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REAL-LIFE PERSPECTIVES ON THE END-OF-LIFE CARE OF CANCER PATIENTS

Liisa Rautakorpi

TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
SARJA – SER. D OSA – TOM. 1636 | MEDICA – ODONTOLOGICA | TURKU 2022

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To my family

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LIISA RAUTAKORPI: Real-life perspectives on the end-of-life care of cancer patients
Doctoral Dissertation, 112 pp.
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ABSTRACT

Background and Aims: The practices of the end-of-life (EOL) care of cancer patients remain unknown in Finland. The aim of this retrospective study was to study the effects of palliative intervention on cancer patients' EOL, the use of anticancer treatments during the last year of life and the use pain medication in a hospice setting.

Methods: To evaluate the effect of palliative intervention, we performed a single-center study including pancreatic cancer patients treated at Turku University Hospital (TUH) during their last month of life. Of 378 patients, 76 (20%) had a contact to the palliative care unit in addition to their standard care. The use of anticancer treatments during the last year of life was assessed in a cohort study of 11,250 deceased cancer patients, of whom 3,285 received intravenous (IV) chemotherapy (CT) and 2,904 radiotherapy (RT) during the last year of life. Finally, pain medication given to 138 cancer patients was studied after transfer to hospice.

Results: Fewer treatment procedures and lower tertiary care costs during the last month of life were observed for cancer patients who were in contact with the palliative care unit. The use of IV CT remained stable across the 9-year period. Patient's age and diagnosis affected the time from last treatment to death. The time between the last fraction of RT and death varied by diagnosis and was longer for patients living >100km from TUH. The use of single-fraction RT treatments was infrequent, even if the median number of RT fractions decreased during the observation time. In hospice, upon transfer 63% of patients, and 1 day before death 90% of patients, received regularly dosed strong opioids. The use of subcutaneous administration increased significantly during the stay in hospice.

Conclusions: Palliative care intervention should be warranted for patients with aggressive malignancies and a short life expectancy. Significant variations in EOL CT between different diagnoses and age groups were identified. Single-fraction RT should be considered more often, and palliative RT should also be made available to patients living far away from the RT unit. Strong opioids remain the foundation of pain medication in hospice.

KEYWORDS: EOL care, palliative intervention, EOL chemotherapy, EOL radiotherapy, pain medication, opioids

TURUN YLIOPISTO
Lääketieteellinen tiedekunta
Kliininen syöpätautioppi
LIISA RAUTAKORPI: Näkökulmia syöpäpotilaan elämän loppuvaiheen hoitoon
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TIIVISTELMÄ

Tausta ja tutkimuksen tarkoitus: Syöpäpotilaiden elämän loppuvaiheen hoitokäytäntöjä ei ole kuvattu Suomessa kattavasti. Tämän retrospektiivisen väitöskirjatutkimuksen tarkoituksena oli tutkia palliatiivisen intervention vaikutusta syöpäpotilaiden elämän loppuvaiheessa, syöpähoitoja potilaan viimeisen elinvuoden aikana ja kipulääkityksen toteutumista saattohoitokodissa.

Menetelmät: Palliatiivisen intervention vaikutusten arvioimiseksi tutkimme Turun yliopistollisessa keskussairaalassa hoidettuja haimasyöpäpotilaita viimeisen kuukauden aikana ennen kuolemaa. 378 potilaasta, 76:lla (20 %) oli hoitokontakti palliatiiviseen poliklinikkaan muun hoidon lisäksi. Viimeisen vuoden aikana annettuja syöpähoitoja kartoitettiin 11 250 menehtyneen syöpäpotilaan kohortissa. Näistä potilaista 3285 sai suonensisäistä sytostaattihoitoa ja 2904 sädehoitoa. Neljännessä tutkimuksessa tutkittiin 138 syöpäpotilaan kipulääkityksen toteutumista saattohoitokodissa.

Tulokset: Potilaille, joilla oli kontakti palliatiiviseen poliklinikkaan, tehtiin viimeisen kuukauden aikana vähemmän hoitotoimenpiteitä ja tutkimuksia. Lisäksi heidän erikoissairaanhoidon kustannuksensa olivat merkittävästi pienemmät. Yhdeksän vuoden tarkastelujaksona aika suonensisäisen sytostaattihoidon päättymisestä potilaan kuolemaan pysyi vakaana. Potilaan ikä ja syöpädiagnoosi vaikuttivat viimeisen sytostaattihoidon ajankohtaan. Viimeisen sädehoidon ja kuoleman väliseen aikaan vaikutti syöpädiagnoosi ja > 100 km etäisyys potilaan asuinpaikan ja sädehoitoyksikön välillä. Viimeisessä sädehoitosuunnitelmassa fraktioiden määrä väheni tarkastelujaksona, vaikkakin yhden fraktion hoitoja käytettiin vähän. Saattohoitokotiin siirryttäessä 63 % ja päivä ennen kuolemaa 90 % potilaista sai säännöllisenä kipulääkkeenä vahvaa opiaattia. Ihonalainen annostelu muuttui yleisemmäksi kuoleman lähestyessä.

Johtopäätökset: Palliatiivinen interventio tulisi taata kaikille nopeasti etenevää syöpää sairastaville potilaille, joiden elinajanodote on lyhyt. Ikä ja potilaan syöpädiagnoosi vaikuttavat suonensisäisen sytostaattihoidon käyttöön viimeisten elinkuukausien aikana. Yhden fraktion hoitoja tulisi harkita useammin ja niille potilaille, jotka asuvat kaukana sädehoitoyksiköstä, tulisi taata mahdollisuus palliatiiviseen sädehoitoon. Vahvat opiaatit ovat elämän loppuvaiheen syöpäkivunhoidon perusta.

AVAINSANAT: elämän loppuvaiheen hoito, saattohoito, palliatiivinen interventio, elämän loppuvaiheen sytostaattihoito, elämän loppuvaiheen sädehoito, kipulääkitys, opiaatit

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Abbreviations

ASCO	American Society for Clinical Oncology
ASTRO	American Society for Radiation Oncology
CT	Chemotherapy
CoT	Computer tomography
EAPC	European Association for Palliative Care
ED	Emergency department
EOL	End-of-life
ESMO	European Society for Medical Oncology
Gy	Gray
ICU	Intensive care unit
IV	Intravenous
MEDD	Morphine equivalent daily dose
MRI	Magnetic resonance imaging
PC group	Palliative care group
RT	Radiotherapy
SC	Subcutaneous
SC group	Standard care group
TUH	Turku University Hospital
WHO	World Health Organization
WPCA	World Palliative Care Association

List of Original Publications

This dissertation is based on the following original publications, which are referred to in the text by their Roman numerals:

I Liisa Rautakorpi, Sirkku Jyrkkiö, Eliisa Löyttyniemi & Outi Hirvonen. End-of-life care among patients with pancreatic cancer with or without palliative intervention: a retrospective single-centre study, *Acta Oncologica*, 2021 60:1, 106–111.

II Liisa Rautakorpi#, Fatemeh Seyednasrollah#, Johanna Mäkelä, Outi Hirvonen, Tarja Laitinen, Laura L. Elo & Sirkku Jyrkkiö. End-of-life chemotherapy use at a Finnish university hospital: a retrospective cohort study, Acta Oncologica, 2017, 56:10, 1272–1276.
# The first and the second authors contributed equally to this manuscript

III Liisa Rautakorpi, Johanna Mäkelä, Fatemeh Seyednasrollah, Anna Hammais, Tarja Laitinen, Outi Hirvonen, Heikki Minn, Laura L. Elo & Sirkku Jyrkkiö. Assessing the utilization of radiotherapy near end of life at a Finnish University Hospital: a retrospective cohort study, *Acta Oncologica*, 2017 56:10, 1265–1271

IV Liisa Koivu, Tuukka Pölönen, Teija Stormi & Eeva Salminen. End-of-Life Pain Medication among Cancer Patients in Hospice Settings, Anticancer Research, 2014 *34*: 6581–6584.

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Rautakorpi (nèe Koivu)

1 Introduction

Palliative care offers a holistic approach to managing patients' symptoms near the end of life (EOL), with focus on the patient's comprehensive well-being. Palliative care is essential to patients with various diagnoses, but in this thesis the focus is on patients with cancer. Palliative care has been found to improve cancer patients' quality of life and alleviate symptom burden (Bajwah et al., 2020; Kavalieratos et al., 2016). Thus, it should be part of their care concurrent with active anticancer treatments (Ferrell et al., 2017).

When faced with serious illness, most people would choose to improve their quality of life for the time they have left, rather than merely extending it (Higginson et al., 2014). Many cancer patients would prefer being cared for at home and, if possible, would also want to die there (Khanm et al., 2014). The importance of death and dying is recognized also by the public, and there is a concern about the prioritization of quantity over quality of life (Daveson et al., 2014).

In the future, the number of cancer patients will increase as the population in Finland ages (Pitkäniemi et al., 2021). Despite improvements in cancer care, malignant neoplasms are one of the leading causes of death in developed countries (Connor et al., 2020). The need for symptom-alleviating procedures and hospital resources will inevitably increase when the patient's cancer becomes advanced (Crawford et al., 2021). Thus, the demand for EOL care will grow simultaneously.

A major part of the costs of health care arises from treatment during the last year of life (Riley & Lubitz, 2010). Indeed, also in Finland, the costs of care rise tenfold as death approaches (Halminen et al., 2019). Advances in palliative and terminal care may lower the costs of care (Finne-Soveri et al., 2021) and give us an opportunity to target the limited resources of health care more effectively (Hirvonen et al., 2018).

In Finland, active anticancer treatments have been at the center of the oncological approach, whereas EOL care has been provided alongside primary healthcare. Cancer care has traditionally focused on improving the prognosis and overall survival of the patient, and treatment patterns during the last month of life or advanced care planning have only come into focus in recent years. Oncologists have more commonly been involved with treating symptoms such as pain, nausea, and fatigue, rather than managing psychological symptoms and EOL issues (Cherny & Catane, 2003).

According to a report by the World Palliative Care Association (WPCA) (Connor et al., 2020), in Finland the quality of palliative care does not reach the level of other high-income developed countries, and the processes of palliative care need to be developed and harmonized, as stated in a report by the Ministry of Social Affairs and Health (Saarto et al., 2019). To further develop and optimize treatment patterns in the future, a crucial step is to assess current treatment practices.

The aims of this thesis were to evaluate from real-life data the effects of palliative intervention on patients' EOL care and the use of anticancer treatments during the last months of a patient's life, and to assess the aggressiveness of oncological interventions close to death. Finally, the aim was to study the use of opioids in the terminal phase of a cancer patient's disease.

2 Review of the Literature

2.1 Definition of key terms

The definitions of key terms, end of life, palliative care, and advance care planning are given in Table 1.

Table 1. Definition of key terms.

End of life	European Society for Medical Oncology (ESMO)	Care for people with advanced disease once they have reached the point of rapid physical decline, typically the last few weeks or months before inevitable death as a natural result of a disease (Crawford et al., 2021).
	Systematic Review	Life-limiting disease with irreversible decline and expected survival in terms of months or less (Hui et al., 2014).
Palliative care	World Health Organization (WHO)	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. Palliative care should provide relief, affirm life, and regards dying as a normal process. It should be applicable early in the course of illness, in conjunction with other therapies that are intended to prolong life, such as chemotherapy or radiation therapy, and includes those investigations needed to better understand and manage distressing clinical complications (Sepúlveda et al., 2002).
	Association for Hospice and Palliative care	An active holistic care of individuals across all ages with serious health-related suffering due to severe illness and especially of those near the end of life. It aims to improve the quality of life of patients, their families, and their caregivers (Radbruch et al., 2020).
Advance care planning	Consensus Definition from a Multidisciplinary Delphi Panel	A process that supports adults at any stage of health in understanding and sharing their personal values, life goals, and preferences regarding future medical care. The goal of advance care planning is to help ensure that people receive medical care that is consistent with their values, goals, and preferences during serious and chronic illness (Sudore et al., 2017).
	European Association for Palliative Care (EAPC)	The ability to enable individuals to define goals and preferences for future medical treatment and care, to discuss these goals and preferences with family and health-care providers, and to record and review these preferences if appropriate (Rietjens et al., 2017).

2.2 Palliative intervention

Palliative care offers a patient-centered and holistic approach to the care of advanced and lethal diseases. In addition to standard oncological care, it should be routinely included in the care of cancer patients already receiving active anticancer treatment (Kaasa et al., 2018), with a focus on those who have a limited life expectancy. The role of palliative care has been unequivocally acknowledged in the guidelines of ESMO (European Society for Medical Oncology) and ASCO (American Society for Clinical Oncology) (Ferrell et al., 2017; Jordan et al., 2018), and the favorable effects on the patient's quality of life, satisfaction, and symptom control have been established in various systematic reviews (Bajwah et al., 2020; Haun et al., 2017; Kavalieratos et al., 2016).

Palliative intervention is a way to integrate palliative care with the standard oncological care and in this thesis it is referred as the intervention when palliative care specialists meet the cancer patient. It may be executed by interdisciplinary palliative care team in palliative care outpatient clinic, inpatient unit or at patient's home. The essential components of clinical process may include routine symptom and functional status screening, discussion on the disease history and prognosis in addition to clarification of treatment goals. Palliative treatment options including symptom control, medical therapies and radiotherapy needs also to be considered. Advance care planning and discussion on patient's and caregivers wishes should also be included (Ferrell et al., 2017; Hui & Bruera, 2015). The definition and execution of palliative intervention varies in clinical studies as presented in the Table 2.

Table 2. Examples on palliative interventions.

	Intervention	Study design	Outcome measurements	Results
Eychmyller et al, 2021 **Switzerland**	A single intervention performed by a physician and a nurse – a structured conversation	A randomized controlled trial	Patients distress and a health-related quality of life	Intervention did not decrease distress or improve quality of life
Vanbutsele et al, 2018 **Belgium**	Consultation with a palliative care nurse within 3 weeks of enrolment and monthly until death. Physician visit on demand – routine assessments. Palliative care nurse participating in weekly multidisciplinary oncology meetings	A randomized controlled trial	Quality of life	Quality of life was increased for the patients in the intervention group
Groenvold et al, 2017 **Denmark**	Referral to multidisciplinary specialist palliative care team – number and frequency of contacts determined by patients needs during 8-week trial period	A randomized clinical trial	Change in each patient's primary need (problems with physical, emotional or role function, or nausea, pain, dyspnea or lack of appetite) and survival	No difference between the groups were observed
Maltoni et al, 2016 **Italy**	Appointment with palliative care specialist within 2 weeks of enrolment and every 2–4 weeks until death – discussion on pre-determined checklist	A randomized clinical trial	Frequency, type and timing of chemotherapy administration, use of resources, place of death and overall survival	In the experimental arm chemotherapy was used less frequently near EOL, and higher use of hospice services was observed
Zimmermann et al, 2014 **Canada**	A meeting with a palliative care physician and nurse once monthly and more often if necessary – routine assessments	A cluster-randomized controlled trial	Quality of life, symptom severity, satisfaction with care and problems with medical interactions	At 4 months a significant difference in all other measurements but medical interactions
Temel et al, 2010 **US**	A meeting with a palliative care physician and a nurse – 8 weeks after diagnosis and at least monthly until death	A randomized controlled trial	Quality of life and mood	Improvements in quality of life and mood, longer OS
Penrod et al, 2010 **UA**	Palliative care consultation for inpatient patients	An observational study	The costs of care and intensive care unit use	Lower costs of care and less utilization in intensive care unit in the palliative care group
Bakitas et al, 2009 **US**	Advanced practice nurse – 4 weekly educational sessions and monthly follow-up until death or study completion	A randomized controlled trial	Quality of life, symptom intensity, depressed mood	Higher QOL and mood, other measurements were not significant between the groups

2.2.1 Effects of palliative intervention

Studies evaluating the effects of palliative intervention show wide variations in the study design. Settings vary with the population studied, the outcomes chosen, the duration of the study, the type of intervention, and the clinical setting. Nonetheless, in addition to improvements in quality of life and mood, and a trend toward a lower symptom intensity (Bakitas et al., 2009), some studies have suggested a longer overall survival for patients who receive early palliative care (Bakitas et al., 2015; Temel et al., 2010). Lower activity of treatment procedures and fewer hospitalizations near the EOL have also been detected as an impact of palliative care (Jang et al., 2015).

Favorable outcomes extend, however, beyond patient outcomes, as early palliative care improves the psychological wellbeing of caregivers (El-Jawahri et al., 2017) and is associated with lower costs of care, as reported in a systematic review by Yadav et al. (Yadav et al., 2020).

However, it should be noted that despite the many advances brought about by palliative intervention, there are also studies with mixed outcomes. In a Danish randomized trial, specialized palliative care showed no beneficial or harmful effects (Groenvold et al., 2017), even if in the exploratory analyses the intervention group seemed more satisfied with the health care received (Johnsen et al., 2020). In a Canadian cluster-randomized controlled trial of patients with advanced cancer, early referral to a palliative care team significantly improved quality of life on one of the measured scales. Furthermore, patient satisfaction increased. However, changes in symptom severity or problems with medical interactions did not decrease (Zimmermann et al., 2014). Additionally, in the ENABLE II randomized, controlled trial, there were no differences in the use of hospital resources near the EOL (Bakitas et al., 2009).

Indeed, evaluating the effects of palliative intervention may be challenging due to the difficulties of conducting prospective trials of palliative care interventions in a population of patients with advanced cancer (Temel et al., 2020).

2.2.2 Palliative care and the use of hospital resources

The need for palliative care evolves as the disease progresses, and many cancer patients require active non-oncological treatment procedures during the last weeks of life. When health care utilization by patients dying of cancer in seven developed countries was assessed, during the last month of life 43–63% of patients were hospitalized in acute care hospitals. One third of patients in the United States (US) and fewer than 11% in other countries were admitted to the intensive care unit (ICU) (Bekelman et al., 2016).

Emergency department (ED) visits are also common, as 26–75% of patients visit an ED during their last month of life (Bekelman et al., 2016; Urvay et al., 2021). Patients with advanced cancer will have symptoms and a need for specialized medical care, but some of the ED visits could be avoided with advance care planning (Hirvonen et al., 2018; Surakka et al., 2021). Indeed, palliative intervention has been found to decrease the need for hospital services and the use of aggressive EOL care (Bevins et al., 2021; Hirvonen et al., 2020; Jang et al., 2015; Temel et al., 2010; Triplett et al., 2017).

2.2.3 Timing of palliative intervention

Traditionally, palliative care has been associated with EOL care and a poor prognosis. It should, however, be given already at an early stage of the disease. In a systematic review and meta-analysis including over 10 million patients, prior to death the median duration from initiation of palliative care to death was 18.9 days (R. Jordan et al., 2020). Early palliative care might have the most pronounced effect on the patient's quality of life (Haun et al., 2017; Nottelmann et al., 2021) even if it does not necessarily influence the use of hospital resources during EOL (Bakitas et al., 2015). However, also this finding varies with the setting: When the timing of palliative intervention was assessed in an Australian study, early (>90 days) and late (<90 days) specialist palliative care was assessed regarding the aggressiveness of cancer care during the last 30 days of life. Late palliative referral was associated with more ED visits and acute hospital admissions, with no differences in ICU admissions (Michael et al., 2019).

The condition for early palliative referral is recognizing that the patient is approaching the EOL and formulating a moderately accurate survival prediction. When predicting the survival of terminally ill patients, physicians' estimates are often overly optimistic, also for patients with impaired performance status (Christakis & Lamont, 2000). Physicians should be aware of this tendency, even though the importance of clinical prediction should not be underestimated, as prediction and actual survival have been found to be strongly correlated (Glare et al., 2003). Discussing these evaluations with empathy and realism in a way that the patient understands is of utmost importance. Furthermore, the difficulties of prognostic evaluation and the stigma associated with EOL- and palliative care may complicate the discussion and hence referral to a palliative care unit.

2.2.4 Integration of oncology and palliative care

To conclude, the question should not be whether palliative intervention is an essential part of a patient's care, but how it should be arranged (Kaasa et al., 2018). Palliative care interventions should be integrated, dynamic, personalized, and based on best evidence (K. Jordan et al., 2018). Regardless, the coordination of palliative care is demanding and involves a vast number of professionals and multiple transitions from one care level to another throughout the disease trajectory, which makes collaboration and integration of services important (Kaasa et al., 2018). Early and systematic integration may be more beneficial for the cancer patient than consultations offered on demand (Maltoni et al., 2016; Vanbutsele et al., 2018). There are many models of integration of oncology with palliative care (Hui & Bruera, 2015). Of the multiple conceptual models, four essential ones are presented in Table 3.

Even if the need for palliative care already in an early stage of disease trajectory has been recognized in many guidelines there has been a lack of consensus of referral criteria for outpatient palliative cancer care (Hui, Meng, et al., 2016). Thus, to achieve this consensus, an international expert panel was formed. Based on its work consensus on 11 major criteria for outpatient palliative-care referral for patients with advanced cancer being treated at secondary or tertiary care hospital was achieved. The nine need-based criteria and the two time-based criteria are presented in a Table 4.

Table 3. Conceptual models for integrating oncological and palliative care (Modified from Hui & Bruera, 2015.

Name of the model	In short	Division	Highlights
Time-based model	Chronological criterion	Time of intervention: i. when no more treatments are available ii. from time of diagnosis ii. level of integration fluctuates over time	Timing and extent of palliative intervention
Provider-based model	Primary, secondary, and tertiary palliative care	i. primary care by an oncologist and primary care providers ii. secondary care by specialist palliative care teams and consultants in inpatient or outpatient settings iii. tertiary care by a palliative care team in an acute palliative care unit	Patient complexity and setting
Issue-based model	Solo practice, congress, and integrated care approaches	i. solo practice model – oncologist is responsible for anticancer and supportive care ii. congress model – oncologist refers patient to various specialists (generally not recommended) iii. integrated care model – patient is referred to specialist palliative care teams early in the disease trajectory (recommended model)	Supportive care issues
System-based model	Clinical events	i. contemporary model – timing and eligibility for palliative care referral is not standardized ii. integrated system-based model – a patient who meets pre-defined criteria is referred to palliative care	Comprehensive supportive care assessments and treatments provided by the palliative care team

Table 4. Referral criteria for outpatient palliative cancer care by an international expert panel (Modified from Hui et al., 2016).

Needs-based criteria	Severe physical symptoms (scored 7–10 on a ten-point scale)
	Severe emotional symptoms (scored 7–10 on a ten-point scale)
	Request for hastened death
	Spiritual or existential crisis
	Assistance with decision making or care planning
	Patients request
	Delirium
	Brain or leptomeningeal metastases
	Spinal cord compression or cauda equina
Time-based criteria	Within 3 months of diagnosis of advanced or incurable cancer for patients with median survival of 1 year or less
	Diagnosis of advanced cancer with progressive disease despite second-line systematic therapy

Accordingly, patients with aggressive malignancies such as pancreatic cancer should receive palliative consultation. Pancreatic cancer is often associated with poor prognosis with an overall survival rate of only 5–12 % in 5 years after diagnosis and is one of the most lethal diseases and fourth leading cause of cancer deaths for both sexes in Europe (Danckert et al., 2019; Ducreux et al., 2015; Dyba et al., 2021). In a clinical practice guideline for metastatic pancreatic cancer by ASCO, patients with pancreatic cancer should have a full assessment of symptom burden, psychological status, and social support as early as possible, preferably at the first visit (Sohal et al., 2016). Indeed, when discussing integration of palliative care and oncology special attention should be paid to these patients.

Integration of palliative care already occurs, but further developments is needed. In a Nordic survey of the management of palliative care in 21 university hospitals, for patients with head and neck cancer, specialized palliative care services were indeed available but collaboration between surgeons, oncologists and palliative care specialists was not well structured. Early integrated palliative care was suggested to be included as an addition to the existing care pathways (Boëthius et al., 2021).

2.2.5 Palliative care in Finland

When the World Palliative Care Association (WPCA), in collaboration with the WHO, categorized countries into four categories based on the level of palliative care, Finland was placed in category three, with 29 European countries ranking better. In category three, a country is characterized to have palliative care activism in several locations with growing local support in those areas, multiple sources of funding, the availability of morphine, several hospice palliative care services from a range of providers, and the provision of some training and education initiatives by hospice and palliative care organizations. (Connor et al., 2020). This ranking underlines the need for improvements in palliative and EOL care.

For decades in Finland, EOL care was implemented as part of primary healthcare, and most cancer patients died on a primary care ward or in a secondary or tertiary care hospital without specific palliative care consultation. Clinical and organizational problems were present in patient's transition to primary care after the discontinuation of active oncological care. In more detail, in a Finnish study, after the responsibility of palliative care was transferred to primary care after termination of oncological treatment, one third of the outpatients were unaware who was responsible for the care and one third reported poor quality of palliative care in primary care. In addition, most patients were symptomatic while leaving the university hospital and no improvement was seen later (Tasmuth et al., 2006). There were four hospices focused in the EOL care maintained by independent foundations. In 2010, the Ministry of Social Affairs and Health determined the minimum criteria for EOL care and assigned the responsibility to the municipalities (Pihlainen, 2010). Since then, EOL care has improved substantially, and palliative consultation services in addition to several specialized units offering EOL care have been established. Education for professionals has also been more dynamic. Based on the recommendations of the task force appointed by the Ministry of Social Affairs and Health to examine EOL care, this trend is expected to continue (Saarto et al., 2019).

In Finland the attitudes towards EOL care have also changed alongside with the legislation. The transition to a stronger emphasis on patient-centered care and a stronger tendency to avoid futile therapies was observed in a postal survey including the responses of 1372 physicians in 1999 and 2015. In more detail physicians chose palliative approaches more often and were more willing to give a hospice voucher in 2015 (Piili et al., 2019). Finnish physicians with special education in palliative medicine are more likely to make less aggressive decisions in the EOL care (Piili et al., 2018) and the number of physicians with palliative training increases as both Nordic and Finnish training programs are ongoing. In addition to special training aiming for palliative specialization, systematic education in palliative medicine is still needed especially for undergraduate medical students (Alminoja et al., 2019).

In Southwest Finland, where data for the present studies were mainly collected, the outpatient palliative care unit was earlier located in a department of oncology, and it had a physician resource 6 days a month from 2003 to 2015, when a fulltime vacancy was created. In 2020, an independent palliative care unit was established at Turku University Hospital. The unit provides patient care and consultation services.

2.3 Intravenous chemotherapy near the end of life

Intravenous chemotherapy is an essential part of cancer treatment, but due to its potential adverse effects and toxicity, its use should always be critically evaluated near the EOL. Chemotherapy affects both cancer and non-cancer cells, and after traditional intravenous administration it can induce both severe acute and late side effects. In most patients with advanced disease, the aim of the chemotherapy is to improve quality of life or, sometimes, overall survival. However, patient selection is of utmost importance (Cherny et al., 2015).

2.3.1 Advantages and disadvantages

A small proportion of patients may gain clinical benefit from active anticancer treatment also when treated close to death. In a cohort of patients with solid tumors who received systemic anticancer therapy 1 month before death, symptoms were alleviated for 16% of them, and for 12% the disease either remained stable or showed a partial or complete response (Baena-Cañada et al., 2019).

Tumor type should always be considered when planning active anticancer treatment for patients at an advanced stage of their disease. Acute myeloid leukemia, choriocarcinoma, aggressive non-Hodgkin's lymphoma, Hodgkin's disease, and acute lymphoblastic leukemias in children are examples of malignant neoplasms that can be treated with curative intent even in the advanced stages (Cherny et al., 2015). The patient's own wishes and concerns regarding treatment should also be considered.

Despite the potential advantages of chemotherapy, the vast majority of patients do not benefit from treatment when life expectancy is severely limited; therefore chemotherapy should not be used in the last weeks of life (Crawford et al., 2021).

The most common cause of mortality within 30 days of chemotherapy is progression of the underlying malignancy, but also severe side effects may occur (O'Brien et al., 2006). Cancer-directed therapies should not be used at least in patients with the following characteristics: low performance status, no benefit from prior evidence-based interventions, not eligible for a clinical trial, and no strong evidence supporting the clinical value of further anticancer treatments (L. E. Schnipper et al., 2012). Chemotherapy use during the last weeks of life should be critically evaluated, as it increases the need for hospitalization (Keam et al., 2008; Näppä et al., 2011) and is associated with more aggressive EOL care including more ED visits, ICU admissions, and endotracheal intubation (Wu et al., 2016). Indeed, the use of chemotherapy near EOL may increase the costs of care and consume the limited health care resources (Bao et al., 2018) without any obvious benefit for the patient.

2.3.2 End-of-life chemotherapy as a quality indicator

Earle et al. evaluated various measures that could use existing data to assess the intensity of EOL cancer care. In their analysis of over 48,000 patients, they suggested that the use of chemotherapy in the final weeks of a patient's life could be used as a quality indicator of not-overly active cancer care. They concluded that less than 10% of patients should receive chemotherapy during the last 2 weeks of life and that less than 2% should receive a new chemotherapy regimen within the last 30 days of life (Earle et al., 2005). These benchmarking standards have since been commonly acknowledged as a quality indicator of EOL cancer care.

2.3.3 Current practice

Concerns have been raised over a detected increase in the use of chemotherapy during the final weeks of life (Earle et al., 2004; Ho et al., 2011). Prior studies have reported rates of chemotherapy use in the last 30 days of life to vary from 10% to 46%, and, for studies not reporting 30-day numbers, to vary in the last 2 weeks from 5.7% to 3.7%. Numbers of patients receiving chemotherapy during the last month of life are shown in Table 5. These percentages must, however, be critically evaluated as the study designs vary. For example, in the Portuguese study by Braga et al. (2007), the percentages are evaluated as a proportion of patients receiving chemotherapy during the last 3 months of life, and in the Finnish study by Asola et al. (2006) as a proportion of patients who died of breast cancer.

Table 5. Use of chemotherapy during the last weeks of life.

Country	**Treatment**	**Inclusion criteria**	**CT 1 month before death**	**CT 2 weeks before death**	**Median time from last chemotherapy to death**
Greece **(**Edman Kessler et al. 2020)	Chemotherapy	Breast cancer	46.5%	-	-
Sweden (Näppä et al. 2011)	Palliative chemotherapy	Epithelial cancer	23%	-	15–84 days
Portugal (Braga et al. 2007)	Chemotherapy	Solid tumors	37%	21%	27 days
Spain 2019 **(**Baena-Cañada et al. 2019)	Systemic anti-cancer therapy	Metastatic solid tumor	32.6%	-	52 days
Italy (Numico et al. 2014)	Chemotherapy, biological or endocrine therapy	Cancer	26.2%	14.2%	75 days
Turkey (Goksu et al. 2014)	Chemotherapy	Stage IV solid tumor	23.9%	10.5%	-
Sweden **(**Edman Kessler et al. 2020)	Chemotherapy	Breast cancer	23.2%	-	-
Switzerland (Matter-Walstra et al. 2014)	Anticancer drug therapy	Cancer	22.2%	-	-
Finland **(**Asola et al. 2006)	Chemotherapy	Breast cancer	19.7%	-	-
France (Rochigneux et al. 2017)	Chemotherapy	Metastatic solid tumor	19.5%	11.3%	-
China (Zhang et al. 2018)	Palliative chemotherapy	Advanced cancer	15.7%	5.2%	-
Norway (Anshushaug et al. 2014)	Chemotherapy	Cancer	10%	5%	2.2 months
Korea (Keam et al. 2008)	Palliative chemotherapy	Metastatic cancer	-	5.7%	2.02 months
Canada **(**Hu et al. 2014)	Chemotherapy	Colorectal cancer	-	3.7%	-

Age has had the most frequent correlation with the use of chemotherapy near the EOL, but other factors have also been presented. In addition, certain diagnostic groups (breast, lung, ovarian, and pancreatic cancer and hematological malignancies), a Glasgow Prognostic Score of two, performance status, previous cancer treatments, geographic location, laboratory values (albumin levels), patients having no contact with a palliative care unit, higher level of comorbidities, short time from diagnosis, hospital type, and in one study also male sex have been found to be associated with chemotherapy use during the last weeks of life (Braga et al., 2007; Edman Kessler et al., 2020; Ho et al., 2011; Hu et al., 2014; Matter-Walstra et al., 2015; Numico et al., 2014; Rochigneux et al., 2017; Sezgin Goksu et al., 2014; Zhang et al., 2018).

In the Nordic countries, where cultural and social frameworks may be closer to those in Finnish society, EOL chemotherapy has been studied among patients with solid tumors. In Sweden, the use of chemotherapy during the last 30 days of life was evaluated in a cohort of patients with metastatic breast cancer and patients with epithelial cancer. Of these, 23% patients in each study received chemotherapy during the last month of life (Edman Kessler et al., 2020; Nappa et al., 2011). In a study evaluating the use of palliative chemotherapy amongst patients with disseminated cancer, the corresponding percentage was higher 32 % (Randén et al., 2013). For 8% of the patients with breast cancer, a new regimen of chemotherapy was initiated during the last month of life (Edman Kessler et al., 2020).

In Norway, the proportion of cancer patients who received chemotherapy during the last 30 days of life was 10%. For breast cancer patients, the proportion was slightly higher at 12% (Anshushaug et al., 2015).

In a Finnish cohort of breast cancer patients, roughly the same percentage as in the Swedish cohort, 19.7%, received chemotherapy during the last month of life (Asola et al., 2006). To our knowledge, apart from this cohort there are no earlier studies from Finland that describe the use of anticancer treatments in other solid tumors and hematological malignancies during the last months of life. However, since 2017, studies have been published assessing the use of EOL treatments in Helsinki and Turku (Hirvonen et al., 2018, 2019, 2020).

2.4 Radiotherapy near the end of life

2.4.1 Palliative radiotherapy

Most cancer patients, especially those with solid tumors, may require radiotherapy once or several times during the course of their disease. Radiotherapy uses ionizing radiation to cause direct and indirect damage to the DNA. The most common type is external beam irradiation. In brachytherapy, the radioactive source is placed directly onto or within the area to be treated. Systemic radioisotopes can target a specific tissue or pathophysiology (Cherny et al., 2015).

The aim of palliative radiotherapy is to control symptoms with minimum associated acute radiation reaction. A consultation with a radiation oncologist should be considered for any patients with pain, bleeding, local complications, or other tumor-related symptoms (G. Williams et al., 2021). In contrast to palliative radiotherapy, the aim of radical radiotherapy is complete eradication of the tumor cells with minimized long-term normal tissue damage (Spencer et al., 2018). Around 40–50% of radiotherapy treatments are given with palliative intent (Janjan, 1998; M. Williams & Drinkwater, 2009).

To minimize normal tissue damage during radiotherapy, the radiation dose is fractionated and delivered over several weeks. Conventionally, one fraction is given daily, but hyperfractionation delivers the total dose in increased numbers of fractions over the same period. Palliative treatments require lower total doses, with the focus on symptom control, and can be delivered in shorter courses of larger fraction size (hypofractionation) (Spencer et al., 2018).

Use of multiple fractions is less common in patients closer to death (Tiwana et al., 2016), which is justifiable as shorter treatments require fewer visits to the hospital and thus require fewer resources from the radiotherapy unit and may be less burdensome for the patient and caregivers. Risk of discontinuation of radiotherapy may also decrease with shorter treatments as seen in a Norwegian study: Shorter regimens of palliative radiotherapy (<2 weeks) led to decrease in the non-completion of the palliative radiotherapy when compared to those receiving longer treatments (Nieder et al., 2022).

Radiotherapy may be an effective treatment option for advanced and metastatic cancer, even during the last months of life. However, a short life expectancy may erase any potential benefit, as time from treatment to response may take several weeks (van der Linden et al., 2006). Additionally, the potential side effects, which are dictated by which tissues receive a substantial dose, must be considered. Acute side effects usually resolve in 4–6 weeks, and long-term side effects are uncommon in palliative radiotherapy, as stated in a clinical practice update by Spencer et al. (Spencer et al., 2018). Many patients experience fatigue during radiotherapy treatment. Other acute effects may include erythema, nausea, vomiting, diarrhea, cystitis, mucositis, and pneumonitis, whereas late effects may include atrophy, fibrosis, telangiectasia, necrosis, strictures, perforation, bleeding, bowel inflammation, and edema (Cherny et al., 2015).

Some patients may receive up to five or more courses of radiotherapy during their disease history, and the numbers of these patients are reported to be growing. (Christ et al., 2021).

2.4.2 Targets of palliative radiotherapy

Palliative radiotherapy may be considered for all patients for whom a local tumor, whether primary, bone or soft tissue metastasis or lymphadenopathy, is causing symptoms (G. Williams et al., 2021). Examples of these symptoms are listed in Table 6.

Table 6. Indications for radiotherapy in symptom palliation (Modified from Cherny et al., 2015).

Symptom	Cause
Pain	
Bone pain	Bone metastases
Visceral pain	Visceral metastases
Neuropathic pain	Bone metastases Soft tissue primary or metastases Intrinsic tumor in nerve tissue
Local pressure	
Spinal canal compression	Epidural metastases Bone metastases
Cranial nerve palsies	Skull base bone metastases Meningeal metastases Intrinsic brain tumor
Obstruction	
Bronchus	Intrinsic bronchial tumor Extrinsic lymphadenopathy
Esophagus	Intrinsic bronchial tumor Extrinsic lymphadenopathy
Superior vena cava	Primary mediastinal tumor Primary lung or esophageal tumors Metastatic mediastinal lymphadenopathy
Hydrocephalus	Malignant meningitis Primary or metastatic brain tumor
Limb swelling	Metastatic lymphadenopathy
Bleeding	
Hemoptysis	Primary bronchial tumor Metastatic bronchial or lung tumor
Hematuria	Primary tumor in kidney Ureter, bladder, prostate
Vaginal bleeding	Primary tumors of vagina, cervix, or uterus Metastases in vagina
Rectal bleeding	Primary anal or colorectal tumors
Bleeding from cutaneus wounds	Cutaneus primary tumors or metastases

Bone metastases can cause a wide range of symptoms including pain, spinal cord compression, hypercalcemia, and pathologic fracture. External beam radiotherapy is the mainstay of treatment for pain and/or prevention of morbidity caused by bone metastases, as stated in the evidence-based guidelines of the American Society for Radiation Oncology (ASTRO) (Lutz et al., 2011).

Single fraction radiotherapy and multifractionated radiotherapy are equally effective at relieving metastatic bone pain and alleviate pain for some 60% of patients. However, patients treated with single fraction have been reported to have a higher re-treatment rate of radiotherapy (Chow et al., 2012) and a higher pathological fracture rate (Sze et al., 2002). Indeed, one-fourth of patients have been reported to receive a second radiotherapy treatment (van der Linden et al., 2006)

In repeat radiation, the overall pain response rate for both single-fraction 8 Gy radiotherapy and 20 Gy radiotherapy in multiple fractions was 45% and 51% for patients with painful bone metastases, respectively (Chow et al., 2014). Commonly targeted regions among patients with bone metastases are the spine, pelvis, and extremities (Tiwana et al., 2016).

The brain and thorax regions are also commonly treated in palliative radiotherapy, and in these radiotherapy targets both primary and secondary tumors are included. In the thoracic region, for example, incurable non-small cell lung cancer is recommended to be treated with palliative thoracic radiotherapy (Moeller et al., 2018). In addition, symptoms including pain, cough, hemoptysis, post-obstructive pneumonia, and superior vena cava syndrome may be successfully addressed with palliative radiotherapy (Jones et al., 2014).

In the treatment of brain metastases, different approaches are possible. Whole brain radiotherapy, stereotactic radiotherapy, and radiation boost to the resection cavity, are all among possible treatment options which the number of metastases, prognosis, and aim of the treatment affect. Side effects vary with the treatment used, and for example whole brain radiotherapy may affect the patient's neurocognition. (Tsao et al., 2012). Patients with primary brain tumors or metastases may suffer from headaches, seizures, and neurological dysfunction (Jones et al., 2014). Approximately two-thirds of patients who received whole-brain irradiation experienced a relief of symptoms and the dose of corticosteroids could be reduced (Sundströmm et al., 1998). Thus, palliative radiotherapy of the brain may also be a potential treatment option for patients with a somewhat poor prognosis.

2.4.3 Current practice

Palliative radiotherapy is a widely used, well-tolerated, and cost-effective standard of care. Of deceased cancer patients, 22–41% are reported to have received palliative radiotherapy (Huang et al., 2014; Lavergne et al., 2011; Murphy et al., 2013). Both clinical factors such as diagnosis, age, sex, comorbidities, survival time, and patient's ethnic background, and non-clinical such as residency, geographic region and municipality population, and treatment year in addition to income have influenced treatment patterns (Danielson et al., 2008; Guadagnolo et al., 2013; Huang et al., 2014; Kress et al., 2015; Lavergne et al., 2011; Murphy et al., 2013).

In a US study by Guadagnolo et al. of 202,299 patients who died of cancer, 7.6% received palliative radiotherapy during the last month of life. Non-clinical factors such as race, non-referral to hospice care, and treatment in a freestanding versus hospital-associated facility were associated with a greater probability of receiving more than 10 days of radiotherapy in the last 30 days of life (Guadagnolo et al., 2013). In contrast, Huang et al. reported that of 12,300 deceased Canadian cancer patients, 5.0% had received palliative radiotherapy during the last 30 days of life. Radiotherapy utilization varied with age, survival time, and travel time to the nearest radiotherapy center (Huang et al., 2014).

2.5 The use of opioids near the end of life

2.5.1 Prevalence of pain in cancer patients

Many cancer patients suffer from pain and its effects on their quality of life (Breivik et al., 2009). As the cancer progresses, so does the prevalence of pain. Pain prevalence has been reported to rise from 39.3% after curative treatment to 55.0% during anticancer treatment and further to 66.4% for patients with advanced, metastatic, or terminal disease (van den Beuken-van Everdingen et al., 2016).

2.5.2 Management of cancer pain

Opioids are the foundation of pain management in patients with advanced cancer (Fallon et al., 2018). They are divided in to three groups weak, intermediate and strong opioids based on their potency. Weak opioids are referred as codeine and tramadol, intermediate opioid is buprenorphine and strong opioids include fentanyl, methadone, morphine, hydromorphone and oxycodone. Their indisputable role was established by the World Health Organization (WHO) back in 1986 with the publication of the three-step pain ladder. The ladder guides the management of pain from non-opioid analgesics to weak opioids and further to strong opioids when needed. The first step is a non-opioid. If this does not relieve the pain, a weak opioid should be added. When this combination fails to bring relief, an opioid for moderate to severe pain should be substituted. Only one drug from each group should be used simultaneously (World health Organization, 1996). (Figure 1)

In the WHO pain ladder below, ‘adjuvant’ refers to medications that can be used either to treat the adverse effects of analgesics (e.g., laxatives), boost pain relief (e.g., corticosteroid), or treat concomitant psychological symptoms (e.g., insomnia).

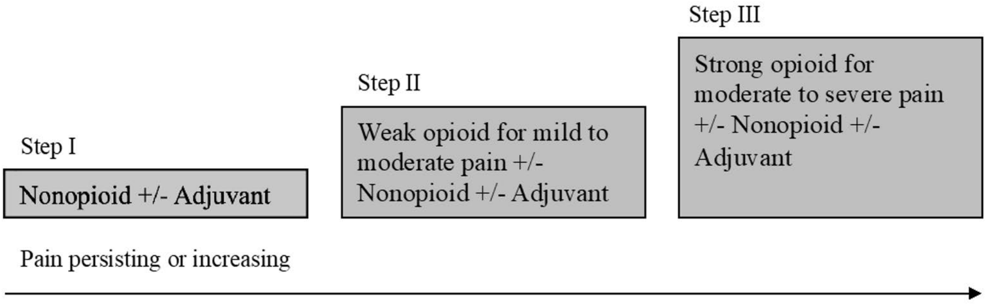

Figure 1. The WHO pain ladder (Modified from World health organization, 1996).

The role of opioids is especially crucial in the care of EOL patients. Strong step-III opioids have been listed by palliative care experts as one of the most essential drugs in the care of the dying (de Lima, 2006; Lindqvist et al., 2013). The use of strong opioids increases in the last months of life (Ziegler et al., 2016) and has been used as one of the quality indicators of good EOL care (Morishima et al., 2013).

The basis for management of moderate to severe pain should be strong opioids administered orally by long-acting formulations. Medication for breakthrough pain and medications for the most common side effects of opioids should be prescribed simultaneously. (Fallon et al., 2018; World health organization, 1996) Transdermal fentanyl and buprenorphine are alternatives to orally administered long-acting strong opioids, especially for patients unable to swallow and for those with nausea and vomiting. Parenteral opioid administration (e.g., subcutaneous, buccal, or intranasal) can also be necessary if the opioid dose needs to be quickly titrated for severe pain. It is also needed for EOL patients who are unable to receive opioids by the oral or transdermal route. Compared with intravenous administration, the subcutaneous route is simple and effective and should be the first-choice alternative route for parenteral opioid administration. (Caraceni et al., 2012; Crawford et al., 2021)

2.5.3 Consumption of opioids

Although the availability of strong opioids is steady in many countries, and guidelines and treatment practice have for decades underlined their importance in the treatment of cancer pain, there are still major differences in their consumption. Globally this is affected by availability and access, which is a huge problem worldwide, but also, for instance, by overly strict regulation and distribution systems (Connor et al., 2020).

When the use of opioids was evaluated in 22 European countries and the US in the mid-2010s, there was a more than tenfold difference between the highest and lowest consumption of opioid analgesics in these countries. In Finland, total opioid consumption dropped between 2004–2006 and 2014–2016 and was the lowest of all the Nordic countries but average for all the analyzed countries (Bosetti et al., 2019). In addition, in Finland the total opioid consumption was also the lowest of all the Nordic countries, and on a global level of 188 countries it was considered adequate, in an earlier comparison (Seya et al., 2011).

There was also variation in the use of different strong opioids. Fentanyl was the most frequently used opioid analgesic in Europe, and in Western and Northern Europe oxycodone was frequently used in addition. The consumption of morphine varied between countries and in Finland increased between 2004–2006 and 2014–2016 (Bosetti et al., 2019).

2.5.4 Factors influencing the use of pain medication

Many factors, including cultural and practical, influence the treatment of EOL cancer pain. For example, in Italy the use of opioids may be more restrained, whereas palliative sedation is used relatively often for cancer patients (Mercadante et al., 2013). The setting also affects the preferred pain medication, as available drugs, equipment, and professional ability vary. The use of morphine and other opioids has been found to be more frequent in the last days of life for patients who were treated in a hospice compared to the those treated in hospital (Raijmakers et al., 2013). Also, hospital case volume influenced the use of opioids during the last months of life (Morishima et al., 2013). Inadequate pain assessment, concerns about high opioid doses and side effects, prescription of inefficient doses of opioids and poor prescription for the treatment of opioid side effects are, on the other hand, examples of physician-related barriers to cancer pain management (Jacobsen et al., 2007). Patient's diagnose may also influence the use of pain medication and in addition to patients with advanced cancer, sufficient pain management needs to be warranted for patients with other end-stage chronic illnesses (Romem et al., 2015).

3 Aims

The aim of this study was to shed light on the end-of-life treatment of cancer patients in Southwest Finland and to study current treatment policies by evaluating retrospectively the use of active oncological treatments and pain medication, and the effect of palliative care intervention as death approaches.

The specific aims were:

1. To evaluate the effect of palliative care intervention on the treatment of pancreatic cancer patients during the last month of life. (Study I)
2. To study the use of chemotherapy and radiotherapy during the last year of life in a cohort consisting of all deceased cancer patients. (Studies II and III)
3. To assess the use of strong opioids in a hospice setting. (Study IV)

4 Materials and Methods

4.1 Study design and methods

This thesis was executed as four independent retrospective studies. A retrospective design enables us to learn from real-life treatment practices and analyze large amounts of information. Executing retrospective studies requires access to comprehensive and reliable patient records, whereby data can be obtained from large databases or extracted manually from patient records. In this study we used both. This registry-based study consisted of three independent patient cohorts and included only deceased patients. All the data analyzed were originally collected as part of routine clinical care.

In ***Studies I, II, and III*** the data was collected in collaboration with Auria Clinical Informatics. In the hospital district of Southwest Finland, Turku University Hospital (TUH) has a catchment area of some 480,000 residents and is the only facility providing cancer care in the area. At TUH, all essential patient records are electronic and have been combined, for secondary use across multiple IT systems in everyday practice, into the Auria Clinical Informatics database. The database provides researchers with patient data and expert services.

In ***Study I*** the cohort consisted of all pancreatic cancer patients who had died during 2011–2016 and had been treated at TUH during their last month of life. Using the database, all pancreatic cancer patients (n=534) treated at TUH and deceased between 2011 and 2016 were identified using ICD-10 code C25. Patients with neuroendocrine tumors (ICD-10 code C25.4 or E34) were not included. Data were validated manually by checking the medical records of all 534 patients to verify the pancreatic cancer diagnosis. Secondary malignant tumors in the pancreas, such as lymphoma metastases, were excluded (n=72). Histological diagnoses were verified from pathologic reports.

Patients were divided into a palliative care group (PC group, n=76) and standard care group (SC group, n=302) based on their possible visit to a palliative care unit. There were no specific referral criteria for palliative care unit. All patients in both groups received standard surgical and oncological treatment. For most patients in the PC group the intervention was an appointment with a physician and a nurse at a palliative outpatient clinic (n=73, 96%). Some patients preferred a call from the clinic due to poor physical performance and persistent symptoms caused by progression of their pancreatic cancer (n=3, 4%). Patients who received only palliative consultation were not included in the PC group. The type of palliative intervention was manually checked from the patient records.

Medical costs at the university hospital have been available in the Auria database since 2012 for all patients (n=244). The information was available for 189 patients (63%) in the SC group and 55 patients (72%) in the PC group. Data on costs of care were based on hospital invoicing. All the costs of hospital treatment are charged to the patient´s local municipality.

In ***Studies II and III*** the cohort comprised all patients with a cancer diagnosis (ICD-10 C00-C97) who were treated at TUH and died between 2005 and 2013 (n=11,250). The patients were identified, and their clinical information retrieved, from the Auria database. The data was manually validated and supplemental information also collected manually from the patients' electronic health records.

Study II included all cancer patients who received intravenous (IV) chemotherapy during the last year of life (n=3285). Data on cause of death (ICD-10 code C00-C97 on the death certificate) was confirmed from the database of Statistics Finland. The data validation was performed by manually revising the patient records of 100 randomly assigned patients to ensure advanced cancer as an indication for IV chemotherapy treatment.

The use of IV chemotherapy was evaluated in terms of the patient´s age, sex, cancer diagnosis, treatment year, and place of death. The patients were divided into five age groups: <50 years (n=308, 9%), 50–59 years (n=584, 18%), 60–69 years (n=1237, 38%), 70–79 years (n=923, 28%), and >80 years (n=233, 7%). Patients were divided into 15 diagnostic groups to evaluate the effect of cancer on the use of IV chemotherapy. The groups were cancer of the head and neck, esophageal and gastric cancer, pancreatic cancer, colorectal cancer, other gastrointestinal cancer, lung cancer, skin cancer, sarcoma, breast cancer, gynecological cancer, prostate cancer, cancer of the urinary tract, hematological malignancies, lymphoma, and other cancer type. If the patient had more than one cancer diagnosis, the patient was classified based on the most recent diagnosis before death. Finally, the patients were divided into three 3-year cohorts: 2005–2007 (n=975, 30%), 2008–2010 (n=1129, 34%), and 2011–2013 (n=1181, 36%). The use of IV chemotherapy was assessed at five time points during the last year of life: 1 year, 6 months, 3 months, 2 months, 1 month, and 2 weeks before death. The number of patients who died in the University Hospital was evaluated using the five time points described above.

In ***Study III*** the study sample consisted of 2,904 patients who had received radiotherapy at TUH during their last year of life. The last radiotherapy treatment and time from last radiotherapy fraction to death were assessed in terms of patient´s age, cancer diagnosis, residency, place of death, and treatment year. Treatments given during the last 14 days of life were further studied to evaluate indications for treatment (palliative or curative) and possible discontinuation.

To assess the use of radiotherapy by age, patients were divided into four groups: age <60 years (n=629, 22%), 60–69 years (n=907, 31%), 70–79 years (n=891, 31%) and >80 years (n=477, 16%). To assess the use of radiotherapy by cancer type, the patients were divided into 14 diagnostic groups: cancer of the head and neck, esophageal and gastric cancer, colorectal cancer, pancreatic cancer, lung cancer, skin cancer, breast cancer, gynecological cancer, prostate cancer, other urological cancer, primary central nervous system (CNS) cancer, lymphoma, hematological malignancies (including leukemia), and ‘other cancers’ including, for example, sarcomas, neoplasm of the mediastinum and pleura, and cancer of unspecified origin. To assess the use of radiotherapy by domicile, the patients were divided into four cohorts by distance from domicile to hospital: <20 km, 20–50 km, 50–100 km, and >100 km. The place of death was assessed as university hospital or other location. To assess the use of radiotherapy by treatment year, the patients were divided into three cohorts by year of radiotherapy administration: 2005–2007 (n=941, 32%), 2008–2010 (n=975, 34%), and 2011–2013 (n=988, 34%). Anatomical radiotherapy targets were divided manually into the following regions: brain, spine, abdomen, thorax, pelvis, extremities, head and neck, prostate, breast, and other. These locations may have included bone, soft tissue, or visceral targets.

In **Study IV** the data were collected manually from the paper patient records of two hospices, Koivikko-koti in Hämeenlinna and Karinakoti in Turku. At the time, they were two of four hospices in Finland providing EOL care mainly to cancer patients. In 2010, altogether 405 patients were treated in these two units.

One hundred and fifty patients treated in 2010 were randomly assigned to the study, 100 from Karinakoti and 50 from Koivikko-koti. The data were mainly collected from the paper archives of the hospices, which included all patient records from arrival at the hospice until death. For patients whose date of cancer diagnosis could not be identified from paper records, this was retrieved from the electronic patient records of the Central Hospital of Kanta-Häme and TUH. The data were collected on a paper form and later transferred to electronic format (excel) for statistical analysis. Twelve patients who died less than 2 days after transfer to the hospice were excluded from the analysis.

For 138 eligible patients, patient characteristics (date of inclusion, date of birth, gender, ethnic group), cancer diagnosis, time of cancer diagnosis, location of metastases, comorbidities, and data on given medications were recorded. The diagnostic groups were i. breast cancer, ii. prostate cancer, iii. lung cancer, iv. gastrointestinal cancer, v. cancer of the female reproductive organs, vi. hematological malignancies, vii. other urological cancer, viii. cancer of unknown origin, and ix. other. Location of metastases was coded as: i. liver, ii. bone, iii. CNS,

iv. lung, v. other and vi. no metastases. Comorbid conditions were divided into eleven categories: i. heart, ii. vascular, iii. lung, iv. gastrointestinal/hepatic, v. kidney, vi. hematological, vii. neurological, viii. psychiatric, ix. musculoskeletal, x. endocrinological, and xi. other.

The medications were studied at five time points: time of transfer to hospice and +2, +14 (2 weeks), +56 (2 months), and 1 day before death. Pain medications were coded as i. regularly dosed strong opioids, ii. opioids given to alleviate breakthrough pain, and iii. other pain medications (including e.g., paracetamol and nonsteroidal anti-inflammatory drugs (NSAIDs)). The total daily dose of pain medications and route of administration was studied, and the daily doses were also reported as morphine equivalent daily doses (MEDD). Other medications were recorded and categorized according to the Finnish pharmacopedia (Pharmaca Fennica): i. cardiovascular drugs and anticoagulants, ii. gastrointestinal and urological drugs, iii. antibiotics, iv. oncological and hematological drugs, v. vitamins and dietary supplements, and iv. sedative, psychonarcotic, and narcotic drugs.

4.2 Statistical analyses

In Studies I-IV, descriptive statistics were used to investigate patient characteristics. Continuous variables were reported as median with range and/or mean together with standard error or standard deviation. Categorical variables were reported as percentages and frequency.

In Study I, patient characteristics between the studied groups was analyzed using Fisher´s exact test (categorical variables like sex) or one-way analysis of variance (ANOVA) when continuous variables were tested to follow normal distributions and Wilcoxon rank sum test otherwise. Interventions and number of interventions between the groups were compared using the same methods. In studies II–III, the Wilcoxon rank sum test or Kruskal-Wallis test was used to compare the medians between two or more comparison groups. Normal distribution assumption was based on original data as well as studentized residuals and checked visually (e.g. using q-q- plots) together with Shapiro-Wilks test.

In Studies II–III, a univariate log-rank test was used to analyze differences in anticancer treatments by year of admission, age, diagnostic groups and, for radiotherapy patients, also target site and domicile. The time from last treatment to death was illustrated using Kaplan-Meier curve. In addition, Cox regression analysis was used to further investigate the association between EOL chemotherapy treatment and age, year of death, or diagnosis in the same model. In Study IV, a chi-square test was used to investigate changes in administration route and use of breakthrough medications before death (transfer, 2^{nd} day, day before death). In all these analyses patients with missing data are automatically removed from the analyses. No imputation was performed to missing values. In all studies statistical significance was set at $p < 0.05$ (two-tailed).

In Studies I and IV, the analyses were performed using SAS software for Windows, version 9.3 for study IV and 9.4 for study I (SAS Institute Inc., Cary, NC, USA). In Studies II–III, analyses were performed using R version 3.1.3. (R Core Team (2015). R: A language and environment for statistical computing. R foundation for Statistical Computing, Vienna, Austria).

All statistical analysis methods used in the publications were standard methods for survival analyses, starting with Kaplan-Meier curve with log-rank test and continued with Cox’s proportional hazard model. Cox’s proportional hazard model enables to include several explanatory variables in the same model and outline the bigger picture in the collected data. Also, when values of continuous response are compared between some categories of explanatory variable it is crucial to first study whether response follow normal distribution or not. In datasets where patients are having the final stage cancer, distributions are quite commonly skewed or having outliers and therefore nonparametric methods (only order in data are used in data analysis) are commonly used.

4.3 Ethical considerations

These registry-based studies included only deceased patients and all the data used in the analyses were obtained as part of routine clinical assessments. No patient interventions were performed. The data was handled anonymously and the data privacy was carefully considered. All the patients had died before the data collection started and informed consents were not collected. However, the approval of institutional review boards was requested. In more detail the studies were executed with the permission of TUH and the Koivikko Foundation. Permission for data collection was requested from Turku Clinical Research Centre, Turku CRC. According to Finnish law, the legislation does not mandate any Ethics Committee approval for retrospective registry-based studies. However, all the studies in this thesis were conducted in accordance with the institutional guidelines and regulations and the principles outlined in the declaration of Helsinki were followed.

5 Results

5.1 End-of-life care with or without palliative intervention (Study I)

The study included 462 pancreatic cancer patients treated at TUH who died during the 6-year period between 2011 and 2016. Of these patients, 378 had contact with tertiary care during the last 30 days of life and were thus eligible for the study. Of these patients, 53% (n=199) were female and 47% (n=179) male. The median age was 72 years (range 32–100 years). The patient characteristics of the study population are presented in Table 7. All these patients received standard care with the option of having surgical and/or oncological treatment. In addition, one fifth (n=76, 20%) of the patients received palliative intervention in a palliative outpatient clinic (PC group). Consequently, 302 patients (80%) received only standard care.

Table 7. Characteristics of pancreatic cancer patients who were in contact with tertiary care during the last 30 days of life (Modified from Study I).

	All	**Palliative intervention**	**No palliative intervention**	**P**
Number of patients (n)	378	76	302	
Gender				
M (n)	179 (47%)	41 (54%)	138 (46%)	0.202*
F (n)	199 (53%)	35 (46%)	164 (54%)	
Age (years)				
Min-max	32–100	47–90	32–100	0.558**
Mean	71	71	71	
Med	72	72	72	
PAD verification				
No (n)	268 (71%)	57 (75%)	211 (70%)	0.401*
Yes (n)	110 (29%)	19 (25%)	91 (30%)	
Chemotherapy				
Yes (n)	151 (40%)	33 (43%)	118 (39%)	0.514*
1 line (n)	93 (25%)	22 (29%)	71 (24%)	0.686*
2 lines (n)	31 (8%)	7 (9%)	24 (8%)	
>2 lines (n)	27 (7%)	4 (5%)	23 (8%)	
Radiotherapy				
Yes (n)	21 (6%)	2 (3%)	19 (6%)	0.273*
Total dose (Gy)				
Min-max	8–76	29–50	8–76	0.859***
Mean	37	40	37	
Med	45	40	45	
OS (months)[1]				
Min-max	0.1–51.8	0.3–37.8	0.1–51.8	**<0.0001*** **
Mean	6.2	9.0	5.5	
Median	2.6	5.4	1.9	

1 OS = overall survival from the pancreatic cancer diagnosis to death
* Fisher´s Exact test (Two-sided Pr)
** One way anova
*** Wilcoxon Two-Sample Test (Two-sided Pr)

The patient characteristics and distribution of PAD verifications (25% vs 30%) did not differ between the PC and SC groups. In addition, there were no significant differences between oncological treatments, including the number of patients receiving chemotherapy and radiotherapy, number of chemotherapy lines, and total dose of radiotherapy. However, overall survival from pancreatic cancer diagnosis to death differed in the study groups: patients in the PC group had longer overall survival than those in the SC group (mean 9.0 months vs 5.5 months, median 5.4 months vs 1.9 months, p<0.0001).

When evaluating the treatment procedures in tertiary care during the last 30 days of life, patients in the PC group had fewer interventions in all studied categories, and the difference was statistically significant in all other categories except surgical interventions (Figure 2). Patients in the PC group had fewer radiological examinations (50% vs 75%, p<0.0001), hospitalizations (47% vs 78%, p<0.0001), and ED visits (36% vs 51%, p=0.021) and were less likely to die in the university hospital (8% vs 21%, p<0.011). (Table 8). For radiological examinations the difference was statistically significant in the use of CoT imaging between the PC and SC groups (14% vs 43%, p<0.0001), ultrasound (17% vs 32%, p=0.024), and x-ray (33% vs 48%, p=0.021). However, stenting and other procedures were available and were needed as frequently in both groups (22% vs 32%, p=0.124).

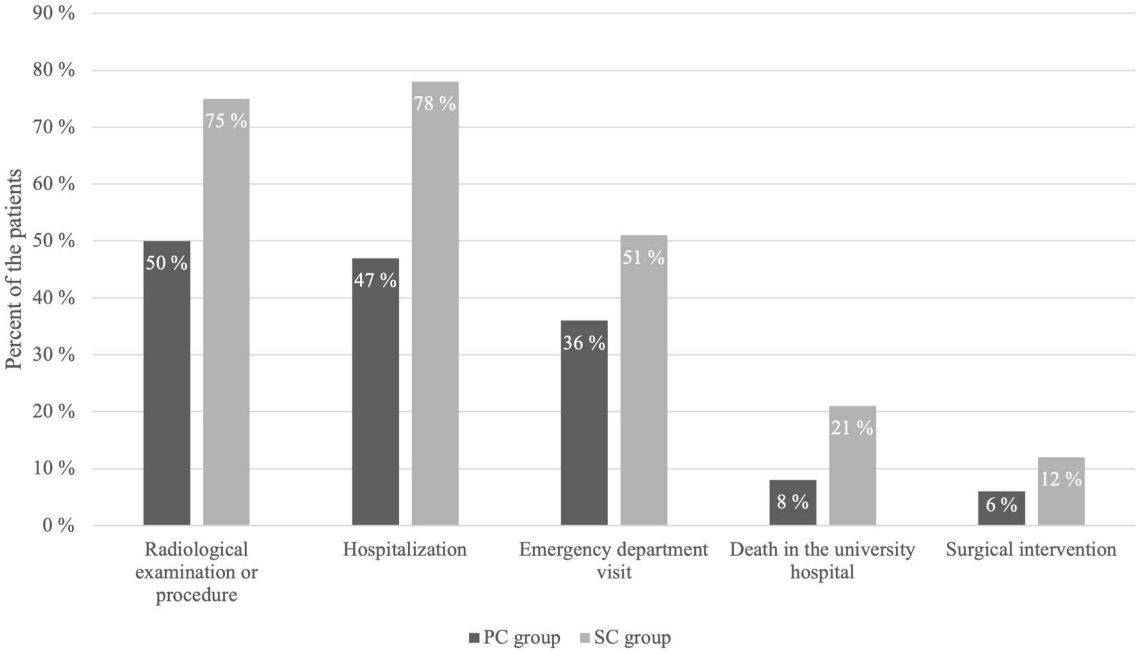

Figure 2. Use of hospital resources during the last 30 days of life (Modified from Study I).

Table 8. Number of interventions for patients with pancreatic cancer in the university hospital during the last 30 days of life (Modified from Study I)

	All	Palliative intervention	No palliative Intervention	P
Number of patients (n)	378 (100%)	76 (100%)	302 (100%)	
Chemotherapy (n)	12 (3%)	1 (1%)	11 (4%)	0.473*
Radiotherapy (n)	5 (1%)	0 (0%)	5 (2%)	0.588*
Radiological examination or procedure (n)	265 (70%)	38 (50%)	227 (75%)	**<0.0001***
Number of interventions (n)				
Min – max	0–16	0–8	0–16	**<0.0001****
Median	2	1	3	
Mean	2	1	2	
Ultrasound	110 (29%)	14 (17%)	96 (32%)	**0.024***
X-ray	169 (45%)	25 (33%)	144 (48%)	**0.021***
CT	141 (37%)	11 (14%)	130 (43%)	**<0.0001***
MRI	5 (1%)	0 (0%)	5 (2%)	0.588*
Other (f.e. stenting and other procedures)	114 (30%)	17 (22%)	97 (32%)	0.124*
Hospitalization (n)	272 (72%)	36 (47%)	236 (78%)	**<0.0001***
Number of days spent in hospital (n)				
Min – max	0–30	0–30	0–30	0.257**
Median	7	6	7	
Mean	9	7	9	
Emergency department (ED) visits (n)	180 (48%)	27 (36%)	153 (51%)	**0.021***
Number of ED visits (n)				
Min – max	1–7	1–4	1–7	0.349**
Median	1	1	1	
Mean	1.7	1.5	1.7	
Death in the University Hospital (n patients)	68 (18%)	6 (8%)	62 (21%)	**0.011***
Surgical intervention (n)	40 (11%)	5 (6%)	35 (12%)	0.203*
Number of interventions per patient (n)				
Min - Max	1–6	1–4	1–6	
Median	2	2	2	
Mean	3	2	3	

* Fisher´s Exact test (Two-sided Pr)

** Wilcoxon Two-Sample Test

In the PC group, 48% of the patients (n=39) were in touch more than twice, 20% (n=16) twice, and 32% once with the palliative care unit. There was a wide range of time, from 0 to 1070 days, between the first contact with the palliative care clinic and the patient´s death. The median time was 2 months (62 days), but 25 patients first made contact with the unit during their final month and six during their last week of life. For patients receiving late palliative consultation during the last 30 days of life (n=25), the median overall survival was significantly shorter (2.9 months, range 0.4–17.8 months) than for patients visiting the palliative care unit sooner (6.98 months, range 0.33–39.53 months, p<0.0001).

The costs of care at the university hospital varied between the groups and were significantly lower for patients who received palliative intervention (p<0.0001). The mean cost varied from €2,049 in the PC group to €4,574 in the SC group and the median cost from €591 in the PC group to €3,268 in the SC group (range €1–21,484 vs €1.5–43,603).

5.2 Use of intravenous chemotherapy and radiotherapy during the last months of life (Studies II–III)

From the cancer patients who were treated in TUH, 11,250 patients died during the 9-year period from 2005 to 2013. Of these patients 3,285 (29%) received IV chemotherapy, 2,904 (26%) radiotherapy, and 1,210 (11%) both chemotherapy and radiotherapy during their last year of life.

5.2.1 Use of intravenous chemotherapy

Of the 3,285 patients who received chemotherapy during the last year of life, 47% (n=1547) were female and 53% (n=1738) male and the median age at death was 66 years for both sexes, respectively. The patient characteristics of those receiving chemotherapy are shown in Table 9. The largest diagnostic groups were lung cancer (n=812, 22%) and hematological malignancies and lymphoma (n=479, 15%). The proportion of patients receiving IV chemotherapy during the last months of life was 22% from 1 year to 6 months, 60% from 6 months to 1 month, 11% from 1 month to 2 weeks, and 7% during the last 2 weeks of life. The average time from the last dose of IV chemotherapy until death was 111 days (SE 1.6).

Table 9. Characteristics of patients receiving intravenous chemotherapy during the last year of life (Modified from Study II).

Age at death	**Median**	
Female	66 years	
Male	66 years	
	n = 3285	**%**
Sex		
Female	1547	47%
Male	1738	53%
Diagnostic groups		
Lung cancer	812	25%
Hematological and lymphoma	479	15%
Gynecological cancer	303	9%
Breast cancer	295	9%
Colorectal cancer	295	9%
Pancreatic cancer	235	7%
Gastric cancer and esophageal cancer	169	5%
Prostate cancer	167	5%
Other	530	16%
Age groups (years)		
<50	308	9%
50–59	584	18%
60–69	1237	38%
70–79	923	28%
>80	233	7%
Treatment year		
2005–2007	975	30%
2008–2010	1129	34%
2011–2013	1181	36%

Time between the last dose of chemotherapy and death varied significantly according to the patient´s age, as younger patients received chemotherapy closer to death ($p<0.0001$) (Figure 3). The differences between the age groups were statistically significant in pairwise comparison, except for the groups aged 50–59 and 60–69 ($p=0.22$), and 60–69 and 70–79 ($p=0.13$). Younger patients were treated closer to death.

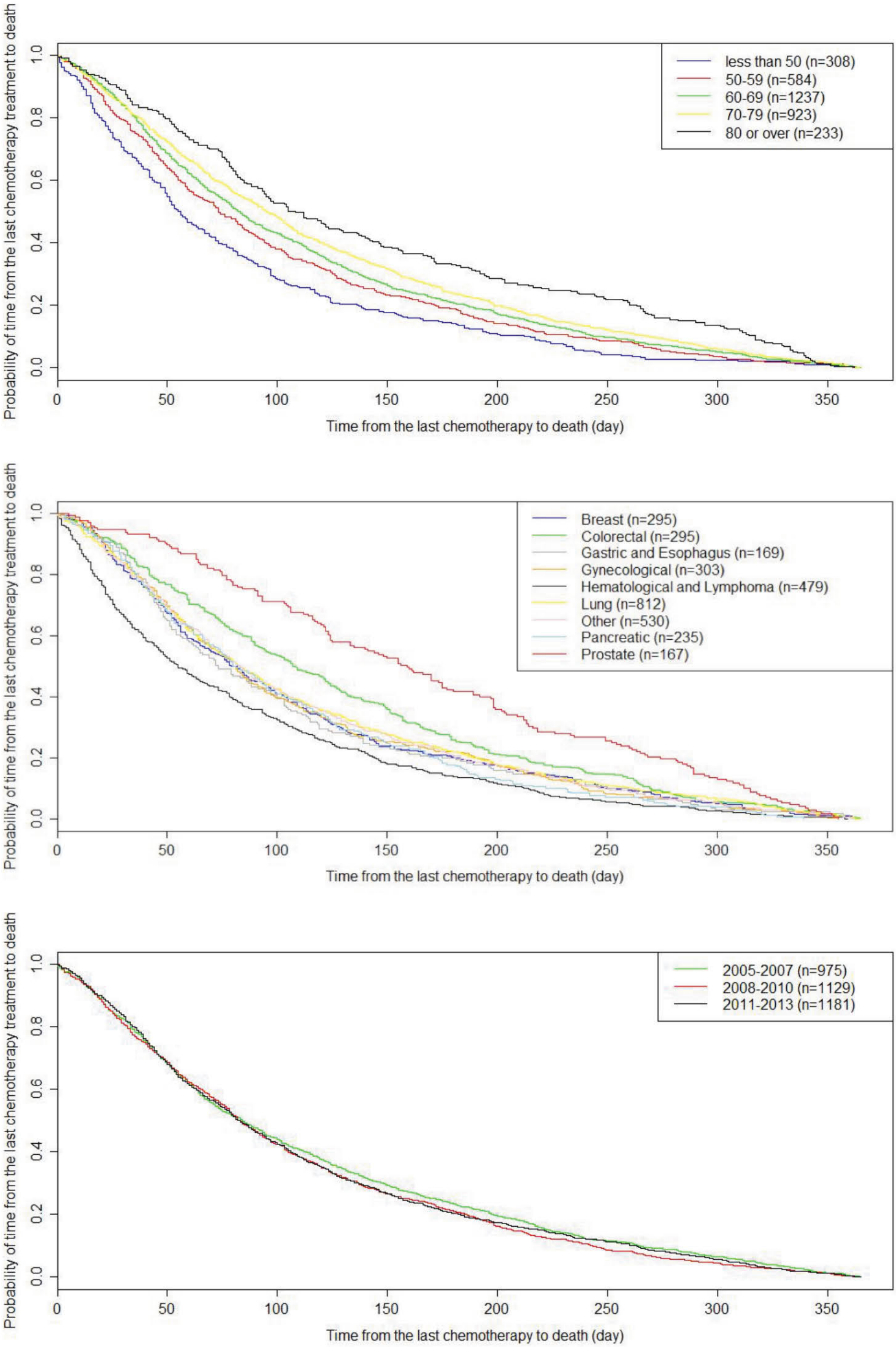

Figure 3. Probability of time between the last IV chemotherapy treatment and death for (A) different age groups, (B) different diagnostic groups and (C) different years (From the original Study II, Published with the permission of the copyright holder).

The use of chemotherapy differed between the diagnostic groups during the last year of life. For prostate cancer patients, IV chemotherapy was emphasized more in earlier months, with 42% of patients having received it earlier than 6 months before death and only 5.4% during the last month of life. For the most actively treated group of hematological malignancies and lymphomas, the corresponding percentages were 13% and 38% (Table 10). In addition, the time between the last dose of chemotherapy and death varied significantly between the diagnostic groups (Figure 3, p<0.0001). Patients with prostate cancer and cancer of the urinary tract were the least frequently treated groups among patients receiving treatment during the last year of life (p<0.05). For patients with lymphoma or hematological malignancies, the time between the last treatment and death was on average the shortest (p<0.05).

Table 10. Number of patients receiving IV chemotherapy during the last year of life in different diagnostic groups.

Diagnostic group	**Number of deceased cancer patients**	**Number of deceased patients receiving iv chemothepapy**				
		One year	6 months	3 months	1 month	2 weeks
Prostate	1011	167(100%)	97(58%)	42(25%)	9(5%)	5(3%)
Breast	872	295(100%)	236(80%)	162(55%)	55(19%)	14(5%)
Colorectal	1043	295(100%)	218(74%)	127(44%)	34(12%)	16(5%)
Gynecological	658	303(100%)	236(78%)	169(56%)	49(16%)	13(4%)
Lung	1934	812(100%)	632(78%)	429(53%)	132(16%)	62(8%)
Esophagus and gastric	709	169(100%)	135(80%)	96(57%)	23(14%)	8(5%)
Pancreatic	772	235(100%)	193(82%)	126(54%)	36(15%)	15(6%)
Other	3010	530 (100%)	421(79%)	288(54%)	87(16%)	29 (6%)
Hematological and lymphoma	1241	479(100%)	412(86%)	307(64%)	161(34%)	76(16%)
Total	**11 250**	**3285 (100%)**	**2580 (79%)**	**1746 (53%)**	**587 (18%)**	**238(7%)**

The time from the last regimen of chemotherapy to death remained stable during the 9-year period, and no significant differences between the years were observed (Figure 3, p=0.20).

To study the combined effect of age, diagnosis, and year of death on the time between last treatment and death, Cox regression analysis was performed. The analysis revealed similar results to those described above, showing that the significant factors in EOL IV chemotherapy treatment were age (p<0.001) and certain cancer types: hematological malignancies (p<0.001), lymphoma (p<0.001), prostate cancer (p<0.001), and cancer of the urinary tract (p=0.020). For the year of death, the effect was not statistically significant (p=0.55).

Of the patients receiving chemotherapy during the last year of life, one third (n=1019, 31%) died at TUH.

5.2.2 Utilization of radiotherapy

There were 2,904 patients who received radiotherapy during the last year of life, of whom 1,251 were female (43%) and 1,653 male (56.9%). The median age at death was 69 years (female 68 years and male 69 years, p=0.11, Wilcoxon test). The largest diagnostic groups were lung cancer (n=596, 21%) and breast cancer (n=335, 12%). The total dose of radiotherapy varied between 1.5 Gy and 70.5 Gy (mean 22.78, median 20.0) during the final radiotherapy course. The characteristics of these patients are presented in Table 11.

Table 11. Characteristics of patients receiving radiotherapy during the last year of life (Modified from Study III).

	Median	Range
Age at death		
Female	68 years	
Male	69 years	
Radiotherapy dose	20.0 Gy	1–70.5 Gy
	n = 2904	**%**
Sex		
Female	1251	43%
Male	1653	57%
Diagnostic groups		
Lung cancer	596	21%
Breast cancer	335	12%
Prostate cancer	319	11%
Primary cns	234	8%
Gastric cancer and esophageal cancer	189	7%
Lymphoma	174	6%
Colorectal cancer	173	6%
Cancer of head and neck	121	4%
Skin cancer	120	4%
Other	643	11%
Age groups (years)		
<60	629	22%
60–69	907	31%
70–79	891	31%
>80	477	16%
Distance between domicile and hospital (km)		
<20	1346	46%
20–50	348	12%
50–100	869	30%
>100	341	12%
Treatment year		
2005–2007	941	32%
2008–2010	975	34%
2011–2013	988	34%

Median time between the last fraction of radiotherapy and death was 84 days (range 0–365 days). The proportion of patients receiving radiotherapy during the last months of life was 24% from 1 year to 6 months, 53% from 6 months to 1 month, 11% from 1 month to 2 weeks, and 12% during the last 2 weeks of life. There was a tendency towards receiving radiotherapy closer to death in the age group 60–69 years compared to groups 70–79 ($p=0.062$) and >80 ($p=0.061$) years, but no significant differences between age groups or between the studied years ($p>0.05$ for all) were detected.

