Early Integration of Specialized Palliative Care with Oncological Treatment

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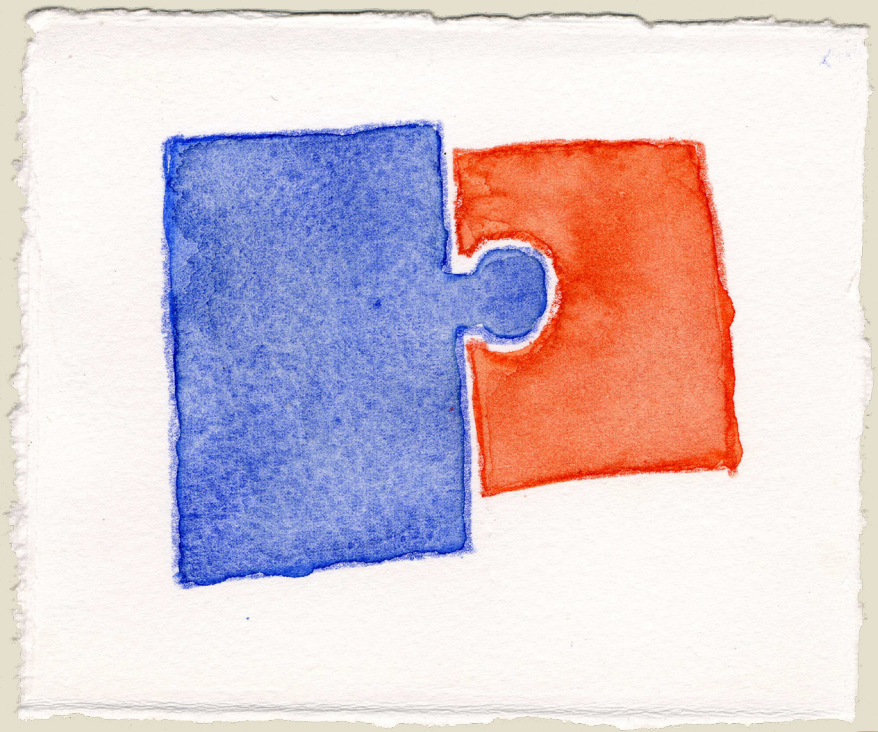

Early Integration of Specialized Palliative Care with Oncological Treatment

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Anders Bojesson MD

LUND
UNIVERSITY

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 8th of November 2024 at 13.00 at the Torsten Landberg Hall, Department of Oncology, Lasarettsgatan 23A, Lund

Faculty opponent

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Abstract:
The primary aim of specialized palliative care (SPC) is to improve the quality of life (QoL) for patients with advanced cancer and other life-threatening diseases by alleviating the burden of symptoms.

Aims

- To examine potential negative prognostic factors at the start of second line (SL) palliative chemotherapy (CHT) and to determine whether enrollment to SPC affects CHT use near death and emergency care utilization, in patients with advanced pancreatic cancer.
- Whether patients with advanced gastrointestinal (GI) cancers who were randomized to early integration of home-based SPC had a better QoL, utilized less emergency healthcare, and received less CHT near the end of life compared to a control group who were referred to home-based SPC as per need in the disease trajectory.

Material and methods
Articles I and II report on retrospective studies including 170 patients with advanced pancreatic cancer receiving palliative CHT. Article III and manuscript IV present results from a randomized controlled trial (RCT) including 118 patients with advanced GI cancer randomized to early integration of home-based SPC (active group) or not (control group) alongside tumor-specific treatment.

Results and conclusion
Hypoalbuminemia and performance status 2 were negative prognostic factors for overall survival (OS) in advanced pancreatic cancer patients starting SL palliative CHT. Those enrolled in SPC for over 30 days before death used less emergency care and had a longer time between last palliative CHT treatment and death compared to those enrolled later or not at all. The RCT showed improved QoL for patients in the active group 24 weeks after randomization. These patients used less emergency care throughout their disease trajectory and had equal OS and use of CHT compared to the control group.
This thesis advocates for the early integration of tumor-specific treatment with home-based SPC for patients with advanced GI cancers.
Key words: Palliative care, early integration of palliative care, quality of life, home-based care, gastrointestinal cancer, advanced cancer and palliative chemotherapy.

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Till mamma och pappa

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Thesis at a glance

#	Aim	Method	Results	Conclusion
I	To study prognostic factors and survival in reference to second-line palliative CHT in patients with advanced pancreatic cancer.	Retrospective single-center study of 170 patients treated at a tertiary cancer center in southern Sweden.	Median OS from start of second-line treatment was 5.0 months for the entire cohort, 2.9 months for patients with PS 2, and 3.5 months for patients with low albumin.	PS 2 and hypoalbuminemia may be negative prognostic factors for survival in patients with advanced pancreatic cancer.
II	To examine whether longer enrollment in SPC (>30 days) affects time from last CHT treatment to death, number of hospitalizations, OS, and place of death, compared to patients with shorter enrollment (≤30 days).	Retrospective single-center study of 170 patients treated at a tertiary cancer center in southern Sweden.	Patients with >30 days in SPC had a median of 73 days between last CHT and death compared to 44 days for those with ≤30 days, as well as fewer hospitalizations (median 1 vs. 2). Only 2% of SPC-referred patients died in the hospital, versus 84% of those never referred.	Enrollment in SPC for >30 days may lower the risk of receiving futile palliative CHT treatment at EOL as well as the risk of dying in the hospital, compared to patients with shorter or no enrollment in SPC.
III	To assess the impact of early integration of home-based SPC alongside tumor-specific treatment on QoL, CHT use, and survival.	RCT of 118 patients with advanced GI cancer randomized to tumor-specific treatment with (active group) or without (control group) early integration of SPC.	Mean total change in FACT-G score between baseline and 24 weeks was 13 points higher (indicating a QoL improvement) in the active group than in the control group. Groups did not differ in terms of OS or time between last CHT cycle and death.	This RCT supports early integration of SPC with tumor-specific treatment for advanced GI cancers, showing improved QoL 24 weeks post-randomization to home-based SPC.
IV	To evaluate the impact of early integration of home-based SPC alongside tumor-specific treatment on emergency care needs, time from CHT treatment to death, and place of death.	RCT of 118 advanced GI cancer patients randomized to tumor-specific treatment with (active group) or without (control group) early SPC integration.	Patients in the active group and the control group had 1 versus 3 emergency ward visits and 1.5 versus 11.5 days of inpatient care, respectively. Groups did not differ in terms of either CHT use near death or place of death.	Early integration of home-based SPC reduces the need for emergency healthcare and hospitalizations in advanced GI cancer patients compared to those randomized to the control group.

CHT – chemotherapy; EOL – end of life; FACT-G, – Functional Assessment of Cancer Therapy - General; GI – gastrointestinal; OS – overall survival; PS – performance status; QoL – quality of life; RCT – randomized controlled trial; SPC – specialized palliative care.

Abstract

Background

The primary aim of specialized palliative care (SPC) is to increase or maintain quality of life (QoL) for patients with advanced cancer and other life-threatening diseases by alleviating disease- and treatment-related symptoms. A close collaboration between oncologic treating units and SPC teams may enhance symptom management in patients with advanced cancer. The American Society of Clinical Oncology (ASCO) suggests integrating SPC with standard oncological therapy for patients with advanced cancer (stage ≥III pancreatic cancer or stage IV solid tumor).

The aim of this thesis was to investigate:

- Potential negative prognostic factors that would argue against starting second line (SL) chemotherapy (CHT) with a palliative intent in patients with advanced pancreatic cancer.
- Whether enrollment to SPC affects palliative CHT use near the end of life (EOL) and emergency care utilization for patients with advanced pancreatic cancer.
- Whether patients with advanced gastrointestinal (GI) cancers who were randomized to early integration of home-based SPC had a better QoL, utilized less emergency healthcare, and received less CHT near the end of life (EOL) compared to a control group who were referred to home-based SPC by a treating oncologist, when need arose, later during the treatment trajectory.

Material and methods

Articles I and II report on retrospective studies including 170 patients with advanced pancreatic cancer who received palliative CHT at Skåne University Hospital. Article III and Manuscript IV describe results from a randomized controlled trial (RCT) involving 118 patients with advanced GI cancer randomized to tumor-specific treatment with or without early integration of home-based SPC.

Results and conclusions

Hypoalbuminemia and performance status (PS) 2 (where 0 is without any negative impact on the general condition and 4 is completely disabled, bedridden) were negative prognostic factors for survival when SL palliative CHT was initiated in patients with advanced pancreatic cancer, compared to patients with normal albumin levels and PS 0–1. Patients with advanced pancreatic cancer enrolled in SPC for more than 30 days

before death utilized less emergency care and had a longer period of time between the last palliative CHT treatment and death compared to patients never enrolled or enrolled for a shorter period of time.

The RCT showed improved QoL for patients with advanced GI cancer 24 weeks after randomization to early integration of home-based SPC. These patients used less emergency healthcare throughout their disease trajectory and had equal overall survival (OS) and CHT use near death compared to the control group, who were referred to SPC if and when the treating oncologist found it indicated.

This thesis advocates for the early integration of tumor-specific treatment with home-based SPC for patients with advanced GI cancers.

List of Articles

Article I

Second-line palliative chemotherapy, survival, and prognostic factors in patients with advanced pancreatic cancer.
Ekström A, Brun E, Eberhard J, Segerlantz M.
Acta Oncologica. 2021;60:1580–1588.

Article II

Integration of specialized palliative care with oncological treatment in patients with advanced pancreatic cancer.
Ekström A, Brun E, Eberhard J, Segerlantz M.
Journal of Pancreatic Cancer. 2022;8:2–8.

Article III

Quality of life for patients with advanced gastrointestinal cancer randomised to early specialised home-based palliative care: the ALLAN trial.
Bojesson A, Brun E, Eberhard J, Segerlantz M.
British Journal of Cancer 131. 729–736 (2024).

Manuscript IV

The ALLAN Trial: Impact of Early Home-Based Palliative Care on Emergency Care and Hospitalisation in Advanced Gastrointestinal Cancer Patients
Bojesson A, Brun E, Eberhard J, Segerlantz M.
To be sent for peer review to the British Journal of Cancer in September 2024.

Abbreviations

ASCO	American Society of Clinical Oncology
ASIH	Advanced care at home
CA 19-9	Carbohydrate antigen 19-9
CHT	Chemotherapy
EOL	End of life
EORTC QLQ-C30	The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire
ESAS	Edmonton Symptom Assessment System
ESMO	European Society of Clinical Oncology
FACT-G	Functional Assessment of Cancer Therapy – General
FL	First line
FLOX	5-fluorouracil, oxaliplatin, and leucovorin
FOLFIRINOX	Oxaliplatin, irinotecan, leucovorin, and fluorouracil
GEM	Gemcitabine
GEM/ABRAX	Gemcitabine plus albumin-bound paclitaxel
GEM/CAP	Gemcitabine and capecitabine
HADS	Hospital Anxiety and Depression Scale
HCC	Hepatocellular carcinoma
IAHPC	International Association for Hospice & Palliative Care
IPOS	Integrated Patient Care Outcome Scale
Nab-Paclitaxel	Albumin-bound paclitaxel
OS	Overall survival
PC	Palliative care
PS	Performance status
QoL	Quality of life
QUAL-E	Quality of Life at the End of Life Scale
RCT	Randomized controlled trial
SL	Second line
SPC	Specialized palliative care
WHO	World Health Organization

Life is pleasant. Death is peaceful.
It is the transition that is troublesome.

Isaac Asimov, *Fantastic Voyage II*: Destination Brain

Populärvetenskaplig sammanfattning

För många av oss blir livets slut och döden en stillsam process. Men ibland innefattar livets sista tid ett stort fysiskt eller psykiskt lidande och experter inom symtomlindring behövs – det specialiserade palliativa teamet.

Palliativ vård uppfattas oftast som vård i livets slutskede men bör ses som den samlade insatsen av symtomlindring, såväl fysisk som psykisk som erbjuds patienter med en besvärande symtombörda i en avancerad sjukdomssituation, oavsett prognos eller annan pågående behandling. Allmän palliativ vård, såsom lindring vid måttlig smärta och ångest, kan ges av all medicinsk personal. Den specialiserade palliativa vården tar hand om patienter med komplexa symtom och förmedlas av läkare som är specialister inom palliativ medicin. I det specialiserade palliativa teamet ingår även specialistutbildade sjuksköterskor, undersköterskor, fysioterapeuter, arbetsterapeuter, kuratorer och även dietist, psykolog och präst.

Specialiserad palliativ vård finns organiserat på olika sätt i Sverige, oftast med möjligheter till inneliggande palliativ vård under en kortare tid. I Skåne finns flera specialiserade palliativa team som bedriver avancerad sjukvård i hemmen, alla under samma huvudman. Där kan teamet till exempel ge intravenös behandling med antibiotika, blod och göra symtomskattningar och därefter ordinera symtomlindrande åtgärder.

Patienter med en avancerad cancersjukdom i mag-tarmkanalen har en hög risk att drabbas av svåra symtom, i första hand smärta, illamående, ångest men löper också risk för komplikationer som tarmvred och svårigheter att få i sig näring. Cancer i den övre delen av magtarmkanalen är oftast aggressiv och drabbade patienter lever i genomsnitt ett år efter diagnosen av en avancerad cancer. Symtomen kan uppträda snabbt och patienterna behöver ofta söka akutsjukvård.

I vår första, retrospektiva journalstudie fann vi att 19% av patienter med avancerad bukspottkörtelcancer, behandlade vid Skånes Universitetssjukhus, fick behandling med cytostatika sista månaden i livet. Utöver det hade patienter med dåligt allmäntillstånd (performance status 2) och lågt äggviteämne (albumin) i blodet ingen förlängd överlevnad av en andra linjes behandling med cytostatika. Vår andra retrospektiva studie undersökte om tiden ansluten till den specialiserade palliativa vården (över 30 dagar eller 30 dagar eller mindre före döden) påverkade antal akutbesök, inneliggande vård och tid mellan sista cytostatikabehandling och död hos patienter med avancerad bukspottkörtelcancer. Resultatet visade att patienter med den längre anslutningstiden (>30 dagar) sökte i mindre utsträckning akutsjukvård, hade färre antal dagar inneliggande på sjukhus och längre tid mellan sista cytostatikabehandling och död

jämfört med patienter med en kortare anslutningstid (≤30 dagar) till den specialiserade palliativa vården.

Mellan åren 2014 och 2021 erbjöds patienter med icke botbar cancer i magtarmkanalen, i samband med att de skulle inleda cytostatikabehandling i lindrande syfte, på Skånes Onkologiska klinik i Lund och i Malmö, att delta i ALLAN studien (tidig pALLiativ ANslutning). Patienter som tackade ja slumpades till att samtidigt med start av cytostatikabehandling anslutas till den specialiserad palliativ vården (aktiv grupp) eller starta cytostatikabehandling och remitteras för anslutning till den specialiserad palliativ vården senare i förloppet, när behov för detta uppstod (kontrollgrupp). Totalt inkluderades 118 patienter, varav 60 hamnade i den aktiva gruppen och 58 i kontrollgruppen. Studiens syfte var att undersöka om det fanns skillnader mellan grupperna avseende livskvalitet, tid mellan sista cytostatikabehandlingen och död, behov av akutsjukvård och sjukhusinläggningar. Den aktiva gruppen befanns ha en bättre livskvalité, mätt efter 6 månader, sökte i mindre utsträckning akutsjukvård, och hade kortare vårdtid på sjukhus jämfört med kontrollgruppen, som anslöts till palliativ medicin vid behov. Patienter i kontrollgruppen som aldrig anslöts till den specialiserade palliativa vården dog i högre utsträckning på sjukhus jämfört med de patienter som anslutits.

ALLAN-studien är den första randomiserade, nordeuropeiska, studien som påvisar positiva effekter av en tidig palliativ anslutning hos patienter med avancerad cancer i mag-tarmkanalen.

1. Introduction

1.1. Palliative medicine and palliative care in cancer

Palliative care (PC) is a complex form of care, for which several definitions have been proposed. The World Health Organization (WHO) describes PC as follows:

> "Palliative care is a crucial part of integrated, people-centered health services. Relieving serious health-related suffering, be it physical, psychological, social, or spiritual, is a global ethical responsibility. Thus, whether the cause of suffering is cardiovascular disease, cancer, major organ failure, drug-resistant tuberculosis, severe burns, end-stage chronic illness, acute trauma, extreme birth prematurity, or extreme frailty of old age, palliative care may be needed and has to be available at all levels of care." [1]

> "Palliative care aims to prevent and relieve health related suffering of adults, children and their families facing problems associated with life-threatening illness. It is based on a comprehensive and person-centred approach, addressing physical, psychological, social and spiritual suffering. Providing equitable and timely access to good palliative care is an ethical duty shared by public health stakeholders and health care workers. Integrated palliative care is part of Universal Health Coverage and is an essential function of Primary Health Care. Special attention has to be given to monitor the quality of palliative care and to asses progresses made in answering people needs and expectations." [2]

The International Association for Hospice & Palliative Care (IAHPC) uses the following definition:

> "Palliative care is the 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.

Palliative care:

- Includes, prevention, early identification, comprehensive assessment and management of physical issues, including pain and other distressing symptoms,

psychological distress, spiritual distress and social needs. Whenever possible, these interventions must be evidence based.

- Provides support to help patients live as fully as possible until death by facilitating effective communication, helping them and their families determine goals of care.
- Is applicable throughout the course of an illness, according to the patient's needs.
- Is provided in conjunction with disease modifying therapies whenever needed.
- May positively influence the course of illness.
- Intends neither to hasten nor postpone death, affirms life, and recognizes dying as a natural process.
- Provides support to the family and the caregivers during the patient's illness, and in their own bereavement.
- Is delivered recognizing and respecting the cultural values and beliefs of the patient and the family.
- Is applicable throughout all health care settings (place of residence and institutions) and in all levels (primary to tertiary).
- Can be provided by professionals with basic palliative care training.
- Requires specialist palliative care with a multi-professional team for referral of complex cases." [3]

The Swedish National Board of Health and Welfare presents a Swedish definition of PC, which when literally translated into English reads as follows:

> "The Swedish National Board of Health and Welfare defines palliative care as healthcare with the aim of alleviating suffering and promoting quality of life for patients with progressive, incurable illness or injury. Palliative care also involves consideration of physical, psychological, social, and existential needs, as well as organized support for caregivers. The Swedish National Board of Health and Welfare's definition concurs with the World Health Organization's (WHO) definition of palliative care.
>
> Palliative care is based on a palliative approach characterized by a holistic view of the individual, supporting them to live with dignity and the highest possible well-being until the end of life, regardless of age or diagnosis.

> Palliative care aims to prevent and alleviate suffering through early detection, analysis, and treatment of physical, psychological, social, and existential issues, achieved through collaboration within multi-professional teams. Palliative care can also be provided early in the course of the illness alongside life-prolonging treatment, which is not addressed here." [4]

While these three definitions of PC converge on a holistic approach, emphasis on quality of life, and support for families, they diverge in scope and specificity. The WHO definition adopts a broader, global, and more policy-oriented perspective; the IAHPC definition is detailed and operational; and the Swedish definition is concise and pragmatic, closely aligning with the WHO definition. The Swedish National Board definition differs as it focuses on patients with a progressive, incurable disease, while the other two definitions focus on patients with a high burden of symptoms.

1.1.2. History and development

Modern PC has its roots in the United Kingdom. In 1967, Cicely Saunders established St. Christopher's Hospice in London to care for cancer patients at the end of life (EOL). Saunders also introduced the concept of "total pain", which embodies a comprehensive understanding of the multifaceted nature of suffering experienced by patients with life-limiting illnesses. Total pain extends beyond physical discomfort to encompass psychological, social, and spiritual dimensions, recognizing that pain is not merely a physiological phenomenon but a complex interplay of various distressing factors. This holistic perspective stresses the need to address all aspects of a patient's suffering, aiming to improve quality of life (QoL) and provide comprehensive support for patients and their families.

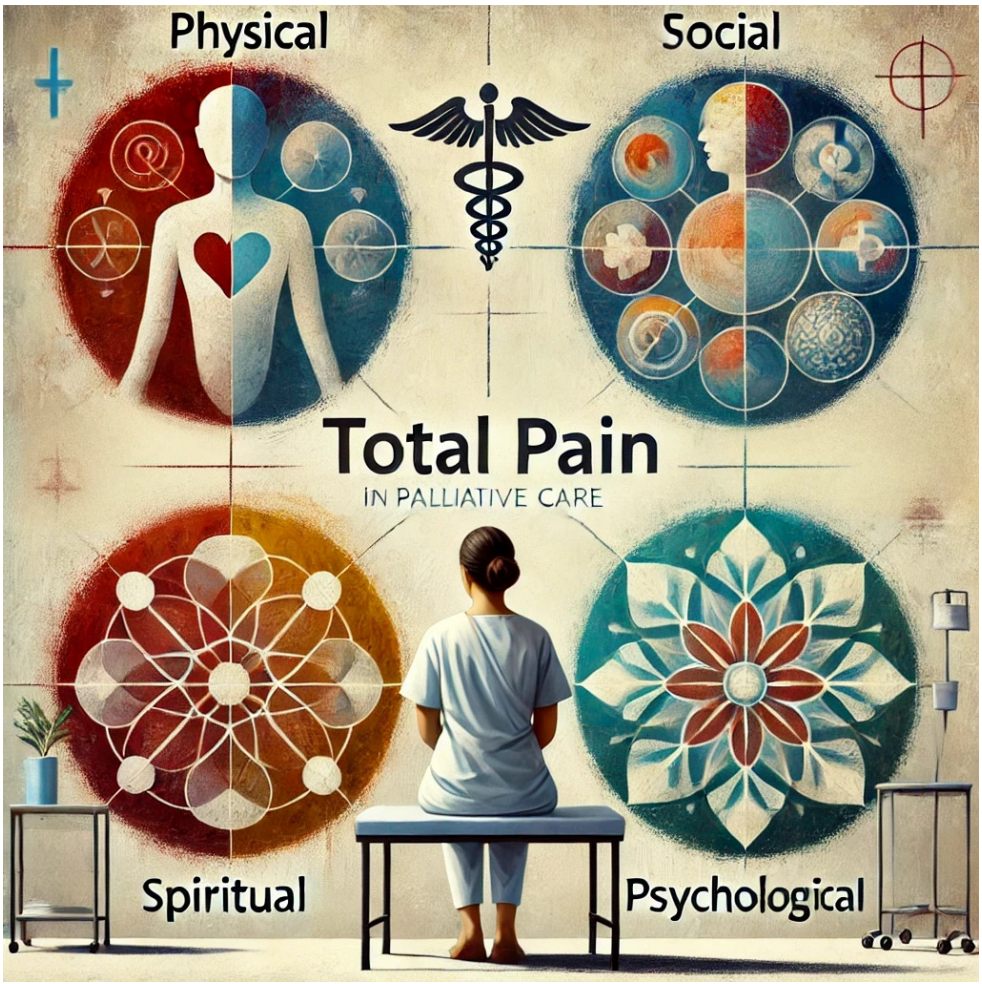

Figure 1. Visual conceptualization of total pain. Image generated by using ChatGPT-4.

Dr. Balfour Mount introduced the term "palliative care" in 1975 to describe his hospice initiative in Canada, a concept subsequently accepted globally [5]. In 1990, the WHO recognized palliative medicine as a specialty in medicine dedicated to relieving suffering and to improving QoL for patients with life-limiting illnesses.

In Sweden, PC has been developed around home care. Dr. Per Arnander organized the first palliative home care service in Jönköping in 1972. In 1977, Dr. Barbro Beck-Friis started a palliative home care service in Motala, focusing on a multi-professional approach to provide holistic care to incurably ill patients [6]. This and other work by Beck-Friis has been important in introducing PC into the Swedish healthcare system.

During the 1990s, several palliative care teams emerged in Sweden, and advanced care at home (ASIH) was initiated. The idea behind ASIH is to provide home-based SPC by a multi-professional team to patients with a high burden of symptoms from an incurable disease [7]. Another contribution to the development of PC in Sweden was made by Dr. Peter Strang, whose efforts led to the establishment of palliative medicine as a recognized specialty in 2015, which in turn led to physicians becoming responsible for specialized palliative care (SPC) within Swedish healthcare. In Sweden, 80% of patients enrolled in SPC have a diagnosis of cancer [8].

During the past 20 years, PC for cancer patients has transformed significantly. A shift has taken place from EOL care, when all oncological treatment was terminated, to a more comprehensive model integrated earlier in the cancer disease trajectory [9]. When referring to EOL, a timeframe of the last 6 months in life is commonly accepted [10, 11].

1.2. Palliative care and cancer

The focus of PC is on optimizing QoL for patients with advanced disease and a high burden of symptoms, addressing physical, emotional, and spiritual needs through comprehensive support and symptom management. Validated assessment methods, such as scales and questionnaires for numerical ratings, are internationally recognized to capture core elements such as QoL and symptom burden. The commonly used methods are presented below. A systematic review indicates that over 50% of patients with incurable cancer report five prevalent symptoms: fatigue, weakness, pain, weight loss, and appetite loss [12].

What is quality of life?

Quality of life is a multidimensional concept that is central both in PC and in healthcare in general. Addressing QoL is essential in providing comprehensive care for cancer patients throughout their disease trajectory. In medicine, QoL is sometimes referred to as health-related QoL; this term can be used interchangeably with QoL [13]. A patient's QoL is highly individual, and there is no strict definition of QoL.

Commonly, QoL is described in terms of physical, psychological, social, and spiritual dimensions [14]. Physical issues might include pain, fatigue, and side effects of disease-specific treatments. Psychological aspects often involve anxiety, depression, and coping with the diagnosis. Social aspects can relate to changes in relationships, social isolation, and role functioning. Spiritual dimensions may involve finding meaning, dealing with

existential questions, and maintaining hope. Additionally, patients may face varying demands for information, economic problems, and difficulties in managing different care situations [14]. These factors collectively impact their overall QoL, and require individualized approaches to support and care in order to maintain or improve QoL in PC [15].

During the disease trajectory, a patient's conception of QoL is challenged and may undergo changes. When people are asked about their priorities and the meaning of QoL, the views of healthy individuals differ from those of patients with newly diagnosed advanced cancer, which in turn differ from those of terminally ill patients [16]. In 1999, Singer et al. conducted, in Canada, a qualitative study using in-depth, face-to-face interviews from 3 previous studies with patients on dialysis, people with HIV, and residents of long-term care facilities [17]. The authors identified five domains affecting QoL in these terminally ill patients. In line with previous research, one of these domains was concerned with pain and other physical symptoms. The remaining domains included social connectedness, with patients expressing a desire to maintain control over their EOL care decisions as long as they were mentally capable. They also aimed to minimize the physical and emotional burden on their loved ones, while actively seeking the involvement of those dear to them during the dying process. The last domain involved avoiding inappropriate prolongation of dying, where study participants were afraid of being kept alive after they were unable to enjoy their lives. Patients may place greater importance on personal dignity and the meaningfulness of life rather than on physical symptoms or functional abilities [18]. However, physical discomfort strongly affects QoL for the dying person, and pain relief is often a dying patient's predominant concern [16].

Burden of symptoms

Symptom burden in patients with advanced cancer refers to the cumulative physical and psychological distress caused by the multiple symptoms associated with the disease, treatment-related side effects, and comorbid conditions [19]. These symptoms often include pain, fatigue, dyspnea, nausea, depression, and anxiety, among others, which can significantly impair the patient's QoL. In addition, there are the so-called "hidden toxicities" of being diagnosed and treated for advanced cancer. Hidden toxicities in advanced cancer patients can arise from psychological challenges, such as the anxiety associated with waiting for computed tomography results and blood samples, as well as financial and logistical burdens, including the costs and difficulties related to transportation, parking, and lodging. These often-overlooked factors significantly increase the overall distress experienced by patients [20]. Symptoms from various

sources collectively contribute to a burden of symptoms representing the patient's subjective experience of disease or treatment burden.

The burden of symptoms can be thought of as the sum of the severity of symptoms reported by a significant proportion of patients with a specific disease or treatment [21]. In short, QoL as measured in patient-reported questionnaires (introduced in detail later in this chapter) is concerned with the burden of symptoms, and hence constitutes a subset of the overall well-being when estimating QoL in terms of life as a whole. In patients with advanced cancer, a high symptom burden is associated with a poor prognosis [22].

Assessment scales

Evaluation of a patient's general well-being and ability to perform activities of daily living is crucial in oncology and in medicine in general. One measure of functional status is the Eastern Cooperative Oncology Group (ECOG) performance status (PS), which has been adopted by the WHO [23] (Table 1). Before its introduction during the 1980s, Karnofsky PS was used for the same purpose. Karnofsky PS is a comprehensive 11-point scale correlating to percentage values ranging from 100% (no evidence of disease, no symptoms) to 0% (death) [24]. Due to its simplicity, ECOG/WHO PS is now broadly in use both in clinical practice and in clinical trials. In this thesis, ECOG/WHO PS will be referred to as PS.

When considering treatment with palliative chemotherapy (CHT) in patients with gastrointestinal (GI) cancers, it is vital to score the PS of a patient. The treating oncologist generally performs this scoring. Clinical trials introducing new treatment options are typically limited to healthier patients, such as those with a PS of 0–1 [25]. Consequently, there is a lack of clinical evidence for treatments suitable for more frail patients with poorer PS who are undergoing palliative CHT.

Table 1. World Health Organization/Eastern Cooperative Oncology Group performance status.

Performance status	Activity
0	Fully active, able to carry on all pre-disease performance without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light housework, office work.
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.

QoL is measured with patient-reported and internationally validated questionnaires. The most common are the Functional Assessment of Cancer Therapy – General (FACT-G), the Edmonton Symptom and Assessment System (ESAS), the Integrated Patient Care Outcome Scale (IPOS), the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30), and the Hospital Anxiety and Depression Scale (HADS). There are also patient-reported and validated questionnaires to assess QoL specifically at the EOL; here, the Quality of Life at the End of Life (QUAL-E) scale is often used.

FACT-G measures health-related QoL in four dimensions according to physical, functional, emotional, and social well-being over the past week, and is designed to assess QoL in patients undergoing cancer treatment [26]. Total score ranges from 0 to 108 points, with higher scores indicating a better QoL. Changes of 4–7 points represent a minimally important difference, while a change of 9–14 points signifies a medium-sized clinically significant effect [27]. Since FACT-G includes questions on symptom control as well as social and emotional well-being, it is hard to separate symptom burden and QoL, which are used interchangeably by researchers [28]. In addition, different disease-specific FACT scales exist tailored to a specific cancer diagnosis; for example, FACT–L for lung cancer patients and FACT-Hep for patients with hepatobiliary cancer.

The ESAS questionnaire assesses the burden of symptoms in PC patients using nine common symptoms: pain, fatigue, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. Each item is rated on a scale from 0 to 10, with 0 indicating the absence of symptoms and 10 representing the worst possible intensity, and so 90 is the highest possible total symptom distress score [13].

The IPOS consists of 20 (for patients to answer) or 19 (for proxy-assessment answered by staff) items, including 17 items on physical, psychological, and spiritual problems, communication needs (including with family), and practical support, all scored on a 5-point scale from 0 (best) to 4 (worst). There are additionally two free-text items, one asking about the patient's main problems and concerns, and one asking about any symptoms other than those covered by the 17 items. The patient version also includes a question asking by whom the measure was completed (patient alone, with help from family or from medical staff). Only the 17 standardized items contribute to the total IPOS score [29]. In PC, the IPOS is used to follow up on the treatment effects of specific symptoms or to map the presence of symptoms at a first visit.

The EORTC QLQ-C30 assesses health-related QoL in cancer patients over the last 7 days [30]. It includes nine multi-item scales: five functional scales (physical, role, cognitive, emotional, and social), three symptom scales (fatigue, pain, and

nausea/vomiting), and one global health and QoL scale. Each scale is scored from 0 to 100. Higher scores on the functional and global health/QoL scales indicate better functioning and QoL, while higher scores on the symptom scales and single items indicate greater symptom burden.

The QUAL-E scale comprises questions from five domains: life completion (issues of transcendence), relationship with a healthcare provider, symptom management, preparation, and effective social support [31]. It is used to measure QoL at the EOL.

The HADS is another commonly used questionnaire for anxiety and depression. It consists of two subscales, each containing seven items: one subscale screens for anxiety (HADS-A) and the other for depression (HADS-D). Subscale scores range from 0 to 21, with 0 indicating no distress and 21 indicating maximum distress. A score of 7 or lower on either subscale is considered normal, a score of 8–10 indicates mild distress, and a score of 11–21 indicates moderate to severe distress.

Terminology in palliative care

The literature on PC for cancer patients includes a number of descriptive terms that lack consistent and clear definitions, and that are interpreted differently around the globe, such as "supportive care," "best supportive care," "palliative care," "end of life care," and "hospice care". Supportive care, PC, and EOL care encompass clinical initiatives designed to evaluate and address the physical and psychosocial challenges experienced by cancer patients and their families. The care involves multidisciplinary assessments and interventions to manage physical symptoms and address psychosocial distress, all while considering the care environment for patients and their families.

The term "supportive care" originates from the discipline of oncology, and includes treatments and other measures to support patients who are undergoing cancer treatment [28]. The National Cancer Institute defines "palliative care" and "supportive care" synonymously. In contrast, some perceive "palliative care" as addressing the needs of patients with incurable illnesses, while "supportive care" is seen as providing care for patients earlier in the disease trajectory [32]. The interchangeable use of these two terms may lead to confusion when studying the literature and publications [33]. However, the term "best supportive care" most often implies that tumor-directed therapy has been discontinued and the treatment now aims at symptom relief.

The term "hospice care" can be used for care that addresses critical EOL concerns: dying with dignity, dying at the preferred place of death and without pain, and reducing the burden placed on family caregivers [34]. Hospice care focuses on bereavement support and community integration.

Home-based SPC refers to the provision of SPC in the patient's home by a specialist team. There is a lack of controlled clinical trials on how the resources in home-based SPC should be optimally employed for patients with advanced cancer, highlighting a critical research gap that needs to be addressed [35, 36].

1.2.1. Specialized palliative care

Whereas general PC is mainly conducted by family physicians, complex symptom management may require a PC specialist. Of the 90,000 deaths occurring annually in Sweden, it is estimated that 75% of individuals had received general PC while another 11% were enrolled in SPC before death [37]. Studies from the United Kingdom and Canada have found that approximately 25% of dying persons are in need of SPC [38, 39].

Key components

In Sweden, SPC and home-based SPC are generally delivered by a multi-professional team, including doctors, nurses, dieticians, physiotherapists, occupational therapists, psychologists, priests and counselors. Doctors and nurses have recognized specializations in PC [6, 40]. Patients enrolled in SPC are offered consultations and homecare around the clock depending on their requirements, and can be admitted for inpatient care if needed. The SPC team provides advanced medical homecare services such as administering intravenous fluids including antibiotics, nutritional support, and blood products, assessing symptoms, and monitoring pain management and side effects of medications or oncological treatment. Admittance to inpatient care at the SPC ward can be arranged, generally for a shorter period, for symptom management and/or to allow for respite for caregivers at home.

The essential components of SPC are listed below:

1. **Symptom management**: It is paramount to maintain effective control of pain and other distressing symptoms such as nausea, shortness of breath, and fatigue. Symptom management often requires pharmacological and non-pharmacological interventions tailored to individual patient needs [41].
2. **Psychosocial support**: The SPC team includes psychologists, social workers, and counselors who provide emotional support, facilitate communication among patients, families, and healthcare providers, and assist with decision-making regarding care options, advance care planning, and EOL preferences [42].

3. **Spiritual care**: Addressing existential concerns and providing spiritual support is vital to SPC. Priests offer guidance, counseling, and rituals according to patients' spiritual or religious beliefs and preferences [43].
4. **Advanced care planning**: The SPC team encourages discussion about the goals of care and preferences for EOL treatment. This involves helping patients and families to understand the patient's prognosis, clarify values and priorities, and make informed decisions about future medical care [44].
5. **Coordination of care**: The SPC team collaborates closely with other healthcare providers involved in the patient's care, including primary care physicians, other specialists, and nurses. The team ensures continuity of care, facilitates transitions between care settings, and optimizes coordination of healthcare services [45].
6. **Bereavement support**: The SPC team extends support to families and caregivers both during the patient's illness and after death. Bereavement services may include counseling, support groups, memorial services, and practical assistance with, for example, funeral planning and paperwork [46].
7. **Education and training**: The SPC team provides education and training to healthcare professionals to enhance their knowledge and skills in palliative care delivery. Educational topics include pain management, communication skills, and ethical considerations in EOL care [47].

1.2.2. Navigating end of life oncology treatment decisions and hospital care utilization

Late in a palliative disease trajectory, the prescribing physician must carefully consider factors such as QoL, symptom control, potential life extension, and the associated side effects of tumor-specific palliative CHT. The overarching challenge in oncological treatment is to carefully balance QoL, potential side effects, and the avoidance of futile treatments, ensuring that valuable time is not wasted for the patient. Determining when an oncological treatment becomes futile or even causes more harm than good is a fundamental clinical problem faced by oncologists and other physicians who prescribe tumor-directed therapies [48]. The challenge of accurately estimating life expectancy in terminally ill cancer patients is widely recognized. More often than not, physicians and patients tend to overestimate a patient's remaining lifespan [49, 50].

Patients with advanced cancer on palliative CHT may perceive a "good doctor" to be one who offers hope of life prolongation, as even a short extension of life translates into additional time spent with one's spouse, children, and grandchildren. This perspective

and the strong desire to live as long as possible, seen among severely ill cancer patients, are in contrast to the perceptions of healthy individuals, who often take their longevity for granted and prioritize QoL over a longer survival time [51].

However, CHT within the final 30 days before death is deemed futile as it poses a risk of decreasing the QoL at EOL [52, 53]. In addition, ASCO states that the use of CHT in patients when there is no evidence of clinical value is a widespread, wasteful, and unnecessary practice in oncology [54]. However, ASCO also states that treatment for metastatic cancer can be recommended even without an improvement in survival as long as it improves the patient's QoL [55].

Emergency care needs and EOL care patterns and preferences

Patients with advanced cancer, and especially GI cancer, commonly experience symptoms such as pain, nausea, vomiting, bowel obstruction, and cachexia, which if not managed sufficiently may lead to the need for emergency care [56]. Aggressive medical interventions for cancer patients in the final weeks of life, including intravenous CHT, emergency department visits, hospital admissions, and intensive care unit stays, are indicators of poor QoL care near death [57].

Merchant et al. examined the delivery of physician-led PC and its association with EOL care in patients with GI cancer. Aggressive EOL care was defined as CHT use, an emergency department visit, or admission to a hospital or intensive care unit within 30 days of death. Of the 34 630 patients included in this retrospective study, 74% had at least one episode of PC service. Patients who did not receive any PC at all experienced more aggressive EOL care than patients receiving such services. Merchant et al. also found that patients who were enrolled in PC for the longest period of time had the least aggressive EOL care [58]. Henson et al. performed a meta-analysis to determine risk factors for cancer patients visiting the emergency department in the last month of life. The analysis, which included 1 181 842 patients, showed that patients receiving any amount of PC were less likely to visit the emergency department in their last month of life [59]. Wright et al. conducted a prospective cohort study involving 386 patients with advanced cancer and an expected survival of less than 6 months, all of whom had experienced disease progression after at least one CHT regimen [60]. The included patients had a median survival of 4 months, and those under treatment with palliative CHT at the start of the study exhibited a lower likelihood of dying at home compared to those not undergoing CHT (47% vs. 66%).

The preferred place of death is defined as the location where patients wish to spend their final days. A systemic overview from Sweden, performed in 2017, showed that an average of 60% of terminally ill cancer patients would prefer to die at home [61]. A

Danish RCT involving 205 patients with late-stage heart or lung disease, or with advanced cancer, investigated whether discussing the preferred place of death with a physician during an advanced care planning meeting would influence the actual place of death [62]. Among patients who participated in an advanced care-plan discussion, 40% died at home compared to 17% of patients not involved in EOL decision-making (p=0.013).

To end palliative oncological treatment

The lack of reliable prognostic factors, the dilemma physicians face when discussing the termination of palliative oncological therapy, and a willingness from the patient to submit to further toxic side effects in order to prolong life are all factors that can result in giving futile treatments with negative consequences for QoL at the EOL, such as severe side effects and need for hospital care [63].

Silvestri et al. investigated patients' views on the values of palliative CHT via an interview study of 81 patients previously treated with cisplatin-based CHT for advanced non-small-cell lung cancer. The aim was to investigate how lung cancer patients valued the trade-off between survival benefits and toxicities of palliative CHT. The survival threshold for accepting CHT varied substantially among the interviewed patients. The median survival criterion for considering CHT was 4.5 months with mild toxicity and 9 months with severe toxicity. A total of 18 patients (22%) said they would choose CHT if it offered a potential survival increase of only 3 months. On the other hand, a larger group comprising 55 patients (68%) said they would choose CHT primarily for its potential to significantly alleviate symptoms, even without a direct extension of life expectancy [64].

The study by Silvestri et al. was not an RCT. However, it highlights the need to individualize the care for patients with advanced cancer, and emphasizes that evidence on effects, survival benefits, and symptom control should be presented to allow patients to make informed decisions on continuing or discontinuing palliative CHT.

1.2.3. Specialized palliative care and timing

There is an ongoing discussion regarding when in the disease trajectory PC should be introduced for patients with advanced cancer. As mentioned, PC has formerly been synonymous with EOL care, and it was common earlier within the medical community, and still, the opinion exists, that tumor-directed treatment should be ended before a referral to PC. Both views are incompatible with the overarching goal of PC, which is to relieve the burden of symptoms for seriously ill patients [65].

American and European oncological societies (ASCO and the European Society for Medical Oncology [ESMO]) have recommended that patients with advanced cancer who are to start oncological therapy should receive integrated PC for management of disease- and treatment-related symptoms in order to improve QoL [66, 67]. The ASCO guidelines also state that early integration of SPC should be initiated within 8 weeks of diagnosis of a stage IV solid tumor or stage ≥III pancreatic or lung cancer. Substantial variation exists in the referral rates to PC units across the United States. A report released by ASCO in 2017 showed that up to 68% of oncologists do not refer their patients to an SPC unit at all, while the remaining 32% do so only within the patient's final month of life [67].

In 2014, Zimmerman et al. investigated the impact of early integration of SPC in the treatment of patients with a wide range of advanced cancers. The results showed that patients referred to early integration of PC had better symptom control after 4 months compared to the controls receiving standard care [45]. In the same cohort of patients, Zimmerman et al. conducted an interview study of patients' views of PC. A total of 48 patients were interviewed about their perception of PC, revealing that these patients had a negative opinion of PC and saw it as being associated with death, hopelessness, and loss of autonomy [68]. One reason for late referral, close to death, is the negative attitude that many patients and families have against PC [69]. In its recommendation on PC for cancer patients, ASCO emphasizes that oncologists should not delay referrals for patients with advanced cancer until EOL.

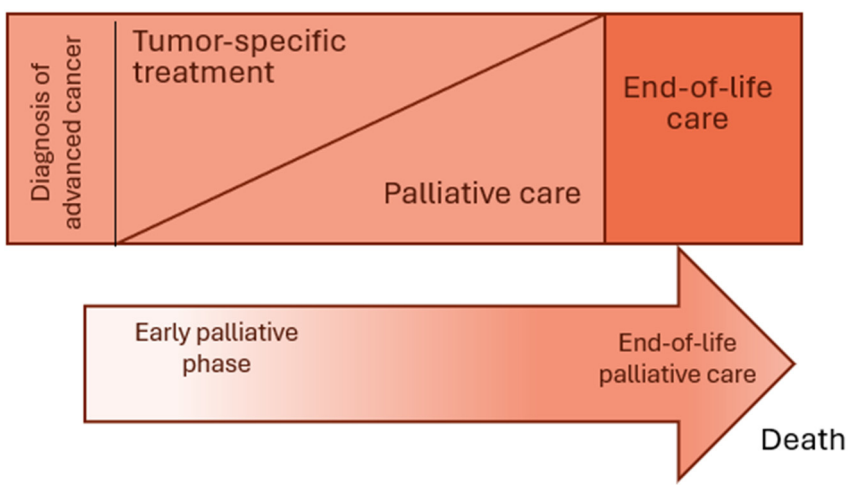

Figure 2. Illustration of early integration of palliative care (PC). Palliative care is integrated with tumor-specific treatment from the time of diagnosis in patients with advanced cancer. At some point, tumor-specific treatment is halted to focus on symptom-relieving PC.

Table 2. Summary of primary and secondary outcomes in randomized controlled trials (RCTs) published between 2000 and 2020 on the integration of palliative care (PC) and specialized palliative care (SPC) for patients with advanced cancer. The most commonly used primary outcome was quality of life (QoL), measured 12–24 weeks after randomization and compared to the control group.

Year Published	Author	Type of Patients	Number of Patients	Intervention	Primary Outcome	Secondary Outcome	Survival	Results
2000	Jordhøy et al.	Advanced cancer	434	SPC vs. standard care	Place of death	Inpatient care	Equal	Early PC group died more often at home and spent less time in institutions
2010	Temel et al.	Advanced non-small-cell lung cancer	151	Early SPC care vs. standard care	QoL at 12 weeks	Mood and survival	Improved	Early palliative care improved QoL, mood, and survival
2013	Eychmüller et al.	Advanced cancer	150	A single PC intervention vs. usual care	Patient distress	QoL	Equal	No improvement in patient distress or QoL
2014	Zimmerman et al.	Advanced cancer	461	Early SPC vs. standard care	QoL at 12 weeks	QoL at 16 weeks	Not specified	PC improved QoL at 16 weeks but not at 12 weeks
2017	The DanPaCT trial	Advanced cancer	297	Early SPC vs. standard care	QoL at 8 weeks	Survival	Equal	No difference in QoL
2018	Vanbutsele et al.	Advanced cancer	186	Early SPC vs. standard care	QoL at 12 weeks	Mood	Equal	Improved QoL for the early PC group, but no difference in mood
2018	Scarpi et al.	Advanced gastric cancer	207	Early SPC vs. standard care	QoL at 12 weeks	Mood and survival	Equal	No significant differences in QoL or mood
2020	The PALINT trial	Advanced cancer	126	Early SPC vs. standard care	QoL at 12 and 24 weeks.	Survival	Equal	No significant difference in QoL or mood at 12 and 24 weeks

PC – palliative care; QoL – quality of life; SPC – specialized palliative care.

The first RCT on SPC was published in the Lancet in 2000 by Jordhøy et al. [70]. This Norwegian randomized trial studied patients (n=395) with advanced cancers and an expected survival of 2–9 months. Patients randomized to the active group maintained regular consultations with their community healthcare professionals, but they also had access to a multidisciplinary PC team that coordinated their care, remained available to offer advice, and could participate in home visits. Patients in the control group received conventional oncological care without any contact with the PC team. The main outcomes were differences in place of death (home, nursing home, or hospital) and time spent in different levels of care in the last month of life. Patients in the active group were more likely to die at home (25% vs. 15%) and spent less time in nursing homes in the last month of life compared to patients in the control group. Need for hospital care and number of hospital deaths were similar in the two groups.

In 2010, Temel et al. investigated patients with advanced non-small-cell lung carcinoma randomized to early integration of SPC or not at diagnosis, alongside oncological tumor-specific treatment [71]. The control group received a referral to SPC when deemed necessary. Patients randomized to early integration of SPC had a better QoL 12 weeks after randomization, received less aggressive EOL treatment (CHT within 14 days before death, no hospice care, or admission to hospice ≤3 days before death), and had an increased median OS (11.6 vs. 8.9 months) compared to patients assigned to the control group. This study was conducted in the ambulatory setting; patients had to attend a highly specialized institution to receive the SPC consultations, and hence their PS had to be good enough to allow them to travel to this tertiary care center.

In 2014, Zimmerman et al. explored the impact of early integration of SPC in the treatment of patients with a wide range of advanced cancers [45], using the ESAS [72] to assess symptom burden. Patients referred to early integration of PC had better symptom control after 4 months compared to the controls receiving standard care. Temel et al. also investigated differences in symptom control in their trial from 2010, in patients with advanced lung cancer. In the early palliative care group, 16% of the patients had depressive symptoms 12 weeks after randomization compared to 38% of patients in the control group [71].

Vanbutsele et al. randomized patients with advanced solid tumors within 12 weeks of diagnosis and with an estimated life expectancy of 12 months to early integration, or not, of SPC while tumor-specific treatment was given [73]. The control group received standard oncological treatment in a setting where all patients were offered multidisciplinary oncological care by medical specialists, psychologists, social workers, dieticians, and specialist nurses. Patients in the active group received home visits once a month from nurses specialized in SPC. In comparison to the control group, the active

group had a better QoL as assessed with the EORTC QLQ C30 questionnaire at 12 weeks after randomization.

However, some RCTs do not show improved QoL when SPC is integrated early. A Danish RCT (the DanPaCT trial) included patients with advanced cancer, who were randomized between early integration or not of SPC and standard oncological care [74]. This multicenter RCT involved 6 medical centers offering SPC to the active group, with home visits and inpatient consultations. Eight weeks after randomization, the trial showed no improvement in QoL for the active compared to the standard care group. The short follow-up time (8 weeks) and the heterogeneity of cancer diagnoses among the included patients might be reasons for the negative outcome of the study. In 2018, Scarpi et al. conducted a multicenter RCT in patients with advanced gastric cancer. Patients in the active group were referred early to a physician specialized in PC, whereas the control group did not have any appointments with a PC physician unless such contact was requested by the patients, their families, or the treating oncology specialist. Patients randomized to the early referral to a PC specialist had structured meetings with the physician every 2–4 weeks until death. The study revealed no statistically significant differences in QoL between the groups [75].

In 2019, Franciosi et al. reported on a multicenter RCT for patients with advanced cancer comparing the addition of early PC delivered by a specialized physician and nurse with standard oncology care alone; the results demonstrated no significant difference in QoL [76]. The PALINT trial included patients with advanced cancer receiving early integration of SPC with a low-intensity follow-up program with the PC team every 6–8 weeks, while the control group received standard care. No differences in QoL were found between the study groups at 3 and 6 months [77]. Eychmüller et al. found no significant improvement in QoL measured at 2, 4, and 6 months following randomization to a single early consultation with an SPC team compared to standard care in patients with advanced cancer [78].

1.3. Palliative chemotherapy and therapeutic considerations in gastrointestinal cancers.

Gastrointestinal cancers encompass a group of malignancies affecting the digestive system, including the esophagus, stomach, liver, pancreas, biliary tract, colon, rectum, and anus [79]. Despite advances in early detection and treatment options, many patients present with advanced disease at the time of diagnosis, leading to limited curative options and a poor prognosis [80]. Palliative chemotherapy focuses on controlling disease progression and managing associated symptoms such as pain, nausea, and obstruction. By employing cytotoxic drugs (mainly 5FU, irinotecan, taxanes, gemcitabine, and platins) and targeted agents as antibodies against EGFR and VEGF, palliative treatments aim to induce tumor regression, alleviate symptoms, and enhance patients' overall well-being; in other words, the aim is to improve QoL [81].

The overall survival (OS) for patients with pancreatic cancers, considering all stages and all treatments, is 4.6 months [82]. For the minority of patients where macroscopically radical surgery and adjuvant medical treatment is an option, a median OS of 28 months is reported [83]. The decision to initiate palliative chemotherapy must be weighed against potentially serious side effects. Negative prognostic factors, such as a PS of 2 or more, and a high burden of comorbidities can be contraindications for chemotherapy.

For patients with advanced pancreatic cancer, with tumor progress or lack of tolerance on first line (FL) palliative CHT, second line (SL) CHT treatment can be offered. Here, poor PS and comorbidities are even more important to consider in balancing disease control and side effects. Various studies have reported median OS from the start of SL treatment to death ranging from 4.8 to 8.8 months [84-86]. However, the survival advantage of SL treatments remains uncertain, as clinical trials have not consistently demonstrated prolonged OS from any specific SL CHT regimen [87, 88]. Gill et al. observed no survival improvement among patients treated with oxaliplatin plus fluorouracil compared to those receiving fluorouracil monotherapy following progression on FL gemcitabine treatment [89]. Conversely, Oettle et al. found improved OS following disease progression on gemcitabine-based FL treatment among patients with advanced pancreatic cancer [90]. The increased OS was found in patients treated with oxaliplatin plus fluorouracil as SL therapy compared to those who received fluorouracil alone. Similarly, Dadi et al. found that patients with metastatic pancreatic cancer who received SL therapy based on nab-paclitaxel demonstrated improved OS

compared to those treated with a non-nab-paclitaxel regimen [91]. This effect was seen subsequent to FL treatment with gemcitabine in monotherapy.

In colorectal cancers, the 5-year OS of 69% [83] by far exceeds that of pancreatic cancer. Local treatments such as ablative treatment including surgery, stereotactic radiotherapy, and radiofrequency treatments of metastatic lesions have contributed to increased survival time for patients with metastasized disease, though this has been shown only for patients with a low number of metastases. Approximately 50–70% of patients with metastatic colorectal cancer undergo SL CHT treatment [92, 93]. A meta-analysis of patients with metastatic colorectal cancer showed an OS of just over 20 months measured from diagnosis [94].

The OS for metastatic esophageal cancer is poor, with a 5-year survival rate of less than 5% [95]. In terms of efficacy, the benefit of combination CHT compared to monotherapy is only marginal, with the increase in duration of disease control and survival typically spanning from weeks to a few months. Numerous studies have demonstrated that monotherapy with paclitaxel or docetaxel for patients with advanced esophageal cancer resulted in response rates ranging from 15% to 24% [96, 97].

Regarding hepatobiliary cancer, there are only a few hepatocellular and biliary cancer treatment options for non-resectable and metastasized cases, and the prognosis is dismal. For these patients, as for patients with GI cancers as a whole, new possibilities have been introduced with immunotherapy agents such as PD 1 and PD L1 inhibitors, although response rates are low [98]. The median OS for patients with advanced biliary tract cancer not receiving tumor-directed therapy is poor, ranging from 2.5 to 4.5 months [99]. Advanced gastric cancer is also associated with a dismal prognosis, with a median OS of about 12 months for those receiving combination CHT and 4 months for those not treated with any tumor-directed therapy [100].

2. Aims of the thesis

The aim of this thesis was to examine the impact of home-based SPC integrated with oncological treatment on QoL, hospitalizations, time between last CHT and death, emergency care utilization, survival, and place of death for patients with advanced GI cancers. Another aim was to evaluate prognostic factors in patients with pancreatic cancer, with special reference to SL palliative CHT.

3. Material and methods

3.2. Articles I and II

Shared features of Articles I and II

Articles I and II both describe retrospective studies of medical records. The studies encompassed patients with histopathologically confirmed pancreatic adenocarcinoma (ICD codes: C25.0–C25.3, C25.7–C25.9) who underwent palliative CHT at the Department of Oncology, Skåne University Hospital, and died during the study period (1 February 2015 to 31 December 2017). A combined cohort of 170 patients with advanced pancreatic cancer treated with palliative CHT was analyzed across the two retrospective studies.

Article I

Patient data, including age, gender, date of diagnosis, and the extent of the disease (local or generalized) at the initial visit to the oncology department and upon tumor progression during FL palliative CHT, were retrieved from the patient's medical record. Additionally, the date of death was recorded. In patients with generalized disease, the number of metastatic sites was assessed, where distant lymph nodes, liver, lungs, skeletal or "other" sites were regarded as different metastatic sites, and survival was analyzed according to 1 or >1 metastatic site. Primary surgery was documented as microscopically radical (R0), macroscopically radical (R1), or not radical (R2).

Data regarding the CHT regimens, the number of treatment cycles of each regimen, the number of lines of palliative CHT, and the day of the last CHT treatment were collected. To qualify as a genuinely adjuvant treatment, the patient had to exhibit no signs of disease at the therapy assessment CT conducted 24 weeks after the last adjuvant treatment. If there was evidence of disease within these 24 weeks, the given treatment was reclassified as FL palliative CHT instead.

Laboratory data were collected on carbohydrate antigen 19-9 (CA 19-9) (U/mL), bilirubin (μmol/L), PS (0–4), serum albumin (g/L), and patient weight (kilograms) at the start of FL palliative CT and at the time of verified radiological progression on that treatment. Upon analysis, albumin was dichotomized as normal if ≥36 g/L and hypoalbuminemia if lower. Furthermore, CA 19-9 was dichotomized as doubled or not, including only values paired with bilirubin in the normal reference interval (<26 μmol/L). Patients were classified into three weight groups based on the percentage of

weight loss: <5%, 5% to <10%, and ≥10%, measured from initiation to completion of FL palliative therapy. Time to progression following FL CHT (in days) was recorded and then dichotomized to ≥100 versus <100 days. Response to treatment was generally evaluated 3 months after initiating therapy with a CT scan.

The aim of Article I was to examine clinical characteristics in patients with advanced pancreatic cancer undergoing palliative CHT, evaluating prognostic factors and survival, with special reference to SL therapy.

3.2.1. Statistics

Given their skewed distribution, descriptive statistics were expressed as median and range for continuous variables and as number (%) for categorical variables. Survival analysis using Kaplan-Meier curves was employed to assess survival over time both in the entire study population and in subgroups. The OS time was defined as the duration between diagnosis and death. Overall survival following SL palliative CHT was measured from the initiation of treatment to death, including only those patients commencing SL treatment due to disease progression on FL palliative CHT and excluding those initiating SL therapy due to toxicity on FL treatment. The log-rank test was applied to examine differences in survival between groups receiving SL palliative CHT.

Article II

Age, gender, date of diagnosis, PS (0–4) at the start of palliative CHT, date of enrollment in PC, and date and place of death were extracted from the records. Overall survival was calculated from the date of pancreatic cancer diagnosis. The extent of the disease, whether localized, generalized, or postoperatively without evidence of remaining tumor, was recorded at the initial visit to the oncologist.

Information was gathered on the frequency of emergency department visits, number of hospitalizations, and the duration of inpatient care in days. If an emergency department visit led to inpatient care, the emergency department visit was not noted as a separate emergency department visit. For patients enrolled in SPC, the duration of their inpatient stay within PC facilities was not categorized as hospitalization, as this in many cases was respite care. Additionally, the date of the final CHT treatment before the date of death was recorded.

The length of time enrolled in SPC was recorded. Patients enrolled for more than 30 days before the date of death were assigned to group A, and those enrolled for 30 days or less (including patients never enrolled in SPC) were assigned to group B.

Statistics

Descriptive statistics were calculated as medians and ranges for continuous variables (due to skewed distribution) and percentages for categorical variables. Kaplan–Meier curves were used to assess OS (defined as time between diagnosis and death) and proximity of CHT treatment to death. [101]. The dataset was stratified into groups A (enrolled in SPC for over 30 days) and B (enrolled for 30 days or less) for analyzing emergency ward visits, inpatient care days, and the interval between the last CHT treatment and death. Place of death was categorized as home, hospital, palliative care ward, or assisted living, with the dataset further subdivided into two new groups for analysis based on admission times in SPC.

3.3. Article III and Manuscript IV

Shared features of Article III and Manuscript IV

Article III and Manuscript IV were based on a prospective RCT known as the ALLAN trial (Swedish acronym for "tidig pALLiativ ANslutning"). Participants were recruited between 18 December 2014 and 29 April 2021 at a tertiary cancer center in the southern Swedish healthcare region. Inclusion required patients to reside within the catchment area of the two primary SPC units, encompassing a population of 0.5 million residents. The final follow-up date for the study was 1 March 2023.

Patients with upper GI cancers (esophageal, gastric, hepatobiliary, and pancreatic cancer) eligible for FL palliative CHT and patients with lower GI cancer (colorectal cancer) eligible for SL palliative CHT were recruited. As patients with colorectal cancer became eligible for SL treatment, they were invited to participate in the study with the anticipation that their survival outcomes would align with those of patients diagnosed with upper GI cancers. Patients accepted were randomized 1:1 to either intervention with early integration of home-based SPC alongside tumor-specific treatment, or tumor-specific treatment alone. Patients assigned to the active arm had scheduled meetings with the SPC team at home within 6 weeks of randomization, followed by at least monthly consultations. In contrast, patients in the control group were not planned for meetings with the SPC team unless specifically referred by the treating oncologist. They remained in the control group for the entirety of the analysis, regardless of whether and when they were eventually referred to SPC. Informed consent was obtained from all participating patients.

Inclusion criteria

The patient-cohort in Article III and Manuscript IV comprised ambulatory adults (>18 years) diagnosed with advanced GI cancer that was confirmed through histological verification. Individuals eligible for palliative CHT as part of their FL treatment for upper GI cancer were invited to join the study. Likewise, those with histologically confirmed advanced lower GI cancers were eligible for enrollment when they became eligible for SL palliative CHT.

Exclusion criteria

Patients with ongoing palliative CHT at randomization (except those with lower GI cancer) were excluded, as were patients already included in SPC. Moreover, patients with neuroendocrine tumors were excluded.

Intervention

The active study group received outpatient tumor-directed treatment at the oncology department and home evaluations by an SPC physician together with a palliative care nurse within 6 weeks of randomization. A multidisciplinary team of dieticians, occupational therapists, counselors, and physiotherapists provided additional support, including home care and the option for inpatient care at the SPC ward if needed. The SPC team delivered advanced homecare services, and an assessment guided by a structured study report was conducted every 6 weeks, covering prognosis, symptom control, anti-tumoral treatment, patients' awareness of their incurable disease, and their ability to live a satisfactory life. During these visits, the IPOS was used for systematic symptom assessment.

In contrast, patients in the control group received tumor-specific therapy and were referred to the SPC team at the discretion of the treating oncologist.

Article III

The aim of Article III was to evaluate the impact of early integration of home-based SPC alongside tumor-specific treatment on QoL assessed at 6, 12, and 24 weeks, as well as at the last evaluation before death, following randomization in the ALLAN trial for patients with GI cancers undergoing FL palliative CHT (esophageal, gastric, hepatobiliary, and pancreatic cancer) or SL CHT (colorectal cancer).

Baseline questionnaires (FACT-G and HADS) were completed by the participants immediately post-randomization, with follow-up assessments conducted every 6±1 weeks until the patient's passing.

Demographic data, including age, gender, diagnosis, enrollment date in SPC, and CHT use, were recorded and extracted from medical records along with PS at the time

of inclusion and the number of contacts, homecare visits, and telephone contacts with the SPC team.

Statistics

To detect a significant difference of 6 points on the FACT-G scale between the active and control groups, each with a standard deviation of 11, a sample size of 108 patients was estimated for 80% power at a 5% significance level. To account for potential dropouts and incorrectly included patients, a total of 124 patients were enrolled in the trial. Patient characteristics at randomization were summarized using absolute and relative frequencies for categorical variables, mean with standard deviation for normally distributed continuous variables, and median with range for non-normal variables.

Differences in FACT-G and HADS scores between the two groups at baseline were evaluated using Welch's t-test. Mean changes in FACT-G, HADS-A, and HADS-D from baseline to weeks 6, 12, 24, and the last assessment were computed and compared using Welch's t-test. The Bonferroni correction was applied to adjust p-values for multiple comparisons. All analyses were conducted on an intention-to-treat basis. Median OS was estimated using the Kaplan-Meier method, with patients alive at the last follow-up (1 March 2023) being censored on that date. Survival in the two arms was compared using a log-rank test.

Manuscript IV

Manuscript IV was also based on the ALLAN cohort of patients. The endpoints of this controlled RCT were differences between the active and control groups in emergency care utilization, place of death, and time between the last palliative CHT treatment and death.

Medical records were analyzed for data on the frequency of emergency department visits, hospitalizations, and the duration of inpatient care in days. Notably, for patients enrolled in SPC, the days spent in the palliative care ward were not categorized as hospital care and therefore were not included in the count. Demographic data as age, gender, cancer diagnosis, enrollment date in SPC, place of death, amount of, and last date of palliative CHT were recorded. Furthermore, data on PS at the time of inclusion and the number of contacts, homecare visits and telephone calls with SPC were extracted from patients' medical records.

The aim was to assess how early integration of home-based SPC alongside tumor-specific treatment influences emergency care utilization, number of hospitalizations and length of in-patient care, place of death, and the time from the last palliative CHT

treatment to death in patients with GI cancers undergoing either FL (esophageal, gastric, hepatobiliary, and pancreatic cancer) or SL CHT (colorectal cancer).

Statistics

Numerical data were expressed as medians and ranges, while categorical data were expressed as absolute numbers and percentages. Emergency healthcare usage was compared between the two groups using the Mann-Whitney U test, and boxplots were generated to display the results. The median OS, calculated from the date of inclusion to the last chemotherapy treatment, was estimated using the Kaplan-Meier method. Patients who were alive at the last follow-up (1 March 2023) were censored at that time. Survival rates between the two groups were compared using the log-rank test. The proportion of patients receiving palliative chemotherapy within 30 days before death was compared using the chi-squared test. All statistical analyses were conducted using version 4.2.2 of R.

3.4. Ethical considerations

3.4.1. Articles I and II

Ethical approval for these two retrospective studies was received from the Swedish National Ethics Committee (ref: 2019-01093). No new data were sought beyond the existing data in medical records, and except for the intrusion in these records nothing that could compromise the deceased patients would be brought up. All data was pseudonymized prior to the analysis, with the key held only by the main responsible researcher. Due to the retrospective design and the fact that all patients were already deceased at the time of inclusion, the ethical committee accepted the trial without discussion at one of their meetings. In short, they saw no ethical issues with our retrospective trial.

3.4.2. Article III and Manuscript IV

The ethical dilemma inherent in clinical trials stems from the inequity between individuals who stand to gain from the trial results and those who bear the responsibilities and potential adverse effects associated with participating in the trial [102]. The research subject of early introduction of SPC is relatively new, with previous studies showing promising results in terms of increasing QoL while decreasing futile CHT use close to death [103]. Our intervention, which comprised early integration of

SPC, gave the patients access to SPC, not as a novel treatment but as an existing multi-professional care, albeit introduced early in the disease trajectory in the present study. The participants, therefore, had no risk of receiving any harmful treatment; however, they still were burdened with issues related to being part of an RCT, such as filling out self-reported questionnaires, the intrusion calls from research nurses, and the extra home visits in accordance with the research protocol.

The ALLAN trial was approved by the Swedish National Ethics Committee (2014-03-18, ref: 2014/118). All patients included in this RCT provided their signed informed consent. A total of six patients, all in the control group, later withdrew consent and were only included in analyses until the date of withdrawal. However, they were included in the survival analysis. Our prospective RCT had several ethical aspects that merited consideration. For example, patients eligible for inclusion had to be informed about their incurable disease and their possible future need for PC on their first visit to the oncologist. Information about having an incurable disease is not always easy to deal with, and may cause distress to the patient. In addition, both patients and healthcare professionals commonly misinterpret PC as EOL care. One can argue that this communication about the palliative situation is truthful and gives patients and families the opportunity to adapt to this reality to make way for advanced care planning and personal arrangements.

4. Results

4.1. Article I

A cohort of 170 patients diagnosed with advanced pancreatic cancer who received palliative CHT at the Department of Oncology, Skåne University Hospital was enrolled in the trial. The median age of these patients was 68 years (range 37–85), and they comprised 90 women and 80 men. Additional patient characteristics are detailed in Table 3. Progression-free survival was ≥100 days in 102 (60%) of the 170 patients on FL treatment, who were then regarded as responders to FL palliative CHT.

Table 3. Characteristics of the patients in Article I at the first visit to the oncology department and at the start of second-line (SL) treatment after the progression of first line (FL) palliative chemotherapy.

Patients' characteristics at first oncology visit	**Number of patients (%)**
Age, median [min–max]	**68 [37–85]**
Gender	
Male	80 (47)
Female	90 (53)
Performance status	
0	85 (50.0)
1	70 (41)
2	15 (9)
Extent of disease at start of chemotherapy	
Metastatic	91 (54)
Locally advanced	55 (32)
Postoperative, no macroscopic disease	24 (14)
Pathology report in operated patients (n=30) [a]	
R0	12 (7)
R1	14 (8)
R2	4 (2)
FL chemotherapy [b]	
FLOX	2 (1)
FOLFIRINOX	59 (35)
GEM	88 (52)
GEM/ABRAX	7 (4)
GEM/CAP	14 (8)
Received genuine adjuvant chemotherapy	
Yes	6 (4)

No	164 (96)
Progression-free survival on FL treatment <100 days ≥100 days	 68 (60) 102 (40)
Reasons for not receiving SL treatment Progressive disease and/or poor PS Death before radiological evaluation Toxicity	 61 (69) 14 (16) 13 (15)
Patients' characteristics at the start of second-line chemotherapy	Number of patients (%)
Age, median [min–max]	64 [37–81]
Gender Male Female	 36 (50) 36 (50)
Performance status 0 1 2 Missing value	 21 (29) 43 (60) 8 (11) 0 (0)
Hypoalbuminemia (<36 g/L) Yes No Missing value	 44 (61) 20 (28) 8 (11)
Weight loss <5% 5% to <10% ≥10% Missing value	 38 (53) 11 (15) 19 (26) 4 (6)
Doubled value of CA 19-9 Yes No Missing value/elevated bilirubin	 30 (42) 27 (37) 15 (21)
Extent of disease Locally advanced Metastatic	 9 (13) 63 (87)
Number of metastatic sites (n=63) 1 metastatic site >1 metastatic site	 32 (51) 31 (49)
Pathology report in operated patients [a] Surgery R0 R1 R2 No surgery	 17 (23) 6 (8) 8 (11) 3 (4) 55 (77)
Received genuine adjuvant chemotherapy Yes No	 2 (3) 70 (97)
First line chemotherapy [b] FOLFIRINOX GEM GEM/ABRAX	 35 (49) 26 (36) 2 (3)

GEM/CAP	9 (12)
Second-line chemotherapy [b]	
FLOX	9 (13)
FOLFIRINOX	6 (8)
GEM	19 (26)
GEM/ABRAX	22 (31)
Other	16 (22)

A total of 170 patients started FL palliative chemotherapy, and 72 (42%) patients started SL treatment after progression on FL treatment. Of the 24 patients who started postoperative adjuvant chemotherapy, 6 (25%) were disease-free at the follow-up CT performed 24 weeks after the last (genuine) adjuvant treatment.

[a] R0 – resection with clear margins ; R1 – no clear margins, microscopic residual tumor; R2 – macroscopic residual tumor.

[b] FOLFIRINOX – oxaliplatin, irinotecan, leucovorin, and fluorouracil; FLOX – 5-fluorouracil, oxaliplatin, and leucovorin; GEM – gemcitabine; GEM/ABRAX – gemcitabine and albumin-bound paclitaxel; GEM/CAP – gemcitabine and capecitabine; Nab-Paclitaxel – albumin-bound paclitaxel.

[c] Distant lymph nodes, liver, lungs, skeletal, or "other" sites were regarded as different metastatic sites.

Second-line palliative chemotherapy

Second-line palliative CHT was initiated in 82 patients (48%) following progression (n=72) or side effects (n=10) during FL treatment (Figure 3). The median number of treatment cycles administered in SL therapy was 3 (range: 1–15).

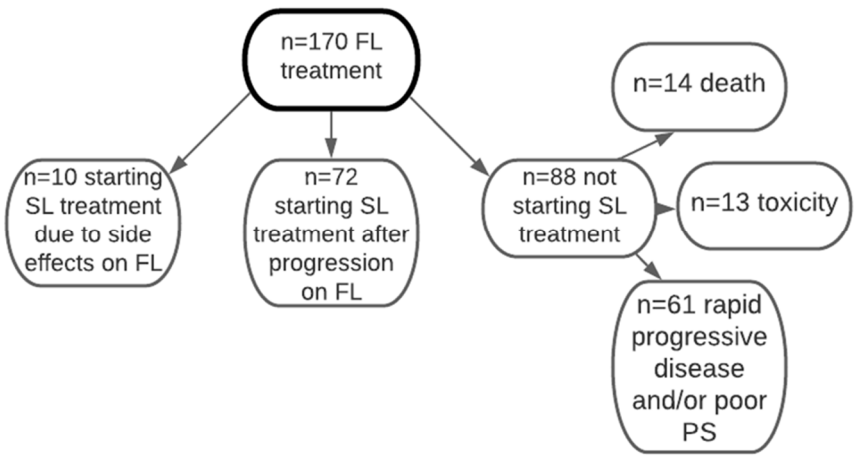

Figure 3. Flowchart of all patients starting first line (FL) chemotherapy. PS – performance status; SL – second-line.

Overall survival

The median OS for the study cohort (n=170) was 11 months (95% CI: 9.2–12).

Time between end of chemotherapy and death

The median duration from the final CHT treatment to death in the whole study cohort was 57 days (range: 3–340), with seven outliers living for ≥200 days (Figure 4). Chemotherapy was administered within the last month of life for 33 patients (19%) and within the last 14 days of life for 12 patients (7%). No discernible differences in age (<60 years vs. ≥60 years) or gender were observed between patients who received CHT within a month before death and those who did not.

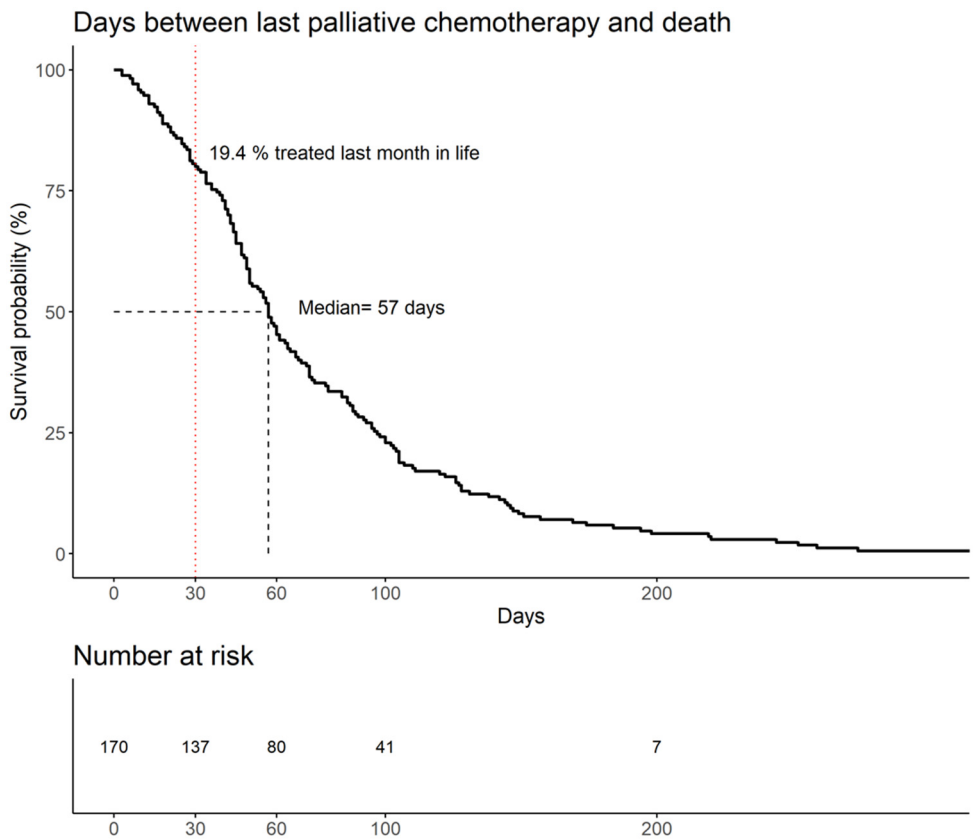

Figure 4. Kaplan-Meier curve for palliative chemotherapy in the last 30 days of life.

Survival following second-line treatment

The median OS from the initiation of SL treatment was 5.0 months (95% CI: 4.0–6.1). Patients with locally advanced disease exhibited significantly longer survival compared to those with metastatic disease, with OS of 9.6 months (range: 2.9–20.2) and 4.8 months (95% CI: 3.4–7.3), respectively (p=0.03). The number of metastatic sites did not impact OS; patients with a single location had a median OS of 4.6 months (95% CI: 3.6–7.3), while those with multiple locations had a median OS of 4.9 months (95% CI: 3.4–6.1).

Association between patient-specific data and survival

In univariate analysis, patients with hypoalbuminemia (n=44) at the initiation of SL therapy exhibited a median OS of 3.5 months (95% CI: 3.0–5.4), whereas those with normal albumin levels (n=20) had a median OS of 8.0 months (95% CI: 5.3–11.1) (p=0.009; Figure 5). Furthermore, patients with a PS of 2 (n=8) before starting SL therapy had a median OS of 2.9 months (range: 0.4–9.5), contrasting with 5.3 months for patients with PS 0 (95% CI: 3.5–11.1) and PS 1 (95% CI: 4.0–7.6) (p=0.03; see Figure 6).

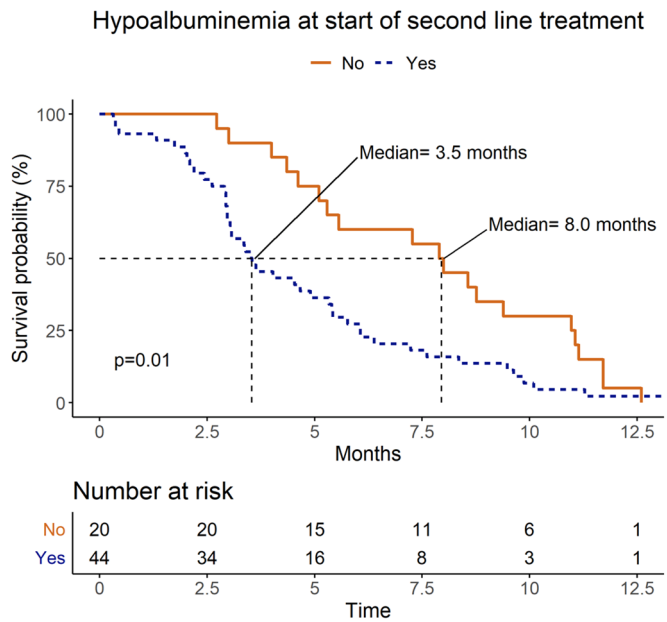

Figure 5. Kaplan-Meier curve comparing patients with and without hypoalbuminemia (albumin <36 g/L) at the start of second-line chemotherapy.

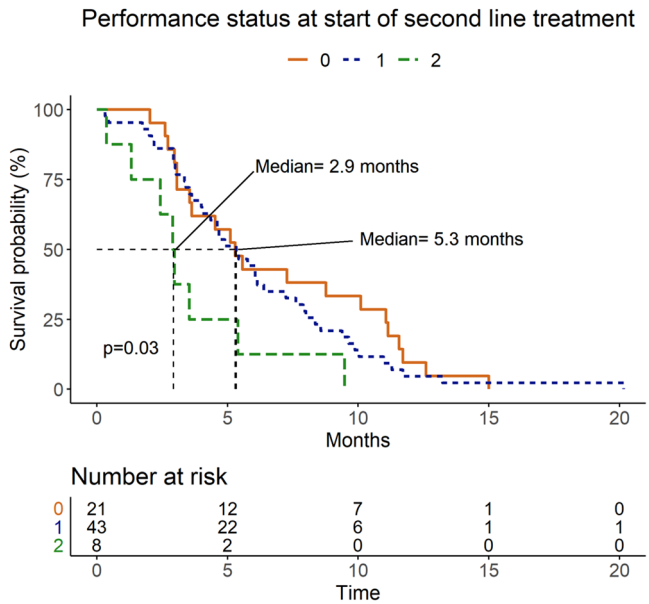

Figure 6. Kaplan-Meier curve for overall survival in terms of performance status at the start of second-line chemotherapy.

No association was found between the length of progression-free survival following FL therapy and the median OS after SL treatment. Weight loss during FL therapy was not significantly linked to OS, with patients experiencing weight loss of <5%, 5% to <10%, and ≥10% exhibiting median survival times of 5.5, 5.3, and 4.0 months, respectively (p=0.5). Similarly, there was no noticeable association between survival and the presence or absence of doubling CA 19-9 after FL therapy; the median OS was 6.6 months among patients with doubling CA 19-9 and 3.6 months among those without (p=0.4).

4.2. Article II

The patient cohort in Article II was the same as in Article I; the median age was 68 years (range: 37–85), and 53% (n=90) were women. Additional patient characteristics are detailed in Table 3 and Table 4.

Table 4. Characteristics of the patients in Article II.

Variable	Admitted to palliative care for >30 days, n=97	Admitted to palliative care for ≤30 days, n=73
Overall survival in months, median (95% confidence interval)	11.2 (8.6–14.2)	10.9 (8.3–12.0)
Days enrolled in specialized palliative care, median [min, max]	84.0 [31, 675]	13.5 [0, 30] [a]
Gender, n (%) Male Female	 38 (39.2%) 59 (60.8%)	 42 (57.5%) 31 (42.5%)
Age [b], median [min–max]	67.0 [37–85]	70.0 [45–83]
Extent of disease b, n (%) Metastatic Locally advanced Radically resected (no macroscopic disease) [c]	 58 (59.8%) 30 (30.9%) 9 (9.3%)	 33 (45.2%) 25 (34.2%) 15 (20.6%)
Performance status at the start of chemotherapy [b], n (%) 0 1 2	 46 (47.4%) 43 (44.3%) 8 (8.3%)	 39 (53.4%) 27 (37.0%) 7 (9.6%)

[a] Patients never admitted to specialized palliative care were excluded from this analysis.
[b] Age, extent of disease, and performance status were collected at the first visit to the oncological department.
[c] These patients were evaluated for adjuvant chemotherapy.

Of the 170 patients, 151 (89%) were enrolled in SPC, with 97 (57% of 170) enrolled for more than 30 days (group A). Group B (n=73) consisted of 54 patients enrolled in SPC for 30 days or less and the 19 patients who were never enrolled. There was no significant difference in age (over vs. under 65 years) between patients enrolled in SPC or not. The median time of enrollment in SPC before death was 84 days in group A and 13.5 days in group B, excluding the 19 patients who were never enrolled (see Table 4).

Patients in group A lived a median of 73 days (95% CI: 59–89) after the last palliative CHT treatment, whereas patients in group B lived for a median of 44 days (95% CI: 41–55) ($p<0.001$). Among patients in group A, 12% (n=12) received palliative CHT within the last 30 days of life, and 2% (n=2) received it within the last 14 days. In contrast, in group B, 30% (n=21) received palliative CHT within the last 30 days of life, and 14% (n=10) received it within the last 14 days (see Figure 7).

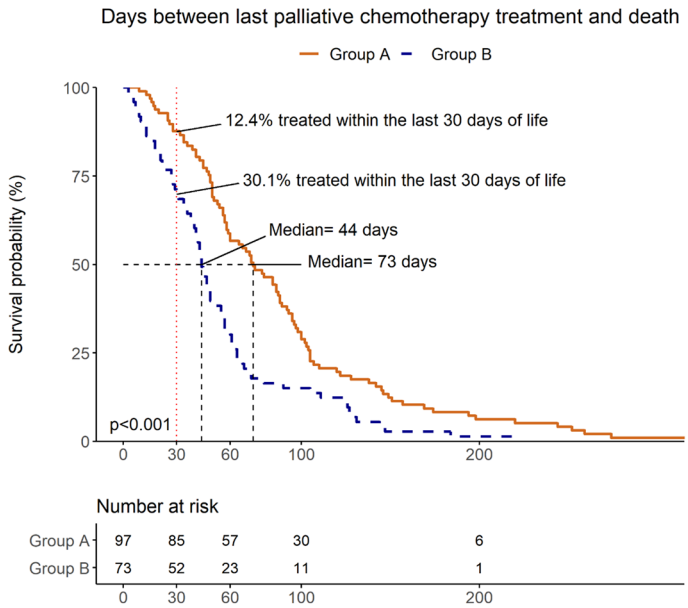

Figure 7. Kaplan-Meier curve for chemotherapy in the last 30 days of life.

Patients in group A had a median of two visits to the emergency department (range: 0–9), one hospitalization episode (range: 0–6), and 8 days of inpatient care (range: 0–70). In contrast, patients in group B had a median of one visit to the emergency department (range: 0–15), two hospitalization episodes (range: 1–10), and 17 days of inpatient care (range: 8–93).

Of the 19 patients not referred to SPC, one died at home (5%), 16 died in the hospital (84%), and two (11%) died within an assisted living facility. Of the 151 patients enrolled in SPC, 72 (48%) died at home, three (2%) died in the hospital, 75 (50%) died within the inpatient SPC ward, and one died within an assisted living facility.

Median OS was 11 months (95% CI: 9.2–12) in the entire study group, 11.2 months (95% CI: 8.6–14.2) in group A, 10.9 months (95% CI: 8.3–12.0) in group B, and 10.0 months (95% CI: 7.6–17.7) among the 19 patients never enrolled in SPC.

4.3. Article III and Manuscript IV

Initially, 124 patients were considered for inclusion. However, six were excluded for various reasons: two did not meet the inclusion criteria, one met an exclusion criterion,

one withdrew consent shortly after randomization, one refused randomization to the control group, and one did not sign the informed consent form. Subsequently, 118 patients were randomized, comprising 55 women with a median age of 70 years (range: 45–83) and 63 men with a median age of 74 years (range: 49–85). Six additional patients later withdrew their consent and were only included in the survival analysis. Baseline PS was as follows: PS 0 in 18 (30%) and 26 (45%) patients, PS 1 in 28 (47%) and 21 (36%) patients, and PS 2 in 14 (23%) and 11 (19%) patients in the active study group (n=60) and control group (n=58), respectively. For additional data see Table 5.

Table 5. Baseline characteristics of the patients in Article III and Manuscript IV, including specialized palliative care use and overall survival.

Variable	Whole study cohort (n=118)	Active group (n=60)	Control group (n=58)
Age, median [min–max]	71.5 [45–85]	71 [51–83]	72 [45–85]
Female gender, n (%)	55 (46.6)	24 (40.0)	31 (53.4)
Cancer diagnosis, n (%)			
Pancreatic	66 (55.9)	35 (58.3)	31 (53.4)
Hepatobiliary	25 (21.2)	11 (18.3)	14 (24.1)
Gastric	11 (9.3)	7 (11.7)	4 (6.9)
Colorectal	9 (7.6)	4 (6.7)	5 (8.6)
Esophageal	7 (5.9)	3 (5.0)	4 (6.9)
Performance status, n (%) [a]			
0	44 (37.3)	18 (30.0)	26 (44.8)
1	49 (41.5)	28 (46.7)	21 (36.2)
2	25 (21.2)	14 (23.3)	11 (19.0)
Palliative CHT lines, n (%) [b]	(n=112)	(n=60)	(n=52)
0	2 (1.8)	1 (1.7)	1 (1.9)
1	66 (58.9)	34 (56.7)	32 (61.5)
2	27 (24.1)	14 (23.3)	13 (25.0)
3	17 (15.2)	11 (18.3)	6 (11.5)
Anticancer therapy, n (%) [c]	(n=110)	(n=59)	(n=51)
Nab-paclitaxel/gemcitabine	25 (22.7)	14 (23.7)	11 (21.6)
FOLFIRINOX	24 (21.8)	12 (20.3)	12 (23.5)
Gemcitabine	24 (21.8)	13 (22.0)	11 (21.6)
Combination CHT	14 (12.7)	8 (13.6)	6 (11.8)
FOLFOX	12 (10.9)	8 (13.6)	4 (7.8)
GEMOX	8 (7.3)	2 (3.4)	6 (11.8)
Single-agent CHT	3 (2.7)	2(3.4)	1 (2.0)
Number of CHT cycles, median [range]	6.0 [0.0, 34.0]	6.0 [0.0, 34.0]	6.0 [0.0, 33.0]
	(n=118)	(n=60)	(n=58)

Baseline FACT-G, mean (SD) [d]	71.3 (14.8)	70.2 (14.9)	72.4 (14.9)
Baseline HADS-A, mean (SD) [e]	5.8 (3.8)	5.1 (3.4)	6.5 (4.0)
Baseline HADS-A, n (%)			
Normal (0–7)	80 (71.4)	43 (76.8)	37 (66.1)
Mild (8–10)	17 (15.2)	8 (14.3)	9 (16.1)
Moderate/severe (11–21)	15 (13.4)	5 (8.9)	10 (17.9)
Baseline HADS-D, mean (SD)	6.2 (2.8)	6.0 (2.7)	6.4 (2.9)
Baseline HADS-D, n (%)			
Normal (0–7)	82 (73.2)	43 (76.8)	39 (69.6)
Mild (8–10)	19 (17.0)	9 (16.1)	10 (17.9)
Moderate/severe (11–21)	11 (9.8)	4 (7.1)	7 (12.5)
Days enrolled in SPC, median [range]		167 [4, 987]	39 [0, 1152]
Assessments by SPC, median [range]			
Physician		10 [1, 34]	2 [0, 24]
Nurse		36 [0, 330]	13 [0, 210]
Telephone		22 [0, 79]	4 [0, 135]
Survival in months, median (95% CI)	7.6 (6.0–10.2)	6.6 (4.9–10.7)	8.7 (6.5–12.2)

FOLFIRINOX – oxaliplatin, irinotecan, leucovorin, and fluorouracil; FOLFOX – 5-fluorouracil, oxaliplatin, and leucovorin; GEMOX – gemcitabine and oxaliplatin; Nab-paclitaxel – albumin-bound paclitaxel.
[a] WHO performance status of 0 indicates that the patient is asymptomatic, 1 that the patient is symptomatic but fully ambulatory, and 2 that the patient is symptomatic and in bed less than 50% of the day.
[b] Six patients withdrew consent and are excluded from this analysis.
[c] Two patients did not start palliative chemotherapy, and six patients withdrew consent and are excluded from this analysis.
[d] Quality of life (QoL) was evaluated with the Functional Assessment of Cancer Therapy-General (FACT-G) questionnaire, measuring health-related QoL in four dimensions according to physical, functional, emotional, and social well-being over the past week. The total FACT-G score ranges from 0 to 108 points, with a higher score indicating better QoL.
[e] Mood was assessed with the Hospital Anxiety and Depression Scale (HADS). The patient-reported HADS questionnaire has two subscales of seven items each, screening for anxiety (HADS-A) and depression (HADS-D). Subscale scores range from 0, indicating no distress, to 21, indicating maximum distress. A score of 7 or lower on either HADS subscale is considered to be normal; 8–10 points indicate mild distress, and 11–21 points indicate moderate to severe distress.

The cancer diagnoses were evenly distributed between the two patient groups, see Table 5.

Quality of life

The baseline total scoring of FACT-G at randomization did not show any significant difference between the study groups. At weeks 6, 12, 24, and the last assessment before death, there were 108, 97, 68, and 112 patients alive, respectively, with corresponding response rates on the FACT-G questionnaire of 91.7%, 86.6%, 79.4%, and 60.7%, respectively.

When examining the mean total change in FACT-G score compared to baseline, the difference in this change between patients assigned to early integration of SPC and controls was 5.2 points (95% CI: -0.1–10.5, p=0.216) at week 6, 6.7 points (95% CI: 0.2–13.3, p=0.172) at week 12, and 13 points (95% CI: 5.7–20.2, p=0.004) at week 24, with all numerical differences favoring the early-integration group. At the last assessment, which occurred a median of 4.1 weeks (range 0.4–6.7 weeks) before death, the difference between the two groups regarding the mean change in FACT-G score was 3 points (95% CI: -4–9.9, p=1.0) (Figure 8 and Table 6).

The mean total FACT-G scores in the active and control groups at weeks 0, 6, 12, and 24, and at the last assessment were 70.2 versus 72.4 points, 74.4 versus 71.5 points, 77.2 versus 73.2 points, 82.6 versus 72.4 points, and 65.9 versus 61.9 points, respectively.

Baseline HADS at randomization did not differ between the study groups. There were no statistically significant differences in mean change in HADS-A/HADS-D from baseline to any of the measurement points in weeks 6, 12, 24, and at the last assessment before death (Tables 4 and 5).

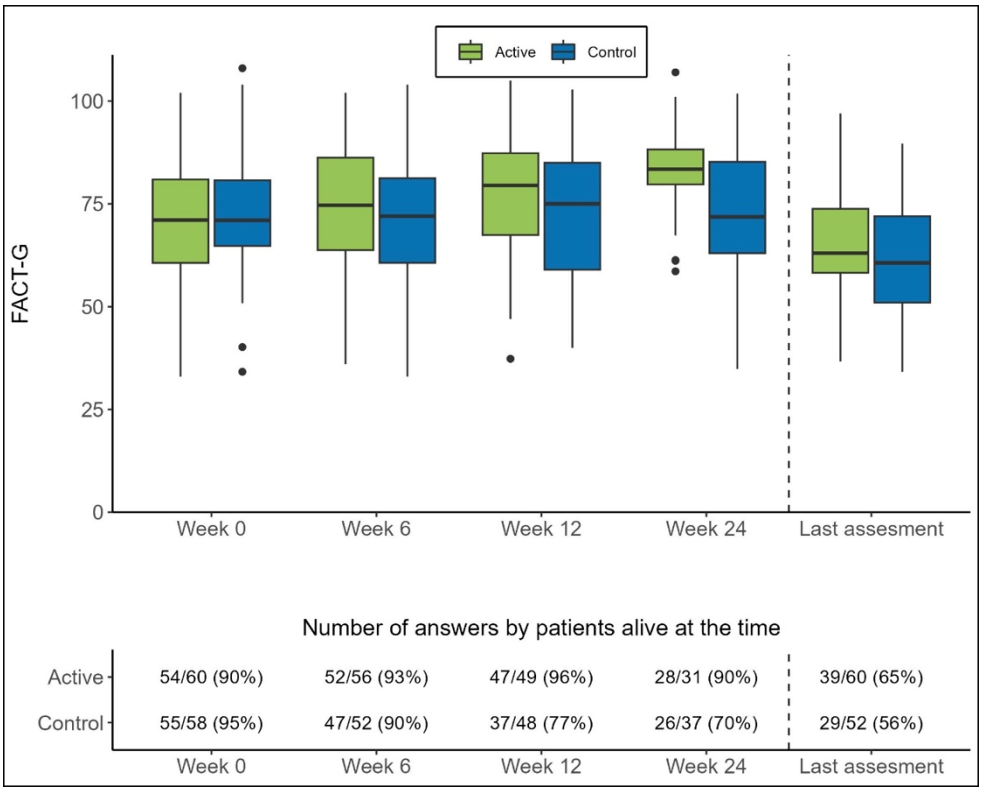

Figure 8. Boxplot of total FACT-G score in the active and control groups at baseline, weeks 6, 12, and 24, and the last assessment before death. The interquartile range covers 25%–75% of the patients at each measurement point, while the whiskers represent 1.5 times the interquartile range. Any markings outside these whiskers are considered outliers. The last assessment before death occurred a median of 4.1 weeks (range: 0.4–6.7 weeks) prior to death.

Table 6. Changes in Functional Assessment of Cancer Therapy-General (FACT-G) and Hospital Anxiety and Depression Scale (HADS) scores from baseline to weeks 6, 12, and 24, and the last assessment before death.

Outcome	Week	Mean change, active group	Mean change, control group	Difference (95% CI)	p-value
FACT-G	6	3.6	-1.5	5.2 (-0.1 – 10.5)	0.216
	12	5.9	-0.9	6.7 (0.2 – 13.3)	0.172
	24	10.8	-2.2	13 (5.7 – 20.2)	0.004
	Last	-6.7	-9.7	3 (-4 – 9.9)	1.000
HADS-A	6	-1.3	-0.5	-0.9 (-2.1 – 0.4)	0.728
	12	-0.7	-0.9	0.2 (-1.1 – 1.5)	1.000
	24	-1.4	-1.1	-0.3 (-2.6 – 1.9)	1.000
	Last	0.5	-0.3	0.8 (-1.1 – 2.7)	1.000
HADS-D	6	-0.3	0.2	-0.5 (-1.5 – 0.6)	1.000
	12	-0.3	0.3	-0.6 (-1.8 – 0.6)	1.000
	24	-0.8	0.4	-1.2 (-2.6 – 0.3)	0.472
	Last	2.0	0.7	1.4 (-0.4 – 3.2)	0.520

Bonferroni correction was used for each outcome to adjust the p-values for multiple comparisons, and so these values are already multiplied by four. The last assessment before death was made a median of 4.1 weeks (range: 0.4–6.7 weeks) before death.
The FACT-G questionnaire evaluates quality of life (QoL), with a higher score indicating better QoL.
The HADS questionnaire assesses mood on two subscales, one for anxiety (HADS-A) and one for depression (HADS-D). Scores range from 0, indicating no distress, to 21, indicating maximum distress.

Specialized palliative care

The median time of enrollment in SPC was 167 days (range: 4–987) in the active group and 39 days (range: 0–1152) in the control group. Among the 58 patients in the control group, 50 (86%) were referred to SPC at some point during the disease trajectory.

In terms of homecare visits, the active group had a median of 10 visits (range: 1–34) from an SPC team physician, 36 visits (range: 0–330) from an SPC nurse or other healthcare professional, and 22 telephone calls (range: 0–79) with any healthcare professional. In comparison, the control group had a median of 2 visits (range: 0–24) from an SPC team physician, 13 visits (range: 0–210) from an SPC nurse or other healthcare professional, and four telephone calls (range: 0–135) with any healthcare professional.

The active and control groups received a median of 6.0 cycles of palliative CHT (0–34 and 0–33, respectively) (Table 5).

Emergency ward visits and the need for inpatient hospital care

Patients in the active study group had a median of one visit to the emergency department (range 0–6) and a median of one hospitalization episode (range: 0–5), and stayed in the hospital for a median of 1.5 days (range: 0–30). In contrast, patients in the control group utilized significantly more emergency and inpatient hospital care. Specifically, patients in the control group had a median of three visits to the emergency department (range: 0–11) and a median of two hospitalization episodes (range: 0–8), and spent a median of 11.5 days in the hospital (range: 0–33) ($p<0.001$) (Figure 9).

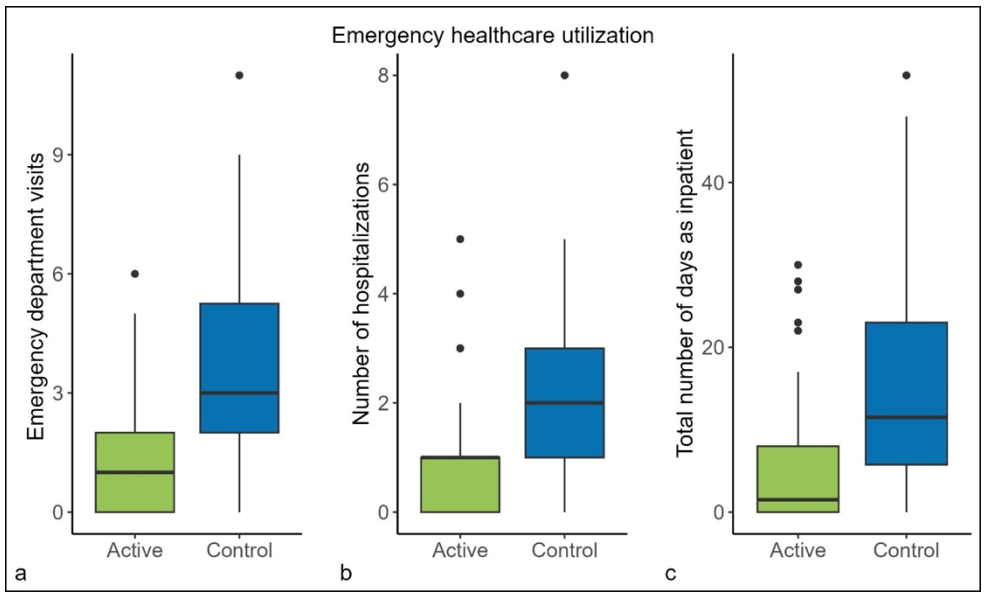

Figure 9. Boxplots showing emergency care use and inpatient care.

A) Numbers of emergency department visits in the two study groups.

B) Numbers of hospitalization episodes in the two study groups

C) Numbers of days of inpatient care in the two study groups.

The interquartile range represents 25%–75% of the patients at each measuring point, the whiskers represent 1.5 times the interquartile range, and the markings outside are outliers.

Chemotherapy treatment close to death

No statistically significant difference between the two groups was observed regarding the time from the last CHT treatment to death. Patients in the active study group survived a median of 48 days (95% CI: 33–58) from their last CHT treatment, compared to 69 days (95% CI: 47–109) for those in the control group ($p=0.053$). Moreover, 33% of patients in the active group received palliative CHT within the last 30 days of life, compared to 22% in the control group ($p=0.28$).

Place of death

At the end of the study, 58 out of 60 patients in the active group had died. Of these, 40% (n=23) died at home, 57% (n=33) died in the inpatient SPC ward, and 3% (n=2) died in the hospital. In the control group, 51 patients had died and six others had withdrawn their consent. Of the deceased, 41% (n=21) died at home, 45% (n=23) died in the inpatient SPC ward, 12% (n=6) died in the hospital, and 2% (n=1) died in an assisted living facility. Among the eight patients in the control group who were never referred to SPC, 75% (n=6) died in the hospital and 25% (n=2) died at home.

Overall survival

Three patients were still alive at the time of analysis. No statistically significant differences in OS were found between the study groups. The median OS for the cohort of 118 patients was 7.6 months (95% CI: 6.0–10.2). In the active study group, the median OS was 6.6 months (95% CI: 4.9–10.7) versus 8.7 months (95% CI: 6.5–12.2) in the control group (p=0.675).

5. Discussion

Our results show the beneficial impact on QoL from early integration of home-based SPC in patients with advanced GI cancers. This is in concordance with earlier studies regarding the advantages of integrating SPC at an earlier stage compared to the conventional practice of introducing PC during the later phases of the disease trajectory; that is, close to the EOL. The findings consistently demonstrate positive impacts on patient-reported outcomes, specifically improvements in QoL and mood, observed around 3–4 months after receiving a diagnosis of advanced cancer [45, 71, 104-106]. Timely integration of SPC in patients with advanced GI cancer allows for a more proactive approach that might lead to better symptom control, psychological support, and improved QoL, compared to patients referred to SPC close to death. Early integration gives time for discussion with patients and families on priorities and preferences, and allows patients to make informed decisions on therapy strategies, such as when to discontinue CHT.

We failed to find any differences between the study groups regarding QoL as measured with FACT-G at the last assessment before death. This was not a primary endpoint, and the negative result could be attributed to several factors. There was a wide variation in the timing of the last assessment before death (0.4–6.7 weeks), which may have influenced the observed outcomes, and nearly all patients in the control group were admitted to SPC at some point during the disease trajectory, thus receiving specialized supportive care close to death.

In contrast, Vanbutsele et al. evaluated QoL at the EOL in patients with advanced cancer, all with an estimated survival of 12 months, and randomized to early integration of SPC or standard of care with referral to SPC when needed. In this trial, QoL was assessed using the EORTC QLQ-C30 questionnaire, and the authors found a better QoL 1, 3, and 6 months before death in the SPC group compared to patients assigned to standard of care [107]. Zimmerman et al. also examined QoL at the EOL in patients with advanced cancer, using the QUAL-E scale measured at baseline and monthly for 4 months [45]. At inclusion, oncologists chose patients with advanced cancers with an estimated survival of 6–24 months. The active group received at least monthly assessments from the palliative team, and the control group received standard care with

a referral to PC when deemed needed. Patients randomized to early integration of PC demonstrated improved QoL at 12 and 16 weeks post-randomization compared to the standard care group. Zimmerman et al. did not report the patient cohort's median OS, and so it is not clear whether a prognosis of 6–24 months at inclusion can be considered EOL.

A patient's perceived QoL is highly personal, and individual preferences and values must be taken into consideration. While PC is frequently linked to the concept of QoL, it is crucial not to overlook the significance of life prolongation. Life prolongation *per se* may be of importance for a patient within their overall QoL, as the persistent threat of death can render even a modest life extension highly valuable [108]. Conversely, other patients may prioritize a better QoL over longevity, preferring to avoid aggressive treatments that may worsen their overall well-being. The ethical principle of beneficence involves acting in the patient's best interest, which includes relieving suffering. Non-maleficence, or "do no harm", suggests that treatments should not add to the patient's burden of symptoms. Shared decision-making between patients and healthcare providers should ensure that treatment goals are aligned with the patient's values. Ideally, advance care planning discussions should occur to empower patients and their families to make informed and well-grounded treatment decisions. Additionally, when treating a patient at the EOL with uncontrolled symptoms and significant suffering, it is unethical to continue life-prolonging treatments such as nutritional support and intravenous antibiotics. These treatments may extend the patient's suffering rather than to improve their QoL [49, 109].

When is the integration of SPC timely?

Nearly 90% of the patients in the ALLAN control group was admitted to SPC at some point, with a median enrolment duration of 39 days (ranging from 0 to 1152 days). The analysis showed that 39 days in SPC was insufficient to abolish the difference in QoL between the two randomization groups.

Previous RCTs have demonstrated an improvement in QoL when PC is initiated early, specifically 12–24 weeks after randomization to SPC, compared to control groups receiving standard of care with SPC introduced late in the disease trajectory or not at all. Zimmerman et al. did not manage to find a statistically significant improvement in QoL, compared to controls, at 12 weeks in their group of advanced cancer patients subjected to early integration of SPC. However, 16 weeks of SPC produced a statistically significant improvement in QoL, compared to the control group receiving standard of care [45].

A European study from 2016 investigated the impact on QoL and symptom burden in patients with inoperable pancreatic cancer receiving early SPC versus SPC when deemed necessary by the patient, their family, or the treating oncologist. The active group met with the SPC team a median of 9 times versus 4 times in the standard care group. Three months after randomization, the active group had better QoL than the control group, with a score of 120 points versus 113 points on the FACT-Hep scale, which has a maximum score of 180 points [106].

Emergency care utilization, hospitalization, and chemotherapy close to death

Intense medical actions performed in the final weeks of life, including emergency room visits and hospitalization in critical care units, are generally considered indicators of poor quality of care [57, 110]. In Manuscript IV, we analyzed data from ALLAN with a focus on the early integration of SPC and potential effects on emergency care utilization, palliative CHT use close to death, and place of death. We found decreased emergency healthcare utilization for patients with advanced GI cancer randomized to early integration of SPC, compared to patients in the control group who only received SPC when deemed necessary by the treating oncologist, patient, or their family. The differences in emergency care utilization were statistically significant ($p=<0.001$), with the control group spending 10 more days as inpatients than patients in the active group.

These findings on lesser emergency care utilization and hospitalizations in the active group of the ALLAN study are corroborated by others. A retrospective cohort study by Hui et al. from 2014 examined whether the timing of referral to PC was associated with the quality of EOL care among 366 patients who had a palliative consultation before dying of advanced cancer. The material was divided into patients who were referred to PC more than 3 months before death and those who were referred closer to death. Patients enrolled in PC for a more extended period had fewer emergency department visits (39% vs. 68%), experienced fewer hospitalizations during the last 30 days of life (48% vs. 81%), and died less often at a hospital (17% vs. 31%) compared with patients enrolled in PC 3 months or less before death [111].

Hospitalizations, including emergency care visits, often include diagnostic procedures such as imaging and excessive blood sampling. These actions can be regarded as futile given the patient's medical situation, and may thus contribute to poorer quality of death for patients near the EOL. As mentioned in the introduction, these "hidden toxicities" (as futile imaging and blood sampling) add to the burden of symptoms for patients with an advanced cancer in a palliative situation [20].

Cochrane reviews from 2013 and 2021 showed inconclusive evidence regarding the impact of home-based PC on QoL, but patients had a higher probability of dying at

home compared to patients subjected to standard of care [36, 112]. We, on the other hand, did not find any difference in the place of death between the two groups in the ALLAN trial. It must be borne in mind that all ALLAN patients except eight were admitted to SPC at some point. Of the eight never admitted, six died at a hospital, and the remaining two died at home or in assisted living.

Spending inpatient time with an advanced disease and with a poor prognosis is often associated with negative effects that contribute to a perceived poor quality of death. These effects include disruption of personal relationships and familiar surroundings, medical interventions and aggressive treatments without any positive consequences for the patient, exposure to unknown staff, and busy hospital surroundings that are poorly fitted for the patient near EOL. With less hospital care, the active group was treated by the familiar staff in the SPC team, providing a patient-centered home-based care plan

We found in the retrospective study that 19% of the patients with advanced pancreatic cancer received palliative CHT in their last month of life [113]. These findings align with those of other studies involving patients with solid tumors undergoing palliative CHT, suggesting a potential overuse of CHT [49]. Administered CHT within the last 30 days of life is generally regarded as futile, carrying a risk of diminishing QoL as patients approach death, and might be associated with intense medical care, such as cardiopulmonary resuscitation or mechanical ventilation, and delayed hospice referrals for patients [52, 60].

In Article II, we further found that patients who were enrolled in SPC for more than 30 days (group A) experienced a longer interval between their last palliative CHT treatment and death compared to those with less or no time enrolled in SPC (group B). However, no difference in OS from date of diagnosis was seen between the two cohorts. Patients in group B utilized more emergency healthcare compared to patients in group A. Also, patients never admitted to SPC were more likely to die in the hospital than patients ever admitted to SPC.

In the prospective ALLAN trial, where 56% of the participants had pancreatic cancer, we did not find any statistically significant differences in time between the last palliative CHT treatment and death. The active group received palliative CHT a median of 48 days before death, compared to 69 days in the control group (p=0.053). This is in contrast to the findings of Greer et al. regarding patients with NSCLC, where those randomized to early PC had half the odds of receiving intravenous CHT during the final 2 months of life compared to the group randomized to standard oncological care alone [114]. The numerical difference and the nearly significant p-value in the ALLAN trial may suggest that patients in the active group underwent palliative CHT closer to death. The SPC team's comprehensive symptom management and supportive care

likely contributed to the sustained and improved functional status observed in the active group. As a result, we hypothesize that these patients could have been considered suitable for palliative CHT for a longer period of time than those in the control group, which may explain the shorter interval between the last CHT treatment and death in the active group.

The previously discussed trial by Temel et al. revealed a statistically significant gain in OS for patients randomized to early integration of SPC, with an OS of 11.6 months versus 8.9 months compared to patients randomized to standard of care (p=0.02) [71]. Similarly, in the ENABLE II study, patients with advanced cancer who were randomized to early PC plus a comprehensive educational program had significantly higher 1-year survival rates than those who received usual oncological care (63% vs. 48%, p=0.038) [104]. On the other hand, a meta-analysis including seven RCTs, pooling 2184 patients, showed no association between PC and improved survival [115]. Overall, the survival benefit of integrating SPC early in patients with advanced cancer is unclear, and there is a need for more studies with similar methodological approaches. The ALLAN trial saw no statistically significant differences in OS (6.6 months in the active group vs. 8.7 months in the control group, p=0.675), adding to the growing body of evidence that SPC does not improve or reduce survival.

There is an inherent contradiction in discussing advanced care planning while simultaneously initiating tumor-specific treatment, as the treatment often sparks hope in the patient for a positive response. Furthermore, medical professionals and patients are reluctant to refer and to be referred to PC [116], with the underlying misinterpretation of this being equal to EOL care. Emerging therapeutic methods in oncology show promise in yielding positive outcomes for severely ill cancer patients. These approaches also bring forth new challenges in terms of prognosis, as individuals who were previously ineligible for treatment with CHT owing to factors such as age or comorbidities may now be assessed as treatable with the new toxicity profiles of these therapies [117]. Despite this, novel treatment opportunities with targeted therapies and immunotherapies show promising results, but possible treatment benefits must again be balanced against the adverse effects [118]. Treatment suggestions should, therefore, be firmly grounded, emphasizing the necessity for strong prognostic indicators. These factors are essential to facilitate informed discussions regarding palliative treatment and to establish realistic expectations from the patient and the treating physician.

Intensity of care

Patients in the ALLAN trial was provided with high-intensity home-based SPC, which is resource-demanding. Scaling this up to the full number of patients who could benefit would be challenging for the healthcare system.

Of all SPC conducted in Sweden, 73% is home-based, 15% is hospice-based, and 12% is hospital-based. Additionally, the proportion of patients receiving SPC varies geographically; in terms of having any contact at all with the SPC team, this proportion ranges from 10.5% (Västernorrland) to 25.8% (Gotland) [119]. There is no national coordination of how SPC is to be arranged, such as within homecare or provided by hospital-based consultation teams, and access varies, resulting in inequality within the country.

As mentioned earlier, ASCO recommends that an integration between oncological care and PC should take place within 8 weeks of a diagnosis of advanced cancer. This recommendation has little in common with the present clinical situation and workforce, as in the United States, where it is estimated that an additional 6 000–10 000 PC specialists would be required to be able to follow the ASCO guidelines [120].

Thus, there is a need for further studies on how to customize PC for optimal utilization of the components of care. Eychmüller et al. found no significant improvement in QoL at 2, 4, and 6 months following randomization to a single early consultation with an SPC team compared to standard of care in patients with advanced cancer [78]. This indicates that a single palliative intervention is not sufficient to improve QoL throughout the disease trajectory. The DanPaCT randomized trial of early integration of palliative care showed no improvement in QoL, indicating that an 8-week follow-up is too short to improve QoL in patients with advanced cancers [74].

Previous studies regarding the early integration of PC have included patients with different diagnoses, and exhibited eclectic patterns and intensity of PC care. Some patients received around-the-clock home-based SPC, while others received palliative consultations at a clinic or had their consultations by telemedicine, and most studies have reported positive results regarding QoL as a single-point measurement [71, 74, 103, 121]. There is currently a range of delivery modes and intensities of care, with most patients internationally seen at multidisciplinary hospital-based outpatient clinics (predominantly in the United States, Australia, and Italy) [122].

Intense PC for patients with serious illnesses inevitably comes with costs. We have shown a decreased utilization of hospital resources, but no healthcare cost analysis has yet been performed on the ALLAN trial. In a Canadian retrospective study of 144 306 patients who had died from cancer, healthcare costs were analyzed according to whether the patient received early integration of PC or not. In the last month of life, patients who had received early PC exhibited lower overall healthcare costs compared to patients without PC. The reduction in costs was primarily through reduced costs of hospitalizations [123].

Selection of patients to early palliative care

Today, patients are generally referred to the SPC team because of a short expected time of survival, not primarily because of symptom severity [124, 125]. However, we propose that a high symptom burden should be the primary factor triggering a referral to SPC.

A randomized cross-over study conducted by Kim et al. revealed that patients (under 70 years of age) newly diagnosed with metastatic pancreatic cancer experienced an enhanced QoL following 16 weeks of outpatient SPC compared to their baseline levels [126]. Moreover, Kim et al. found that patients with metastatic pancreatic cancer exhibited lower QoL scores at baseline compared to those with locally advanced disease. The improvement, with a decrease in the total symptom distress score (evaluated using ESAS), was observed solely in patients with metastatic pancreatic cancer. Rodin et al. conducted a secondary analysis of the RCT conducted by Zimmerman et al. in 2014 [45], with early integration of PC in a group of patients with stage IV cancers. The results showed that independent of diagnosis, an improvement in QoL at 4 months was only seen in patients with a high burden of symptoms at baseline [127].

These findings by Kim et al. and Rodin et al. suggest the potential for selecting patients for early integration of SPC based on the severity of symptoms. The studies presented in this thesis included patients with GI cancers, who comprise a group of patients that are regarded as having a high burden of symptoms in the palliative situation [59, 128]. Thus, assessing the burden of symptoms may be one way to select patients for referral to early SPC, with the goal of identifying patients who would benefit the most from early multi-disciplinary palliative interventions [121]. As in the ALLAN trial [129], the symptom burden can be measured using the FACT-G questionnaire. In concordance, Hui et al. have proposed a framework for when and to whom PC should be introduced. This framework proposes routine systematic screening of supportive care needs, consensus referral criteria, timely triage, and targeted services to ensure that PC services focus on the patients with the highest need [41].

In Article I, we identified possible prognostic factors linked to inferior chances of any gains from SL palliative CHT for patients with pancreatic cancer. These factors, comprising a PS of ≥2 and hypoalbuminemia, are straightforward clinical assessments. This prognostic information could be incorporated into the considerations when discussing referral to SPC in addition to informed treatment planning discussions with the patients [113]. We anticipate that additional prognostic factors will be identified that can aid doctors and patients in deciding whether to refer patients to PC.

In summary, early integration of SPC in patients with advanced GI cancers can enhance QoL by providing better symptom control and psychological support. However, the

timing and intensity of SPC are crucial, as a short duration may not yield the full benefits. Personalized care that aligns with patient values and ethical considerations is essential, and further research is needed to optimize the delivery and impact of SPC in improving patient outcomes at the end of life.

I'm the one that's got to die when it's time for me to die,
so let me live my life the way I want to.

Jimi Hendrix, "If 6 Was 9"

6. Conclusion

This thesis strengthens the argument for early integration of home-based SPC with tumor-specific treatment in patients with advanced GI cancers. We found an improved QoL 24 weeks following admission to SPC, and a significant reduction in usage of emergency healthcare services and inpatient care for patients with advanced GI cancer after randomization to early integration of SPC. A longer time of enrollment was of importance for the improvement of QoL and decreased hospital care utilization.

7. Future perspectives

There is still insufficient knowledge of which component(s) of PC or SPC lead to the improved QoL seen in the RCTs on integrating PC with oncological treatment. Several questions remain; for example, whether patients provided with home-based SPC benefit the most regarding QoL, and whether the multi-professional structure of the SPC team is fundamental for its success.

We hypothesize that an "ALLAN 2.0" study could include patients with advanced cancers using a cross-over design based on symptom burden. Patients with a high symptom burden, identified using the FACT-G questionnaire, should be enrolled in SPC. Once symptom control is achieved, these patients could transition from an intensive, home-based follow-up to a consultation program. The consultation program would include follow-ups by telephone as needed, initiated by the patient, with the SPC team available to adjust medications or allow the patient to re-enter the home-based program based on a FACT-G score indicating high symptom burden. Some patients will continue deteriorating after SPC enrollment and remain in the home-based program. Others may be on the consultation list for months, enabling SPC to accommodate more patients with advanced illnesses. This approach is ethically preferable to providing continuous home-based SPC to patients after symptom control, while other patients with high symptom burden receive general PC and lack access to inpatient PC and PC specialists.

SPC is predominantly home-based in Sweden, while larger units also operate outpatient clinics. Internationally, only a few RCTs have been performed in the home-based setting of SPC [112], and, as mentioned, there is an ongoing discussion on how to optimally provide SPC and how the expertise of the multi-professional SPC team is best utilized. Several models are seen as hospital-based SPC teams provide consultations for in-patients, outpatient clinics, and home-based care. The timely implementation, with patients included in one or more models depending on their present requirements, needs to be studied and defined

Caregivers represent another key area of unmet need in SPC. There is little caregiver-focused work in the present PC literature, yet many reasons exist to think that caregivers have unique needs requiring novel solutions. Our randomized controlled ALLAN trial

collected data on the patient's next of kin regarding QoL and sick leave rate, with a follow-up a year after the patient's death. We hypothesize that the next of kin in the active group would be less burdened by responsibilities, worries, and navigating the healthcare system and that they would be able to maintain their everyday life less burdened than the corresponding next of kin in the control group. These data remain to be analyzed.

The term "palliative care" may convey the misconception that only patients in the very advanced and/or terminal stages of illness are eligible for enrollment in SPC. Remembering the definitions of palliative care by WHO and IAHPC, presented at the beginning of this thesis, PC is not exclusively for patients in a palliative situation but applicable to all patients with a high burden of symptoms. Thus, patients undergoing aggressive cancer treatments with toxic side effects could gain much from the support of an SPC team. Effectively managing these side effects at home, with antibiotics, pain treatment, nutritional support, etc, would lessen the need for emergency ward visits and hospitalizations. Whether the treatment's intent is curative, symptom palliation, or prolonging survival, the focus should be on treating patients with a high symptom burden.

Ju mer man tänker desto mer inser man
att det inte finns något enkelt svar
Nalle Puh

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