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TURUN YLIOPISTON JULKAISUJA – ANNALES UNIVERSITATIS TURKUENSIS
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## University of Turku

Faculty of Medicine
Department of Clinical Medicine
Clinical Oncology
Doctoral Programme in Clinical Research

## Supervised by

Professor Outi Akrén, MD, PhD
Palliative Care Center
Comprehensive Cancer Center
Helsinki University Hospital
Helsinki, Finland and
Faculty of Medicine
Department of General Medicine
University of Turku
Turku, Finland

Adjunct Professor Sirkku Jyrkkiö, MD, PhD
Department of Oncology and Radiotherapy
Turku University Hospital
Turku, Finland

## Reviewed by

Professor Jussi Koivunen, MD, PhD
FICAN North
Oulu University Hospital and
University of Oulu
Oulu, Finland

Emerita Professor Dagny Faksvåg Haugen, MD, PhD
Department of Clinical Medicine K1
University of Bergen
Bergen, Norway

## Opponent

Adjunct Professor Vesa Kataja, MD, PhD
Department of Oncology
South Savo Social and Health Care Services
Mikkeli, Finland

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*Life is meaningful because it is a story, and in stories, endings matter*
*- Atul Gawande*

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## ABSTRACT

Patients with pancreatic cancer often face a heavy symptom burden and low quality of life (QoL). Continuing anticancer therapy or extensive hospital service use near the end of life (EOL), as well as delayed initiation of palliative care (PC), may further impair QoL. Early integrated palliative care (EIPC) is recommended but remains underutilized.

The aim of this dissertation was to assess EOL care in patients with pancreatic cancer. Studies I and II were retrospective registry-based cohorts that evaluated whether the timing of the formal transition to PC—the PC decision—affected hospital resource use, access to specialized PC (SPC), and the extent to which EIPC was implemented. Study III was a prospective study examining the ability of three QoL questionnaires to monitor symptoms and QoL over a 4-month follow-up period.

Across Studies I and II, nearly half of the patients had a PC decision made within the last month of life or not at all. Such late or absent decisions were consistently associated with higher healthcare use in the last month, including more emergency department visits, more hospitalizations, and anticancer therapies being continued closer to death. Late or missing PC decisions were also linked with more deaths in secondary or tertiary hospitals. In contrast, early PC decisions resulted in earlier and more frequent SPC engagement. However, only 36% of patients received PC integrated with ongoing anticancer treatment.

In Study III, the short QLQ-C15-PAL provided an efficient overview of well-being, while QLQ-PAN26 contributed valuable pancreatic cancer-specific information. No major changes in symptoms or QoL were observed, although missing data, primarily due to non-completion of follow-up questionnaires as patients' health declined or because of death, increased over time. The most common reported concern was worry about future health.

In conclusion, a timely transition to PC is associated with less aggressive EOL care and earlier involvement of PC services. QoL questionnaires offer a practical tool for guiding communication and care in this highly symptomatic patient population.

KEYWORDS: Pancreatic cancer, palliative care, end-of-life care, quality of life, healthcare utilization

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## TIIVISTELMÄ

Haimasyöpäpotilailla on merkittävä oirekuorma ja heikko elämänlaatu. Elämän loppuvaiheessa jatkuvat syöpähoidot tai runsas sairaalahoidon tarve sekä viivästynyt palliatiivisen hoidon aloitus voivat edelleen heikentää sitä. Palliatiivisen hoidon varhainen integraatio on suositeltua, mutta edelleen alihyödynnettyä.

Tämän väitöskirjan tavoitteena oli arvioida haimasyöpäpotilaiden elämän loppuvaiheen hoitoa. Tutkimukset I ja II olivat retrospektiivisiä rekisteritutkimuksia, joissa tarkasteltiin miten palliatiiviseen hoitoon siirtymisen ajankohta vaikutti sairaalapalvelujen käyttöön ja erityistason palliatiivisen hoidon saavutettavuuteen sekä kuinka hyvin varhainen palliatiivinen hoito toteutui. Tutkimus III oli prospektiivinen tutkimus, jossa arvioitiin kolmen elämänlaatumittarin soveltuvuutta oireiden ja elämänlaadun kartoittamiseen neljän kuukauden seuranta-ajalla.

Tutkimuksessa I ja II lähes puolella potilaista palliatiivisen hoidon päätös tehtiin vasta viimeisen elinkuukauden aikana tai ei lainkaan. Tämä liittyi selvästi lisääntyneeseen sairaalahoidon tarpeeseen, useampiin päivystyskäynteihin ja syöpähoitojen jatkumiseen lähempänä kuolemaa. Myöhäinen päätös lisäsi myös sairaalakuoleman riskiä. Varhaisen päätöksen omaavilla potilailla oli aiemmin ja useammin toteutunut erikoistason palliatiivisen hoidon kontaktiin. Vain 36 % potilaista sai palliatiivista hoitoa meneillään olevan syöpähoidon aikana.

Tutkimuksessa III QLQ-C15-PAL-kysely tarjosi tiiviin kokonaiskuvan potilaiden voinnista, ja QLQ-PAN26-kysely täydensi sitä kartoittaen haimasyöpään liittyviä oireita. Oireissa tai elämänlaadussa ei havaittu suuria muutoksia seurannan aikana, mutta puuttuvan tiedon määrä kasvoi terveydentilan heikkenemisen tai kuoleman vuoksi. Yleisin huolenaihe koski tulevaa terveydentilaa.

Johtopäätöksenä voidaan todeta, että oikea-aikainen siirtyminen palliatiiviseen hoitoon on yhteydessä vähemmän aggressiiviseen elämän loppuvaiheen hoitoon ja varhaisempaan palliatiivisten palveluiden käyttöön. Elämänlaatumittarit tarjoavat käytännöllisen välineen keskustelun tueksi ja hoidon ohjaamiseen tässä voimakkaasti oireilevassa potilasryhmässä.

AVAINSANAT: Haimasyöpä, palliatiivinen hoito, elämän loppuvaiheen hoito, elämänlaatu, terveydenhuollon resurssit

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# Abbreviations

| | |
|---|---|
| ACP | Advance care planning |
| AE | Adverse effects |
| ASCO | American Society of Clinical Oncology |
| BRCA | Breast cancer gene |
| CA19-9 | Carbohydrate antigen 19-9 |
| CT | Computed tomography |
| DFS | Disease-free survival |
| dMMR | Deficient mismatch repair |
| DNA | Deoxyribonucleic acid |
| DNR | Do not resuscitate |
| ED | Emergency department |
| EMA | European Medicines Agency |
| EOL | End of life |
| EORTC | European Organisation for Research and Treatment of Cancer |
| EORTC QLQ-PAN26 | 26-item, pancreas cancer–specific quality-of-life module used alongside the QLQ-C30 |
| EORTC QLQ-C15-PAL | A 15-item, cancer-specific palliative care quality-of-life questionnaire, shortened from the QLQ-C30 |
| EORTC QLQ-C30 | A 30-item cancer-spesific core quality-of-life instrument |
| ePROM | Electronic patient-reported outcome measure |
| ERCP | Endoscopic retrograde cholangiopancreatography |
| ESAS | Edmonton Symptom Assessment System, a patient-reported scale assessing symptom severity in palliative and cancer care |
| ESMO | European Society for Medical Oncology |
| EUS | Endoscopic ultrasound |
| EQ-5D | Generic 5-item health status measure plus a Visual Analog Scale |
| FACT-G | A 28-item general cancer quality-of-life measure |
| 5-FU | Fluorouracil |

| | |
|---|---|
| HRQoL | Health-related quality-of-life |
| HUH | Helsinki University Hospital |
| i.e. | id est, that is |
| IPC | Integrated palliative care |
| LAPC | Locally advanced pancreatic cancer |
| mFOLFIRINOX | Modified 4-drug chemotherapy regimen containing folinic acid, fluorouracil, irinotecan, and oxaliplatin |
| MRI | Magnetic resonance imaging |
| MSI-H | Microsatellite instability high |
| NCCN | National Comprehensive Cancer Network |
| NTRK | Neurotrophic tyrosine receptor kinase |
| OS | Overall survival |
| PC | Palliative care |
| PFS | Progression-free survival |
| PS | Performance status |
| PROM | Patient-reported outcome measures |
| SPC | Specialist palliative care |
| QoL | Quality of life |
| WHO | World Health Organization |

# List of Original Publications

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

I Miinalainen S, Rissanen A, Leskela RL, Saarto T, Hirvonen O, Anttonen A. Effect of Palliative Care Decision on Use of Hospital Services in Pancreatic Cancer Patients: A Retrospective Study. *Anticancer Research* 2022 Nov;42(11):5457-5463. https://doi.org/10.21873/anticanres.16050

II Koivusalo S, Kitti P, Nåhls NS, Carpén T, Leskelä RL, Saarto T, Akrén O. The Impact of Early Palliative Care Decisions on Hospital Service Utilization and End-of-Life Care in Patients with Pancreatic Cancer – a retrospective study. *Journal of Palliative Care* 2026;0(0). https://doi.org/10.1177/08258597261436077

III Miinalainen S, Löyttyniemi E, Jyrkkiö S, Akrén O. Assessing Quality of Life in Patients with Pancreatic Cancer in a Prospective Single-Center Observational Study. *Journal of Palliative Medicine* 2025 Oct 3. https://doi.org/10.1177/10966218251383708. PMID: 41043869.

# 1 Introduction

Pancreatic cancer is one of the most lethal malignancies, characterized by a heavy symptom burden and poor quality of life (QoL) (Bray et al., 2024). Only a minority of patients are eligible for potentially curative surgery, and even then, recurrence is common and prognosis remains poor (Tempero et al., 2019; Park et al., 2021). Despite advances in oncology, survival outcomes in pancreatic cancer have shown minimal improvement over the past decades, with a 5-year survival rate of only 5–12% (NORDCAN; Arnold et al., 2019; Bray et al., 2024).

Standard management of advanced pancreatic cancer relies primarily on systemic chemotherapy. Most patients receive one or two lines of treatment until disease progression, unacceptable toxicity, or declining functional status leads to discontinuation (Conroy et al., 2023). Administering chemotherapy near the end of life (EOL) offers limited benefit and may expose frail patients to disproportionate harm, emphasizing the need for careful and timely treatment cessation. Because the majority present with incurable disease, management is predominantly palliative, aimed at symptom relief and maintenance of QoL (Latenstein et al., 2020; Radbruch et al., 2020).

The World Health Organization (WHO, 2002) defines palliative care (PC) as active, comprehensive care for patients and families facing life-limiting illness aimed at improving QoL by preventing and relieving suffering through early identification and management of pain and other physical, psychosocial, and spiritual problems. Early integration of PC into oncology is likewise supported by oncology societies like the European Society for Medical Oncology (ESMO) and the American Society of Clinical Oncology (ASCO) (Ferrell et al., 2017; Jordan et al., 2018). Early involvement of PC has been shown to offer multiple benefits, including improved QoL, more effective symptom control, and higher satisfaction among patients and caregivers (Bakitas et al., 2009; Temel et al., 2010; Zimmermann et al., 2014; Kavalieratos et al., 2016; Vanbutsele et al., 2018). In addition, early PC reduces overly aggressive EOL care by limiting inappropriate treatments, decreasing hospital utilization, and promoting timely access to specialist PC (SPC) (Temel et al., 2010; Greer et al., 2012; Maltoni, 2016). Nevertheless, late initiation of PC remains common, including among patients with pancreatic cancer (Zimmermann et al.,

2014; Bhulani et al., 2018; Bevins et al., 2021). EOL refers to a phase characterized by progressive physical or functional decline, during which worsening symptoms signal that death is approaching, although the exact timing is often uncertain (Schüttengruber et al, 2022). In contrast to PC which may be delivered throughout the disease course, EOL care refers specifically to the final stages of life.

Pancreatic cancer is associated with substantial morbidity, including anorexia, cachexia, abdominal pain, fatigue, and other symptoms that significantly impair QoL, and therefore systematic evaluation of symptoms and QoL is critical throughout the disease trajectory (Bauer et al., 2018; Yoo et al., 2022; Conroy et al., 2023).

QoL encompasses patients' perceptions of their physical, psychological, and social well-being. Validated QoL questionnaires not only capture the patient's condition but can also support shared decision-making, ensuring that care aligns with patients' priorities and functional capacity (Witvliet-Van Nierop et al., 2017; Macarulla et al., 2020).

Given the well-recognized symptom burden and aggressive disease course of pancreatic cancer, systematic QoL assessment and early integration of PC are important components of high-quality EOL care. The aim of this dissertation was to assess EOL care in pancreatic cancer, including the role of QoL questionnaires in clinical practice and the impact of PC timing on EOL care.

# 2 Review of the Literature

## 2.1 Pancreatic cancer

Most pancreatic cancers (>90%) are infiltrating pancreatic ductal adenocarcinoma, which originates from the exocrine ductal cells of the pancreas (Conroy et al., 2023). Unless otherwise specified, the term *pancreatic cancer* generally refers to this histological subtype. Less common forms include pancreatic neuroendocrine tumors (PNETs), acinar cell carcinomas, adenosquamous carcinomas, and mucinous cystic neoplasms and intraductal papillary mucinous neoplasms (IPMNs) (Conroy et al., 2023). These rarer entities are beyond the scope of this dissertation.

### 2.1.1 Epidemiology and prognosis

Pancreatic cancer is among the deadliest malignancies worldwide. It ranks as the 12$^{th}$ most frequently diagnosed cancer globally and the 6$^{th}$ in Europe, while its mortality burden is higher, being the 6$^{th}$ leading cause of cancer-related deaths worldwide and 4$^{th}$ in Europe in 2022 (Globocan Factsheet Pancreatic Cancer, Bray et al., 2024). The global burden of this highly aggressive cancer is rising. In 2022, 511,000 new pancreatic cancer cases were reported worldwide (Bray et al., 2024). While prevalence remains greater in males, the relative increase in incidence is occurring faster in females (Hesami et al., 2024).

In Finland, approximately 1,300 new cases are diagnosed annually. The disease accounted for 1,266 deaths in 2022, making it the third leading cause of cancer-related mortality in Finland (Finnish Cancer Registry). This high mortality rate is primarily due to early micrometastatic spread, the rarity of early detection, and the often asymptomatic nature of the disease until advanced stages, with cachexia and metabolic dysfunction additionally contributing to the poor prognosis (Cascinu et al., 2010; Grossberg et al., 2020; Sohal et al., 2020). Furthermore, pancreatic cancer displays pronounced chemoresistance, driven by a complex tumor microenvironment and metabolic adaptations, which restrict the efficacy of standard chemotherapy regimens (Lu et al., 2019; Kaoutari et al., 2021).

Most pancreatic cancer patients present with advanced disease. Approximately 50% have metastatic disease, 10–15% have localized disease suitable for surgical

resection, and the remaining 30–35% have locally advanced, mostly unresectable tumors, typically due to extensive vascular involvement (National Cancer Institute; Balaban et al., 2016; van Veldhuisen et al., 2019; Park et al., 2021; Mazur and Trna, 2023).

Despite advances in cancer care, the 5-year overall survival (OS) of pancreatic cancer has barely changed over the past decades, ranging from 5% to 12% in the Nordic countries (NORDCAN) to 3–15% worldwide (Arnold et al., 2019; Wild et al., 2020; Bray et al., 2024). Overall, the 5-year relative OS across all stages is only 9–13% (Wild et al., 2020; Siegel et al., 2025).

### 2.1.2 Risk factors

Increasing age is the strongest risk factor for sporadic pancreatic cancer, with peak incidence between 65 and 74 years (National Cancer Institute). Additional risk factors include smoking, high consumption of alcohol or red meat, low intake of fruits and vegetables, as well as obesity, type 2 diabetes mellitus, and chronic pancreatitis (Wild et al., 2020; Conroy et al., 2023). Hereditary predisposition accounts for only about 10% of cases (Pereira et al., 2020; Conroy et al., 2023).

### 2.1.3 Diagnosis and staging

Most pancreatic cancers (≈75%) arise in the head of the pancreas, while 17–26% occur in the body or tail, and 5–8% present diffusely (Conroy et al., 2023). Tumors in the head often cause bile or pancreatic duct obstruction, leading to jaundice as a first clinical presentation, which may allow earlier diagnosis and surgical intervention. Other frequent presenting symptoms include abdominal pain, appetite loss, fatigue, weight loss, and exocrine insufficiency. Duodenal obstruction from tumor invasion is also common, and sometimes new-onset or worsening diabetes and pancreatitis can be the first clinical sign (Park et al., 2021; Conroy et al., 2023).

Computed tomography (CT) is the standard imaging modality for diagnosing and staging. Beyond defining tumor location and size, CT is essential for evaluating vascular involvement, thrombosis, and local or distant metastases (Khorana et al., 2019; Conroy et al., 2023; Basturk et al., 2025).

Carbohydrate antigen 19-9 (CA19-9) is the most used tumor marker in pancreatic cancer (Ducreux et al., 2015), though its specificity is limited by elevations in biliary obstruction and lack of expression in Lewis antigen-negative individuals (Conroy et al., 2023; Basturk et al., 2025). Despite this, baseline levels remain useful for prognosis and treatment monitoring. A baseline value exceeding 500 U/mL predicts worse outcomes, even when imaging suggests resectability, and may shift the treatment strategy toward neoadjuvant therapy (Isaji et al., 2018). Additional

imaging modalities, such as magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), or staging laparoscopy, can provide further diagnostic and staging value in selected cases. Endoscopic retrograde cholangiopancreatography (ERCP), however, is reserved for therapeutic, rather than diagnostic, purposes (Conroy et al., 2023; Basturk et al., 2025).

Due to its retroperitoneal location, biopsy sampling may be challenging. Histological confirmation is not necessary if upfront surgical resection is planned (Basturk et al., 2025). When metastatic lesions are present, biopsy is usually performed from the most accessible tumor, often in the liver, under ultrasound or CT guidance. In cases with classic clinical and radiological features and markedly elevated CA19-9, biopsy may be omitted to avoid treatment delays, after careful multidisciplinary evaluation (Conroy et al., 2023).

### 2.1.4 Treatment strategies

Management of pancreatic cancer is primarily guided by tumor stage, which is classified as resectable, borderline resectable, locally advanced, or metastatic disease, and by patient-specific factors, such as nutritional status, performance status (PS), and comorbidities (Conroy et al., 2023).

**Resectable disease** accounts for approximately 10–15% of new diagnoses and is potentially curable with radical surgery combined with (neo)adjuvant chemotherapy. Resectable tumors are defined by the absence of distant metastases, no arterial involvement, and limited venous contact without contour irregularity (Tempero et al., 2019). **Borderline resectable** and **Locally Advanced Pancreatic Cancer (LAPC)** represent roughly 30–40% of non-metastatic cases (Ducreux et al., 2015; Gemenetzis et al., 2019; van Veldhuisen et al., 2019). Borderline resectable tumors have limited vascular involvement but remain surgically feasible, whereas locally advanced tumors involve extensive vasculature involvement and are typically unresectable even after neoadjuvant therapy (National Cancer Institute). For patients who are not candidates for curative treatment, management primarily focuses on symptom control. **Advanced or metastatic disease** occurs when the tumor cells have spread to distant organs, representing 50–55% of new diagnoses. Poor prognostic factors in this population include reduced functional status (Eastern Cooperative Oncology Group performance status (ECOG PS) ≥2), age >65 years, hypoalbuminemia (<35 g/L), hepatic or multiple metastatic sites, and elevated serum CA19-9 levels, all of which independently predict reduced OS (Conroy et al., 2011; Von Hoff et al., 2013). The distribution of pancreatic cancer by disease stage is shown in Figure 1.

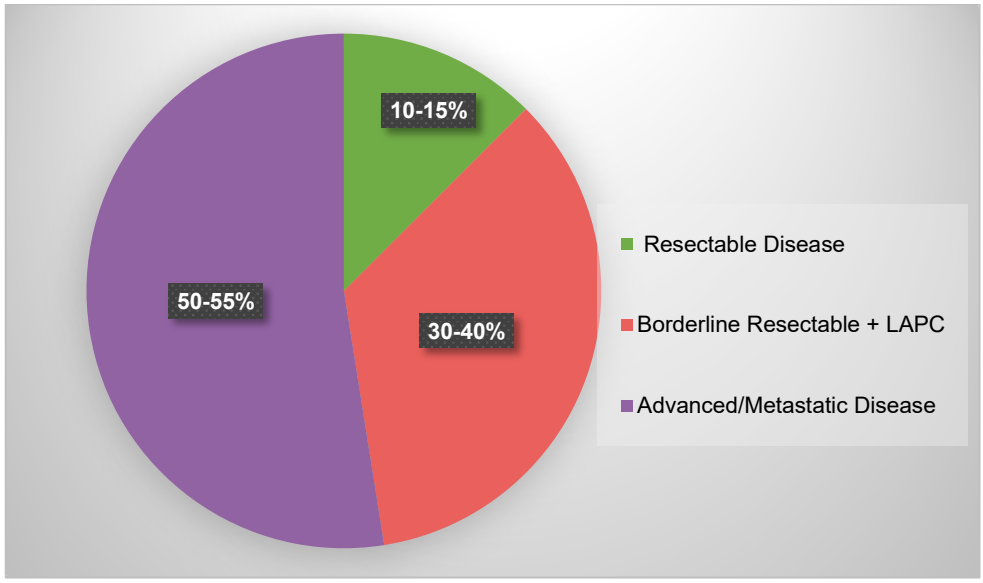


**Figure 1.** Distribution of pancreatic cancer by disease stage

### 2.1.5 Curative-intent treatments

Surgical resection remains the only potentially curative option in pancreatic cancer, yet only 10–15% of patients are eligible at diagnosis (Park et al, 2021). Even after surgery, prognosis remains poor, with a median OS of approximately 2 years (Tempero et al., 2019). Current guidelines of the ASCO, ESMO, and National Comprehensive Cancer Network (NCCN) (Khorana et al., 2019; Conroy et al., 2023; Basturk et al., 2025) recommend 6 months of adjuvant chemotherapy to improve survival.

The CONKO-001 trial demonstrated that gemcitabine significantly prolongs both disease-free survival (DFS) and OS (Oettle et al., 2013). The modified FOLFIRINOX regimen (including folinic acid, fluorouracil, irinotecan, and oxaliplatin) further improved median OS compared to gemcitabine (19.4 vs. 8.8 months), though with greater toxicity, and is now the preferred option for fit patients (Conroy et al., 2018, 2022). For patients with limited tolerance, gemcitabine–capecitabine doublet therapy or single-agent gemcitabine or fluorouracil/folinic acid may be used. The ESPAC-4 trial showed a modest but significant survival benefit, with gemcitabine–capecitabine, particularly after complete R0 resection, with microscopically negative surgical margins for residual tumor (Neoptolemos et al., 2017). Neoadjuvant chemotherapy can increase the likelihood of R0 resection and improve survival in borderline resectable cases (van Dam et al., 2022; Ghaneh et al., 2023), using regimens such as FOLFIRINOX or gemcitabine–nab-paclitaxel, sometimes followed by chemoradiotherapy (Basturk et al., 2025). After tumor

downstaging and CA19-9 decline, selected patients may undergo surgical resection (Conroy et al., 2023; Basturk et al., 2025).

In LAPC, the treatment objective is disease control, symptom relief, and maintenance of QoL, as curative outcomes are rare (Balaban et al., 2016; Seufferlein et al., 2019). Systemic chemotherapy, with or without subsequent radiotherapy, is used (Ducreux et al., 2015; Balaban et al., 2016; Wang et al., 2023; Basturk et al., 2025). The same regimens used for metastatic disease (FOLFIRINOX or nab-paclitaxel and gemcitabine) are applied (Suker et al., 2016; Seufferlein et al., 2019). Neoadjuvant therapy may allow surgery in 12–35% of patients, improving progression-free (PFS) and OS (Gemenetzis et al., 2019; Seufferlein et al., 2019; van Veldhuisen et al., 2019; Wang et al., 2023). Reported median survival for LAPC varies widely from 9 to 35 months (Vernerey et al., 2016; Taieb et al., 2017; Gemenetzis et al., 2019; Lambert et al., 2019), reflecting heterogeneity in study definitions, patient selection, and treatment strategies.

### 2.1.6 Life-prolonging treatments

More than half of pancreatic cancer cases are diagnosed at a stage beyond curative intent (Ducreux et al., 2015; van Veldhuisen et al., 2019; Mazur and Trna, 2023). In these cases, anticancer treatment aims to extend survival and, since survival benefits are often modest, it also plays a role in improving QoL and/or relieving symptoms (Kristensen et al., 2016). Chemotherapy remains the cornerstone of treatment and may be given as monotherapy or in combination, typically for up to two lines, until disease progression, unacceptable toxicity, or functional decline.

Until 1997, fluorouracil was standard, before gemcitabine demonstrated improved clinical benefit (pain, functional status, weight), and a modest OS gain (from 4.4 to 5.7 months) (Lambert et al., 2019). Currently, FOLFIRINOX is the preferred first-line treatment for metastatic pancreatic cancer in fit patients (Sohal et al., 2020; Conroy et al., 2023; Basturk et al., 2025), providing a median OS benefit of 4.3 months and delayed QoL deterioration compared to gemcitabine (Gourgou-Bourgade et al., 2013). Nab-paclitaxel plus gemcitabine is an alternative, improving OS by 1.8 months versus gemcitabine alone (Von Hoff et al., 2013), albeit with increased toxicity. Patients with good PS are characterized by an ECOG score of 0–1, adequate biliary drainage, and maintained nutrition, whereas those with intermediate PS have an ECOG score of 2. For these patients, single-agent gemcitabine or capecitabine may be considered, while PC is appropriate for frailer patients (Basturk et al., 2025).

Second-line therapy depends on prior treatment, patient PS, and molecular profile. After gemcitabine, 5-fluorouracil (5-FU) with oxaliplatin or (nanoliposomal) irinotecan is preferred; capecitabine with oxaliplatin is another option. After

fluoropyrimidine-based first-line therapy (e.g. FOLFIRINOX), gemcitabine ± nab-paclitaxel is recommended. According to current treatment guidelines (ESMO, ASCO, NCCN), targeted therapy options for pancreatic cancer remain limited. Patients with hereditary BRCA1/2 mutations may benefit from platinum-based chemotherapy and olaparib maintenance. Immunotherapy with pembrolizumab can be considered for tumors with certain DNA repair deficiencies (MSI-H/dMMR tumors), though it is not formally approved for pancreatic cancer in Europe. Rare NTRK gene fusions may be treated with selective kinase inhibitors (larotrectinib or entrectinib).

Third-line therapy is not standardized. Although an increasing number of patients receive it (Martín et al., 2018), evidence supporting its efficacy is limited, and current guidelines do not recommend routine use (Conroy et al., 2023). In carefully selected cases, further chemotherapy with previously unused agents may be considered, but shared decision-making and individualized assessment are essential.

### 2.1.7 Treatment-specific survival outcomes

Survival varies markedly by disease stage and treatment strategy. Table 1 summarizes the survival outcomes according to disease stage.

**Table 1.** Survival outcomes according to disease stage.

| Disease stage | Treatment strategy | Median OS | 5-year survival | References |
|---|---|---|---|---|
| Resectable | Surgery + adjuvant chemotherapy (gemcitabine) | ~23 months | ~20% | Oettle, 2013 |
| Resectable (fit patients) | Surgery + adjuvant modified FOLFIRINOX | 54 months | ~40% | Conroy, 2018 |
| Borderline resectable | Neoadjuvant therapy ± surgery if feasible | 29 months (if resected) | — | van Dam, 2022 |
| LAPC (unresectable) | Chemotherapy ± radiotherapy | 9–24 months | <5% | Suker, 2016; Wang, Ma & Meng, 2023; Vernerey, 2016 |
| LAPC converted to resectable) | Neoadjuvant therapy followed by surgery | 20–35 months | — | Vernerey 2016; Gemenetzis, 2019; Seufferlein 2019; |
| Metastatic | Combination chemotherapy | 9–12 months | 35–48% (1 year) | Conroy 2011b; