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General introduction



“Life is pleasant. Death is peaceful. It’s the transition that’s troublesome.”
 Isaac Asimov, American science fiction novelist & scholar (1920 – 1992)

Death comes to us all

At the beginning of the 20th century, death was often a sudden event, with infectious diseases, accidents and death in relation to childbirth as leading causes. Nowadays, sudden deaths are less common, especially in Western societies, where most people can anticipate death at an advanced age from a progressive illness which is preceded by a period of gradual decline^{1,2}. Each year, 1.6 million patients in Europe will die from cancer and around 5.7 million from non-malignant chronic diseases³. In The Netherlands the total number of deaths in 2016 was approximately 149.000, of which 89.000 were non-sudden deaths^{4,5}. Half of the patients (53%) die at home, 19% die in hospital and 28% in a nursing home⁵.

Palliative care

As a chronic disease progresses, the emphasis in treatment goals shifts from prolonging life to preservation of quality of life³. This transition from curative care to palliative care is often a gradual process. The World Health Organization (WHO) defined palliative care in 2002 as “an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness, through the prevention and relief of suffering by means of early identification and impeccable assessment and treatment of pain and other problems, physical, psychosocial and spiritual”⁶. It has been estimated that in high income countries, up to 82% of people who are approaching the end of life may benefit from palliative care⁷.

Palliative care is mostly provided to patients suffering from advanced cancer, despite the fact that patients with a non-cancer diagnosis, like organ failure, neurological disease or dementia, may have the same palliative care needs as cancer patients^{3,8}. Several studies have shown that early provision of palliative care can improve the quality of life of people with cancer or other life-threatening illnesses⁹⁻¹¹. However, the start of palliative care is often delayed until the last weeks or days of life, when the disease is far advanced and disease focused treatments are no longer effective¹². Three distinct trajectories of functional decline in patients with progressive chronic illness (see Figure 1¹³) have been described by Lunney et al, illustrating the characteristic dynamic patterns of patients with different underlying diseases¹⁴. The first trajectory, typically associated with cancer, involves a reasonably predictable decline in physical health over a period of weeks, months, or, in some cases, years, followed by a fast deterioration in the last few weeks. The second trajectory, typically associated with organ failure, features a gradual decline with intermittent severe symptomatic crises. Each exacerbation may result in death, but the patient may also survive several of such episodes. The third trajectory, typically associated with dementia or frailty, shows a

progressive erratic decline from an already low baseline of cognitive or physical functioning^{13 14}. Insight into these trajectories can assist healthcare professionals in estimating when palliative care should commence. However, with multimorbidity, which has become the norm at the end of life, patients may present with a combination of one or more trajectories, making this estimation more complex¹⁵.

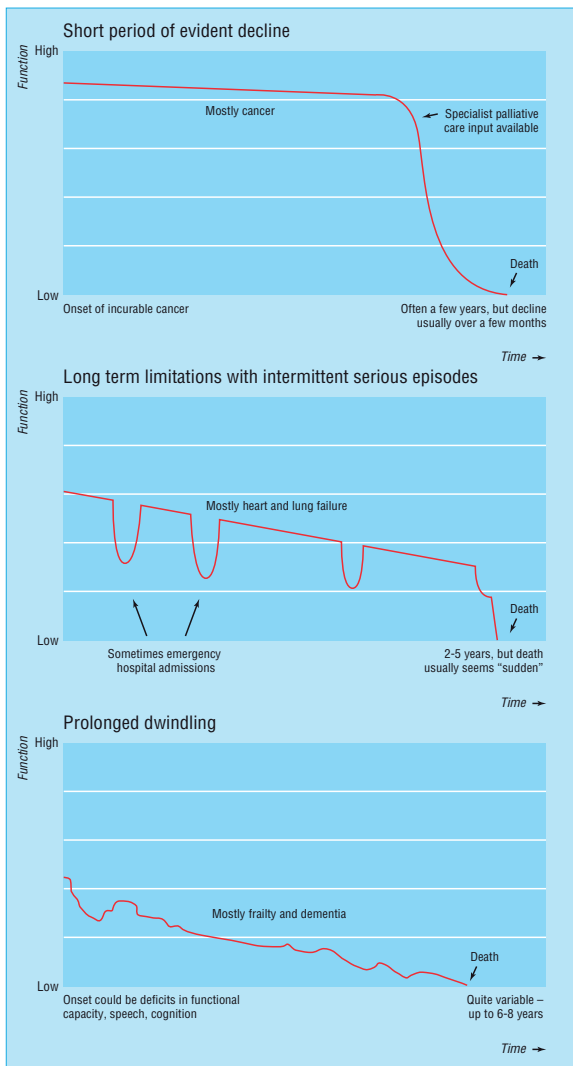


Figure 1, Typical illness trajectories for people with progressive chronic disease. From Murray et al., 2005

Symptoms

In order to deliver good palliative care it is important to know which symptoms may occur during a specific disease trajectory or disease phase and what their impact on daily

functioning is. The New Oxford Dictionary provides the following definition of a symptom: “A physical or mental phenomenon, circumstance or change of condition arising from and accompanying a disorder and constituting evidence for it.” Symptom expression varies from patient to patient, depending on the individual patient’s perception and on other factors, such as psychosocial issues. While symptoms are often addressed separately, patients frequently have multiple coexisting symptoms¹⁶⁻¹⁸. Moreover, when evaluating symptoms, it is important to be aware of their multidimensional nature. Evaluation of a symptom should not be limited to its mere presence but also includes its severity and/or impact. The mere presence of a symptom does not imply that it is distressing or that there is a need for action¹⁶.

Symptoms in patients with advanced disease

The last 25 years, the number of studies focusing on symptoms in patients with advanced diseases has increased steadily (see figure 2). Symptom related aspects that are covered in these studies are the prevalence, burden (i.e. impact or distress) or management (i.e. symptom control or interventions) of symptoms; the development, validation or translation of tools for screening or assessment of symptoms; a focus on specific symptoms or specific diagnoses; symptom aspects in relation to specific locations of care, care providers, (palliative) care teams, countries or regions of the world; and comparisons between different symptom assessors (e.g. patients or proxies such as family members or healthcare professionals).

A number of systematic reviews on symptoms in patients with advanced diseases (i.e. cancer, chronic organ failure, dementia) have been published this last decade¹⁹⁻²¹. Teunissen et al. performed a review on symptom prevalence in patients with cancer which showed that during the palliative phase fatigue, pain, lack of energy, weakness and appetite loss were all highly prevalent symptoms, being present in more than 50% of patients²⁰. Janssen et al. reviewed studies on the prevalence of symptoms in patients with advanced chronic organ failure and found that fatigue, dyspnoea, insomnia and pain were frequently reported in all patient groups¹⁹. Lastly, van der Steen showed that patients with advanced dementia are often reported as having pain, shortness of breath, discomfort, restlessness, and difficulty with swallowing²¹. There seems to be a certain degree of concordance when looking at highly prevalent symptoms in patients with different types of advanced disease.

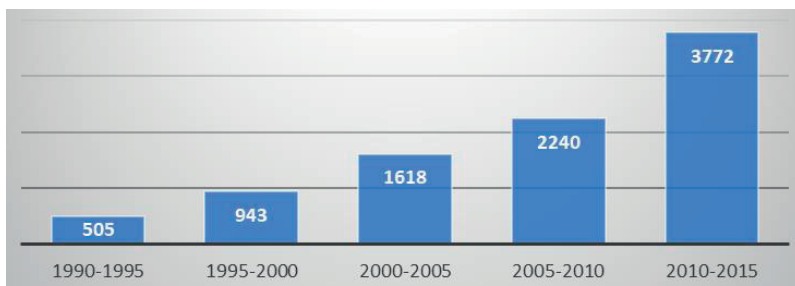


Figure 2 Number of published studies on symptoms in advanced diseases between 1990 and 2015 in English

Although the number of studies on symptoms in patients with advanced diseases increases, evidence remains scarce or lacking for some subgroups. Of the approximately 9000 studies published between 1990 and 2015 on symptoms in patients with advanced diseases, around 56% focused on symptoms in relation to cancer compared to 9% that focused on chronic organ failure (i.e. chronic heart failure, chronic obstructive pulmonary disease or chronic renal failure) and 2% that focused on dementia²². Furthermore, also in the studies in cancer, various cancer types were not evenly represented. Especially, patients with specific cancer types, as for example head and neck cancer, were barely studied. Moreover, almost all research has focused on patients in high-income countries^{19 20 23 24}, whether patients in developing parts of the world experience the same symptoms and functional limitations remains unclear.

Diagnosing dying and awareness of dying

Recognition of the dying phase (i.e. the phase when death is expected to occur within hours or days^{25 26}) is an important prerequisite to enable patients and their families to prepare for their impending death and saying goodbye²⁷. Being aware that death is imminent is often seen as one of the features of a good death in modern Western culture²⁸⁻³¹. Awareness that a patient's death is imminent allows healthcare professionals to appropriately reset the goals of care to prevent possible harmful treatment. Diagnosing dying has been described as being partly 'art' and partly science³². On the one hand, it has been repeatedly shown that physicians are inaccurate in their prognoses for terminally ill patients. Mostly they overestimate patients' life expectancy, although more experienced physicians have shown to have greater prognostic accuracy^{33 34}. On the other hand, nurses have been described as perceiving signs and symptoms of dying earlier than physicians do³⁵. This seems to be related to the intensity, frequency and duration of their contact with patients. Besides spending more time with a patient, intuition or a 'sixth sense' have also been suggested to be part of nurses' assessment of imminent death^{36 37}. Hence, a diagnosis of dying should preferably be established by physicians together with nurses, i.e. by an interdisciplinary team. It is not clear to what extent patients recognize their own dying.

Symptoms in the dying phase

Several studies have focused on the relation between symptoms and patients' impending death³⁸⁻⁴¹. Rigorous scientific evidence on which signs or symptoms could indicate imminence of death is still lacking. Benedetti et al. performed a Delphi study to establish expert consensus on clinical phenomena indicating that a person will die within the next hours or days⁴². Death rattle, no food or fluid intake and changed breathing rhythm were judged by these experts as having the highest relevance.

A reduced oral intake is a common phenomenon at the end of life. This may be due to illness- or treatment-related symptoms or complications, such as dysphagia, nausea or vom-

iting, mechanical or functional obstruction in the digestive tract, generalized weakness, and in the last days of life by a decreased level of consciousness or a loss of desire to drink^{43,44}. The evidence that artificial hydration may be beneficial when patients have a reduced oral intake at the end of life is limited and inconclusive⁴⁵⁻⁴⁷. Common arguments against artificial hydration are that it may increase the risk of complications such as oedema, ascites, and death rattle^{43,48,49}. On the other side, artificial hydration has been suggested to reduce the risk of delirium or terminal restlessness^{47,50,51}. To be able to provide good quality of care at the end of life it is important to know which symptoms or phenomena can occur, but also how symptoms or interventions interact.

Patients with an advanced disease (cancer or non-cancer) have been reported to experience many symptoms in their last week or days of life⁵²⁻⁶². Pain (reported prevalence between 30%-60%)^{20,52,56,58,60,62}, shortness of breath (22%-62%)^{20,52,56,58,60}, restlessness (42%-51%)^{52,62}, dysphagia (16%-46%)^{20,58}, confusion (30%-68%)^{56,57,60,62} and death rattle (39%-56%)^{52,58} have all been reported to be common in the last week or days of life. Insight into commonly occurring symptoms in the dying phase enables healthcare professionals to be proactive in the care they provide and enables them to explain to patients and family members what they can expect during the dying phase.

AIM AND OVERVIEW OF THE THESIS

In this thesis, we focus on the impact of symptoms in the last phase of life. The studies described in this thesis were aimed at providing insight into various aspects of symptoms and symptom relief during the last phase of life. The following research questions will be addressed:

Research question 1 *What is the prevalence and impact of symptoms in two understudied patient groups: patients with incurable head and neck cancer and patients in a developing country with advanced heart failure?*

To answer this research question data were used from two survey studies.

To explore the prevalence and impact of symptoms in patients with incurable head and neck cancer, a cross-sectional descriptive study was performed at Erasmus MC. This study consisted of two parts. First, data from questionnaires filled in by patients between October 2006 and October 2008 as part of normal care were used to establish symptom prevalence for 30 symptoms, of which 9 psychosocial. Second, data were prospectively gathered from February 2009 up to May 2009 to establish the impact of those 30 symptoms for patients and potential discrepancies between the ratings from patients and their family caregivers (see chapter 2).

To explore the prevalence and burden of symptoms in patients with advanced heart failure in a developing region of the world, a cross-sectional observational study was performed at Groote Schuur Hospital in Cape Town, South Africa. Patients were recruited for this study between August and November 2012 from several inpatient facilities (i.e., an emergency unit, emergency ward, cardiology ward, and general medicine wards) and the outpatient cardiology clinic. Patients provided information on symptom prevalence of 28 physical and 4 psychological symptoms and the associated burden (see chapter 3).

Research question 2 *What is the prevalence and impact of death rattle and terminal restlessness and does fluid intake influence their occurrence?*

To answer this research question, first a systematic review focused on death rattle was performed in 2012. Several databases were searched for empirical studies on death rattle. We investigated which labels and definitions of death rattle were used, the prevalence of death rattle, the impact of death rattle on patients, relatives, and professional caregivers, and effects of medical and nonmedical interventions (see chapter 4).

As fluid intake is suggested to be related to the occurrence of death rattle and terminal restlessness, a multicentre prospective observational study was performed. Data were collected in 8 hospitals (one to three wards per hospital) and five hospices, including three palliative care units in nursing homes (PCUs), in the Netherlands. Data collection took place between November 2012 and November 2013 in patients who were, according to the multidisciplinary care team, likely to die within a few days. Data were collected using a digital version of the Care Program for the Dying (CPD), which was supplemented for this study with questions about death rattle, terminal restlessness, use of opioids and patients' fluid intake (see chapter 5). The CPD, a Dutch instrument for multidisciplinary care can be used to support care and symptom management during the last days of life. The CPD was originally based on the Liverpool Care Pathway for the dying patient⁶³ and adapted to the Dutch language and healthcare system. The CPD is started when the multidisciplinary team agrees that the patient is likely to die within a few days. The CPD is a template for multidisciplinary care in the last few days to hours of life and consists of three parts in which different data are recorded by doctors and nurses⁶⁴. The care program assesses the physical, psychological, social, spiritual/religious and information needs of patients and relatives at 4 hourly intervals^{59,64}. Between 2010 and 2012 a digital version of the CPD was developed in the Netherlands to comply with the need for digitalization in healthcare

Research question 3 *To what extent are patients aware of the imminence of their death?*

To answer this research question, we performed a secondary analysis of data that were collected in a study that investigated the effect of using the CPD on the care and quality of

life during the last 3 days of life. Patients were recruited from hospitals, nursing homes and home care services and data collection took place between November 2003 and February 2006. Nurses and family caregivers were requested to fill out a questionnaire with questions about the last 3 days of life. Both groups were asked whether a patient had been aware of the imminence of death. Also, medical records were screened for statements indicating that the patient had been informed of the imminence of death (see chapter 6).

Research question 4 *Do nurses experience moral distress in relation to the practice of palliative sedation?*

Patients who are nearing death sometimes experience symptoms that cannot be relieved with conventional therapeutic interventions, such as intractable pain, dyspnoea, and delirium⁶⁵⁻⁶⁶. Palliative sedation is a medical intervention used to alleviate unbearable and refractory suffering in the last phase of life by the deliberate lowering of a patient's level of consciousness to induce decreased awareness of symptoms⁶⁷⁻⁶⁹. Palliative sedation is a practice of last resort and is therefore often used in complicated cases, under stressful conditions and with time constraints, it has been linked to (emotional) burden for nurses⁶⁸⁻⁷⁴. To answer this research question, a secondary analyses of qualitative interview data was performed. Qualitative interviews with nurses were collected as part of a larger project about the practice of palliative sedation in the Netherlands after the introduction of a national guideline on palliative sedation. Nurses were interviewed between October 2008 and April 2009. Analyses were performed with the constant comparative method. (see chapter 7).

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