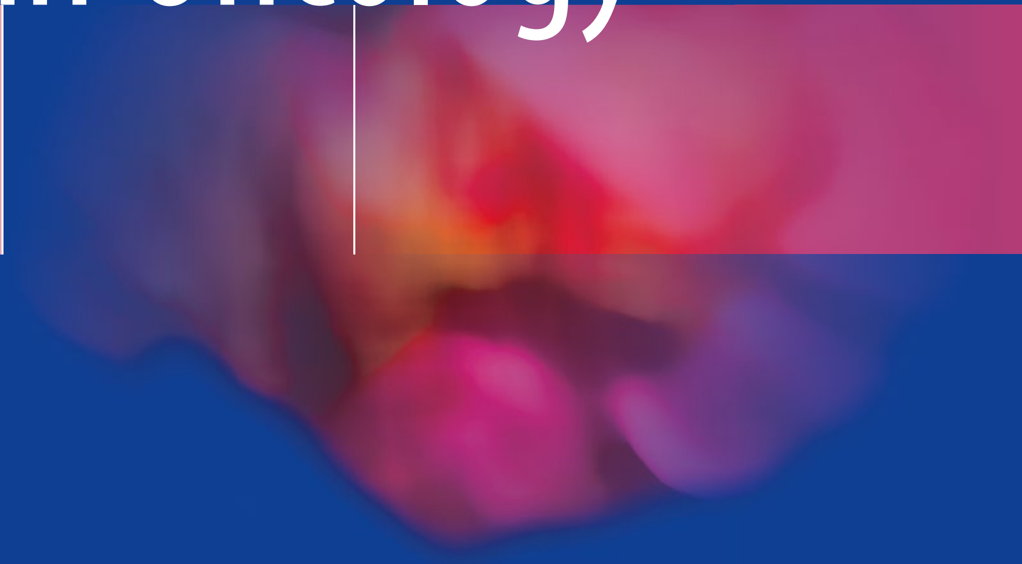
Dying and Death in Oncology



Lawrence Berk
Editor

Springer

Dying and Death in Oncology

Lawrence Berk
Editor

Dying and Death in Oncology

Springer

Editor
Lawrence Berk
Morsani School of Medicine
Tampa General Cancer Center
University of South Florida
Tampa, FL
USA

ISBN 978-3-319-41859-9 ISBN 978-3-319-41861-2 (eBook)
DOI 10.1007/978-3-319-41861-2

Library of Congress Control Number: 2016954970

Printed on acid-free paper

This Springer imprint is published by Springer Nature
The registered company is Springer International Publishing AG Switzerland
The registered company address is: Gewerbestrasse 11, 6330 Cham, Switzerland

Contents

Art of Dying

1

Lawrence Berk

There'll come a time when all of us must leave here
Then nothing sister Mary can do
Will keep me here with you
As nothing in this life that I've been trying
Could equal or surpass the art of dying
Do you believe me?

There'll come a time when all your hopes are fading
When things that seemed so very plain
Become an awful pain
Searching for the truth among the lying
And answered when you've learned the art of dying

But you're still with me
But if you want it
Then you must find it
But when you have it
There'll be no need for it

There'll come a time when most of us return here
Brought back by our desire to be
A perfect entity
Living through a million years of crying
Until you've realized the Art of Dying
Do you believe me?

Written by George Harrison and published by Harrisongs Ltd 1970
Published with permission, Hal Leonard Corporation 2016

L. Berk, MD, PhD
Morsani School of Medicine, University of South Florida, Tampa, FL, USA
e-mail: lberk@health.usf.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_1

Everyone diagnosed with cancer will die. But then, everyone without cancer will also die. It is an inescapable fact that we all will die. What is the risk of dying at any moment in time? The first statistical analysis of the rate of risk of dying was published by the British actuary Benjamin Gompertz in 1825 (Gompertz 1825). He developed the formula now called the Gompertzian function in which the rate of risk of death increases exponentially as we age. This holds for almost all animals, from fruit flies to humans. For humans, the rate of dying doubles every 8 years. This formula is accurate for most of the human life span, but it underestimates the rate of death at very early ages and overestimates it among the very old. The current survival and death probabilities in the United States, based on US census data, was graphed by Brian Skinner on his blog Gravity and Levity (Skinner 2009). As the figures show, the risk of dying starts to rapidly rise at about age 60 (Fig. 1.1).

Skinner's data from 2005 had a doubling of the death rate every 8 years, just as did Gompertz' in 1825. That is not to say life expectancy has not changed. Figure 1.2 shows the life expectancy in Britain over the last 450 years, and there has been a marked increase in life expectancy, from 41 years in 1840 to 79 years in 2010. However, the rate of change of the curve has held constant. What is also clear from the data in Fig. 1.2 is that the maximum life span has changed very little over 160 years, despite the

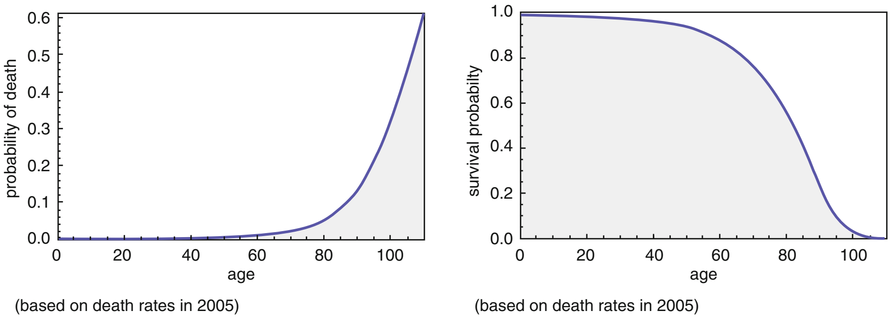


Fig. 1.1 Death and survival in the United States in 2005 (Skinner 2009)

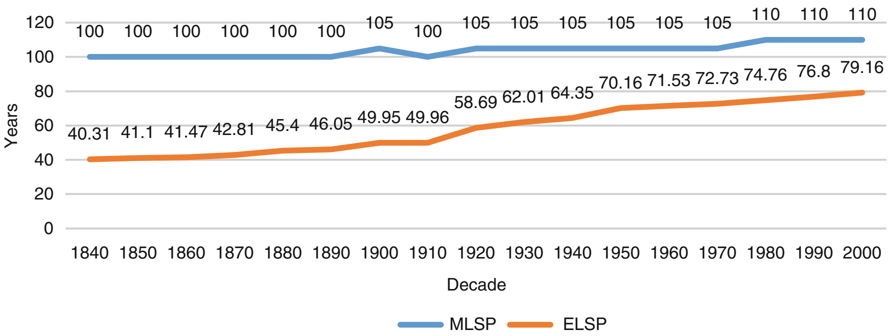


Fig. 1.2 Life expectancy and maximum life span in Britain 1840–2010 (Data are from the human mortality database (http://www.mortality.org/)

dramatic improvement in expected life span. The maximal life span was taken to be the age when less than three standard deviations of the population were alive, that is, less than 0.27 % of the population born in the reference period was still alive.

Gompertz' equation is from line fitting the data and is not explanatory. Why is man designed to die? Why has not natural selection directed us to immortality? Attempts have been made to explain the underlying mechanisms of aging and, ultimately, death. There are three types of explanations. One is an overall theory about the inevitability of aging without specifics as to causes. An example is the utilization of Information Theory and the Second Law of Thermodynamics. The Second Law of Thermodynamics states that entropy (i.e., the randomness of a system) is always increasing (Riggs 1993). As described by Riggs, the entropy that is increasing in the cell and leading to death is an increase in informational entropy of the genome. The informational order in the genome is due to genomic redundancy (the genome has a lot of redundancy, and therefore it has low informational entropy). As people, and more specifically the cells of people, age, there is a rate of error during cell division which causes increased randomness of information and increased entropy, ultimately leading to death. The same approach, but on a more direct causal level, was developed by Bolt and Bergman under the somewhat heavy-handed acronym BOLT (Burn Out Lifespan and Thermosensitivity) (Bolt and Bergman 2015). In their approach, they utilize a systems biology model centered on the sensitivity of proteins to slight variations in temperature, and the resultant loss of redundancy of important proteins leads to aging effects. "To review, BOLT theory suggests that minor fluctuations in thermal energy are the antagonizing agents of age-related changes that result in functional decline. In network terms, we can say that heat alters the properties of nodes (biomolecules) or hubs (highly connected biomolecules) such that the edges (the nature of interactions) between them are modified and topological changes to network architecture allow new properties to emerge." Further, "We can think of a phenotype as the path taken by a ball rolling down that {epigenetic] landscape. Just as in energetics, the ball will follow negative gradients: often moving through narrow canals formed by closely related by relatively unfavorable options. To alter the scaffold and landscape is to alter the route a ball will take and thus an individual's phenotype. The BOLT theory suggests that thermal energy warps the scaffold to elicit different phenotypic outputs" (Bolt and Bergman 2015). This strongly suggests the entropic/heat model of the Second Law of Thermodynamics, and thus evokes the Informational Entropy theory of Riggs.

Another explanatory approach to the cause of aging that has had long-term popularity and a reasonable amount of supporting experimental data is that aging is a function of free radical formation within cells (Perez-Campo et al. 1998). In particular, the formation of free radicals in the mitochondria is at the heart of aging. Early studies suggested that the level of antioxidants correlated with maximal life span. Further studies found that maximal life span correlated better with mitochondrial fee radical formation rate, suggesting that the immediate damage was more important than the ability to detoxify the free radicals (Perez-Campo et al. 1998). There are many other models of aging, but no definitive answer as to the underlying process (DiLoreto and Murphy 2015).

Aging and cancer are mechanistically related. Many of the processes of aging (senescence) are the same processes that lead to the development of cancer (Finkel et al. 2007; Loaiza and Demaria 2016; Serrano and Blasco 2007). As discussed in the chapter on Programmed Cell Death, cells normally stop growing, and ultimately die. Those cells that lose the ability to die become tumor cells. The common term used in the laboratory for cells that continue to grow is “immortal.” Thus, normal cells, such as fetal fibroblasts, may grow in cell culture for a time, but ultimately, after about 50 divisions, they die. This was first noted by Hayflick and Moorhead in 1961 (Hayflick and Moorhead 1961). The first immortal cell line was developed by George and Martha Gey from the cervical cancer of Henrietta Lacks, the HeLa cells (Scherer et al. 1953). Although Henrietta Lack’s cancer cells are immortal, she unfortunately died 8 months after her diagnosis (Finkel et al. 2007). The difference between the eternal growth patterns of cancer cell lines and limited growth of normal cell lines suggests that cell senescence can lead to either of two endpoints: the planned outcome of cell death or the more catastrophic outcome of cancer.

If death is universal, why does it evoke such fear? Some level of death anxiety is part of the human condition. It is doubtful that any other animal has sufficient self-awareness to be able to imagine its own death. In Ancient Greek mythology, it was stated that one of the greatest gifts of Prometheus to man was that he took away the foreknowledge of the time of each person’s death. As Aeschylus wrote in the fifth century BCE:

> “Chorus: Did you perhaps transgress even somewhat beyond this offence? Prometheus: Yes, I caused mortals to cease foreseeing their doom (*moros*).
> Chorus: Of what sort was the cure that you found for this affliction?
> Prometheus: I caused blind hopes (*elpides*) to dwell within their breasts
> Chorus: A great benefit was this you gave to mortals.” (Smyth 1926)

Freud stated that people do not fear death because they have not and cannot experience death. Rather, the fear of death is a representation of another unconscious fear, such as abandonment (Drobot 2015). However, the fear of death (thantophobia) is now often considered a psychological driving force. The most utilized of the current theories on the psychological response to death anxiety is terror management theory (TMT). In TMT, an individual faced directly or indirectly with death (i.e., the death of themselves or others) aim for cultural worldview validation by showing that their core beliefs are correct and culturally accepted and enhanced self-esteem by showing others that they represent these worldviews well. The identification with the culture gives them a feeling that they will have continuity after death through this culture.

> The central premise of this theory is that people have developed two defense mechanisms, namely cultural worldview validation and self-esteem enhancement, in an effort to avoid the terror associated with death. The former defense consists of symbolic social constructions that provide a sense of meaning, order, and permanence. High self-esteem is achieved when an individual believes that he or she meets culturally prescribed standards of value. (Mosher and Danoff-Berg 2007)

Death anxiety can present from a personal risk of death or as a reaction to another person's risk of dying or dying. Thus, TMT predicts that interacting with patients with cancer should cause a negative emotional response. A study by Mosher and Danoff-Berg did not support this conclusion (Mosher and Danoff-Berg 2007). In this trial, college students were presented different vignettes of a man or a woman with cancer, with variation of the type of cancer, and if the person smoked. Only females with high death anxiety showed the expected increased negative response to various vignettes, suggesting that TMT does not predict response to cancer well.

What about death anxiety in patients with advanced cancer? Although all humans know they are mortal, the diagnosis of death strips away much of the temporal distance normally associated with death. Neel and colleagues found that about one-third of patients with advanced cancer had significant death anxiety, as measured on the Death and Dying Distress Scale. They found that death anxiety had a negative correlation with self-esteem (i.e., low self-esteem was associated with higher death anxiety) and positive correlation with age, increased symptom burden, and having younger children (Neel et al. 2015).

Do cancer survivors have increased death anxiety? Is there increased social and familial bonding, as predicted by Terror Management Theory? In looking at this, Little and colleagues define three terms (Little and Sayers 2004):

- Mortality salience: knowing that all people die, but an impersonal knowledge
- Death salience: knowing that I am eventually going to die
- Dying salience: knowing that I am actively dying

The diagnosis of cancer increases mortality salience. It is common for families to unite to ”fight” the cancer. In the modern era, they scour the Internet for hidden cures and bond online with others who have battled cancer. Often, the oncologist, who is not a fellow sufferer, is seen as less invested in their cure than the family or their Internet colleagues. During treatment, they are part of a community of cancer patients, meeting in waiting rooms and chemotherapy infusion centers. But, then the treatment stops, and there are two categories of cancer patients: those that may be cured and those that are not. Those that are cured may still face death salience due to their experience. Those that are not cured now face dying salience. Acceptance of the eventuality of death has to come to all three partners in the disease: the patient, the family, and the medical community. Patients may accept their imminent death, that is, have dying salience, but defer to their families who reject dying and demand that the patient seek further therapy. In a recent survey of families after the patient's death, they stated that the goal of the patient and family even at the end of life was to prolong survival in 30 % of patients and to provide comfort in 70 % of patients (Wright et al. 2016). The physician may find it easier to avoid the inevitability of the patient's death by offering ineffective treatments and false hope, rather than directly address the issue of death. Thirteen percent of patients in the United States receive chemotherapy within the last 30 days of their life and 33 % have chemotherapy within the last 180 days of their life. Forty percent of patients in the United States have an intensive care unit admission in the last 180 days of their life and 11 % within the last 30 days of life (Bekelman et al. 2016).

Thus, we return to the "Art of Dying". In this book, we expand beyond the medical aspects of dying and into the physical, cultural, historical, economical, and theological aspects of dying, with the focus on cancer. The goal is help educate all of the parties involved in the process to assist them in learning the art of dying. And I hope this book gives a modicum of increased peace to the survivors.

References

Bekelman JE, Halpern SD, Blankart CR, Bynum JP, Cohen J, Fowler R, Kaasa S, Kwietniewski L, Melberg HO, Onwuteaka-Philipsen B, Oosterveld-Vlug M, Pring A, Schreyogg J, Ulrich CM, Verne J, Wunsch H, Emanuel EJ, International Consortium for End-of-Life Research (ICELR) (2016) Comparison of site of death, health care utilization, and hospital expenditures for patients dying with cancer in 7 developed countries. JAMA 315:272–283

Bolt K, Bergman A (2015) Systems biology of aging. Adv Exp Med Biol 847:163–178

DiLoreto R, Murphy CT (2015) The cell biology of aging. Mol Biol Cell 26:4524–4531

Drobot A (2015) Freud on death. Romanian Association for Psychoanalysis Promotion. http://www.freudfile.org/psychoanalysis/papers_11.html. Accessed 02/05 2016

Finkel T, Serrano M, Blasco MA (2007) The common biology of cancer and ageing. Nature 448:767–774

Gompertz B (1825) On the nature of the function expressive of the law of human mortality, and on a new mode of determining the value of life contingencies. Phil Trans Royal Soc Lond 115:513–583

Hayflick KL, Moorhead PS (1961) The serial cultivation of human diploid cell strains. Exp Cell Res 25:585–621

Little M, Sayers EJ (2004) The skull beneath the skin: cancer survival and awareness of death. Psychooncology 13:190–198

Loaiza N, Demaria M (2016) Cellular senescence and tumor promotion: is aging the key? Biochim Biophys Acta 1865:155–167

Mosher CE, Danoff-Berg S (2007) Death anxiety and cancer-related stigma: a terror management analysis. Death Stud 31:885–907

Neel C, Lo C, Rydall A, Hales S, Rodin G (2015) Determinants of death anxiety in patients with advanced cancer. BMJ Support Palliat Care 5:373–380

Perez-Campo R, Lopez-Torres M, Cadenas S, Rojas C, Barja G (1998) The rate of free radical production as a determinant of the rate of aging: evidence from the comparative approach. J Comp Physiol B 168:149–158

Riggs JE (1993) Aging and mortality: manifestations of increasing informational entropy of the genome? Mech Ageing Dev 66:249–256

Scherer WF, Syverton JT, Gey GO (1953) Studies on the propagation in vitro of poliomyelitis viruses. IV. Viral multiplication in a stable strain of human malignant epithelial cells (strain HeLa) derived from an epidermoid carcinoma of the cervix. J Exp Med 97:695–710

Serrano M, Blasco MA (2007) Cancer and ageing: convergent and divergent mechanisms. Nat Rev Mol Cell Biol 8:715–722

Skinner B (2009) Your body wasn't built to last: a lesson from human mortality rates. at https://gravityandlevity.wordpress.com/2009/07/08/yourbody-wasnt-built-to-last-a-lesson-from-human-mortality-rates/

Smyth H (1926) Aeschylus vol 1: promethus bound. Harvard University Press, Cambridge, MA

Wright AA, Keating NL, Ayanian JZ, Chrischilles EA, Kahn KL, Ritchie CS, Weeks JC, Earle CC, Landrum MB (2016) Family perspectives on aggressive cancer care near the end of life. JAMA 315:284–292

Dying: What Happens in the Cells and Tissues

2

Lawrence Berk

2.1 History of the Studies on the Cellular Basis of Death

There are various formulations of the question as to why we die. This is often asked in a philosophical sense or theological sense. It is also an important question in cell biology. The last several decades have had an exponential increase in the knowledge of the mechanisms of cell death. However, interest in the question of the biology of death arose with the beginning of Western science. For example, the question of why the corporeal body dies was analyzed in detail by Aristotle in 350 BC. In *On Youth and Old Age, On Life and Death, On Breathing*, he states: "To be born and to die are common to all animals, but there are specifically diverse ways in which these phenomena occur; of destruction there are different types, though yet something is common to them all. There is violent death and again natural death, and the former occurs when the cause of death is external, the latter when it is internal, and involved from the beginning in the constitution of the organ, and not an affection derived from a foreign source. In the case of plants the name given to this is withering, in animals senility" (Aristotle (Translated by G. R. T. Ross) 2009). Aristotle held that death is caused by the exhaustion of the heat of the body. Heat is generated from nutrition, and this heat is counterbalanced by the cooling of respiration. This cooling occurs in the lungs among air-breathing animals and from water in aquatic life. The heat can be dissipated through excessive cooling, such as when the body is opened by violence to the air. It can also be dissipated during illness, when there is too much heat consumed without sufficient fuel to replenish it. Natural death, that is, death from old age, like the withering of a plant, is from the gradual exhaustion of the inner, innate nutrient that is needed for life. This is the fate of all living objects if they escape an unnatural death.

L. Berk, MD, PhD
Morsani School of Medicine, University of South Florida, Tampa, FL, USA
e-mail: lberk@health.usf.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_2

The modern exploration of cell death got its impetus from investigations into embryology and the growth and development of organisms. The first modern description of cell death was given by Carl Vogt in 1842 based upon his investigation on the development of the midwife toad (Vogt 1842). In his discussion, he described the loss of original cells and their replacement with new ones during development. Rudolph Virchow commented on natural versus unnatural cell death in his 1859 textbook *Cellular Pathology*: "Necrobiosis is death brought on by (altered) life, a spontaneous wearing out of living parts, the destruction and annihilation consequent upon life, natural as opposed to violent death (mortification)" (Virchow as quoted in Majno and Joris (1995)). Improved microscopes and tissue preparation techniques available in the latter half of the nineteenth century accelerated the research into cell death.

The modern science of cell death has evolved over the last 40–50 years. In analogy to Aristotle, natural cell death is separated from cell death due to violence. Natural cell death, called programmed cell death, is broadly broken down into three types: Type 1 (apoptosis), Type 2 (autophagy), and Type 3 (programmed necrosis). The term programmed cell death was coined in the 1970s to describe controlled cell death involved in tissue development. The field traces its modern development to the work on the development of the nematode worm *Caenorhabditis elegans* embryo (reviewed in (Lockshin and Zakeri 2001)). It was shown that specific genes were involved in controlled cell death during development. It was also found that many of these genes were also expressed in other animal genomes, including the human genome.

2.2 Programmed Cell Death

This is the only chapter that embraces death as the desired outcome. The cellular basis of cancer is the inability of a cell to appropriately die. As described by Cooper, "The fundamental abnormality resulting in the development of cancer is the continual unregulated proliferation of cancer cells. Rather than responding appropriately to the signals that control normal cell behavior, cancer cells grow and divide in an uncontrolled manner, invading normal tissues and organs and eventually spreading throughout the body. The generalized loss of growth control exhibited by cancer cells is the net result of accumulated abnormalities in multiple cell regulatory systems and is reflected in several aspects of cell behavior that distinguish cancer cells from their normal counterparts" (Cooper 2000).

2.2.1 Apoptosis

The most common, and most studied, form of programmed cell death is apoptosis. The first descriptions of apoptosis focused on the morphological changes seen in cells. Apoptosis is characterized by changes in the nucleus, with chromatin condensation and nuclear fragmentation (Fig. 2.1). As described by Ziegler and Groscurth,

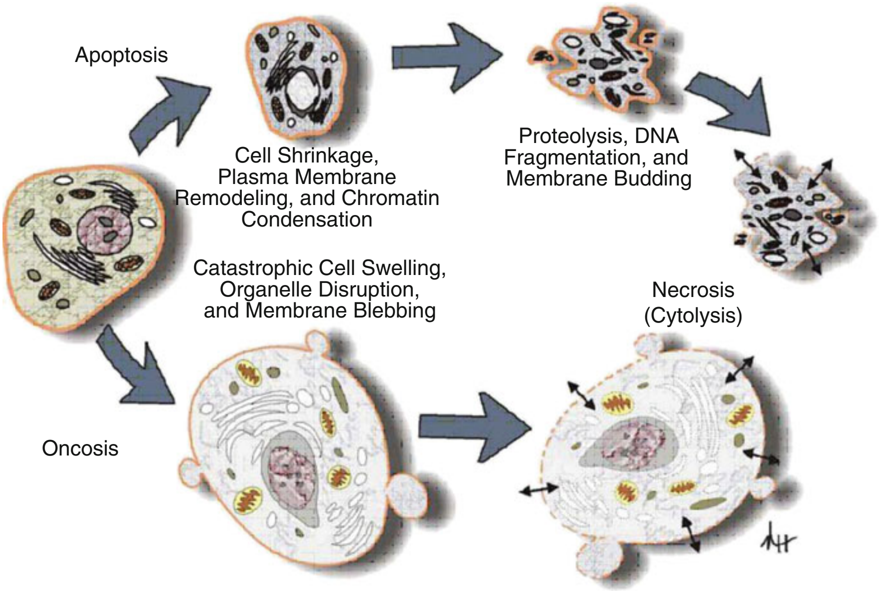


Fig. 2.1 Morphology of cell deaths (Grasso et al. 2012)

"The condensation starts peripherally along the nuclear membrane, forming a crescent or ringlike structure. During later stages of apoptosis the nucleus further condenses, and finally it breaks up inside a cell with an intact cell membrane, a feature described as karyorrhexis" (Ziegler and Groscurth 2004). Early in the apoptotic process, the dying cells pull away from the other cells. The cells develop blebs which are protrusions of the cell surface membrane. Then, the blebs, containing cell organelles and the cell debris generated during the apoptosis, break off from the cell and are engulfed by phagocytic cells and then degraded within the phagocytic cells. Thus, as stated in the Nomenclature Committee on Cell Death statement on the definition of apoptosis, " Apoptosis is accompanied by the rounding-up of the cell, retraction of pseudopods, reduction of cell volume (pyknosis), chromatin condensation, nuclear fragmentation (karyorrhexis), classically little or no ultrastructural modifications of the cytoplasmic organelles, plasma membrane blebbing (but maintenance of its integrity until the final stages of the process) and engulfment by resident phagocytes (in vivo)" (Kroemer et al. 2009). Apoptosis occurs without significant surrounding inflammation, because the entire lytic process takes place within intact cell membranes.

The molecular and genetic basis of apoptosis has been extensively explored. Defining programmed cell death by biochemical processes rather than morphological changes allows better elucidation of differences in processes, because the end result of many different biochemical processes can look the same. Based on a molecular–mechanistic approach, apoptosis can be further divided into extrinsic apoptosis and intrinsic apoptosis. Figure 2.2 from (Vucic et al. 2011) shows a model

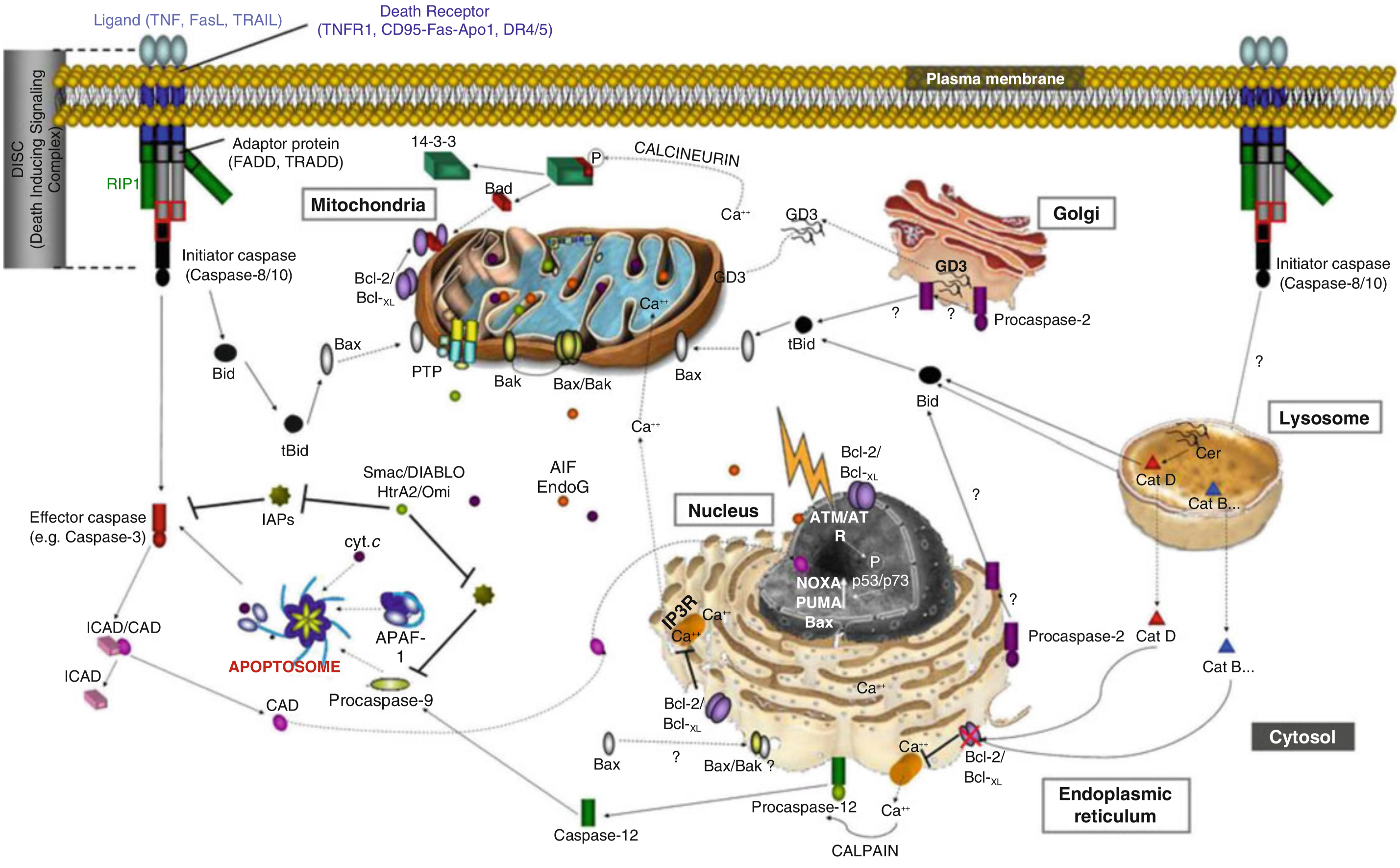


Fig. 2.2 Apoptosis from Apraiz et al. (2011)

of the intrinsic and extrinsic pathways. The extrinsic pathway initiates cell death by activation of cell surface receptors. The surface receptors that initiate the process are called death receptors, and these include the receptors for CD95 (Fas/Apo1), tumor necrosis factor-related apoptosis-inducing ligand (TRAIL), and tumor necrosis factor alpha (TNFα). These receptors all have a trans-cytoplasmic “death domain” that transmits the signal from the extracellular milieu to inside of the cell (Ashkenazi and Dixit 1998). Binding of the cognate ligand (e.g., TNFα with the surface membrane TNFα receptor) activates a process leading to the formation of the death-inducing signaling complex (DISC). The DISC then initiates the activation of procaspase 8. Caspases are aspartic proteases that require the presence of a cysteine to be active (i.e., cysteine-dependent aspartate-specific protease, or caspase). Caspases are primarily involved in two processes – apoptosis and inflammation (McIlwain et al. 2013). Caspases 3, 6, 7, 8, and 9 are involved in apoptosis, and 1, 4, 5, and 12 in inflammation. Because the caspases involved in apoptosis will lead to cell death, when not involved in apoptosis they are in the cell in the inactive state as procaspases.

The extrinsic apoptosis process continues with the conversion and activation of procaspase 8 to caspase 8 by dimerization and cleavage of the procaspase. Caspase 8 is an initiator caspase, and it then converts the procaspases 3 and 7 into the executioner caspases 3 and 7, which then initiate the apoptosis process and cell death. Apoptosis is a rapid process, and leads to the elimination of the cell often in less than 24 h. As noted previously, this process occurs without developing an inflammatory response. The caspase mechanisms in apoptosis are shown in Fig. 2.3.

The other mechanism of apoptosis is termed intrinsic apoptosis and is induced by intracellular stress or damage. It can also occur during normal development. Intrinsic apoptosis starts when caspase 9 is activated. This occurs when a stress causes the mitochondria to release cytochrome c, and the cytochrome c then binds with the adapter protein, apoptotic protease activating factor-1 (APAF1). Seven activated APAF-1 molecules assemble with caspase 9 monomers and cytochrome c to activate the caspase 9 by dimerization. The complex of the cytochrome c, APAF-1, and active caspase 9 is called the apoptosome (McIlwain et al. 2013). The active caspase 9 then activates caspase 3 and enters into the same executioner phase as the extrinsic apoptosis process.

Intrinsic apoptosis is not receptor-initiated, but is controlled by stimuli that change the internal milieu (Elmore 2007). For example, the absence of growth factors can cause a failure of the suppression of intrinsic apoptosis and therefore the start of the death cascade. The cascade can be stimulated by stresses such as hypoxia and by cell-damaging agents such as radiation and free radicals. Whatever might be the agent, there is induction of changes in the mitochondrial membrane which opens the mitochondrial permeability transition (MPT) pore which then allows the release of cytochrome c into the cytosol (as described above). Mitochondrial membrane integrity is regulated by the Bcl-2 family of proteins. These can be pro-apoptotic or anti-apoptotic. Among the Bcl-2 proteins that inhibit apoptosis are Bcl-2, Bxl-2, Bcl-w, Mcl-1, and Bcl2L10. Those that promote apoptosis include Bax, Bak, Bok,

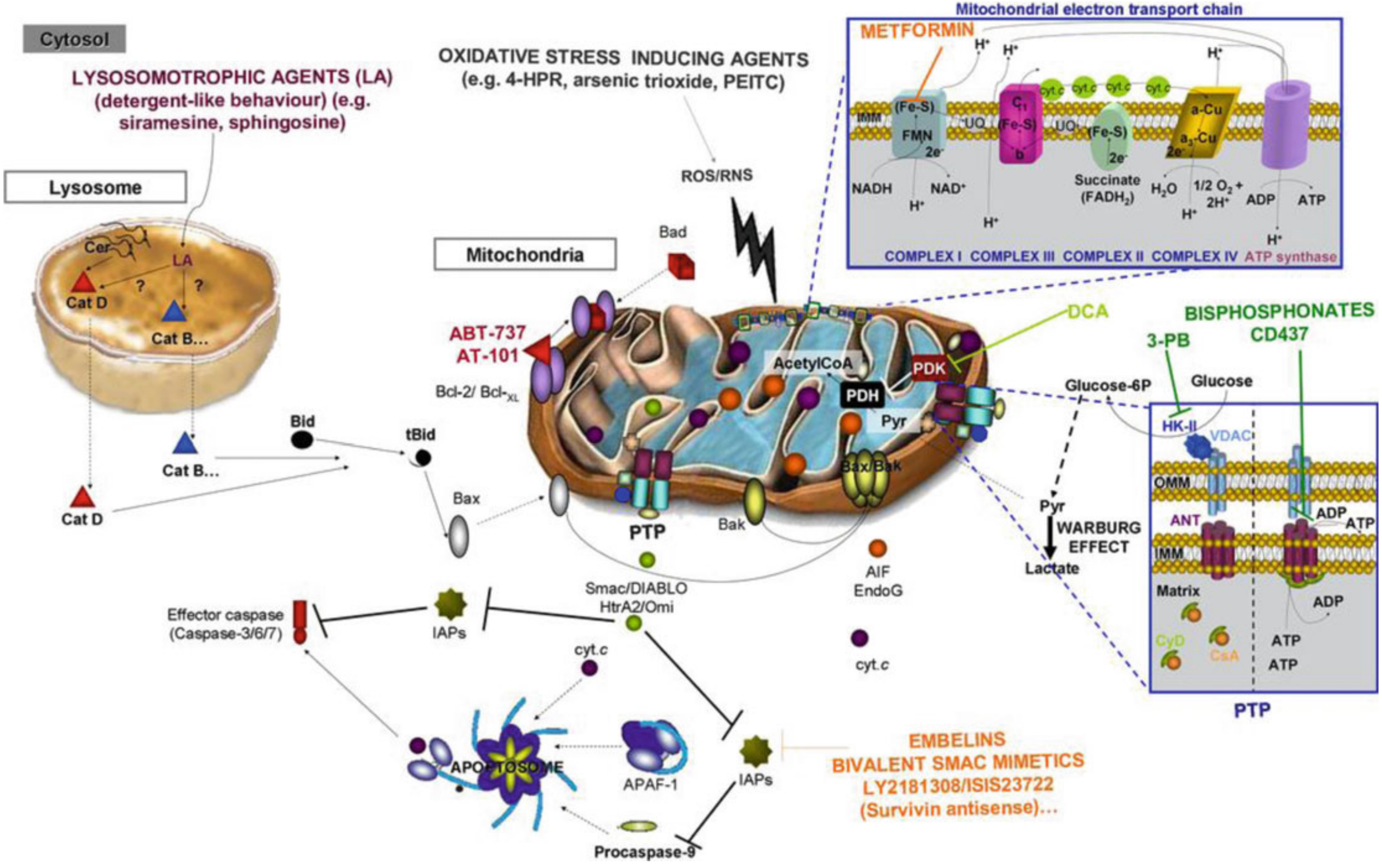


Fig. 2.3 Mechanisms of cancer treatment induction of apoptosis (Apraiz et al. 2011)

Bid, Bad, Noxa, Puma, and Bim (Arya and White 2015). This will be discussed as part of the role of apoptosis in cancer treatment.

2.2.2 Autophagy

The second major form of programmed cell death is autophagy. The majority of research on autophagy has been on yeast, but similar pathways are in mammalian cells. There are three forms of autophagy: microautophagy, macroautophagy, and chaperone-mediated autophagy. In all the three cases, the goal of autophagy is the proteolysis of cytosolic contents by lysozymes. In microautophagy, this occurs by direct incorporation of the material into lysosomes through membrane invagination. In chaperone-assisted autophagy, the material is directed across the lysosomal membrane by a protein complex. In macroautophagy, the material to be degraded is first encased in a membrane and then degraded after this complex fuses with a lysosome (Glick et al. 2010). This latter process, macroautophagy, will be discussed here and will be called by the generic term "autophagy." Autophagy is initiated when there is a stress on a cell such as starvation or hypoxia. On the morphological level, autophagy is characterized by degenerating cytoplasmic material inside double-membraned vesicles called autophagosomes, which then merge with lysosomes to form autolysosomes. Within the autolysosome, the cellular debris and the inner membrane of the autolysosome are dissolved by the acidic lysosomal hydrolases (Kroemer et al. 2009).

As mentioned previously, autophagy has been primarily studied in yeast. Autophagy in mammals is not as well elucidated. Macroautophagy (again, generally referred to as autophagy) is nonspecific, with the cellular debris swept randomly into the autophagosomes. The cause of the formation of the autophagosome membranes in man is unknown. In yeast, the phagophore membrane is formed around the preautophagosomal structure (PAS), but a similar structure has not been found in mammals (Glick et al. 2010). The primary proteins involved in autophagy in yeast are the Atg proteins. The homologs in mammals are called the ATG proteins. The primary Atg protein is the Atg1 kinase complex. The homolog in mammals is the ULK1/2 complex (Feng et al. 2014).

Selective autophagy is similar to macroautophagy, except that there is receptor-mediated binding of specific compounds into the autophagosomes rather than random debris. An example is mitophagy, in which senescent mitochondria are degraded by autophagy (Youle and Narendra 2011). It is uncertain if autophagy is an important form of cell death. Although autophagosomes are seen in dying cells, they may represent failed protection of the cells rather than a mode of death of the cells (Fuchs and Steller 2015). A review of 1400 active or potential anticancer agents showed that none caused autophagic cell death, although signs of autophagy could be found. Further, elimination of genes necessary for autophagy, such as *ATG5* and *ATG7*, accelerated rather than inhibited cell death (Shen et al. 2012).

2.2.3 Necrosis

The third major classification of programmed cell death is death by necrosis. This was the last to be understood to be under the control of molecular mechanisms. Historically, it was thought that necrosis was a passive form of cell death, similar to Aristotle's death by violence (Ziegler and Groscurth 2004). It is now recognized that there are distinct regulatory proteins that can be involved in necrosis (Feoktistova and Leverkus 2015). The morphological changes of necrosis include increased cell volume, swelling of the cellular organelles, and then rupture of the cell membrane with cell death (Kroemer et al. 2009). The most studied form of programmed necrosis is necroptosis. In necroptosis, TNF-1 stimulates the TNF receptor 1 (TNFR1). The receptor-interacting protein kinase 1 (RIPK1) then binds with the TNFR1-associated death domain (TRADD) to form the RIPK1- and TRADD-dependent receptor-bound complex 1. This complex then activates nuclear factor-kB (NF-kB), which causes inhibition of apoptosis and ultimately the formation of a cytosolic death-inducing signaling complex (DISC) and a cascade that results in regulated necrosis and cell death (Vanden Berghe et al. 2014). Necroptosis is defined as necrosis involving activation of RIPK1 and RIPK. The RIPK1–RIPK3 complex is called the necrosome (Feoktistova and Leverkus 2015). Much of the pathway leading from TNF stimulation of the cell surface membrane death receptors (discussed above in relation to apoptosis) through to necroptosis is shared with apoptosis, and necroptosis primarily occurs when the apoptotic pathway is inhibited (Vanlangenakker et al. 2012). Necroptosis can also be stimulated by viruses such as human immunodeficiency virus type 1 (HIV-1), herpes simplex virus type-1 (HSV-1), the West Nile virus (WNV), and the murine cytomegalovirus (MCMV). Bacterial infections, such as *Shigella flexneri*, *Neisseria gonorrhoeae*, and *Klebsiella pneumoniae*, can also stimulate necroptosis. Physicochemical stressors such as radiation and chemotherapy can also induce necroptosis (Vanlangenakker et al. 2012). There are other forms of programmed necrosis using other pathways to a similar morphological endpoint. These include ferroptosis, oxytosis, ETosis, NETosis, cyclophilin D-mediated necrosis, parthanatos, pyroptosis, and pyronecrosis (see (Vanden Berghe et al. 2014) for a review).

2.3 Phagosomes and Lysosomes and Cell Content Degradation

All of the programmed and necrotic cell death mechanisms ultimately must degrade the components of the cells back into their original building blocks, such as fats, amino acids, and nucleic acids. This process is accomplished by phagosomes and lysosomes. Phagocytes are cells that can ingest other cells and cellular debris. Whereas the elimination of a pathogen, such as bacteria, can induce an immune response, clearance of the products of apoptosis usually induces no immune response. One suggestion is to call the latter process "efferocytosis," based on the Latin term "efferre" meaning "to take to the grave" or "to bury" (Henson and Hume 2006). This process can be broken down into four steps: the dying cell sends out a "find me" signal; then the phagosome finds and recognizes the dying cell; next the phagocytes engulf the dying cell; and finally the phagosome digests the cell (Ravichandran and Lorenz 2007). The "find me" signals from the dying cell include the nucleotides ATP and UTP, the chemokine fractalkine (CX3CL1), and the lipids lysophosphatidylcholine (LPCAT1) and sphingosine-1-phosphate (S1P, lysosphingolipid) (Arandjelovic and Ravichandran 2015). The apoptotic cell presents a surface signal on its surface, such as the lipid phosphatidylserine (PtdSer). In healthy cells, this lipid is only on the inner side of the membrane, and it is exposed in apoptotic cells (Balsubramanian and Schroit 2003). Healthy cells can also avoid engulfment with protective surface signals, including CD47 and CD31 (Arandjelovic and Ravichandran 2015). Once the phagosome has identified the cell to be degraded, it then starts the engulfment process. This engulfment is macroautophagy, as described above, in which an autophagosome is formed. This starts with the formation of the phagophore membrane, probably from multiple sources including the Golgi complex, the endoplasmic reticulum, and mitochondria. The membrane then grows circularly around the contents to be engulfed (such as cells or organelles) and ultimately forms a complete membrane around the cargo, which is called an autophagosome. The autophagosome can then fuse with other endosomes containing debris to be degraded. Finally, the autophagosome fuses with a lysosome (or lysosomes) for the final processing of the cargo (Mijaljica et al. 2012).

Lysosomes are single-membrane vesicles that contain hydrolytic enzymes to degrade cell contents (Boya 2012). The enzymes within the lysomes are only active at acidic pH, and ATPase proton pumps maintain an intra-vacuole pH of 4.6–5.0 (Mellman et al. 1986). The mechanism of fusion of the lysosomes with the autophagosomes is not completely elucidated. The current belief, based on time-lapse focal microscopy, is that there is a combination of fusion of the two organelles and of "kissing" in which there is contact and transfer of the autophagosome contents into the lysosome for degradation (Luzio et al. 2007). There, the cellular contents are degraded and then transported back to the cytosol for reuse.

Lysosomes are also involved in apoptosis (Mrschtik and Ryan 2015). Induction of lysosomal membrane permeation, for example, through proteins accumulated in the lysosomal membrane or from reactive oxidative species generated within the lysosome, can cause release of lysosomal enzymes. The enzymes implicated in lysosomal induction of apoptosis include the aspartic cathepsin D and the cysteine cathepsins B, C, F, H, K, L, O, S, V, W, and X (Mrschtik and Ryan 2015). Cathepsin D may be directly involved in apoptosis initiation through interaction with the proapoptotic Bcl-2 proteins Bax and Bid. Other studies suggest that the released lysosomal enzymes may not initiate apoptosis but can enhance it (Oberle et al. 2010).

2.4 Programmed Cell Death and Cancer

A cancer cell can be described as a cell that has malfunctioning normal cell death mechanisms. That is, programmed cell death, primarily apoptosis, is not active, allowing the cells to have unchecked growth. Autophagy is also malfunctioning, both in allowing the abnormality to occur rather than removing it and in allowing the cells to survive. The normalization of programmed cell death is therefore a prime target for the treatment of cancer. As stated earlier, cell death is perhaps the only area of cancer where death is welcomed.

Resistance to apoptosis can be seen in carcinogenesis, tumor progression, and the development of resistance to treatment (Mohammad et al. 2015). Apoptotic activity is a function of balance between the pro-apoptotic proteins and the anti-apoptotic proteins. Disruption of this normal balance toward the anti-apoptotic proteins can encourage cancer cell growth (Kang and Reynolds 2009). For example, the Bcl-2 family contains both pro-apoptotic and anti-apoptotic members. Pro-apoptotic Bcl-2 proteins such as BAX and BAK are required for activation of the mitochondrial outer membrane permeabilization (MOMP) process of the intrinsic apoptotic pathway. These two proteins can be stimulated by BIM, BID BAD, and PUMA. They are inhibited by Bcl-2, BCL-X, Bcl-2A1, BCL-W, and MCL-1. The overexpression of anti-apoptotic proteins can be found in different cancer clones. Some cancer cells are "Bcl-2 dependent" for survival, and as such are dependent on Bcl-2 or Bcl-2-like proteins for apoptotic inhibition and growth (Juin et al. 2013). Figure 2.4 highlights the potential therapeutic intervention sites in the apoptosis pathway.

A potentially efficacious therapeutic modality is to activate apoptosis and cancer cell death through manipulation of the Bcl-2 interactions. This has been explored in the laboratory and in the clinic. One approach is with BH3 mimetics. The BH3 domain is a sequence of 15 amino acids that binds to a hydrophobic groove in the

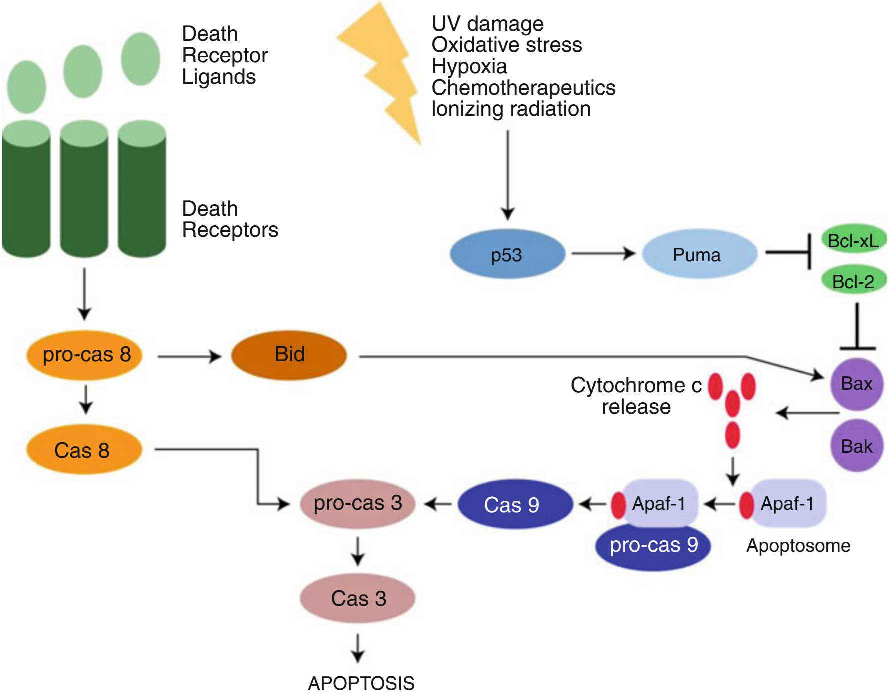


Fig. 2.4 Caspase mechanisms (Panayi et al. 2013)

anti-apoptotic proteins of the Bcl-2 family, thereby inhibiting their anti-apoptotic activity and activating apoptosis. At least 20 compounds have been explored as BH3 mimetics to stimulate apoptosis (see the review by Vela and Marzo (2015)). Of these, the two most studied are the natural product gossypol and ABT-737.

Gossypol is extracted from cottonseed oil. Along with being explored for use to treat cancer, it is also being looked at as a male contraceptive, to lower cholesterol, and as an antibacterial and antiviral agent (Keshmiri-Neghab and Goliaei 2014). Gossypol is a polyphenolic bis-sesquiterpene that is extracted from cottonseed oil as a racemic mixture. Both the natural racemic mixture and the more active R-(-) enantiomer (AT-101) have been explored for cancer treatment. Gossypol has multiple activities, including inhibiting DNA replication and repair, inhibiting cell cycling, as well as inducing apoptosis (Keshmiri-Neghab and Goliaei 2014). The mechanisms inhibiting apoptosis include inactivation of cMyc, post-translational modification of the Akt, and downregulation of inhibitors of apoptosis, including inhibitors of apoptosis (IAPs). Gossypol also induces release of cytochrome c from mitochondria, thereby initiating the intrinsic apoptosis pathway, and acts as a BH3 mimetic and induces apoptosis. So far in Phase II clinical trials, AT-101 was found to be tolerable to patients but showed no significant survival advantage in prostate cancer, small cell lung cancer, or nonsmall cell lung cancer (Baggstrom et al. 2011; Ready et al. 2011; Sonpavde et al. 2012).

There is also extensive preclinical research on the Bcl-2 mimetic ABT-737 and its oral form ABT-263 (navitoclax). ABT-737 binds to Bcl-2, BCL-X_L, and BCL-W. In-vitro ABT-737 induces apoptosis in a wide variety of tumor cell lines (Billard 2013). Single agent navitoclax was active in a Phase I study of leukemia (Roberts et al. 2012) and not active as a single agent in a Phase II study in relapsed small cell lung cancer (Rudin et al. 2012).

An alternative approach to modulating Bcl-2 overexpression is to inhibit the synthesis of Bcl-2. Oblimersen sodium is an 18 mer antisense oligonucleotide that targets the first six codons of Bcl-2 RNA. It attaches to the Bcl-2 RNA and inhibits its transcription (No author listed 2007). Preclinical research suggested that oblimersen is synergistic with chemotherapy (Moreira et al. 2006). A randomized Phase III trial for high-risk melanoma patients of dacarbazine with or without oblimersen showed no survival advantage for the oblimersen (Bedikian et al. 2014). A randomized trial of fludarabine and cyclophosphamide with or without oblimersen for relapsed or refractory chronic lymphocytic leukemia showed no overall advantage with oblimersen, but there was a higher response rate, and for patients who responded to treatment there was a significant increase in 5-year survival (O'Brien et al. 2009). A trial of dexamethasone with or without oblimersen for patients with refractory or relapsed advanced multiple myeloma showed no time to progression or response advantage with oblimersen (Chanan-Khan et al. 2009). A trial for castration-resistant prostate cancer of docetaxel with or without oblimersen showed no increase in response rate with oblimersen. Similarly, a randomized study of patients with extensive staged small cell lung cancer comparing carboplatin and etoposide with or without oblimersen did not show any outcome improved by oblimersen (Rudin et al. 2008).

Myeloid cell leukemia-1 (Mcl-1) is a prosurvival Bcl-2 protein which is overexpressed in many cancers (Akgul 2009). Inhibition of Mcl-1 sensitizes cancer cells to both chemotherapy and radiation therapy (Warr and Shore 2008). The levels of Mcl-1 in cells can be increased due to stimulation of transcription of Mcl-1, as seen in myeloma cells. In myeloma cells, the upregulation involves the JAK/STAT pathway which induces IL-6 and IFN-α signaling and Mcl-1 transcription (Puthier et al. 2001). Mcl-1 translation is under the control of the micro-RNA mir-29b (Mott et al. 2007). Mcl-1 has a short post-translation lifetime and is degraded through ubiquitin-dependent protein degradation by the 26S proteasome (Warr and Shore 2008). Inhibition of the degradation leads to inhibition of apoptosis and protection from cisplatin and etoposide treatments (Zhong et al. 2005). Mcl-1 dependence was shown to predict outcome to treatment of patients with acute myeloid leukemia receiving vorinostat and gemtuzumab ozogamicin (Pierceall et al. 2014). Similarly, Mcl-1 expression predicts progression-free survival in patients with chronic lymphocytic leukemia treated with pentostatin, cyclophosphamide, and rituximab (Awan et al. 2009). As of yet, no intervention has been tested that is designed to increase Mcl-1 degradation and allow increased apoptosis.

Autophagy is in general thought to be involved in the resistance and sensitivity to cancer treatments, and to carcinogenesis (Panda et al. 2015). Hydroxychloroquine has been studied in several cancers as an autophagy inhibitor. The goal is to increase sensitivity of the cancer cells to the stress of radiation therapy or chemotherapy. The addition of increasing doses of hydroxychloroquine with temozolomide and radiation therapy did not show significant inhibition of autophagy at the maximum dose used (600 mg/g) and did not show an improvement in survival (Rosenfeld et al. 2014). Hydroxychloroquine and temozolomide for solid tumors and melanoma showed some evidence of autophagic inhibition (Rangwala et al. 2014b). A similar trial for the same patients but using hydroxychloroquine and temsirolimus showed similar results (Rangwala et al. 2014a). There have been similar trials with hydroxychloroquine and the HDAC inhibitor vironostat and with bortezomib which show potential activity (Mahalingam et al. 2014; Vogl et al. 2014). These studies are looking at inhibiting autophagy to increase sensitivity to treatment. No studies have looked at increasing autophagy as a mode of cancer cell death. As discussed above, there is a question as to whether autophagic cell death has any role in cancer (Shen et al. 2012).

Finally, there are no clinical trials of necroptosis-specific agents for cancer, although many agents in use may induce necroptosis (Fulda 2014).

Conclusion

Cancer is a disease that often leads to death. On the cellular level, cancer is a disease that is based on the lack of death. Causing the increased programmed cell death of cancer cells has extensive preclinical data suggesting that reversing the inhibition of cell death through activating apoptosis or necroptosis should improve the outcomes of the patients. However, this has not been borne out in clinical trials. As is very often the case, the treatment of human cancer is far more complex and difficult than the treatment of in vitro and in vivo models of cancer.

Nonetheless, this is an intriguing area of potential treatment, and of the use of dying and death for the good of the patient.

References

Akgul C (2009) Mcl-1 is a potential therapeutic target in multiple types of cancer. Cell Mol Life Sci 66:1326–1336

Apraiz A, Boyano MD, Asumendi A (2011) Cell-centric view of apoptosis and apoptotic cell death-inducing antitumoral strategies. Cancers (Basel) 3:1042–1080

Arandjelovic S, Ravichandran K (2015) Phagocytosis of apoptotic cells in homeostasis. Nat Immunol 16:907–917

Aristotle (Translated by G. R. T. Ross) (2009) On youth and old age, on life and death, on breathing. MIT, Boston. Available at http://classics.mit.edu/Aristotle/youth_old.html

Arya R, White K (2015) Cell death in development: Signaling pathways and core mechanisms. Semin Cell Dev Biol 39:12–19

Ashkenazi A, Dixit VM (1998) Death receptors: signaling and modulation. Science 281:1305–1308

Awan FT, Kay NE, Davis ME, Wu W, Geyer SM, Leung N, Jelinek DF, Tschumper RC, Secreto CR, Lin TS, Grever MR, Shanafelt TD, Zent CS, Call TG, Heerema NA, Lozanski G, Byrd JC, Lucas DM (2009) Mcl-1 expression predicts progression-free survival in chronic lymphocytic leukemia patients treated with pentostatin, cyclophosphamide, and rituximab. Blood 113:535–537

Baggstrom MQ, Qi Y, Koczywas M, Argiris A, Johnson EA, Millward MJ, Murphy SC, Erlichman C, Rudin CM, Govindan R, Mayo Phase 2 Consortium, California Consortium (2011) A phase II study of AT-101 (Gossypol) in chemotherapy-sensitive recurrent extensive-stage small cell lung cancer. J Thorac Oncol 6:1757–1760

Balsubramanian K, Schroit AJ (2003) Aminophopholipid asymmetry: a matter of life and death. Annu Rev Physiol 65:701–734

Bedikian AY, Garbe C, Conry R, Lebbe C, Grob JJ, Genasense Melanoma Study Group (2014) Dacarbazine with or without oblimersen (a Bcl-2 antisense oligonucleotide) in chemotherapy-naive patients with advanced melanoma and low-normal serum lactate dehydrogenase: 'The AGENDA trial'. Melanoma Res 24:237–243

Billard C (2013) BH3 mimetics: status of the field and new developments. Mol Cancer Ther 12:1691–1700

Boya P (2012) Lysosomal function and dysfunction: mechanism and disease. Antioxid Redox Signal 17:766–774

Chanan-Khan AA, Niesvizky R, Hohl RJ, Zimmerman TM, Christiansen NP, Schiller GJ, Callander N, Lister J, Oken M, Jagannath S (2009) Phase III randomised study of dexamethasone with or without oblimersen sodium for patients with advanced multiple myeloma. Leuk Lymphoma 50:559–565

Cooper GM. (2000) The development and causes of cancer. In: The cell: a molecular approach, 2nd edn. Sinnauer Associates, Sunderland MA Available from: http://www.ncbi.nlm.nih.gov/books/NBK9963/

Elmore S (2007) Apoptosis: a review of programmed cell death. Toxicol Pathol 35:495–516

Feng Y, He D, Yao Z, Klionsky DJ (2014) The machinery of macroautophagy. Cell Res 24:24–41

Feoktistova M, Leverkus M (2015) Programmed necrosis and necroptosis signalling. FEBS J 282:19–31

Fuchs Y, Steller H (2015) Live to die another way: modes of programmed cell death and the signals emanating from dying cells. Nat Rev Mol Cell Biol 16:329–344

Fulda S (2014) Therapeutic exploitation of necroptosis for cancer therapy. Semin Cell Dev Biol 35:51–56

Glick D, Barth S, Macleod KF (2010) Autophagy: cellular and molecular mechanisms. J Pathol 221:3–12

Grasso S, Meléndez-Guitiérez P, Carrasco-Garcia E, Mayor-López L, Tristante E, Rocamora-Reverte L, Gómez-Martinez A, Grarcia-Morales P, Ferragut J, Saceda M, Martinez-Lacaci I (2012) Cell death and cancer, novel therapeutic strategies. In: Ntuli T (ed) Apoptosis and medicine. In Tech, Croatia. accessed at http://www.intechopen.com/books/apoptosis-and-medicine/cell-death-and-cancer-novel-therapeutic-strategies

Henson PM, Hume DA (2006) Apoptotic cell removal in development and tissue homeostasis. Trends Immunol 27:244–250

Juin P, Geneste O, Gautier F, Depil S, Campone M (2013) Decoding and unlocking the BCL-2 dependency of cancer cells. Nat Rev Cancer 13:455–465

Kang MH, Reynolds CP (2009) Bcl-2 inhibitors: targeting mitochondrial apoptotic pathways in cancer therapy. Clin Cancer Res 15:1126–1132

Keshmiri-Neghab H, Goliaei B (2014) Therapeutic potential of gossypol: an overview. Pharm Biol 52:124–128

Kroemer G, Galluzzi L, Vandenabeele P, Abrams J, Alnemri ES, Baehrecke EH, Blagosklonny MV, El-Deiry WS, Golstein P, Green DR, Hengartner M, Knight RA, Kumar S, Lipton SA, Malorni W, Nunez G, Peter ME, Tschopp J, Yuan J, Piacentini M, Zhivotovsky B, Melino G, Nomenclature Committee on Cell Death 2009 (2009) Classification of cell death: recommendations of the Nomenclature Committee on Cell Death 2009. Cell Death Differ 16:3–11

Lockshin RA, Zakeri Z (2001) Programmed cell death and apoptosis: origins of the theory. Nat Rev Mol Cell Biol 2:545–550

Luzio JP, Pryor PR, Bright NA (2007) Lysosomes: fusion and function. Nat Rev Mol Cell Biol 8:622–632

Mahalingam D, Mita M, Sarantopoulos J, Wood L, Amaravadi RK, Davis LE, Mita AC, Curiel TJ, Espitia CM, Nawrocki ST, Giles FJ, Carew JS (2014) Combined autophagy and HDAC inhibition: a phase I safety, tolerability, pharmacokinetic, and pharmacodynamic analysis of hydroxychloroquine in combination with the HDAC inhibitor vorinostat in patients with advanced solid tumors. Autophagy 10:1403–1414

Majno G, Joris I (1995) Apoptosis, oncosis, and necrosis. An overview of cell death. Am J Pathol 146:3–15

McIlwain DR, Berger T, Mak TW (2013) Caspase functions in cell death and disease. Cold Spring Harb Perspect Biol 5:a008656

Mellman I, Fuchs R, Helenius A (1986) Acidification of the endocytic and exocytic pathways. Annu Rev Biochem 55:663–670

Mijaljica D, Prescott M, Devenish RJ (2012) The intriguing life of autphagosomes. Int J Mol Sci 13:3618–3635

Mohammad RM, Muqbil I, Lowe L, Yedjou C, Hsu HY, Lin LT, Siegelin MD, Fimognari C, Kumar NB, Dou QP, Yang H, Samadi AK, Russo GL, Spagnuolo C, Ray SK, Chakrabarti M, Morre JD, Coley HM, Honoki K, Fujii H, Georgakilas AG, Amedei A, Niccolai E, Amin A, Ashraf SS, Helferich WG, Yang X, Boosani CS, Guha G, Bhakta D, Ciriolo MR, Aquilano K, Chen S, Mohammed SI, Keith WN, Bilsland A, Halicka D, Nowsheen S, Azmi AS (2015) Broad targeting of resistance to apoptosis in cancer. Semin Cancer Biol 35(Suppl):S78–S103

Moreira JN, Santos A, Simoes S (2006) Bcl-2-targeted antisense therapy (Oblimersen sodium): towards clinical reality. Rev Recent Clin Trials 1:217–235

Mott JL, Kobayashi S, Bronk SF, Gores GJ (2007) mir-29 regulates Mcl-1 protein expression and apoptosis. Oncogene 26:6133–6140

Mrschtik M, Ryan KM (2015) Lysosomal proteins in cell death and autophagy. FEBS J282:1058–1070

No author listed (2007) Oblimersen: Augmerosen, BCL-2 antisense oligonucleotide – Genta, G 3139, GC 3139, oblimersen sodium. Drugs R D 8:321–334

Oberle C, Huai J, Reinheckel T, Tacke M, Rassner M, Ekert PG, Buellesbach J, Borner C (2010) Lysosomal membrane permeabilization and cathepsin release is a Bax/Bak-dependent, amplifying event of apoptosis in fibroblasts and monocytes. Cell Death Differ 17:1167–1178

O'Brien S, Moore JO, Boyd TE, Larratt LM, Skotnicki AB, Koziner B, Chanan-Khan AA, Seymour JF, Gribben J, Itri LM, Rai KR (2009) 5-year survival in patients with relapsed or refractory chronic lymphocytic leukemia in a randomized, phase III trial of fludarabine plus cyclophosphamide with or without oblimersen. J Clin Oncol 27:5208–5212

Panayi N, Mendoza E, Breshears E, Burd R (2013) Aberrant death pathways in melanoma. In: Davids L (ed) Recent advances in the biology, therapy and management of melanoma, http://www.intechopen.com/books/recent-advances-in-the-biology-therapy-and-management-of-melanoma/aberrant-death-pathways-in-melanoma

Panda PK, Mukhopadhyay S, Das DN, Sinha N, Naik PP, Bhutia SK (2015) Mechanism of autophagic regulation in carcinogenesis and cancer therapeutics. Semin Cell Dev Biol 39:43–55

Pierceall WE, Lena RJ, Medeiros BC, Blake N, Doykan C, Elashoff M, Cardone MH, Walter RB (2014) Mcl-1 dependence predicts response to vorinostat and gemtuzumab ozogamicin in acute myeloid leukemia. Leuk Res 38:564–568

Puthier D, Thabard W, Rapp M, Etrillard M, Harousseau J, Bataille R, Amiot M (2001) Interferon alpha extends the survival of human myeloma cells through an upregulation of the Mcl-1 anti-apoptotic molecule. Br J Haematol 112:358–363

Rangwala R, Chang YC, Hu J, Algazy KM, Evans TL, Fecher LA, Schuchter LM, Torigian DA, Panosian JT, Troxel AB, Tan KS, Heitjan DF, DeMichele AM, Vaughn DJ, Redlinger M, Alavi A, Kaiser J, Pontiggia L, Davis LE, O'Dwyer PJ, Amaravadi RK (2014a) Combined MTOR and autophagy inhibition: phase I trial of hydroxychloroquine and temsirolimus in patients with advanced solid tumors and melanoma. Autophagy 10:1391–1402

Rangwala R, Leone R, Chang YC, Fecher LA, Schuchter LM, Kramer A, Tan KS, Heitjan DF, Rodgers G, Gallagher M, Piao S, Troxel AB, Evans TL, DeMichele AM, Nathanson KL, O'Dwyer PJ, Kaiser J, Pontiggia L, Davis LE, Amaravadi RK (2014b) Phase I trial of hydroxychloroquine with dose-intense temozolomide in patients with advanced solid tumors and melanoma. Autophagy 10:1369–1379

Ravichandran K, Lorenz U (2007) Engulfment of apoptotic cells: signals for a good meal. Nat Rev Immunol 7:964–974

Ready N, Karaseva NA, Orlov SV, Luft AV, Popovych O, Holmlund JT, Wood BA, Leopold L (2011) Double-blind, placebo-controlled, randomized phase 2 study of the proapoptotic agent AT-101 plus docetaxel, in second-line non-small cell lung cancer. J Thorac Oncol 6:781–785

Roberts AW, Seymour JF, Brown JR, Wierda WG, Kipps TJ, Khaw SL, Carney DA, He SZ, Huang DC, Xiong H, Cui Y, Busman TA, McKeegan EM, Krivoshik AP, Enschede SH, Humerickhouse R (2012) Substantial susceptibility of chronic lymphocytic leukemia to BCL2 inhibition: results of a phase I study of navitoclax in patients with relapsed or refractory disease. J Clin Oncol 30:488–496

Rosenfeld MR, Ye X, Supko JG, Desideri S, Grossman SA, Brem S, Mikkelson T, Wang D, Chang YC, Hu J, McAfee Q, Fisher J, Troxel AB, Piao S, Heitjan DF, Tan KS, Pontiggia L, O'Dwyer PJ, Davis LE, Amaravadi RK (2014) A phase I/II trial of hydroxychloroquine in conjunction with radiation therapy and concurrent and adjuvant temozolomide in patients with newly diagnosed glioblastoma multiforme. Autophagy 10:1359–1368

Rudin CM, Hann CL, Garon EB, Ribeiro de Oliveira M, Bonomi PD, Camidge DR, Chu Q, Giaccone G, Khaira D, Ramalingam SS, Ranson MR, Dive C, McKeegan EM, Chyla BJ, Dowell BL, Chakravartty A, Nolan CE, Rudersdorf N, Busman TA, Mabry MH, Krivoshik AP, Humerickhouse RA, Shapiro GI, Gandhi L (2012) Phase II study of single-agent navitoclax (ABT-263) and biomarker correlates in patients with relapsed small cell lung cancer. Clin Cancer Res 18:3163–3169

Rudin CM, Salgia R, Wang X, Hodgson LD, Masters GA, Green M, Vokes EE (2008) Randomized phase II Study of carboplatin and etoposide with or without the bcl-2 antisense oligonucleotide oblimersen for extensive-stage small-cell lung cancer: CALGB 30103. J Clin Oncol 26:870–876

Shen S, Kepp O, Kroemer G (2012) The end of autophagic cell death? Autophagy 8:1–3

Sonpavde G, Matveev V, Burke JM, Caton JR, Fleming MT, Hutson TE, Galsky MD, Berry WR, Karlov P, Holmlund JT, Wood BA, Brookes M, Leopold L (2012) Randomized phase II trial of docetaxel plus prednisone in combination with placebo or AT-101, an oral small molecule

Bcl-2 family antagonist, as first-line therapy for metastatic castration-resistant prostate cancer. Ann Oncol 23:1803–1808

Vanden Berghe T, Linkermann A, Jouan-Lanhouet S, Walczak H, Vandenabeele P (2014) Regulated necrosis: the expanding network of non-apoptotic cell death pathways. Nat Rev Mol Cell Biol 15:135–147

Vanlangenakker N, Vanden Berghe T, Vandenabeele P (2012) Many stimuli pull the necrotic trigger, an overview. Cell Death Differ 19:75–86. doi:10.1038/cdd.2011.164

Vela L, Marzo I (2015) Bcl-2 family of proteins as drug targets for cancer chemotherapy: the long way of BH3 mimetics from bench to bedside. Curr Opin Pharmacol 23:74–81

Vogl DT, Stadtmauer EA, Tan KS, Heitjan DF, Davis LE, Pontiggia L, Rangwala R, Piao S, Chang YC, Scott EC, Paul TM, Nichols CW, Porter DL, Kaplan J, Mallon G, Bradner JE, Amaravadi RK (2014) Combined autophagy and proteasome inhibition: a phase 1 trial of hydroxychloroquine and bortezomib in patients with relapsed/refractory myeloma. Autophagy 10:1380–1390

Vogt C (1842) Untersuchungen über die Entwicklungsgeschichte der Geburtshelferkrte (Alytes obstetricans). Jent und Grassmann, Solothurn

Vucic D, Dixit VM, Wertz IE (2011) Ubiquitylation in apoptosis: a post-translational modification at the edge of life and death. Nat Rev Mol Cell Biol 12:439–452

Warr MR, Shore GC (2008) Unique biology of Mcl-1: therapeutic opportunities in cancer. Curr Mol Med 8:138–147

Youle RJ, Narendra DP (2011) Mechanisms of mitophagy. Nat Rev Mol Cell Biol 12:9–14

Zhong Q, Gao W, Du F, Wang X (2005) Mule/ARF-BP1, a BH3-only E3 ubiquitin ligase, catalyzes the polyubiquitination of Mcl-1 and regulates apoptosis. Cell 121:1085–1095

Ziegler U, Groscurth P (2004) Morphological features of cell death. News Physiol Sci 19: 124–128

Dying: What Happens to the Body After Death

3

Vernard Adams

3.1 Physical Decomposition of the Body

The tissue of the body begins to decay or decompose immediately after death, but few decompositional changes are immediately visible to the naked eye.

3.1.1 Autolysis

Within seconds of the circulation of blood ceasing, the tissues become acidic as the cells turn to anaerobic means of deriving energy from glucose or fatty acids. When anaerobic energy sources are depleted, the cells begin their own dying process, which is called autolysis. Cell nuclei and cytoplasmic organelles swell and become distorted. These changes are visible with an electron microscope within seconds. Red blood cells in the blood stream take on water, swell, and burst, releasing free hemoglobin and potassium into the plasma. Underperfusion of tissues by blood is called ischemia. The results of ischemia can be seen using an ordinary light microscope within an hour or two in tissues such as brain and heart muscle, and within a day or two in other tissues. The organ most sensitive to the lack of blood flow is brain. Cartilage, ligaments, tendons, and gristle tissue in general are the most resistant to ischemia.

V. Adams, MD
Consulting Forensic Pathologist, 400 North Ashley Drive, Suite 1900, Tampa,
FL 33602, USA
e-mail: viadams@vernardadamsmd.com

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_3

3.1.2 Classical Signs of Death

Algor mortis is an old-fashioned term for postmortem cooling of a dead body. In general, a dead body cools to ambient temperature after death. In warm climate, anaerobic bacterial metabolism in the large intestine may produce a brief rise in rectal temperature after the human host is dead.

Livor mortis, also known as postmortem lividity, denotes the apparent staining of skin caused by gravitational settling of red blood cells within the blood vessels after death. In a supine body (lying on the back), the blood settles in the back. Because the blood is not oxygenated, the skin appears purple. The first hint of livor can appear in half an hour in good light. Livor is especially prominent when death is by heart attack or asphyxia, and is minimal when death is by exsanguination or trauma of the brainstem or cervical spine. In the presence of carbon monoxide poisoning, the livor is red rather than purple. If a body is put into a new position within hours of death, the blood will shift into a new pattern of lividity that reflects the new position. Later, as capillary vessels become so engorged that they cannot drain, the livor will not shift, and is said to be fixed. When livor involves the face, family members and funeral directors can mistakenly think that they are seeing bruises from trauma.

Muscle relaxation is a high-energy state. In the absence of oxygen, muscles have inadequate access to energy and become stiff, whether the person is alive or dead. In a dead person, muscle stiffening is called *rigor mortis*. If a muscle is being heavily exercised just before death, that muscle can go into rigor almost immediately after death; this effect was once known as "cadaveric spasm." In the absence of heavy exercise, rigor mortis becomes readily apparent within a few hours of death, builds to a maximum for some hours, and then fades in parallel with the onset of putrefactive decomposition. If a body is moved after rigor mortis has set in, the original attitude of the limbs will be preserved. However, rigor can be overcome by passive stretching of a joint, and once the rigor is overcome in the muscles holding a joint in flexion, the rigor does not return. Funeral directors sometimes must overcome rigor in the limbs in order that the body lie properly for transport and viewing. The apparent strength of fully developed rigor mortis is directly proportional to the muscle mass of the dead person.

3.1.3 Putrefaction

In temperate climates, if a dead body is left at ambient temperature, putrefactive decomposition ensues. Putrefaction is the bane of funeral directors. Putrefaction begins with the indigenous bacteria of the intestines. After death, when the intestines are deprived of oxygenated blood, the cells in the intestinal wall that normally keep bacteria confined to the inside of the intestine fail and thereby permit bacteria to migrate across the intestinal wall into the stagnant blood in the blood vessels serving the intestine. From those local vessels, the bacteria make their way into systemic blood vessels. When intestinal bacteria such *E. coli* reach this blood, they begin to use the blood as a nutritional source, just as they would in a petri dish filled with blood-enriched agar. When bacteria consume glucose and other nutrients in the blood, the bacteria extract energy and emit gases such as carbon dioxide, methane, and sulfurous gases. Carbon dioxide and methane are produced in large quantities and cause gaseous swelling of the organs and limbs. Hydrogen sulfide, the gas that has the odor of rotten eggs, contributes to the foul odor of putrefactive decomposition. Bacterial consumption of amino acids and peptides derived from proteins produce particularly foul gases. The hydrogen sulfide interacts chemically with the iron in hemoglobin and myoglobin and changes the color to black-green. The first appearance of this green color is often in the skin of the right lower abdominal area. The production of gases by bacteria can be so prodigious as to float a dead body that is chained to barbell weights and thrown into the sea. The pressure of gases inside the torso often forces red-brown froth from the lungs to discharge from the mouth and nose.

While a body is bloating from the gases and discoloring from the sulfides, the top layer of the skin (epidermis) begins to detach from the underlying dermis, due to lack of an oxygenated blood supply to the desmosomes. Desmosomes are like biological rivets that are visible with an electron microscope and that serve to keep the epidermal cells attached to the dermis. The sloughing of epidermis in a decaying body is usually called skin slippage by forensic pathologists.

The odors of putrefaction attract flies, which then lay their eggs on or near the body. The eggs hatch, and the larvae, known as maggots, feed on the decomposing flesh. After going through up to three growth stages, the maggots crawl away, pupate, and then emerge as flies.

As the mass of the body is reduced by the feeding of maggots, beetles are attracted. The beetles feed on the gristly tissue that is too tough for the maggots. At any of these stages, if carnivores have access to the body, they may feed on it, or drag the body parts several feet away.

Putrefaction and insect activity are so unattractive and repulsive that great efforts are made to prevent or retard putrefaction, by refrigerating the body, or substituting a different form of decomposition.

Refrigeration will cool a body of normal habitus quickly enough to prevent overt putrefaction and permit embalming. However, obese bodies have so much insulation afforded by the layer of subcutaneous fat that overnight refrigeration may often fail to cool the internal organs and blood vessels, so that putrefaction can ensue in an obese body even while it lies in refrigerated storage. This can be prevented by having an autopsy soon after death. At autopsy, the opening of the body cavities and removal of organs cool them, the drainage of blood incident to the autopsy removes the nutrition source for the bacteria, and the opening and cleaning of the intestines remove the bulk of the bacteria.

3.1.4 Mummification

Mummification, otherwise known as desiccation, simply means alteration of the composition of a dead body by extraction of moisture. Extreme drying creates an environment that is unfavorable for putrefactive bacteria. It occurs naturally in some desert environments. However, except in very small or very thin bodies, mummification is usually preceded by some degree of putrefaction. Mummification is accompanied by darkening of the skin.

The following forms of decomposition are uncommon in the natural state but are often employed to retard putrefaction:

3.1.5 Freezing

Freezing is a form of decomposition, because it causes damage to cells. Freezing is most notable for its ability to completely retard putrefaction. However, when a frozen body thaws, putrefaction ensues even more rapidly than is the case with a body cooling from a recent death. Some medical examiner offices freeze unclaimed putrefied bodies in order to control odor.

3.1.6 Incineration

Consumption of a dead body by fire has been known for centuries. It certainly prevents putrefaction if the incineration is complete. Incineration at temperatures of about 1800°, until nothing is left but a few calcined fragments of bone (notably the dense heel bone and the even more dense inner ear bone), is known in the funeral industry as cremation. Cremation releases hot carbon dioxide up the incinerator stack and leaves a few pounds of bone fragments. The bone fragments are ground to a fine consistency and termed "ashes" by the funeral industry.

3.1.7 Chemical Fixation

A number of chemicals have the property of cross-linking protein molecules, stiffening the tissues, and greatly retarding the growth of putrefactive bacteria. The stiffening of tissues is referred to as fixation. Examples of such chemicals are ethanol, isopropyl alcohol, and formaldehyde. Formaldehyde as a gas solution in water is called formalin. Formalin fixation is used by the funeral industry for embalming, and by pathologists for preparation of tissues for microscopic work.

3.2 Autopsy

Procedure An autopsy is an examination of the outside and inside of a dead body by a physician for a medical or legal purpose. An autopsy report is traditionally divided into at least two sections: external and internal examinations.

The external examination is a visual inspection of the outside surfaces of the body. The external examination may be accompanied by the collection of trace evidence in criminal cases, by the recording of handwritten notes on a preprinted body diagram, or by the taking of photographs.

The internal examination consists of opening the torso and head, inspecting the organs as they lie, and then removing the organs from the head, neck, chest, abdomen, and pelvis, and dissecting the organs. An internal examination is usually accompanied by the collection of specimens for toxicological analysis in medical examiner or coroner autopsies. During the internal examination, small tissue specimens are taken for histological preparation and examination under the microscope. Other parts of the body such as the limbs are dissected only for special purposes such as tracing the path of a bullet or finding the seat of deep vein clots.

Purpose An autopsy may be conducted to aid in determining the cause of death or extent of disease, to collect specimens or evidence, to identify the body, or simply to raise the level of certainty for the cause-of-death opinion. Medical examiner and coroner autopsies are most often done to help in determining the cause of death. Hospital autopsies are most often done to determine the extent of disease.

Authority to Perform Autopsy Under common law, the next-of-kin have a right to claim a reasonably intact dead body for the purpose of burial or other disposition. That right can be overridden by statutory law or voluntarily suspended by permission of the next-of-kin. Medical examiners and coroners have the authority under their enabling statutes to perform autopsies without the permission of the next-of-kin. Hospital and private autopsies are done after the family gives permission for the autopsy, usually in writing.

Who Performs Autopsies Medical examiner and coroner autopsies are usually performed by forensic pathologists trained in the recognition of wounds and determination of cause of death, while hospital autopsies are usually performed by pathologists whose primary job is to examine surgical biopsies under the microscope to diagnose cancer. In some areas of the United States, the so-called private autopsies are performed by pathologists not working in a hospital or medical examiner office, to satisfy the market need for autopsies requested by family members.

Determination of Cause of Death Contrary to the impression conveyed by television shows and detective novels, the autopsy rarely determines the cause of death. Rather, it provides information, both inclusionary and exclusionary, like a battery of laboratory tests or X-rays, which, taken in concert with the medical and social history, and the circumstances of death (what the person was doing when he or she died), permit the pathologist to form an opinion as to the cause of death. At this point, a few definitions are in order:

The *cause of death* is the underlying disease or wound that ultimately culminates in death. For example, cancer of the breast or gunshot wound of the head with perforation of the brain are competent causes of death.

In contrast, congestive heart failure, brain edema, and septic shock are physiological derangements set into motion by the underlying disease or wound. These physiological derangements are customarily called *mechanisms of death* by forensic pathologists.

The *manner of death* is an ancient classification system that classifies deaths by whether they be natural or unnatural, and intentionally or nonintentionally caused. The four manners of death are natural, homicide, suicide, and accident. If a manner of death cannot be determined, the manner may be said to be unclassified or undetermined.

3.3 Embalming and Cremation

Purpose of Embalming The purpose of embalming is to retard putrefaction in order to display a body at an open casket service or transport it over a long distance without refrigeration. Embalming is generally not required by law.

Embalming Procedure Embalming by the ancients may have involved the use of pleasant-smelling salves applied to the outside of the body to cover the odor of putrefaction; hence the term “embalm.” Modern embalming procedures attempt to prevent putrefaction by killing the bacteria responsible for it. *Arterial embalming* uses a machine to inject a mixture of liquid fixative chemicals into the blood vessels to flush out the blood and perfuse the organs and tissues with the fluid. This process deprives the bacteria of food, and kills the bacteria. In addition, for an unautopsied body, the embalmer uses a hollow pipe called a trocar to perforate the abdominal wall, aspirate any fluids, and directly inject concentrated embalming fluid. *Trocar embalming* is directed at the intestines, where the feces represents a reservoir of bacteria. A side effect of trocar work is the creation of numerous perforations in multiple organs. Parts of the body not reached by arterial injection or trocar injection are embalmed by the use of syringes and needles. Trocar work is not needed after an autopsy. After arterial and trocar embalming, the body is dressed, the hair is styled, and cosmetics are applied.

Cremation “Cremains” are the finely ground bone fragments left from cremation of a dead body. Because cremation is considered a form of final disposition of a dead body, and the cremains pose no biological risk, the cremains can be displayed, stored, interred, or discarded at will, with no permit required.

3.4 Death Certificate

History The registration of vital events has a long ecclesiastical history, but only in recent times has been the responsibility of governments. For centuries, the established churches in Europe recorded baptisms, marriages, and burials. The first government to require the collection of vital statistics was Massachusetts Bay Colony, which has required the town clerks to collect birth, marriage, and death events since the 1630s. The other New England colonies followed suit, and the data collection has continued uninterrupted to this day despite the change in oversight of the towns from colonies to provinces, and provinces to states. Other states began to require the registration of births, marriages, and deaths as late as the early part of the twentieth century.

Purposes The purpose of death registration on the part of the state is twofold: to establish that death occurred, and to collect cause-of-death statistics in the interest of public health. The registered information is made available to private citizens in the form of death certificates issued by the health department, or in New England, the town clerk. Life insurance companies use the death certificate to establish that death occurred, and to determine if the death was by suicide or accident. Most life insurance policies exclude any payment for a suicide within 1 or 2 years of the taking out of the policy. If a death occurs exclusively by wound or injury under accidental circumstances, many whole life insurance policies pay double the face value. Banks and other financial institutions need to know if a person has died in order to close an account, but ordinarily do not need to know the cause of death. Depending on the US state, the death certificate may or may not be a public record. For example, Florida issues two types of death certificates: the long form includes the cause of death and is not a public record; the short form, which has the identification and disposition data but does not include the medical component and cause of death, is a public record.

Structure of Death Certificate A death certificate has data that fall into three categories: (1) identification of the decedent; (2) method and place of disposition of the body; and (3) place, date, cause, and circumstances of death. The funeral director provides a signature for the first two parts, and the physician or medical examiner signs for the third part. Identification of the decedent includes not only the decedent's name and date of birth, but also the names of the decedent's parents, the decedent's occupation, and the name of the informant providing this information.

Time of Death On a death certificate, the time of death can be given as the actual time of witnessed death, the time a dead body is found after an unwitnessed death, or the time that a physician "pronounces" a person dead. Pronouncing a person dead is an administrative event rather than a biological event, and is done out of long custom and habit in hospitals, or to establish a legal time of death when the biological time of death is not ascertainable because of resuscitation efforts or transportation. Examples:

Found dead. A boy scout on a hike finds a partly decomposed body found hanging in the woods. A suicide note is found at the decedent's home. The time of death is not known, and most of the time does not need to be known. Death does not need to be pronounced; it is obvious to any nonmedical person of sound mind. The death certificate will, depending on local practice, probably list the date the body is found rather an unsupportable opinion as to the actual date of death.

Witnessed death. A man playing golf is witnessed to suddenly collapse. He has received no wounds. Bystanders find no pulse and detect no breathing. The death probably occurred from a sudden stoppage of the heart caused by an interruption in the propagation of the electrical impulses that cause it to pump blood. If there is no resuscitation effort, he is legally dead because there is no pulse or respiration. The time of death is the time that he collapsed.

Pronounced death. A woman playing tennis has a witnessed collapse. Her tennis partner thinks he feels a pulse and initiates chest compressions and mouth-to-mouth breathing. Paramedics arrive, find no pulse, and determine that the heart is in asystole (flat-line) on the heart monitor. Because the paramedics are not in radiocommunication with a physician, they do not stop the resuscitation efforts, and continue them while transporting to the hospital emergency room. There, a physician determines that the tennis player is indeed dead, and records a time of pronouncement of death. Delaying the determination of death until a physician can make a death pronouncement makes it easy to define the place and time of death by an artificial convention whereby death is said to occur at the hospital and at the time of pronouncement. No one has to develop an opinion as to whether the death occurred on the golf course or en route to the hospital. Pronouncement of death as an administrative convenience is especially useful if a patient is transported across international, state, or county lines.

Quality of Life at the End of Life

4

Lodovico Balducci and Miriam Innocenti

4.1 Introduction

Ultimately every form of medical care is palliative, as life may be considered a terminal disease (Cleese). The promotion of quality of life is inextricable from any other goal of care (cure, prolongation of survival, symptom relief) throughout the trajectory of human life (Schnipper et al. 2015). When death is proximate and unavoidable, quality of life (QOD) becomes the predominant goal of care (Peppercorn et al. 2011).

In this chapter, the factors that may affect QOD are explored. The goal of the chapter is fourfold:

- To offer a blueprint to assist busy practitioners in negotiating their way through QOD issues
- To describe the methodological limitations in studying QOD
- To outline QOD issues deserving further research
- To provide a construct of a "good death"

4.2 The Sources of Information

In 1997, the Institute of Medicine recommended the development of clinical studies related to end-of-life care, with particular focus on QOD (Institute of Medicine 1997). The difficulties in conducting such studies soon became apparent (Hales et al. 2010). In addition to methodological issues, there were several variables that were not addressed. These included: (1) the different diseases that may cause death;

L. Balducci, MD (✉) • M. Innocenti, LCSW
Moffitt Cancer Center, University of South Florida College of Medicine,
12902 Magnolia DR, Tampa, FL 33612, USA
e-mail: Lodovico.balducci@moffitt.org

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_4

(2) age, sex, race, and ethnicity of dying individuals; (3) cultural issues; and (4) the need to use proxies (the family caregivers or the health care providers) to assess QOD in certain circumstances (Prigerson et al. 2015), even if it is known that determination by proxies may be unreliable (Crocker et al. 2015; Jones et al. 2011). This last factor is particularly true during the emotional conflicts that may accompany end of life, when different caregivers may have opposite perceptions of the QOD of the same patient (Zhang et al. 2012; Fukui et al. 2011). Of special interest are studies asking terminal patients and their caregivers (Steinhauser et al. 2000), or the general population (Hales et al. 2012), which factors may influence their QOD. Delineation of these factors provides practical indications for organizing the care of the terminally ill and their families. Also, traditional methods of assessing quality of life may not address all the dimensions of death, especially the relationship between QOD and such factors as meaning of life, spirituality, and religion, or the interactions that may be in conflict, between the patient, the family caregiver(s), and the medical staff. For this reason, a host of qualitative research based on narrative and language analysis has explored QOD (Melin-Johansson et al. 2008; Shah et al. 2015). An important reference in the following discussion is the "Coping with Cancer (CwC1)" study (Zhang et al. 2012; Abbott et al. 2015). This is a multisite prospective and longitudinal study of the QOD of 396 dying U.S. patients and their informal caregivers conducted between 2002 and 2008. The patients enrolled in CwC1 are representative of the diversity of the population.

In this chapter, we will focus on end of life of cancer patients, which has been studied extensively, to build a frame of reference to assess and promote QOD in different clinical situations. We will examine the factors that affect QOD and discuss controversies surrounding specific factors.

Discussion of cultural issues is a necessary preface to this chapter. Culture plays an important role in shaping one's perception of QOL (Wright et al. 2013; Mack et al. 2010), and cultural sensitivity is essential to effective intercultural communication (Martin and Nakayama 2013).

4.3 Cultural Issues and QOD

For the purpose of this chapter, culture is defined as the complex of "shared language, beliefs and values" of a group of individuals (Collier et al. 2002). Clearly, the construct of culture overlaps to some extent those of race and ethnicity that are poorly defined and often interchangeable in the medical literature (Lee 2009).

While it might be relatively easy to identify a predominant culture in a small community with limited external contact, this is not the case in the modern world and especially in the West, where culture is continuously evolving due to multiple factors. These include unprecedented waves of immigration, interfaith and interracial marriages, and more frequent cultural interactions through travels and media (Martin and Nakayama 2013). Even in a multicultural society, it is possible to find enclaves of people who preserve their cultures by establishing close communities such as the Amish (Cacciatore and Thieleman 2014) and Orthodox Jewish (Prossr et al. 2012) communities in the United States. In addition, immigrants from different cultures, especially first generation immigrants, are more likely to maintain their culture of origin when they live in the same neighborhood and communicate in their primary language (Goldstein et al. 2002). It is important for the practitioner to become familiar with the values, beliefs, and communication styles of communities they serve.

Searight and Gafford have identified "points of cultural diversity in health care" (Searight and Gafford 2005). These include:

- Emphasis on individualism (as is common in North America) or on collectivism (as may be the case among some Muslim, Orthodox Jewish, and Hasidic Jewish communities).
- Definition of family: extended, nuclear, and even including nonblood kinship; it is common in some Middle Eastern populations to refer to close friends as "brothers and sisters."
- Roles within the family: Who is responsible for child rearing, taking care of older adults, and making financial decisions? In some African societies, the maternal uncle, rather than the father, is responsible for child rearing.
- Views about marriage and other types of relationships.
- Communication patterns (direct vs indirect; relative emphasis on nonverbal communication; meaning of nonverbal gestures). For example, in some Asian languages, the word "no" does not exist, and the negation is expressed in a roundabout way; in some Asian populations, a smile indicates embarrassment rather than amusement.
- Religious and spiritual belief systems. The monotheistic religions of the West emphasize the unique sacredness of each human being subjected to the justice of the same god. Some of the Eastern beliefs hold that each person is assigned by the deity a social situation that is unchangeable for a person's lifetime.
- Views about physicians.
- Views about suffering.
- Views about the afterlife.

A discussion about each point is beyond the scope of this chapter, but it is important to highlight the cultural differences in end-of-life care pertaining to the four principles of medical ethics: autonomy, beneficence, nonmaleficence, and justice. In the Western world, the principle of autonomy trumps the other principles, and in the United States, it has been enshrined in the 1990 Patient Self-Determination Act (42 USC 1395). The Act states that an individual is ultimately responsible for his/her health care decisions. In other cultures, however, concerns about beneficence and nonmaleficence may be predominant. For example, advance directives that were devised to preserve the patient's autonomy (even when he/she has lost the ability to make decisions) may be perceived by family/caregivers as a threat to the patient's well-being. Family and caregivers may fear that asking to sign the advance directive documents may be perceived as a sign that there is no hope of recovery. In these cultures, the principles of beneficence and nonmaleficence outweigh

Table 4.1 Factors that determine QOD (Zhang et al. 2012; Black et al. 2011; Hermann and Looney 2011)

Symptoms
Pain
Fatigue
Nausea
Appetite
Discomfort
Dyspnea
Sleep disturbance
Depression
Anxiety
Existential/psychic pain
Health care related
ICU stay
Chemotherapy at the end of life
Hospital death
Use of feeding tubes
Religion and spirituality
Religious practices
Pastoral care
Therapeutic alliance

autonomy, and the ultimate health care decisions are trusted to the most authoritative family members. The ethical principles may be the same in many cultures, but the emphasis on a particular principle varies. To accept different perspectives on end-of-life issues may require health care providers to set aside their own point of view. Cultural sensitivity is essential to effective communication and establishing trust, which are crucial in preserving QOD (Mack et al. 2009).

4.4 Factors That Influence QOD

A number of factors determine QOD (Table 4.1).

Symptom Control It has been repeatedly demonstrated that symptom control affects a patient's QOD (Black et al. 2011; Hermann and Looney 2011). Symptoms are interwoven, and management of one symptom may worsen or improve another. For example, opioids may increase the risk of nausea and constipation and may cause delirium or "emotional numbness," which may impair social interaction (Maciejevsky and Prigerson 2013). In this situation, QOD may be better served by minimizing opiates if the patient voices the desire to remain alert and oriented and is able to tolerate some degree of pain. Anxiolytics may be more effective than opioids in preserving a patient's QOD when the pain has an intense emotional component (Veinante et al. 2013) and is aggravated by anxiety.

For effective symptom management, the distinction between physical pain and discomfort is essential (Maciejevsky and Prigerson 2013). Occasionally, one may have pain without discomfort and discomfort without pain. For example, a Catholic priest with metastatic prostate cancer felt that the pain from bone metastases allowed him to participate in the redemptive pain of Christ, and he tolerated the most atrocious pain with a smile on his face (Balducci 2008). Clearly, relief of pain would have worsened rather than improved his QOD, because it would have deprived him of a very meaningful spiritual experience. It is not uncommon for patients at the end of life to experience a generalized discomfort due to a combination of factors, such as fear of the unknown and concern about people left behind, even when physical pain is well controlled. Many patients can benefit from an open discussion of their concerns, pastoral assistance, or social work intervention for emotional concerns, rather than pain or antianxiety medications alone (Kirsten et al. 2014). *Depression* may be considered a "symptom hub" in the terminally ill. Depression may intensify physical and emotional pain which in turn may exacerbate depression (Pinquart et al. 2006; Mehta and Roth 2015). It is also important to distinguish depression that may respond to medication from depression related to existential pain (Balducci 2011), which may respond better to empathy and listening than to medications. In these situations, the management of depression requires a multipronged approach, including psychotherapy and in some cases psychiatric evaluation for psychotropic medications.

Fatigue is the most common end-of-life symptom for cancer patients (Black et al. 2011) and can be a major threat to QOD (Luciani et al. 2008; Tang et al. 2014). The management of cancer-related fatigue is problematic and controversial (Balducci and Fossa 2013). QOD may be preserved by helping the patient acknowledge the need for help with activities of daily living and the need for caregivers to demonstrate their love for the patient. Often caregivers feel helpless and frustrated when a patient refuses to accept their help.

Sleep disturbances include insomnia and alterations in circadian sleep-wake rhythm, and may represent an additional cause of fatigue, anxiety, and discomfort (Dahiva et al. 2013), as they affect more than 50 % of terminally ill patients with cancer. Patients should be encouraged to go to bed only when they are sleepy, to avoid long naps, and to engage in activities like walking and interacting with others, if only briefly. Educating patients about sleep hygiene is important; however, many sleep difficulties are related to anxiety, depression, and worry. Counseling is very useful to address these issues. Pharmacological treatment in general has a limited role, as the majority of these individuals are already overmedicated; however, medication for sleep may in some cases be required, especially at the end of life. Management of polypharmacy and elimination of drugs that are not strictly necessary may also help sleep disorders (LeBlanc et al. 2015).

Anorexia is common in cancer patients especially at the end of life, and questions about nutrition at the end of life and in relation to QOD are common. In general, anorexia seems to be more troubling to the caregiver than to the patient. A common perception is that starvation may kill the patient before the cancer does. This concern should be relieved, as it has been repeatedly demonstrated that hyperalimentation accelerates cancer growth in the absence of antineoplastic treatment (Balducci and Hardy 1987). Appetite stimulants including alcohol in small doses, progestins, and corticosteroids may improve the QOD of some patients by allowing them to enjoy a pleasant meal. In a randomized controlled study, a ghrelin synthetic derivative, anamorelin (Temel et al. 2014) improved the appetite and the nutritional status of patients with advanced cancer. If approved in the United States, this drug may represent effective management of anorexia.

4.4.1 Health Care-Related Issues

Place of Death and Aggressive End-of-Life Treatment All studies agree on these facts: QOD is worsened by death in the hospital (especially in the ICU) and by chemotherapy at the end of life (Prigerson et al. 2015; Crocker et al. 2015; Jones et al. 2011; Zhang et al. 2012; Fukui et al. 2011; Steinhauser et al. 2000)· Several authors have found that a patient has a better QOD in the comfort of his/her home (Prigerson et al. 2015; Crocker et al. 2015; Jones et al. 2011; Zhang et al. 2012; Fukui et al. 2011; Steinhauser et al. 2000; Teno et al. 2004; Collier et al. 2015; Fleming et al. 2015; Wright et al. 2010a, b). Among patients dying at home or in an institution, hospice care significantly improved QOD thanks to better symptom control (Teno et al. 2004). These data were obtained primarily from interviews of caregiver of patients who had died, but the conclusions need to be mitigated by a number of considerations.

Patients were more likely to die in the ICU if they asked for life-extending treatment up to the very last minute (Wright et al. 2010a). When death in the ICU is unavoidable, the patient's QOD may be improved when health care providers strive to communicate with the patient and family. The Three Wishes Project (Cook et al. 2015) represents a successful example of this approach. In the few days preceding death, physicians and nurses working in a 21-bed ICU of a major hospital endeavored to fulfill three wishes that the patient and family recognized as particularly meaningful. The wishes, expressed in an informal conversation were varied, but essentially belonged to five categories: humanizing the ICU environment, paying a personal tribute to the patient, reconnecting with family members and friends, celebrating a ritual, and paying forward. This approach preserved the patient's dignity, gave a voice to the family, and fostered compassion and empathy in the staff.

Studies reporting that chemotherapy worsened QOD may be slanted toward this conclusion, because they were focused on patients who died shortly after receiving chemotherapy. A number of patients who received chemotherapy in the same conditions might have achieved a more prolonged survival and a better quality of life. In other words, it might have not been established that the patients who eventually died and did not benefit from treatment were close to the end when they did receive chemotherapy, as predictions of impending death are notoriously unreliable (Rose et al. 2000).

Finally, and most importantly, the concept of home needs to be qualified. By necessity, all studies indicating that home was the ideal place of death involved patients with a home and a stable, loving family. It excluded the homeless, those with a conflicted or dysfunctional family life, and those where the family caregiver was torn by competing responsibilities, such as raising children and putting bread on the table in addition to taking care of the dying (Woodman et al. 2015). Also, a number of studies established that the concept of home for dying patients may be a dynamic one (Collier et al. 2015). Home indicates a place where the dying person feels safe and comfortable because he/she is surrounded by familiar objects and by loving people and is confident they will receive the best palliative care. Patients receiving end-of-life care in a facility rather than at home and assisted by skilled personnel are less likely to experience hospital admission at the end of life (Henson et al. 2015; Kaspers et al. 2013).

Clearly, end-of-life care may be influenced by cultural and religious beliefs. For example, for devout Muslims, it is the family's responsibility to take care of a person at the end of life, and it is inconceivable that the person may die in any other place but home (Padela and Mohiuddin 2015).

Open communication between health care professionals and patients and families is essential to ensure that everybody's goals of care are reconciled and respected in the treatment plans. It is desirable to avoid death in the hospital and in the ICU for patients whose disease is clearly terminal, but not at the price of overruling a patient's desires. When a home is available and the family is able to manage the dying, home is the preferred site of death. The concept of home should be conceived in a dynamic sense, however, and ultimately home is the place where most patients feel safe and comfortable.

Tube Feeding In general, the presence of feeding tubes at the end of life has been perceived as a barrier to QOD. The issue is controversial both from medical and ethical standpoints (Nowarska 2015). The problem hinges on the question as to whether nutrition and hydration increase discomfort in these patients. Not surprisingly, the clinical evidence is inconclusive (Gent et al. 2015; Wiffen et al. 2014). A reasonable approach to the issue is the following:

- The patient and his/her health care surrogate have the right to request or refuse a gastric or a nasogastric tube for nutrition and hydration in any circumstance, according to the principle of autonomy.
- In patients who have a terminal disease such as advanced cancer, are unconscious and unresponsive to treatment, and have no health care surrogate, it is reasonable to provide hydration through an NG tube if it appears to decrease discomfort from dehydration. In view of the lack of any evidence that nutrition and hydration in these circumstances are beneficial, an NG tube should not be routinely inserted.

Religion and Spirituality Epidemiological studies suggest that belonging to a religious community is associated with increased life expectancy, improved health and function, and more successful outcome of substance dependence treatment

(Balducci and Mayer 2001). In a recent white paper from a consensus conference, it is stated that palliative care should include spiritual and religious domains, and every member of the care team should be able to recognize issues related to these domains (Puchalski et al. 2009). Failure to do so may jeopardize the patient's QOD and ultimately the success of palliative care. The professional properly trained to address these issues is the chaplain on the team who has undergone clinical pastoral training (CPT).

Despite the fact that many patients and families consider spiritual assistance and pastoral care at the end of life desirable (Zhang et al. 2012; Peteet and Balboni 2013), the evidence that these interventions are beneficial is inconclusive (Puchalski et al. 2009; Candy et al. 2012; Cobb et al. 2012). This is not surprising, given the large number of variables involved. In part, the confusion may derive from the lack of clear distinction between religion and spirituality. Religion involves the adherence to beliefs shared by a community, commonly expressed by rituals and common prayers (Balducci and Mayer 2001). The concept of spirituality is more vague and refers to that which gives an individual meaning in life without necessarily embracing a specific creed. A recent review of the literature (Stephenson and Berry 2015) identified five attributes of spirituality: meaning, beliefs, connecting, self-transcendence, and value. It is not clear whether any of the instruments available to assess these domains reflects the complexity of the issue, as the spiritual attributes are interwoven. By necessity, the data on spirituality and QOD are fragmented and in part anecdotal.

Another unsettled issue is the matter of which professional is qualified to provide spiritual and religious care, the minister of the religious community to which the patient belongs or a member of the palliative care team. The CwC study showed that patients receiving their religious support from a community minister were less likely to enroll in hospice, more likely to receive aggressive treatment for their cancer at the end of life and die in the ICU (Balboni et al. 2013). The reverse was true for patients who received religious and spiritual support from the medical team (that included a chaplain and a social worker). This discrepancy is puzzling, and one may suppose that ministers in the religious communities may have sometimes unrealistic expectations of health care providers and their ability to prolong life. They may also have the erroneous belief that cessation of treatment and referral to hospice imply the patient and medical team are "giving up." The hope for a miracle cure may influence this attitude. More studies of this issue are necessary to confirm these initial data and also to study the effects on QOD of these different attitudes toward and approaches to end of life. Sharing the concept of "letting go" rather than "giving up" is one that improves the QOD for many patients and families.

One may anticipate several benefits at the end of life from religious and spiritual care, including fostering hope (Hawthorn 2015), facilitating forgiveness (Wittemberg et al. 2015), promoting communication (Wittemberg et al. 2015), implementation of prayer (Tomkins et al. 2015) and other rituals, and the discovery of meaning of life (Stephenson and Berry 2015). In addition, a spiritual perspective may help ameliorate caregiver stress and make caregiving more effective, rewarding, and meaningful (Kim et al. 2011).

One may also be concerned about the potential negative effects of spiritual and religious intervention (Van Laarhoven et al. 2012), which may include unrealistic expectations from medical care, although spiritual care may help to address issues like guilt and fear of the afterlife.

One may draw the following conclusions from this discussion:

- Religion and spirituality are human domains that may influence all aspects of health care, including QOD.
- Health care providers may have limited influence on these dimensions; however, they cannot ignore these dimensions in ministering to the dying. A number of patients decry the failure of the medical team to address these aspects of care.
- Religious and/or spiritual intervention may be helpful in fostering a sense of meaning, accomplishment, and fulfillment in the dying. This intervention may also help patients accept death with grace and may render the endeavors of family caregiver more meaningful and rewarding.
- Spiritual and religious interventions may have different effects on end-of-life care. In some cases, it may promote aggressive treatment; in others, it may promote acceptance of death. There are no data to determine how these different effects influence QOD.
- Every member of the treatment team should be able to recognize spiritual and religious issues and refer the patient to the proper professional. It goes without saying that the focus of this communication should be the patient's beliefs, and in no circumstances the provider should attempt to prevail on these beliefs.

A recent study showed that the management of religious and spiritual issues is more effective when these issues are addressed at the beginning of patient-physician relationship (Roscoe and Tullis 2015). A simple instrument called FICA (Faith, Importance, Community Assessment) is designed to obtain this information and may be utilized in the course of later care (Puchalski et al. 2009).

Therapeutic Alliance In addition to effective communication, therapeutic alliance (Mack et al. 2009) plays a crucial role in the care of the terminally ill patient and family. Therapeutic alliance preserves the dignity of the patient and is based upon empathy, respect, open-mindedness, acceptance, availability, and humility. These elements are included in "The Human Connection (THC) Scale" (Mack et al. 2009) – a validated scale to assess therapeutic alliance. High scores in THC were associated with higher level of QOD among patients dying with cancer. The palliative care team is instrumental in establishing the therapeutic alliance, and the patient benefits from the ability to engage in life review at the end of life. Relating one's history is an important part of bringing one's life to a close. It helps affirm one's life has had meaning and for some individuals may help come to terms with lost relationships and regrets. Hospice social workers are uniquely trained to assist patients with these issues and work with families at the end of life.

Controversial Issues The previous discussion revealed a number of controversies in the care of the dying. While there is general agreement that spiritual and religious assistance may improve QOD, there were questions about the best way to provide it.

In this section, we examined two issues that are controversial: whether to fully disclose the patient's status and whether palliative sedation may improve QOD.

End-of-Life Discussion Therapeutic alliance is one pillar of QOD, and trust is the pillar of therapeutic alliance. Clearly, it behooves the practitioner to provide honest, clear, and complete information when answering the patient's questions. The issue is how to deal with the patient who is reluctant to discuss prognosis or avoids it completely and how to formulate answers to questions in a way that does not cause stress, depression, and withdrawal. It is also important to recognize that the family may want to shield the patient from a honest discussion even when the patient requests it.

The literature suggests that end-of-life discussions are not stressful for the majority of patients (Emanuel et al. 1999–2004) and that they improve QOD, patients' ability to cope, medical care near death, and caregiver bereavement (Wright et al. 2008; Lee et al. 2013; Balducci 2012). End-of-life discussion more than 30 days prior to death was associated with decreased use of aggressive therapy near death in terminal cancer patients, which may have led to improved QOD (Mack et al. 2012). A randomized controlled study examined the value of palliative care since the beginning of treatment with chemotherapy in patients with metastatic lung cancer. The study showed that early palliative consultation which included an honest discussion of prognosis and treatment goals was associated with improved QOL, improved survival, decreased incidence of ICU death and of third line chemotherapy, and reduced cost (Temel et al. 2011).

While the data overwhelmingly suggest the benefit of honest end-of-life discussion, this conclusion should be mitigated by the following considerations.

- The studies of the issue may be biased as they involved selected patients who were willing and able to give informed consent. They provide no information related to the QOD of the patients who were unable or unwilling to provide consent, which may involve patients from different cultural, socioeconomic, and educational backgrounds.
- The studies were not geared to establish the results of end-of-life discussion in individual patients, that is, to establish whether in some patients this discussion resulted in worsening of QOD. One learns that the discussion was beneficial to the majority of patients, not whether it was hurting some of the patients. Information on how to differentiate between patients who might benefit and those who might be harmed by this discussion was not provided.
- In all studies, the end-of-life discussion was conducted by highly trained professionals; so, the conclusions cannot be applied to discussion on end of life by

> nonprofessionals. It is not far-fetched to imagine that these discussions may be harmful when led by people who are uncomfortable with death and dying and/or lack adequate education to prepare them for end-of-life discussions. It is important to be able to identify individual psychological and emotional nuances which require empathy, compassion, and skillful communication techniques. At least anecdotally it is clear that some patients avoid engaging in discussions about end of life and may be hurt by professionals who insist upon having this discussion (Balducci 2012).

In conclusion, open and honest communication is the key to trust, and untruthful communication should be avoided, to preserve therapeutic alliance. This may not always be clear-cut, however. Although some patients may appreciate the team's honest communication about their prognosis, others may label this as "doom and gloom." An empathic discussion of end-of-life issues, however, including prognosis and realistic treatment goals, is beneficial to the QOD of the majority of patients. It is up to the practitioner to be sensitive to individual patient preferences and recognize when a patient is uncomfortable. This discussion is crucial at the initial visit when the patient should be asked the degree to which he/she wishes to know about the disease in general and as treatment progresses, prognosis. It is also important to inform the patient and family that it is sometimes very difficult to make predictions. Survival information should be provided when the patient asks or is concerned about his/her ability to bring to terms some specific plans (Balducci 2008). Last, but not least, the practitioner should respect the patient's right not to be informed and to trust the management decisions to his/her provider (Rosembaum 2015).

Palliative Sedation Pharmacological induction of unconsciousness up to the time of death is almost universally accepted in the management of terminal patients in whom life-supporting treatment, including artificial ventilation, is discontinued (Claessens et al. 2008). However, the practice of terminal or palliative sedation is controversial for the management of terminal suffering, including pain, anxiety, and in particular for the management of "existential pain" (Claessens et al. 2008; Papavasiliou et al. 2014). Existential pain sometimes is referred to as psychic pain. The controversy hinges on whether or not terminal sedation is a form of euthanasia. Euthanasia by definition cannot be considered a means to improve QOD, as the goal of euthanasia is to facilitate death rather than improve life. The controversy is further complicated by the fact that the protocol for terminal sedation is not standardized. Terminal sedation may be delivered in different ways, with different drugs, and at different levels of consciousness (Claessens et al. 2008; Papavasiliou et al. 2014). Clearly more studies of the issue are necessary.

From an ethical standpoint, palliative sedation appears acceptable when it is utilized to alleviate pain or other symptoms that cannot be otherwise relieved (Boyle 2004). In the case of "existential suffering," however, the issue remains controversial (Putman et al. 2013). For the majority of physicians interviewed, it is a statement that death is a better condition than life, and as such it should not be utilized for improving QOD.

4.5 The Construct of a Good Death

Ira Byock, a renowned scholar of palliative care, claims that dying well is important, rather than obtaining a "good death" (Byock 1997), implying that death, like any other human experience, is a process that involves multiple actors including the patient, the medical team, and the patient's family and friends. Byock provides an emotional blueprint to "well dying" that includes expression of love, repentance, and forgiveness that lead to a peaceful and loving separation, in addition to symptom control. Indeed, symptom control primarily represents a precondition to a satisfactory final goodbye. To this blueprint, we would like to add: the finding of meaning of one's own existence; the satisfaction of knowing that one's life has had meaning. Irrespective of whether one believes in the afterlife, one may feel the need to transcend himself/herself at the end of life, to collocate him/herself as an essential pebble of the greater human mosaic.

The question we would like to ask at the end of this chapter is "Is a good QOD equivalent to dying well?" We believe it is important to distinguish between two concepts. A good QOD may facilitate the process of dying well and is generally associated with well dying. But as long that she/he has discovered the ultimate sense of his/her life, even a patient crucified to a ventilator, with tubes spurting from each one of his/her natural or artificial orifices, may enjoy the experience of dying well.

Conclusions

QOD is a complex construct. Complex, from the Latin term "*cum plexere*" is "to weave together," which means that it results from a number of tightly interwoven factors. A treatment team involving different health care providers is crucial in providing end-of-life care and should, in addition to physicians and nurses, include social workers and chaplains. In addition, cultural sensitivity is essential to establish good communication and foster an atmosphere of mutual respect.

The factors that may affect QOD include symptom control, dying at home, avoidance of chemotherapy or other heroic treatments near death, adequate spiritual and religious support, and most of all, the therapeutic alliance, based on trust. As explained in the text, each of these factors needs to be managed in the dynamic individual context of each patient. One may accept some level of pain if absolute pain control is associated with delirium, emotional numbness, or severe nausea and vomiting. Likewise, aggressive treatment close to the time of death may be necessary for patients who have difficulty facing death or wish to prolong life to reach an important milestone.

A good QOD may facilitate the process of "dying well" that involves peace with oneself and one's relations, and discovery of the ultimate meaning of one's life.

References

Abbott CH, Prigerson HG, Maciejegewski PK (2015) The influence of patients quality of life at the end of life on bereaved caregiver suicidal ideation. J Pain Symptom Manage 48:459–464

Balboni TA, Balboni M, Enzinger AC et al (2013) Provision of religious support to patients with advanced cancer by religious communities and association with medical care at the end of life. JAMA Intern Med 173:1109–1117

Balducci L (2008) And a time to die. J Med Person 6:99–103

Balducci L (2011) Suffering and spirituality: analysis of living experiences. J Pain Symptom Manage 42:479–486

Balducci L (2012) Death and dying: what the patients want. Ann Oncol 23(Suppl 3):56–61

Balducci L, Fossa SD (2013) Rehabilitation of older cancer patients. Acta Oncol 52:233–238

Balducci L, Hardy C (1987) Cancer and nutrition: a review. Compr Ther 13:60–69

Balducci L, Mayer R (2001) spirituality and medicine: a proposal. Cancer Control 8:368–376

Black B, Herr K, Fine P et al (2011) The relationship among pain, non pain symptoms, and quality of life measures in older patients with cancer. Pain Med 12:880–889

Boyle J (2004) Medical ethics and double effect: the case of terminal sedation. Theor Med Bioeth 25:51–60

Byock I (1997) The prospective of death at the end of life. Riverhead book, New York

Cacciatore J, Thieleman K (2014) We rise out of the cradle into the grave: an ethnographic exploration of rituals, mourning, and death on a Hutterite colony. Omega 69:357–379

Candy B, Jones L, Varagunam M et al (2012) Spiritual and religious intervention for well being of adults in terminal phase of disease. Cochrane Database Syst Rev (5):CD007544. doi:10.1002/14651858.CD007544.pub

Claessens P, Menten J, Shotsman P et al (2008) Palliative sedation: a review of the research literature. J Pain Symptom Manage 36:310–333

Cleese J. http://WWW.thejohncleese.com

Cobb M, Dowrick C, Lloyd Williams M (2012) What can we learn about the spiritual needs of palliative care patients from the research literature. J Pain Symptom Manage 43:1105–1119

Collier MJ, Hedge P, Lee N et al (2002) Dialogues on the edges: ferments in communication and culture. In: Collier MJ (ed) Transforming communication about culture. Sage, Thousand Oaks, pp 229–230

Collier A, Phillips JL, Iedema R (2015) The meaning of home at the end of life: a video-reflexive ethnography study. Pall Med 29:695–702

Cook D, Swinton M, Toledo F et al (2015) Personalizing death in the Intensive Care Unit: the three Wishes Project. Ann Intern Med 163:272–280

Crocker TF, Smith JK, Skevington SM (2015) Family and professionals underestimate quality of life across different cultures and health conditions: a systematic review. J Clin Epidemiol 68:584–595

Dahiva S, Ahluwalia MS, Walia HK (2013) Sleep disturbances in cancer patients: under recognized and undertreated. Cleve Clin J Med 80:722–732

Emanuel EJ, Fairclough DL, Wolfe P (1999–2004) Emanuel LL: talking to terminally ill patients and their caregivers about death, dying and Bereavement: Is it stressfull? Is it helpful? Arch Intern Med 2004:164

Fleming R, Kelly F, Stillfried G (2015) 'I want to feel at home": establishing what aspects of environmental design are important to people with dementia at the end of life. BMC Palliate Care. doi:10.1186/s12904-015-0026-y

Fukui S, Yoshiuchi K, Fjita J et al (2011) Japanese People's preference for place of end-of life care and death: a Population-Based Nationwide Survey. J Pain Symptom Manage 42:882–892

Gent MJ, Fradsham S, Whyte T et al (2015) What influences attitudes toward clinically assisted hydration in the care of dying patients? A review of the literature. BMJ Supp Pall Care 5:223–231

Goldstein D, Thewes W, Butow P (2002) Communicating in a multicultural society: Greek communities attitudes toward cancer in Australia. Int Med J 32:289–296

Hales S, Zimmermann C, Rodin G (2010) Review: the quality of dying and death: a systematic review of measures. Palliat Med 24:127–144

Hales S, Gagliese L, Nissim R et al (2012) Understanding bereaved caregiver evaluation of dying and death: an application of cognitive interviewing methodology to the a quality of life and death questionnaire. J Pain Symptom Manage 195–204

Hawthorn M (2015) The importance of communication in sustaining hope at the end of life. Br J Nurs 24:702–705

Henson LA, Gao W, Higginson IJ et al (2015) Emergency department attendance by patients with cancer in their last months of life: a systematic review and meta-analysis. J Clin Oncol 33:370–376

Hermann CP, Looney SW (2011) Determinants of quality of life in patients near the end of life: a longitudinal perspective. Oncol Nursing Forum 38:23–31

Institute of Medicine (1997) Approaching death: improving care at the end of life. National Academy Press, Washington, DC

Jones JM, McPherson CJ, Zimmermann C et al (2011) Assessing agreement between terminally ill cancer patients' reports of their quality of life and family caregiver and palliative care physician proxy rating. J Pain Symptom Manage 42:354–365

Kaspers PJ, Pasman HR, Onwuteaka-Phillipsen VD et al (2013) Changes over a decade in end of life and transfers during the last three months of life: a repeated survey among proxies of deceased older people. Palliat Med 27:544–552

Kim SS, Reed PJ, Hayward RD et al (2011) Spirituality and psychological well being: testing a theory of family interdependence among family caregivers and their elders. Res Nurs Health 34:103–115

Kirsten AT, Lars JD, Kari K et al (2014) The power of consoling presence: hospice nurses-lived experience with spiritual and existential care of the dying. BMC Nurs 13:25

LeBlanc TW, McNeil MJ, Kamal AH et al (2015) Polypharmacy in patients with advanced cancer and the role of medication discontinuation. Lancet Oncol 16:e333–e341

Lee C (2009) "Race" and "Ethnicity" in Biomedical research: how do scientists construct and explain differences in health? Soc Sci Med 68:1183–1190

Lee MR, Baek SK, Kim S et al (2013) Awareness of incurable cancer status and health-related quality of life among advanced cancer patients: a prospective cohort study. Pall Med 27:244–254

Luciani A, Jacobsen PB, Extermann E et al (2008) Fatigue and functional dependence in older cancer patients. Am J Clin Oncol 31:424–430

Maciejevsky PK, Prigerson HG (2013) Emotional numbness modifies the effect offend-of –life discussion and end-of –life care. J Pain Symptom Manage 45:841–847

Mack JW, Block SD, Nilsson M et al (2009) Measuring therapeutic alliances between oncologists and patients with advanced cancer: The Human Connection Scale. Cancer 115:3302–3311

Mack JW, Paulk ME, Viswanath K et al (2010) Racial disparities in outcome communication on medical care received near death. Arch Int Med 170:1533–1540

Mack JW, Cronin A, Keating NL et al (2012) Association between end-of-life discussion characteristic and care received near death: a prospective cohort study. J Clin Oncol 30:4387–4395

Martin JN, Nakayama TK (2013) Intercultural communication in contexts. McGraw Hill, Boston

McCreery E, Costello J (2013) providing nutritional support to patient with cancer cachexia. Int J Pall Nurs 19:32–37

Mehta RD, Roth AJ (2015) Psychiatric considerations in the oncology setting. CA Cancer J Phys 65:299–314

Melin-Johansson C, Odling G, Axelsson B et al (2008) The meaning of quality of life: narrations by patients with incurable cancer in palliative care home. Palli Support Care 6:231–238

Nowarska A (2015) Clinically assisted hydration and the liverpool care pathway: Catholic ethics and clinical evidence. J Med Ethics 41:645–649

Padela A, Mohiuddin A (2015) Ethical obligations and clinical goals in end-of-life care: deriving a quality of life construct based on the Islamic concept of accountability before God. Am J Bioeth 15:3–13

Papavasiliou ES, Brearley SG, Seymour EG et al (2014) From sedation to continuouis sedation until death: how has the conceptual life of sedation at the end of life changed over time? J Pain Symp Manage 47:891–706

Patient self-determination act 19090, 42 USC 1395 cc (a)

Peppercorn JM, Smith TJ, Helft PR et al (2011) American Society of Clinical Oncology. American Society of Clinical Oncology statement: toward individualized care for patients with advanced cancer. J Clin Oncol 29(6):755–760

Peteet JR, Balboni MR (2013) Spirituality and religion in oncology. CA Cancer J Clin 63:280–289

Pinquart M, Koch A, Eberhardt B et al (2006) Association of functional status and depressive symptoms with health-related quality of life in cancer patients. Qual Life Res 15:1565–1570

Prigerson HG, Bao Y, Shah M et al (2015) Chemotherapy use, performance status, and quality of life at the end of life. JAMA Oncol. doi:10.1001/jamaoncol.2015.2378

Prossr R, Korman D, Feinstein RA (2012) An orthodox perspective of the Jewish end-of-life experience. Home Healthc Nurse 30:579–585

Puchalski C, Ferrell B, Virani R et al (2009) Improving the quality of spiritual care as a dimension of palliative care: the report of the consensus conference. J Palliat Med 12:885–904

Putman MS, Yoon JD, Rasinsky KA et al (2013) Intentional Sedation to unconsciousness to the end of life: findings for a National Physician Survey. J Pain Symptom Manage 46:326–334

Roscoe L, Tullis J (2015) The meaning of everything: communication at the end of life. J Med Person 13:81–86

Rose JH, O’toole EE, Dawson NV et al (2000) Generalists and Oncologists show similar care practices and outcomes for hospitalized late-stage cancer patients. SUPPORT investigators. Study to understand Prognoses and preferences for Outcomes and Risks of Treatment. Med Care 38:1103–1118

Rosembaum L (2015) The paternalism preference-choosing unshared decision making. N Engl J Med 373:589–592

Schnipper LE, Davidson NE, Wollins DS et al (2015) American Society of Clinical Oncology statement: a Conceptual Framework to assess the value of cancer treatment options. J Clin Oncol 23:2563–2577

Searight HR, Gafford J (2005) Cultural diversity at the end of life: Issues and guidelines for family physicians. Am Fam Physician 71:515–522

Shah SK, Kaspar K, Millar FG (2015) A narrative review of the empirical evidence on public attitudes on brain death and vital organ transplantation: the need for better data to inform policy. J Med Ethics 41:291–296

Steinhauser KE, Christakis NA, Clipp EC et al (2000) Factors considered important at the end of life by patients, family, physicians, and other care providers. JAMA 284:2476–2482

Stephenson PS, Berry DM (2015) Describing spirituality at the end of life. West J Nurs Res 27:1229–1247

Tang ST, Liu LN, Kin LC et al (2014) Trajectories of the multidimensional dying experience for terminally ill cancer patients. J Pain Symptom Manage 48:863–874

Temel JS, Greer JA, Adamane S et al (2011) Longitudinal perceptions of prognosis and goals of therapy in patients with metastatic non-small-cell lung cancer: results of a randomized study of palliative therapy. J Clin Oncol 29:2319–2329

Temel J, Currow D, Fearon K et al (2014) Anamorelin for the treatment of cancer anorexia/cachexia in NSCLC. Results from the phase III studies Romana 1 and 2. Ann Oncol 25:1–41

Teno JM, Clarridg BR, Casey V et al (2004) Family perspective on end-of-life care at the last place of care. JAMA 292:88–93

Tomkins A, Duff J, Fitzgibbon A et al (2015) Controversies in faith and health care. Lancet pii: S0140-6736(15)60252-5. doi:10.1016/S0140-6736(15)60252-5

Van Laarhoven SW, Schilderman J, Verhagen CA et al (2012) Comparison of attitudes of guilt and forgiveness in cancer patients without evidence of disease and advanced cancer patients in a palliative care setting. Cancer Nurs 35:483–492

Veinante P, Yalcin I, Barrott M (2013) The Amygdala between sensations and affect: a role in pain. J Mol Psych. doi:10.1186/2049-9256-1-9

Wiffen PJ, Derry S, Moore RA (2014) Impact of morphine, fentanyl, oxycodone, or codein on patients'consciousness, appetite and thirst when used to treat cancer pain. Cochrane Database Syst Rev (5):CD011056. doi:10.1002/14651858.CD011056.pub2

Wittemberg E, Ferrell B, Goldsmith J et al (2015) Providers difficulties with spirituality and forgivness communication at the end of life. Am J Hosp Pall Care 2015. pii: 1049909115591811

Woodman C, Baillie J, Sivell S (2015) The preferences and perspectives of family caregivers toward the place of care for their relatives at the end of life. A systematic review and thematic synthesis of qualitative evidence. BMJ Supp Pall Care. pii: bmjspcare-2014-000794. doi:10.1136/bmjspcare-2014-000794

Wright AA, Zhang B, Ray A et al (2008) Associations between end of life discussions, patient mental health, medical care near death, and caregiver bereavement adjustment. JAMA 30:1665–1673

Wright AA, Mack JW, Kritek PA et al (2010a) Influence of patients' preferences and treatment site on cancer patients' end-of-life care. Cancer 116:4656–4663

Wright AA, Keating NL, Balboni TA et al (2010b) Place of death: correlations with quality of life of patients with cancer and predictors of bereaved Caregivers' Mental Health. J Clin Oncol 28:4457–4464

Wright AA, Stieglitz H, Kupersztoch YM et al (2013) United States acculturation and cancer patients end of life care PLoS One 8(3):e58663. doi:10.1371/journal.pone.0058663. Epub 2013 Mar 11

Zhang B, Nilsson ME, Prigerson HG (2012) Factors important to patient's quality of life and the end of life. Arch Intern Med 172:1133–1142

Legal Aspects of Oncology Care for Dying Patients

5

Marshall B. Kapp

5.1 Introduction

A variety of potential legal issues, both personal and financial in nature, are relevant to cancer patients who are approaching the end of their lives. These include such matters as estate planning needs, attaining eligibility for public or private disability benefits, and health care insurance coverage disputes (Rodabaugh et al. 2010). However, these individuals and their families, as well as their professional caregivers, also often confront difficult decisions regarding medical care at this point and those choices must be made within the prevailing legal environment. The legal environment surrounding and shaping medical decision making and care for dying cancer patients is explored in this chapter.

The focus here is on medical-legal questions impacting dying adult cancer patients and their families and caregivers in the United States. It is noteworthy, however, that most of these same issues also have application internationally and a comparison of different national approaches may usefully inform American practice (Foster et al. 2014; Kerrigan and Ormerod 2010).

5.2 Distinguishing Living Patients from Dead Bodies

Medical decision making pertains to living patients. Postmortem rights and duties (briefly outlined in Sect. 5.7 of this chapter) apply to dead bodies. Legal definitions of death, embodying societal values, are central to distinguishing living patients from dead bodies.

M.B. Kapp
Florida State University Center for Innovative Collaboration in Medicine and Law,
Tallahassee, FL, USA
e-mail: marshall.kapp@med.fsu.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_5

Historically, permanent cessation of cardiorespiratory functioning has served adequately as a definition of death for all purposes. However, the continued utility of the heart-lung definition has been seriously called into question in the past half century as technical advances in medicine have enabled us to sustain cardiorespiratory functioning artificially in some individuals almost indefinitely. Hence, the states have had to come up with an alternative definition of death that is comprehensive (legal, ethical, and clinical) and that provides clear guidance about precisely when the duty, and the authority, to provide life-sustaining medical treatment ceases.

In 1981, the President's Commission for the Study of Ethical Problems in Medicine and Biomedical and Behavioral Research recommended a Uniform Determination of Death Act (UDDA), which stated the following:

> An individual who has sustained either (1) irreversible cessation of circulatory and respiratory functions, or (2) irreversible cessation of all functions of the entire brain, including the brain stem, is dead.

The UDDA states that a "determination of death must be made in accordance with accepted medical standards." All state statutes in this sphere agree.

The clinical state of the art continues to evolve. The Harvard Criteria, published in 1968 and regularly updated to respond to advances in medical knowledge and technology, proposed that a permanently nonfunctioning brain (i.e., patient death) could be diagnosed accurately on the basis of four findings:

1. The person is neither receptive nor responsive.
2. The person has no spontaneous movements and no spontaneous breathing.
3. The person has no detectable reflexes.
4. As a confirmatory measure only, flat electroencephalograms are taken twice within at least a 24-h intervening period.

Because state law leaves to clinical discretion the selection of which specific tests to perform to confirm a patient's death, individual hospitals frequently develop their own policies to guide physicians declaring death within the institution.

Either by statute of judicial decision, all the states have adopted the UDDA. Nonetheless, ethical and clinical controversies persist and threaten to disturb the prevailing consensus regarding the definition of death for all purposes and its legal consequences (Pope 2014). A thorough explication of those controversies is beyond the scope of this chapter; the point here is simply to set out the legal importance of the fundamental alive-versus-dead person dichotomy.

5.3 Informed Choice and Confidentiality

5.3.1 Informed Consent and Refusal

Adult patients have the right to make their own health care choices about the initiation, continuation, withholding, or withdrawal of various forms of medical intervention. This right is not in any way diminished because of a diagnosis of irreversible, incurable cancer.

The informed choice doctrine, encompassing both consent to and refusal of specific aspects of medical intervention, is predicated on the ethical principles of respect and autonomy or self-determination, especially regarding the physical integrity and dignity of one's own body (del Carmen and Joffe 2005) An additional rationale for the doctrine is the belief that participating in the medical decision making process generally confers therapeutic benefit—a positive feeling of maintaining some degree of control—on the patient (Schachter and Fins 2008).

A health care provider may be held civilly liable, usually under a negligence theory but in rare cases under a battery or intentional tort theory (intentional acts that are or can be predicted to cause harm and do so) for subjecting a person to any diagnostic, therapeutic, or research-related intervention without that person's effective consent to the intervention. The substance of the informed consent rule has evolved over time, on a case-by-case basis, as a function of state common (judge-made) law. Moreover, the majority of states have enacted statutes and regulations spelling out a jurisdiction's specific details regarding informed consent for clinical care generally, including end-of-life care for oncology patients.

For a patient's decision about whether to accept or reject a suggested medical intervention to be considered legally valid, three separate but interrelated elements must be present. First, the patient's participation in the decision making process and the final decision(s) regarding intervention must be voluntary, rather than unduly influenced by force, fraud, duress, or any other actual or perceived form of constraint or coercion. Second, the patient's agreement or disagreement with recommended interventions must be adequately informed. The professional is obligated to disclose sufficient information about the proposed intervention to empower the patient to give or withhold a knowledgeable, intelligent consent or refusal. The third essential element of legally effective medical decision making is adequate cognitive and emotional capacity on the part of the patient to appreciate and manipulate relevant information about his or her medical care.

Regarding the informed part of the informed consent doctrine, there are two competing standards for determining how much information about a proposed medical intervention must be disclosed to the patient in advance. The medical custom or reasonable professional standard mandates the sharing of such information that a reasonable, prudent professional would disclose under similar circumstances. In other words, the health care professional's disclosure behavior is judged against the customary disclosure behavior of that person's professional peers. By comparison, the materiality or patient orientation standard compels the sharing of information that might make a difference (i.e., might be "material") to the decision making of a reasonable, average (in other words, objectively determined) patient in the same or similar circumstances. The different states are approximately evenly split between these two competing standards of information disclosure.

Under either the materiality or the reasonable professional standard, certain basic items of truthful information disclosure emanate from the professional's fiduciary or trust obligations to the patient (Tabak et al. 2012). These include the following: diagnosis or nature of the patient's medical problem; prognosis; nature and purposes (expected benefits) of the proposed interventions; reasonably foreseeable risks associated with the intervention, specifically, the probability of a risk actually occurring and the severity if it does materialize; and reasonable alternative interventions and their anticipated risks and benefits. The professional also must explain the reasonably foreseeable risks and benefits of foregoing available interventions. For example, a patient possesses the right to voluntarily stop eating and drinking (VSED) (Pope and Anderson 2011), but needs to be properly informed of the likely consequences (namely, death) of that action.

Other pieces of information that a health care professional should carefully consider disclosing to the patient are: complementary and alternative medicine alternatives; cost ramifications to the patient of proposed alternatives; professional-specific information pertinent to the particular intervention (for instance, the professional's own individual track record with the particular intervention or any financial incentives that professional has regarding the patient's course of care); and the level of uncertainty within the medical community concerning the particular intervention being contemplated.

This latter piece of the decisional puzzle—medical uncertainty—is particularly important in the oncology arena, where "clinical equipoise" between multiple alternatives often is present (van Laarhoven et al. 2014). Frequently, there is no clear, definitive clinically "correct" answer and competing quality of life considerations are attached to different choices, enhancing the wisdom of patient-centered shared decision making (Ellor et al. 2014) rather than the traditional physician-dominated paternalistic approach.

The patient's informed consent to a medical intervention may be implied or expressed. There are many situations in which a patient's permission to proceed with a medical intervention does not need to be put into words but, instead, may be implied from the circumstances. This happens when, through demonstrative actions or passive compliance, the patient indicates a wish (or at least willingness) to undergo a specific intervention by voluntarily submitting to it in a manner that the health care professional can reasonably rely on to conclude that the intervention has been authorized. Implied consent is appropriate for most routine, noninvasive, relatively low risk kinds of medical interventions such as taking a patient's blood pressure or listening to the heart. Implied consent is not an exception to the general informed consent requirement, but instead a different (created by behavior instead of words) form of permission.

Express consent (put into spoken or written words), by contrast, is more appropriate when the proposed medical intervention is intrusive and/or significantly more risky than ordinary, everyday life. With a small number of exceptions created by particular state statutes for designated kinds of interventions (such as testing for the HIV virus), implied consent in the form of spoken rather than written patient words is legally adequate, so long as the consent is given voluntarily, competently, and on the basis of sufficient information being disclosed. However, for particularly intrusive or risky interventions, the provider should consider documenting the patient's decision to consent or refuse by asking the patient to sign a separate written form, in addition to the professional always completing a thorough, timely progress note in the patient's medical record (Treleaven et al. 2012). Also, voluntary accreditation standards with which the provider complies, such as those of the Joint Commission, may require the use of separate written consent forms for particular sorts of medical interventions.

In communicating information to a patient, and in interpreting a patient's response to information provided, the health care provider should be attuned to cultural aspects of the patient's background that might contribute to a tension or even outright conflict between the patient's underlying values and those embodied in predominant American society and law. Especially in the end-of-life context, the culturally influenced attitude of patients and their families regarding such matters as the role of individual autonomy, advance medical planning (see Sect. 5.4, below), and the propriety of literal and transparent medical communication should be factored into planning precisely how the provider's legally required fact disclosures will be sensitively broached with the patient, family, and/or surrogate (Chew 2012). In a similar vein, the structural aspects (the where, when, and how aspects of presenting choices to the patient) of decision making guide the effective degree of patient participation determining a particular decision (Salloch et al. 2014); health care providers are obliged to manipulate those structural aspects as creatively as possible to maximize the patient's contribution to shared decision making.

5.3.2 Right to Control Medical Information

The right of cognitively and emotionally capable adult individuals or their surrogates to make personal medical decisions is paralleled by a right to exercise control over distribution of the patient's personal medical information. In other words, the medical decision maker in the specific situation ordinarily is the one with authority to dictate details regarding the keeping or disclosure of personally identifiable information concerning the patient.

In the course of providing care, health care professionals routinely come into the possession of very private information about patients and their families. Professionals owe patients a fiduciary or trust responsibility to hold in confidence all sensitive patient information entrusted to them through the professional/patient relationship. This is both an ethical obligation, based on the patient's important autonomy interest in protecting personal privacy and avoiding the social stigma and potential discrimination that breach of one's medical privacy might entail (particularly in the oncology context), and a legally enforceable duty.

5.3.2.1 State Law

Every state, both within its various state professional Practice Acts and in separate statutes pertaining to particular health care delivery settings, has enacted provisions pertaining to the confidentiality duties of health care professionals, institutions, and agencies. Administrative regulations often are published to spell out how those duties will be implemented at the ground level. Moreover, a strong common law health care confidentiality doctrine has evolved through state court decisions delivered over time. Violation of state common law or relevant statutory or regulatory requirements regarding the confidentiality of patient information may expose transgressing health care providers to civil damage suits, brought by or on behalf of the patient whose privacy was improperly infringed; additionally, violation of state Practice Act provisions may subject the violator to administrative sanctions by the state, including license suspension or even revocation.

However, there are numerous exceptions to the general confidentiality rule. Several of these exceptions are not really relevant to the oncology context, but a few do apply to the current discussion. The most pertinent exception in the oncology context occurs when a patient voluntarily and knowingly waives, or gives up, the right to assert the confidentiality of particular information. These waivers take place daily, either expressly or by implication, through which patients make their information available to third-party payers (for instance, Medicare claims processors and private health insurers), quality of care auditors (such as Joint Commission surveyors), and other public and private entities like health care surrogates authorized to make medical decisions on behalf of decisionally incapacitated patients. Also, because the modern delivery of oncology care is a team effort, each patient implicitly gives permission for the sharing of certain otherwise private pieces of information among the members of the care team. Internal information sharing of this nature is essential to optimal patient care. Indeed, failures in communication among the multiple providers involved in the care of a dying cancer patient who needs such coordination and continuity may lead to negligence liability claims when harm results.

Further, a health care professional may be compelled to reveal otherwise confidential information about particular patients by the force of legal process, namely, when a judge issues a court order requiring such release. This is a possibility in any civil or criminal lawsuit involving a factual dispute about a patient's physical or mental condition, for instance, in a personal injury suit stemming from an automobile accident. A court order (as opposed to a subpoena or subpoena *duces tecum*, which is issued simply as an administrative, nondiscretionary matter by the court clerk rather than by a judge) may overrule the state's professional/patient testimonial privilege statute. That statute ordinarily would prohibit the provider from testifying in a legal proceeding regarding private patient information, but a court order could require the professional to produce personally identifiable patient information. Every state testimonial privilege statute provides for judicially compelled testimony on the part of the health care professional when, for example, the patient has placed his or her own health condition and medical treatment in issue in a lawsuit.

5.3.2.2 Federal Law

Federal confidentiality regulations are codified at Title 45, U.S. Code of Federal Regulations Parts 160 and 164.These regulations implement the Health Insurance Portability and Accountability Act (HIPAA) of 1996 (Public Law No. 104–191, title XI, Part C). These regulations, published in the form of a Privacy Rule and a Security Rule, impose on covered health care entities (defined as, among certain others, any health care providers who transmit any patient-related information electronically) an extensive set of requirements regarding the handling of personally identifiable medical information contained in patient records. These regulations authorize significant criminal and civil sanctions for unauthorized disclosures of personal health information. Substantively, HIPAA and its implementing regulations in essence codify preexisting state statutory and common law protections for patients, with some additional provisions clarifying that patients have a right to access the information recorded in their own medical records. (Previously, state law had varied or was unclear regarding the issue of patient access to records.) HIPAA contains provisions authorizing covered entities to transmit personal health information to certain others for purposes of "treatment, payment, and health care operations" such as quality assurance or marketing. These and other exceptions explicitly contained in HIPAA are consistent with pre-existing state statutes and common law precedent.

5.4 Advance Health Care Planning

5.4.1 Decisional Capacity Issues

The law begins with a presumption that all adults are able to make and communicate autonomous decisions about their own medical care. Sometimes, though, a patient is not mentally and/or emotionally capable of assimilating pertinent information and taking an active part in a rational, voluntary decision making process about medical interventions. Oncology patients approaching end-of-life situations may become (or already may be) so impaired that they fall into this category. When the patient personally lacks adequate decisional capacity, the health care professional is not relieved of the duty to obtain informed consent but, instead, must work with someone else who is willing and available to act as a surrogate on the patient's behalf.

Assessing decisional capacity entails a functional inquiry. The basic questions to be posed are the following: (1) Can the person make and communicate any decisions at all? (2) Is the person able to offer reasons for the choices made, indicating any degree of reflection and consideration? (3) Are the reasons given based on logical reasoning proceeding from factually accurate suppositions? (4) Can the patient appreciate the probable consequences (i.e., the likely risks and benefits) of the alternatives outlined and the choices expressed, and comprehend that these consequences apply to that particular patient? (5) Does the individual actually understand the practical implications of his or her choices?

A patient's cognitive and emotional capacity should be evaluated on a decision specific, rather than a global or all-or-nothing, basis. A patient may be capable of making some kinds of decisions, but not others; partial or limited capacity is possible even when total capacity is not. Moreover, capacity may fluctuate within a specific patient according to variables such as time of day, day of the week, physical location, acute and transient physical problems, other persons available to support or coerce the patient's choice, and medication reactions. Some of these factors may be susceptible to manipulation by caregivers (e.g., through changes in the timing of drug administration) so that discussions with the patient (rather than or in addition to discussions with the surrogate) about the care plan can take place under the most lucid circumstances possible.

5.4.2 Advance Health Care Planning Opportunities

A number of legal instruments have evolved over the past several decades and are available to empower a patient who presently is decisionally capable to plan ahead for a future time when medical decisions regarding the initiation, continuation, withholding, or withdrawal of life-sustaining medical treatment may need to be made but that person will then lack sufficient capacity to exercise autonomous choice (Sabatino 2014). A recent report of the Institute of Medicine (2014), *Dying in America*: *Improving Quality and Honoring Individual Preferences Near the End of Life*, confirms the observations of many health practitioners and legal commentators (Sico 2013) that current methods of advance health care planning are hardly a panacea for difficulties that may arise in this arena. Nonetheless, advance planning does help patients who have the foresight and wherewithal to look ahead to maintain some degree of prospective medical autonomy. Advance planning also may help individuals and their families avoid court involvement in medical decisions, conserve limited health care resources in a way that is consistent with patient self-determination, and reduce emotional stress on families in crisis circumstances. Thus, health care professionals have an obligation to assist patients to be aware of and take advantage of available planning opportunities.

Although an advance directive (AD) may be oral, it is much more likely to be followed if it is a written document. An instruction (living will)–type AD contains an individual's instructions about wanted, limited, or unwanted interventions in case that person subsequently becomes incapacitated. These instructions may be detailed (e.g., relating to specific medical treatments in specific situations), general (for instance, requesting "no extraordinary measures"), or phrased in terms of a patient's personal values and goals (like "keep me alive forever no matter what pain or expense" or "avoiding suffering is my main concern").

By contrast, a proxy directive (usually a durable power of attorney [DPOA]) is an AD that permits an individual to designate another person—called a health care agent, surrogate, proxy, or attorney-in-fact—to make health care decisions if the principal (the person who delegates away decision making authority) later loses decision making capacity. In states that have default surrogate consent laws (which are statutes that designate a legal hierarchy of family members and others who may make decisions on behalf of incapacitated patients when there is no court-appointed guardian or instruction directive present), a DPOA can clarify which person has authority to decide when two persons have equal status (such as siblings) in the hierarchy. Additionally, a DPOA is very valuable when a person prefers a nonrelative as the future decision maker. For example, in the gay community, it is common for individuals to appoint a domestic partner or friend rather than a family member as the health care agent (Persinger 2010). Some AD documents combine the instruction and proxy elements.

Only a presently capable person may execute a valid AD. The AD becomes effective only when that individual subsequently lacks decisional capacity regarding a particular medical treatment issue. States have enacted detailed statutes that outline conditions under which an AD is legally valid, and there is some inconsistency among the various state statutes (Maron 2011). In practice, health care providers are often unclear about when a living will applies and are uncomfortable about deciding when a patient is on a dying trajectory that warrants triggering or operationalizing a living will's instructions. Furthermore, health care providers sometimes find a living will's directions either too broad or too narrow to provide useful guidance in a particular situation. Thus, appointing a proxy with power to make real time medical choices, based on the best available up-to-date information, may be more useful.

The Patient Self-Determination Act (PSDA) became effective in 1991. The PSDA mandates that hospitals, nursing homes, home health agencies, hospices, health maintenance organizations, and preferred provider organizations participating in the Medicare or Medicaid government financing programs (1) provide written information to individuals about their right to participate in medical decision making consistent with applicable state law; (2) ask patients whether they have completed an AD already and, if the answer is affirmative, have a system for recording the patient's AD; (3) offer decisionally capable patients an opportunity to execute an AD if the document does not already exist; (4) not discriminate in the provision of care based on the presence or absence of an AD; (5) have a system to comply with applicable state laws on medical decision making; and (6) educate staff and the community about medical decision making rights.

Despite substantial public attention, psychological resistance to the contemplation of illness and death, coupled with inertia and legal complexities complicating the execution of an AD (Castillo et al. 2011), keeps the rate of AD completion low among the general public. There is evidence, however, that patients with a cancer diagnosis are more likely than others to engage in advance care planning (Lovell and Yates 2014). Still, "[e]ven individuals with advanced illness, including metastatic cancer, may receive more-aggressive treatment than they want because they have not discussed their end-of-life care preferences with their doctor" (Wilson et al. 2014).

The PSDA expressly forbids any health care provider from requiring a patient to execute an AD as a condition of admission or receipt of services. Nevertheless, the health care team, with the oncologist taking the lead, should attempt to discuss end-of-life preferences with seriously ill cancer patients and help them complete ADs if desired. Changes in physician reimbursement practices may encourage physicians to undertake this role (Halpern and Emanuel 2014). Public health agencies also should be involved in educating patients and families about their options at this stage of life (Rao 2014). Many people in this patient population group want to talk about end-of-life care and are willing to fill out an AD if given the opportunity. Discussions may focus on specific interventions and/or on an individual's remaining life and health care goals and priorities. Although physicians should be centrally involved in the communication process (Billings and Krakauer 2011), the active participation of nurses, physician assistants, and social workers may also be highly valuable.

Timing of communication about end-of-life care is key. Discussions ideally should occur in advance of a medical crisis, during regularly scheduled appointments with the oncology team. Periodically, and following significant health events, health care providers should review with patients who retain decision making capacity their ADs to ascertain the continued accuracy of their listed preferences and other information. Patients should be advised to give copies of the AD to their designated health care agents, family members, and close friends, as well as make sure that all of the patient's physicians have a copy in the medical records, thus assuring easy accessibility in an emergency. In emergency situations outside of health care institutions (e.g., a cardiac arrest in the patient's own home), emergency medical service providers may not recognize and follow an AD unless it takes the form of a physician's order made in conformity with the state's applicable out-of-institution treatment statute. (See discussion of POLST in Sect. 5.4.3 below.)

No person, whether living in the community or temporarily or permanently being cared for in an institution, is legally or ethically required to execute an AD. Individuals (and their families) should be informed—and providers must understand—that the person will not be abandoned, ignored, or otherwise discriminated against regarding treatment because of failure to execute an AD. (See discussion of palliative treatment in Sect. 5.5.2.)

5.4.3 Physician Orders for Life-Sustaining Treatment

For patients with advanced, irreversible illness who may become decisionally incapacitated, growing frustration with the inherent limitations of existing advance health planning instruments (Nachman 2011) has led many attorneys, health care professionals, and commentators to advocate as the next step in the evolution of health care advance planning law and policy the use of POLST (Physician Orders for Life-Sustaining Treatment) forms. (Exact nomenclature varies among different jurisdictions; e.g., New York State refers to its physician order instrument as a MOLST, for Medical Orders for Life-Sustaining Treatment (Bomba 2011)). From a variety of perspectives, the POLST paradigm offers a number of opportunities for going beyond the status quo, including our present strong reliance on ADs, to potentially improve the care of individuals with advanced, irreversible illness (Wolf et al. 2014).

Unlike a traditional AD executed by a patient while still decisionally capable, POLST entails a medical order written by a physician (with the concurrence of the patient or surrogate) instructing other health care providers such as emergency medical squads about the treatment of a patient with advanced, irreversible illness under specific factual circumstances. "The POLST form is a more uniform, comprehensive, and portable method of documentation of patients' end-of-life treatment desires. Although the POLST form is not intended to replace ADs executed by patients, it corrects many of the inadequacies of current forms and intends to lessen the discrepancy between a patient's end-of-life care preferences and the treatment(s) eventually provided by the patients' health care providers" (Spillers and Lamb 2011). In many respects, a POLST is an expansion of the Do Not Resuscitate (DNR) concept that has become well-accepted and widely utilized in appropriate circumstances for patients for whom cardiac arrest would not be unexpected or welcomed (O'Shea et al. 2002).

As of the end of 2014, 15 states had formally implemented the POLST Paradigm into clinical practice, with national coordination efforts being administered through the Center for Ethics in Health Care at the Oregon Health & Science University. Many more states are in the process of developing and implementing their own versions of POLST.

5.4.4 Making Medical Decisions in the Absence of Advance Planning

It is foreseeable that a significant number of seriously ill patients with cancer will become decisionally incapacitated without having written an instruction directive or appointed a decision making agent, and for whom no POLST has been created by the patient's physician. An overwhelming majority of states have statutes that empower family members and specified other individuals to make certain choices for incapacitated persons in this situation (Pope 2012). In states that have enacted surrogate default legislation, the approved procedure usually involves documenting unanimous agreement among professional caregivers, specified relatives, and sometimes others who are enumerated in a particular priority order. Even in the minority of states that lack surrogate default legislation, the courts (on the very rare occasions that they become involved) uphold as a matter of common law or a state's own constitution the family's power to exercise the incapacitated person's decision making rights for that person.

When no durable power of attorney has been appointed, there is no applicable surrogate default statute or judicial precedent authorizing family members or others to decide (or the patient is "unbefriended" and without family members or friends to act on his or her behalf (Volpe and Steinman 2013)), and/or family members vehemently and irreconcilably disagree among themselves about the best course of care for the decisionally impaired individual, establishing a guardianship or conservatorship may be necessary. A guardianship or conservatorship order (terminology varies among different jurisdictions) has the effect of formally transferring decision making power from an incapacitated person to an officially authorized substitute decision maker. However, the formal legal process involved in producing a guardianship/conservatorship order (with its accompanying financial and human costs) should only be initiated as a last resort after other strategies, such as referral to an institutional or organizational Ethics Committee or attempts at collaborative or supported decision making (Kohn et al. 2013) have failed in attempting to reconcile the conflicting positions of the interested stakeholders.

5.5 Standards of Care and Medical Malpractice Liability

5.5.1 Standards of Care Pertaining to the Dying Cancer Patient

In a private civil lawsuit predicated on a theory of professional negligence, the plaintiff is required to establish four distinct elements by a preponderance of the evidence (a more likely than not burden of proof). First, the patient/plaintiff has the burden of proving that the professional defendant owed the patient an obligation defined by the appropriate standard of care. The existence of this duty ordinarily is established by showing that there existed, within the relevant time frame, a professional relationship between the patient and caregiver, that is, the plaintiff was a patient of the professional for diagnostic and/or therapeutic purposes.

Second, the plaintiff must present sufficient evidence that the professional breached or violated the appropriate standard of care arising within the professional relationship. The professional does not guarantee particular results, let alone perfection. By the same token, however, it is not enough for professionals to simply "do their best" if their conduct does not rise to the applicable level of care, even when errors or omissions were unintentional (i.e., just negligent).

The third element that a medical malpractice plaintiff is required to prove is the occurrence of some financially compensable injury or damage. Besides special or economic (pecuniary) damages that include such quantifiable items as lost income and past and future health care–related costs, plaintiffs may be awarded general or noneconomic (nonpecuniary) damages for such difficult-to-quantify things as pain and suffering, mental anguish, grief, loss of enjoyment of life (hedonic damages), and other emotional complaints. In very rare circumstances, punitive or exemplary damages may be awarded over and above compensatory damages, where the defendant's conduct has been not merely negligent but actually reckless or malicious (and thus grossly negligent).

The final component of proof in a professional malpractice lawsuit is the element of causation. To succeed, a plaintiff must persuade the jury, to a reasonable (not an absolute) degree of medical certainty, that his or her injuries were the result of the defendant's negligence. A plaintiff must prove not only that the defendant's negligence was a "substantial factor" in bringing about the injury or that "but for" (sine qua non) the defendant's negligence the injury would not have happened, but further that there were no intervening, unforeseeable events of forces that acted to break the chain of proximate or direct causation between the defendant's negligence and the patient's injury.

Legal standards of care have been established mainly by the courts as a matter of common law on an incremental, case-by-case basis. State statutes, such as those containing professional licensure requirements, also help to define the required standards of care.

Ordinarily, expert witnesses are allowed to testify, and thereby educate the lay jurors, regarding the appropriate professional conduct under the circumstances. To establish what conduct would have been reasonable, the parties may also introduce other kinds of evidence to supplement the testimony provided by the expert witnesses. Additional forms of evidence introduced for this purpose may include professional codes of ethics, medical journal literature, textbooks (learned treatises), the *Physician's Desk Reference* (PDR) and pharmaceutical package inserts (PPIs) pertaining to the correct use and dosage of prescription drugs, pertinent statutes or regulations, voluntary accreditation standards such as those of the Joint Commission, and pertinent clinical practice guidelines or parameters.

5.5.2 Basis for Malpractice Claims

Malpractice claims, other than those based on an allegation that the physician's negligence resulted in a delayed diagnosis that, in turn, reduced the possibility of successful curative treatment (Casaceli 2014), are rarely brought by or on behalf of seriously ill or deceased cancer patients. Because the realistic prognosis for this patient subgroup is (or was) so dire, it would be difficult for a plaintiff to prove that, even if the physician or other caregiver negligently breached an applicable standard of practice, the breach directly caused a legally compensable injury. Nonetheless, a couple of potential legal risk areas are worth noting.

First, as noted in Sect. 5.3, patients have a right (exercised either personally or through a surrogate) to have their bodily integrity respected by others and therefore the right to refuse any particular type of medical intervention. Thus, health care providers who impose even a benevolently intentioned medical intervention on a patient in the absence of informed, voluntary, express, or implied consent by the patient or the patient's surrogate expose themselves to potential civil, criminal, and disciplinary liability for battery (an unconsented-to touching) and/or negligence (Pope 2013–2014, 2013). In some cases, overtreatment of a patient at the end of life could be categorized as elder mistreatment (Teaster and O'Brien 2014).

Second, there is growing support among health law and bioethics scholars for recognition and legal enforcement of a duty on the part of health care providers to offer patients nearing the end of life clinically appropriate forms of palliative care. There is evidence that palliative care is routinely underutilized as a strategy to try to alleviate the suffering of dying oncology patients (Oken 2001–2002). It is important that palliative care "extend beyond the hospital into the ambulatory, community, and home settings to optimize its effect" (Pizzo 2014), including extension into the hospice arena (Smith and Himmel 2013).

The right of a suffering dying patient to be treated effectively with palliative care, up to and including the possibility of terminal sedation, has been argued as an ethical, and even a religious, imperative (Smith 2014). According to one prominent physician who began his medical career in the 1940s:

> Going back to my internship days, I can remember many patients in pain, sometimes in coma or delirious, with late, hopeless cancer. For many of them we wrote an order for heavy medication to be given regularly by the nurses. Morphine by the clock. We were assisting with a softer exit from this world. Nurses helped willingly. This was not talked about openly, and little was written about it. It was essential, not controversial. (Moore 1995)

The corresponding legal duty to make an offer of palliative intervention in proper circumstances may be established by state statute and/or regulation (Ledden 2013; Leven 2013–2014) or common law judicial precedent (Tucker 2011–2012) as one component of the standard of care that society reasonably expects health care providers to satisfy in their fiduciary or trust relationships with patients. Once that duty has been established more firmly, the failure to comply with the resulting standard of care will expose a physician to professional malpractice claims based on the theory of negligence. Financial damages under such a doctrine would compensate the patient or family (bringing a wrongful death claim after the patient's death) for pain and suffering that could have been avoided if the professional had exercised reasonable care (by offering palliative intervention in a timely fashion) under the circumstances.

Some physicians are apprehensive about possible exposure to adverse professional disciplinary sanctions to be inflicted by state medical licensing boards on physicians who treat pain in oncology patients too aggressively with controlled substances. As explained by one pharmacologist:

> Medical decisions about opioid use have long been influenced by fears of regulatory scrutiny. Such fears have impacted negatively on opioid prescribing for pain control, even for persons with pain related to cancer. Yet there is no evidence that this patient population is a source of drug diversion and no evidence that oncologists have been the target of overzealous drug regulators. (Dahl 2005, p. 387)

The Federation of State Medical Board published *Responsible Opioid Prescribing* in 2014 (Fishman 2014). This publication includes Model Guidelines for regulating physician conduct in this arena and many states have adopted some version of those Model Guidelines that recognize the importance of fostering legitimate access to pain medications.

5.6 Limits on the Rights of Patients and Families

Within the health care enterprise, and the provider/patient relationship particularly, the rights of patients and their families or other surrogates are very extensive. However, those rights are not absolute or unlimited. With special attention to the oncology sphere, there are several relevant limits on the rights of patients and families.

One limitation presently applicable in the majority of states is the denial of a patient's right to obtain the assistance of a physician in actively hastening that patient's death. The prohibited behavior could take the form of either an act of euthanasia performed by the physician (e.g., injecting a toxic substance into the patient for the purpose of hastening death) or the physician prescribing a lethal dose of a medication to a patient with the knowledge that the patient intends to use that lethal dose to hasten the patient's own death. The United States Supreme Court has rejected a federal constitutional right for the patient regarding the procuring of a physician's assistance in such acts, leaving the extent of patients' rights regarding this matter to be delineated by the individual states (Vacco v. Quill 1997; Washington v. Glucksberg 1997). Only a handful of states have explicitly recognized a patient's right to physician-assisted death (PAD) as a matter of state constitutional law, statute, or public ballot initiative. In the vast remainder of the states, the legal status of PAD is either unsettled (Tucker 2012) or clearly in violation of a state's general homicide statute or specific PAD prohibitory statute.

Another limitation of patient or family rights concerns demands for futile medical interventions. In some situations, the patient, or more usually the family, insists on initiation or continuation of medical treatment ("doing everything possible") that the clinician judges to be worthless or very nearly worthless in terms of benefit to the patient. Neither a patient nor the family has a legal right to, nor does a physician owe an obligation to provide, medical intervention that would not be beneficial. On the very rare occasions that courts have been involved prospectively with the futility issue, their holdings have been confusing, inconsistent, and poorly reasoned. However, no court has ever imposed liability on a health care professional for failure to begin or perpetuate futile interventions for a critically ill patient, even in the face of family insistence on doing everything technologically possible. In practice, though, clinicians usually seem to take the path of least resistance and comply with the family's morally unreasonable demands, often out of mistaken apprehension about their own potential liability exposure. Most of the time, better physician-family communication, perhaps supplemented with formal or informal dispute resolution mechanisms such as Institutional Ethics Committees (Pope 2013–2014), during which the realistic implications of "doing everything possible" are spelled out clearly and placed in reasonable perspective, can mediate serious disagreements over how to proceed.

In a related vein, the courts have refused to recognize a constitutional right on the part of critically ill patients to demand that they be allowed, with proper informed consent, to enroll in research protocols, even if there is no available standard treatment or what is accepted as standard treatment for their condition has been tried and found ineffective. The broad topic of human subject participation in biomedical and behavioral research projects is beyond the scope of this chapter, but the point for this discussion is that an oncology patient's right to autonomously accept or refuse offered therapeutic or research interventions does not translate into a legal right to demand participation in any particular research trial, even if there is some possibility that participation might confer a benefit on the individual (Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach 2007).

There are a couple of notable caveats to this discussion about patient access to investigational interventions. First, the federal Food and Drug Administration (FDA) operates a limited "compassionate use" or "expanded-access" program. A patient may be granted access to investigational (i.e., unapproved) drugs and devices outside of a formal research protocol if the patient's condition is severe enough, other avenues of treatment do not exist or have been exhausted, the potential patient benefit justifies the potential risks, the patient cannot obtain the drug in a clinical trial or other expanded-access protocol, and providing the drug to the patient will not interfere with the initiation, conduct, or completion of a clinical investigation

(Darrow et al. 2015). From a public policy perspective, regulatory standards must attempt to balance effective protection of terminally ill patients from additional suffering and the loss of quality time with family and friends with the strong desire of some patients for access to experimental treatment alternatives (Malinowski 2014).

Similarly, a handful of states have adopted "right-to-try laws" that permit a patient to get off-protocol access to an investigational drug or device after it has passed through Phase 1 of a clinical trial and has been found initially, after being tried on a small group of people, to be safe (Turkewitz 2015). Requirements vary among these states, but they generally require the patient's physician to recommend the experimental therapy and to attest to the inadequacy of FDA-approved treatment alternatives (Darrow et al. 2015). Consideration of patient applications under both the federal "compassionate use" and state "right-to-try" programs is completely discretionary on the part of the FDA or the particular state, with limited funding available to pay for the investigational drugs and devices, and, therefore, these programs do not create any sort of enforceable entitlement on the part of patients to off-protocol interventions.

Another area in which family decision making prerogatives may be restricted concerns family refusals to consent to the provision of palliative care for relatives who are dying because of cancer. Family refusal in this context presents difficult emotional dynamics for the health care team, but ultimately ethics and law condemn family actions that are not consistent with the patient's best interests. In recognition of the consensus that family refusal of comfort measures for a suffering, decisionally incapacitated patient fall into that category, at least one state has enacted a statute authorizing health care providers to overrule family refusal of palliative care when that care is clinically indicated (Blinderman 2012).

5.7 Postmortem Rights and Duties

Death is not the end of attention to the rights and duties of various involved actors. Several key details surrounding the death of an oncology patient have important legal ramifications.

Upon a patient's death, the attending physician ordinarily is responsible for filling out the medical portion of the death certificate. Physicians and other health care professionals should be familiar with the requirements of their own state's vital records statute. They also should be knowledgeable about appropriate techniques for filling out death certificates accurately. Properly completed death certificates provide information that is vital for public health purposes and also can be useful as a risk management tool in defending against claims of substandard medical treatment.

In certain circumstances, the attending physician is required by state statute to report the circumstances of a patient's death to a local public official. That official is either a coroner or a medical examiner, depending on the public death-investigation system in place in the particular jurisdiction (Jentzen 2009). This public official then determines what steps, including an autopsy, are appropriate to investigate the deceased's death. When a case is within the jurisdiction of the coroner or medical examiner, the deceased's family may not prevent the public investigation from proceeding; the family's consent for autopsy or other investigative methods is not necessary legally in such circumstances.

State statutes differ in detail concerning when an attending physician is mandated to report a patient's death to the coroner or medical examiner. Physicians should be aware of the specific triggers in their own jurisdiction's mandatory death-reporting statute. Most cases in which cancer was the cause of death do not fall within any of the categories encompassed in state mandatory death-reporting statutes. The most important exceptions might be provisions in some state statutes for mandatory reporting to the coroner or medical examiner of deaths occurring within a certain time period after hospital admission, deaths involving an apparent suicide, or the death of a patient who had not recently been attended by a physician. Once the office of a coroner or medical examiner has conducted an autopsy, some states treat the results as an easily accessible public record, but some prevent the public from obtaining the resulting information.

There are cases in which referral to the coroner or medical examiner is not legally mandated, but the attending physician may recommend that a private hospital autopsy be performed. This recommendation may be motivated by family, research, educational, or public health considerations. An autopsy also may be advisable to clarify legal concerns involving such matters as estate (probate) distribution and potentially disputed life or health insurance claims. By dispelling family suspicions about improper medical care of the deceased, the autopsy can be a valuable risk management device for the health care team.

In situations in which referral to the coroner or medical examiner is not required by statute, an autopsy may be performed only upon obtaining valid informed consent. Anyone who alters the deceased's body without consent may be held liable civilly to the survivors and sometimes even prosecuted criminally. State statutes enumerate who is legally authorized to consent to an autopsy; states vary in terms of the specific priority order of potential consenters. Consent also must be obtained for partial autopsies of specific organs. Individual state statutes should be consulted to determine who has the legal right to access information derived through a private autopsy.

All 50 states plus the District of Columbia have adopted some version of the Uniform Anatomical Gift Act (UAGA) proposed in 1968 by the National Conference of Commissioners on Uniform State Laws (NCCUSL). Under these state statutes, the expressed (usually on a driver's license) wishes of a decisionally capable adult to donate cadaveric tissues and organs after death cannot be vetoed by family members or others. However, tissues and organs to be extracted from deceased donor patients who have died after a long struggle with cancer often will be considered clinically unacceptable for transplantation purposes.

Authority to direct disposition of a deceased's bodily remains is determined by state statute or common law. Most states recognize the surviving next of kin's right to immediate possession of the deceased's body (assuming the coroner or medical examiner is not involved in the death investigation) for preservation and burial or cremation. The family's interest is generally classified as a quasi-property right, or the "right of sepulcher." However, many states also permit a living person to create prospective instructions regarding the disposition of his or her bodily remains post-death and to have those instructions respected. However, state law is not entirely uniform in this regard (Farmer 2015), so health care institutions where oncology patients die, as well as mortuaries, need to be attuned to the relevant statutes and case law in their particular jurisdiction.

References

Abigail Alliance for Better Access to Developmental Drugs v. von Eschenbach 2007, 495 F.3d 695 (D.C. Cir.) (en banc), cert. denied, 552 U.S. 1159 (2008)

Billings JA, Krakauer EL (2011) On patient autonomy and physician responsibility in end-of-life care. Arch Intern Med 171:849–853. doi:10.1001/archinternmed.2011.180

Blinderman CD (2012) Do surrogates have a right to refuse pain medications for incompetent patients? J Pain Symptom Mgt 43:299–305

Bomba P (2011) Landmark legislation in New York affirms benefits of a two-step approach to advance care planning including MOLST: a model of shared, informed medical decision-making and honoring patient preferences for care at the end of life. Widener Law Rev 17:475–500

Casaceli B (2014) Losing a chance to survive: an examination of the loss of chance doctrine within the context of a wrongful death action. J Health Biomed Law 9:521–552

Castillo LS, Williams BA, Hooper SM, Sabatino CP, Weithorn LA, Sudore RL (2011) Lost in translation: the unintended consequences of advance directive law on clinical care. Ann Intern Med 154:121–128. doi:10.7326/0003-4819-154-2-201101180-00012

Chew PK (2012) A case of conflict of cultures: end-of-life decision making among Asian Americans. Cardozo J Conflict Resolution 13:359–391

Dahl JL (2005) How to reduce fears of legal/regulatory scrutiny in managing pain in cancer patients. J Supportive Oncol 3:384–388

Darrow JJ, Sarpatwari A, Avorn J (2015) Kesselheim. Practical, legal, and ethical issues in expanded access to investigational drugs. N Engl J Med 372:279–286. doi:10.1056/NEJMhle1409465

del Carmen MG, Joffe S (2005) Informed consent for medical treatment and research: a review. Oncologist 10:636–641. doi:10.1634/theoncologist.10-8-636

Ellor SV, Pagano-Young TA, Avgeropoulos NG (2014) Glioblastoma: background, standard treatment paradigms, and supportive care considerations. J Law Med Ethics 42:171–182

Farmer TJ (2015) Don't die in Iowa: restoring Iowans' right to direct final disposition of their bodily remains. Iowa Law Rev 100

Fishman SM (2014) Responsible opioid prescribing: a clinician's guide, 2nd edn. Federation of State Medical Boards, Washington, DC

Foster C, Herring J, Doron I (eds) (2014) The law and ethics of dementia, Hart Publishing, Portland, OR

Halpern SD, Emanuel EJ (2014) Can the United States buy better advance care planning? Annals Intern Med. doi:10.7326/M14-2476

Institute of Medicine (2014) Dying in America: improving quality and honoring individual preferences near the end of life. National Academies Press, Washington, DC

Jentzen JM (2009) Death investigation in America. Harvard University Press, Cambridge, MA

Kerrigan S, Ormerod I (2010) Advance planning in end-of-life care: legal and ethical considerations for neurologists. Pract Neurol 10:140–144. doi:10.1136/jnnp.2009.200113

Kohn NA, Blumenthal JA, Campbell AT (2013) Supported decision making: a viable alternative to guardianship. Penn State Law Rev 117:1111–1157

Ledden KB (2013) A nudge in the right direction with a stick the size of CMS: physician-patient communication at the end of life. Saint Louis U J Health Law & Pol'y 6:389–424

Leven DC (2013–2014) Health justice denied or delayed at the end of life: a crisis needing remedial action. A crisis needing remedial action. N Y Law School Law Rev 58:403–415

Lovell A, Yates P (2014) Advance care planning in palliative care: a systematic literature review of the contextual factors influencing its uptake 2008-2012. Palliative Med 28:1026–1035. doi:10.1177/0269216314531313

Malinowski MJ (2014) Throwing dirt on Doctor Frankenstein's grave: access to experimental treatments at the end of life. Hastings L J 65:615–660

Maron RF (2011) Who has the will to live? Why state requirements for advance directives should be uniform(ly revised). Regent Univ Law Rev 24:169–203

Moore FD (1995) A miracle & a privilege: recounting a half century of surgical advance. Joseph Henry Press, Washington, DC, p 333

Nachman DD (2011) Living wills: is it time to pull the plug? Elder Law J 18:289–333

O'Shea EM, Penson RT, Stern TA, Younger J, Chabner BA, Lynch TJ Jr (2002) A staff dialogue on do not resuscitate orders: psychosocial issues faced by patients, their families, and caregivers. Oncologist 7(Suppl 2):36–42. doi:10.1634/theoncologist.7-suppl_2-36

Oken RJ (2001–2002) Curing healthcare providers' failure to administer opioids in the treatment of severe pain. Cardozo Law Rev 23:1917–1992

Persinger A (2010) Still pioneers: special social and economic hardships for elderly gays and lesbians. Hastings Women's Law J 21:137–157

Pizzo PA (2014) The doctor: for life and at the end of life. Annals Intern Med. doi:10.7326/M14-2399

Pope TM (2012) Legal fundamentals of surrogate decision making. Chest 141:1074–1081. doi:10.1378/chest.11-2336

Pope TM (2013–2014) Dispute resolution mechanisms for intractable medical futility disputes. N Y Law School Law Rev 58:347–368

Pope TM (2013) Clinicians may not administer life-sustaining treatment without consent: civil, criminal, and disciplinary sanctions. J Health Biomed Law 9:213–296

Pope TM (2014) Legal briefing: brain death and total brain failure. J Clin Ethics 25:245–257

Pope TM, Anderson LE (2011) Voluntarily stopping eating and drinking: a legal treatment option at the end of life. Widener Law Rev 17:363–427

Rao JK (2014) Engaging public health in end-of-life issues: it is time to step up to the plate. Ann Intern Med. doi:10.7326/M14-2479

Rodabaugh KJ, Hammond M, Myszka D, Sandel M (2010) A medical-legal partnership as a component of a palliative care model. J Palliative Care 13:15–18. doi:10.1089/jpm.2009.0203

Sabatino CP (2014) Advance care planning tools that educate, engage, and empower. Pub Pol'y Aging Rept 24:107–111. doi:10.1093/ppar/pru018

Salloch S, Ritter P, Wäscher S, Vollmann J, Schildmann J (2014) Medical expertise and patient involvement: a multiperspective qualitative observation study of the patient's role in oncological decision making. Oncologist 19:654–660. doi:10.1634/theoncologist.2013-0268

Schachter M, Fins JJ (2008) Informed consent revisited: a doctrine in the service of cancer care. Oncologist 13:1109–1113. doi:10.1634/theoncologist.2008-0101

Sico R (2013) End-of-life care: the legal, cultural, and interdisciplinary barriers hindering the effective use of advance directives. Ann Health Law 22:44–63

Smith GP II (2014) Cura personalis: a healthcare delivery quandary at the end of life. Saint Louis U J Health Law & Pol'y 7:311–330

Smith F, Himmel S (2013) Changing the way we die: compassionate end-of-life care and the hospice movement. Berkeley, CA, Viva Editions

Spillers SC, Lamb B (2011) Is the POLST model desirable for Florida? Fla Pub Health Rev 8:80–90

Tabak N, Itzhaki M, Sharon D, Barnoy S (2012) Intentions of nurses and nursing students to tell the whole truth to patients and family members. J Clin Nursing 22:1434–1441. doi:10.1111/j.1365-2702.2012.04316.x

Teaster PB, O'Brien JG (2014) The elder mistreatment of overtreatment at end of life. Pub Pol'y & Aging Rept 24:92–96. doi:10.1093/ppar/pru025

Treleaven J, Gadd E, Cullis J, Favre J, McLeod A, Meller S et al (2012) Guidelines on obtaining consent for systemic anti-cancer therapy in adults. Hematology 17:249–254. doi:10.1179/1607845412Y.0000000022

Tucker KL (2011–2012) When dying takes too long: activism for social change to protect and expand choice at the end of life. Whittier Law Rev 33:110–160

Tucker KL (2012) Aid in dying: an end of life-option governed by best practices. J Health Biomed Law 8:9–26

Turkewitz J (2015) Patients seek "right to try" new drugs. N Y Times 10:A16

Vacco v. Quill. 1997, 521 U.S. 793

van Laarhoven HWM, Henselmans I, de Haes JHC (2014) To treat or not to treat: who should decide? Oncologist 19:433–436. doi:10.1634/theoncologist.2013-0258

Volpe RL, Steinman D (2013) Peeking inside the black box: one institution's experience developing policy for unrepresented patients. Hamline Law Rev 36:265–274

Washington v. Glucksberg. 1997, 521 U.S. 702

Wilson KS, Kottke TE, Schettle S (2014) Honoring Choices Minnesota: preliminary data from a community-wide advance planning model. J Am Geriatr Soc'y 62:2420–2425. doi:10.1111/jgs.13136

Wolf RB, Maag MJ, Gallant KB (2014) The Physician Orders for Life-Sustaining Treatment (POLST) coming soon to a health care community near you. Real Prop Trust Estate Law J 49:71–161

Spiritual Care: An Essential Aspect of Cancer Care

6

Kenneth J. Doka

6.1 Introduction

As an enduring gift of the hospice movement, led by openly spiritual Dame Cicely Saunders, spirituality re-emerged as a critical aspect of medical care. In recent years, varied initiatives such as the National Consensus Project emphasizing the value of spirituality as an aspect of palliative care, The ACE (Achieving Clinical Excellence) project offering training in palliative care to chaplains and psychosocial professionals, and The Hospice Foundation of America's Teleconference on Spirituality at the End-of-Life all stressed the importance of spiritual care in death and bereavement.

Spiritual care is particularly important in cancer care – as cancer has long been viewed as a dreaded disease – one that carries, in many cases, a sense of moral opprobrium and spiritual abandonment. For much of its long history, cancer was an unspoken disease – the big "C" – a fearful disease dreaded for its mysterious causation slow and painful, sometimes disfiguring progression. Even now with far better treatment, diagnosis, and survival rates, cancer still is viewed as a spiritual curse. And it still carries a sense, at least in some sites of the disease, of opprobrium. Tell someone of another's death by lung cancer and a likely question is "how long did the victim smoke?" A question that implies the individual with the disease is less deserving of sympathy or support.

This chapter explores the nature of spirituality both during the course of illness, and should death occur, in bereavement. It begins by defining spirituality and exploring the ways that spirituality may affect health care. It then addresses the spiritual issues that may be experienced throughout the course of an illness – from diagnosis to chronic care, recovery, or death as well as the spiritual issues that arise in grief. Finally, the chapter focuses on both spiritual assessment and intervention.

K.J. Doka, PhD
The Graduate School of The College of New Rochelle, New Rochelle, NY, USA

The Hospice Foundation of America, Washington, DC, USA
e-mail: KnDok@aol.com

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_6

6.2 Defining Spirituality

Religion and spirituality are often elusive concepts that are difficult to define and differentiate. A Consensus Conference funded by the Archstone Foundation brought together scholars and practitioners from a broad range of fields and disciplines in 2009. The agreed upon definition emerging from the Consensus Conference was that: *Spirituality is the aspect of humanity that refers to the ways that individuals seek and express meaning and purpose and the way they experience their connectedness to the moment*, *to self*, *to others*, *to nature*, *and to the significant or sacred* (Puchalski et al. 2009, p. 887). The International Workgroup on Dying, Death and Bereavement defines spirituality as "concerned with the transcendental, inspirational, and existential way to live one's life" (1990, p. 75). I have always preferred Miller's far more poetic definition:

> Spirituality relates to our souls. It involves the deep inner essence of who we are. It is an openness to the possibility that the soul within each of us is somehow related to the Soul of all that is. Spirituality is what happens to us that is so memorable that we cannot forget it, and yet we find it hard to talk about because words fail to describe it. Spirituality is the act of looking for meaning in the very deepest sense; and looking for it in a way that is most authentically ours (1994).

To Miller, spirituality is inherently individual, personal, and eclectic. Religion, however, is more collective. Religion is a belief shared within a group of people. Miller again offers a lyrical perspective:

> Now religion works in a very different way. While spirituality is very personal, religion is more communal. In fact, if you take the words back to its origins, "religion means that which binds together," "that which ties things into a package." Religion has to do with collecting and consolidating and unifying. Religion says, "Here are special words that are meant to be passed on. Take them to heart." Religion says, "Here is a set of beliefs that form a coherent whole. Take them as your own." Religion says, "Here are people for you to revere and historical events for you to recall. Remember them." Religion says, "Here is a way for you to act when you come together as a group, and here's a way to behave when you're apart" (1994).

Thus while spirituality is very personal, a person's spirituality may very well be shaped by an individual's religious beliefs. Yet, because of the individual nature of spirituality, religious affiliation is not likely to be the sole determinant of spiritual beliefs. Often developmental outlooks, personal experiences, and cultural perspectives will join with religious beliefs in shaping an individual's spirituality.

6.3 Spirituality, Religion, and Health

There is research that religion and spirituality can both facilitate and complicate responses to life-threatening illness and grief. Here, both terms are used together as the ways researchers define *spirituality* and *religion* differ. Much of this research supports the spirituality and religion can have positive roles in assisting individuals who struggle with life-threatening illness or grief.

Religion and spirituality can offer a sense of meaning in the illness that facilitates coping (Siegel and Schrimshaw 2002) as well as a sense of resilience and hope (Pentz 2005). Often the diagnosis of a life-threatening illness challenges an individual's assumptive world as the person struggles with attempting to make sense of the illness. Later in the illness, individuals may seek to make sense of their suffering, their death, or their life. Throughout this existential endeavor, religious and spiritual perspectives offer meanings. Religious and spiritual perspectives may reassure persons with life-threatening illness that their illness is part of a larger plan or that the illness experience may offer lessons to self or others, or that suffering may offer a cosmic connection to humankind. Even as an individual faces death, there is some evidence that religious and spiritual beliefs may minimize fear and uncertainty (Siegel and Schrimshaw 2002).

Religion and spirituality enhance a sense connection on a number of levels. There can be a sense that a God or some Higher Power will sustain and protect. This connection may be more tangible as well. Many individuals may benefit from the social support available through the ministries of a chaplain, clergy, spiritual advisor, ministry team, or even within the larger faith community. The sense that one is not alone and others are caring, visiting, and praying seems to provide benefit (Siegel and Schrimshaw 2002; Townsend et al. 2002).

Religious and spiritual practices and beliefs can enhance health. Most spiritual belief systems suggest either abstinence or moderation in behaviors such as alcohol or tobacco use. Spiritual and religious beliefs also may enhance coping by encouraging self-esteem as most religious and spiritual systems emphasize an individual's inherent worth. This belief in a loving and forgiving deity – or the intrinsic value of an individual may be especially important in a life-threatening illness or in grief when self-blame may loom large and self-acceptance is in jeopardy. There is also some speculation that spiritual and religious beliefs may have physiological benefits such as lowering blood pressure or enhancing immune function though here the research has shown some inconsistency (Dane 2000; Sephton et al. 2001; Miller and Thoresen 2003; Lin and Bauer-Wu 2003; Olive 2004; Stefanek et al. 2005).

Religious and spiritual beliefs also may influence an individual's sense of control. In a time of life-threatening illness, an individual may feel that they have little or no control. Religious and spiritual beliefs reaffirm a sense of personal control. Individuals now have a sense of interpretive control – the ability to find meaning or benefit from the experience, or vicarious control – leaving the illness in the hands of a Higher Power. In some cases, the control may be of a predictive nature; perhaps believing that God will cure them or be with them throughout this experience.

Yet, this sense of control also demonstrates the ways that religious and spiritual beliefs may complicate the response to a life-threatening illness or grief. For example, a person with life-threatening illness may be convinced that he or she may be cured by a divine intervention. If death ensues, such an individual or other family members may become immobilized, unrealistic in decisions, or even despondent. In other cases, the illness may be viewed as a punishment for prior acts.

Certain religious or spiritual beliefs may serve to increase rather than decrease death anxiety or complicate grief. For example, fears over divine judgment or uncertainty in an afterlife may not offer comfort to a dying person (Neimeyer 1994). Moreover, religious and spiritual perspectives can sometimes conflict with medical practices and advice. For example, some spiritual systems such as Christian Science may eschew any medical treatment while others such as the Jehovah Witnesses may prohibit certain medical practices such as blood transfusions or blood-based therapies. In other cases, a fatalistic spirituality may inhibit health-seeking behaviors or adherence to a medical regimen. Pargement et al. (2004) found in a longitudinal study that certain types of religious coping such as seeking spiritual support or believing in a benevolent God were related with better health while other spiritual coping behaviors and beliefs such as a perspective of a punishing God or religious discontent were predictive of declines in health.

Religious and spiritual beliefs also may be evident in reactions to illness. For example, anger could be directed toward God. There may be anger that one has the disease or that the disease has come at an inopportune or unfair time. Guilt may be clouded by a moral guilt – a belief that this illness is a punishment for some transgression. Fear and anxiety, as mentioned earlier, can also have a religious or spiritual root, as one may fear the wrath of God in this world or the next. There may even be an existential sense of abandonment – a sense that one is facing the crisis alone, alienated from God. In all of these cases, religious and spiritual beliefs may intertwine with psychological and affective reactions to the illness.

6.4 Spiritual Tasks in Life-Threatening Illness

Throughout the illness, an individual may have to cope with distinctly spiritual tasks. In an earlier work (Doka 1993a, b, 2014), I proposed, building on the work of both Weisman (1980) and Pattison (1978), that life-threatening illness can best be viewed as a series of phases. These phases are:

- *The Prediagnostic Phase* – This phase is generally characterized as the period prior diagnosis – generally a health-seeking phase. In cancer care, this is likely to come in one two ways. Often, it may result from a patient seeking evaluation of a troublesome symptom such as unexpected bleeding, some lump, or perhaps a new mole. In other cases, it may merely be a routine physical or screening that leads to a cancer diagnosis. Retrospectively analyzed, prediagnostic behavior can indicate much about the patient's style of coping. For example, did the patient suspect cancer? How long did the patient delay before seeking medical attention? Did the patient self-diagnose? Prior to seeking medical examination, did the patient engage in any self-treatments or spiritual coping (praying, etc.)? Even in routine examinations, it is always worthwhile to examine the patient's concerns, anxieties, and expectations.
- *The Diagnostic Phase* – Here as Weisman (1980) notes, even when the diagnosis is expected or feared, it still comes as a shock, creating a sense of "existential plight" where one's very existence is threatened. Often it is a life divide. Even if

the patient survives the encounter, he or she will often talk about this as a turning point wrought with implications that follow for the rest of life.

- *The Chronic Phase* – Often, especially in cancer care, this is a long and difficult period wrought with anxiety and uncertainty as the patient struggles with the treatment, side effects, and the ongoing demands of life. Often this is a lonely time. As friends and family rally at the time of diagnosis or as death nears, many patients may not find as much social support in this chronic phase as others resume their lives.
- *The Recovery Phase* – Not every disease, and certainly not cancer, inexorably leads to death. In many cases, patients may experience long periods of remission or even cure. Yet, the encounter with disease leaves all types of residues – physical scaring, deformity, or disability as well as psychological, social, economic, and spiritual implications. Individuals may have an enhanced sense of their fragility, feeling that they are living under a sword that can strike at any time (Koocher and O'Malley 1981).
- *The Terminal Phase* – Here the goal is no longer to cure or even extend life but rather palliative, that is, comfort care as the patient approaches death.

Obviously not every patient experiences all of these phases. In any particular cancer case, individuals may jump from one phase to another. For example, in some cases, a successful removal of a tumor may place an individual right into a recovery phase with virtually no chronic phase. In another disease, diagnosis may be immediately followed by a steep and inexorable decline toward death. While each phase encompasses a variety of issues and tasks including psychological, social, and medical issues or tasks (see Doka 2014), there are spiritual issues that arise in each phase as well.

In the prediagnostic and diagnostic phases, the spiritual issue is incorporating the present reality of illness into one's sense of past and future. Questions such as: "Why did I get this disease, now?" loom large here. An individual now struggles to make sense of the disease and of the new reality of his or her life. Spiritual and religious beliefs may offer an answer to these questions or at least provide direction for further quest. Given the fears that cancer generates, the diagnosis may arouse a sense that one is being punished. This may lead to a sense of moral guilt or even a deep sense of anger at God or the cosmos.

In the chronic phase, suffering may become a major spiritual issue. "Why am I suffering through this disease and treatment?" "Is it all worth it?" Persons will often look to their religious or spiritual beliefs to make sense of this suffering. Their beliefs may vary. Again some may see the suffering as retribution for sins in this or another life. Some may even find comfort in that thought; believing that suffering now may offer recompense or even purification that will mollify God or better prepare them for an afterlife. Others may see suffering as random. Still others may see their suffering as a learning experience allowing greater empathy. Others may see it as sacrifice, offering it as a way to gain a greater connection to God or others. Such beliefs can strongly influence patients' receptiveness to pain management (Doka 2006).

Spiritual issues arise in recovery as well. Individuals may struggle with a sense of "the bargain." It is not unusual for persons to make spiritual commitments and promises in a cosmic deal to surmount the illness. Now that they have recovered from this threat, individuals may now feel they have to fulfill their promises. A failure to fulfill such commitments may loom large should a person experience a relapse or even encounter another disease. There may be other spiritual changes in recovery as well. Some individuals may move closer to their religion or become more spiritually aware and active. Others may feel alienated either from their God or their spiritual community. Some may actively seek a new spirituality, perceiving that their past beliefs did not serve them well in this crisis.

During the course of a life-threatening illness, patients and their families will have to make critical ethical decisions about care. How long should active medical treatment persist even if it is perceived a futile? When should treatment cease and who should be empowered to make such determinations? Should the patient receive artificial hydration and nutrition? Can treatments be withheld, or if administered, withdrawn? Is assisted suicide ever a valid ethical choice in life-threatening illness?

Health professionals have long realized that religious and spiritual systems play a significant role in the ways that patients and their families make end-of-life decisions and resolve ethical dilemmas (Koenig 2004). As patients and their families struggle with these decisions, they often turn to their religious and spiritual values, and even to their clergy or spiritual mentors, for guidance.

In the terminal phase, individuals often struggle with three spiritual needs (Doka 1993a, b). The first is to have lived a meaningful life. Individuals may assess their life to find a sense of meaning and purpose. Here individuals may struggle seeking forgiveness for tasks unaccomplished or for hurtful acts that they may have committed. Therapeutic approaches such as Life Review, Reminiscence Therapy, and Dignity Therapy (Chochinov 2012) can assist individuals in achieving a sense of meaningfulness. Individuals may struggle with a second goal – to die an appropriate death, however that is individually defined. A final spiritual need is to find hope beyond the grave. This means that the individual needs a sense that life will continue – in whatever appropriate way is supported by the person's spiritual sense. This can include living on the memories of others, in the genes of family members, within one's community, in the creations and legacies left, in a sense of "eternal nature" (i.e., that one returns to the cycle of life), in some transcendental mode, or in an afterlife (Lifton and Olsen 1974; Doka 1993a).

6.5 Spirituality and Grief

After the individual dies, the family may still spiritually struggle, trying to reconstruct their own faith or spiritual system that may have been challenged by that loss (Doka 1993b). There may be very significant spiritual issues as individuals experience grief. Bereaved individuals may experience a number of spiritual reactions.

Some may be complicating. There may be a loss of faith. Individuals who are grieving may have a spiritual or cosmic anger – alienating them from sources of spiritual strengths such as their beliefs, rituals, faith practices, or even their faith community. They may experience a sense of "moral guilt" – or a belief that the death of the deceased is due to some moral failing or sin that is now being punished. Other beliefs can be troubling as well such as beliefs that the individual who died is condemned in some way for some transgression.

However, spirituality is often a facilitating factor in grief. Spiritual beliefs allow a sense of meaning – that this loss fulfills some purpose or is part of a cosmic plan. Spirituality also can offer a sense of connection – a belief that the deceased is now safe or happy, or a belief that even entertains a possibility of future contact or reunion. Spiritual beliefs and practices can even allow a continuing connection – through, for example, prayer, and veneration of ancestors.

6.6 Spiritual Assessment

Effective spiritual care begins with spiritual assessment. The Consensus Conference suggested a threefold process that incorporated a quick spiritual screening to assess whether the illness has created a spiritual crisis; a spiritual history to understand the patient's needs and resources; and a full spiritual assessment completed by a board-certified chaplain (Puchalski et al. 2009).

There are a number of tools for spiritual histories and assessment (Hodge 2005; Ledger 2005). In recent years, there has been emphasis on using objective assessment instruments in order to standardize assessments. While there may be value in using uniform and standardized instruments, it should not impede the ability to create a dialog that allows individuals opportunities to explore their spiritual journeys and assess how their spirituality speaks to their current situation. Naturally, an assessment will begin with questions of religious affiliation – whether they identify with a particular faith, regularly practice that faith in rituals such as prayer or meditation, and whether they are active in a faith community, attending a church, temple, synagogue or mosque?

Spirituality is more than affiliation and membership. It is important to consider with individuals the times they feel most spiritually connected. What practices they utilize when they are stressed, anxious, or depressed? What are the stories, prayers, or songs that offer spiritual comfort? How important is their faith system in making medical and other life decisions? A spiritual assessment should offer information on the spiritual strengths that an individual possesses, themes within an individual's spirituality (such as grace, karma, fate, or retribution, etc.), and experiences that have tended to challenge that person's spirituality. Occasionally, such an assessment may uncover forms of spiritual abuse – spiritual beliefs or practices or behaviors of spiritual mentors that have resulted in a sense of spiritual alienation.

6.7 Spiritual Interventions

Once an assessment of spirituality is made, an individual can be encouraged to connect with their spiritual community. Clergy visits throughout the illness may be valued. Clergy, chaplains, and other spiritual advisors may be sought as an individual or family member responds to the spiritual questions inherent in the experiences of grief and illness. Despite the importance of ministry to the ill, the dying, and bereaved, many clergy reported little formal seminary education on dealing with dying patients and their families (Doka and Jendreski 1985; Abrams et al. 2005). Faith communities too can offer spiritual comfort and connection; visits, calls, cards, and letters that show support and ease isolation; and assistance with tangible tasks such as cooking, home maintenance, transportation, and caregiving. In addition to the patient's own clergy, hospital chaplains, especially board-certified chaplains, are specifically trained to offer spiritual care to patients with life-threatening illness.

Naturally spiritual beliefs and practices also are sources of strength. A person's spiritual beliefs may be critical in making meaning throughout an illness and for family, after the death. Often a simple question such as, "How do your beliefs speak to you in this situation?" can engage the person in spiritual exploration. It may also be useful to investigate the ways that the individual's beliefs assisted and helped the person make sense of the experience in earlier crisis. There may be situations where the individual's beliefs seem inadequate or dysfunctional.

Spiritual practices such as prayer and meditation also may have a role in the illness. At the very least, intercessory prayer (i.e., the prayer of others) is a tangible sign that the individual is not facing this crisis alone. It offers family and friends a tangible thing to do – reaffirming a form of vicarious control in an unsettled time. Individuals who are struggling with physical illness often use prayer as a form of coping (Ribbentrop et al. 2005). There is some evidence that prayer and meditation do affect physical health in a number of ways including lowering stress levels and blood pressure (Mayo Clinic Health Letter 2005). Schroeder-Sheker (1994) has even pioneered the field of musical thanatology, using spiritual music as a way to ease the transition to death.

Rituals also can be a source of comfort to both the ill or dying patient as well as family. Many faith traditions that have rituals for the sick and the dying, such as the Roman Catholic Rite for Anointing of the Sick (popularly known as "Last Rites") or rituals at the time of death such as washing or preparing the body. Individuals who do not have distinctive rituals as part of their tradition may be invited to create one at the time of death. These can include such acts as lighting a candle, anointing the dead person, and joining in prayer or meditation, singing a spiritual hymn or song, or in other, individual ways saying a final goodbye to mark the transition from life to death. Rituals work well in these liminal or transitional moments – offering participants away to acknowledge loss and transition.

Certainly rituals after the death such as funerals can be critically important to families and others as they cope with loss. Funerals can allow mourners a sense of reality of death, a chance to ventilate feelings, meaningful actions in a disorganized time, opportunities to remember the deceased, bring together supportive others, and interpret the death according to their own philosophical or spiritual background (Rando 1984). The value of funerals can be enhanced when mourners have opportunities to plan and participate in the ritual (Doka and Jendreski 1985).

Conclusion

Spiritual support can be a challenge. Many health professionals have little specialized training in spirituality. Moreover, there may be concern lest one impose his or her own spirituality upon a patient or family member. Sometimes out of respect for the diversity and individuality of a person's spiritual beliefs, health professionals may be reluctant to enter into conversations involving religion or spirituality. Thus, there often is temptation to leave these issues to chaplains, clergy, or other spiritual mentors. Such delegation to spiritual mentors is unlikely to suffice. Spiritual concerns arise throughout the entire experience of the illness. Patients and families will choose when, where, and with whom they share their spiritual needs and concerns. These choices may not always fit into neat organizational charts or job descriptions. They are the responsibility of the team.

Spiritual concerns cannot be neglected. Holistic care entails that spiritual concerns are both acknowledged and validated. A true respect for spirituality means that such concerns and struggles need be addressed by every professional. Spirituality therefore cannot be ignored. Death, after all, may be the ultimate spiritual journey.

Note Portions of this work were drawn from previous pieces published by the author and noted in the bibliography.

References

Abrams D, Albury S, Doka K, Crandall L, Harris R (2005) The Florida Clergy End-of-Life Education Enhancement Project: a description and evaluation. Am J Hosp Palliat Med 22(3):181–187

Chochinov HM (2012) Dignity therapy: final words for final days. Oxford, New York

Dane B (2000) Thai women: mediation as a way to cope with AIDS. J Relig Health 38:5–21

Doka J (ed) (2006) Pain management at the end of life: Bridging the gap between knowledge and practice. The Hospice Foundation of America, Washington, DC

Doka K (1993a) Living with life-threatening illness: a guide for patients, their families, and caregivers. Lexington books, Lexington, MA

Doka K (ed) (1993b) Death and spirituality. Baywood Press, Amityville

Doka KJ (2014) Counseling individuals with life-threatening illness, 2nd edn. Springer, New York

Doka K, Jendreski M (1985) Clergy understandings of grief, bereavement and mourning. Res Record 2:105–114

Hodge D (2005) Developing a spiritual assessment toolbox: a discussion of the strengths and limitations of five different assessment methods. Health Soc Work 30:314–323

International Work Group on Death, Dying, and Bereavement (Spiritual Care Work Group) (1990) Assumptions and principles of spiritual care. Death Stud 14:75–81

Koenig H (2004) Religion, spirituality, and medicine: research findings and implications for clinical practice. South Med J 97:1194–1200

Koocher G, O'Malley J (1981) The Damocles syndrome: psychological consequences of surviving childhood cancer. McGraw-Hill, New York

Ledger S (2005) The duty of nurses to meet patients' spiritual and/or religious needs. Br J Nurs 14:220–225

Lifton R, Olsen G (1974) Living and dying. Bantam Books, New York

Lin H, Bauer-Wu S (2003) Psycho-spiritual well being in patients with advanced cancer: an integrative review of the literature. J Adv Nurs 44:69–90

Mayo Clinic Health Letter (2005) Meditation 23(3):3–4

Miller J (1994) "The transforming power of spirituality". Presentation to a conference on transformative grief. Burnsville, NC, November

Miller W, Thoresen C (2003) Spirituality, religion, and health: An emerging research field. Am Psychol 58:1–19

Neimeyer R (ed) (1994) Death anxiety handbook: research, instrumentation, and application. Taylor & Francis, Washington, DC

Olive K (2004) Religion and spirituality: Important psychosocial variables frequently ignored in clinical research. South Med J 97:1152–1153

Pargament K, Koenig H, Tarakeshwar N, Hahn J (2004) Religious coping methods as predictors of psychological, physical, and spiritual outcomes among medically ill elderly patients: a two-year longitudinal study. J Health Psychol 9:713–730

Pattison EM (1978) The living-dying process. In: Garfield C (ed) The psychosocial care of the dying patient. McGraw-Hill, New York

Pentz M (2005) Resilience among older adults with cancer and the importance of social support and spirituality-faith: "I don't have time to die". J Gerontol Soc Work 44(3-4):3–22

Puchalski C, Ferrell B, Virani R, Otis-Green S, Baird P, Bull J, Chochinov H, Handzo G, Nelson-Becker H, Prince-Paul M, Pugilese K, Sulmasy D (2009) Improving the quality of care as a dimension of palliative care: The report of the Consensus Conference. J Palliat Med 12:885–904

Rando TA (1984) Grief, dying, and death: clinical interventions for caregivers. Research Press, Champaign, Il

Ribbentrop E, Altmaier E, Chen J, Found E, Keffala V (2005) The relationship between religion/spirituality and physical health, mental health, and pain in a chronic pain population. Pain 116:311–321

Schroeder-Sheker T (1994) Music for the dying: a personal account of the new field of Music-Thanatology – History, theory and clinical narratives. J Holist Nurs 12:83–99

Sephton S, Koopman C, Shaal M, Thoresen C, Spiegel D (2001) Spiritual expression and immune status in women with metastatic cancer: an exploratory study. Breast J 7:345–353

Siegel K, Schrimshaw E (2002) The perceived benefits of religious and spiritual coping among older adults living with HIV/AIDS. J Sci Study Religion 41:91–102

Stefanek M, McDonald P, Hess S (2005) Religion, spirituality and cancer: current status and methodological challenges. Psychooncology 14:450–463

Townsend M, Kladder V, Mulligan T (2002) Systematic review of clinical trials examining the effects of religion on health. South Med J 95:1429–1434

Weisman A (1980) Thanatology. In: Kaplan O (ed) Comprehensive textbook of psychiatry. Williams & Williams, Baltimore

Religious Views of the Afterlife

7

Christopher M. Moreman

7.1 Judaism

The history of Judaism spans a period of well over 2,000 years of recorded history (traditionally extending as far as 2,000 years and beyond that). Over these many years, Jewish belief has evolved and adapted, with disagreement a hallmark of Jewish theology. In modern times, perhaps as a result of attempts to divest Judaism of any semblance of superstition, the Jewish faith has often been characterized as a pragmatic, “here and now” religion. Moreover, the horrors of the Holocaust had a massive effect on Jewish identity, with views of death and the afterlife among the most strongly affected.

The Jewish story is long and wrought with hardship, as depicted in the Hebrew Bible, or *Tanakh* (what Christians refer to as the Old Testament). Beginning with the story of Adam and Eve (Gen. 2: 4–3:24), it is clear that God had given them every opportunity to enjoy life and all its pleasures, with but one rule – that they should not eat the fruit of the Tree of Knowledge of Good and Evil lest they should die. In disobeying this one rule, Adam and Eve were thus cast from the garden and cut off from the Tree of Life, which bore fruit that gave them immortality, thereby forced to live a mortal existence ending in death. As such, life remained God’s gift, but it would be limited according to one’s divergence from His command.

The Patriarch Abraham represents a potential starting point for a historical understanding of Jewish origins, with an estimated lifetime in around 1800 BCE. It is at this point that we begin to have some written historical records with which to corroborate biblical accounts from multiple cultures with which to compare and contrast beliefs and practice. The Bible itself was not written until several hundred years after this, though the stories contained therein purport to date back thousands

---

C.M. Moreman, PhD
Department of Philosophy, California State University, East Bay,
25800 Carlos Bee Blvd., Hayward, CA 94542, USA
e-mail: christopher.moreman@csueastbay.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_7

of years before Abraham (into a history that includes such stories as Noah and the Flood; Sodom and Gomorrah; the Tower of Babel; and of Adam and Eve).

With Abraham, we have a figure whose story begins in Mesopotamia, a land of which much is known from historical records. For instance, the Epic of Gilgamesh, the oldest extent written text in Western civilization, tells the story of Utnapishtim, a man warned by a God to build a large boat in order to save his family from an impending flood. The similarities between this and the story of Noah are striking. That Abraham came from the land of Gilgamesh to occupy lands in modern Israel, it should be of no surprise that he would have brought some of that culture with him!

In terms of an afterlife, the ancient Mesopotamians held the view that life was a gift from the Gods, and that a person's lot in life was but to honor and worship the Gods (their failure to do so was the reason for the Flood). Death was an unpleasant end, with the dead residing in a dark and dreary underworld with the only respite coming in the form of sacrificial offerings shared with them from the living. This ancestral cult formed the basis of religious life in that the living were expected to make offerings in honor of the Gods, and also to the dead, and to teach their children to do likewise into the future.

Similarly, the earliest Jewish ideas of life after death describe the place of the dead as a dark underworld called *Sheol*, literally a hole in the earth. There is no good said of this place as *Sheol* is described as, "A land of thick darkness, as darkness itself; a land of the shadow of death, without any order, and where the light is as darkness" (Job 10: 22), and elsewhere, "the nether-most pit, in dark places, in the deeps" (Ps. 88: 7). The author of one of the Psalms (88:5) laments: "I am counted with them that go down into the pit; I am become as a man that hath no help." And again, in Job the life of a person is summed up: "He cometh forth like a flower, and withereth; he fleeth also as a shadow, and continueth not" (Job 14: 2). The scripture makes no mention of any reprieve for the dead, focusing squarely on life itself as the gift of God.

The story of Abraham marks a turning point away from the Mesopotamian tradition of ancestor worship, most explicitly revealed in the story of the sacrifice of Isaac (Gen. 22: 1-19). In this episode, God provides Abraham and his wife Sarah a miraculous child, their only son. Given their cultural background, the fact that they had had no children into old age would have represented a serious problem for their afterlife state, being one in which there were no living ancestors to offer sacrifices for them. God seemingly corrected this by allowing the elderly Sarah to become pregnant.

It is important to know that Abraham's importance is cemented in his forming the covenant with God that defines Jewish identity ever after: Abraham agreed to a pact by which God would guarantee that he and his descendants would live peacefully and forever in a promised land (roughly modern Israel); in exchange, Abraham and his descendants would have to agree to do everything that God asked them to.

Isaac being born, God then asked Abraham to sacrifice his one and only son to Him, creating a paradoxical scenario in which Abraham knew that he had committed to doing everything God would ask of him, while the reward for doing so would be a guarantee of peace and life for him and his descendants. On the other hand, the

Mesopotamian tradition from which Abraham emerged taught that Abraham should have children who would outlive him, thereby guaranteeing respite through sacrifices after death. With Abraham's willingness to kill his son, a task that God released Abraham from at the moment he was about to complete it, Abraham not only showed his loyalty to God, but also his willingness to forgo the promises of an ancestral cult and to instead embrace the covenantal promise of eternal life and peace in the promised land of God.

Over the centuries since the time of Abraham, the Hebrew people have striven to live peacefully according to God's commandments, but have found themselves time and again the victims of persecution and oppression. The land promised by God has been plagued by disruption, as waves of conquerors captured and abused her people. Israel was dominated by the likes of the Assyrians, Babylonians, Persians, Greeks, Romans, Christians, and Muslims. The Jewish people were forcibly removed from the land in 70 CE, existing in an anti-Semitic Diaspora that culminated in the horrors of the Holocaust. Over and over, Jewish thinkers have had to grapple with the problem of God's promise of peace and everlasting life in the promised land against the reality of suffering heaped upon suffering.

God had promised an everlasting life of peace provided His chosen people did as He commanded, and yet a great many who strove to follow God died without ever tasting a moment of peace let alone everlasting life. Recognizing human limitations in understanding, Jewish thinkers were open to new interpretations provided they could be backed by scripture. One important innovation was the concept of resurrection, predicting an eventual restoration to life of all those who had died without ever experiencing God's promised reward for loyal dedication to Him. Since God had promised an eternal life of peace, the only way that the dead could enjoy such a promise was by being restored to life at some future point.

Under Hellenistic influence (circa late-third to mid-first century BCE), Jewish thinkers had to contend with competition from Greek conceptions of the afterlife, which included a dualism whereby the spirit might survive bodily death to exist in some paradisiacal realm. Among a range of cultural tensions, resurrection asserted a distinctly Jewish view of afterlife that emphasized the need for *both* body *and* spirit combined just as God had created life.

By the time of Jesus of Nazareth, Jewish religious leaders had established a scriptural basis for resurrection. The prophet Isaiah, for example, includes the prediction: "Thy dead shall live, my dead bodies shall arise – awake and sing, ye that dwell in the dust – for Thy dew is as the dew of light, and the earth shall bring to life the shades" (Is. 26: 19). The most often cited passage, though, is Ezekiel 37: 5–10. Here, the prophet has vouchsafed a vision of the remnants of the people of Israel:

> 'Thus saith the L-rd GOD unto these bones: Behold, I will cause breath to enter into you, and ye shall live. And I will lay sinews upon you, and will bring up flesh upon you, and cover you with skin, and put breath in you, and ye shall live; and ye shall know that I am the Lord.' So I prophesied as I was commanded; and as I prophesied, there was a noise, and behold a commotion, and the bones came together, bone to its bone. And I beheld, and, lo, there were sinews upon them, and flesh came up, and skin covered them above; but there was no breath in them. Then said He unto me: 'Prophesy unto the breath, prophesy, son of

> man, and say to the breath: Thus saith the L-rd GOD: Come from the four winds, O breath, and breathe upon these slain, that they may live.’ So I prophesied as He commanded me, and the breath came into them, and they lived, and stood up upon their feet, an exceeding great host.

While Jesus himself agreed with the doctrine of resurrection, it is clear that not all Jewish leaders accepted it. Even among those who accepted resurrection, there was no small debate on when it would occur, what the nature of the resurrected body would be, the state of the dead while awaiting resurrection, or on who would be resurrected.

The cadaver itself was thought to remain sensitive to its surroundings. There were many who believed that at the time of resurrection, the individual would be raised in the same clothes he had been buried in, encouraging many to bury their loved ones in the best clothes available. The *luz*, a small bone at the base of the spine which was the only part of the body thought to survive decomposition, was considered the kernel around which the resurrected body would be built. For this reason, cremation was impossible lest the resurrection of the person be prevented. Even the paradise of the eventual world to come had been conceived of as a sensual place, with the three main pleasures being Shabbat (worship of God), sunshine, and sexual intercourse (with one’s spouse, of course) (Sonsino and Syme 1994: 29).

The Jewish view of life after death remained relatively unchanged over the next several hundred years until religious philosophers began to move away from a strictly physical view of the resurrection and to place an increasing emphasis on the spiritual side of things. The great Jewish philosopher and scriptural scholar, Maimonides (1135–1201), citing Daniel,[1] argued that resurrection was a certainty and that it entailed both a physical restoration to life and also a spiritual hereafter beyond even that. From the Middle Ages through the eighteenth century, alongside Christian interpretations of resurrection, the doctrine of spiritual immortality overtook that of bodily resurrection and eventually became the more accepted position in Jewish belief.

Further emphasis on the divergence of spirit and body in Jewish thought appears in the mystical school of *Kabbalah*. One of the main mystical texts of this esoteric movement, the *Zohar*, has been described as containing “some of Judaism’s most sophisticated teachings on the afterlife” (Raphael 1994: 273). Here, the soul is believed to come from God and to eventually be destined to reunite with Him. In the meantime, souls will transmigrate from one body to the next, even through multiple levels of reality, always learning until they can finally leave the cycle of life and simply return to God. While there is no evidence of reincarnation appearing in any Jewish philosophy before the twelfth century, *Kabbalists* found references in the writings of certain *Talmudic* rabbis, as well as in the *Tanakh* itself. One rather vague passage used to illustrate this notes: “One generation passeth away, and another

---

[1] Dan 12: 2: “Multitudes who sleep in the dust of the earth will awake; some to everlasting life, others to shame and everlasting contempt;” and 13: “As for you, go your way till the end. You will rest, and then at the end of the days you will rise to receive your allotted inheritance.”

generation cometh; and the earth abideth for ever" (Eccl. 1:4). Similarly: "For I the Lord thy God am a jealous God, visiting the iniquity of the fathers upon the children unto the third and fourth generation of them that hate Me" (Ex. 20: 5). In any event, the *Kabbalists* took reincarnation for granted from their earliest writings. King David was said to be the reincarnation of Adam, who was then meant to later reincarnate as the Messiah.

Ultimately, the most profound challenge to the Jewish covenant with God has been the Holocaust. That God should allow His chosen people to suffer to such an extreme shattered many peoples' faith (see Rubenstein 1966), leading to a secular Judaism that focuses strongly on life in the here-and-now. For others, in the depths of immense suffering a renewed sense of meaning was discovered. The psychologist and Holocaust survivor, Victor Frankl (Frankl 1984: 98), explains:

> We had to learn ourselves and furthermore, we had to teach the despairing men, that *it did not really matter what we expected from life, but rather what life expected from us.* We needed to stop asking about the meaning of life, and instead to think of ourselves as those who were being questioned by life – daily and hourly. Our answer must consist, not in talk and meditation, but in right action and in right conduct. Life ultimately means taking the responsibility to find the right answer to its problems and to fulfill the tasks which it constantly sets for each individual.

Today, the many branches of Judaism embrace various forms and combinations of the beliefs described above. As the *Tanakh*, being the ultimate authority in all schools of Judaism, makes so little mention of the afterlife, it is largely considered an open question. Only the most orthodox Jews hold onto the notion of a literally physical resurrection, others preferring to view things metaphorically. The resurrection which is to take place is more often considered to be one of a purely spiritual nature. The concept of reincarnation is not widespread in Judaism in the least, but it remains a valid alternative all the same, the *Kabbalah* having been largely absorbed into the larger Jewish tradition. In any event, a life after death is expected at some point within Judaism despite the "this-life" orientation of many modern Jews.

7.2 Christianity

For Christians, the story begins with Jesus of Nazareth and the story of Jesus begins with the Gospels. Written several decades after his death, the Gospels describe the teachings of Jesus in the context of intertestamental religious debates. Jesus teaches his particular interpretation of scripture, sometimes in agreement with other Jewish spiritual leaders, and sometimes at odds with them. On the topic of the afterlife, there are few clear details, though Jesus is certainly on the side that argues for the truth of an impending resurrection.

In one episode, a group of Sadducees, conservative Jews opposed to the notion of resurrection, posed what was meant to be a tricky question, confronting Jesus on the issue of resurrection (Mark 12: 18–27 & Luke 20: 27–38). Their proposed hypothetical involves a woman obliged by tradition to marry her husband's brother after his death. To the question of to whom the woman should be married after the resurrection, Jesus answered simply: "Do ye not therefore err, because ye know not the scriptures, neither the power of God? For when they shall rise from the dead, they neither marry, nor are given in marriage; but are as the angels which are in heaven" (Mark 12: 24–25). Jesus's reply not only stumps the Sadducees, but also, while supporting the notion of an eventual resurrection of the dead, also suggests that one's state after resurrection will be somehow different from that before. The exact nature of this postresurrected state has been hotly debated ever since.

The Jewish thinking on resurrection had emphasized physical bodily return in contrast to the Greco-Roman dualism of body and spirit. As Christianity spread, though, and moved away from Judaism, it leaned into dualism. Other books of the New Testament, particularly those attributed to St. Paul who was writing largely to non-Jewish Christians, confirm the truth of resurrection, but muddy the waters on to whether it will be a physical or a spiritual one. In his first letter to the Corinthians, for instance, Paul summarizes the individual's fate thus: "It is sown a natural body; it is raised a spiritual body. There is a natural body, and there is a spiritual body" (I Cor. 15: 44). Clearly, Paul indicates that the postresurrection man is fundamentally changed from his present state. The corruptible, physical body is dead and gone and in its place is a fresh, incorruptible spiritual body, however paradoxical the notion of a spiritual body is.

The Church Fathers, who laid down the basis for Christian doctrine from the second century AD, encouraged a physicalist interpretation. Growing slowly out of Judaism and still unable to conceive of a life without a body, they leaned more heavily upon the Hebrew tradition over the Hellenized intertestamental ideas that seem to have influenced Jesus and the biblical accounts of his resurrection.

Augustine (354–430 AD), accepting what might seem to be a dualistic compromise, proclaimed that at death the soul left the body for an intermediary state where it awaited the coming resurrection. Upon an individual's death, Augustine taught, the soul left the body and if not immediately taken up to Heaven – a privilege reserved for the most pure of men, including Elijah in the Old Testament – it went to a *Sheol*-like transitional state – the first inklings of purgatory, an interim where souls would be purged of their sins before finally being judged on the Last Day and either resurrected to live eternal life with God, or sent back to Hell to suffer the eternal damnation described by Jesus. The philosopher of religion, John Hick, sees this as the beginning of a trend in Christian thought moving away from a focus on the resurrection and looking more purposefully to the immediate fate of one's soul upon death (Hick 1976).

As the clouds of the Dark Ages parted, medieval Christians had all but relegated the final resurrection to some distant and unimaginable future. The official doctrine still held to that delineated by Augustine, but for the average believer, the resurrection was a far-off anticlimax. With purgatory, each individual was judged at death to determine the level of purgation required; some would go directly to Heaven, some to Hell, but most required some degree of purification. With this initial judgment rendered, the idea of a Final Judgement seems no more than a reiteration of one's immediate death.

As time went on, the emphasis on the immediate afterlife took an increasingly ominous turn. The fate of the soul became a matter of everyday concern for the general population. One could die at any moment and immediately face judgment. According to Aquinas, man was placed upon this earth with the sole intention of aspiring toward Heaven. As for descriptions of Heaven, the scripture is sparse. John's Apocalypse reports witnessing God's Holy City, the New Jerusalem, descending from the heavens:

> It shone with the glory of God, and its brilliance was like that of a very precious jewel, like a jasper, clear as crystal. It had a great, high wall with twelve gates, and with twelve angels at the gates. […] The wall was made of jasper, and the city of pure gold, as pure as glass. The foundations of the city walls were decorated with every kind of precious stone. The first foundation was jasper, the second sapphire, the third agate, the fourth emerald, the fifth onyx, the sixth ruby, the seventh chrysolite, the eighth beryl, the ninth topaz, the tenth turquoise, the eleventh jacinth, and the twelfth amethyst. The twelve gates were twelve pearls, each gate made of a single pearl. The great street of the city was of gold, as pure as transparent glass. (Rev. 21: 11–12 & 18–21)

Though the Pearly Gates come from this biblical description, the association of St. Peter as the gatekeeper is traditional, perhaps drawn from Jesus's declaration that Peter would be the "rock" of the Church, and "I will give you the keys to the kingdom of heaven" (Matt. 16: 19). In fact, both Sts. Paul and Peter are depicted as psychopomps, advocating for the dead in purgatory and introducing the faithful to Heaven, in catacomb paintings from as early as the second or third centuries AD.

Though the image of riches might encourage many to strive after it, Revelation indicates that only the "victorious will inherit all of this," while "the cowardly, the unbelieving, the vile, the murderers, the sexually immoral, those who practice magic arts, the idolaters and all liars – they will be consigned to the fiery lake of burning sulfur" (Rev. 21: 8). Perhaps because of the prevalence of cowards and liars among the general population (for who among us is not one sometimes?), this striving quickly evolved to an overwhelming fear of facing Hell, which had people scrambling to atone for sins before it was too late. As Hick suggests (p: 198), Dante's *Divine Comedy* and Milton's *Paradise Lost* depict the medieval idea of the afterlife as conceived in the popular imagination, doing more to define most people's conceptions of Heaven and Hell than official Church doctrine. Both of these works deal almost exclusively with the immediate fate of the individual upon death, ignoring any idea of a future resurrection. Dante contrasts the light and love of the heavenly spheres with a series of detailed tortures for various sins in concentric circles of Hell; Milton brings to life the ambition of Satan's war over Earth, bookended by the desolation of Hell and the lushness of Eden's garden.

With a growing fear of Hell, and of the tortures meted out in purgatory, many worried for the fates of their departed loved ones. Prayers on behalf of the dead were thought helpful and the Church began to accept alms in exchange for such prayers as services on behalf of the dead. Alternately, the living could also see their sins absolved by similarly paying the local clergy in order to ensure safe passage to Heaven after death. Purgatory thus became a profitable venture for the Church as souls gathered there in wait of the Final Judgement, leading to one of the most prominent criticisms of the Protestant Reformation.

The Reformation called for a return to direct scriptural interpretation, much like what the Jews had been doing for centuries, away from Church authority and the edifice of doctrine that the Fathers had built over time. Problematically, though, once undermining one authority, Protestantism opened the door for a myriad claims to authority, resulting in widespread disagreement on all manner of scriptural detail. Anyone could pick up a Bible and read the Word of God for themselves. Luther believed purgatory to be no more than a tool used by the Church to fleece believers as they paid tribute in order to "save" deceased souls (Luther 1915). Instead, Luther readopted the Judaic concept, whereby a person would simply sleep dreamlessly until being awakened at the Last Day. Among Reformers there was not agreement, however, as Calvin argued against Luther's torporific state, positing that the souls of the dead were transported immediately to either Heaven or Hell, there sampling their eventual fates, the reunion of body and soul at the resurrection intensifying the joys or pains of the afterlife (Calvin 1958). While Protestants rejected the Catholic notion of purgatory as an intermediary spiritual existence, they maintained themes of Heaven, Hell, and even the Final Resurrection, though the details of timing, nature, and of who might endure what fate remains an ongoing debate.

As to the Final Judgement, the Gospels warn that the means to salvation are difficult and that many will fail to achieve it:

> Enter ye in at the straight gate: for wide is the gate, and broad is the way, that leadeth to destruction, and many there be which go in thereat.
>
> Because straight is the gate, and narrow is the way, which leadeth unto life, and few there be that find it. (Matt. 7: 13–14)[2]
>
> And if thy hand offend thee, cut it off: it is better for thee to enter into life maimed, than having two hands go into hell, into the fire that never shall be quenched […] And if thine eye offend thee, pluck it out: it is better for thee to enter into the kingdom of God with one eye, than having two eyes to be cast into hell fire: Where their worm dieth not, and the fire is not quenched. (Mark 9: 43–48)

On the other hand, the path requires Jesus himself, as John quotes him famously: "No one comes to the Father but through Me" (John 14: 6). Paul is clear as well: "If you declare with your mouth, 'Jesus is Lord,' and believe in your heart that God raised him from the dead, you will be saved. For it is with your heart that you believe and are justified, and it is with your mouth that you profess your faith and are saved" (Rom. 10: 9–10). The primary (and perhaps only depending on interpretation) requirement for salvation and resurrection into Heaven is a true and professed belief in Jesus as Christ.

Jesus, though, was particularly interested in the salvation of the more unfortunate members of society. Matthew recounts an episode in which a rich young man is advised by Jesus to sell off his belongings and give them to the poor, so that he can receive rewards in Heaven. When the man walks away displeased, Jesus reminds his

---

[2] Echoed in Luke 13: 23–24.

disciples: "Truly I say to you, it is hard for a rich man to enter the kingdom of heaven […] it is easier for a camel to go through the eye of a needle, than for a rich man to enter the kingdom of God" (Matt. 19: 23–24). Luke similarly recounts the parable of two men, one rich and one poor. Throughout life, the poor man, Lazarus, suffered a life of hardship. The rich man, Dives, lived in the lap of luxury, ignoring the plight of his poor neighbor. In death, Dives suffers the torments of Hell while Lazarus is accepted into the bosom of Abraham. When Dives begs for some respite, Abraham answers, "Son, remember that thou in thy lifetime receivedst thy good things, and likewise Lazarus evil things: but now he is comforted, and thou are tormented" (Luke 16: 19–31). While the importance of charity and care for the poor would seem to be clear in these passages, interpretations range from an ascetic call to renounce attachments to material goods at one extreme to the glorification of the wealthy (whose millions and billions awarded by God for purity allow for a greater capacity to give charitably) found in prosperity theology. Part and parcel with belief in Jesus and Lord and savior comes some commitment to his teachings, however much the interpretative details may vary.

One area of constant conjecture over the two millennia since Jesus lived relates to the timing of the end times. Since Jesus, his followers have been impressed with the nearness of the resurrection; that Jesus himself was resurrected was taken as evidence that the end times had begun and that a general resurrection was imminent. Attempts at predicting the end times have been made by legitimate religious authorities throughout Christian history, including Church Fathers and popes. Catholic tradition has largely given up on trying to predict the timing of the resurrection, citing that only God knows. Many Protestants continue prognosticating, though, with recent attempts by Pat Robertson, Jerry Falwell, and Harold Camping, among others.

Of particular interest to the afterlife is the innovation of dispensationalism, which divides human history into distinct periods differing in God's relation to humankind in order to understand revelation and prophecy. Largely the result of teachings by John Nelson Darby (1800–1882) and Cyrus Scofield (1843–1921), dispensational thinking has encouraged the popularity of apocalyptic expectation among the American public, perhaps especially stoked by the recent turn of millennium. Periods of a thousand years are specifically mentioned in John's Apocalypse:

> And I saw an angel coming down out of heaven […] He seized the dragon, that ancient serpent, who is the devil, or Satan, and bound him for a thousand years. He threw him into the Abyss, and locked and sealed it over him, to keep him from deceiving the nations anymore until the thousand years were ended. After that, he must be set free for a short time. […] And I saw the souls of those who had been beheaded because of their testimony about Jesus and because of the word of God. They had not worshiped the beast or its image and had not received its mark on their foreheads or their hands. They came to life and reigned with Christ a thousand years. (The rest of the dead did not come to life until the thousand years were ended.) This is the first resurrection. Blessed and holy are those who share in the first resurrection. […] When the thousand years are over, Satan will be released from his prison and will go out to deceive the nations in the four corners of the earth […] (Rev. 20: 1–8).

Dispensationalists take such passages as literal prophecy for the future (or present) and expect that the righteous will be taken away, raptured, from the period of tribulation during which Satan is released upon the Earth. As the millennium drew nearer, apocalyptic thinking became increasingly popular, and works like Hal Lindsey's *The Late Great Planet Earth* (Lindsey 1970) and the immensely popular *Left Behind* series of books and films (LaHaye and Jenkins 1995) have firmly planted the concept of a rapture and tribulation in the American imagination. While Lindsey and LaHaye (whose fiction has been described by Jerry Falwell as having greater impact on Christianity than any other modern book, aside from the Bible itself [quoted in TIME 2005]) are avowed Christians, the concept has moved into the mainstream with the likes of HBO's *The Leftovers* and Casey La Scala's horror film *The Remaining* (2014).

The resurrection, for the most part, has been completely relegated to some distant metaphor. It is still referred to as something that makes Christianity different from anything else, but there is general agreement that at death, the individual immediately goes to either Heaven or Hell. Certainly, most Christians now believe that they and their loved ones are destined for Heaven, and that the dead are already there, with Hell reserved for only the most hated and despised. Even then, many Christians believe that Hell is not truly a place of eternal damnation but rather some state in which the soul is purified in order to share in the eternal life with God after the resurrection, essentially taking the place of purgatory. Rather than eternal torment, the punishment for sin is now seen as isolation from the grace of God, and a temporary one at that, for an all-loving God must forgive even the most evil among us.

7.3 Islam

The latest of the Abrahamic traditions, Islam traces its origins to the Prophet Muhammad, born over 500 years after the death of Jesus, in a part of the Arabian peninsula largely ignored by the two world superpowers, Zoroastrian Persia and the Christian Roman Empire. Muhammad grew up in Mecca, where his family was charged with the care of an important religious center, the Kaaba. Though he would later cleanse the temple of its idols and rededicate it to the one true God, Allah, the Kaaba served as a spiritual center for the diverse spirituality of the pre-Islamic Arabs and their neighbors. Importantly for our present context, many among the pre-Islamic Arabs practiced a form of ancestral veneration, whereby the dead would be tied to the place of their individual burial, but also somehow connected to the tribe as it moved from place to place. There was no real sense of an afterlife in the sense of a Heaven or Hell, instead seeing death as a negative state, though mediated by sacrifices and honor for the dead from the living.

As Muhammad grew older, he traveled the peninsula, encountering Jews, Christians, and Zoroastrians, all of whom agreed on some key doctrines, including the imminent end times, the resurrection, and a judgment of the dead. All of these people also warned that failure to obey the one true God would result in damnation, a charge that if true would condemn the pre-Islamic Arabs, Muhammad's people, for all time. While meditating on these matters, Muhammad became a prophet when the archangel Gabriel appeared to him and delivered the Qur'an, the holy text of Islam. What he learned from his revelation was that the basic tenets of the other Abrahamic faiths, especially concerning the afterlife, were correct, though substantial details had been corrupted over time. God had given Muhammad the revelation to fix all previous errors in human understanding.

The Qur'an agrees that the end times are near, that there will be a general resurrection of the dead who will be judged by God, followed then by either eternal reward in Heaven or damnation in Hell.

> When the sun ceases to shine; when the stars fall down and the mountains are blown away; when camels big with young are left untended and the wild beasts are brought together; when the seas are set alight and men's souls are reunited; when the infant girl, buried alive, is asked for what crime she was slain; when the records of men's deeds are laid open and the heaven is stripped bare; when Hell burns fiercely and Paradise is brought near: then each soul shall know what it has done. (Qur'an 81: 1–14)

All who have died will be raised up from their graves to experience the Last Day. The deeds of every person are made clear and revealed to all:

> Frail and tottering, the sky will be rent asunder on that day, and the angels will stand on all sides with eight of them carrying the throne of your Lord above their heads. On that day you shall be displayed before Him, and all your secrets shall be brought to light. (Qur'an 69: 13–18)

The deeds, good and evil, of every person are recorded in books, which are then handed back to each individual as a sign of the judgment rendered. If the book is given into the right hand of a person, they are destined for Paradise. A book placed in the left, however, is a condemnation to Hell:

> Truly, the record of the sinners is in Sidjeen […] a sealed book […] But the record of the righteous shall be in Illiyun […] a sealed book, seen only by those who are closest to Allah. (Qur'an 83: 6–7 & 18–19)
>
> He who is given his book in his right hand will say to his companions: "Take this, and read it! I knew that I should come to my account." His shall be a blissful state in a lofty garden with clusters of fruit within reach […] But he who is given his book in his left hand will say: "Would that my book were not given me! Would that I knew nothing of my account!" […] We shall say: "Lay hold of him and bind him. Burn him in the fire of Hell." (Qur'an 69: 18–28)

Those who have led their lives according to the will of Allah and have been good and just, will be granted access to Paradise, which is described as lush gardens with flowing streams and cool breezes. The blessed can indulge in all manner of feasting and are wedded to lovely virgins. On the other hand, sinners are cast into Hell, which is consistently described with allusions to fire and boiling water and where they have no joys and no pleasures at all.

> This is the Paradise which the righteous have been promised. There shall flow in it rivers of unpolluted water, and rivers of milk for ever fresh; rivers of delectable wine and rivers of clearest honey. They shall eat therein of every fruit and receive forgiveness from their Lord.

> Is this like the lot of those who shall abide in Hell for ever and drink scalding water which will tear their bowels? (Qur'an 47: 15)
>
> Garments of fire have been prepared for the unbelievers. Scalding water shall be poured upon their heads, melting their skins and that which is in their bellies. They shall be lashed with rods of iron […] And for those that have faith and do good works, Allah will admit them to gardens watered by running streams. They shall be decked with pearls and bracelets of gold, and arrayed in garments of silk. (Qur'an 22: 19–23)
>
> They shall recline on couches ranged in rows. To dark-eyed *houris* [maidens] We shall wed them […] Fruits We shall give them, and such meats as they desire. They will pass from hand to hand a cup inspiring no idle talk, no sinful urge; and there shall wait on them young boys of their own as fair as virgin pearls. (Qur'an 52: 20–24)
>
> The wrongdoers shall be known by their looks; they shall be seized by their forelocks and their feet […] They shall wander between fire and water fiercely seething […] But for those that fear the majesty of their Lord there are two gardens […] planted with shady trees […] Each is watered by a flowing spring […] Each bears every kind of fruit in pairs […] They shall recline on couches lined with thick brocade, and within their reach will hang the fruits of both gardens […] They shall dwell with bashful virgins whom neither man nor jinnee will have touched before […] Virgins as fair as corals and rubies […] And beside these there shall be two other gardens […] of darkest green […] A gushing fountain shall flow in each […] Each planted with fruit-trees, the palm and the pomegranate […] Dark-eyed virgins sheltered in their tents […] whom neither man nor jinnee will have touched before […] They shall recline on green cushions and rich carpets. (Qur'an 55: 37–76)

Scholars and theologians have debated the words of the Qur'an and whether they should be taken literally in all cases, especially where the issue of life after death appears. Some elements above are familiar to Christian apocalyptic, such as the emphasis on the contrast between Heaven as a bejeweled place with lush gardens and the fires of Hell. Descriptions of the sensuous pleasures of Paradise, especially the dark-eyed virgins which seem directed largely at male enjoyment, have stirred some degree of controversy. There has been some sense in modern times that these depictions are not to be taken literally.

Annemarie Schimmel suggests that, "One could, however, interpret the houris and the fruits as symbolizing the greatest happiness, that of perfect union with the Beloved, and of the ancient belief that one can attain union with the Holy by eating it" (Schimmel 1994: p 238). Sometimes, the virgins are reinterpreted in a gender-neutral sense in order to accommodate women in Paradise as well, the chaste virgins seen as "perfect" spouses of either sex. One can also point to the presence of the youths, "fair as virgin pearls," as an indication that women will receive similar treatment to men in Paradise. Gender equality in the eyes of God is guaranteed by the Qur'an explicitly (3: 195). The *hadith*, which details the deeds and sayings of Muhammad that were not part of the divine revelation, provides several examples of women in Paradise. For instance, the following passage concerns Khadija, the first wife of Muhammad:

> "What did he (the Prophet) say about Khadija?" He (Abdullah bin Aufa) said, "(He said) 'Give Khadija the good tidings that she will have a palace made of Qasab [precious stones] in Paradise and there will be neither noise nor any trouble in it.'" (Khan nd.: *Sahih Bukhari*: Vol. 3, Bk 27, no. 19)

However broadly it is interpreted, it is clear that the Qur'an deliberately depicts a sensual Paradise, promising physical rewards in the hereafter. However, not only do the good benefit from those bodily pleasures described, but they are also granted the vastly more important reward of spending eternity in the presence of God: "And what is more, they shall have grace in His sight. That is the supreme triumph" (Qur'an 9: 72). It has been suggested since at least the tenth century (by Muslim philosopher, al-Farabi) that physical descriptions of the afterlife were the only means, however inadequate, to portray the true splendors of the afterlife to the common human mind. (Goodman 1992, p 127).

The Qur'an also states that once a person has died, "Behind them there shall stand a barrier till the Day of Resurrection" (Qur'an 23:100). The barrier, and the intermediary state in which the dead remain until resurrection, is called *barzakh*. For a description of this purgatory-like state, one must turn to the *hadith* literature, in combination with a variety of commentary, philosophy, theology, and pre-Islamic traditional folklore to learn of the chain of events that befall one at the end of life. At the moment of death, the individual is visited by the angel of death, 'Izra'il, thought to be a fearsome being of immense power, symbolizing the fact that no one can escape his or her mortal fate. The person is then approached by two angels who question the dead. Failure to answer correctly proves one as a sinner, while a true Muslim would have the answers at hand. The sinner is beaten and tormented by these angels, and then sealed into the grave with the body. While the sinner feels the worms chewing upon his or her corpse, the angels open a small window to allow them to gaze into Hell while awaiting this eventual fate. On the other hand, if the person has followed the ways of Islam, the angels are kind and open a window looking out onto awaiting Paradise. In either case, the dead remain in their grave until the time of resurrection, in a kind of dreamless sleep.

There is one exception to this intermediary fate – martyrs are exempted from the purgatorial *barzakh* and are brought directly to Paradise. In one instance, the Qur'an explains: "Think not of those who are slain in Allah's way as dead. Nay, they live, finding their sustenance in the presence of their Lord. They rejoice in the Bounty provided by Allah: And with regard to those left behind, who have not yet joined them (in their bliss), the (Martyrs) glory in the fact that on them is no fear, nor have they (cause to) grieve" (Qur'an 3: 169–170). Some of the *hadith* literature depicts the martyrs embodied as green birds in Paradise. The notion that martyrs will receive 72 virgins stems from a single weak *hadith*, though its exorbitance has gained traction in the popular imagination, especially among those who would seek to discredit Muslims.

The dominant opinion in Islam, then, is that, upon death, the individual soul is thought to remain in the grave either in a state of sleeplike torpor or experiencing a taste of the fate to come, perhaps experiencing the intermediary *barzakh* state as a kind of purgatory in preparation for judgment, until the eventual Final Resurrection. Martyrs, however, may travel immediately to Paradise, while everyone awaits the judgment before receiving the fullness of either Heaven or Hell. Some modern scholars prefer to see the torment of Hell as temporary, dependent upon the severity of the sin, thereby allowing potentially all people to achieve Paradise. All in all, Islam presents a sophisticated eschatology clearly in the mold of the Abrahamic tradition.

7.4 Hinduism

The distinctly Indian religion of *Sanatana Dharma* (Eternal Teaching), with a history at least as ancient as Judaism, is, in fact, a conglomeration of spiritual philosophies and practices that have been collected together under the umbrella of Hinduism. Over centuries, new interpretations and innovations in practice have been added to previous ones, while allowing the older traditions to continue rather than superseding them entirely. Modern Hinduism can best be described as a multifaceted system with multiple paths all leading to the same divine source.

In terms of the afterlife, differences in approach all sit cleanly within the context of reincarnation, the idea that an individual will be reborn into subsequent lifetimes after death. That these incarnations are not necessarily constrained to human form allows for the possibility of births in alternate, spiritual worlds.

The oldest traditions described in the earliest *Vedas* (the Hindu scriptures) depict a form of ancestor worship, with spirits of the dead residing in the *Pitrloka*, or Land of the Fathers. The "Fathers," ancestors, themselves form a collective, invocations being directed toward the group as a whole more so than to any individual among them. While the Fathers might be encouraged to help the living with special offerings, regular offerings are necessary simply to ensure that the ancestors would not cause harm. Entry to the *Pitrloka* requires prescribed ritual actions as outlined in the *Vedas*. Essentially, the rituals involve a continual recognition of the importance of the ancestors, and the expectation that one will have children who learn the importance of continuing the rituals on into the future. Offerings of food and such were intended as sustenance for the dead and the means by which they might continue to "live" in the *Pitrloka*.

Many continue some form of these rituals today, with offerings made for the dead from the moment of death as a means of appeasing the deceased and to help prepare the spirit for its journey to the afterlife. *Vedic* priests are typically needed to perform these rituals, as most Hindus simply have inadequate access to the scriptures. For 13 days, offerings of food (normally milk and a rice-ball mixture called *pinda*) and money are given to both the priests and to the dead. While acting as a form of payment for the priests, the act also prepares the dead for the afterlife as well.

The *Pitrloka* itself is described as a place of idyllic beauty. According to the *Atharva Veda*, those who perform the requisite rituals are promised the sensuous rewards of women, food, and drink in the comfort of a lush, breezy landscape (Whitney 1971: AV. 4.34). The dead are also described in the *Rig Veda* as sharing rich banquets with the Gods in a realm of light (Griffith 1973: RV. 7.76.4). Such images are contrasted with a simple, albeit bleak, alternative being simply a dark abyss for those who have failed to conduct the rituals accordingly. Some of the later *Vedas* seem to imply divine retribution, particularly for transgressions against the priestly classes or for failure to adhere to sacred norms. The *Atharva Veda*, for instance, provides the following rather gruesome example: "They who spat upon a Brahman, or who sent [their] mucus at him – they sat in the midst of a stream of blood, devouring hair" (Whitney 1971: AV 5.19.4). Another late *Vedic* text simply states that one who spills the blood of a *Brahman* shall, "not get to see the world of fathers" (Oldenberg 1988: 320. Quoting *Taiit. samhita* II, 6, 10, 2). The overwhelming emphasis rests on the performance of the rituals and respect for those who know the details of them.

While the *Vedas* themselves offer little detail on the afterlife, later commentaries (*Brahmanas*) and further philosophical writings (*Upanishads*) offer a much more sophisticated and complex system within which the above resides. The primary innovation in thinking is the incorporation of reincarnation as a system allowing individuals to live multiple lifetimes, removing the sense that one might be condemned for eternity for mistakes made during one lifetime, while also encouraging good behavior as leading to increasingly greater rewards; and discouraging evils by pointing to their attracting painful punishments. The priests describe an evolutionary progress through successive lifetimes:

> Now as a caterpillar, when it has come to the end of a blade of grass, in taking the next step draws itself together towards it, just so this soul in taking the next step strikes down this body, dispels its ignorance, and draws itself together [for making the transition].
>
> As a goldsmith, taking a piece of gold, reduces it to another newer and more beautiful form, just so this soul, striking down this body and dispelling its ignorance, makes for itself another newer and more beautiful form like that either of the fathers, or of the Gandharvas, or of the gods, or of the Prajapati, or of Brahma, or of other beings. (Hume 1921: BA 4.4.3–4)

The question of divine justice is addressed in the *Upanishads* in several ways, including an expanded interpretation of *karma*, from ritual action to *right* action generally. Relatedly, the notion of *dharma*, one's duty in life, what one ought to do, is a more intricate force driving all action. All of one's actions in one life will affect the form they take upon reincarnation, with each new life reflecting the actions they had taken in past ones.

> either as a worm, or as a moth, or as a fish, or as a bird, or as a lion, or as a wild boar, or as a snake, or as a tiger, or as a person, or as some other in this or that condition, he is born again here according to his deeds (*karman*), according to his knowledge. (Hume 1921: KU 1.2)

And that which moves through incarnations is described here as the *atman*, roughly equivalent to the soul or Self. The incarnations take place within the ongoing cycle of birth, life, and death, in whatever realm, that is collectively known as *samsara*. So, according to the *Upanishads*, the individual *atman* is incarnated (in whatever form) within *samsara*, where it undertakes its actions (*karma*). In order to encourage a positive rebirth in subsequent lifetimes, one must ensure that one's actions (*karma*) align with one's *dharma* (duty). Importantly, though, this process is not endless, but there is an endpoint to which everyone might endeavor. Contrasted with the *atman* as individual, there is also the *Brahman*, which is the essential element of which all of reality is composed – it might be imagined as the soul of the entire universe. Through successive incarnations, the individual is supposed to grow closer to a realization of one's connection with the universal reality of *Brahman*. One analogy describes the individual as a single drop of water, and *Brahman* as the ocean itself. The ocean requires every drop, and it is but a matter of perspective as to the form of the individual drop of water once added to the ocean. The realization of this interconnection is called *moksha*, which stands in contrast to *samsara* – the former takes the view of the ocean as whole, while the latter focuses on the individual droplet moving from place to place through the sea.

The system recognizes that this rather esoteric view of the individual's place in the universe will not be readily understood by all people, and thus the older system of ancestor veneration remains in place. So long as the average person does their own individual duty in life, which will include marriage and children, veneration of ancestors, respect for the priestly class, and the performance of specific societal functions according to one's birth, one can be said to accomplish one's *dharma*. It is only the priestly class whose societal dharma includes understanding and teaching the above system of thought, and it is therefore this class of people who are deemed closest to achieving the state of *moksha*. Until a person achieves a birth as a Brahmin priest, one can expect a great many lifetimes, including those as humans, animals, and as spirits in various other realms.

According to tradition, as recorded in the *Puranas* (extra-*Vedic* compilations of legend and lore), there are said to be seven heavens, seven nether regions, and twenty-one hells. The denizens of these realms range from demons, ghosts, and ghouls to angelic *devas* and the spirits of the dead. The *Vedic* World of Fathers appears among the seven heavens, as do the World of the Gods and the Ultimate Reality of *Brahmaloka*, the World of *Brahman*, found in the *Upanishads*. The layers of Hell are described as equally radiant as the heavens, but provide homes for the myriad demons believed to share space with human beings. The Nether World, on the other hand, is the place where tortured souls reside. Any of these multiple worlds might be the future birthplace of any given person after death.

The greatest sins reported are those of neglecting family responsibility, performing rituals poorly or incorrectly, and disrespecting Brahmin priests; murder, theft, and slander are among the next-most severe wrongs. Methods of punishment for such beings who had failed in their duties or committed other evils predominantly involve either physical mutilation or the forced ingestion of all manner of gruesome matter. Having one's intestines plucked out by birds; being forced to hold hot metal balls in the mouth; being torn in half; ingesting blood, pus, and urine; having one's eyes blown out of one's head – all examples of tortures one might endure for bad *karma* (Dimmitt and van Buitenen 1978).

Devotional theism, being devotion (*bhakti*) to a specific divinity in the hopes that this particular God will provide a propitious rebirth, sprung from a need for *personal* salvation, especially as contrasted with the *Brahmanic* notion of *moksha*. Ramakrishna, the nineteenth-century yogi, summed up the sentiment when he said, "I want to taste sugar, not become sugar" (Hopkins 1992: 152). This new idea does not deny the cycle of rebirth cited in the *Upanishads*, nor that one might eventually achieve *moksha*. Instead, it proposes a new path to *moksha*, a way of devotion that is simpler to understand and that provides a more personally rewarding relationship with one's God. Simply put, not every person is born into the same position in life, whether by caste, station, or other factors, but *bhakti* offers everyone some measure of control over their immediate fate after death. Krishna, in the immensely popular *Bhagavad Gita*, promises that through devotion and faith in him, Krishna will guarantee salvation:

> Listen! I tell thee for thy comfort this. Give me thy heart! Adore Me! Serve me! Cling in faith and love and reverence to Me! So shalt thou come to Me! I promise true, for thou art sweet to Me! And let go those – rites and write duties! Fly to Me alone! Make Me thy single refuge! I will free thy soul from all its sins! Be of good cheer! (Arnold 1961: Bk 18: 109)

Hinduism thus offers a complex array of possibilities, all working within the grand narrative of reincarnation through successive lifetimes. One's actions in life will have an impact on one's future incarnations. One may dream of release from successive lifetimes in order to enjoy some blissful reunion with everything, but the concept is difficult to imagine and so many might prefer simply to aim for reincarnation into a higher social class, or perhaps choose to venerate a particular God in order to enjoy some heavenly existence, however temporary it may be. Remembering the importance of the ancestors remains important as well, being part of one's duties in life and a show of respect for the dead.

7.5 Buddhism

Buddhism is based on the teachings of the Siddhartha Gautama, who became the Buddha with an epiphany about the nature of suffering and the place of humankind in the universe. His enlightenment included a rejection of the Brahmin priests and their hierarchical interpretation of the *Vedas*, and introduced new perspectives on familiar themes. Like the later emphasis of the *Puranas* and *Gita* in Hinduism, the Buddha democratized the afterlife by making every individual, regardless of station or class, responsible for one's own state of being.

The Buddha accepted reincarnation in principal and the connection between what one does (*karma*) and what one ought to do (*dharma*), but whereas the Hindu focuses on the permanency of the *atman* through successive lifetimes, the Buddha focuses on the impermanence of all things as change is inevitable and occurring at every moment. The Buddha rejects the notion of a permanent Self residing unchanged through time, emphasizing that it is just such a concept that fosters suffering in giving us a sense of continuity that allows or encourages us to become attached to things, wishing that they would not change despite the fact that they always do. Aging, sickness, and death, especially, cause suffering exactly because we see these as negative changes destroying our attachments to people, especially ourselves, as permanent, ongoing entities. To overcome suffering, the Buddha urges his followers to be aware of the impermanence of things at all times, especially of one's self. In effect, death is occurring at all times as change is ever present. The person I was before is gone, and the person I am now is not only different from that before, but is also temporary. With this in mind, Buddhists are encouraged to focus on the moment and to live within each moment accordingly, following the Buddha's teachings (his *dharma*, being a guide to how we all ought to live), which essentially urges selfless compassion. Since the self that I am at this moment will soon be gone, there is no point in being selfish – any pain I suffer will be gone with the passing moments, as will any material goods that I might enjoy.

With this in mind, it is possible to speak of rebirth as related to *karma* and the individual. One's actions lead to karmic consequences along a linear chain of cause and effect linked with a series of ever-changing thought-moments. A selfless perspective, living according to the Buddha's *dharma*, naturally results in a peaceful, pain-free existence, whereas neglecting the *dharma* and living selfishly perpetuates its own suffering. The maxim that the more you have, the more you have to worry about holds true here. As long as I remain focused on the self as permanent, then I will continue to hold onto past sufferings as if they were relevant to the present moment, and I will cling to material things and wish they would not change, despite the knowledge that they certainly will. In this way, each individual is the architect of his or her own suffering.

Rebirth occurs so long as a person is attached to the self as an ongoing entity, and can take many forms, depending upon the *karma* involved. There are basically six modes of existence: the three higher modes consist of humans, lesser divinities (*asuras*), and Gods (*devas*); the three lower modes include animals, hungry ghosts (*pretas*), and hell-beings (*naraka*). As the Buddha explains:

> Because of their wicked conduct, their unjust conduct […] some beings with the break up of the body, after death […] go the bad way, come to places of pain, to hell […] Owing to their conduct in agreement with the teaching, their considerate conduct, some beings with the break up of the body, after death, go the good way, come to the heavenly world. (Schumann 1973: 55 f. Quoting *Anguttaranikaya* 2, 2, 6, I)

None of these states is permanent, however, and progress to the next mode of being is dependent on perspective and whether one elects to follow the *dharma* of selflessness or not. Performing good deeds leads to a better life, while evil ones lead invariably to a hellish one. People who give gifts of food will live long and healthy lives; those who offer houses gain palaces full of wealth; those who dig wells for the public will never need water; those who offer medicine are forever free from disease. And so the list goes. The same is true of sinners and their punishments. Those who oppress others by confining them suffer madness; those who physically assault others become lepers; those who steal cannot earn money even with great effort.

Another common form of punishment comes from being reborn as a hungry ghost. Individuals whose sins may not have been grave enough to warrant Hell, but who continue to harbor base attachments to the material world may be reborn as ghostly beings continually starved but never able to satiate themselves. The *Petavatthu* details a number of tales involving these tortured spirits in various forms, some withered and emaciated, others bleeding and full of pus. As a whole, these spirits take on a form that is sufficiently horrible to reflect their Hell-like state, and like other forms of purgation, such existence often teaches the individual the error of his or her ways and leads to a better life when this one ends.

Over the centuries since Gautama's death, and as his teachings spread from India across Asia, different interpretations have emerged. The oldest form remaining, Theravada Buddhism, which is now dominant in Sri Lanka, Thailand, and Cambodia, places a heavy emphasis on personal responsibility and meditation as a means to achieving nirvana (the release from suffering attained through complete understanding of the *dharma* of selflessness), which has resulted in a distinct separation between the monks and laity. Essentially, monks are seen as closest to achieving nirvana, while most laypeople might aspire toward it with the hope of being reborn as a monk along the way. Since laypeople can expect successive incarnations in their future, the practice of ancestral veneration remains common, similar to how it remains prominent in India and China.

Mahayana Buddhism, however, which is dominant in China, Japan, Vietnam, and other parts of Asia, allows for a form of spiritual assistance to alleviate some of the pressures of personal responsibility for *karma* in the form of the *bodhisattvas*. Upon achieving the realization of utter selflessness that is nirvana, one becomes a *bodhisattva* intent on assisting every other person to achieve the same. Total selflessness could not, it is reasoned, result in an abandonment of the world, but rather the compassion elicited would require a selfless being to remain somehow available to help those left behind.

It is thought that because of their desire to see every person released from suffering, *bodhisattvas* are incapable of refusing any request for help. In exchange for this help, however, the supplicant agrees to commit to the strict morals of compassion espoused by the *bodhisattva*s themselves. For those for whom strict adherence to such a code would prove difficult, even maintaining faith in the Buddha and the *bodhisattvas* can help.

Of the many schools of Mahayana thought that have arisen, Pure Land Buddhism dominates the Far East. Of the three main texts of Pure Land Buddhism, the *Larger* and *Smaller sutras* originated in India, while the third, the *Meditation sutra*, or *Kuan Wu-liang-shou ching*, shows the distinct Chinese influences of the fifth century CE. The older sutras describe how the *bodhisattva* Dharmakara vowed to forgo his own entrance into nirvana until every person who called him to mind had first entered before him, in the process becoming Amitabha Buddha. According to his vow, the mere act of invoking the name of Amitabha, or Amida, at the moment of death would enable one to be reborn in the Pure Land of his Western Paradise. The *Larger sutra* describes the Pure Land as a realm of eternal light, filled with lakes and rivers. Flowers bloom in abundance while jewels grow upon trees and music whistles through their branches. Evil is nonexistent and there is no need for food to survive (Kotatsu 1996). Being born into the Pure Land was seen as a stepping stone before the inevitable entrance into nirvana, but the sensual images of paradise appeal much more readily to the more immediate concerns of the average person.

The *Meditation sutra* points out that these heavenly realms are not mere fantasies, but actual places that can be seen through the practice of sincere meditation. Through practicing various visualization techniques, anyone can receive visions of the world to come. Similarly, it is crucial to continue the meditative process on one's deathbed and focus the mind on the image of Amitabha, while reciting his name. The *Meditation sutra* describes how different types of meditation and varying levels of faith will result in different deathbed experiences. To the most accomplished meditators, Amitabha appears in his full brilliance. Others see only flowers and splendid colors, while the lowest of the worthy must first get a brief taste of Hell before being reborn in the Pure Land (Becker 1984). The *Ching-t'u-lun* lists twenty accounts of deathbed visions in which monks and laypeople report seeing various spiritual beings, including the Buddha, Amitabha, and the popular Kuan-yin. Reports such as these have been used as proof of existence of the Pure Land and the continuing presence of the *boddhisattvas*.

Another school of Buddhism, Vijrayana, is the unique product of Tibet, incorporating elements of pre-Buddhist spirituality with Buddhist philosophy. The most famous unique contribution of Tibetan Buddhism is the *bardo* state, outlined in the *Tibetan Book of the Dead*. The purpose of this great text, written by the "great adept's adept" (Thurman 1994: p. 83), Padma Sambhava around the eighth century CE, is to help guide the dying and the dead through the period in-between incarnations. It is thought that one maintains the capacity for change while dying and can still influence one's impending reincarnation while dead. The readings in the text are aimed not only at providing instructions for the subsequent journey, but also at maintaining a clear and positive mental state upon entering death. The Dalai Lama (1979: 8) points out that, "the attitude just before death is very important; for, if even a moderately developed practitioner is disturbed at that time, manifest desire or hatred will be generated." During the *bardo* state, which may last for as long as 49 days, the individual adopts a spiritual body, and without guidance, might not realize that he or she is dead and wander in a ghostly form until the next birth. The constant presence near the body of a reader of the Book of the Dead, though, will guide the deceased through the in-between space of *bardo* and help them to attain a beneficial reincarnation.

Whatever the form Buddhism takes, the core perspective remains the same – death should not be seen as a source of suffering but as an inevitable aspect of the ongoing process of change. Those who are unable or unwilling to accept this reality can expect subsequent incarnations, through which one can expect to continue suffering in the ways that we all do out of our desires to avoid the inevitability of change and of death. The end of suffering comes through the change of perspective recommended by the Buddha, which is one of selflessness and acceptance.

References

14th Dalai Lama (1979) Foreword. In: Rinbochay L, Hopkins J (eds) Death, intermediate state and rebirth in Tibetan Buddhism. Rider, London

Arnold E (ed) (1961) The song celestial or Bhagavad-Gita. Routledge & Kegan Paul, London

Becker CB (1984) The pure land revisited: Sino-Japanese meditations and near-death experiences of the next world. Anabiosis J Near-Death Stud 4:51–68

Calvin J (1958) Psychopannychia. In: Torrance TF (ed) Tracts & treatises on the reformation of the church, vol 3. Grand Rapids, Eerdmans

Dimmitt C, van Buitenen JAB (eds) (1978) Classical Hindu mythology: a reader in the Sanskrit Puranas. Temple UP, Philadelphia

Frankl VE (1984) Man's Search for Meaning. 1959. Rev. and updated. Washington Square, New York

Girffith RTH, trans. (1973) The hymns of the Rgveda. Shastri JL (ed) Motilal Banarsidass, Delhi

Goodman LE (1992) Avicenna. Routledge, London

Hopkins Thomas J (1992) Hindu views of death and afterlife. In: Hiroshi O (ed) Death and afterlife: perspectives of world religions. Greenwood, New York

Hick J (1976) Death and Eternal Life. Collins, London

Hume RE (ed) (1921) The thirteen principle Upanishads. Oxford UP, Delhi

Khan MM, trans. nd. Sahih Bukhari, Volume 3, Book 27, Number 19. Online: http://www.sahih-bukhari.com/Pages/Bukhari_3_27.php. Accessed 3 July 2015

Kotatsu F (1996) Pure Land Buddhism in India. Translated by Taitetsu Unno. In: James F, Michael S, Richard KP (eds) The pure land tradition: history and development. Regents of the University of California, Berkeley

LaHaye T, Jenkins JB (1995) Left behind. Living Books, Boston

Lindsey H (1970) The late great planet earth. Zondervan, Grand Rapids

Luther M (1915) Disputation of Doctor Martin Luther on the power and efficacy of indulgences. Works of Martin Luther. 6 volumes. Translated & edited by Adolph Spaeth, et al. A. J. Holman, Philadelphia

Oldenberg H (1988) The religion of the Veda. Translated by Shridhar B. Shrotri. Motilal Banarsidass, Delhi

Raphael SP (1994) Jewish Views of the Afterlife. Jason Aronson, London

Rubenstein RL. After Auschwitz: Radical Theology and Contemporary Judaism. Indianapolis: Bobbs-Merrill, 1966

Schimmel A (1994) Deciphering the signs of god. SUNYP, New York

Schumann HW (1973) Buddhism: an outline of its teachings and schools. Translated by Georg Fenerstein. Rider, London

Sonsino R. Daniel B. Syme (1994) What Happens After I Die?: Jewish Views of Life After Death. Jason Aronson, Northvale, NJ

TIME Staff (2005) "The 25 Most Influential Evangelicals in America: Tim and Beverly LaHaye" Monday, Feb. 7. TIME. Online: http://content.time.com/time/specials/packages/article/0,28804,1993235_1993243_1993291,00.html. Accessed 26 June 2015

Thurman RAF (ed) (1994) The Tibetan book of the dead. Bantam, New York

Whitney WD (ed) (1971) Atharva-Veda-Samhita. Motilal Banarsidass, Delhi

A Historical Perspective of Death in the Western World

8

David San Filippo

8.1 Introduction

Humans appear to have had awareness from their early consciousness that none of us get out of this life alive. Death beliefs and practices have changed throughout history due to changes in social, spiritual, and religious beliefs and practices. A belief in the immortality of the spirit has been present in most religions and spiritual practices for centuries. The belief that there is a life after death is one of the oldest concepts of human history. Freud (1961) when reflecting on how we think of death and immortality commented,

> Our own death is indeed unimaginable, and whenever we make an attempt to imagine it we can perceive that we really survive as spectators. Hence the psychoanalytic school could venture on the assertion that at bottom no one believes in his own death, or to put the thing in another way, in the unconscious everyone of us is convinced of his [or her] own immortality (p. 154).

Religions and spiritual practices throughout history have provided structures that support the religious and social needs of practitioners regarding death and an existence after life. Rituals and sacred writings support the various religious and spiritual interpretations of what death is and what it will be like in the afterlife. However, even with the differences in religious beliefs, there are similarities between many different religious groups regarding afterlife beliefs. One similarity among religious groups is the belief in an afterlife following physical death. Another similarity is the presence of "the two polar images of life after death – the abode of the righteous, heaven or paradise, and the place for the wicked, or hell" (Grof and Grof 1980, p. 13).

D.S. Filippo, PhD
National Louis University, Chicago, IL, USA
e-mail: David.SanFilippo@nl.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_8

Death beliefs and practices throughout history have been influenced by environmental, social, religious, and spiritual factors. Environmental factors are based upon the external elements to the person such as climate, predators, food, water supply, and health risks. Social factors included the socialization practices of societies, class structures, governmental structures, and social practices for caring for the dead and bereaved. The spiritual factors include a belief in a life after death, or not, and spiritual practices for the caring for the dying, dead, and the bereaved.

Historical changes in the beliefs of death, dying, and bereavement have also influenced how medical practices approach this final stage of life. This chapter will examine the historical perspective of death beliefs and practices over the span of human history from pre-historical times to the present day focusing on the beliefs in death, dying, afterlife, the final disposition of the dead, and some of the bereavement practices during the span of human history.

8.2 Pre-history (Before 10,000 Years Ago)

The life span of prehistoric humans was about 30 years old. Our historical knowledge of early humans' death and afterlife beliefs and practices have been developed through archeological finds of early human remains. Death came to the prehistoric humans in the way of illness and/or injury. The survival of children was poor as a result of the lack of nutrition and/or illness and rudimentary medical practices. Adults perished as a result of the same issues with the addition of predators both animals and other humans.

Death was an accepted part of life to the prehistoric human because of the high rate of death as a result of illnesses, accidents, and the attack of predators. The process of dying was often painful and quick. Cro-Magnon humans had a concept of death and an anticipation of life after death. They buried their dead in or near their caves or huts along with the dead person's tools, weapons, jewelry, and other favorite possessions. The dead were also attired in the favorite formal clothing. The burial of the person, along with her or his belongings, are considered to be prehistoric humankind's anticipation of needing these things in life after death (San Filippo 1998). Many primitives believed that death was a change in existence in which the essence, the soul, of the individual passes from this realm to another realm.

The dying person was often prepared for death by various pre-death rituals and funeral practices. There was a fear that if the dead were not treated properly in their death and final disposition the departed spirit would interfere in the lives of the living.

Funeral practices were not based upon the containment of potential illness to the living due to decomposition of the corpse but on the fear of offending the spirit of the dead or the gods. Funeral rituals therefore were often designed to honor the dead or "to offset fears about the potential malevolence of the dead towards the living" (DeSpelder and Strickland 1983, p. 36). The primitive corpse was buried in the belief that it would someday grow again like a plant (Aiken 2000).

8.3 Antiquity (Before AD 500)

The expected life span of a person born into the ancient world was approximately 35 years old. Tombs and other final resting places provide a view into the dying, death, and afterlife beliefs and practices of ancient societies. Ancient Hebrews recognized the existence of a soul but did not dwell on life after death. Ancient Egyptians, Greeks, and Romans had an expressive perspective toward death and the existence of life after death and their practices of dealing with the dying and death reflected their perspectives. The Greek and Roman perspectives of death were similar as a result of ancient Roman culture incorporating aspects of early Greek culture into Roman culture.

Ancient Egyptians focused a great deal of time, energy, and resources in order to prepare for the next life. They perceived life as a dream that was quickly over and thought that death was eternal. Ancient Egyptians believed that in order to enjoy eternity in another life, the body of the deceased had to survive into eternal life (San Filippo 1998).

Egyptians believed that humans had a dual soul, "Ka" and "Ba." One soul, "Ka" remained close to the body after death. The "Ba" soul was a living soul that resided in the spiritual domain. The Egyptians believed that the dead crossed the river of death to the House of Osiris, the god of the dead, where they were to spend eternity. To guide the dead on their journey to the House of Osiris, the Book of the Dead was buried with the deceased. Entrance into eternity was dependent on judgment of Osiris of the individual's life (Assmann 2005).

The Egyptians also believed the preservation of bodies provided for a happy afterlife. Additionally, they believed that "Ba" survived by preserving the body of the dead through mummification in order for "Ba" to be able to recognize the body upon the soul "Ba's" return. A widely used method of mummification in ancient Egypt was the preserving the dead by leaving their remains in the hot, dry deserts of Egypt to mummify.

Ancient Greeks perceived death as a release of the soul from the body. The soul, which was believed to be part of the mind, was believed to be immortal. It was considered that the soul lived before the birth of the body and would live again after the death of the body in another life. Death was feared by some in ancient Greece out of fear of the repercussions by the gods and goddess or a spirit of someone who died. Others, in contrast, saw death as passage to another existence and a natural occurrence to be embraced. Socrates and Plato believed that ending your life when your usefulness ended was an acceptable practice. Plato wrote,

> It has been proved to us by experience that if we would have pure knowledge of anything we must be quit of the body the soul in herself must behold things in themselves: and then we shall attain the wisdom which we desire, and of which we say that we are lovers; not while we live, but after death; for if while in company with the body, the soul cannot have pure knowledge, one of two things follows either knowledge is not to be attained at all, or, if at all, after death. (Plato, trans. 1976, p. 204)

Socrates' death provides an example of how Greeks wanted to view death as the end of this existence and not to be afraid when it happened. When Socrates was condemned to die for supposedly corrupting the young by asking too many questions, he accepted death gracefully. In the dialogue "Phaedo," Plato recorded Socrates' final evening with his friends. After ingesting the poison hemlock, Socrates commented to his friends,

> And therefore I go on my way rejoicing, and not only, but every other man who believes that his mind has been made ready and he is in a manner purified. And what is purification but the separation of the soul from the body.... I have been told a man should die in peace. (Plato 1976, p. 277)

Socrates then lay down and covered himself with a sheet. Just before he died, thinking of the life he was leaving, he sat up and addressed a friend, "Crito, I owe a cock to Asclepius; will you remember to pay the debt?" and then he lay back down and died (Plato, trans. 1976, p. 278). This readiness and matter-of-fact approach to death by Socrates illustrates how ancient Greeks considered death to be a passage to greater existence than this life, and that one should prepare for death just as one would prepare for any journey. Socrates' remembrance that he owed Asclepius a debt is similar to how one may remember an unfinished task before one embarks on any journey (San Filippo 1998).

Some Greeks believed the soul was reincarnated many times until the soul was pure. Other Greeks believed in an active afterlife with a connection to the living by providing favor or ill will upon the living. Many Greeks believed that after death the soul of the person continued to live in the "underworld" (Edmonds 2013).

Early Roman beliefs in regard to death, dying, and an afterlife were similar to early Greek beliefs. The dead were either buried or cremated. Poor citizens were often buried in a common grave, without a ceremony, and at night. However, the more prominent citizens were mourned with style and pomp. Their bodies were laid out for people to come by and pay their last respects.

The Greeks and Romans shared the belief in the dead souls being ferried across the river Styx. The Romans also placed coins on the dead person's mouth to pay the boatman, Charon, who transported the dead across the river Styx. The river Styx, in Greek mythology, was the river that separated the living world and the underworld called Hades.

Ancient Greeks and Romans believed that a proper burial and respect for the gods was important to avoid the ghosts of the dead coming back and/or the gods interjecting themselves into the living world. Out of fear of reprisal by and offended god or goddess, ancient Greeks followed strict rituals to appease the gods and the spirits of the dead. Additionally, Toynbee comments,

> All Roman funerary practice was influenced by two basic notions – first, that death brought pollution and demanded from the survivors acts of purification and expiation; secondly, that to leave a corpse unburied had unpleasant repercussions on the fate of the departed soul. (Toynbee 1971, p. 43)

The burial placement of the dead had some significance. The practice of burying the deceased facing east began as a practice of having the dead face the rising sun (Decker 2010).

Greeks and Romans believed that one's immortality was only assured by the memories of those of the living world. As a result of this belief, monument, tombs, and earth mounds were erected to remember the deceased. Many early Romans would have their tombs erected long before their death. Later in Roman history the dead were often cremated and their cremains would be placed in urns and buried or placed in catacombs. For those who were cremated, often a finger was removed prior to cremation, as part of the practice "os resectum," in order to have a body part to bury (Kyle 1994). Some ancient Greeks and Romans pacified the potential evil that departed spirits might make on the living by providing food for the dead. In some cases, feeding tubes were inserted into the grave, sarcophagus or the urn to provide food and wine to the deceased (Toynbee 1971).

8.4 Middle Ages (Sixth to Eighteenth Century)

The Middle Ages are considered to have been from the sixth to the thirteenth century. The "Dark Ages" began the Middle Ages. Similar to ancient humans, the expected life span of a person born into the Middle Ages was approximately 35 years old. Death was common and often violent during the Middle Ages. The French historian Philippe Ariès, in his seminal study of death and dying across human history, *Western Attitudes towards Death from the Middle Ages to the Present*, identified three periods of development concerning understandings of death in post-antiquity Western culture (Ariès 1974). The first period is considered to be between the sixth and the early twelfth century, the time of the Dark Ages. The second period is identified as being between the later twelfth century and the seventeenth century. This includes the periods known as the Renaissance and the Reformation. The third period began toward the late seventeenth century and has run through the twentieth century. Attitudes toward death changed significantly during this final period and can be subdivided into two periods: the seventeenth century through the nineteenth century, and the twentieth century (San Filippo 1998). Ariès additionally considered that people's beliefs and practices concerning death are changed over time based upon their experiences and understanding of death. Ariès named these changes in death beliefs and practices as periods in which death was considered to be a "tame death," "one's own death," "thy death," and "forbidden or wild death" (Ariès 1974; Wood and Williamson 2004).

Ariès considered the "tame death" period to a period in the late antiquity and early Middle Ages. According to Wood & Williamson, the Middle Ages, was a period

> when material conditions were unimaginably horrid and death was a common event. War, famine, pestilence, and childbirth made living a perilous endeavor. A span of 30 years often constituted a full life. The decline of the Roman Empire returned urban populations

> to the familiarity of towns and villages. Roads declined, and people did not travel long distances, usually living in one location for the entirety of their lives. If death was "tame," it was because people died frequently, in plain view of their townsmen or fellow villagers; in such times, it would have been difficult to die a private death. (Wood and Williamson 2004, p. 4)

During the Middle Ages, effective sanitation and hygiene practices were not practiced to control disease due to the rudimentary medical knowledge of public safety and welfare. The Middle Ages was a period of strife with wars and plagues an everyday part of life. The multiple wars of this era were the Crusades, the Hundred Years' War, the French War of Religion, the 30 Years' War, and the Deluge (A8). The Crusades provided the clash between the Christian and Islamic faith. During the Middle Ages, until the Reformation, the Roman Catholic Church and its teaching were the accepted source of knowledge and hope concerning dying, death, and afterlife beliefs. A great part of society was controlled by religious teachings of the Church and these teachings were used to control social and personal behavior.

Death was accepted as enviable but was still feared during the Middle Ages. People dealt with death as a community. Medical practice during the Middle Ages was rudimentary and therefore death was often prolonged and painful. This prolonged approach to death allowed the dying to prepare for their death by putting their affairs in order and confessing their misdeeds and sins before they died (Bynum and Freedman 2012). Medieval people believed that individuals had a premonition of their own death as they were in the dying process. Sudden, non-violent or non-medical related deaths were often viewed superstitiously since they did not follow the painful process of dying which was normal for so many people in the Middle Ages. The fears associated with dying and death heightened during the mid-1300s as a result of the Black Death pandemic that killed an estimated 75-200 million people in Europe (Health 2001).

According to Ariès, during the "tame death" period there were four basic characteristics associated with a "tame" death (Ariès 1974):

1. The dying person would be in a supine position, often on a bed. Christians usually lay face-up toward heaven.
2. The dying person presided over her/his own death. The dying person was aware of the religious rituals and customs. The dying person controlled when the priest would be called and when family members could pay their respects.
3. Death was not hidden. It was a public event with family and friends, including children, present with the dying person. It was acceptable to be surrounded by family and friends.
4. Death was considered normal and there were no "theatrics" or a "great show of emotions" on the part of the friends and family.

In the Middle Ages, a person's grave was only temporary. Because the graveyards became overcrowded, after the body had decomposed the bones of the deceased were exhumed and stored in a charnel house close to the cemetery (Dizdar 2010). A charnel house was a building or vault that housed the bones of the dead and was usually close to a church.

The practice of burying the deceased facing east continued from antiquity. The Judeo-Christian societies continued this practice. The Judeo-Christian practice was based upon the belief that Jesus would come from the east.

Ariès observed another change to society's view of death during the eleventh and twelfth centuries. It changed from a "tame death" attitude to a "one's own death" perspective in which people saw their connection with nature by accepting the fact that all living things die, most importantly including themselves. According to Ariès, "the twelfth century reveals the importance given throughout the entire modern period to the self, to one's own existence, and can be expressed by [the] phrase, la mort de soi, one's own death" (Ariès 1974, p. 55). "The act of dying became an important personal experience. A belief in a personal afterlife became more important than what happened to others after death" (San Filippo 1998, p. 11).

According to AC, "one's own death" was personalized in that the individual was considered more important than the death of others. He identified four indications in society's changes in attitudes practices surrounding death:

1. According to early Christian belief in the "Last Judgement," believers and non-believers would be separated at death during God's judgment of the dead. A change in the meaning of the Last Judgement occurred during the "one's own death" period. In the age of "one's own death," God's judgment occurred after death based upon weighting one's good and bad deeds to determine whether the deceased would go to Heaven or Hell.
2. Christians believed that one's deathbed behavior and their consideration of their deeds in life made the moment of death more significant in its impact on the judgment of God after death.
3. People being present at the death of another continued to be important but it was for a different reason. People now would be present not to witness the death but to witness the moment before judgment following death.
4. Art forms that depicted artifacts of death, such as skeletons and corpses, became more prevalent. Personal tombs became more prevalent. Death, and the dying and final disposition of the body became more personal as a reminder of the person's life.

During the later centuries of the Middle Ages, death took on a more romantic perspective. Many scenes in art and literature were associated with love, and with Thanatos and Eros – the god of the dead and the instinct of death and the goddess of love and the instinct of life. According to San Filippo (1998), death was romanticized in its depiction as a human companion in art and literature. Dying and life after death were believed to be beautiful, peaceful experiences. One romantic depiction of death compared dying with the emergence of a butterfly from a cocoon. DeSpelder and Strickland stated, "(t)he old notions of Heaven and Hell that had so motivated people in an earlier time were replaced by a hoped for immortality of the soul and an eventual reunion of loved ones in an afterlife" (DeSpelder and Strickland 1983, p. 60). Mozart, in a letter to his father in 1787 shared his romantic view of death:

> As death, when we come to consider it closely, is the true goal of our existence, I have formed during the last few years such close relations with this best and truest friend of mankind, that his image is not only no longer terrifying to me, but is indeed very soothing

> and consoling! And I thank my God for graciously granting me the opportunity… of learning that death is the key which unlocks the door to our true happiness. (Anderson 1966)

The Middle Ages began to close with the advent of the Renaissance, between the thirteenth to fifteenth century. During the early Renaissance, death became both feared and routine as a result of the prevalence of the "Black Death," or bubonic plague. The Renaissance was followed by the Reformation, which took place approximately between the sixteenth to seventeenth centuries. The life expectancy of Western human beings during the Renaissance and Reformation improved slightly. Humans were living into their forties. Medical science also continued to advance. It was during the Renaissance that Leonardo da Vinci dissected corpses and recorded his anatomical findings and *The Book of Healing and the Canon of Medicine* was written and published by Avicenna of Persia. The Renaissance was also marked by the development of the Guttenberg press and a renewed interest in the arts, sciences, and literature.

Also during the Renaissance the Catholic Church introduced a third option to the beliefs of what happens when a person dies. Prior to this time it was believed a person either went to Heaven or Hell upon her or his death. The concept of a Purgatory was introduced as another disposition of the soul (Dizdar 2010). Many of the art forms, reborn during the Renaissance depicted the souls of the dead now residing in Heaven, Hell, or Purgatory.

As commented earlier, the Catholic Church was a powerful social architect during the Middle Ages and the period of the Renaissance. Christian dying and burial practices were opportunities for Christians to remember that death was not the end of a person's existence. This remembrance of a life after death provided hope to the Christian faithful. Visiting the dying, as discussed in Ariès, was an important social practice even though many feared the contraction of a disease from the dying (Ariès 1974).

The Islamic faith, which had gained influence in Western Europe following the Crusades, had its own death practices. Cleanliness, in the name of Allah, was a central part of the Islamic faith. The bodies of the dead were thoroughly washed with water. The female dead were washed several times with water and berry leaves and camphor. Once the dead were washed, they would be placed in linen for burial. The washing and cleansing of the dead was to honor God and as a preparation for the deceased to enter paradise.

The remembrances to the dead were mostly created for the wealthy. The common person was usually buried in a graveyard without a marker or headstone. Grave sites of the wealthy were often adorned in artistic depictions of the deceased. The graves and tombs became places the bereaved could come to mourn. According to Dizdar, there were three major structural aspects to the tombstones of medieval time (Dizdar 2010). The first element was the artistry of the tomb chest – the vault or chamber a body was interned. The tomb chests were artistically decorated, similar to the ancient sarcophagus. The second element were the "canopied tomb-niches," similar to the ancient catacombs. These niches were artistically decorated with mosaics and paintings above the tomb chests and stones. The third element was the artistry within the tombs of the dead. The art represented the dead person's death bed scene in different forms from a simple engraving to the more sophisticated sculptures of the deceased.

The Protestant Reformation, which began during the sixteenth and eighteenth century, created some uncertainties about death and dying as a result of the Reformation's emphasis on the individual nature of a person's salvation. The control of the Catholic Church on Christians was usurped as a result of the Reformation's focus on individuality. Additionally, during the seventeenth century social thought began to shift from a theocratic approach to an emphasis on the advances of the sciences and medicine in daily life and death.

Knowledge of the human anatomy and medical knowledge and practices was more readily shared as a result of the printing press. William Harvey published *An Anatomical Study of the Motion of the Heart and of the Blood in Animals* which leads to an understanding and future research into the human cardiovascular system. Blood cells and bacteria also began to be studied as a result of the invention of the microscope.

During the seventeenth century, there was a medical and social belief, by some, that when a person died their body retained some type of awareness. This resulted in a renewed practice of preserving the corpses of the dead. In contrast, for those who continued to prescribe to the Catholic teaching, it was believed that when the body died the soul was released into an afterlife. As a social perspective, it became the practice that when a person died a physician would declare the person dead (Library Index n.d. a).

As the seventeenth century came to a close, the period of death being considered "one's own death" began to evolve to what Ariès calls the period of "thy death." At this same time, Western civilization began to expand to the New World and move into the pre-modern age.

8.5 Pre-modern Age (Eighteenth and Nineteenth Century)

During and after the eighteenth century, the Western world expanded to include the migration of people to the "New World" that would eventually include the United States of America. Although the New World would create some if its own attitudes, beliefs, and practices concerning death and dying, the early beliefs from Western Europe would also be brought to the New World. Medical science knowledge continued to expand. During the eighteenth century, the value of citrus fruit for the prevention of scurvy was discovered, the first successful appendectomy was performed and a vaccine for smallpox was found. However, despite the evolving medical skills and knowledge to prevent or treat fatal illnesses, diseases, or treat many injuries, death continued to be an accepted and common occurrence in life. People during the pre-modern age viewed death as a fact of life and lived their lives in preparation for death and judgment after death. Children were also taught to prepare for death.

Ariès observed that in the eighteenth century the period he calls "thy death" began to emerge (Ariès 1974). In the "thy death" period death was "exalted" and often "dramatized." Death was thought of as being "disquieting" and "greedy" (Library Index n.d. b). People had less concern for their own death and begin to focus more on the death of others, "la mort de toi." This was a significant shift in death attitudes from "one's own death" to "thy death." According to San Filippo, concerns about one's own death were overshadowed by a social awareness of the death of others (San Filippo 1998).

According to Ariès, the "thy death" period was marked by the following observations:

1. Attitudes regarding death ranged from death being exalted, to being feared and in some cases worshipped by others. Death was dramatized in art and literature, in contrast to the romanticism of death in the late Middle Ages.
2. People participated in the social and ritualistic practices of death and dying but the former purpose of being a witness of the dying person's passing changed. People were now present to mourn the passing of the dying person. Although mourning was practiced in earlier ages as part of the death ritual, it became more dramatic and spontaneous and often was accompanied by excessive displays of emotion, such as wailing.
3. Death was no longer accepted. Death was lamented and the bereaved were preserved the memory of the deceased in rituals and keepsakes.
4. An important aspect of the period of "thy death" was the memorialization of the dead. The memorialization practices for the dead lead to a renewed consideration of the final resting place for the dead and markers for these resting places.

Many early New World settlers, when considering death and afterlife, believed in the predestination of the soul. Therefore, nothing could influence the fate of the dead after death, and the dying and funeral practices reflected the predestination belief. They believed there was no significance to the body after the person died; therefore, there was no need for bodies to be buried in a sacred location. Cemeteries were called a "burying yard," "burying ground," "burying place," "bone yard," and "graveyard" (McGowan 2008). This was a departure from the earlier terminology for cemeteries, based upon the early Greek, in which cemeteries were a "sleeping place." Early pilgrims viewed the burial grounds as meadows as opposed to sacred ground. Markers were placed on grades with simple words.

In the nineteenth century, people were beginning to live longer. The average life span of a person grew to the late 40s and early 50s. This was a due, in part, to the continued advancement of new medical knowledge and practices. Anesthetics were more generally used in surgical and dental procedures. The stethoscope was invented and the first human transfusion of blood took place. Additionally, the syringe was invented and Luis Pasteur identified that germs were the cause of disease and, with Robert Koch, developed the germ theory of disease. Vaccine for different diseases, such as cholera, anthrax, rabies, typhoid fever, and the Bubonic plague were discovered. Tetanus and diphtheria vaccines from antitoxins were also discovered. With these advances in medical science, people began to live longer lives.

In the mid-nineteenth century, Western society entered the period Ariès describes as the "forbidden death" period. People began to consider death "shameful and forbidden." During this time, death was not openly spoken of and when someone was dying they were not told of their pending death. This was justified by trying to spare the person pain. In many ways we continue this by isolating the dying from the living and not speaking openly about death and dying. In contrast to death being exalted or dramatized in the previous "thy death" period and the control the dying person had on his or her death, the "forbidden death" period took that control away from the person and the dying were left to the perils of early modernity medical practices and the wishes of others.

The nineteenth century was marked by the Victorian Age, roughly from 1837 through 1901. Queen Victoria of England became the face of the elaborate grieving and death practices of the nineteenth century as a result of her grieving the death of her husband, Prince Consort Albert. The Victorian age represented a time of history in which practices and rituals associated with death were an important aspect of social change in the Western world. A "cult of death" was prevalent in the Victorian age through the use of icons and rituals to remember the dead and express the grief of the bereaved (Library Index-19th n.d c).

During the Victorian age, the mourning periods, the attire of the bereaved, and the funeral and internment of the deceased became more elaborate. The rule of the funeral director grew in stature, as the person to direct the extensive Victorian funerals. Many of the funeral directors grew into their roles as former carpenters who built coffins or livery keepers who rented out the funeral horses and carriage (Hotz 2008).

During the mid-nineteenth century, graveyards began to be beautified and families would picnic in the cemeteries. Before the Civil War, family members and friends would be responsible for the care of the dead. The dead body would be laid on a board and washed by a female member of the family. The body then would be wrapped in a burial cloth. The undertaker, often a carpenter, would make a simple wood coffin with a lid. He would bring it to the home of the dead person and place the corpse in the coffin. The minister would then perform the appropriate ritual, dependent on the deceased religious beliefs, with the family of the deceased and friends in attendance. The undertaker would then take the coffin to the graveyard to be buried.

Embalming practices resurged during the Civil War years in order to preserve the dead soldiers' bodies for transport home. Caring for the dead became a business by the late nineteenth century. Embalming took place at the funeral home instead of the home of the deceased. Embalming was promoted as a public health practice. Caskets, formerly referred to as coffins, were made in various styles to fit with the deceased and the family of the deceased's desires (Schroeder-Lein 2008).

During the nineteenth century, the dying process was considered as a time to allow the dying person to take care of her or his final affairs and prepare spiritually for death. Death was believed, by many, to be the beginning of a new existence in which the deceased would wait for other family members to join them upon their death. Mourning was not considered to be as much for the loss of a loved one but the indefinite time between the death of the loved one and the eventual reunion with the loved one in the afterlife.

A common bereavement practice in the nineteenth century was for bereaved family and friends to have their pictures taken with the deceased, and to create memorial cards and jewelry – such as a locket with lock of the deceased's hair, to memorialize the death of a family member or friend. During this period in history, death was an accepted part of life and in most cases not hidden from others. Most people died at home with family and friends around them. In many cases, the dead's passing was heralded as the spirit moving on into an afterlife.

8.6 Modernity (Twentieth and Twenty-First Century)

During human history, death has always been present and a part of normal life, regardless if it was accepted, feared, revered, or romanticized. People of the twentieth century and the beginning of the twenty-first century lived, and are living, longer than their ancestors. The average life span is now 78 years old. Ariès' "forbidden death" became more prominent as death was fought by the advances of medicine to prolong life, the dying were most often confined to hospitals instead of dying at home, and the final care and internment for the deceased was relegated to the funeral industry.

Attitudes about death and dying began to change during the twentieth century and became more remote and a subject that was not discussed. During the twentieth century death was normally concealed in hospitals and death became a fearful occurrence. The fear of death and dying, as reflected in Ariès' "forbidden death" period, was exacerbated by a reduced confidence in organized religious doctrines regarding death and an increase in medical science's intervention in the dying process. Scientific advances also increased the secularization of social and intellectual thought, supplanting religious doctrines. Modern scientific advances have caused many people to lose touch with longstanding religious and cultural beliefs and practices, which have left a void in many people's ability to deal with death (San Filippo 1998). According to Wood & Williamson,

> Thus Ariès proposes an alternative historical scheme in which death had gradually become less familiar to the living, moving initially from what he calls the "tame death" of the ancients and the early Middle Ages to the "wild [forbidden] death" of the modern world. (Wood and Williamson 2004, p. 2)

Dylan Thomas reflected how death should be fought in the modern era when he wrote in the poem, *Do Not Go Gentle into that Good Night*, "Rage, rage against the dying of the light" (Thomas 1952).

Ariès concluded that there were two social trends in the twentieth century that impacted death practices and customs. These two trends were:

1. Hospitals became the place to go or be sent to die in contrast to the home often being the place one went to die. Advances in medical science and treatment required specialized facilities and equipment and hospitals had what the dying person needed to stay alive as long as possible.
2. The growing belief that life should be happy, therefore, death was denied because it was sad and unpleasant. As a result of this belief, children were shielded from death by the use of various euphemisms to describe death and dying.

Most people fear death at some level but because of the “forbidden” nature of talking about death, it is not often a topic of conversation. People’s fears of death are associated with the dying process, being dead, and what happens after death. Many people fear death and/or dying. These fears can be summarized as fearing the pain and loneliness of dying, the fear of non-existence, and the fear of the unknown after death. The most common fear, in Western society, is that the process of dying will be painful, prolonged, and will reduce the quality of life. Many also fear dying alone. Another fear is that of not existing and no longer participating in life. Many people cannot conceive life without their involvement. Humans also fear death because they view death as an annihilation of their person, a radical personal transformation, a threat to the meaningfulness of life, and a threat to the completion of life projects. Not knowing what happens after death has been linked both to eternal questions of mortality and immortality and to the fear of the unknown by many human beings.

During the latter part of the twentieth century, significant changes in the attitudes and approaches people had for death began to change with the advent of hospices for the dying and publications of books and articles on the topics of death and dying. Dame Cicely Saunders created the first modern hospice in London in 1967. In 1969 Dr. Elizabeth Kübler-Ross wrote the seminal book *On Death and Dying*. Dr. Kübler-Ross identified that five stages that dying patients often passed back and forth through in their journey to death. These stages are denial, anger, bargaining, depression, and acceptance (Kübler-Ross 1969). With acceptance the patient has come to accept their circumstance and inevitability of his death. These new approaches to death began to bring death out of the shadows of fear and slowly into a period of acceptance.

With the growth of the hospice movement in the Western world and as Kübler-Ross’ teaching became more mainstream, many dying people were discharged from hospitals and returned to their home or a hospice to prepare to die. As family members became more involved with their dying loved ones’ care and comfort, death became better understood and accepted in Western society. The final disposition of the deceased continues to be primarily burial or cremation.

Additionally, in the twentieth and into the twenty-first century, the social positions concerning euthanasia and the advances in medical sciences to prolong life have become the concerns of Western societies. According to Foley, defining life is more difficult than defining death,

> Adopting a single definition for life would have heavy implications for divisive issues such as abortion, birth control, in vitro fertilization, and stem cell research. If the law defined life to begin at conception, for example, the legality of all of these activities would be brought into serious question…
>
> The legal definition of death, by contrast, is arguably less political, due to the genesis and nature of the definitions of death that have been devised thus far. Historically, death was determined by the cessation of heart and/or lung function (cardiopulmonary death). Later, the law expanded the definition of death to also include cessation of the functioning of the entire brain (brain death) (Foley 2011, p. 8).

The Uniform Determination of Death Act (UDDA) is the definitive voice in how death is determined by the legal community and medical communities. The act was written in 1980 and was approved by the American Medical Association and the American Bar Association as a model for the states of the United States of America to adopt as a uniform definition of death. All of the states have adopted the UDDA with some states adding some additional criteria for determining death.

According to the UDDA, there are two methods for ascertaining death:

1. The irreversible cessation of circulatory and respiratory functions
2. The irreversible cessation of all functions of the entire brain, including the brain stem

As medical knowledge continues to grow and the medical skills and technologies continue to be refined, the guidelines presented in the UDDA provide guidance when dealing with issues concerning organ donation and harvesting, cryonics as a method to preserve the body after death, and legal actions such as criminal cases, torts actions, and estate law.

A 2013 Pew Research Center survey of North Americans' views on end-of-life medical treatments provides a contemporary analysis of US perspectives concerning dying and death. The aging of the US "baby-boomer" population and the advances in medical sciences that are prolonging life have created the need for modern individuals to think about their end of life desires and to share these desires with others. Hafiz identified 12 facts from the Pew Research Center survey on American attitudes about death (Hafiz 2013). These facts are:

1. America's elderly population has more than tripled in size over the last century.
2. Over a quarter of U.S. adults haven't really thought about future medical treatment at the end of their lives.
3. Most Americans are expected to live well into their seventies.
4. The majority of U.S. adults would want to stop medical treatment if they were suffering a lot of pain without hope for improvement.
5. About one third of Americans would fight for life no matter what.
6. A majority of adults believe in a moral right to suicide, if a person was in great pain with no hope of getting better.
7. There is large disagreement on the issue of the legitimacy of physician-assisted suicide.
8. Race greatly affects the answers of whether people would want to fight to stay alive in great pain and with little hope of improvement.
9. Death has affected most people in the United States.
10. A majority of U.S. adults believe that an infant should receive as much treatment as possible in the case of a life-threatening birth defect, even if parents want to refuse treatment.
11. Religion and race greatly affect people's response to the idea of a moral right to suicide in case of great pain.
12. Optimism for the future is harder to find in the older generation

The presence of death in our society will always be a constant reminder of our personal mortality. Medical sciences will continue to discover new practices to improve and prolong life. However, eventually all organic material dies and that cannot be stopped. Society's approach to death, dying, and bereavement will continue to reflect the collective attitude of society concerning the individual's mortality and beliefs in life after death.

Steve Jobs at the Stanford University graduation ceremony in June 2005 summed up a reflective way to look at the final reality that death is as a part of life,

> No one wants to die. Even people who want to go to heaven don't want to die to get there. And yet death is the destination we all share. No one has ever escaped it. And that is as it should be, because Death is very likely the single best invention of Life. It is Life's change agent. It clears out the old to make way for the new. (Jobs 2005)

Robin Williams provided his students the film Dead Poets Society with a view of death and the importance to live "extraordinary" lives as they were viewing pictures of long dead school alumni,

> Now I would like you to step forward over here and peruse some of the faces from the past. You've walked past them many times. I don't think you've really looked at them. They're not that different from you, are they? Same haircuts. Full of hormones, just like you. Invincible, just like you feel. The world is their oyster. They believe they're destined for great things, just like many of you. Their eyes are full of hope, just like you. Did they wait until it was too late to make from their lives even one iota of what they were capable? Because you see gentlemen, these boys are now fertilizing daffodils. But if you listen real close, you can hear them whisper their legacy to you. Go on, lean in. Listen. Do you hear it? Carpe. Hear it? Carpe. Carpe Diem. Seize the day boys. Make your lives extraordinary. (Dead Poets' Society 1998)

It is important to understand how our collective beliefs, attitudes, and practices concerning death have developed and how we live with the reality that none of us get out of this life alive. This knowledge can guide society into a fuller life by not being fearful of death but by living life with meaning.

Carpe' Diem

References

Aiken L (2000) Dying, death, and bereavement, 4th edn. Psychology Press, Hove, Retrieved from http://www.ebrary.com

Anderson E (ed) (1966) The letters of Mozart and his family, 2nd edn. St. Martin's Press, New York

Ariès P (1974) Western attitudes towards death from the middle ages to the present. Johns Hopkins University Press, Baltimore

Assmann J (2005) Death and salvation in Ancient Egypt. Cornell University Press, Ithaca, Retrieved from http://www.ebrary.com

Bynum CW, Freedman P (eds) (2012) Middle Ages Series: last things: death and the apocalypse in the Middle Ages. University of Pennsylvania Press, Philadelphia, Retrieved from http://www.ebrary.com

Dead Poets Society [Motion picture] (1998) Touchstone Home Video

Decker S (2010) Why do tombstones often face east? Demand Media, Inc., Retrieved from http://www.ehow.com/about_6671751_do-tombstones-face-east_.html

DeSpelder LA, Strickland AL (1983) The last dance encountering death and dying. Mayfield, Berkeley

Dizdar G (2010) The culture of death in late medieval and early Renaissance Italy. Retrieved from https://www.academia.edu/432885/The_Culture_of_Death_in_Late_Medieval_and_Early_Renaissance_Italy

Edmonds RG (2013) Redefining ancient orphism: a study in Greek religion. Cambridge University Press, Cambridge, Retrieved from http://www.ebrary.com

Foley EP (2011) Law of life and death. Harvard University Press, Cumberland, Retrieved from http://www.ebrary.com

Freud S (1961) Thoughts for the times on war and death. In: Strachey J (Trans.), The standard edition of the complete psychological works of Sigmund Freud, vol 14. Hogarth Press, London (Original work published 1915)

Grof S, Grof C (1980) Beyond death – the gates of consciousness. Thames and Hudson Ltd., London

Hafiz Y (11/21/13) American attitudes towards death: 12 facts from new Pew Research Center Survey. The Huffington Post: The Huffington Post Media Group

Health (2001) De-coding the black death. British Broadcasting Corporation (BBC). Retrieved 13 Aug 2015

Hotz ME (2008) SUNY series, studies in the long nineteenth century: literary remains: representations of death and Burial in Victorian England. State University of New York Press, Ithaca, Retrieved from http://www.ebrary.com

Kübler-Ross E (1969) On death and dying. Collier Books, New York

Kyle DG (1994) Spectacles of death in Ancient Rome. Routledge, Florence, Retrieved from http://www.ebrary.com

Library Index (n.d. a) Death through the ages: a brief overview – The Renaissance [cultural rebirth from the 14th through the middle of the 17th centuries. Early Renaissance, mostly in Italy, bridges the art period during the fifteenth century, between the Middle Ages and the High Renaissance in Italy]. Retrieved from http://www.libraryindex.com/pages/539/Death-Through-Ages-Brief-Overview-RENAISSANCE.html

Library Index (n.d. b) Death through the ages: a brief overview – The Eighteenth Century [1701–1800] Retrieved from http://www.libraryindex.com/pages/540/Death-Through-Ages-Brief-Overview-EIGHTEENTH-CENTURY.html

Library Index (n.d. c) Death through the ages: a brief overview – The Nineteenth Century Retrieved from http://www.libraryindex.com/pages/541/Death-Through-Ages-Brief-Overview-NINETEENTH-CENTURY.html

McGowan S (2008) Death and dying in the 18th and 19th centuries., Retrieved from http://memorialhall.mass.edu/classroom/curriculum_8th/lesson1/bkgdessay.html

Plato (1976) The portable Plato. (S. Buchanan, Ed.). Penguin Books, New York

San Filippo D (1998) The value of the awareness of near-death experiences for reducing fears of death for elderly persons, Doctoral dissertation. Retrieved from WorldCat. (51720750)

Sanford Report (2005) Commencement address delivered by Steve Jobs

Schroeder-Lein GR (2008) Encyclopedia of civil war medicine. M.E. Sharpe, Inc., Armonk, Retrieved from http://www.ebrary.com

Thomas D (1952) The poems of Dylan Thomas. New Directions Publishing, New York

Toynbee JMC (1971) Death and burial in the Roman world. Thames & Hudson, London

Wood WR, Williamson JB (2004) Historical changes of the in the meaning of death in the western tradition. In: Bryant CD (ed) Handbook of death and dying. Sage Publications, Thousand Oaks

Economic Aspects of Death and Dying in Oncology

9

Vlad Dolgopolov

9.1 Economics and Economic Tools in the Analysis of Death and Dying in Oncology

The study of economic issues relevant to oncology, death, and dying is – and should be – an important component of a multifaceted analysis of our healthcare system. This includes the analysis and design of practices and policies of healthcare providers and individual physician and patient-consumer decision-making processes.

In this chapter, we explore economic issues and data that are relevant to healthcare in general, oncological treatment, end-of-life care, and dying, and discuss the frameworks and economic tools available to a medical practitioner for analysis of such issues.

Economics is a social science concerned with decisions about allocation of limited resources to satisfy unlimited wants of individuals, firms, governments, and on a larger scale, nations, and societies. There always existed and there will always exist a chasm between what we have and we want. Thus, we need to make choices about the best use of our scarce resources.

The emphasis on the *best*, or *most efficient*, use of resources is at the heart of economics. All economic actors (or, in other words, participants in economic transactions) prefer to use their limited resources efficiently so that such resources can be stretched to extract the most satisfaction for individuals, the most profit for firms, the highest level of service for governments' constituents, and the most optimal outcomes for societies. Best use of resources will differ based on the objectives of economic actors. What an individual considers to be best may not be the best from the point of view of a government policy maker or another stakeholder in the economic transaction.

V. Dolgopolov
National Louis University, 122 S Michigan Ave, Chicago, IL 60603, USA
e-mail: vdolgopolov@nl.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_9

9.2 Economics of Healthcare: Costs, Trends, and Consequences

9.2.1 Cost of Healthcare and Cancer Care

As a society, we allocate considerable resources to spending on healthcare, including spending on cancer treatment care and end-of-life care. Such spending accounts for some of the highest absolute levels of spending (measured in dollars) and relative levels of spending (measured as proportion of total spending on final goods and services) in the world.

The Centers for Medicare & Medicaid Services (CMS) estimates that in 2013, United States' healthcare spending[1] reached $2.9 trillion, or approximately $9255 per capita, and accounted for approximately one-sixth of our gross domestic product (GDP) in 2013 (CMS 2015). Much of this spending is attributable to spending in the later years in life. For example, CMS attributes 25.2 % of total personal healthcare spending to individuals between the ages of 65 and 84, and another 8.7 % to individuals aged 85+ in 2010, with per capita spending for each group at $15,857 and $34,783, respectively. For comparison, such spending for the 19–44 group is $4098 per capita (CMS 2010).

Cancer-related care accounts for approximately 10 % or more of total healthcare expenditures (Lyman 2007). Approximately 6 out of every 100 adults in the United States reported being afflicted with cancer in 2012–2013 (known as prevalence of disease) (National Center for Health Statistics 2014, Table 42, p. 161), with an incidence rate of new cases estimated at 0.438 % of the total population per year in 2011 (ibid, Table 40, p. 156).

9.2.2 Trends and Outcomes

Over 1960–2013, healthcare spending increased considerably, with national health expenditure rising from $147 to $9255 per capita, and the relative weight of healthcare expenditures growing from 5.0 % of GDP to 17.4 % of GDP as shown in Table 9.1.

For decades, the growth rate of healthcare spending has exceeded the growth rate of the GDP. Thus, healthcare costs increased as a percentage of total national spending. For example, as GDP grew by 7.1 % in 1970, the national health expenditures grew by 10.6 %; and this trend only slowed down in 2009–2013, with growth rates slightly below to slightly above the overall GDP growth rate, as shown in Table 9.2.

This trend indicates a cause for concern. It is clear that healthcare spending has grown considerably over the past 50 years, at a rate much higher than the average

---

[1] National health expenditures includes health consumption expenditure (inclusive of personal health care, administration and net cost of private health insurance, and public health spending), as well as investment in health care.

Table 9.1 Comparative data, U.S. national health expenditures

Category/year	1960	1970	1980	1990	2000	2009	2010	2012	2013
National health expenditures, in billions	$27.4	$74.9	$255.8	$724.3	$1378.0	$2505.8	$2604.1	$2817.3	$2919.1
National health expenditures as percent of GDP	5.0	7.0	8.9	12.1	13.4	17.4	17.4	17.4	17.4
National health expenditures per capita	$147	$356	$1110	$2855	$4881	$8175	$8428	$8996	$9255

Source: National Center for Health Statistics (2014), Table 102, p. 302

Table 9.2 Average annual percent change from previous year in GDP and health expenditures

Category/year	1970	1980	1990	2000	2009	2010	2012	2013
GDP	7.1	10.3	7.6	5.6	3.8	3.8	3.9	3.7
National health expenditures	10.6	13.1	11.0	6.6	6.9	3.9	4.0	3.6
National health expenditures per capita	9.2	12.0	9.9	5.5	5.9	3.1	3.3	2.9

Source: National Center for Health Statistics (2014), Table 102, p. 302

for all other spending. At the same time, the slowdown in the last 5 years also indicates that we may have reached a steady state in healthcare expenditure dynamics. The recent slowdown in healthcare inflation may also be just a temporary phenomenon, explained by the recession and the loss of healthcare coverage by the unemployed workers. However, we also suspect that the Patient Protection and Affordable Care Act (PPACA) of 2010, commonly known as Obamacare, may have contributed to a more permanent reduction in healthcare inflation through its focus on expanding coverage and curbing costs.

Even if the healthcare spending is stabilized at approximately 17.4 % (or a little more than one-sixth) of US GDP (and that is an assumption that remains to be tested by future data), this level of spending by far exceeds comparable spending of other industrialized nations. Canada, for example, spent only 10.2 % of its GDP on healthcare in 2013 (and appears to have spent only 10 % in 2014); Germany spent 11.0 %; Japan – a country with a much older population than the United States – spent 10.2 %; the United Kingdom, 8.5 %; and France, 10.9 % (OECD 2015).[2] The

---

[2] Per OECD methodology, the United States spends 16.4 % of its GDP on healthcare in 2013, rather than 17.4 %, as calculated by the US National Center for Health Statistics.

average for healthcare spending for all nations that belong to OECD, a group that generally includes some of the most industrialized and prosperous countries in the world, is 8.9 % of GDP. The United States spends approximately 80 % more than average on healthcare and almost 50 % more than the second-highest spender in the OECD group, the Netherlands.

Are we paying more for exceptional health outcomes? Unfortunately, this does not appear to be the case. The United States underperforms in some of the most common measurements of health outcomes, such as life expectancy at birth (a child born in the United States in 2013 could expect to live to 78.8 years of age on average, as compared to Canada's 81.5 years, France's 82.3 years, Japan's 83.4 years, and the OECD average of 80.5) and infant mortality rate (6.0 deaths per 1,000 live births in 2012, as compared to Canada's 4.8, France's 3.6, Japan's 2.1, and the OECD average of 4.1) (OECD 2015).

9.2.3 Allocation of Resources in Society and the Role of Markets; Healthcare Markets as a Special Case

Economists posit that certain structures and institutions contribute considerably to the most efficient use of resources. For example, economists consider *markets* to be one of the best ways to achieve optimal allocation of resources, with buyers and sellers coming together to determine an equilibrium price for goods and services traded in the markets with little to no outside interference. The price is established at the level where the quantity demanded is exactly equal to the quantity supplied, and price will fluctuate according to the changes in factors that influence demand or supply. If the sellers make profits that are higher than the average in other marketplaces, more providers will enter the market and drive the price down; if the sellers' profits are lower than average or if they lose money, they will exit the market, and the price will go up.

Efficient marketplaces, however, require certain conditions to exist. First, the *rules of the game*, such as the structure for assuring property rights and efficient trading mechanisms must be in place, so that both the seller and the buyer can engage in transactions freely, without fear of loss of their property yet with little undue interference that creates artificial barriers to the market functioning. Second, both the seller and the buyer must have the same level of knowledge about the characteristics of goods or services being traded; this condition is known as *symmetrical information*. Third, *competition* must exist on both sides, as unregulated marketplaces with one or few sellers (or one or few buyers, for that matter) will result in artificially high (or in some cases, artificially low) prices and inefficient transfer of resources from one marketplace participant to another. Finally, decisions made by economic actors *should not impact third parties*. In other words, one's decision to take an action should not impose a cost or confer a benefit on anyone else but oneself.

How different are the healthcare markets from the marketplace described above? In one word: considerably. First, healthcare providers are heavily regulated by multiple agencies on the federal, state, and local levels, with some private and quasiprivate regulators and organizations involved in the process (such as The Joint Commission, or JCAHO). Field notes that such oversight is widely acknowledged as necessary, since human lives are at stake. The debates, however, revolve around the optimal way of structuring the regulations and the regulating agencies, which often operate without coordination, and may create a regulatory maze for bringing new treatments to the market (Field 2008).

Second, the providers and the patients have vastly different knowledge available to them, as described in the later part of this chapter – which can be an even greater issue in the markets for health insurance.

Third, local markets for healthcare tend to be dominated by large networks of healthcare providers and large insurance companies. Federal and state governments and agencies are also some of the largest buyers and providers of healthcare and related services.

Finally, decisions that individuals make have an impact on the rest of us: the uninsured transfer costs of their treatment onto providers and insured individuals; those receiving flu vaccinations provide a benefit to the rest of the society by reducing the risk of their getting sick; and perhaps most importantly, insurance reduces or eliminates the incentive to shop for better healthcare prices by transferring the cost of treatment to someone else.

Thus, healthcare markets are complex and tend to be less than fully efficient. They function differently from typical markets. The tools of economic analysis can still assist healthcare practitioners, administrators, and policy makers to navigate such complex markets with greater efficiency.

9.3 Cost-Benefit Analysis

9.3.1 The Cost-Benefit (CBA) Approach

Cost-benefit analysis (CBA) is perhaps one of the best-known and most-used tools in economics, public policy, and business. In fact, the US government has since 1981 required all new federal regulations to undergo the cost-benefit analysis process to demonstrate their value to the taxpayers.

The approach sounds simple: we compare the costs and the benefits of various choices, and choose the one that maximizes the difference between benefits (B) and costs (C), discarding those where such difference (B-C) produces a negative result. The difference on its own represents an absolute value. To improve this analysis even more, we may simply take the ratio of benefits to costs (B/C); discard those choices resulting in a ratio of less than 1; and select the choice with the highest benefit-to-cost ratio from the remainder.

9.3.2 Assigning Monetary Values to Benefits and Costs of Treatment

In practice, however, cost-benefit analysis tends to be complicated. The nature of the cost-benefit analysis requires us to compute both costs and benefits in the same unit of measurement (e.g., dollars). The costs are easily tallied in dollars, but the benefits are normally made through gains in health outcomes. Such nonmonetary benefits, which may include gains in life years or in quality of life, will then require translation into a monetary equivalent.

How do we value a life then? This question is morally distasteful to many. However, economists and policymakers would argue that the decisions people make and the policies we develop both at national (macro) and organization/individual (micro) levels actually require us to engage in some level of valuation of a human life. More importantly, these studies of the value of statistical life (VSL) also allow us to engage in marginal analysis of costs of reduction of risks to human lives. Table 9.3 summarizes some of the major approaches to valuation of life for the purpose of CBA.

Cropper and colleagues, in summarizing the results of multiple meta-analyses of US hedonic wage studies conducted over 1974–2002 and normalized to $2009, noted estimates of valuation of statistical life (VSL) that ranged from $2.0 million to $11.1 million (Cropper et al. 2011). For stated preference/contingent valuations studies, estimates ranged from $2.7 to $8.5 million. Thus, valuations in the middle of this range would be considered reasonable by most economists.

Table 9.3 Selected approaches to life valuation

Approach	Description
Human capital/ wage-based valuation	This methodology assigns a value to human life based on expected economic productivity of an individual. Not surprisingly, lives of highly educated and professionally successful individuals earning high wages will be valued very highly, while the lives of those of retirement age will be valued lower.
Willingness to pay	Estimated through studying decisions in which individuals demonstrate willingness to pay for reducing risks to their life. For example, if an individual is willing to pay $1000 for a medical procedure that reduces the risk of death by 0.01 %, that decision places a valuation of $1000/0.01 % = $10 million.
Willingness to accept	Estimated through studying the individuals' willingness to accept situations associated with higher risks to life and health for a certain premium, such as high-risk occupations (firefighters, policemen, etc.). Many US government agencies use the method of compensating wage differentials (wage premiums associated with risks of fatal injuries in the workplace) as the method for estimating the value of mortality risk reduction (Cropper et al. 2011).
Stated preferences/ contingent valuation	In this approach, the researcher poses hypothetical questions about premiums the individual is willing to pay for various reductions in risk to their life, and collects individual's stated preference for analysis.

9.3.3 Intertemporal Nature of Costs and Benefits

We encounter a disconnect in timing between incurring costs and receiving benefits of a decision, when costs are incurred now (cost of providing treatment, which may include cost of chemotherapy, surgery, hospital stay, ambulatory care, follow-up care, medication, possible lost wages, pain and suffering associated with undergoing invasive treatment, and other direct and indirect opportunity costs) but benefits are derived in the future over many years (such as improved quality of life, extended life expectancy, higher productivity, and higher wages through lower absenteeism in the workplace).

Future costs and benefits are also not certain. They represent our best estimate as to what may happen in the future. This will require us to engage in the discounting of future costs and/or benefits to the present day, thus making decisions about the appropriate discount rate to be used in the present value formula:

$$\mathrm{PV} = \sum_{t=1}^{t=n} \frac{\left(B_t - C_t\right)}{\left(1+d\right)}$$

In this formula, *Bt* is the benefit derived in time period *t*; *Ct* is the cost incurred in time period *t*; and *d* denotes the discount rate applied to the future benefits and costs over *n* time periods. Clearly, the higher the discount rate, which may be driven by the higher uncertainty of a benefit, the lower the net present value of future benefits and future costs of a choice.

Cost-benefit analysis may be used to evaluate a single choice or multiple choices. Most of us perform a version of cost-benefit analysis in our minds on a daily basis without realizing it when making decisions that involve choices.

9.3.4 Cost-Effectiveness Analysis (CEA)

Cost-effectiveness analysis (CEA) attempts to establish a specific performance threshold for benefits to be achieved by a project or medical intervention, and similar to the CBA methodology, CEA measures the total direct and indirect costs of attaining such a goal. To eliminate the issue of converting benefits to monetary values, the benefit goals are expressed in nonmonetary terms, such as achievement of a specific live expectancy for the population, number of lives saved, or reduction of incidence of disease in population. The change in costs is then compared to the change in performance in the metric of interest to obtain a CEA ratio, and the projects are prioritized based on their ratios.

9.3.5 Quality Adjusted Life Year

The cost-utility analysis (CUA) is a special case of the CEA approach, and is utilized extensively in healthcare. Prior to jumping into the discussion of the methodology of cost-utility analysis, it will be useful to review the concept of quality adjusted life year (QALY). QALY is a measure of health improvement widely used in assessing cost-effectiveness of therapies both in the United States and the United Kingdom, and thus, in making decisions about efficient allocation of scarce resources in healthcare interventions (known as productive efficiency). QALY allows us to recognize that quality of life matters greatly in the assessment of efficiency of treatments; and that gaining a year of life that is fully functional and allows the individual the full freedom of productive and leisure activities and free of pain and suffering is much more valuable than gaining a year of life confined to a bed and spent in constant pain.

The basic approach of QALY is to recognize a scale of health states that range from zero to one, where zero corresponds to being dead, and one corresponds to being in perfect health. The other health states can be rated as between zero and one. In rare circumstances, it is possible to rate a state of health as a negative QALY value (i.e., worse than the state of death), thus subtracting from total QALYs accumulated over period studied. QALY scales are constructed in such a way that they can be aggregated for analysis (Weinstein et al. 2009).

For example, when comparing two cancer interventions which result in an average gain of 2.0 years (Intervention A) and 3.0 years (Intervention B) of life expectancy for intervention recipients, we may be tempted to identify Intervention B as a superior choice. However, if Intervention A results in an aggregate QALY gain that exceeds that of Intervention B through allowing the patient higher quality of life and better state of health, we may argue Intervention A to be a better choice from a utilitarian point of view, and likely, from a point of view of many patients as well.

The QALY approach has its limitations as well, and has attracted its share of criticism. First, QALY health state valuations are those of policy makers, and not those of people on whose behalf decisions are being made (and who may not be fully able to assess the implications of the state of health if they are not currently in that state of health). Second, QALY computations by their design imply that the value of an intervention is proportional to the recipient's capacity to benefit (Nord et al. 2009). For instance, younger patients who may gain more years of life at higher QALY rating from a treatment will be favored over older patients, thus raising concerns about societal equity issues. Another concern yet is that chronic conditions, such as cancer, will be discounted in favor of prevention of fatal accidents in people with normal health (ibid).

There is also some disagreement on whether QALY is an appropriate measure for evaluating health states for individuals receiving end-of-life care. Round (2012) notes that the arguments typically advanced against using the QALY approach include: lack of expected survival gain from an intervention and thus inappropriateness of a time-based measure such as QALY; priority of other dimensions of quality of life over health status; measure that uses death as an anchor point invalid when death is imminent; unstable patient preferences and time valuation at the end of life; and disconnect between cost-effectiveness and desirability of certain treatments. Round (2012) argues that while such arguments have some weight, there is still no acceptable robust alternative to QALY that can be used for policy- and decision-making in valuing and assessing the health states of those receiving end-of-life care, and using such data for allocating appropriate resources.

9.3.6 The Cost-Utility Analysis Approach

Cost-utility analysis (CUA) is an alternative approach to cost-benefit analysis, which does not require conversion of benefits derived from medical intervention into dollars, and thus allows us to avoid the often difficult and controversial exercise of computing the value of statistical life or value of incremental gains in life. Rather, cost-utility analysis measures the costs of gains in QALYs made in various healthcare interventions, and considers the total costs and the cost per QALY gained.

By way of illustration, when engaging in CUA, we may compare two cancer interventions that on average result in gains of 2.3 and 2.5 quality adjusted life years, and cost $20,000 and $2,000,000, respectively. Intervention A is somewhat less effective in terms of total QALYs gained (8 % less effective, as measured in QALYs), but it costs much less than Intervention B. Intervention A's cost is $8696 per QALY and Intervention B's cost is $800,000 per QALY gained. The gain in the life expectancy needs to be balanced against the cost-utility analysis issues identified.

9.3.7 Other Approaches to Economic Evaluation of End-of-Life Care and Experiences

All three economic evaluation approaches identified above (cost-benefit analysis, cost-effectiveness analysis, and cost-utility analysis that incorporate QALY as a measure of outcomes) may generally be used in evaluating end-of-life care. In recent years, however, additional research targeting economic evaluation of such care has emerged that offers additional perspectives to be considered.

Coast notes there are "three broad normative theoretical bases that economists are likely to choose from: welfarism, narrow extra-welfarism interpreted as health maximization or an alternative extra-welfarist perspective focusing on opportunity for a good death," and offers the extrawelfarist capability approach as a starting point for thinking about economic analysis of end-of-life care (Coast 2014). The capability approach, based on the work by the Nobel Laureate Amartya Sen, evaluates interventions based on their impact to the individual's "capability well-being," or what the individual is capable of doing rather than what the individual chooses to do with their life. Such an approach, Coast argues, allows us to analyze quality of life and quality of death to the dying individual and their family and friends.

The challenges associated with this approach are considerable. Coast notes the methodological challenges in determining what capabilities are important to individuals at the end of life, measuring such capabilities, valuing such capabilities, and using such capabilities in decision making. This, undoubtedly, will continue to be an area of future research in economics.

9.4 Costs of Cancer, Cancer Treatment, and Death

9.4.1 Direct and Indirect Costs to Individuals, Families, Providers, Insurers, and Other Parties

The costs of cancer treatment include both direct and indirect costs of inputs or resources consumed in the course of treatment. Such costs are incurred by both patients and providers, as well as by third parties, which include patients' families, employers, insurance providers, and the society at large.

Direct costs are typically defined as the resources involved in the treatment of the disease and controlled by the medical sector. *Indirect costs* are resources lost due to illness and its treatment (Uyl-de Groot 1995).

Table 9.4 identifies potential direct and indirect costs to various parties.

In estimating the costs of treatment, it is important to include not only direct medical costs, but also direct nonmedical costs borne by the patients, and often, by their families. Such costs may include the costs of traveling to receive treatment, maintaining a special diet (insomuch as it exceeds the cost of a normal diet, as an economist would consider the marginal cost only), and other similar costs that would not have been incurred otherwise. Economists also advocate for considering the indirect costs from the perspective of human capital theory in such analyses. For instance, what impact would treatment have on the patient's ability to maintain employment, and thus, draw income, both now and in the future? Since individuals ultimately maximize not income but utility (or enjoyment of life, in other words), what impact would treatment have on their quality of life, both positive and negative?

The death of an individual brings its own set of costs as well. National Funeral Directors Association compiles annual data on the average cost of funeral services. As of 2014, the median cost of an adult funeral with viewing and burial reached $7181, an increase of 28.6 % from 2004 (NFDA 2015). The loss of a companion who also serves as a source of economic support in a family unit also imposes an economic cost on the survivors. Research conducted on the impact of death and burial costs on widows' and widowers' economic well-being had found such impact

Table 9.4 Direct and indirect costs of cancer treatment and death

Direct costs	Indirect costs
Medical (treatment and associated) costs: radio-/chemotherapy, surgery, hospital stay, ambulatory care, follow-up visits, readmission costs, diagnostics, drugs, home care costs, hospice and palliative care costs, and other costs	*Patient/family income loss*: loss of resources due to treatment/illness, such as decrease in or loss of employment income, and decrease in quality/satisfaction of life
Nonmedical costs: patient's and family's travel cost, special diet cost, housekeeping and related services costs, and other costs	*Societal costs*: temporary/permanent decrease in productivity from society member(s)
Death costs: funeral and burial expenditures, legal costs associated with transfer of assets/wealth/probate, and related costs	*Mortality costs*: estimates of value of the foregone years of life due to a premature death, such as value of foregone productivity

to be significant, exceeding the household financial wealth for the 10th and 25th percentile of households and equal to almost 40 % of financial wealth of the 50th percentile of households (Fan and Zick 2004). The impact of final medical and burial expenses would, therefore, have a considerable expense on the economic position of the surviving spouse. Banks noted that even the least expensive final disposition method, cremation, will create a burden equivalent to 8 % of income for the median US household (Banks 1998).

9.4.2 Empirical Data on Direct Costs of Cancer

9.4.2.1 Current Prevalence and Costs

Cancer remains the second-highest condition-related expenditure in healthcare spending in 2012, at $52.7 billion nationally among adults aged 18–64, preceded only by trauma-related disorders ($56.7 billion) and succeeded by mental disorders ($51.1 billion), heart conditions ($45.0 billion), and arthritis and other nontraumatic joint disorders ($43.3 billion). For the individuals aged 65 and over, cancer is also the second-highest expenditure, at $34.5 billion. Table 9.5 indicates the prevalence, total cost, and average cost of treatment of cancer in both subsets of the population and for all civilian noninstitutionalized population (Soni 2015b).

The prevalence of cancer in population aged 18–64 is lower than that of other top five most costly conditions (compare 6.5 million cancer cases to 21.8 million cases of trauma-related disorders and 29.6 million cases of mental disorders). Yet, the average cost of treating cancer in this group is much higher at $8125. The next highest average expenditure per adult is that of heart conditions, $4825, or 40 % less.

The prevalence of cancer in population aged 65 or over increases considerably, but average expenditure is reduced, and becomes comparable to average spending for heart conditions and trauma-related disorders (Soni 2015b). This can be attributed to different tactics used in treatment and management of cancer and different type of cancers experienced by the population.

For civilian noninstitutionalized population, cancer is the third costliest condition in 2012 at $87.5 billion (after heart conditions, $101.0 billion, and trauma-related disorders, at $93.1 billion). The prevalence of cancer is the lowest of the five costliest conditions at 15.5 million cases; and average expenditures are the highest at $5631 (Soni 2015a) compared to other five highest condition-related expenditures.

Table 9.5 Prevalence, total cost, and average cost of cancer in the United States

	Population aged 18–64	Population aged 65+	All civilian noninstitutionalized population
Total 2012 expenditure, in billions US$	$56.7	$34.5	$87.5
Number of adults with expenses for condition in 2012, in millions	6.5	9.0	15.5
Average expenditure per adult in 2012	$8125	$3839	$5631

Source: Soni (2015a; b)

Table 9.6 Share of direct medical expenditure on cancer treatment by site of service

	Population aged 18–64 (%)	Population aged 65+ (%)
Outpatient and office-based	39.4	47.7
Hospital stays	46.3	33.9
Emergency room	0.9	0.5
Prescribed medicine	12.0	5.2
Home health	1.4	12.6

Source: Soni (2015b)

The distribution of spending on direct medical expenditures also differs by the age group. For adults aged 18–64, the expenses are heavily biased toward hospital stays (46.3 % of spending) and then to outpatient and office-based expenses (39.4 %). For the 65+ population, the main expenditure source is outpatient and office-based expenses (47.7 %), with a much smaller share in hospital stay expenses (33.9 %). Table 9.6 illustrates exact share of each expense by site of service.

9.4.2.2 Dynamics and Projections of Cancer Costs

Over the period of 2002–2012, the total economic burden of direct costs of cancer has increased considerably, from total spending of $59.8 billion to $87.5 billion (as measured in 2012 dollars). This is largely due to an increase in the number of individuals living with cancer from 10.9 to 15.5 million, and to some extent, to an increase in the average direct cost of treatment from $5509 to $5631 (as measured in 2012 dollars) (Soni 2015a).

What accounts for such increases? Yabroff et al. note that “the economic burden of cancer in the United States is substantial and expected to increase significantly in the future because of expected growth and aging of the population and improvements in survival as well as trends in treatment patterns and costs of care following cancer diagnosis” (Yabroff et al. 2011). As we make advances in screening, detection, and treatment of cancer, and as we improve patient outcomes, these typically come at the expense of higher consumption of healthcare resources.

Based on medical advances, dynamics of escalation of prices for new treatments, and the aging of the US population, national cancer spending is projected to be growing relatively fast. Mariotto et al., based on cancer incidence, survival, and medical cost of care data in the United States, project a variety of scenarios that assume varying trajectories of change of these three variables (Mariotto et al 2011). Under a relatively reasonable scenario of incidence and survival trends similar to the past and a 2 % increase in the initial and last year of life phases,[3] and with population aging at the rate indicated by its current state, the total spending is expected to increase by 39 % from 2010 to 2020, to $173 billion. With the same assumptions,

---

[3] Direct medical costs of cancer treatment are generally U-shaped. The spikes in direct costs are associated with initial period following the diagnosis and end-of-life period; and direct costs are typically lowest in the period between the two, as in the case of colorectal cancers of varying survival rates (Yabroff et al. 2008).

but an increase of 5 % in the initial and last year of life, the total spending is expected to increase by 66 %, to $207 billion. These predictions indicate a considerable challenge for the policymakers, healthcare institutions, researchers, and pharmaceutical companies, as well as for the healthcare consumers.

9.5 Shifting Costs and Economic Issues in Insurance

9.5.1 Cost Burden and Health Insurance Coverage in the United States

The burden of healthcare costs is borne by different parties. Much of the burden of illness in general and cancer specifically is suffered by the patients and their families. Direct medical expense payments, however, are largely made by third-party payers. In 2013, out of $2468.6 billion spent on all personal healthcare expenditures, $339.4 billion (13.7 %) was covered by out-of-pocket payments, and $1907.9 billion (77.3 %) was covered by various insurance programs (National Center for Health Statistics 2014). Many are surprised to find out that the various federal and state government programs (Medicare, Medicaid, CHIP, etc.) accounted for almost 51 % of all insurance spending, and private insurance for slightly less than 45 %. We can make an argument, then, that the costs of these direct medical expenses are collectively borne by the taxpayers at large through redistribution of income, employers and employees (patients themselves) through tax-advantaged workplace deductions, and in some cases, by the medical providers through provision of charitable care.

Health insurance programs present both unique benefits and unique challenges. They are much valued by general population – and many consider the quality and generosity of a health insurance program to be one of the most important benefits a company may offer to its employee, as well as an important component of a social compact between the citizens and their governments. At the same time, the universal health insurance mandate established by the Patient Protection and Affordable Care Act of 2010 was a subject of much public debate and disagreement, despite the fact that the United States remains the country with the lowest health insurance coverage rate among its peer industrialized nations, with 16.7 % of nonelderly population uninsured as of 2013 and 18.2 % uninsured in 2010 prior to the implementation of PPACA (Keiser Family Foundation 2015).

Why do health insurance programs exist? In general, the concept of insurance is closely related to that of *risk aversion*. Most people are risk averse, and would like to avoid an unexpected large expenditure when an illness requiring expensive treatment strikes. Thus, a large group of individuals (say, 100 people) may get together, estimate the total medical spending among the members of the group (say, $10,000) and the cost of administering the program (let us allocate another $100 to expenses such as paper and pens for recordkeeping), and divide such total into the annual premiums that each person will contribute to the total ($101 each). If the total medical spending increases, the group's premiums will increase; if the total medical spending decreases, the group's premiums will decrease. Over time, provided that the probability of being impacted by an illness is relatively random and that the group is large enough, this insurance program is likely to work well.

Health insurance programs, however, are rarely that simple. First, as data previously discussed shows, the most prevalent health insurance coverage in the United States is not private health insurance, but rather a set of government-provided social insurance programs, distinguished by the fact that the eligibility for such programs is established by specific rules and premiums do not reflect the true cost of operating such programs. Second set of issues is related to the concepts of *moral hazard* and *adverse selection* in purchasing insurance.

9.5.2 Moral Hazard and Demand for Healthcare

The concept of *moral hazard* refers to the phenomenon of changing behavior in the presence of an economic incentive to do so. An often-used but rather unlikely example is that of an individual who chooses to engage in bungee-jumping because he has health insurance, and who would not have done so otherwise. However, a scenario that is much more likely, and that has likely happened to many of us, is making healthcare decisions based on reduced prices or prices of zero that are discounted or completely covered by the healthcare plan, which result in increasing our consumption of such services beyond optimal.

In a previous example of a cost-utility analysis, we reviewed two hypothetical cancer interventions. On average, Intervention A resulted in a gain of 2.3 quality adjusted life years (QALYs) and cost $20,000 and Intervention B resulted in a gain of 2.5 QALYs and cost $2,000,000. Respective costs were $8696 and $800,000 per QALY. Given the relatively small difference between the total QALY gains between the two interventions, and the considerable cost difference between the two, one would argue that most individuals, when paying out of pocket, would select Intervention A. However, if both interventions were covered by a health insurance program with no difference in out-of-pocket payment to the individual, it is highly likely that most patients would select Intervention B, as it provides a marginal improvement in benefits over Intervention B (an increase in 0.2 QALYs) at zero marginal cost. Such a decision would exemplify moral hazard in health insurance.

Unabated, moral hazard leads to an increase in health insurance costs, which in turn leads to an increase in premiums, which in turn leads to the healthiest members of the insurance pool dropping out of the insurance plan. Thus the spiral of escalating costs, increasing premiums, and even more loss of membership continues. The changes in behavior brought by the changes in incentives caused by the health insurance plans also result in a loss of efficiency in the use of scarce resources. Reducing the incidence of moral hazard in health insurance requires providing an incentive for patients to modify their behaviors in a way that would more closely resemble what they would do in a marketplace, yet minimize the adverse impact of consumer underspending on health and preventive care.

There are a number of economic tools that can be used to manage moral hazard. One set of tools includes *restrictions* levied on eligibility of medical interventions for reimbursement by insurance companies, such as preauthorization requirements, establishing lists of approved/unapproved therapies, requirements to substitute brand name drugs by less expensive generic drugs, and establishing lists of preferred providers of various treatments based on their costs and effectiveness. Another set of tools aims at creating incentives for making decisions based on prices that at least somewhat mimic the cost of medical treatment to the third-party payer through *copays and co-insurance*, which require the patient to pay either a set amount or a percentage of cost of treatment. Such an approach makes the cost of healthcare at least one of the considerations in the decision-making process for the patient. In countries where single-payer national insurance systems are present, *rationing* is also utilized as one of the mechanisms for controlling the moral hazard and cost issues.

One of the more recent experiments for addressing the moral hazard issue and controlling the growth in the health costs is the health savings account (HSA), authorized by the Medicare Prescription Drug Improvement and Modernization Act of 2003. HSAs are used as a part of a high-deductible health insurance plan (HDHP) which essentially results in a creation of a dual vehicle for both insurance and saving. High deductible health insurance plans require cash payments between $1250–6350 (individual) and $2500–12,700 (family) before insurance coverage becomes effective (AHIP Center for Policy and Research 2014). By requiring the individuals to use their health savings accounts for the first few thousand dollars of healthcare expenditures, we provide them with an incentive to be more sensitive to prices of healthcare services as well as to the quantity of healthcare services consumed. Since its introduction in 2004, HDHPs account for approximately 20 % of all health plan enrollments for covered workers (Kaiser Family Foundation 2014).

9.5.3 Adverse Selection

Adverse selection is a common issue in health insurance – or, for that matter, any insurance program where one party (the insured) may have more knowledge about their health condition than the other (the provider). At heart, adverse selection arises due to information asymmetry, which tends to make markets inefficient, and was originally identified by George Akerlof (1970).

To illustrate adverse selection, let us return to our previous example of a simple health insurance pool of 100 people, average annual medical expenditure of $10,000, average administration cost of $100, and an average premium of $101. Provided that the incidence of illness is random and unpredictable, and the cost of administration of the health insurance pool is relatively low, the program is likely to run well. However, given that some illnesses are chronic, it makes sense that the individuals who experience them and who know that they are likely to continue experiencing them will want to join the health insurance pool. As they do so, the pool's total healthcare expenses will rise faster than the total premiums; and thus, the individual premiums will increase. As premiums increase, at least some of the healthier individuals will decide that they will be better off on their own as uninsured or self-insured (saving money); as they leave the pool, the revenues will decrease but the costs will stay relatively constant and thus, individual premiums will need to be increased again. At the same time, to reduce the information asymmetry, the pool administrators will attempt to engage in additional monitoring of new applications and expenditures of existing members, attempting to reduce the entrance of those with chronic illnesses – or even to expel those with chronic conditions out of the pool. These actions will increase administrative costs (and thus reduce value created by the insurance program) and create considerable conflict between the purpose of the program and its operations. As a result, the insurance program will continue suffering in the vicious cycle of shrinking member base, rising premiums, higher administrative costs, and membership more prone to illness.

How do insurance companies deal with the adverse selection? In the past, prior to the introduction of the Patient Protection and Affordable Care Act (PPACA) of 2010, they would commonly exclude preexisting medical attention from coverage – at least, for a given time period – to prevent individuals with an existing health condition to become instantly eligible for coverage. The insurers' ability to exclude preexisting coverage was taken away by PPACA, in exchange for the universal health insurance mandate. The mandate penalizes individuals for leaving the general health insurance pool or for remaining uninsured through imposing tax penalties, and provides income-based subsidies for health insurance purchase.

Insuring groups of individuals, based on a common set of characteristics, such as shared employment, tends to be another way to avoid adverse selection. Health insurance, due to a historical phenomenon with roots in aftermath of World War II, is most commonly obtained through employers, rather than purchased directly through individuals. Thus, insurance companies also engage in assigning an experience rating to companies that, among other factors, depends on the history and volume of claims, and impacts the premiums charged. The timing of enrollment in health insurance plans is also typically limited to a given window in the calendar year or tied to a life event (such as marriage, child birth, divorce, etc.), which is designed to prevent enrollment in insurance plans that coincides with onset of an illness.

9.6 Economic Benefits of Cancer Treatment

In a previous section of this chapter, we have discussed approaches to calculating economic costs of cancer treatment. In this section, we concentrate on the economic benefits of cancer treatment, which typically include gains in years or quality adjusted life years (QALYs) – and associated gains in economic productivity of the affected individual.

Sun et al. have identified the gains in overall survival by cancer type between 1988 and 2000, separating the impact of detection and improvement in care (Sun et al. 2008). Overall gain in life expectancy was estimated at 3.9 years for all cancers; 3.5 years for non-Hodgkin's lymphoma; 1.7 years for colorectal cancer;

0.8 years for lung cancer; 0.5 years for pancreatic cancer; and 3.6 years for breast cancer. The estimated improvements in life expectancy due to improved treatment are considerable, and account for 77.9 % of life expectancy gain for all cancers (or approximately 3 years out of 3.9-year improvement in survival), with the remaining gains due to improvements in screening and other factors.

In a follow-up analysis, the researchers estimated the economic gains made from improvements in survival rates. A hallmark of their study was the separation of social welfare gains into gains made by producers and gains made by patients and a comparison of these benefits against imputed profits made by cancer care providers over the time period (Sun et al. 2009). The analysis indicated that the improvements in survival generated approximately 23 million additional (quality-unadjusted) life years, which were valued at $1.9 trillion by the patients (or $86,000 for the average life year gained, and well in line with statistical life valuations suggested by many other studies). At the same time, imputed profits made by cancer care providers for the period were estimated to be at most $433 billion. Thus, net consumer (patient) surplus generated by the improvements in cancer survival rates were $1.5 trillion.

The overall results suggest considerable gains made from advances in treatment and detection of cancers. However, the overall positive gains may not mean that we are making positive economic gains with all new cancer therapies uniformly. A set of considerations in the analysis of individual therapies should include not only gains made in years of life but also gains in quality adjusted life years (QALYs) – as well as the analysis of transfers of wealth from consumers to producers. Such transfers of wealth may take place of payments (including copayments and co-insurance) from the patients who are undergoing therapy, but even when made by the insurance company or federal government as a third-party payment, these payments will ultimately result in higher premiums paid by all customers or redistribution of wealth by taxpayers. Some of the recently approved drugs are priced in excess of $10,000 per month of therapy, and result in marginal improvements in median life expectancies for their recipients. Additional economic studies that evaluate not only gains in life expectancy but also gains in QALYs as well as associated redistributions of consumer welfare are strong topics for further research.

9.7 Economic Issues in Patient Care: Alignment of Incentives and Principal/Agent Conflict

The patient-physician relationship is that of trust: a patient trusts that the physician keeps the best interests of the patient in making physician's decisions and in advising the patient. The physician is the expert in this relationship; and the patient relies on the physician's unique expertise. In economic terms, the relationship is that of *agency*, or a *principal-agent relationship*. The physician is the agent, and the patient is the principal.

An agency relationship is inevitably made more difficult by the issue of asymmetrical information, which often contributes to inefficiency in economics. In this case, asymmetrical information – the case of the physician knowing a lot and the patient knowing relatively little about the conditions, its treatment, and the prognosis for recovery – is what makes the agency relationship necessary in the first place. However, given the different set of incentives that the patient and the physician have, it has the potential to contribute to economically inefficient outcomes.

The patient's incentive is to improve their health (and for many patients, there may be other preferences as well, such as minimizing monetary outlay, maintaining their eating or leisure habits that may conflict with health improvement, etc.). The physician's incentives are not necessarily tied to the incentives of the patient, as the physician's income is driven, in most cases, not by the patient's health status outcomes and preferences (recovery and spending on healthcare) but by the volume of visits, procedures, and services performed. The conflicting incentives of the two parties, and the asymmetrical information which provides a greater amount of power in this relationship to the physician, has the potential to – and often results in – unnecessary and wasteful spending.

Atul Gawande, a general surgeon with specialty in tumors of the thyroid and other endocrine organs, eloquently describes in his 2015 New Yorker article what he terms "America's epidemic of unnecessary care" – or even "low value to no value care" (Gawande 2015). He notes that the dual phenomena of information asymmetry and rewarding healthcare providers for volume of procedures, rather than for the health outcomes of their patients, are largely to blame for the escalation in medical costs, and advocates approaches that concentrate on prevention and management of conditions such as high blood pressure and diabetes rather than overtesting.

Better alignment of incentives of healthcare providers and patients is one of the goals of the healthcare reform in the United States. Patient Protection and Affordable Care Act of 2010, commonly known as Obamacare, has established several pilot programs known as "pay-for-performance." For example, some hospital payments will be indexed to reward hospitals that perform better on quality metrics established by the Centers for Medicare & Medicaid Services. The hospitals with a high 30-day patient readmission rate for some of the conditions are also penalized, with penalty expressed as a percentage of their Medicare reimbursement. Additionally, pilot programs that provide flat-rate payments per patient per year (practice known as capitation and followed by national healthcare systems in countries like the United Kingdom for primary healthcare), rather than pay a fee per service are introduced.

We should note that these are undoubtedly interesting initiatives; and as with everything else with economics, the execution and detail of these initiatives will prove the key to their success. Improvement in patient outcomes is often difficult to measure, and it may be influenced by factors outside of the healthcare practitioner's control. Thus, factors that we choose to measure will often be proxies for quality, with some of the proxies being imperfect.

9.8 Alternative Approaches in Cancer/End-of-Life Care

The last few years have seen a considerable amount of public interest in the end-of-life care, exemplified by the interest in the New York Times bestseller "Being Mortal: Medicine and What Matters in the End" (2014). The argument made by the author, Atul Gawande, is that at the end of life we overutilize intensive medical interventions, underuse low-cost palliative care that also contributes to higher quality of life for the patient, and do not meet patients' top concerns that extend beyond simply prolonging their lives but rather include "avoiding suffering, strengthening relationships with family and friends, being mentally aware, not being a burden to others, and achieving a sense that their life is complete" (Gawande 2014). Gawande makes an argument for improved communication to the patients and their families, better assessment by physicians of the outcomes of various therapies and their side effects, and a more honest conversation about the experiences connected to death and dying.

Most economists would agree with the logic of statements. The surveys that Gawande refers to are consistent with the tenets of economic theory that posit that individuals value utility (happiness or satisfaction) rather than extension of life at any price. Given our general knowledge of incentive structures, we would suspect that at least some of use of intensive interventions for end-of-life care is related to financial reimbursement under the fee-for-service model. Indeed, we know that approximately a quarter of all Medicare spending in the United States is for the 5 % of patients in the last year of their lives (Riley and Lubitz 2010). While it is expected that there will be a spike in the expenses related to the end-of-life care, may it be reasonable to suspect that at least some – and potentially many – of these expenses are economically inefficient?

Home care can often be an effective substitute for hospital-based care for cancer patients. Home care benefit was originally authorized as an eligible Medicare benefit for some categories of patients in 1965; and economic studies (such as Van Houtven and Norton 2004) indicate that both informal (family-provided) and formal home healthcare are strong substitutes for each other, and that home healthcare provides considerable reductions in hospitalization spending.

Hospice care, including home-based hospice visits and separate hospice facilities, had been approved for Medicare reimbursement since 1983, and is increasingly used for end-of-life care and palliative care as an alternative to hospital-based care. The National Hospice and Palliative Care Organization estimates that in 2014, 1.6 to 1.7 million patients received services from a hospice; and that by 2007, 43.3 % of Medicare patients with cancer diagnosis received 3 or more days of hospice services (NHPCO 2015). Approximately half of the hospice patients receive 14 or less days of hospice services, while about 19 % receive 90 or more days of such services (NHPCO 2015). 35.9 % of hospice service recipients receive care at a private residence; 31.8 % receive care at a hospice inpatient facility; and the rest at a nursing home, residential facility, or an acute care hospital. The most common diagnosis for hospice patients (36.6 %) is cancer.

Conclusions

As a society, we have made considerable progress in treatment of cancer through advances in treatment and early detection practices over the last several decades. Such progress, however, has been economically costly, as healthcare and cancer care account for an increasingly large share of national spending, government budgets, and consumer spending; yet – as research shows – gains made are of high value to patients. There is much room for improvement, as the United States spends more than a sixth of its gross domestic product (GDP) on healthcare spending. This is a much greater share than other industrialized nations, with national health outcomes that are below such counterparts' outcomes.

Economics provides us with a set of tools that evaluate the use of limited resources for their most efficient use and recommend changes to their allocation. In healthcare in general, and in the evaluation of cancer interventions, to achieve such allocative efficiency we can incorporate the use of cost-benefit and cost-utility analysis in making decisions about appropriate courses of actions; analyzing not just gains in life years but in quality adjusted life years (QALYs) and other factors that contribute to higher quality of life for patients in evaluating alternative treatments; improve alignment of incentives among patients, physicians, healthcare institutions, and insurance programs; and consider all costs and benefits in treatment and policy decisions.

References

AHIP Center for Policy and Research (2014) January 2014 census shows 17.4 million enrollees in Health Savings Account—eligible High Deductible Health Plans (HSA/HDHPs). America's Health Insurance Plans, Washington, DC

Akerlof G (1970) The market for "lemons": quality uncertainty and the market mechanism. Quart J Economics 84(3):488–500

Banks D (1998) The economics of death? A descriptive study of the impact of funeral and cremation costs on U.S. households. Death Stud 22(3):269–285

Centers for Medicare & Medicaid Services (2015) National health expenditure fact sheet. Retrieved from https://www.cms.gov/research-statistics-data-and-systems/statistics-trends-and-reports/nationalhealthexpenddata/nhe-fact-sheet.html

Centers for Medicare & Medicaid Services (2010) Statistics, trends, and reports: National health expenditure data. Retrieved from https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/Downloads/2010GenderandAgeTables.pdf

Coast J (2014) Strategies for the economic evaluation of end-of-life care: making a case for the capability approach. Expert Rev Pharmacoecon Outcomes Res 14(4):473–482

Cropper ML, Hammitt JK, Robinson LA (2011) Valuing mortality risk reductions: progress and challenges, NBER Working Paper Series. National Bureau of Economic Research, Cambridge, MA, Retrieved from http://www.nber.org/papers/w16971.pdf

Fan JX, Zick CD (2004) The economic burden of health care, funeral, and burial expenditures at the end of life. Consum Aff 38(1):35–55

Field RI (2008) Why is health care regulation so complex? Pharm Therap 33(10):607–608

Gawande A (2014) Being mortal: medicine and what matters in the end. Metropolitan Books/MacMillan, New York

Gawande A (2015) Overkill. New Yorker

Kaiser Family Foundation (2014) 2014 Employer Health Benefits Survey. Retrieved from http://kff.org/report-section/ehbs-2014-summary-of-findings/

Kaiser Family Foundation (2015) Key facts about the uninsured population. Retrieved from http://kff.org/uninsured/fact-sheet/key-facts-about-the-uninsured-population/

Lyman GH (2007) Economics of cancer care. J Oncol Pract 3(3):113–114. doi:10.1200/JOP.0731501

Mariotto AB, Yabroff KR, Shao Y, Feuer EJ, Brown ML (2011) Projections of the cost of cancer care in the United States: 2010-2020. J National Cancer Inst 103:117–128

National Center for Health Statistics (2014) Health, United States, 2014: with special features on adults aged 55-64. U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, Hyattsville, Retrieved from http://www.cdc.gov/nchs/data/hus/hus14.pdf#103

National Funeral Directors Association (2015) Median cost of an adult funeral. NFDA, Brookfield, Retrieved from http://nfda.org/about-funeral-service-/trends-and-statistics.html

National Hospice and Palliative Care Organization (2015) NHPCO's facts and figures: Hospice care in America (2015 ed.). NHPCO, Alexandria. Retrieved from http://www.nhpco.org/sites/default/files/public/Statistics_Research/2015_Facts_Figures.pdf

Nord E, Daniels N, Kamlet M (2009) QALYs: some challenges. Value Health 12:S10–S15. doi:10.1111/j.1524-4733.2009.00516.x

Organization for Economic Co-operation and Development (2015) OECD health statistics 2015: Frequently requested data. Retrieved from http://www.oecd.org/els/health-systems/health-data.htm

Riley GF, Lubitz JD (2010) Long-term trends in Medicare payments in the last year of life. Health Serv Res 45(2):565–576. doi:10.1111/j.1475-6773.2010.01082.x

Round J (2012) Is QALY still a QALY at the end of life? J Health Econ 31(3):521–527. doi:10.1016/j.jhealeco.2012.01.006

Soni A (2015a) Trends in the five most costly conditions among the U.S. Civilian Noninstitutionalized Population, 2002 and 2012. Statistical Brief #470. Agency for Healthcare Research and Quality, Rockville. Retrieved from http://www.meps.ahrq.gov/mepsweb/data_files/publications/st470/stat470.shtml

Soni A (2015b) Top five most costly conditions among adults age 18 and older, 2012: estimates for the U.S. Civilian Noninstitutionalized Population. Statistical Brief #471. Agency for Healthcare Research and Quality, Rockville. Retrieved from http://meps.ahrq.gov/mepsweb/data_files/publications/st471/stat471.shtml

Sun EC, Jena AB, Lakdawalla DN, Reyes CM, Philipson TJ, Goldman DP (2009) An economic evaluation of the war on cancer, NBER Working Paper Series. National Bureau of Economic Research, Cambridge, MA, Retrieved from http://www.nber.org/papers/w15574.pdf

Sun E, Jena AB, Lakdawalla D, Reyes CM, Philipson TJ, Goldman DP (2008) Relative contribution of better treatments and improved detection: an analysis of cancer survival gains from 1988-2000 using SEER data. RAND Corporation, Santa Monica

Uyl-de Groot CA (1995) Economic evaluation of cancer treatments. Thesis Erasmus Universiteit Rotterdam. Erasmus University Rotterdam, Rotterdam

Van Houtwen CH, Norton EC (2004) Informal care and health care use of older adults. J Health Econ 23(6):1159–1180. doi:10.1016/j.jhealeco.2004.04.008

Weinstein MC, Torrance G, McGuire A (2009) QALYs: the basics. Value Health 12:S5–S9. doi:10.1111/j.1524-4733.2009.00515.x

Yabroff KR, Lund J, Kepka D, Mariotto A (2011) Economic burden of cancer in the United States: estimates, projections, and future research. Cancer Epidemiol Biomarkers Prev 20(10): 2006–2014

Oncologists and Death

10

Lawrence Berk

10.1 Introduction

> AGAINST his will he dieth that hath not learned to die. Learn to die and thou shalt con[1] to live, for there shall none con to live that hath not learned to die; and he shall be cleped[2] a wretch that cannot live and dare not die.
>
> If thou wilt live freely learn to die wilfully[3]; and if thou ask of me how many it learneth, I shall tell it thee anon.
>
> Thou shalt understand that this life is not else but death; for death is a passing as every man knoweth well. Wherefore men say of a man when he dieth that he passeth;

I will admit that I am writing this chapter at the last minute. The original author of this chapter got his outline to me and some of the text, but despite very polite cajoling, he never finished the manuscript. On reviewing his outline, I realized that the information he wanted to present was very appropriate but also mundane. It is already well known that palliative medicine can improve medical care for the dying patient and at the same time save costs for the medical system. It is also known that palliative care and hospice care are underutilized and often introduced to patient care too late to make a significant difference. Therefore, I want to look at the dying patients from another point of view – that of the physician. What is it like for oncologists to have to face dying patients? How do they communicate? How do they handle the prolonged and almost inevitable progression to death of many patients? How does this affect these physicians?

---

[1] Learn.

[2] Called.

[3] Willingly.

L. Berk, MD, PhD
Morsani School of Medicine, University of South Florida, Tampa, FL, USA
e-mail: lberk@health.usf.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_10

There is very little information in the literature on these questions, but I will review what I could find.

10.2 What Are the Attributes of a Good Oncologist?

> Now Lord hast Thou forsaken me. Thy servant. Thou wouldest teach me wisdom enough, but I am almost brought to the death. O my God, how much bindeth me the presence of death that I have seen! Now the Image of Death hath so overlaid all my mind that unnethes[4] wot I whether I have seen the Image of Death or not; for I am so greatly astonied that unnethes wot I whether this that I have seen be so in deed, or in likeness. (Comper 1917) p. 119

The best place to begin is the beginning, and the beginning of the process is training. What are the characteristics of a physician who chooses to be an oncologist? A PubMed search of various permutations of "oncologist" and "characteristics," and similar words produced no relevant articles. However, one of the constant findings in the literature is that physicians who are having discussions of impending death with the patient and family need to have empathy. For example, in the oft-quoted article by Rabow and McPhee, giving the ABCDEs of telling families bad news, "D"is "Deal with patient and family reactions" and specifically "Listen actively, explore feelings, express empathy" (Rabow 1999). Empathy, as described by Burton, is the ability to share someone else's perspectives and imagine oneself as the other person in that situation (Burton 2015). Empathy is the intellectual understanding of the other's situation, and this understanding allows better care of the person. In contrast, pity is an emotional reaction, and sympathy is a feeling of concern for the other that does not necessarily require the intellectual understanding of the other's situation. Sympathy and empathy can coexist or exist independently. One can have sympathy for a dead butterfly, but it would be difficult to have empathy. In Gelhaus' series on the moral attitude of the physician, he first discussed empathy, in which he defines empathy as "the adequate understanding of the inner processes of the patient concerning his health-related issues" (Gelhaus 2012a). He finds that empathy is necessary as an intellectual component of moral health care, but not sufficient for defining moral health care. There should also be compassion, as discussed below. This call for empathy is a call for understanding the dying person's situation, not for an emotional exchange with him. Similarly, feeling sympathy or pity does not help give insight into how to improve his situation. But, this leaves a problem – empathy is a term and not an object. Empathy only exists within a definition, and there is no universal definition. To measure temperature, one measures it in relation to a defined standard (e.g., a relative scale based on the freezing and melting of water). This measurement is only useful because of the universal agreement within the Celsius measurement system for this scale. What is empathy measured relative to? Only an arbitrary definition. For example, Hojat et al. developed "The Jefferson Scale of Physician Empathy"

---

[4] Scarcely.

(Hojat et al. 2001). They reviewed the literature and chose 90 questions they thought reflected empathy. This was tested on a group of 55 physicians and narrowed down to 45 questions. This was then tested on 41 Internal Medicine residents and 193 third year medical students, and narrowed down to 20 items. This, despite the best intentions of the authors, is not a measurement of empathy but a definition of what Hojat and colleagues think empathy is. They then do a host of tests to show it has interreliability with other made up definitions and that it has good consistency when the same person is tested more than once. This then proves the scale's "validity." Actually, this proves no more than that it is precise, not accurate. Precision is the ability to do the same thing many times. Accuracy is doing it correctly. There is no test for accuracy, because you cannot say what the right answer is. So, rather than valid, the appropriate term for their testing is reproducibility. Using this to test physician empathy represents what Bridgman called "operationalism" (Bridgman 1927). Per the *Stanford Encyclopedia of Philosophy* "Operationalism is based on the intuition that we do not know the meaning of a concept unless we have a method of measurement for it" (Hasok 2009). Further, Bridgman stated (as quoted in (Hasok 2009)) "we mean by any concept nothing more than a set of operations; the concept is synonymous with the corresponding set of operations." Although operationalism long ago fell out of favor as a philosophy, I find it is a fundamental problem in humanistic medical sciences in that measurements become confused with the abstract term with the same name. Thus, we say empathy as if it is something concrete, whereas the opposite is true; empathy only exists as an abstract term, and therefore what can be taught is only how to improve on the measurement. So, how do Hojat and colleagues define empathy? What do they think makes an empathetic physician? The items of the Jefferson Scale are as follows (Hojat et al. 2002a):

1. I try to imagining myself in my patients' shoes when providing care to them.
2. My understanding of my patients' feelings gives them a sense of validation that is therapeutic in its own right.
3. An important component of the relationship with my patients is my understanding of the emotional status of themselves and their families.
4. I try to understand what is going on in my patients' minds by paying attention to their nonverbal cues and body language.
5. I try to think like my patients in order to render better care.
6. I believe that empathy is an important therapeutic factor in medical treatment.
7. Empathy is a therapeutic skill without which my success as a healthcare provider would be limited.
8. Patients' illnesses can only be cured by medical treatment; therefore, affection ties to my patients cannot have a significant place in this endeavor.
9. I do not allow myself to be touched by intense emotional relationships between my patients and their family members.
10. I believe that emotion has no place in the treatment of medical illness.
11. Because people are different, it is almost impossible for me to see things from my patients' perspectives.
12. Attentiveness to my patients' personal experiences is irrelevant to treatment effectiveness.
13. My patients feel better when I understand their feelings.
14. I have a good sense of humor that I think contributes to a better clinical outcome.

15. I consider understanding my patients' body language as important as verbal communication in caregiver–patient relationships.
16. I try not to pay attention to my patients' emotions in interviewing and history-taking.
17. I consider asking patients about what is happening in their lives as an unimportant factor in understanding their physical complaints.
18. It is difficult for me to view things from my patients' perspectives.
19. I do not enjoy reading nonmedical literature and the arts.
20. My understanding of how my patients and their families feel is an irrelevant factor in medical treatment.

Knowing the questions thus makes it easy to make a physician more empathetic, as measured by the scale. And the authors misinterpret their scale by analyzing the data to show that physicians in "people-oriented specialties" outscored those in "technology-oriented" specialties in empathy, especially in question 3 (Hojat et al. 2002b). It is probably true that a radiologist or a pathologist or probably even an anesthesiologist do not improve their performance by understanding the emotional status of their patients. That does not make them less empathetic. It makes their practice of medicine require less empathy (as defined by this scale). What is important to note is that this scale, as it reflects what empathy might mean, strongly emphasizes that it is an intellectual and not an emotional process. One has to understand the patient and the patient's family, not grieve for them. An oncologist can be empathetic and yet maintain an emotional distance and professional objectivity.

What is the evidence that having empathy leads to a better death for the patient? There are little prospective data, apart from patients saying they prefer empathetic physicians. There are articles, particularly in the nursing literature, stating patients prefer caring physicians. But there are no data showing that empathetic physicians give better care and that the patient's outcome improves. Some measurements of empathy also include compassion. Again, a term is being used that has no definition and cannot be objectively defined. Most definitions include empathy as part of compassion, but compassion is not part of empathy. Joan Halifax, known for her work with dying, and her book *Being With Dying*, states "The very act of training others, including clinicians in the end-of-life care field, in the cultivation of compassion, necessitates exploration of what in fact is compassion, what comprises compassion, what are the interactive processes that prime compassion, and what optimizes and sustains compassion. To summarize then, enactive compassion is an emergent process that arises out of the interaction of a number of non-compassion processes. Putting it simply, compassion is composed of non-compassion elements" (Halifax 2012). In the same article, she concludes "In sum, it is the experience of the author of this article that one cannot directly train in compassion per se. Compassion is an emergent process rising out the interaction of a number of interdependent somatic, affective, cognitive, attentional, and embodied processes, all of which themselves can be trained in. There is no compassion without attentional and affective balance. Compassion is not possible without altruistic intention and insight, including insight about the distinction between self and other. And compassion is an embodied and engaged process that can lead to a direct and transformative relationship with suffering and be enacted in the world" (Halifax 2012). In Gelhaus' previously mentioned series on the desired moral attitude of the physician, he also explores compassion (Gelhaus 2012b). Gelhaus calls compassion the "morally emotional part" of the moral attitude. Compassion is seen by Gelhaus as a more complex trait. What is generally known as compassion, he defines as C_{SE}, the spontaneous emotion of compassion. This emotion is characterized by the recognition of suffering, benevolence, a feeling of being personally addressed, and an inclination to relieve the suffering. He notes that this is a personal emotion that can vary from patient to patient. If this type of compassion is acted on, it will direct the physician to treat some patients differently, and therefore better or worse, than others. He therefore defines a second type of compassion, C_{PA}, compassion as a general medical attitude. This compassion is still an emotion, but a more general emotion that is incorporated into the general attitude of the practitioner, and therefore applied to all of the patients (ideally) equally. This not only removes the inequalities that spontaneous compassion involves, but also depersonalizes the compassion and may reduce the risk of excess burn out. C_{PA} combined with empathy can give the physician a sustainable professional medical ethic that will maximize the quality of all of the patients' experiences with the physician. This background gives a semantic and practical foundation to the vague statement that dying patients should be treated with empathy and compassion. To be more concrete, the physician should incorporate compassion, the general emotion (perhaps desire) to help all of his patients while approaching the individual patient through his empathy, which is focused on the individual needs and experiences of the patient.

So, what to make of a study by McFarland et al. showing that residents' empathy levels decrease while on a hematology–oncology rotation (McFarland et al. 2015; McFarland et al. 2016). This study was with Mount Sinai Internal Medicine residents at Memorial Sloan Kettering Cancer Center, both in New York City. Empathy was measured with the Interpersonal Reactivity Index (IRI). This scale is completely different than the Jefferson Scale of Physician Empathy in that it is not focused on empathetic interaction of a physician with a patient, but on general public empathy (Davis 1983). As stated in the article by Davis on the IRI, "Empathy in the broadest sense refers to the reactions of one individual to the observed experiences of another" (Davis 1983). Further, he states "Rather than treating empathy as a single unipolar construct (i.e., as either cognitive or emotional), the rationale underlying the IRI is that empathy can best be considered as a set of constructs, related in that they all concern responsivity to others but are also clearly discriminable from each other" (Davis 1983). The 28 items in the IRI are in four subscales: Perspective-Taking which is the tendency to spontaneously adopt the psychological point of others; Fantasy which is the tendency to transport oneself into the feelings and actions in fictitious characters in books, movies, and plays; Empathic Concern which assesses "other-oriented" feelings of sympathy and concern for unfortunate others; and the Personal Distress Scale which measures "self-oriented feelings of personal anxiety and unease in tense interpersonal settings (all of these are directly from (Davis 1983)). Thus, this general survey uses a totally different set of questions than the more medically defined Jefferson questionnaire. What were McFarland's results? The scale has 28 questions scored 0–4, and so the range of potential scores is 0–112. The overall scores changed from 58.9 before the rotation to 56.8 after the rotation, a change of 2. The standard for a "significant" change in the values of surveys such as this is not the statistically significant changes, which is dependent on the number of surveys but a minimum clinically relevant change, such as 20 %. The change here was 4 %, which has no clinical significance (despite the *p* value was 0.018). Further, the analysis of the four subgroups showed that the only significant decrease was in the personal distress scale. What type of questions are there in this subscale?

- In emergency situations, I feel apprehensive and ill-at-ease.
- I sometimes feel helpless when I am in the middle of a very emotional situation.
- Being in a tense emotional situation scares me.
- I tend to lose control during emergencies.

Thus, improvement in the very qualities that make a good physician – control in a stressful situation – is defined as a loss of empathy by McFarland. This highlights that an abstract term such as empathy has no meaning outside of a measurement called empathy. The conclusion of the article is that Internal Medicine residents have a decline in empathy during a hematology–oncology rotation. The actual conclusion is that the authors ran an inappropriate clinical trial due to the use of a misapplied measurement.

10.3 Discussing End of Life

> And there ought not to be given to any sick person over much hope of recovering his bodily health. Howbeit oft times many do the contrary, in prejudice of their souls, yea, to them otherwhile[5] that draw to their death. And it happeth oft that they will not hear of death, and so by such false comfort, and by such faint trust of health, the sick person falleth into damnation. (Comper 1917) p. 75

How should an oncologist approach end-of-life discussions? Jors et al. surveyed German physicians and nurses working in 10 cancer centers to ask what changes they recommended to end-of-life curriculum (Jors et al. 2015). One of the main responses was a desire to have increased skills training in communication. Communication is a more easily defined and accepted word than is empathy – it is the mutual exchange of information. The statement can be muddied by calling for "empathetic" communication. However, good communication should involve the give and take of ideas and therefore encompass the generally accepted meaning within medicine for empathy. Tulsky et al. reported on a computer-based training program for enhancing communication between oncologists and patients (Tulsky et al. 2011). The specific goal of the training was to teach the oncologists how to address patients' emotions. The physicians were randomized to either a lecture or a

---

[5] At times.

lecture with a tailored CD-ROM course. Pre-intervention and post-intervention audio recordings of patient interactions were then analyzed for "empathic" statements. The number of empathic statements increased from 0.4 per interaction in the control group to 0.7 in the group with advanced training. There was clinically insignificant difference in the patients' reactions to the trained and control physicians, with very slight differences in perceived empathy and trust. Moore et al. published a Cochrane Review of communication skills training for healthcare professionals working with people who have cancer (Moore et al. 2013). After analyzing all the randomized trials available until February 2012, they concluded "We found no evidence to support a beneficial effect of CST [communication skills training] on HCP [health care provider] 'burnout', patients' mental or physical health, and patient satisfaction." A systematic review of interventions to cultivate physician empathy found that "Overall, the 64 included studies were characterized by relatively poor research designs, insufficient reporting of intervention procedures, low incidence of patient-report empathy assessment measures, and inadequate evaluations of long-term efficacy. 8 of 10 studies with highly rigorous designs, however, found that targeted interventions did increase empathy" (Kelm et al. 2014). They did not evaluate whether the training had any effect on patient or physician satisfaction. A cynic, such as myself, would conclude that if you teach the test you will improve the score on the test. But you may not change anything else.

10.4 The Life of an Oncologist

> Since it is that death nought to man, but rather from him, taketh, and priveth him of that he hath, whereof profiteth this doctrine of death? Say me it seemeth wonderful, and therefore teach me heavenly master. (Comper 1917) p. 105

How does all of these weigh on the oncologist? Are oncologists happy in a field that treats large numbers of patients, who, from their first meeting they know will die despite treatment? A survey was done in by Shanafelt et al. of US Medical Oncologists, using the Maslach Burnout Inventory (Shanafelt et al. 2014). Because "burnout" is an artificial construction, it is important to know what Maslach and Jackson were asking in the survey. The original description of their scale was published by Maslach and Jackson in 1981. They defined burnout as "a syndrome of emotional exhaustion and cynicism that occurs frequently among individuals who do 'people-work' of some kind." They identified three aspects of burnout (Maslach and Jackson 1981):

1. Increased feelings of emotional exhaustion
2. Development of negative, cynical attitudes and feelings about one's clients
3. The tendency to evaluate oneself negatively

They based this on prior qualitative research they had done. They then formulated a larger survey with 47 items using a dual scoring of frequency and intensity. This was pared down with factor analysis to 25 questions, maintaining at that time the dual scoring. The dual scoring is not used on the current instrument; only frequency is scored. This was then tested for reproducibility on a separate cohort of people. People included in both cohorts were police, social workers, nurses, physicians, and others. The scale has three subscales (Maslach and Jackson 1981):

1. "Emotional Exhaustion describing "feelings of being emotionally overextended and exhausted by one's work."
2. Depersonalization describing "an unfeeling and impersonal response toward recipients of one's care or service."
3. Personal Accomplishment describing "feelings of competence and successful achievement in one's work with people."

Increased burnout correlated with higher scores on the first two subscales and lower scores on the third subscale. The personal accomplishment subscale is independent of the scores on the other subscales. That is, you can still feel good about yourself even if you do not like what you are doing. In the article by Shanafelt et al., they conducted surveys from October 2012 to March 2013 among 2000 US oncologists, and 1490 responded (Shanafelt et al. 2014). The oncologists were evenly distributed through academic practice and private practice. The oncologists worked on average about 60 h a week. Of these physicians, 45 % had burnout on the emotional exhaustion or depersonalization subscales discussed above. The number of hours worked correlated with the risk of burnout. Despite the high burnout rate, over 80 % of the oncologists were satisfied with their career choice. The burnout rate is similar to the 45 % burnout rate that is seen among all doctors (Shanafelt et al. 2012). The authors noted that the 80 % satisfaction rate was the highest among all of the specialties they have surveyed. The same group looked at surgical oncologists. Here, 36 % of 1581 surgical oncologists responded to the survey (Kuerer et al. 2007). Using the same Maslach scale, only 28 % had burnout, with this higher among women and younger (less than 50) surgeons. A similar study among gynecological oncologists elicited a 40 % return among 1086 solicited physicians (Rath et al. 2015). Here, the burnout rate was 30 % for emotional exhaustion and 10 % for depersonalization with an overall 32 % burnout rate. A randomized trial of "19 biweekly facilitated physician discussion groups incorporating elements of mindfulness, reflection, shared experience, and small-group learning for 9 months" was done with 74 physicians at the Mayo Clinic in Rochester, Minnesota (West et al. 2014). This intervention slightly but statistically significantly improved the personal accomplishment subscale and had a more marked effect on decreasing depersonalization. However, there was no effect on emotional exhaustion.

Conclusion

Unfortunately, there are no clear conclusions to be reached. What are the ideal attributes of physicians who are treating dying patients, such as oncologists? The literature often states that they should be empathetic and compassionate. However, neither term has a concrete meaning. It is perhaps better to say that open communication between the patient and the oncologist is very important. Giving realistic expectations to the patient and sufficient information throughout the treatment process may lessen the acute burden of telling the patient she is dying because it will not be as great an emotional shock to either the patient or the family. Do oncologists seem to have a higher emotional burden than other physicians due to the constant specter of death over their patients? The answer appears to be no, at least as far as measured by the Maslach burnout scale. It is worthwhile to reiterate that this is not a measure of burnout; it is the score on the scale and what the authors decided burnout means. Perhaps, oncologists are better at managing death than other groups. Most of the treatments given by oncologists have such little effect on the cure rates that it lessens the burden on the oncologist. Dying of an infection after being given antibiotics is seen as unusual. Dying after being given chemotherapy is seen as the natural history of the patient and cancer. Thus, in the end, much of the emotional burden of the oncologist in facing the dying patient is removed, because we are so limited in what we do. Discussing death with the patient is much easier if it is not my fault.

References

Bridgman P (1927) The logic of modern physics. Macmillan, New York

Burton N (2015) Empathy Vs Sympathy. Psychology Today. https://www.psychologytoday.com/blog/hide-and-seek/201505/empathy-vs-sympathy

Comper FMM (1917) The book of craft of dying and other early English tracts concerning death

Davis MH (1983) Measuring individual differences in empathy: evidence for a multidimensional approach. J Personal Soc Psychol 44:113–126

Gelhaus P (2012a) The desired moral attitude of the physician: (I) empathy. Med Health Care Philos 15:103–113

Gelhaus P (2012b) The desired moral attitude of the physician: (II) compassion. Med Health Care Philos 15:397–410

Halifax J (2012) A heuristic model of enactive compassion. Curr Opin Support Palliat Care 6:228–235

Hasok C (07/16/2009) Operationalism. Stanford encyclopedia of philosophy. http://plato.stanford.edu/entries/operationalism/. Accessed 3/12/2016 2016

Hojat M, Gonnella JS, Nasca TJ, Mangione S, Veloksi JJ, Magee M (2002a) The Jefferson Scale of Physician Empathy: further psychometric data and differences by gender and specialty at item level. Acad Med 77:S58–S60

Hojat M, Gonnella JS, Nasca TJ, Mangione S, Vergare M, Magee M (2002b) Physician empathy: definition, components, measurement, and relationship to gender and specialty. Am J Psychiatry 159:1563–1569

Hojat M, Mangione S, Masca T, Cohen M, Gonnella J, Erdmann J, Veloski J, Magee M (2001) The Jefferson Scale of Physician Empathy: development and preliminary psychometric data. Educ Psychol Measurement 61:349–365

Jors K, Seibel K, Bardenheuer H, Buchheidt D, Mayer-Steinacker R, Viehrig M, Xander C, Becker G (2015) Education in end-of-life care: what do experienced professionals find important? J Cancer Educ 31:272–278

Kelm Z, Womer J, Walter JK, Feudtner C (2014) Interventions to cultivate physician empathy: a systematic review. BMC Med Educ 14:219

Kuerer HM, Eberlein TJ, Pollock RE, Huschka M, Baile WF, Morrow M, Michelassi F, Singletary SE, Novotny P, Sloan J, Shanafelt TD (2007) Career satisfaction, practice patterns and burnout among surgical oncologists: report on the quality of life of members of the Society of Surgical Oncology. Ann Surg Oncol 14:3043–3053

Maslach C, Jackson S (1981) The measurement of experienced burnout. J Occup Behav 2:99–113

McFarland DC, Malone AK, Roth A (2016) Acute empathy decline among resident physician trainees on a hematology-oncology ward: an exploratory analysis of house staff empathy, distress, and patient death exposure. Psychooncology epublished ahead of print January 2016

McFarland DC, Holland J, Holcombe RF (2015) Inpatient hematology-oncology rotation is associated with a decreased interest in pursuing an oncology career among internal medicine residents. J Oncol Pract 11:289–295

Moore PM, Rivera Mercado S, Grez Artigues M, Lawrie TA (2013) Communication skills training for healthcare professionals working with people who have cancer. Cochrane Database Syst Rev (3):CD003751

Rabow MW, McPhee SJ (1999) Beyond breaking bad news: how to help patients who suffer. West J Med 171:260–263

Rath KS, Huffman LB, Phillips GS, Carpenter KM, Fowler JM (2015) Burnout and associated factors among members of the Society of Gynecologic Oncology. Am J Obstet Gynecol 213:824.e1–824.e9

Shanafelt TD, Gradishar WJ, Kosty M, Satele D, Chew H, Horn L, Clark B, Hanley AE, Chu Q, Pippen J, Sloan J, Raymond M (2014) Burnout and career satisfaction among US oncologists. J Clin Oncol 32:678–686

Shanafelt TD, Boone S, Tan L, Dyrbye LN, Sotile W, Satele D, West CP, Sloan J, Oreskovich MR (2012) Burnout and satisfaction with work-life balance among US physicians relative to the general US population. Arch Intern Med 172:1377–1385

Tulsky JA, Arnold RM, Alexander SC, Olsen MK, Jeffreys AS, Rodriguez KL, Skinner CS, Farrell D, Abernethy AP, Pollak KI (2011) Enhancing communication between oncologists and patients with a computer-based training program: a randomized trial. Ann Intern Med 155:593–601

West CP, Dyrbye LN, Rabatin JT, Call TG, Davidson JH, Multari A, Romanski SA, Hellyer JM, Sloan JA, Shanafelt TD (2014) Intervention to promote physician well-being, job satisfaction, and professionalism: a randomized clinical trial. JAMA Intern Med 174:527–533

Pediatric Cancer and End-of-Life

11

Kathleen G. Davis

11.1 Introduction

Children continue to die from cancer. Despite the decline in mortality, pediatric cancer remains the leading cause of death from disease in children ages 1–14, exceeded only by accidental death. Childhood deaths due to cancer represent 58 % of disease-related deaths, outnumbering all other causes of death by disease combined (Curesearch 2015). An estimated 1,250 cancer deaths were expected to occur among children 0–14 years of age in 2015 and an additional 610 among adolescents 15–19 years of age, totaling almost 2,000 annual cancer-related deaths in children and adolescents between birth and 18 years of age (American Cancer Society 2015). For the remainder of this chapter, the term child or children will be used to describe individuals from birth to age 19.

The population referred to as Adolescents and Young Adults (AYAs) with cancer overlaps the adolescent population included in pediatric cancer statistics. The AYA population includes individuals with pediatric forms of cancer, between the ages of 15 and 40, treated on pediatric protocols. The treatment may occur in either a pediatric or adult program, and patients between 15 and 19 who are treated in an adult program will typically be counted in the adult statistics. As a result, it is difficult to accurately identify the number of 15–19 year olds diagnosed with or who have died with cancer. In 2011, an estimated 69,212 AYAs were diagnosed with cancer, which represented the leading cause of disease-related death in this age group (National Cancer Institute 2014).

Each day in the United States, approximately 43 children receive a new diagnosis of cancer (American Cancer Society 2015). In 2014, an estimated 15,780 new cases of pediatric cancer were diagnosed among children birth to 19 years in the

---

K.G. Davis, PhD, MSEd
Pediatric Palliative Care and Ethics, University of Kansas Medical Center,
3901 Rainbow Blvd., Kansas City, MO MS4004, USA
e-mail: kdavis2@kumc.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_11

United States. Overall, childhood cancer incidence rates increased by 0.6 % per year from 2007 to 2011. However, the 5-year relative survival rate increased from an average of 58 % in the mid-1970s to 83 % from 2004 to 2010 (Ward et al. 2014).

Despite improvements in diagnosis and treatment of pediatric cancer, it remains impossible to predict the outcome for a specific child. Thus, many children and families continue to struggle with the diagnosis, treatment, and unknown prognosis of pediatric cancer. Pediatric cancers may be cured, become a long-standing chronic condition, or lead to death. Regardless of the trajectory of a child's cancer, all children with cancer benefit from support and assistance in maintaining or improving quality of life while on cancer treatment. In caring for children with cancer, therefore, it is prudent to follow the words of Benjamin Disraeli, "I am prepared for the worst, but hope for the best" (Disraeli 1833).

Whole-patient cancer care includes not only medical therapies, but also treatment directed at the psychosocial well-being of patients and their families (Adler and Page 2008). Whole-patient care enables continued cognitive, emotional, and social development in children living with or dying with cancer. Recent literature has called for the integration of psychosocial care into standard medical oncology practice including routine screening for psychological distress and identification of those in need of additional support (Carlson et al. 2012; Jacobsen and Wagner 2012). There is inconsistency of available psychosocial resources among pediatric cancer treatment sites. In the past, psychosocial care for children with cancer was initiated when problems such as depression, anxiety, or school avoidance became evident. Today, it is widely recognized that psychosocial care should be provided early in the trajectory of the child's cancer experience. Children with cancer, and their family members, have multiple psychosocial issues and require a unique set of supports to help them conceptualize and operationalize the issues they will confront during treatment.

Coping strategies will vary from child to child, disease to disease, and age to age. The strategy may change as the child moves through developmental stages. Children undergoing cancer treatment need healthcare professionals, family, friends, teachers, coaches, spiritual leaders, and others in their natural environment to recognize their needs and that they differ from those of adults. Only then can young patients develop the necessary trust to allow those same individuals in to provide support when they are dying. The psychosocial state of the dying child is affected by developmental stage, the effectiveness of the child's support system, symptom burden, relapse of cancer, pain and symptom management, treatment modalities and a wide range of other factors. The child's developmental level will inform how well he is able to process the reality that some diseases are incurable and result in death. How the child transitions out of life will also be affected by the family's level of distress. Many variables will impact the child's final days and hours. The period leading up to the child's death requires a great deal of sensitivity, honesty, and courage on the part of the healthcare team as they help the parent, child, siblings, and others assign meaning to the process and prepare for the child's death (Lee et al. 2006).

The goal of this chapter is to provide a foundation for the development or growth of pediatric psychosocial care in various settings by addressing the psychosocial needs of the child before and during the end-of-life (EoL) period, and the needs of family and community before, during, and after the child's death. This chapter will discuss the need to assess and treat a child's pain as a prerequisite to addressing the child's psychosocial needs; elucidate the role of developmental stages in the child's response to having cancer and to dying; examine the unique needs of family members of the child with cancer; discuss end-of-life decision making; identify resources for families in the development of posttraumatic growth and resilience; and synthesize this information alongside the role of pediatric palliative care in partnership with the pediatric psycho-oncology team.

11.2 The Child with Cancer

11.2.1 Child Development in the Child with Cancer

A child's experiences while living with cancer may have a significant impact on the experience of the child dying with cancer. Prior to discussing ways to care for the dying child and his family, a brief discussion of child development is warranted. The development of the child continues throughout cancer treatment and affects the manner in which the child lives and dies. In parallel, the cancer experience has a separate impact on the child's development.

The psychosocial impact of cancer is significant from toddlers to teens. Children are dynamic beings who develop as a result of their experiences. Cancer impacts growth and development as the child is limited in participation at school, isolated from friends, undergoing painful procedures, encountering physical changes, and suffering from the symptoms of the disease and treatment. It is no surprise that ongoing evaluation and treatment of the youngster's psychosocial needs is a prerequisite to ensuring optimal comprehensive child-centered cancer care. It is recommended that the child with cancer and his family members receive routine systematic assessments of their psychosocial healthcare needs (Kazak et al. 2015) and the provision of psychosocial supports and interventions, including psychiatry as needed, indicated by the assessment (Steele et al. 2015).

Child development does not occur in a static environment but the cancer experience may create such an environment. The infant who is confined to a crib does not have the opportunity to explore his environment. Toddlers, preschoolers, and young school-aged children learn through play and experiences with objects and may experience isolation and disruption in their active play and learning opportunities during cancer treatment. Older school-age children and adolescents are engaged in developing relationships with their peers and gaining independence from their parents. Suddenly, dependence on parents returns right at a time when they yearn to branch out on their own. Amputation, limb-sparing surgery, hair loss, or weight changes may result in reluctance to engage with peers. As cancer treatment progresses, some children see friends less often and may feel that interactions with peers no longer afford the rich opportunities they once did. It becomes difficult to identify characteristics that inform who they will be as an adult. Social skills, academic achievement, and answering the question "Who am I?" are threatened by the cancer diagnosis. This is challenging for the child whose treatment lasts a few months but devastating for the child who spends months or years on treatment and who may be facing death. Children with cancer are often described as wise beyond their years but they may also be socially, emotionally, and spiritually delayed due to the interruptions and negative impact of cancer on development.

11.2.2 A Steep Learning Curve for Children

Despite similarities in diagnoses and treatment children are not little adults in their adaptations to cancer. When an adult is diagnosed with cancer, they have already defined many aspects of who they are. They recognize the uniqueness and qualities of various relationships, how they cope with adversity, who can assist them during the course of their disease, and how they will navigate their world of work. Adults can make decisions that will lighten the psychosocial, emotional, and spiritual challenges of the cancer experience, identify who will be instrumental in helping them through the diagnosis, request help in developing coping strategies, and ask family and friends for assistance during difficult times.

The cancer experience presents very different challenges for a child. Although most children have parents and other caring adults who provide significant support throughout the cancer journey, children sometimes have needs that those adults cannot identify or address. For example, young children may not yet have the vocabulary to articulate their fears, and older children may not yet be able to define their needs, or may be hesitant to verbalize their needs to parents for fear of adding to their parents' burden. Children usually cannot ask friends to step in or to be with them, even during critical stages of development when peer friendships are the most important relationships. Approaching the EoL as a child is the ultimate assault of feeling different and intensifies the child's awareness that they are not "normal." If the dying child has not continued his relationships with friends throughout his illness, he may feel very abandoned at the EoL and his friends may have more difficulty with grief.

As children progress through the cancer experience, they may also move through new developmental stages that bring increased understanding and anxiety regarding their diagnosis. For example, the 5-year-old diagnosed with stage IV rhabdomyosarcoma may be unaware of the significance of his diagnosis but in a year or two he may question if he is dying from the disease. He may feel a lack of trust toward parents and healthcare providers if they have not previously communicated honestly with him. Or the adolescent with acute myelogenous leukemia, who previously allowed parents to assume all responsibility for decision making, may suddenly exert his autonomy and choose to make his own decisions about his impending death. Similarly, children may grieve anew and with more intensity as they pass through developmental stages that bring with them a new understanding of their losses or impending EoL. Healthcare providers and parents should anticipate that these changes will occur and attempt to understand upcoming developmental stages before the child needs intensified support.

11.3 First: Pain and Symptom Management

Pain in a dying child may prevent him from being able to identify how to express his needs or where to go for help. Healthcare professionals should assess the child's pain frequently, seek to understand the child's pain, and work until adequate pain control has been achieved. Simultaneously, psychosocial care team members should partner with the pediatric oncologist to identify physical, psychological, social, emotional, and spiritual needs that impact the experience of pain. Pain and symptom management enables the child to focus on the psychosocial and existential pain and suffering that intensify at the EoL.

Being a child dying of cancer-related causes is even more difficult than being a child living with cancer. It is a challenge for the child to be heard in the healthcare setting. Pediatric patient reports risk being overshadowed by the reports of parents, especially as the child approaches death. Healthcare providers must work to hear the voice of the dying child related to pain, symptoms, concerns, and health-related quality of life (HRQL). Patient-reported outcomes, or PROs, are not often found in pediatric research. Rather, many studies opt to report parent or healthcare professional responses or extract data from the medical record. About 85 % of studies on children with cancer at the EoL did not include PRO measurements. One reason cited was the lack of reliable and valid instruments for use in clinical care (Hinds et al. 2007). In addition, measuring patient-reported pain can vary based on the developmental stage of the child and can be impacted by other psychosocial variables present in the ill or dying child.

HRQL measures can provide insight into the experiences of children with cancer at EoL. Measuring HRQL in children with cancer is complicated by the unique symptoms and disease burdens that make comparison to peers with or without disease difficult. Thus, it is not surprising that parent reports of HRQL have been more frequently used in research (Hinds et al. 2007). Despite the challenges, it remains best practice to attempt to gather PROs to most effectively assess the child's pain and symptoms. The recommendations from a joint workshop of the Institute of Medicine and the American Cancer Society suggest that researchers routinely collect and integrate a core group of PROs and parent reports, into the healthcare delivery system as a method to improve clinical care (Nass et al. 2015).

Children with cancer at EoL require close psychosocial surveillance in an attempt to provide intervention in remediable areas. Sadness, pain, nausea, lack of appetite, and feeling irritable were reported by one-third of children at EoL with the majority rating their pain as moderate to severe and half describing their pain as "highly distressing." Children who had received chemotherapy within the past 4 months reported greater symptom burden (Collins et al. 2000). More research is needed to determine if children who are not on active treatment or who are at home may experience less significant symptoms at the EoL. Still, parent reporting may be the only available report of a dying child's experience. Interviews of parents whose children died of cancer a mean of 3 years previously found that fatigue, pain, dyspnea, and poor appetite were the most frequent symptoms at their child's EoL, with 89 % of parents reporting that their child suffered "a lot" or "a great deal" (Wolfe et al.

2000). A decade later, 84 % of parents at a mean of 4.5 years after their child died of cancer still reported that their child had suffered “a lot” or “a great deal” from the same symptoms of pain, fatigue, and poor appetite (Heath et al. 2010).

The World Health Organization guidelines acknowledge the large proportion of children with cancer who experience pain and the “widespread inadequacy” of pain management efforts (WHO 1998). The data suggest that the majority of children diagnosed with cancer each year in the United States experience moderate-to-severe pain throughout their treatment (Mercandante 2004; Gordon et al. 2005). Painful procedures, disease- and treatment-related pain, and pain at the EoL continue to result in physical and psychosocial distress for the child with cancer. There may be a variety of reasons why pain and symptom management remains onerous. Palliative and hospice models of care are assumed to afford an increased focus on pain management. However, pediatric oncologists acknowledge that they do not always refer patients to pediatric palliative care. They would be more likely to refer patients if hospice facilities would admit a child who was still receiving chemotherapy, if palliative care was renamed “supportive care” or if palliative care was not perceived negatively by their patients (Wentlandt et al. 2014). Children who receive Medicaid are eligible for concurrent care under the Affordable Care Act of 2010. They may continue aggressive, life-prolonging, or curative treatment along with hospice care.

There is increasing responsibility for parents to manage their child’s pain at home both during treatment and possibly at the EoL. Parental attitude about children’s pain may play a significant role in the administration of pain medication. Parents are identified as most likely to undermedicate a dying child’s pain due to misconceptions regarding appropriate analgesic use and how children express pain (Fortier et al. 2012). Parents and children may be concerned about addiction, the side effects of medications, or may believe that cancer pain at the EoL is unavoidable (Ameringer et al. 2006). Adolescents may hesitate to report pain if they feel that their opinions will be ignored, that their social activities will be restricted (Wild and Espie 2004), or that they may have to undergo undesirable diagnostic tests (Ameringer 2009). Assessing a child’s cancer pain and its impact on function and quality of life requires conscientious and continuous communication, ideally with a variety of individuals, always including the child and, whenever possible, the parents, bedside nurse, child life specialist, and others who have the opportunity to observe the child in various settings.

A multimodal approach to pain treatment maximizes function by providing children with a degree of control over their pain. Utilizing complementary pain management strategies to supplement pharmacologic methods may best improve function as the child’s pain decreases. Complementary strategies including distraction, breathing for relaxation, progressive muscle relaxation, and guided imagery are among the techniques that psychologists, psychiatrists, social workers, and other healthcare professionals may employ with children with cancer and their parents. Hypnosis has been suggested to have efficacy in the reduction of pain and anxiety during venipuncture, bone marrow aspirate, and lumbar puncture. Additional research is needed that incorporates adequate power, appropriate control populations, objective measurement of results, and long-term follow-up to further legitimize hypnosis as a care modality for children living and dying with cancer (Wild and Espie 2004). It is recommended that parents learn complementary strategies so they may act as their child's coach and have the opportunity to directly contribute to their child's pain management. In addition, parents may opt to employ the strategies for personal use in coping with stress and anxiety.

The developing child brings changing physical, psychological, social, emotional, and spiritual needs to the EoL. Achieving adequate pain and symptom management is the first step in developing a healthy psychosocial foundation from which the child can move forward in their personal experience. The existence of pain may disable the dying child as he attempts to address the psychological, social, emotional, and spiritual issues that intensify near the EoL.

11.4 The Family

Cancer in childhood can impact HRQL, mental and physical health, activities of daily living, family dynamics, identity formation, parental and sibling roles, school success, a sense of meaning, and spirituality (Jones 2012). Pediatric cancer is a family illness and in order to "die well" from cancer, a child and his family must first learn to navigate all of those issues to first live well with cancer. When a child has cancer, the roles of each family member change, and the family's balance may be threatened or lost entirely. As the needs of each family member come into focus it is hoped that resources will more fully address those needs.

The challenges begin at the time of diagnosis, and follow each family member for the rest their lives. When a child dies, it is not unusual for family members to have very different experiences during the dying process and in bereavement. Some individuals may experience posttraumatic growth, or the concept that difficult life struggles can lead to an individual's growth in positive life-changing directions (Calhoun and Tedeschi 2004), and resilience will be realized. For others, struggling with anxiety, depression, guilt, and other negative emotions may become a lifelong reality. Healthcare professionals within the field of psycho-oncology assess family members for psychosocial needs and treat those issues. The recent development of psychosocial standards for children with cancer and their families, from diagnosis through bereavement, may begin to bridge the gap and ensure that all children dying with cancer and each family member will receive optimal psychosocial assessment and treatment (Wiener et al. 2015).

11.4.1 Parents

Although research regarding parents' experience at the EoL of their child is increasing, there are still more questions than answers. Culture, ethnicity, and religion should be considered to ensure that healthcare providers are sensitive to family needs and beliefs. However, the broad overview of cultural beliefs should be used only to identify the most cultural sensitive and effective way to start the conversation about EoL with the family. Despite religion or ethnicity, every child and parent is an individual and each will express unique beliefs and needs that will guide the EoL discussion. The needs of dying children and their parents become evident when trusting relationships with HCPs develop. Ongoing, thoughtful, effective, and compassionate communication can open doors that inform healthcare providers about the best care for that individual child, parent, or family member.

Parents' needs are most critical at three stages surrounding their child's EoL: when making decisions related to their child's impending death, immediately preceding and at the time of death, and during bereavement. Parents have extremely difficult decisions to make when their child is dying with cancer and it is important for healthcare professionals to work with parents and support them in decision making. The personal preferences or beliefs of the healthcare professional must be removed from the decision making process unless there is concern that the child is suffering or being harmed in some way by parental decisions. Some parents want their child to receive aggressive life-sustaining treatment (LST) until the child's body stops functioning. Other parents request that all life support be removed for fear that their child will suffer or to ensure that the child dies with dignity. It is agonizing for parents to make decisions that will have some impact on either their child's quality of quantity of life. Parents may state that they cannot possibly make a decision and may ask the physician to make the decision regarding when LST should cease. It is widely accepted that parents should make these decisions in the best interest of their child. Regardless of what decision a parent makes, they will carry the decision with them for the rest of their life. Compassionate, gentle support and guidance from the healthcare team will enable parents to make the choice that they believe is in the best interest of their child.

The current orthodoxy is that most people would prefer to die at home. However, freedom from distress and pain and being surrounded by loved ones tends to trump location of death as EoL approaches (Waghorn et al. 2011). Dying at home does not constitute a "good death" for all individuals. Parents should feel supported in whichever location is chosen for their child's death. Some children and parents prefer to continue to receive care and support in the hospital, especially when strong relationships have developed with the cancer care team. Children who are permanently ventilator dependent may have to live in a ventilator care center or a nursing home. Healthcare professionals should support the family with their choice regarding location of death and focus on identifying ways to improve quality of care in all places children with cancer die, including hospitals, nursing homes, and the child's own home. When a child is dying in the hospital parental needs increase. These needs include a place to sleep; the ability to participate in their child's care; the opportunity to be with their child and to be able to talk to, touch, hold, and protect their child; to know that their child's pain is adequately controlled; to receive complete information about their child in a way that they can understand; to feel free to ask questions; and to have their authority as a parent respected. When these needs are not adequately met parents report higher levels of complicated grief symptoms 6 months after the child's death (Meert et al. 2012).

For some children with cancer, a consequence of extended medical treatment is significant changes in their physical appearance. Parents vividly remember these changes and may feel frustrated and hurt that their child had to suffer. Many parents find it helpful to share in their child's daily care during this process. Parents report sadness when they cannot hold their dying child and that they feel comforted when they are physically close to the dying child, lying with the child in one bed, holding the child in the hour of or after death, and washing the child after death (Falkenburg et al. 2016). Parents' transition from providing active care for their child in the hospital to the days after the child's death is a stark change. Offering tangible memories of the child may aid in reducing the contrast of having a child one day and not having their child the next. Blankets, pillowcases, stuffed animals, or articles of clothing that carry the scent of the child may be treasured by parents. Other memories may be created by nurses or child life specialists and placed in a box to be given to the parents. Locks of hair, molds of hands and feet or photographs of the child and family may provide additional comfort in coming days. Advance care planning should include an understanding of what will bring comfort to the individual family during the days, hours, and minutes prior to the child's death.

Retrospective studies reveal common themes of what is important to parents when a child is dying with cancer. In a meta-ethnography of parental decision making at the EoL of their child, three major themes were identified by parents as being of the greatest importance as their child was dying. First, a multifaceted concept of communication emerged to include comprehensive discussions regarding all aspects of their child's diagnosis, prognosis, positive and negative effects that might alter treatment decisions, and emotional communication including comforting the parent. Next, parents expressed wanting more time with their child as a key factor in considerations and decision making. Parents shared a desire to have both palliative care and cancer-directed therapy concurrently. Some parents, in hindsight, would have chosen to stop medical care sooner. Finally, a desire to understand their child's prognosis was cited as a factor when making EoL decisions for their child. Many parents acknowledged that their goals approximated those of their child's oncologist when the doctor communicated effectively regarding prognosis. Differences between the oncologist's prognosis and that of others, such as the intensivist or palliative care specialist, for example, were difficult for parents to understand (Heinze and Nolan 2012). These themes may serve to provide a point of reference for healthcare professionals as they work to communicate effectively with the child's family as the child is dying.

11.4.2 Siblings

Siblings of children with cancer have long been a population whose needs are recognized but not always addressed. While the body of research regarding bereaved parents' psychosocial outcomes increases, there continues to be a paucity of literature regarding the needs of siblings when a brother or sister dies (Rosenberg et al. 2012). Siblings of children dying with cancer are a psychosocially at-risk group and should be provided with appropriate supportive services. Parents and professionals should be advised about ways to anticipate and meet siblings' needs, especially when siblings are unable to visit the hospital regularly (Gerhardt et al. 2015).

Increased rates of anxiety, depression, and illicit substance use during the year after their loss was reported in a study of siblings who had lost a brother or sister about 12 years previously. The participants cited lack of communication, poor preparation for their sibling's death, not getting to say goodbye and a perception that the cancer experience had a negative impact on relationships in their family as the reasons for their challenges, which returned to baseline after the first year. It was agreed among nearly all siblings that, despite those improvements, they still were affected by the loss 12 years later and about half reported that the experience affected their career and educational goals (Rosenberg et al. 2015). Other investigations identified siblings with a higher risk of anxiety when their social support needs were unmet the last month of their brother or sister's life (Eilertsen et al. 2013) and lower self-esteem, difficulties falling asleep, and lower maturity levels 2–9 years post the death of a brother or sister (Eilegård et al. 2013). Of note is that siblings may also experience posttraumatic growth after their brother or sister's death. Nearly all siblings report changes in perspectives, interests, and relationships in the year after their brother or sister has died. These changes include positive alterations, which include personal growth, new meaning, or purpose (Foster et al. 2012). Severe psychopathology is rare but there are several reviews that identify anxiety, depression, post-traumatic stress, lower quality of life, decreased healthcare utilization, and disruption to academic and social functioning as long-term problems for bereaved siblings of children who died with cancer (Alderfer and Hodges 2010; Alderfer et al. 2004; Sveen et al. 2014; Kacel et al. 2011). Bereaved siblings also frequently exhibit greater challenges than peers who are not bereaved (Wilkins and Woodgate 2005).

The field of psycho-oncology may have the chance to learn from missed opportunities. Of note is The International Society for Pediatric Oncology guidelines for the support of siblings of children with cancer published almost 20 years ago (Spinetta et al. 1999). The guidelines called for healthcare professionals and parents to involve siblings immediately after the child's diagnosis with cancer and to keep them informed throughout the cancer trajectory, emphasizing the positive and optimistic aspects of treatment whenever possible. Despite these recommendations, supports for siblings continue to be sparse in many programs. Access constitutes a significant challenge as most healthcare professionals involved in sibling support are not at the hospital or treatment center when siblings typically visit on nights and weekends. Some siblings may have limited or no opportunities to visit if the family lives a distance away from the cancer treatment center.

A new opportunity to identify ways to support siblings presents in a more recent set of guidelines (Gerhardt et al. 2015). The guidelines describe broad categories that should be considered in the standard of care for siblings of children with cancer including sibling stressors, communication needs, psychosocial impact, bereaved siblings, supportive care and barriers. The findings related to bereaved siblings describe siblings' desire to be involved and informed when their brother or sister is dying. In addition, the guidelines emphasize the potential for bereaved siblings to have increased incidence of internalizing problems, difficulties in peer relationships, and long-term outcomes affecting educational and career goals. It is recommended that ongoing support is provided to families, especially following the death of a child.

Siblings usually want to be where their brother or sister and parents are at the end of the child's life. Parents' desire to protect their healthy child(ren) may result in denying visits so the sibling does not have to see his brother or sister as they are dying. Parents should receive counseling and support in how to address this issue with their other child(ren). Siblings should be offered the opportunity, with age-appropriate guidance and preparation, to see their brother or sister who is dying to be able to say their good-byes (Giovanola 2005) and to participate as much as they desire in funeral planning and attendance.

Including the adult caregivers in the sibling's natural environment is another opportunity to improve support when a child is losing or has lost a brother or sister with cancer. It is impractical to assume that siblings' needs can all be assessed and addressed in the healthcare environment when siblings spend minimal time there. Siblings live in their own natural environments of school, activities, worship, friendships, and family. As psychosocial palliative care for dying children and their families expands, creative ways of addressing siblings' needs should be considered. Teachers, counselors, coaches, spiritual leaders, and others may be provided with the resources to enable them to be the youngster's coach or mentor during their brother or sister's illness, death, bereavement, and beyond. Investigation is needed to better understand the relationships between identifiable risk factors such as a bereaved sibling's gender, age, and developmental level. Development of better communication with siblings and a comprehensive understanding of long-term outcomes may afford additional opportunities for improved psychosocial care for siblings.

11.4.3 Grandparents

Grandparents may be a disenfranchised group during the EoL of a child with cancer. Very limited research exists on the psychosocial impact on grandparents when a grandchild dies of cancer (Wakefield et al. 2015). A higher proportion of grandparents of children with cancer report clinically relevant distress, depression, and anger when compared to controls. Grandparents more often seek religious or spiritual support but rarely (<5 %) seek evidence-based psychosocial support when grieving the death of a grandchild. Untreated distress of grandparents may reduce their capacity to support their families (Wakefield et al. 2014).

Grandparents play a significant role in the family and in society and may have complex and demanding expectations within those roles (Thiele and Whelan 2008). Grandparents of children with cancer report feeling helpless as they watch both their child and their grandchild suffer. Their role in the family of a dying child may be poorly defined and they may not know how to help. They express a desire to trade places with their grandchild because of their own advanced age (Moules et al.

2012a). A study of the physical and mental health, grief, and role functioning for 136 grandparents in the first year after the death of their young grandchild (newborn through age 6) found grandparents experienced clinical depression (31 %), PTSD (35 %), physical illnesses (28 %), hospitalizations, new chronic health conditions (mental disorders, hypertension, angina, cancer), and medication changes (Youngblut et al. 2015).

Grandparents suggest that additional information would be helpful, including information about their grandchild's chance of survival, side effects of the treatment or symptoms of the cancer (Moules et al. 2012b), and the chance for a relapse or recurrence of the disease (Wakefield et al. 2014). Grandparents may be reluctant to ask their child about their grandchild's cancer for fear of adding additional stress to their child (Moules et al. 2012a). With the consent of their adult child, and, when appropriate, grandparents' access to information may prove beneficial to all stakeholders. Siblings are often in the care of the grandparents while the parents go back and forth to the hospital and, with guidance about what to tell the sibling, grandparents could offer support to the siblings by helping address their fears and concerns.

11.4.4 Extended Family and Community

A diagnosis of cancer in a child results in an individual and group impact in the community; for example, in the school, place of worship, baseball team, ballet class, Boy or Girl Scout troop, within the child's circle of friends, and among their extended family. Peers are often confronting their first experience of the death of someone they know and care about. Most community members are not comfortable in knowing what to say, what to do, and how to help the child when he returns after being away from activities. Acknowledging this discomfort and addressing individual and group concerns may provide those who care about the child with the opportunity to support the child and family during the illness, around the time of death, and through bereavement.

The best manner in which to address the child's peers will be dependent upon the age of the child with cancer and his cohorts. Children's inquisitiveness suggests the need to provide developmentally appropriate, accurate information about the child's disease while also affording an opportunity for peers to begin to learn how to support others during difficult times. A preschool-age child might worry that they caused their peer's illness because they fought with the child on the playground and the early elementary-age child's concerns might be the belief that cancer is contagious so they may catch it if they play with the child with cancer. An older elementary or middle-school child is likely to be uncomfortable with the child's hair loss or any other physical changes that make him "different" from the norm. A slightly more mature high schooler might attempt to distance himself from his friend with cancer or engage in early separation in fear of how they will feel if their friend dies. With parental and child consent, healthcare professionals may be in a position to offer accurate information to peers by providing classroom presentations, science lessons, or group assemblies at the child's school. Professionals can also provide suggestions to families about posting information and needs on a social media site to keep information flowing while simultaneously reducing the need for parents to make frequent phone calls or emails to update individuals.

Despite these challenges, most individuals are able to get beyond their personal concerns and begin to provide support to the child and family. It is common to observe schools, places of worship, or other groups work in tangible ways to help the child and family. In the early days and weeks after the diagnosis, dinners are brought to the family, fund-raisers occur, and offers to help typically pour in. However, when the child and family have to be away from home for an extended period of time, if the child has a relapse or recurrence of the cancer, or if the group does not receive feedback regarding their contributions, support begins to wane. As days turn into weeks and weeks become months, the child's cancer begins to take on a "normalcy" and supportive community involvement decreases. When death is imminent there may be a renewed sense of shock among those who care about the child and family with an associated resurgence of support.

One solution is to keep the child visible to those with whom he would typically interact in his natural environments. Maintaining close relationships throughout the child's disease and treatment helps lay a strong foundation of support for the child and family throughout the child's disease trajectory. The dying child's ability to reach out and have meaningful end-of-life conversations is probably limited. To hear from his teacher, baseball coach, Boy Scout leader, and friends may bring great comfort to the child in the final days or weeks of life. For peers, developing skills to express support for friends who are dying will likely be beneficial when losses occur in their future.

11.5 EoL Decision Making and Communication

As the EoL approaches, the child, family, and healthcare professionals, each experiences increased tension and sadness. Feelings become more intense, confusing, and often overwhelming. This time calls for the healthcare team to provide focused, comprehensive, and compassionate family-centered care to the child and family. Frequent and effective communication becomes even more critical as the oncologist and other professionals talk with the child and parents, sometimes several times a day, while lending support and guidance in decision making.

For some families, developing an advance directive (AD) may be a powerful and unifying experience. Advance care planning may demystify death and allow the child, parents, and siblings the opportunity to talk about shared feelings, hopes, and fears. Solutions to concerns may become evident when fears are exposed and loved ones can understand and help one another. The dying child may experience a normalizing effect when each family member fills out an AD form.

Minor children may assent to EoL decisions despite being unable to complete a legally binding AD. Several options are available, most of which are listed on the International Children's Palliative Care Network (ICPCN) site (ICPCN 2015). Hearing the child's hopes for his EoL experience, memorial service, and his concerns about leaving his family may result in discussions that will be treasured by parents and siblings and bring comfort to the child who is dying. Parents may experience pride and relief as they later realize that they carried out their child's wishes during and after his death. For healthcare professionals, encouraging families to engage in informal advance care planning from diagnosis forward may result in making the process familiar and nonthreatening when formalized EoL discussions are indicated. Although it may be difficult to know the best time to introduce advance care planning to the child and family, the outcomes make it a critical part of psychosocial care.

Healthcare professionals often report being hesitant to talk to young people about end-of-life due to concern about taking away the child's hope or increasing fear and anxiety (Lyon et al. 2004, 2009; Wiener et al. 2015). The end result of this selective communication by healthcare professionals may be a false sense of child and parental hope, which may not allow the patient and family to adequately prepare for the possibility of a poor outcome (Meert et al. 2008). Pediatric healthcare professionals, typically, agree that advance care planning has benefits including providing a sense of security and control, improving quality of care, and ensuring respect for patient's and parents' wishes. However, providers also cite barriers to advance care planning discussions as including unrealistic expectations by parents, differences between patients'/parents' and physicians' understanding of prognosis, parents' lack of readiness for such discussions, fear of taking away hope, physician uncertainty about prognosis, and uncertainty about how to address the topic of advance care planning (Lotz et al. 2014). Additional training may benefit healthcare professionals who must have difficult EoL discussions patients and parents. However, studies of the patients themselves indicate that they are actually comfortable having discussions about their preferences at the end-of-life, and want to be included in such decisions (Moules et al. 2012a).

When adolescents with cancer and parents join one another to discuss family-centered advance care planning, parents have the opportunity to hear their adolescent's fears, hopes, and preferences including choices that may include discontinuation of unnecessary or unwanted care (Lyon et al. 2009). Further, parents verbalize a commitment to honor these decisions. Adolescents who participated in advanced care planning demonstrated decreased anxiety and these changes increased over time. These teens thought that the best times to bring up EoL discussions were before being sick (19 %), at the time of diagnosis (19 %), when dying (25 %), and 38 % agreed that any of those times would be appropriate. Of note is the fact that none of the teens thought that the first hospitalization was the appropriate time (Lyon et al. 2013).

The preferences of adolescents with advanced cancer who had recently made end-of-life decisions were found to have views regarding treatment which were very similar to those of their parents and physicians. Key areas of agreement among the three groups included considering the preferences of others, preventing or reducing suffering, and ensuring that all treatment options are exhausted. Holding on to hope, communicating honestly, striving for relief from symptom burden, and caring for one another were found to be mutual themes across stakeholders (Weaver et al. 2016).

When the point comes that children can no longer speak on their own behalf due to their illness, parents have a unique challenge as the sole decision maker for their child. Parents express a strong need to be perceived as a "good parent," and they may need reinforcement from their child's HCPs to acknowledge that they are acting in their child's best interest or that the decisions that they are making would be embraced by their child (Feudtner et al. 2015). Healthcare professionals can reassure parents by acknowledging that any decision they make for their child will be the correct decision because it is being made from a place of love and respect for their child. Little is known regarding how parents make decisions about their child's EoL but an early study to address parents' EoL decision making for their child with cancer revealed the complexity of the process (Hinds 1997). Parents must consider the impact both on the comfort of the dying child (Kars et al. 2011) and the well-being of surviving family members (Kreicbergs et al. 2004). Healthcare providers can best support families when they understand end-of-life decision making from the parents' point of view.

Communication is especially important among children with cancer, parents/families, and healthcare professionals at the time a patient begins to experience health decline. Techniques that are essential to effective communication between stakeholders have been identified as including patients in treatment decisions, continuing relationship building, ensuring caring and empathy guide communications, using an interdisciplinary team for additional child and family support, and pairing bad news with an action plan (Snaman et al. 2016). Parents and patients begin cancer care hoping for the best from treatment and, when treatment fails, families may hope that their child will be the recipient of a miracle. As the last shred of hope abates, parents are overwhelmed.

Patients, parents, and professionals may all agree that communication, especially near the EoL, should be frequent, open, honest, and provide families the information they need to make decisions regarding the child's care. Parents may also find that too much information also leads to confusion and stress. Parents' request for a plan of action suggests that they also need reassurance that the team understands the difficulty the family faces and that trusted healthcare professionals will continue to be there for the child and family.

11.6 Pediatric Palliative Care

Pediatric palliative care (PPC) has been described as a competent, compassionate, and consistent mode of healthcare for children with life-limiting diagnoses or chronic complex conditions and their families (Friebert 2009). PPC has several purposes, the first being to improve the quality of life of the child and family. In addition, PPC works to minimize physical pain and symptoms, as well as to address psychosocial, emotional, and spiritual needs. In order for palliative care to have the greatest impact, collaboration is needed between the patient, family, friends, and healthcare professionals (Finlay et al. 2008). Palliative care in adult oncology is often synonymous with EoL care. It is not unusual for an adult oncology patient to receive palliative care in the last days or weeks of life. In pediatrics, palliative care provides a very different model of care, which supports the developing child with a life-limiting diagnosis to continue to grow and achieve as typically as possible. Individual prognosis is unknown at diagnosis and it is too late to begin to address a child's needs when EoL is approaching. Ideally, PPC begins at the time a child is diagnosed with cancer and addresses the child's needs throughout the cancer experience, whether that ends in cure, a long-term chronic illness, or death.

The American Academy of Pediatrics (AAP) suggests the integration of pediatric palliative care into the care continuum.

PPC-PHC (pediatric hospice care) should be provided as collaborative integrated multimodal care, including cure-seeking, life-prolonging (when in the child's best interest), comfort-enhancing, and quality-of-life enriching modes of care, along with psychological, spiritual, and social support for the family. Collaboration is essential; patient, parents, other involved extended family members and friends, schools, parental employers, and all involved members of the primary and specialty healthcare team must collaborate to meet the needs of patients most effectively.

For all patients, high-quality PPC-PHC should routinely prevent and treat distressing symptoms such as pain, nausea, or anxiety, and seek to maximize quality of life, which may entail various interventions depending on the patient's specific goals. Dedicated specialty PPC-PHC teams should be consulted for advanced clinical treatments and complicated decision making and for social and spiritual needs beyond what the primary care team can provide. These consultations can occur throughout the child's illness experience, including at initial diagnosis, when the goals of care are focused on cure. PPC-PHC should be integrated throughout the illness course, providing interventions to support the goals of care, which often shift over time. After initiating a PPC or PHC consultation, the patient's medical home and all providers (including primary pediatricians or family medicine physicians, pediatric specialists, and surgeons) should remain fully engaged in the well-coordinated care for the child (AAP 2013).

Emotional domains of care at the EoL were statistically improved with introduction of comprehensive palliative care interventions for children with cancer (Wolfe et al. 2008). Today, most children's hospitals and many pediatric departments in larger hospitals have developed palliative care teams. Some hospice agencies also incorporate palliative supports into the care plans of children who are living with chronic conditions. Services address the physical, psychological, social/emotional, and spiritual needs of the child and family. The pediatric oncology team directs the physical care of the child, while the PPC team focuses on the other domains. The time that children spend at the hospital is usually limited. More time is spent at school, with friends and in activities. Therefore, psychological, social/emotional, and spiritual needs exist outside the hospital setting. When palliative care programs can partner with the professionals in the child's natural environments, children receive comprehensive palliative supports in the locations where they continue to grow, play, learn, and develop. Education and support from the healthcare palliative team can support and empower caring adults in the child's natural environments.

PPC is not a familiar concept in all pediatric oncology programs. In 1998, the American Society of Clinical Oncology (ASCO) surveyed its membership in an effort to determine attitudes, practices, and challenges associated with EoL care for patients with cancer (Hilden et al. 2001). The pediatric oncologists who responded cited a lack of formal courses in pediatric palliative care, a strikingly high reliance on trial and error in learning to care for dying children, and a need for strong role models in the area of EoL care. Most cited the lack of an accessible palliative care team or pain service as a barrier to optimal care. Communication challenges were described between parents and oncologists, mostly in regard to pain management and the shift to EoL care. The cry for increased resources was heard. Commencing in April 2013, Education in Palliative and End-of-life Care for Pediatrics (EPEC) training is offered online and at national oncology conferences (EPEC 2016). When PPC is at its best, pediatric oncologists and pediatric palliative care providers collaborate to support the provision of pediatric palliative care by an interdisciplinary team model that is accessible in all patient settings, including outpatient clinics, acute and long-term care facilities, and private homes (Ferris et al. 2009).

The intersection of oncology and palliative care has resulted in a relatively new field, psychosocial oncology or psycho-oncology. This field includes the study of the psychological reaction of patients at all stages of cancer as well as of the reactions of the family and oncology staff. Ensuring that all children with cancer receive a timely referral to PPC will also ensure that psycho-oncology is a standard part of ongoing care for children with cancer.

11.7 Posttraumatic Growth and Resilience in Children and Families

The concept of posttraumatic growth (PTG) is a construct of positive psychological change that occurs as the result of one’s struggle with a highly challenging, stressful, and traumatic event. Posttraumatic growth is described as the ability to make sense or find meaning from a traumatic experience (Calhoun and Tedeschi 2004). Healthcare professionals have an ethical responsibility to support families of children who are dying. This responsibility is predicated on (1) the best interest of the child and (2) nonabandonment. Reducing parent distress and increasing the opportunity to experience posttraumatic growth in parents is a benefit of providing this type of psychosocial care for family members of children with cancer (Jones et al. 2014). Further, parents who evidence higher levels of self-esteem, find meaning in caregiving, and have a defined sense of spirituality are found to have higher levels of posttraumatic growth. Conversely, higher depression scores were correlated with caregiver burden and feelings of abandonment (Calhoun and Tedeschi 2004).

Resilience is also believed to be correlated to parent and family well-being when a children has cancer. Resilience suggests an ability to withstand stress and to recover significantly, if not completely, from traumatic events. Resilience research holds the promise of avenues to promote positive psychosocial outcomes while minimizing negative ones in children with cancer and their parents (Rosenberg et al. 2013a).

11.8 Bereavement

After a child dies with cancer, bereavement is experienced by families, friends, the community, and the healthcare team. For the family, strong communication and compassion around the time of a child’s death better enables them to begin the grief or bereavement process, models ways to effectively provide support for one another and will, hopefully, decrease the incidence of complicated grief (Rosenberg et al. 2013b). Complicated grief is a chronic debilitating condition characterized by intense yearning for the deceased, frequent thoughts and images of the deceased, feelings of shock and disbelief, extreme loneliness, a lack of purpose, avoiding reminders of the deceased, or excessive proximity seeking (Cadell et al. 2012). Symptoms are often persistent and may last for months or years, leading to impaired function in occupational, social, and relational realms (Shear et al. 2011).

The pediatric oncology patient's family becomes an extension of the child's care after his death as the same physical, emotional, and spiritual care that was provided the child follows his family into bereavement. Parents often report, anecdotally, that they continue to struggle with adjusting to the loss of a child for the remainder of their lives, particularly if they feel that their child suffered or did not have the type of death that the child or parents would have preferred. After the death of a child, parents are at higher risk for complicated grief and associated challenges, while siblings, especially sisters, may have difficulty adjusting after the loss of a brother or sister (Machajewski and Kronk 2013). Surviving siblings exhibit irritability, sullenness, loneliness, and require increased attention as they are expressing grief over the death of a brother or sister (Dickens 2014). Both parents and teachers suggest that grieving siblings perform significantly lower in social competence, higher in social withdrawal, and higher in aggression than standardized norms or control groups (Silverman et al. 2003). As a result, the care provided by the healthcare team after the death of a child is of great importance to the individual surviving family members and to the family unit. Evidence suggests that the standard of care should include at least one bereavement meeting between the healthcare team and bereaved parents in order to identify parents at risk for negative psychosocial outcomes and to provide them with bereavement resources (Lichtenthal et al. 2015).

Pediatric oncologists report a wide range of feelings when a patient dies, including sadness, crying, sleep loss, exhaustion, physical illness, and a sense of personal loss. In addition to these typical feelings of grief, feelings of self-questioning, guilt, failure, and helplessness are experienced by those who were interviewed. Feeling irritable at home, disconnected from family members and friends, becoming more desensitized toward death, and gaining a greater and more appreciative perspective on life were described as pediatric oncologists expressed concern about burnout as well as improving holistic care due to experiencing the death of patients. Recommendations to aid in avoiding those adverse effects include training in communication and in developing resiliency, education about avoiding burnout, strategies for improving methods of delivering bad news, and a strong focus on work-life balance (Granek et al. 2016).

Conclusion

Children are dynamic beings who are constantly developing and changing in their ability to comprehend illness and death. A child who is facing his own death benefits from whole-person care that includes a strong child and family-centered approach. From toddlers to teens, children respond best to adults who engage in effective communication with the child and in whom the child feels a sense of trust. Talking with and listening to the child may enable the child to have a relationship with HCPs that lead him to a better understanding of his illness, treatment, and EoL issues. The ability to communicate with HCPs also enables the child and parents to express their wishes regarding advance care planning. When decisions are made about what will occur during routine treatment, it becomes easier for the child and parents to later talk about Do Not Attempt Resuscitation or other EoL topics when they must do so.

Children who are dying have needs across physical, psychosocial, and spiritual domains and, therefore, require effective and ongoing assessment and treatment by professionals in pediatric oncology, palliative care, and psycho-oncology. The child may benefit from interventions provided by child life therapy, music and/or art therapy, occupational and/or physical therapy, speech and language pathology, spiritual advisors, friends and volunteers. In addition, schoolteachers, athletic coaches, Girl/Boy Scout leaders, religion teachers, and others with whom the child has a meaningful relationship should be considered as important partners who may bring an added dimension to the child's EoL experience.

In addition, those who care about the dying child are also experiencing a unique and personal loss of their own. A child's death has an impact on friends, cousins, aunts and uncles, teachers, teammates, other community members and healthcare professionals. Psychosocial care and support should be available to all individuals who care about the child. If there are not adequate resources in the dying child's healthcare environment to provide support, referrals should be made to outside counselors, mental health facilities, school professionals, and other providers. Self-care and coping strategies are critical to HCPs who frequently care for children who die.

Addressing the widespread impact of the death of a child with cancer is a first step that enables healing to begin. The experience may have a strong influence on future experiences of loss for each family member or friend who grieves the child. Acknowledging one's grief, and the opportunity to engage in grief work, may enhance the opportunity for all who cared about the child to develop posttraumatic growth and resilience and be prepared to support others with similar needs.

References

Adler NE, Page AEK (eds) (2008) Cancer care for the whole patient: Meeting psychosocial health needs. Institute of Medicine (US) Committee on the Psychosocial Services to Cancer Patients/Families in a Community Setting. National Academies Press (US). Institute of Medicine, Washington, DC

Alderfer MA, Hodges J (2010) Supporting siblings of children with cancer: a need for family-school partnerships. School Ment Health 2(2):72–81

Alderfer MA, Labay LE, Kazak A (2004) Brief report: does posttraumatic stress apply to siblings of childhood cancer survivors? J Pediatr Psychol 28(4):281–286

American Academy of Pediatrics, Section on Hospice and Palliative Medicine and Committee on Hospital Care. Policy Statement. Pediatric Palliative Care and Hospice Commitments, Guidelines, and Recommendations. http://pediatrics.aappublications.org/content/pediatrics/132/5/966.full.pdf. Accessed 15 Feb 2016

American Cancer Society (2015) Cancer facts and figures 2015. American Cancer Society, http://www.cancer.org/research/cancerfactsstatistics/cancerfactsfigures2015/. Accessed 14 May 2016

Ameringer S (2009) Barriers to pain management among adolescents with cancer. Pain Manag Nurs 11(4):224–233

Ameringer S, Serlin RC, Hughes SH, Frierdich SA, Ward S (2006) Concerns about pain management among adolescents with cancer: developing the Adolescent Barriers Questionnaire. J Pediatr Oncol Nurs 23(4):220–232

Cadell S, Kennedy K, Hemsworth DJ (2012) Informing social work practice through research with parent caregivers of a child with a life-limiting illness. Soc Work End Life Palliat Care 8(4):356–381

Calhoun LG, Tedeschi RG (2004) The foundations of posttraumatic growth: new considerations. Psychol Inquiry 15:93–102

Carlson LE, Waller A, Mitchell AJ (2012) Screening for distress and unmet needs in patients with cancer: review and recommendations. J Clin Oncol 30:1160–1177

Collins JJ, Byrnes ME, Dunkel IJ, Lapin J, Nadel T, Thaler HT, Polyak T, Rapkin B, Portenoy RK (2000) The measurement of symptoms in children with cancer. J Pain Symptom Manage 19(5):363–377

Curesearch (2015) Childhood cancer deaths per year. CureSearch for Children's Cancer, http://curesearch.org/Childhood-Cancer-Deaths-Per-Year. Accessed 14 May 2016

Dickens N (2014) Prevalence of complicated grief and posttraumatic stress disorder in children and adolescents following sibling death. Fam J Counsel Ther Couples Fam 22:119–126

Disraeli B (1833) The Wondrous Tale of Alroy, the Rise of Iskander (Saunders and Otley, London), Part 10, Chapter 3. Accessed at http://www.rc.umd.edu/editions/alroy/novel/p10c3.html. 12 May 2016

Eilegård A, Steineck G, Nyberg T, Kreicbergs U (2013) Psychological health in siblings who lost a brother or sister to cancer 2 to 9 years earlier. Psychooncology 22(3):683–691

Eilertsen ME, Eilegård A, Steineck G, Nyberg T, Kreicbergs UJ (2013) Impact of social support on bereaved siblings' anxiety: a nationwide follow-up. Pediatr Oncol Nurs 30(6):301–310

EPEC (2016) Education in Palliative and End-of-Life Care. Accessed on January 13, 2016 at http://www.epec.net/

Falkenburg JL, Tibboel D, Ganzevoort RR, Gischler S, Hagoort J, van Dijk M (2016) Parental physical proximity in end-of-life care in the PICU. Pediatr Crit Care Med. Accessed 27 Feb 2016 [Epub ahead of print] http://www-ncbi-nlm-nih-gov.proxy.kumc.edu:2048/pubmed/?term=Falkenburg+JL%2C+Tibboel+D%2C+Ganzevoort+RR%2C+Gischler+S%2C+Hagoort+J%2C+van+Dijk+M+(2016)+Parental+physical+proximity+in+end-oflife+care+in+the+PICU.+Pediatr+Crit+Care+Med.+Accessed+27+Feb+2016+%5BEpub+ahead+of+print%5D

Ferris FD, Bruera E, Cherny N, Cummings C, Currow D, Dudgeon D, JanJan N, Strasser F, von Gunten CF, Von RoennAm JH (2009) Palliative cancer care a decade later: accomplishments, the need, next steps—from the American society of clinical oncology. J Clin Oncol 27(18):3052–3058

Feudtner C, Walter JK, Faerber JA, Hill DL, Carroll KW, Mollen CJ, Miller VA, Morrison WE, Munson D, Kang TI, Hinds PS (2015) Good-parent beliefs of parents of seriously ill children. AMA Pediatr 169(1):39–47

Finlay F, Lewis M, Lenton S, Poon M (2008) Planning for the end of children's lives – the lifetime framework. Child Care Health Dev 34:542–544

Fortier MA, Wahi A, Bruce C, Maurer EL, Stevenson R (2012) Pain management at home in children with cancer: a daily diary study. Pediatr Blood Cancer 61(6):1029–1033

Foster TL, Gilmer MJ, Vannatta K, Barrera M, Davies B, Dietrich MS, Fairclough DL, Gerhardt CA (2012) Changes in siblings after the death of a child from cancer. Cancer Nurs 35(5):347–354

Friebert S (2009) NHPCO facts and figures: pediatric palliative and hospice care in America. National Hospice and Palliative Care Organization, Alexandria

Gerhardt CA, Lehmann V, Long KA, Alderfer MA (2015) Supporting siblings as a standard of care in pediatric o(ncology. Pediatr Blood Cancer 62(Suppl 5):S750–S804

Giovanola J (2005) Sibling involvement at the end of life. J Pediatr Oncol Nurs 22(4):222–226

Gordon DB, Dahl JL, Miaskowski C, McCarberg B, Todd KH, Paice JA, Lipman AG, Bookbinder M, Sanders SH, Turk DC, Carr DB (2005) American pain society recommendations for improving the quality of acute and cancer pain management: American Pain Society Quality of Care Task Force. Arch Intern Med 165(14):1574–1580

Granek L, Barrera M, Scheinemann K, Bartels U (2016) Pediatric oncologists' coping strategies for dealing with patient death. J Psychosoc Oncol 34(1-2):39–59

Heath JA, Clarke NE, Donath SM, McCarthy M, Anderson VA, Wolfe J (2010) Symptoms and suffering at the end of life in children with cancer: an Australian perspective. Med J Aust 192(2):71–75

Heinze KE, Nolan MT (2012) Parental decision making for children with cancer at the end of life: a meta-ethnography. J Pediatr Oncol Nurs 29(6):337–345

Hilden JM, Emanuel EJ, Fairclough DL, Link MP, Foley KM, Clarridge BC, Schnipper LE, Mayer RJ (2001) Attitudes and practices among pediatric oncologists regarding end-of-life care: results of the 1998 American Society of Clinical Oncology survey. J Clin Oncol 19(1):205–212

Hinds PS, Brandon J, Allen C, Hijiya N, Newsome R, Kane JR (2007) Patient-reported outcomes in end-of-life research in pediatric oncology. J Pediatr Psychol 32(9):1079–1088

Hinds PS (1997) Revising theories on adolescent development through observations by nurses. J Pediatr Oncol Nurs 14(1):1–2

International Children's Palliative Care Network (ICPCN) End-of-life planning, http://www.icpcn.org/resources-for-end-of-life-planning-and-care/. Accessed 12 Dec 2015

Jacobsen PB, Wagner LI (2012) A new quality standard: the integration of psychosocial care into routine cancer care. J Clin Oncol 30:1154–1159

Jones B (2012) The challenge of quality care for family care-givers in pediatric cancer care. Semin Oncol Nurs 28(4):213–220

Jones BL, Contro N, Koch KD (2014) The duty of the physician to care for the family in pediatric palliative care: context, communication, and caring. Pediatrics 133(Suppl 1):S8–S15

Kacel E, Gao X, Prigerson HG (2011) Understanding bereavement: what every oncology practitioner should know. J Support Oncol 9(5):172–178

Kars MC, Grypdonck MH, van Delden JJ (2011) Being a parent of a child with cancer throughout the end-of-life course. Oncol Nurs Forum 38(4):E260–E271

Kazak AF, Abrams AN, Banks J, Christofferson J, DiDonato S, Grootenhuis MA, Kabour M, Madan-Swain A, Patel SK, Zadeh S, Kupst MJ (2015) Psychosocial assessment as a standard of care in pediatric cancer. Pediatr Blood Cancer 62(Suppl 5):S426–S459

Kreicbergs U, Valdimarsdóttir U, Onelöv E, Henter JI, Steineck G (2004) Anxiety and depression in parents 4-9 years after the loss of a child owing to a malignancy: a population-based follow-up. Psychol Med 34(8):1431–1441

Lee V, Cohen SR, Edgar L, Laizner AM, Gagnon AJ (2006) Meaning-making and psychological adjustment to cancer; development of an intervention and pilot results. Oncol Nurs Forum 33(2):291–302

Lichtenthal WG, Sweeney CR, Roberts KE, Corner GW, Donovan LA, Prigerson HG, Wiener L (2015) Bereavement follow-up after the death of a child as a standard of care in pediatric oncology. Pediatr Blood Cancer 62(Suppl 5):S834–S869

Lotz JD, Jox RJ, Borasio GD, Führer M (2014) Pediatric advance care planning from the perspective of health care professionals: a qualitative interview study. Palliat Med 29(3):212–222

Lyon ME, Jacobs S, Briggs L, Cheng YI, Wang J (2009) A longitudinal, randomized, controlled trial of advance care planning for teens with cancer: anxiety, depression, quality of life, advance directives, spirituality. J Adolesc Health 54(6):710–717

Lyon ME, Jacobs S, Briggs L, Cheng YI, Wang J (2013) Family-centered advance care planning for teens with cancer. JAMA Pediatr 167(5):460–467

Lyon ME, McCabe MA, Patel KM, D'Angelo LJ (2004) What do adolescents want? An exploratory study regarding end-of-life decision-making. J Adolesc Health 35(6):529.e1–6

Machajewski V, Kronk R (2013) Childhood grief related to the death of a sibling. J Nurse Practitioners 9:443–448

Meert KL, Eggly S, Pollack M, Anand KJ, Zimmerman J, Carcillo J, Newth CJ, Dean JM, Willson DF, Nicholson C (2008) Parents' perspectives on physician-parent communication near the time of a child's death in the pediatric intensive care unit. National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network. Pediatr Crit Care Med 9(1):2–7

Meert KL, Templin TN, Michelson KN, Morrison WE, Hackbarth R, Custer JR, Schim SM, Briller SH, Thurston CS (2012) The Bereaved Parent Needs Assessment: a new instrument to assess the needs of parents whose children died in the pediatric intensive care unit. Crit Care Med 40(11):3050–3057

Mercandante S (2004) Cancer pain management in children. Palliat Med 18(7):654–662

Moules NJ, Laing CM, McCaffrey G, Tapp DM, Strother D (2012a) Grandparents' experiences of childhood cancer, part 1: doubled and silenced. J Pediatr Oncol Nurs 29(3):119–132

Moules NJ, McCaffrey G, Laing CM, Tapp DM, Strother D (2012b) Grandparents' experiences of childhood cancer: part 2. The need for support. J Pediatr Oncol Nurs 29:133–140

Nass SJ, Patlak M, Rapporteurs (2015) National Cancer Policy Forum; Board on Health Care Services; Institute of Medicine; The National Academies of Sciences, Engineering, and Medicine. Comprehensive Cancer Care for Children and Their Families: Summary of a Joint Workshop by the Institute of Medicine and the American Cancer Society. National Academies Press (US), Washington (DC)

National Cancer Institute (2014) A Snapshot of Adolescent and Young Adult Cancers – Cancers Affecting Adolescents and Young Adults AYAs). http://www.cancer.gov/research/progress/snapshots/adolescent-young-adult. Accessed 17 Sept 2015

Rosenberg AR, Baker KS, Syrjala K, Wolfe J (2012) Systematic review of psychosocial morbidities among bereaved parents of children with cancer. Pediatr Blood Cancer 58(4):503–512

Rosenberg AR, Baker KS, Syrjala KL, Back AL, Wolfe J (2013a) Promoting resilience among parents and caregivers of children with cancer. J Palliat Med 16:645–652

Rosenberg AR, Dussel V, Kang T, Geyer JR, Gerhardt CA, Feudtner C, Wolfe J (2013b) Psychological distress in parents of children with advanced cancer. JAMA Pediatr 167(6): 537–543

Rosenberg AR, Postieer A, Osenga K, Kreichbergs U, Neville B, Dussel V, Wolfe J (2015) Long-term psychosocial outcomes among bereaved siblings of children with cancer. J Pain Sym Manage 49(1):55–65

Shear MK, Simon N, Wall M, Zisook S, Neimeyer R, Duan N, Reynolds C, Lebowitz B, Sung S, Ghesquiere A, Gorscak B, Clayton P, Ito M, Nakajima S, Konishi T, Melhem N, Meert K, Schiff M, O'Connor MF, First M, Sareen J, Bolton J, Skritskaya N, Mancini AD, Keshaviah A (2011) Complicated grief and related bereavement issues for DSM-5. Depress Anxiety 28(2):103–117

Silverman PR, Baker J, Cait C, Boerner K (2003) The effects of negative legacies on the adjustment of parentally bereaved children and adolescents. Omega 46:335–352

Snaman JM, Torres C, Duffy B, Levine DR, Gibson DV, Baker JN (2016) Parental perspectives of communication at the end of life at a pediatric oncology institution. J Palliat Med. Accessed 21 Feb 2016 [Epub ahead of print] http://www.ncbi.nlm.nih.gov/pubmed/26862782

Spinetta JJ, Jankovic M, Eden T, Green D, Martins AG, Wandzura C, Wilbur J, Masera G (1999) Guidelines for assistance to siblings of children with cancer: report of the SIOP Working Committee on Psychosocial Issues in Pediatric Oncology. Med Pediatr Oncol 33(4):395–398

Steele AC, Mullins LL, Mullins AJ, Muriel AC (2015) Psychosocial interventions and therapeutic support as a standard of care in pediatric oncology. Pediatr Blood Cancer 62(Suppl 5):S585–S618

Sveen J, Eilegård A, Steineck G, Kreicbergs U (2014) They still grieve-a nationwide follow-up of young adults 2–9 years after losing a sibling to cancer. Psychooncology 23(6):658–664

Thiele DM, Whelan TA (2008) The relationship between grandparent satisfaction, meaning, and generativity. Int J Aging Hum Dev 66(1):21–48

Waghorn M, Young H, Davies A (2011) Opinions of patients with cancer on the relative importance of place of death in the context of a ‘good death’. BMJ Support Palliat Care 1(3): 310–314

Wakefield C, Lin S, Drew D, McLoone J, Doolan E, Young A, Fardell J, Cohn R (2015) Development and evaluation of an information booklet for grandparents of children with cancer. J Pediatr Oncol Nurs(Accessed 12 Sept 2015) [Epub ahead of print]

Wakefield CE, Drew D, Ellis SJ, Doolan EL, McLoone JK, Cohn RJ (2014) Grandparents of children with cancer: a controlled study of distress, support, and barriers to care. Psychooncology 23(8):855–856

Ward E, DeSantis C, Robbins A, Kohler B, Jemal A (2014) Childhood and adolescent cancer statistics. CA Cancer J Clin 64(2):83–103

Weaver MS, Heinze KE, Bell CJ, Wiener L, Garee AM, Kelly KP, Casey RL, Watson A, Hinds PS, Pediatric Palliative Care Special Interest Group at Children’s National Health System (2016) Establishing psychosocial palliative care standards for children and adolescents with cancer and their families: an integrative review. Palliat Med 30(3):212–223

Wentlandt K, Krzyzanowska MK, Swami N, Rodin G, Le LW, Sung L, Zimmermann C (2014) Referral practices of pediatric oncologists to specialized palliative care. Support Care Cancer 22(9):2315–2322

Wiener L, Kazak AE, Noll RB, Patenaude AF, Kupst MJ (2015) Standards for the psychosocial care of children with cancer and their families: an introduction to the special issue. Pediatr Blood Cancer 62:S419–S424

Wild MR, Espie CA (2004) The efficacy of hypnosis in the reduction of procedural pain and distress in pediatric oncology: a systematic review. Dev Beh Pedia 25(3):207–213

Wilkins KL, Woodgate RL (2005) A review of qualitative research on the childhood cancer experience from the perspective of siblings: a need to give them a voice. J Pediatr Oncol Nurs 22(6):305–319

Wolfe J, Grier HE, Klar N, Levin SB, Ellenbogen JM, Salem-Schatz S, Emanuel EJ, Weeks JC (2000) Symptoms and suffering at the end of life in children with cancer. N Engl J Med 342(5):326–333

Wolfe J, Hammel JF, Edwards KE, Duncan J, Comeau M, Brey-er J, Aldridge SA, Grier HE, Berde C, Dussel V, Weeks JC (2008) Easing of suffering in children with cancer at the end of life: is care changing? J Clin Oncol 26(10):1717–1723

World Health Organization (1998) Cancer pain relief and palliative care in children, http://apps.who.int/iris/bitstream/10665/42001/1/9241545127.pdf. Accessed 14 Nov 2015

Youngblut JM, Brooten D, Blais K, Kilgore C, Yoo C (2015) Health and functioning in grandparents after a young grandchild’s death. J Community Health 40(5):956–966

Symptom Management of the Dying Oncology Patient

12

Lawrence Berk

12.1 Introduction

> Dar'st thou die?
> The sense of death is most in apprehension;
> And the poor beetle that we tread upon,
> In corporal sufferance feels a pang as great
> As when a giant dies.
>
> William Shakespeare, Measure for Measure Act III, scene 1.

The goal for everyone, the patient, the family, and the medical staff, is for a death without suffering, a peaceful death. But, often the process of dying is complicated by unwanted symptoms. The appropriate treatment of these problems will improve the quality of the death. The most common problems include pain, nausea, dyspnea, delirium, and death rattle. This chapter reviews various approaches to these problems. This is not intended to be a systematic review, but rather to give insights into the problems and to offer potential treatments. There are many other approaches available in the literature than the ones discussed here, and these treatments are based on the present evidence from clinical trials and common usage.

12.2 Pain

Pain is a multidimensional problem, combining both the physical stimulation of nociceptors and the cognitive reaction to the stimulus that becomes the unpleasant emotional response of pain. Pain can therefore be treated by eliminating the

---

L. Berk, MD, PhD
Morsani School of Medicine, University of South Florida, Tampa, FL, USA
e-mail: lberk@health.usf.edu

L. Berk (ed.), *Dying and Death in Oncology*, DOI 10.1007/978-3-319-41861-2_12

stimulus, preventing the transmission of the pain to the brain or inhibiting the cerebral sensation of pain. Treatments for cancer patients which eliminate the stimulus include surgery, radiation therapy, and chemotherapy. These treatments are often too aggressive for the dying patient during the last days. Therefore, treatment focuses on pharmacological management of the pain rather than physical relief of the pain.

The primary pharmacological treatment for moderate to severe pain in dying patients is opioids. As a brief aside, opium is a mixture of alkaloids from the poppy seeds; opiates are medications which are derived from the naturally occurring alkaloids of opium; and opioids are any medications that react with the opiate receptors in the brain, including opiates (Trescot et al. 2008). The primary target for pain relief is the activation of the opiate receptors in the brain and spinal cord. There are three opiate receptors associated with pain relief, the mu receptor, the delta receptor, and the kappa receptor. The International Union of Basic and Clinical Pharmacology (IUPHAR) recommends these be called MOR, DOR, and KOR, respectively (Toll). The three most commonly used opiates are morphine, oxycodone, and hydromorphone. The two most commonly used synthetic opioids are fentanyl and methadone.

In 1996, the World Health Organization published the "pain ladder: for analgesia." In this scheme, mild pain should be treated with a nonopioid, such as a nonsteroidal anti-inflammatory drug (NSAID), with or without an adjuvant such as gabapentin. Moderate pain should be treated with a weak opioid such as tramadol, propoxyphene, or hydrocodone with or without a nonopioid and/or adjuvant. Severe pain should be treated with a strong opioid with or without a nonopioid and/or adjuvant. The basis for using a weak opioid was never stated, given that they have lower efficacy and higher risk for toxicity. For example, a randomized trial with cancer patient in moderate pain compared low-dose morphine to tramadol +/− acetaminophen or codeine with acetaminophen. The morphine had higher efficacy (Bandieri et al. 2015). Many pain professionals do not use the second step of the WHO ladder and instead start with strong opiates. This is especially true for the dying patient in which efficacy must be maximized and toxicity minimized. Therefore, the weak opioids will not be discussed here.

12.2.1 Morphine

Morphine (the structure of morphine is shown in Fig. 12.1) was the first opiate isolated from opium and is the prototypical agent. It is primarily a MOR receptor and has weak KOR activity. It is most often used orally and intravenously, but can be given intramuscularly, subcutaneously, and intrarectally. It comes as immediate-relief tablets, immediate-relief liquid, and slow-release (12 and 24 h) tablets/capsules. The time to maximum pain relief through oral administration of immediate release morphine is 30–60 min, and its duration of action is 3–4 h. Its elimination half-life is about 120 min (Trescot et al. 2008). The time to onset of IV morphine is about 5 min with a 20 min time to peak effect and a 4 h duration. It is metabolized

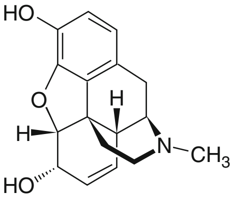


Fig. 12.1 Structure of morphine. “Morphin – Morphine” by NEUROtiker – Own work (Licensed under Public Domain via Commons – https://commons.wikimedia.org/wiki/File:Morphin_-_Morphine.svg#/media/File:Morphin_-_Morphine.svg)

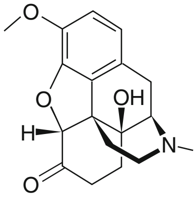


Fig. 12.2 Structure of oxycodone. “Oxycodone” by Fvasconcellos (talk contribs) – Own work (Licensed under Public Domain via Commons – https://commons.wikimedia.org/wiki/File:Oxycodone.svg#/media/File:Oxycodone.svg)

in the liver primarily by glucuronidation to morphine-6-glucuronide (M6G) and morphine-3-glucuronide (M3G) (Hasselstrom and Sawe 1993). M6G is a much more potent analgesic than morphine (Armstrong and Cozza 2003). M3G may be involved in hyperalgesia, in which high doses of morphine induce an increase in pain. Patients differ in their innate glucuronidation activity and will generate differing amounts of M6G, which may be the source of variation of the response of patients to morphine.

12.2.2 Oxycodone

Oxycodone is a phenanthrene class opioid. Its structure is shown in Fig. 12.2. It is marketed as oxycodone alone or combined with acetaminophen, ibuprofen, or aspirin. The prudent approach is to give the oxycodone alone and give an adjuvant medication separately. This allows titration of the oxycodone without the risk of unnecessary toxicity from increasing dosage of the adjuvant drug. The receptor site of activity of oxycodone is controversial. Animal studies suggest it primarily binds to KOR receptors, but its analgesic activity is more in line with a MOR receptor agonist (Kalso 2007). The parent compound, oxycodone, has direct analgesic effect. It has a time to maximum onset of 30–60 min and a half-life of 2.5–3 h. It is metabolized in the liver by glucuronidation to minimally active noroxycodone and to the active drug oxymorphone (Trescot et al. 2008).

12.2.3 Hydromorphone

Hydromorphone is a semisynthetic opioid derived from morphine. Its structure is shown in Fig. 12.3. It functions primarily as a MOR agonist with less DOR activity. The time to maximum activity for oral administration is about 30 min and its duration of activity is about 4 h. Given intravenously, hydromorphone's time to maximum activity is about 10–15 min, with the maximum effect at about 20 min and a duration of effect of about 4 h. It is metabolized in the liver to hydromorphone-3-glucurinode (H3G) (Trescot et al. 2008). H3G has no analgesic effect but can cause toxicity.

12.2.4 Fentanyl

Fentanyl is a synthetic opioid, as shown in Fig. 12.4. It is a MOR agonist. It undergoes rapid metabolism in the liver and cannot be given orally. It is available in IV, transdermal, transoral, mucosal, and inhaled formulations. Its time to onset after IV administration is less than a minute, with a peak onset time of about 5 min. However, it has a short half-life of 30–60 min. Transmucosal and inhaled fentanyl also have rapid onset of pain relief. Transdermal fentanyl has a 6–8 h of onset, and the pain relief equilibrates after several days. Subcutaneous fat acts as a reservoir for the transdermal fentanyl and can be active for 24 h after discontinuation of the transdermal drug. Fentanyl is metabolized in the liver to inactive and nontoxic metabolites

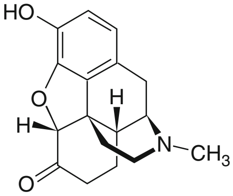


Fig. 12.3 Structure of hydromorphone. "Hydromorphone – Hydromorphon" by Yikrazuul – Own work (Licensed under Public Domain via Commons – https://commons.wikimedia.org/wiki/File:Hydromorphone_-_Hydromorphon.svg#/media/File:Hydromorphone_-_Hydromorphon.svg)

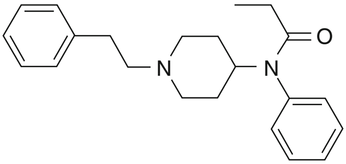


Fig. 12.4 Structure of fentanyl. "Fentanyl2DCSD" by Fuse809 (talk) – Own work (Licensed under Public Domain via Commons – https://commons.wikimedia.org/wiki/File:Fentanyl2DCSD.svg#/media/File:Fentanyl2DCSD.svg)

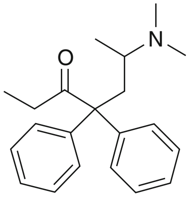


Fig. 12.5 Methadone. "Methadone" by Calvero – Selfmade with ChemDraw (Licensed under Public Domain via Commons – https://commons.wikimedia.org/wiki/File:Methadone.svg#/media/File:Methadone.svg)

(Trescot et al. 2008). With its rapid time of onset and short half-life without toxicity metabolites, it is the preferred drug for use with IV analgesia, including patient-controlled analgesia.

12.2.5 Methadone

Methadone is also a synthetic MOR agonist and is an antagonist of the N-methyl-D-aspartate (NDMA) receptor (see Fig. 12.5). This latter activity suggests it may be useful in neuropathic pain. It has a very complex and variable metabolism. It has a highly variable absorption, and so each patient must be titrated carefully. Also, although methadone has an analgesic duration of action of about 4–8 h, it has an elimination half-life of up to 150 h. Furthermore, methadone induces its metabolism enzymes in the liver, leading to increased methadone metabolism and drug requirements in the first week, but then it has stable metabolism. It is metabolized by the CYP3A4 enzyme, and thus it susceptible to multiple drug interactions, as described in the next section. Thus, it is hard to use at the end of life.

12.2.6 Drug Interactions

Morphine and hydromorphone are metabolized through glucuronidation by the hepatic uridine diphosphate glucuronosyl transferase (UGT) enzymes with little to no P450 involvement. There are not many morphine and hydromorphone drug-drug interactions. Examples of possible interactions are with rifampin, ranitidine, and diclofenac (Armstrong and Cozza 2003).

In contrast, oxycodone and methadone are more prone to drug-drug interactions. Oxycodone is metabolized by the P450 CYP2D6 to oxymorphone, which is an FDA-approved commercially available analgesic. Inhibitors of P450 CYP enzymes have been implicated in oxycodone deaths. Strong inhibitors of CYP2D6 include selective serotonin reuptake inhibitors (SSRIs), such as fluoxetine, paroxetine, and ritonavir (Drummer et al. 1994; Jannetto et al. 2002; Jin et al. 2005) Dexamethasone also induces CYP2D6 and therefore could decrease the efficacy of oxycodone.

Methadone has a very high risk of drug-drug interactions because of its complicated metabolism to toxic and long-lived metabolites. P450 enzymes CYP3A4, CYP2B6, and CYUP2D6 are all involved in methadone metabolism. Curcumin, a popular herbal product, inhibits CYP2B6. In the same vein, grapefruit juice, noni, and pomegranate juice inhibit CYP3A4. Drugs inhibiting CYP3A4 include many antivirals; the azole antifungals including fluconazole, ketoconazole, and itraconazole; some macrolide antibiotics including erythromycin and clarithromycin; and some calcium channel blockers including verapamil and diltiazem. The CYP2D6 inhibitors were mentioned above.

12.2.7 Side Effects

The side effects of opioids are legion, but their efficacy usually outweighs their risks. The three general concerns with opioids in the dying patient are sedation, respiratory depression, and hypotension. Sedation can occur with starting and increasing doses of opioids, but it is usually temporary. Methylphenidate doses of 10–15 mg a day can reverse the sedation (Bruera et al. 1992; Wilwerding et al. 1995).

Respiratory depression can also occur, particularly with opioids that have toxic, long-lived metabolites such as methadone. The respiratory depression can be reversed with the use of naloxone. The half-life of naloxone after IV administration ranges from 30 to 80 min, which is shorter than most opioids. The patient must be observed for recurrence of the sedation. The recommended dose is from 0.4 to 2 mg, with further doses every 2–3 min if there is no response. This can be repeated after 20–60 min for recurrent sedation. Naloxone can also be given intramuscularly or subcutaneously. The lowest dose to reverse the sedation should be used, because the naloxone will also reverse the opioid's analgesia, precipitating a pain crisis.

Cardiovascular effects, including hypotension, are uncommon, except with methadone. Hypotension can occur and appears to be related to histamine release by the opioids (Flacke et al. 1987). H1 blockade can decrease hypotension. This histamine release can also cause pruriitis, which is often mistaken for an allergic reaction. However, there is no mast cell release or IgA response to suggest an allergic component.

Another common, almost universal, side effect is constipation due to interaction with opiate receptors in the bowel inducing low motility. This is treated with fiber and other osmotic agents, stimulants, and hydration. If these are insufficient, then both methylnaltrexone and lubiprostone are effective for opioid-induced constipation (Ford et al. 2013). Both of these are very expensive. Misoprostol, an inexpensive prostaglandin E1 analog, is also effective, but a large percentage of patients cannot tolerate it due to cramping (Roarty et al. 1997; Soffer et al. 1994).

12.2.8 Conversion

The conversion from using one opioid to another is based upon general guidelines and are not based on any rigorous data. Further, there is incomplete cross-resistance between the opioids, and therefore the dose needs to be reduced anywhere from

25 to 50 % of the calculated conversion. Fentanyl cannot be converted from other opioids and must be titrated up from a low dose. Methadone is very difficult to convert to and from, and in the dying patient it may not be worthwhile to convert a patient to methadone, although it may be useful as an adjuvant if the patient is not responding to other opioids (Table *12.1*).

12.3 Nausea

Nausea and/or vomiting occurs frequently in terminal cancer patients. It can arise from mechanical problems, such as constipation, esophageal obstruction or malignant bowel obstruction, metabolic toxicities such as renal failure or hepatic failure, from treatments such as with opioids or other medications, or from unidentified or unidentifiable causes (see Fig. 12.6). Obviously, correction of an identified cause

Table 12.1 Properties of common opioids

Analgesic	Equivalent dosage	Time to maximum effect	Duration of analgesia
Morphine, IV, IM	10 mg	5–10 min	3–4 h
Morphine, PO	30 mg	30–60 min	3–4 h
Oxycodone, PO	20 mg	10–15 min	3–4 h
Hydromorphone, IV, IM	1.5 mg	10–15 min	3–4 h
Hydromorphone, PO	7.5 mg	15–30 min	2–3 h
Fentanyl, IV	0.05–0.1 mg	<1 min	1–2 h
Methadone, PO	Utilize special tables		

Modified from (Lee)

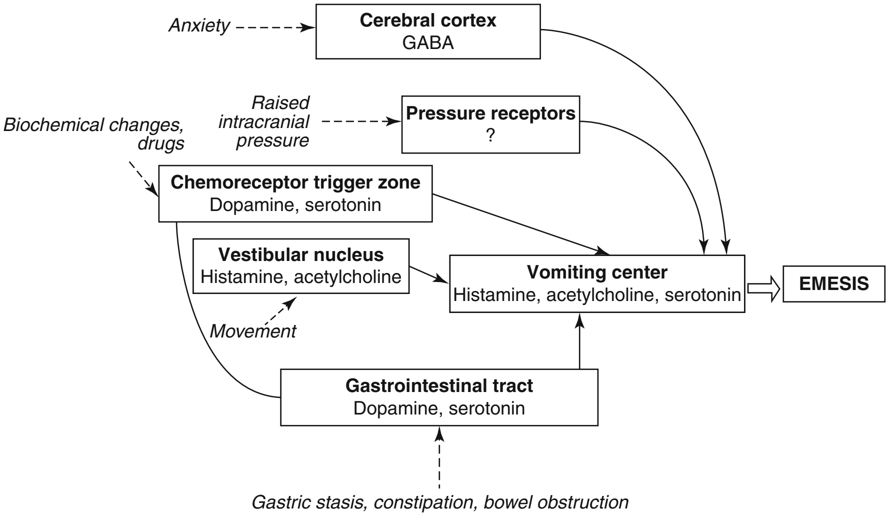


Fig. 12.6 Emetic pathway (From Glare et al. 2011)

such as a metabolic imbalance or medication problem should be the initial step to control nausea and vomiting.

12.3.1 Malignant Bowel Obstruction

A potentially correctable cause of nausea and vomiting in cancer patients is malignant bowel obstruction. High-volume vomiting with minimal odor and with brief episodes of cramping pain is often secondary to small bowel obstruction, whereas small-volume, foul-smelling emesis with more severe colic may represent colonic obstruction (Laval et al. 2014). Malignant bowel obstruction is more common with gynecological and gastrointestinal cancer. Obstruction can be from focal blockage of the bowel, such as from a primary colorectal cancer, or from peritoneal carcinomatosis. Radiographic evaluation can assist with diagnosis. For a patient that presents with abdominal pain, distention, nausea, and constipation, a plain abdominal film or CT scan may show complete or high-grade partial small bowel obstruction with proximal dilated loops of bowel with multiple air-fluid levels (Silva et al. 2009). Peritoneal carcinomatosis may present on CT with ascites, invasion of the fat of the greater omentum with streaking or nodules, invasion of the mesentery with nodules or anomalous fixation of the small intestine, and tumor implants on the walls of the intestine. Diffuse carcinomatosis may not be too small to be imaged (Diop et al. 2014).

Laval and colleagues from the French Society for Palliative Care published guidelines for the treatment of bowel obstruction from peritoneal carcinomatosis (Laval et al. 2014). They state that CT scanning is the gold standard for diagnosis, with a sensitivity of more than 90 %. Once clinical features and imaging confirm obstruction secondary to carcinomatosis, the patient can be evaluated for surgery. Surgery would rarely be recommended for a patient at the end of life. The role of stents in peritoneal carcinomatosis is also limited due to the usually diffuse nature of the obstructions and expected progression elsewhere. Placement of a venting gastrostomy tube is a low-morbidity procedure that can improve the quality of life of patients with obstruction. In a series reported by Issaka et al., there was successful placement of the venting tube in 95 of 96 patients (Issaka et al. 2014). The venting gastric tube provided complete relief from nausea and vomiting in 91 % of the patients.

Medical management of the symptoms of malignant obstruction often includes corticosteroids (Laval et al. 2014). Although the corticosteroids are generally well tolerated, their efficacy is also limited (Feuer and Broadley 1999). Anticholinergics, such as scopolamine and hyoscine butylbromide, act as antisecretory agents to reduce the volume of fluid in the bowels. These drugs have the common anticholinergic side effects such as dry mouth, tachycardia, and agitation. Glycopyrrolate, also an anticholinergic, has little penetration into the central nervous system, and so has fewer side effects (Soriano and Davis 2011). Octreotide can also be given, but at much greater cost. Opioids can be given for the abdominal pain, but opioids can also stimulate the bowel, causing more pain.

In this case, they can be combined with the anticholinergics to reduce the colic (Soriano and Davis 2011).

12.3.2 Pharmaceutical Management

Davis, Walsh and colleagues at the Cleveland Clinic published their approach to the treatment of nausea (Gupta et al. 2013). They use a standard sequential approach to antiemetics. First, they use metoclopramide (a dopamine D_2 antagonist) or haloperidol (a dopamine D_2 antagonist), and then use olanzapine (an atypical antipsychotic medication with dopamine, serotonin, alpha-adrenergic, and cholinergic receptor activity) or chlorpromazine (a dopamine D_2 antagonist) as a second-line treatment, and ondansetron (a selective $5HT_3$ receptor antagonist) as third-line treatment. For patients with ascites, a paracentesis can help relieve nausea. For patients with cerebral brain edema, they use dexamethasone. They recommend gabapentin (or carbamazepine) for relief of nausea from leptomeningeal carcinomatosis, but there are no clinical trials of its use (Gupta et al. 2013). Another approach to choosing an antiemetic treatment is mechanistic, that is, choosing the treatment based on the "emetic pathway" and cause of the nausea (Glare et al. 2011). However, there is no evidence that this approach is more successful than an empirical approach. The article by Glare and colleagues gives an extensive discussion of the medications that can be used for the treatment of nausea and vomiting.

12.4 Dyspnea

The primary pharmacological treatment of dyspnea is morphine. Ben-Aharon and colleagues performed a meta-analysis of randomized trials of morphine versus placebo for cancer-related dyspnea which showed a positive effect for the use of morphine (Ben-Aharon et al. 2012). No serious adverse events, such as respiratory depression and sedation, were reported in the trials. Midazolam has been shown to be efficacious as a supplement to morphine and as an alternative to morphine (Navigante et al. 2006, 2010).

A trial by Abernethy and colleagues randomized 239 patients with a PaO_2 of at least 7.3 kPa (55 mmHg) and dyspnea due to a life-limiting illness (14 % had primary lung cancer and 2 % had lung metastases). Patients were not eligible, by standard guidelines, for oxygen therapy, or have an anemia of <100 g/L (10 mg/dL). Patients were treated for 7 days with either oxygen or medical air. There was no improvement with either air or oxygen in breathlessness level (Abernethy et al. 2010).

Nebulized morphine can also be given for end-stage dyspnea. A systematic review concluded that there is no evidence that nebulized morphine is superior to other forms of administration and that its use should be guided by the goals for each patient (Boyden et al 2015).

12.5 Delirium

Delirium is often underdiagnosed at the end of life. According to the *Diagnostic and Statistical Manual Version 5* (DSM-5), there are five criteria for delirium, as shown in Table *12.2*. Both hyperactive delirium and hypoactive delirium are seen. Delirium can be evaluated by many instruments. De et al. reviewed the delirium-screening tools tested in the literature (De and Wand 2015). They found 21 screening tools. The Confusion Assessment Method was the most widely used instrument. However, this tool requires training to be used effectively. The Single Question in Delirium (SQiD) test has good sensitivity and sensitivity, and by its design requires no special testing. In the SQiD, the patient's friend or relative is asked: "Do you feel that [patient's name] has been more confused lately?" (Sands et al. 2010) The SQiD was tested in 21 patients admitted to an inpatient oncology service. When compared with a psychiatrist's interview, the SQiD had a sensitivity of 90 % and specificity of 71 %. In a study by Lin et al., the SQiD had a sensitivity of 77 %, specificity of 51 %, and a negative predictive value of 83 % (Lin et al. 2015). The Lin study also evaluated the clinician-administered Simple Query for Easy Evaluation of Consciousness (SQeeC). The SQeeC has the clinician ask the patient two questions: "Name a place you would like to visit that you have never been before" and "How would you make the journey?" If the response is ambiguous, two additional questions can be asked, "How would you organize the trip/flight" and "Will the plane fly through water" The SQeeC showed a sensitivity of 83 %, specificity of 81 %, and a negative predictive value of 97 %.

The primary treatment of delirium focuses on identifying the underlying cause. This includes correction of metabolic abnormalities and toxicities from medications. A prospective study by Gaudreau and colleagues showed that delirium among hospitalized cancer patients correlated with daily benzodiazepine dosages of lorazepam above 2 mg (or equivalent), corticosteroid doses above 15 mg dexamethasone (or equivalent), and opioid doses of 90 mg of morphine (or equivalent) (Gaudreau et al. 2005). Metabolic abnormalities, including hepatic encephalopathy and hypercalcemia, can contribute to delirium.

Pharmacological treatment of delirium focuses on the antipsychotic agents, and most often this is haloperidol. A review by Bush et al. found no difference in efficacy of one drug or drug class over another. The agents reviewed included typical and atypical antipsychotics, dexmedetomidine, rivastigmine, and lorazepam (Bush et al. 2014). They note that in one trial rivastigmine had higher mortality compared

Table 12.2 *DSM-5* criteria for delirium

Disturbance in attention and awareness
Development over hours to days and may especially occur at night (sundowning)
Another disturbance in cognition, such as memory, orientation, language, or perception
Findings not better explained by another neurocognitive disorder
Delirium has an underlying cause such as a medical condition or toxin exposure

to placebo. In this trial with 104 critically ill patients with delirium, there was a 22 % mortality during the drug use and an 8 % mortality with placebo ($p = 0.07$) (van Eijk et al. 2010). Rivastigmine is a reversible cholinesterase inhibitor, and thus a cholinergic agent. Bush and colleagues therefore recommend avoiding all cholinergic agents. However, as Schriver et al. concluded in a systemic review of haloperidol for in-hospital delirium prevention and treatment, “Although results on haloperidol for delirium management seem promising, current prevention trials lack external validity and treatment trials did not include a placebo arm on top of standard nonpharmacological care. We therefore conclude that the current use of haloperidol for in-hospital delirium is not based on robust and generalizable evidence” (Schrijver et al. 2016).

Nonpharmacological management of delirium is multifaceted and includes re-orienting the patient, avoiding constipation, maintaining mobility, and trying to avoid sleep disturbances. Behavioral and educational interventions can also be part of the overall management of delirium (Grassi et al. 2015).

12.6 Death Rattle

Death rattle is the noisy breathing that occurs just prior to death. It does not represent suffering from the patient, but can be distressing to the patient’s family and caregivers. The primary treatment is with antimuscarinic drugs to dry out the patient’s oral secretions. However, both a Cochrane review and a systematic review do not support the treatment of death rattle (Lokker et al. 2014; Wee and Hillier 2008).

12.7 Palliative Sedation and Euthanasia

What if the patient is suffering at the end of life and none of these treatments bring relief? The two final interventions are palliative sedation and euthanasia.

Palliative sedation comes in two levels: deep, continuous palliative sedation in which the patient is rapidly put into an unresponsive state, and proportional palliative sedation in which the patient is titrated to the level of sedation needed to relieve the symptoms but not necessarily become completely unresponsive. There are various guidelines for the use of palliative sedation. In Europe, both the European Association for Palliative Care (EAPC) and the European Society of Medical Oncology (ESMO) have published detailed guidelines (Cherny et al. 2009; Cherny and ESMO Guidelines Working Group 2014). The EAPC Guidelines are for any situation with intractable suffering, including potentially reversible situations such as burn patients. The ESMO Guidelines are oncology-specific and focus on refractory symptoms at the end of life, reflecting the historical term “terminal sedation.” Terminal sedation has an overtone of hastening death and has been abandoned for the term palliative sedation. This is reinforced in that studies strongly suggest that palliative sedation does not hasten death (Maltoni et al. 2012). The ESMO Guidelines note that pain, dyspnea, anxiety, and agitated delirium are common terminal symptoms, and that probably 20–30 % of terminal cancer patients have refractory symptoms requiring sedation (Cherny and ESMO Guidelines Working Group 2014). Much of the ESMO guideline focuses on communication with the patient and the patient's family and caregivers to insure a proper understanding of the process. The most common form of palliative sedation is IV midazolam (Maltoni and Setola 2015). IV propofol can also be used (National Comprehensive Cancer 2016). The sedating medication dose is monitored to achieve a balance between relief and awareness, with the focus on relief. Because midazolam and propofol are short-acting, they can be interrupted to awaken the patient if desired.

Although some may consider deep, continuous palliative sedation equivalent to inducing death because the patient is no longer interacting with his environment, the family and supporters can still interact with the patient and provide care. In contrast, euthanasia (death actively chosen by the patient or a decision-making proxy, in which physician-assisted suicide is a subgroup) is the final, irreversible treatment for refractory symptoms and is far more controversial than palliative sedation. In the United States, five states have legalized euthanasia: California, Montana (by court ruling), Oregon, Vermont, and Washington. Four states have no specific laws regarding euthanasia (Nevada, North Carolina, Utah, and Wyoming), and in the remaining 41 states and the District of Columbia, euthanasia is illegal (Procon.org 2016). Elsewhere, only a few countries allow euthanasia. Belgium allows euthanasia, but not specifically physician-assisted suicide (i.e., the patient or a family member can cause the death). Assisted suicide is legal in Switzerland, Columbia, the Netherlands, Belgium, and Luxembourg. In Canada (except Quebec), euthanasia is currently illegal, but the lawmakers are under a Supreme Court mandate to pass a law making it legal. In Columbia, euthanasia is legal, but without supporting regulations to protect doctors, it is unclear what role physicians can play. Germany passed a law allowing euthanasia in November 2015 but banned "commercial" euthanasia, again raising questions about whether physicians can routinely assist in euthanasia.

Conclusion

Suffering at the end of life is multidimensional. It includes physical suffering, emotional suffering, and existential suffering. Although this chapter focuses on the reduction of physical suffering, complete treatment of the patient requires addressing all areas of a patient's pain. In some cases, the suffering cannot be controlled. In these cases, terminal sedation or assisted suicide may be evaluated as options. However, most patients can be adequately treated with standard therapies.

References

Abernethy AP, McDonald CF, Frith PA, Clark K, Herndon JE 2nd, Marcello J, Young IH, Bull J, Wilcock A, Booth S, Wheeler JL, Tulsky JA, Crockett AJ, Currow DC (2010) Effect of palliative oxygen versus room air in relief of breathlessness in patients with refractory dyspnoea: a double-blind, randomised controlled trial. Lancet 376:784–793

Armstrong SC, Cozza KL (2003) Pharmacokinetic drug interactions of morphine, codeine, and their derivatives: theory and clinical reality, part I. Psychosomatics 44:167–171

Bandieri E, Romero M, Ripamonti CI, Artioli F, Sichetti D, Fanizza C, Santini D, Cavanna L, Melotti B, Conte PF, Roila F, Cascinu S, Bruera E, Tognoni G, Luppi M (2015) Randomized trial of low-dose morphine versus weak opioids in moderate cancer pain. J Clin Oncol 34(5):436–442, Online pre-print

Ben-Aharon I, Gafter-Gvili A, Leibovici L, Stemmer SM (2012) Interventions for alleviating cancer-related dyspnea: a systematic review and meta-analysis. Acta Oncol 51:996–1008

Boyden JY, Connor SR, Otolorin L, Nathan SD, Fine PG, Davis MS, Muir JC (2015) Nebulized medications for the treatment of dyspnea: a literature review. J Aerosol Med Pulm Drug Deliv 28:1–19

Bruera E, Miller MJ, Macmillan K, Kuehn N (1992) Neuropsychological effects of methylphenidate in patients receiving a continuous infusion of narcotics for cancer pain. Pain 48: 163–166

Bush SH, Kanji S, Pereira JL, Davis DH, Currow DC, Meagher DJ, Rabheru K, Wright DK, Bruera E, Agar M, Hartwick M, Gagnon PR, Gagnon B, Breitbart W, Regnier L, Lawlor PG (2014) Treating an established episode of delirium in palliative care: expert opinion and review of the current evidence base with recommendations for future development. J Pain Symptom Manage 48:231–248

Cherny NI, ESMO Guidelines Working Group (2014) ESMO Clinical Practice Guidelines for the management of refractory symptoms at the end of life and the use of palliative sedation. Ann Oncol 25(Suppl 3):iii143–iii152

Cherny NI, Radbruch L, Board of the European Association for Palliative Care (2009) European Association for Palliative Care (EAPC) recommended framework for the use of sedation in palliative care. Palliat Med 23:581–593

De J, Wand AP (2015) Delirium screening: a systematic review of delirium screening tools in hospitalized patients. Gerontologist 55:1079–1099

Diop AD, Fontarensky M, Montoriol PF, Da Ines D (2014) CT imaging of peritoneal carcinomatosis and its mimics. Diagn Interv Imaging 95:861–872

Drummer OH, Syrjanen ML, Phelan M, Cordner SM (1994) A study of deaths involving oxycodone. J Forensic Sci 39:1069–1075

Feuer DJ, Broadley KE (1999) Systematic review and meta-analysis of corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancers. Systematic Review Steering Committee. Ann Oncol 10:1035–1041

Flacke JW, Flacke WE, Bloor BC, Van Etten AP, Kripke BJ (1987) Histamine release by four narcotics: a double-blind study in humans. Anesth Analg 66:723–730

Ford AC, Brenner DM, Schoenfeld PS (2013) Efficacy of pharmacological therapies for the treatment of opioid-induced constipation: systematic review and meta-analysis. Am J Gastroenterol 108:1566–1574

Gaudreau JD, Gagnon P, Harel F, Roy MA, Tremblay A (2005) Psychoactive medications and risk of delirium in hospitalized cancer patients. J Clin Oncol 23:6712–6718

Glare P, Miller J, Nikolova T, Tickoo R (2011) Treating nausea and vomiting in palliative care: a review. Clin Interv Aging 6:243–259

Grassi L, Caraceni A, Mitchell AJ, Nanni MG, Berardi MA, Caruso R, Riba M (2015) Management of delirium in palliative care: a review. Curr Psychiatry Rep 17:550

Gupta M, Davis M, LeGrand S, Walsh D, Lagman R (2013) Nausea and vomiting in advanced cancer: the Cleveland Clinic protocol. J Support Oncol 11:8–13

Hasselstrom J, Sawe J (1993) Morphine pharmacokinetics and metabolism in humans. Enterohepatic cycling and relative contribution of metabolites to active opioid concentrations. Clin Pharmacokinet 24:344–354

Issaka RB, Shapiro DM, Parikh ND, Mulcahy MF, Komanduri S, Martin JA, Keswani RN (2014) Palliative venting percutaneous endoscopic gastrostomy tube is safe and effective in patients with malignant obstruction. Surg Endosc 28:1668–1673

Jannetto PJ, Wong SH, Gock SB, Laleli-Sahin E, Schur BC, Jentzen JM (2002) Pharmacogenomics as molecular autopsy for postmortem forensic toxicology: genotyping cytochrome P450 2D6 for oxycodone cases. J Anal Toxicol 26:438–447

Jin M, Gock SB, Jannetto PJ, Jentzen JM, Wong SH (2005) Pharmacogenomics as molecular autopsy for forensic toxicology: genotyping cytochrome P450 3A4*1B and 3A5*3 for 25 fentanyl cases. J Anal Toxicol 29:590–598

Kalso E (2007) How different is oxycodone from morphine? Pain 132:227–228

Laval G, Marcelin-Benazech B, Guirimand F, Chauvenet L, Copel L, Durand A, Francois E, Gabolde M, Mariani P, Rebischung C, Servois V, Terrebonne E, Arvieux C, French Society for Palliative Care, French Society for Digestive Surgery, French Society for Gastroenterology, French Association for Supportive Care in Oncology, French Society for Digestive Cancer (2014) Recommendations for bowel obstruction with peritoneal carcinomatosis. J Pain Symptom Manage 48:75–91

Lee D Opiod Potency Comparison. Emedicine Health. http://www.emedicinehealth.com/opioid_potency_comparison/article_em.htm

Lin HS, Eeles E, Pandy S, Pinsker D, Brasch C, Yerkovich S (2015) Screening in delirium: a pilot study of two screening tools, the Simple Query for Easy Evaluation of Consciousness and Simple Question in Delirium. Australas J Ageing 34:259–264

Lokker ME, van Zuylen L, van der Rijt CC, van der Heide A (2014) Prevalence, impact, and treatment of death rattle: a systematic review. J Pain Symptom Manage 47:105–122

Maltoni M, Setola E (2015) Palliative sedation in patients with cancer. Cancer Control 22: 433–441

Maltoni M, Scarpi E, Rosati M, Derni S, Fabbri L, Martini F, Amadori D, Nanni O (2012) Palliative sedation in end-of-life care and survival: a systematic review. J Clin Oncol 30:1378–1383

Navigante AH, Castro MA, Cerchietti LC (2010) Morphine versus midazolam as upfront therapy to control dyspnea perception in cancer patients while its underlying cause is sought or treated. J Pain Symptom Manage 39:820–830

Navigante AH, Cerchietti LC, Castro MA, Lutteral MA, Cabalar ME (2006) Midazolam as adjunct therapy to morphine in the alleviation of severe dyspnea perception in patients with advanced cancer. J Pain Symptom Manage 31:38–47

National Comprehensive Cancer Network (2016) NCCN Guidelines Version 1.2016 Palliative Care. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/PDF/palliative.pdf

Procon.org (2016) State-by-State Guide to Physician-Assisted Suicide – Euthanasia – ProCon.org.http://euthanasia.procon.org/view.resource.php?resourceID=000132. Accessed 3/20/2016

Roarty TP, Weber F, Soykan I, McCallum RW (1997) Misoprostol in the treatment of chronic refractory constipation: results of a long-term open label trial. Aliment Pharmacol Ther 11:1059–1066

Sands MB, Dantoc BP, Hartshorn A, Ryan CJ, Lujic S (2010) Single Question in Delirium (SQiD): testing its efficacy against psychiatrist interview, the Confusion Assessment Method and the Memorial Delirium Assessment Scale. Palliat Med 24:561–565

Schrijver EJ, de Graaf K, de Vries OJ, Maier AB, Nanayakkara PW (2016) Efficacy and safety of haloperidol for in-hospital delirium prevention and treatment: a systematic review of current evidence. Eur J Intern Med 27:14–23

Silva AC, Pimenta M, Guimaraes LS (2009) Small bowel obstruction: what to look for. Radiographics 29:423–439

Soffer EE, Metcalf A, Launspach J (1994) Misoprostol is effective treatment for patients with severe chronic constipation. Dig Dis Sci 39:929–933

Soriano A, Davis MP (2011) Malignant bowel obstruction: individualized treatment near the end of life. Cleve Clin J Med 78:197–206

Toll L Opiod receptors, introduction. IUPHAR/BPS Guide to PHARMACOLOGY. http://www.guidetopharmacology.org/GRAC/FamilyIntroductionForward?familyId=50

Trescot AM, Datta S, Lee M, Hansen H (2008) Opioid pharmacology. Pain Physician 11:S133–S153 van Eijk MM, Roes KC, Honing ML, Kuiper MA, Karakus A, van der Jagt M, Spronk PE, van Gool WA, van der Mast RC, Kesecioglu J, Slooter AJ (2010) Effect of rivastigmine as an adjunct to usual care with haloperidol on duration of delirium and mortality in critically ill patients: a multicentre, double-blind, placebo-controlled randomised trial. Lancet 376:1829–1837

Wee B, Hillier R (2008) Interventions for noisy breathing in patients near to death. Cochrane Database Syst Rev (1):CD005177

Wilwerding MB, Loprinzi CL, Mailliard JA, O'Fallon JR, Miser AW, van Haelst C, Barton DL, Foley JF, Athmann LM (1995) A randomized, crossover evaluation of methylphenidate in cancer patients receiving strong narcotics. Support Care Cancer 3:135–138