Cancer diagnosis and distance from the patient's domicile to TUH were associated with changes in the time from the last fraction of radiotherapy until death (Figure 4). Of all the diagnostic groups, lung cancer ($p<0.001$), skin cancer ($p=0.01$), lymphoma ($p=0.007$), and 'other cancers' ($p<0.001$) were treated closer to death, whereas gynecological malignancies were treated least frequently near death ($p=0.02$). Patients living >100 km from the hospital were treated least frequently near death and had a median of 110 days to death from the last treatment. For other groups it was 80–83 days. The difference was statistically significant in each pairwise comparison ($p<0.001$).

For patients receiving EOL radiotherapy, the median number of fractions was 7 (mean 9.1) in their last administered radiotherapy course. The distribution of radiotherapy fractions at different time points is presented in Figure 5. Most of the last radiotherapy treatments consisted of ≤10 fractions (77%) and 7% of a single fraction. The median number of fractions dropped over the years from 8 in 2005–2007 to 6 in 2011–2013 ($p=0.032$).

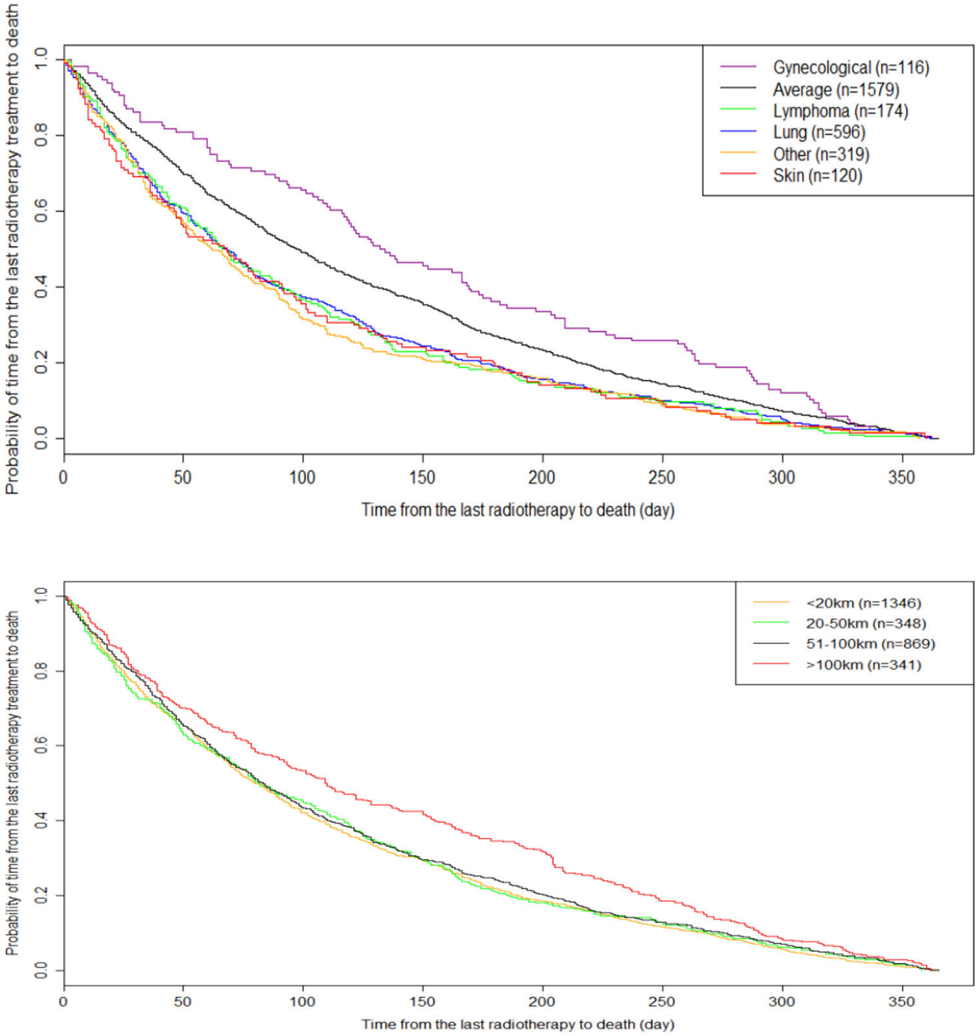

Figure 4. Probability of time between the last radiotherapy treatment and death for (A) different diagnostic groups and (B) patients by distance from domicile to radiotherapy unit (From the original Study III, Published with the permission of the copyright holder).

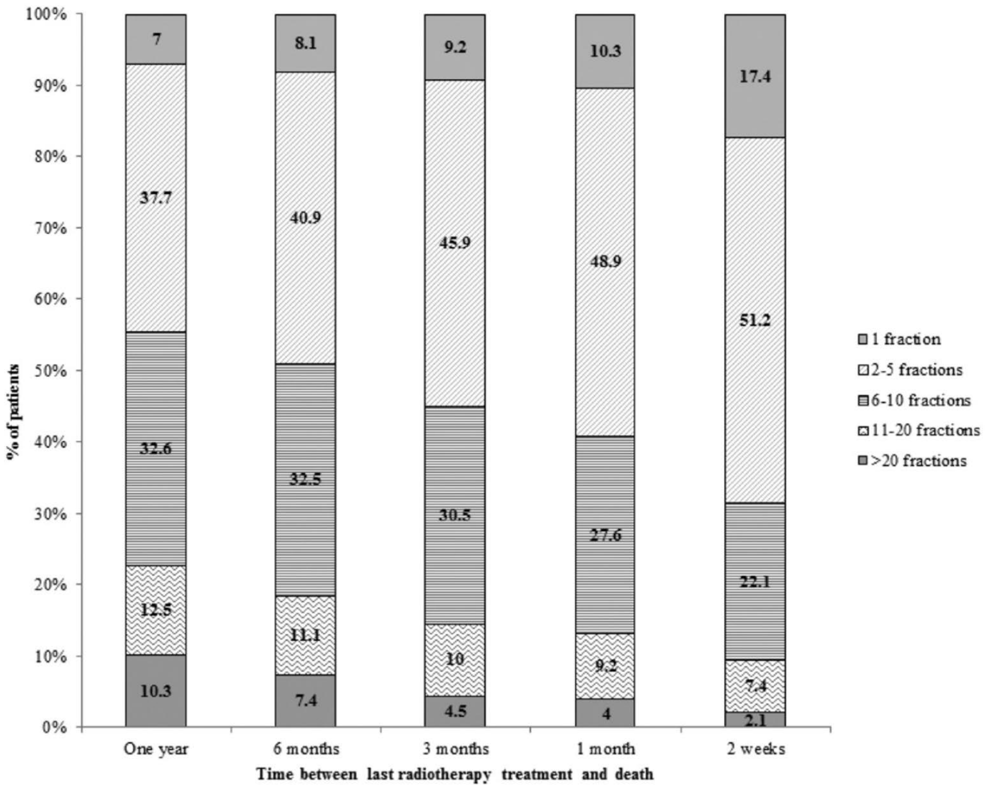

Figure 5. Distribution of radiotherapy fractions given as part of the last treatment plan (From the original Study III, Published with the permission of the copyright holder).

The two most targeted anatomical locations during the last year of life were the brain and thorax. The proportion of primary and secondary tumors was assessed for these two locations. One-third (28%, n=185) of patients receiving radiotherapy to the brain had a primary CNS tumor (C70–C72), the rest (72%) had brain metastases. Of the patients who received radiotherapy to the thoracic region, 45% (N=240) were diagnosed with lung cancer (C34). The spine and pelvis were the third and fourth most treated locations, respectively. The targeted locations at different time points are presented in more detail in Figure 6.

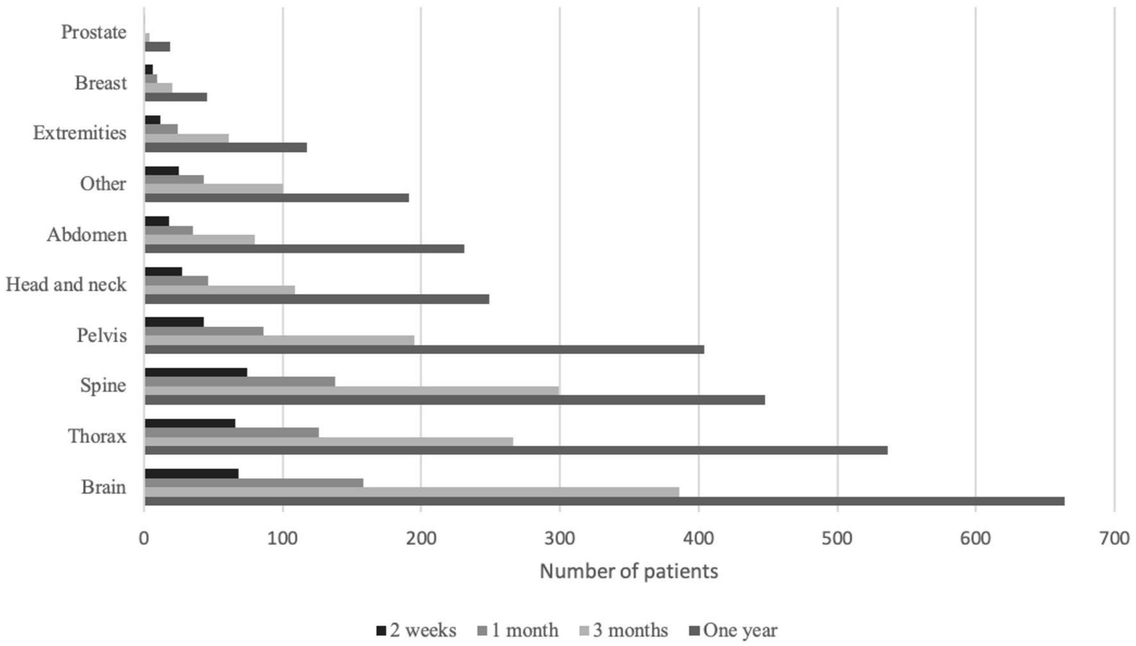

Figure 6. Radiotherapy locations in patients receiving radiotherapy during the last year of life (Modified from Study III)

Of the 340 patients who were treated during the last 2 weeks of life, 97% (n=330) received radiotherapy with palliative intent. Nearly half of these treatments were discontinued (n=138, 41%) due to general worsening of the patient's condition (70%, n=97), death of the patient (21%, n=29), and other reasons such as the patient's own wishes (9%, n=12). The indications for palliative radiotherapy were pain (29%), followed by brain symptoms caused by primary tumor or metastases (20%), local symptoms caused by the tumor, such as hematuria, dysphagia, edema (17%), paraparesis or other radicular or local symptom caused by changes in the spine (12%), dyspnea and other respiratory symptoms (10%), primary or secondary tumor growing through the skin or mucosa (5%), vena cava superior syndrome (2%), and other (1%).

Of the patients receiving radiotherapy during their last year of life, 20% died at TUH, whereas the corresponding percentage of patients treated during the last 2 weeks of life was 46%. Thus, half of the patients who received radiotherapy during the last 2 weeks of life died in hospital. Patients treated closer to death with radiotherapy were more likely to die at TUH.

5.3 Treating end-of-life pain (Study IV)

There were 138 eligible patients who were treated in the two hospices in 2010. Of these, 64% (n=88) were female and 36% (n=50) male. The median age at transfer to hospice was 75 years (range 38–103). The most common cancer diagnoses were gastrointestinal cancer (33%, n=45) and lung cancer (16%, n=22). Mean time from cancer diagnosis to referral to hospice was 2.6 years for Karinakoti and 2.0 years for Koivikko-koti. Comorbid conditions were diagnosed in 83% of the patients, 69% of them from one to three and 14% from four or more categories. The patient characteristics are given in Table 12.

The mean time in hospice was 32 days (range 2–376 days). One-third (28%, n=39) of the patients were in hospice for less than 7 days, 60% (n=82) from 7 days to 2 months, and 12% (n=16) for more than 2 months.

Table 12. Patient characteristics for hospice patients (Modified from Study IV).

Age at death		
Median	75 years	
Range	38–103 years	
Sex		
Female	88	64%
Male	50	36%
Diagnostic groups		
Breast cancer	15	11%
Lung cancer	22	16%
Gastrointestinal cancer	45	33%
Other	56	41%
The number of comorbidities		
Mean	2.2	
Range	0–9	
Time at the hospice		
Mean	32 days	
Range	2–376 days	
<7 days	39	28%
1 week-2 months	82	60%
>2 months	16	12%
Mean time from cancer diagnosis to hospice		
Karinakoti	2.6 years	
Koivikko-koti	2.0 years	

All but five patients received strong opioids during their stay in hospice. At transfer to hospice, 63% of patients received regularly dosed strong opioids. The corresponding percentages on the second day in hospice and 1 day before death were

77% and 90%, respectively. The opioids used were oral morphine, oral oxycodone, transdermal fentanyl, and subcutaneous morphine and oxycodone. A wide range was observed in the individual dose need for opioids, regardless of the mode of administration. At transfer, the median dose of oral morphine was 60 mg/day (24–120 mg). For oral oxycodone the median dose was 40 mg/day (8–280 mg), for transdermal fentanyl 25 µg/day (12–350 µg), for subcutaneous morphine 192 mg (180–336 mg) and for subcutaneous oxycodone 100 mg (30–170 mg), respectively.

In morphine equivalent daily doses (MEDD) the corresponding median for oral morphine and oral oxycodone was 60 mg, for transdermal fentanyl 75 mg, for subcutaneous morphine 576 mg and for subcutaneous oxycodone 300 mg, respectively. MEDD varied from 12 mg to 1050 mg.

In hospice, the routes of opioid administration changed with approaching death as shown in Figure 7. A significant change was seen in more frequent subcutaneous administration ($p<0.0001$).

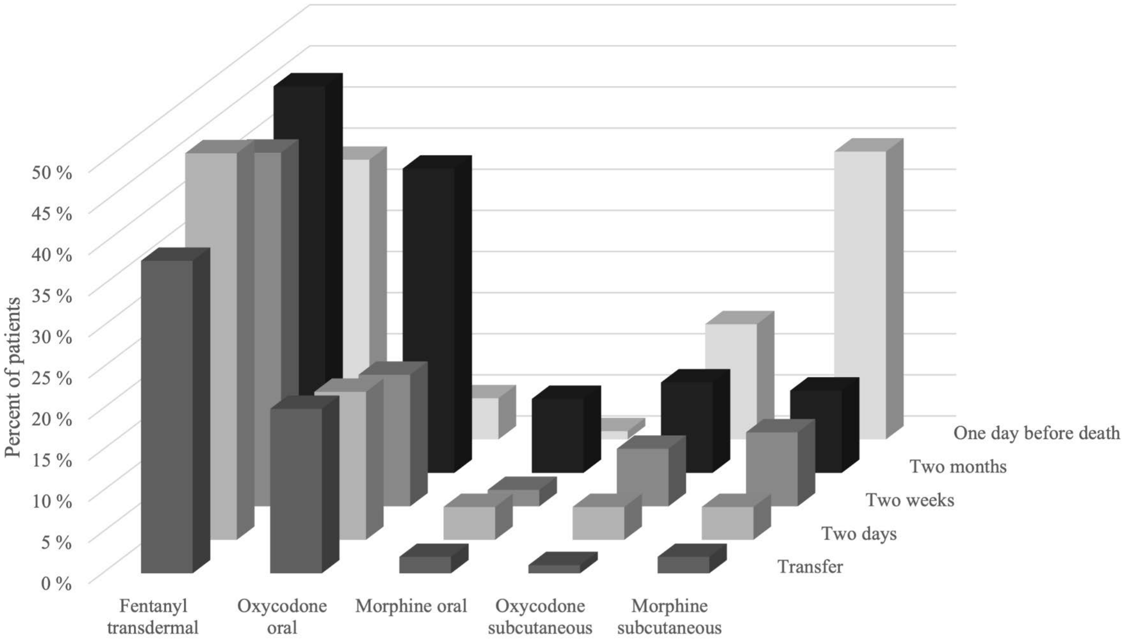

Figure 7. Use of strong opioids in hospice.

Half of the patients (52%) received medication for breakthrough pain on the second day in hospice. The corresponding percentage of patients at 2 weeks and 2 months was 48% and 42%, respectively. On the day prior to death the corresponding percentage was higher 76% ($p<0.0001$).

In addition to strong opioids, other pain medications were also used in hospice. However, less than 10% of the patients received them at each observation point.

The use of other than pain medication showed a decreasing trend as death approached. However, the use of sedative and psychoactive drugs increased during the stay in hospice. At the time of transfer 51% of patients, on the second day 60%, and 1 day before death 70% received medications from this group. The most used were benzodiazepines, with 96 patients (70%) receiving them at least at one point, haloperidol in 44 patients (32%), and SSRIs (selective serotonin reuptake inhibitors) in 14 (10%).

6 Discussion

6.1 Effect of palliative care intervention (Study I)

Our study evaluating the use of hospital resources during the last month of life in patients with pancreatic cancer showed a significant decrease in the use of these resources when the decision was made to change to a symptom-centered goal of care and the patient's care was transferred to the palliative outpatient clinic. This was expected, as the role of palliative intervention has been unanimously recognized in international guidelines (Ferrell et al., 2017; K. Jordan et al., 2018) and improvements in symptom burden and quality of life have been established (Kavalieratos et al., 2016). Nonetheless, there are studies in which no positive effect of a single palliative intervention have been observed (Eychmüller et al., 2021).

Despite the recommendations, only a minority of patients are referred to palliative care units in Finland (Hirvonen et al., 2020), as observed also in our study. Moreover, only 20% of the patients visited a palliative outpatient clinic, while the rest received standard oncological care. In a US study of 54,130 pancreatic cancer patients, the number of patients receiving palliative care consultation was even lower at 5.8% (Bhulani et al., 2018).

Palliative intervention was associated with less use of hospital resources such as radiological examinations, CoT imaging, hospitalizations, and ED visits during the last 30 days of life. This is consistent with the findings reported by Jang et al. (2015) and Hirvonen et al. (2020). Pancreatic cancer patients often have a heavy symptom burden and need tertiary care services near the EOL (Sohal et al., 2016). Indeed, 47% of patients in the PC group and 78% in the SC group were hospitalized during the last 30 days of life. The median time spent in hospital was 6 and 7 days in the PC and SC groups, respectively. In acute hospital wards, patients may receive more aggressive procedures and less frequent pain control and incur higher medical costs than in inpatient palliative care units (Wang et al., 2016).

Nearly half of the pancreatic cancer patients in our series needed ED services during the last month of life. ED visits have been reported to be common also in other countries (Barbera 2010). Many of the ED visits could, however, be avoided even among patients receiving outpatient palliative care (Delgado-Guay et al., 2015). In the study by Delgado-Guay et al a visit to an ED was classified as potentially avoidable if the problem could have been managed at the outpatient palliative care clinic or by telephone (for example cancer pain or gastrointestinal symptoms). One fourth of ED visits were deemed potentially avoidable if proactive efforts to improve communication and increased support between appointments would have been warranted. Additionally in a Finnish cohort study admissions to ED tended to decrease after palliative care intervention including ACP (Hirvonen et al., 2018).

Prior visits to a palliative care clinic have been correlated with more comprehensive advance care planning information, do-not-resuscitate (DNR) order issuance, and connection to primary care amongst patients who visited an ED (Hirvonen et al., 2018). To conclude, wider use of palliative intervention might reduce the pressure on ED clinics and reduce hospitalizations. It should be noted that in our series of patients, reduced use of resources did not affect the availability of stenting and surgical interventions, which indicates that necessary symptom-alleviating procedures were available equally for patients in both groups.

At TUH, patients have traditionally been referred to a palliative care clinic only after discontinuation of active anticancer treatments. In clinical work, evaluating the prognosis remains a challenge and doctors are often overly optimistic (Christakis & Lamont, 2000; Glare et al., 2003). However, even if clinical estimation of survival is challenging, prognostic tools are not superior to clinical prediction (Stone et al., 2021). In our analysis there were no significant differences in patient characteristics, chemotherapy treatments, or radiotherapies received by patients in the PC and SC groups, except for overall survival which varied significantly between the groups (5.4 vs. 1.9 months, respectively). Palliative care consultation should be required also for patients with aggressive disease and short overall survival already concurrent with active anticancer treatments. This could be achieved by active referral to palliative care unit preferably at the visit in the oncology clinic as recommended in the ASCO clinical practice guideline (Sohal et al., 2018). Based on this finding, treatment strategies at TUH have been revised and systematic palliative care intervention is offered for all newly diagnosed pancreatic cancer patients.

Patients receiving hospital-based palliative care are reported to die in their preferred place more often than those receiving regular care (Bajwah et al., 2020). Also in our study, the place of death varied significantly between patients who visited a palliative care unit and those who received only standard care. Moreover, the probability of dying in a tertiary care hospital was nearly threefold among patients who did not visit a palliative care unit.

Palliative care has been associated with lower costs of care for cancer patients (May, Normand, et al., 2018; Penrod et al., 2010; Sheridan et al., 2021; Yadav et al., 2020) and Study I was in line with this finding. The effect may be more pronounced with care in palliative care unit when compared to palliative care consultation (May, Garrido, et al., 2018). Palliative care might lower the health care costs especially in tertiary care (Greer et al., 2016). Indeed, in the present study, where unfortunately primary healthcare costs were not included, the costs of care during the last month of life in tertiary care were significantly lower for patients who had visited a palliative outpatient clinic. Indirect costs including for example productivity costs and informal care explain approximately half of the total costs of cancer patients palliative care period (Haltia et al., 2018) and were not included in the present study.

There is constant pressure against optimizing the use of limited resources in our publicly funded healthcare system. A quarter of all healthcare costs arise from treatment during the last year of life (Riley & Lubitz, 2010); in cancer, metastatic and palliative states incur remarkable costs (Färkkilä et al., 2015; Torvinen et al., 2016). Indeed, the median cost in our study population varied from €591 in the PC group to €3,268 in the SC group with a range of €1–43,603, respectively. Advances in EOL care could be a way to optimize these costs. In Finland, savings could also be achieved by investing in the development of palliative care (Finne-Soveri et al., 2021).

6.2 Use of Intravenous chemotherapy near the end of life (Study II)

IV chemotherapy is an essential part of cancer patients' treatment, occasionally also near the EOL. However, as life expectancy decreases, the potential side effects and effects of consumptive treatment on their general condition and quality of life should be carefully considered, especially if the potential benefits of the treatment are limited.

At TUH, the use of IV chemotherapy near the EOL was in line with previous studies, as 17.9% of the deceased cancer patients who had received IV chemotherapy during the last year of life were treated during the last month of life. The percentage of patients receiving chemotherapy during the last 30 days of life has been reported to be lower in Norwegian (10%) and Chinese (15.7%) cohorts (Anshushaug et al., 2015; Zhang et al., 2018), whereas higher percentages (19.5–46.5%) were previously often reported (Asola et al., 2006; Baena-Cañada et al., 2019; Braga et al., 2007; Earle et al., 2004; Edman Kessler et al., 2020; Hirvonen et al., 2019; Matter-Walstra et al., 2015; Näppä et al., 2011; Numico et al., 2014; Randén et al., 2013; Rochigneux et al., 2017; Sezgin Goksu et al., 2014). The number of patients receiving IV chemotherapy during the last 2 weeks of life (7.2%) met the indicators set by Earle et al., as less than 10% of them did so (Earle et al., 2005).

It has been suggested that there is a trend towards more active cancer care near the EOL (Earle et al., 2004; Ho et al., 2011), while in our series of patients the time between the last IV chemotherapy treatment and death remained stable across the follow-up time of 9 years. Treatment patterns must, however, be critically evaluated, as ASCO has specified EOL chemotherapy as one of the opportunities to improve care and reduce costs in oncology (Schnipper et al., 2012).

Variations in the study design, however, limit the generalization of these results. For example, in a study by Kessler et al. reporting the use of chemotherapy in patients with metastatic breast cancer, peroral cytotoxic agents were also included, and capecitabine and vinorelbine were both used during the last month of life (Edman Kessler et al., 2020). Moreover, in a Norwegian study, one fifth of the patients received hormonal therapy as a last line of anticancer treatment (Anshushaug et al., 2015), and it can be assumed that also in our study the number of patients would have been higher if other than IV chemotherapy treatments had been included. Patients' inclusion criteria may also affect the results, and for example Braga et al. and Baena-Cañada et al. included only solid tumors in their analyses (Baena-Cañada et al., 2019; Braga et al., 2007).

At TUH, the time from the last treatment to death was influenced by both the age and diagnosis of the patient. Regarding the use of chemotherapy in different diagnostic groups, patients with hematological malignancies and lymphoma were treated closer to death than were other groups, which is line with the findings by Hui et al. (Hui et al., 2014). However, as reported in a study by Rochigneux et al., there were no significant differences between the groups of solid tumors (Rochigneux et al., 2017). It should be noted that patients with chemosensitive neoplasms may receive a survival benefit even with second-, third- or fourth-line treatment, and there are also many patients receiving first-line treatment during the last year of life.

Younger patients were treated more actively close to death, which may have been influenced by the patients' and caregivers' wishes or the chemosensitivity of the tumors in this group. Younger age has been associated with more active use of chemotherapy during the last months of life, also in earlier studies (Anshushaug et al., 2015; Braga et al., 2007; Edman Kessler et al., 2020; Sezgin Goksu et al., 2014; Zhang et al., 2018). In our cohort of patients, the treatment of elderly patients did not, however, differ significantly compared to younger patients. This study included only patients who received IV chemotherapy during the last year of life; therefore patients whose general condition was significantly reduced or who had significant comorbidities and were thus not eligible for anticancer treatments after diagnosis were excluded. Despite this, based on clinical experience there might be a need to evaluate the treatment of elderly patients, especially among those with limited performance status. For example, in a study by Rochigneux et al. (Rochigneux et al., 2017), older age was associated with lower rates of chemotherapy, which may be justifiable given poorer levels of tolerance to the treatment.

In addition to evaluating the number of patients receiving treatment close to death, we should also evaluate the wider entirety around EOL chemotherapy, as it may affect the EOL in various ways. In a study by Wu et al. (Wu et al., 2016), patients who did not receive palliative chemotherapy received more hospice care in the last months of life. Additionally, in a study by Baena-Cañada et al., systemic anticancer therapy was associated with more visits to the ED and less care from a palliative care unit (Baena-Cañada et al., 2019). This should also be considered in our clinic, as patients have traditionally been transferred to a palliative outpatient clinic or to hospice services only after finishing anticancer treatments, leaving insufficient time to organize EOL care before the patient's general condition deteriorates, especially for those receiving chemotherapy near the EOL. In addition, the place of treatment also affects the place of death. In our study population, one-third of the patients who were treated during the last year of life died at TUH. Many patients would prefer to die at home (Khanm et al., 2014), which clearly cannot be fulfilled. Indeed, compared to patients not treated with chemotherapy near the EOL, those receiving EOL chemotherapy have been found to be admitted more frequently to hospital, have a significantly shorter survival, more often lack a documented decision to cease treatment, and die less frequently at home (Näppä et al., 2011).

The present study focuses in IV chemotherapy near EOL but the rapid development of other anticancer treatments during the past years cannot be disregarded. Immune checkpoint inhibitors and targeted therapies have revolutionised the management of many cancers, especially advanced melanoma (Carlino et al., 2021; Robert et al., 2019). In addition, combination treatments such as antiangiogenic receptor tyrosine kinase inhibitors and immune checkpoint inhibitors for advanced renal cell carcinoma have improved treatment outcomes (Hofmann et al., 2020). As the treatment options increase and medications with more tolerable adverse effects are available, the possible benefits and disadvantages should still be carefully considered before starting a new anticancer treatment with a special attention paid to elderly patients.

6.3 Use of radiotherapy near the end of life (Study III)

The entirety around EOL radiotherapy differs from chemotherapy, as palliative radiotherapy may be an important way to relieve symptoms (Dennis et al., 2011; Jones et al., 2014; Spencer et al., 2018), even near the EOL. However, time to symptom control limits the use of radiotherapy during the last weeks of life (van der Linden et al., 2006), and in clinical practice it is often recommended to refrain from radiotherapy if the life expectancy is less than 3 months. Nonetheless, radiotherapy is used for patients with a shorter life expectancy; in our patient population, among patients treated during the last 2 weeks of life 97% of the courses were given with palliative intent and for half the patients the indications for radiotherapy were pain (29%) or brain symptoms (20%).

At TUH, 26% of all radiotherapy treatments were given during the last year of life. One-fourth (23%) of the patients treated during the last year and 6% of all treated patients received radiotherapy during the last month of life. These treatments included both curative and palliative treatment plans, although it should be noted that curative and palliative goals may be merged in cancer patients (Jones et al., 2014). The study design varies in previous studies, but 5–29% of patients have been reported to receive radiotherapy during the last 30 days of life (Guadagnolo et al., 2013; Hirvonen et al., 2020; Huang et al., 2014; Tiwana et al., 2016; S. Wu et al., 2019), which is in line with our findings.

Nearly half of the radiotherapy courses given during the last 2 weeks of life were discontinued; the most common reason was worsening of the patient's general condition. In a study by Wu et al., 42% of the patients receiving radiotherapy for metastatic cancer during the last 30 days of life did not complete their final course (Wu et al., 2019). Gripp et al. have also reported high rates of discontinuation of palliative radiotherapy near the EOL (Gripp et al., 2010). Increased age and comorbidities may be significant predictors of death within 2 weeks of receiving radiotherapy (Murphy et al., 2013), and at least for those patients, evaluation of prognosis should be warranted before starting palliative radiotherapy, even if the prognostic models may be inaccurate in predicting the survival of palliative radiotherapy patients (Rodríguez-López et al., 2020).

In previous studies, increased travel time to the radiotherapy unit reduced the use of radiotherapy near the EOL (Danielson et al., 2008; Huang et al., 2014; Lavergne et al., 2011). This was also seen in our series of patients, as those living more than 100 km from the hospital were treated less frequently close to death. In Southwest Finland the only radiotherapy unit is at TUH, and the availability of radiotherapy, especially short courses of palliative radiotherapy, must be guaranteed also for patients living further away. Finland is, however, sparsely populated, and logistical challenges in both the archipelago and rural areas may explain this variation.

Patients' cancer diagnosis affected the time from the last fraction of radiotherapy to death. Specifically, patients with lung cancer, skin cancer (including melanoma), lymphoma, or "other cancers" were more likely to receive radiotherapy closer to death. Tumor site has been recognized as an important factor when evaluating the use of palliative radiotherapy, and especially lung cancer patients have been frequently treated near the EOL (Huang et al., 2014; Lavergne et al., 2011; Murphy et al., 2013; Tiwana et al., 2016; Wu et al., 2019).

Age has been found to have an influence on the use of palliative radiotherapy in multiple studies (Danielson et al., 2008; Huang et al., 2014; Kress et al., 2015; Lavergne et al., 2011; Murphy et al., 2013; Wu et al., 2019), but in our study population no such trend was observed. This raises the question of whether treatment patterns for elderly patients should be further evaluated.

Radiotherapy fractionation should be adjusted to fit the patient’s prognosis (Jones et al., 2014; Mojica-Márquez et al., 2020). This was observed in our study, where the number of short-fraction radiotherapy treatments increased as death approached. The median duration of palliative radiotherapy has been reported to vary between 12 and 16 days (Berger et al., 2014; Murphy et al., 2013), but in our study the median number of fractions in the last treatment plan was 8 in 2005–2007 and down to 6 in 2011–2013. Indeed, 59% of the treatments during the last month of life had <10 fractions. Even if short courses were common, single-fraction treatments were used rather infrequently in our study. ASCO states in a guideline for treating bone metastases that single-fraction 8 Gy is as effective as 20 Gy in 5 fractions, 24 Gy in 6 fractions, and 30 Gy in 10 fractions (Lutz et al., 2011). Shorter courses of radiotherapy have been found to be as effective in treating bone metastases causing pain, even if higher retreatment rates have been detected among patients who have received single-fraction radiotherapy (Chow et al., 2012; Sze et al., 2002). Thus, single-fraction treatments should be preferred for patients with painful bone metastases, also when there is a need for repeat radiation (Chow et al., 2014).

The most targeted radiotherapy locations were the brain, thorax, spine, and pelvis. Especially in the spine and pelvic regions, bone metastases are those generally targeted. However, in the brain, radiotherapy is used to alleviate symptoms caused by both primary tumors and metastases. In whole-brain irradiation, 20 Gy in 5 fractions is preferable for most patients (Rades et al., 2007). Indeed, whole brain external beam radiotherapy is the standard care for patients ineligible for resection or stereotactic radiosurgery, and for patients with a short prognosis shorter treatments are recommended (Jones et al., 2014). Our finding that the fractions received by patients with primary brain tumors and brain metastases were 8 and 5 respectively are in line with these recommendations.

Palliative radiotherapy should be available for patients even when the treatment has been referred to primary care after discontinuation of active anticancer treatments. This must be ensured by providing consultation services at an oncology clinic also in the future. In the US, in a study by Lutz et al. (Lutz et al., 2004) ,hospice professionals recognized the importance of palliative radiotherapy as a treatment option, yet less than 3% of hospice patients needed it. Patients referred to hospice are less likely to receive long courses (>10) of radiotherapy regardless of whether they are enrolled in hospice care before or after radiotherapy (Lavergne et al., 2011).

6.4 Management of pain with strong opioids (Study IV)

Pain alleviation of cancer patients has relied on strong opioids for decades (Fallon et al., 2018; Makhlouf et al., 2020; World Health Organization, 1996) and lacks any significant developments, upgrades, or novel approaches to effective alleviation. As expected, in this series of cancer patients treated in hospice, pain management relied on strong opioids. Indeed, nearly all patients (96%) received strong opioids during their stay in hospice. This is also seen in previous studies, where 79–95% of patients with advanced cancer were reported to have received opioids (Raijmakers et al., 2013; Zerzan et al., 2010). The number of patients receiving opioids increased during the hospice stay, as at transfer 63% and on the day prior to death 89.9% received them regularly dosed. In an Italian multicenter study, 61% of patients received opioids at transfer and only 70% 1 day before death. Thus, in the Italian cohort opioids were prescribed to patients less frequently and the doses were smaller than in our findings (Mercadante et al., 2013).

Wide range in MEDD (12-1050 mg) was observed in the present study outlining the need for individual pain assessment near EOL. The pain medication of imminently dying have been studied in Swedish cohort where corresponding daily doses were reported (Fürst, Lundström, Klepstad, et al., 2020b).

Pain is one of the most common symptoms at the EOL (Breivik et al., 2009; van den Beuken-van Everdingen et al., 2016), and patients should be guaranteed high-quality symptom management to ensure a “good death” (Khanm et al., 2014). In hospice there might be fewer barriers to prescribing and using opioids (Jacobsen et al., 2007) than in a hospital or outpatient setting. Indeed, hospice patients have been more likely to receive opioids than hospital patients (Raijmakers et al., 2013). Fewer barriers might also be associated with more easily recognizing pain. In hospice, pain-related behaviors and discomfort are often well recognized, even when the patient’s ability to communicate declines. However, barriers may remain in patients’ and caregivers’ attitudes and understanding of effective cancer pain management (Makhlouf et al., 2020).

Even if morphine has remained the first treatment of choice for moderate to severe cancer pain (Makhlouf et al., 2020), this is more for reasons of familiarity, availability, and cost than its proven superiority (Caraceni et al., 2012). Novel formulations, especially oxycodone and fentanyl, were frequently used in our patient cohort, which is consistent the general opioid prescribing practice in Finland (Bosetti et al., 2019). Furthermore, compared to morphine, oxycodone may cause less nausea and hallucinations (Kalso & Vainio, 1990). Methadone, as a low-dose add-on to other opioids, has been delineated as an important tool for treating advanced pain in specialized palliative care, but this was not observed in our study (Fürst, Lundström, & Strang, 2020; Fürst, Lundström, Klepstad, et al., 2020a).

Breakthrough cancer pain remains a challenge also for patients with stable and controlled background pain (Margarit et al., 2012). A correlation has been found between the intensity of background pain and breakthrough pain (Mercadante, Caraceni, et al., 2021). The incidence of breakthrough pain alternates in different stages of cancer but is reported by 70–93% of patients (Mercadante, Maltoni, et al., 2021; Swanwick et al., 2001). In our series of patients the need for strong opioids for alleviating breakthrough pain was common, as half of the patients received them on the second day in hospice and 76% on the day before death. It should be remembered that rather than just treating episodic pain with short-onset opioids, careful and continuous assessment could limit the burden induced by breakthrough cancer pain (Mercadante, Caraceni, et al., 2021).

The route of administration of opioids changed significantly, with orally administered medications decreasing while subcutaneous administration became more common. Transdermal fentanyl was used steadily throughout the stay in hospice. The SC administration route is simple and effective for delivering opioids and should be the first choice for patients unable to receive opioids orally or transdermally (Fallon et al., 2018). As death approaches, the need for other than oral administration of opioids increases. Especially in a hospice setting, SC administration of medications is common (Raijmakers et al., 2013). Changing the administration route is justifiable given that severe and/or overwhelming pain has been reported to decrease after starting continuous SC infusion during the final days (Fürst, Lundström, Klepstad, et al., 2020b).

Symptom burden near the EOL is obviously more complex than just treating pain. Opioids can be used to alleviate cancer-related dyspnea (Ben-Aharon et al., 2012) in addition to pain, but other essential medications are also needed. Midazolam, haloperidol, and an antimuscarinic were listed among four essential drugs needed in caring for dying patients (Lindqvist et al., 2013). The list of essential medicines for palliative care by the International Association for Hospice and Palliative care also includes these medications (de Lima, 2006). The use of sedative and psychoactive drugs is common in the EOL care of advanced cancer patients (Raijmakers et al., 2013; Zerzan et al., 2010), and in our study population it increased during the stay in hospice from 51% at transfer to 70% 1 day before death. The most frequently used were the above medications listed as essential, as benzodiazepines were received by 70% and haloperidol by 32% of patients, respectively. Opioid use may increase the symptom burden and its side effects should be treated actively (World health organization, 1996).

Concerns have been raised over the undertreatment of cancer pain. In a Pan-European survey of prevalence, treatment, and patient attitudes towards cancer related pain, 64% of Finnish respondents reported pain. A third of the cancer patients felt that pain was a problem, 42% that their health care provider did not have enough time to discuss it, and 42% that their health care provider did not know how to control pain (Breivik et al., 2009). Underestimation of pain severity and lack of knowledge of adequate pain treatment were named as prior reasons for inadequate treatment of pain by Finnish physicians (Silvoniemi et al., 2012). Even if our analysis did not include the patients' perspective it can be assumed that undertreatment of pain was uncommon, since strong opioids were frequently used.

In 2010, Finland had only four hospices, and patients who received hospice care thus represent a minority of all deceased cancer patients. Nevertheless, these units have been pioneers in treating pain and other symptoms of dying patients. Palliative care processes are evolving and new facilities to offer EOL care are being established. While the need for more training in the treatment of cancer pain has been recognized (Bossi et al., 2021; Silvoniemi et al., 2012), it would be beneficial to include these practical observations as part of the training in future. Specifically, these findings support previous recommendations for units treating EOL cancer patients to assess pain, prescribe both regularly dosed strong opioids and strong opioids for breakthrough pain, and execute administration of pain medication via the SC route when needed.

6.5 Study limitations

The most distinctive limitation of this thesis concerns the retrospective approach of all the studies I-IV. However, there have not been comprehensive population-based studies concerning the EOL cancer care in Finland earlier and therefore the first step in evaluating the current practice was the retrospective, descriptive approach seen in the studies II and III. This was enabled by the high-quality data provided by the Auria Informatics. After the descriptive approach demonstrating the established cancer care practices were studied, more precise research question demonstrating the effect of palliative intervention was assigned. EOL pain medication in two hospices, which are few in Finland, was studied to describe EOL pain medication during last weeks and days of life in highly specialized units.

There are restrictions in retrospective studies, as only data collected systematically as part of routine care could be utilized. Therefore, data on symptom burden, quality of life, performance status, and experiences of the patient and caregiver could not be reliably assessed. Regardless of these limitations, descriptive analysis providing valuable knowledge of current practices were possible. To our believe, the most important variables were included in the studies I-IV and the use of anti-cancer treatments, pain medications and the effect of palliative intervention could be evaluated.

In the study I, diagnose of pancreatic cancer was manually identified from patients' records but the definite cause of death was not verified. Some of the patients may have therefore died for other reason than cancer. The SC and PC groups differed in terms of OS. This difference between the groups should be further investigated on a prospective study design. Indeed, there are no specific referral criteria for palliative outpatient clinic and thus there might be some unidentified bias in the patient selection of these studied groups. The data included only the use of tertiary care resources and therefore hospitalizations and the costs of EOL care in primary care were not included in the present study.

In Studies II–III, the population-based data was to our believe representative as all deceased cancer patients who had a cancer diagnose code were included in the study. However, the first appearance of metastatic cancer could not be identified from patient records. To improve the accuracy of our data only patients receiving anticancer treatments during the last year of life were included. The cause of death was affirmed from death certificates in addition to data validation. In Study II, the data included only IV chemotherapies, with no orally administered cytotoxic agents or hormonal medications. This might have led towards an impression of less active use of chemotherapy near the EOL than occurred in real life. During 2005–2013, checkpoint inhibitors, CDK 4/6 inhibitors, and second-line antiandrogens (enzalutamide or abiraterone) were not used, but for example capecitabine, vinorelbine, tyrosine kinase inhibitors, and temozolomide in addition to hormonal agents were available.

In Study III, the intent of radiotherapy could not be verified from radiotherapy plans, even though the total dose of radiotherapy and fractionation may indicate the intent of the treatment course. Performance status and patient’s symptoms would have provided beneficial information when evaluating the advantage of treatments during the last weeks of life.

In Study IV, the patients were randomly assigned to the study and no selection was made. The cohort was rather small which may decrease the generalization of the results. The most important limitation to the study was the lack of written pain estimates. However, even if this aspect would have been considered in a prospective study design, patients’ severe symptoms, either physical or psychical, are common during the last days of life and could affect the data collection. In addition, only three physicians were working at these two facilities during the time the data were collected.

6.6 Future considerations

Additional studies addressing the optimal timing and execution of palliative intervention also for other than pancreatic cancer patients are recommended. Referral criteria for palliative care should be assessed and harmonized. A prospective trial evaluating the effect of palliative intervention in different settings, could help target the resources in the future. The results of this study could be reinforced by evaluating the hospitalizations and costs of EOL care in primary care. Quality of life and other patient-centered outcomes in Finnish population remain unknown and could be evaluated either by prospective study design or by implementing more precise and structured symptom assessment as a part of routine clinical work.

In the future, the use of all anticancer treatments including orally administered agents with a special focus on elderly patients should be assessed in collaboration with geriatric approach. Development of anticancer treatments including well tolerated orally administered agents has revolutionized cancer care for some diagnose groups and currently there are more treatment options for patients when compared to time when the data was collected for Study II. Lastly, if cancer patients pain medication in terminal phase would be evaluated in a wider range of facilities, education could be targeted to ensure that there are no barriers in the use of strong opioids near EOL.

This thesis aimed not only to describe the cancer patients' treatment patterns near EOL but to raise awareness of the importance of palliative and EOL care. Palliative care is commonly associated with the terminal phase of a disease rather than a patient-centered holistic approach and may be associated with negative stigma (N. Cherny, 2009). The term was once unfamiliar (Koffman et al., 2007), but in recent decades the importance of death and dying has been increasingly recognized by the public (Daveson et al., 2014). However, awareness of palliative care and the importance of communication in addition to emotion management skills, attitudes and beliefs towards palliative care among healthcare professionals should be enhanced (Bennardi et al., 2020). In Finland, attitudes towards EOL care have changed. Patients suffering from cancer or other terminal illnesses require quality palliative care. Patients may still have concerns that palliative intervention hastens death, even if most people would choose to improve the quality of life for the time they have left (Higginson et al., 2014).

An accurate prognosis for an individual patient may be challenging to assess, and further information is needed on the timing of palliative intervention during the cancer pathway. Quality care at the EOL is highly individual and should be achieved through a process of shared decision making and clear communication that acknowledges the values and preferences of patients and their families (Steinhauser et al., 2000). Attention should also be paid to strengthening patient's coping skills (Greer et al., 2018). Indeed, EOL decisions should always be made mutually with the patient and with respect for the patient's own wishes (Rietjens et al., 2017).

7 Summary and conclusions

I Palliative intervention was associated with a decrease in the use of hospital resources during the last month of life of pancreatic cancer patients. The difference was statistically significant in terms of the number of radiological examinations, emergency department visits, hospitalizations, and costs of tertiary care between patients who visited an outpatient palliative care unit in addition to standard oncological care and those receiving only standard oncological care. Systematic palliative intervention should be warranted for all patients with a short prognosis or heavy symptom burden. The limited resources of health care could be better optimized if early palliative intervention were offered to a larger number of patients.

II Over a 9-year period the use of IV chemotherapy remained stable in terms of time from the last treatment to time of death, reflecting established oncological treatment at TUH. The number of patients receiving IV chemotherapy during the last weeks of life was in line with international studies and met the quality recommendations. Young patients and patients with hematological malignancies and lymphoma were treated more frequently close to death than were other diagnostic groups. A third of patients who received IV chemotherapy died in tertiary care. Use of IV chemotherapy should, however, be critically evaluated when the life expectancy is short, as it is unlikely in most cases to extend life and may be associated with aggressive care near the EOL.

III Cancer diagnosis and the distance between the patient’s domicile and the radiotherapy unit affected the time from the last radiotherapy fraction to death. Single-fraction treatments were used infrequently in the last radiotherapy plan, even if the median number of fractions decreased significantly during the 9-year period. During the last 2 weeks of life 97% of patients received radiotherapy with palliative intent, one-third of them to alleviate pain. Nearly half of these treatments given during the last 2 weeks of life were discontinued, and patients treated close to death were more likely to die in a tertiary care hospital. Thus, widespread adoption of prognostic tools to identify EOL patients is warranted. Single-fraction treatments should be considered more often and the opportunity for palliative radiotherapy should be offered also to patients living far from the radiotherapy unit.

IV Pain medication during the last weeks and days of life in hospice relies on strong opioids. The dose range of opioids varies between individuals. While a trend towards more frequent use of subcutaneous administration was significant, the use of transdermal administration was frequent throughout the hospice care. In addition to regularly dosed strong opioids, drugs to alleviate breakthrough pain and mental distress were commonly used. The availability of, and professionals' knowledge of, the use of subcutaneous pain medication should be ensured in units providing EOL care.

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Liisa Rautakorpi

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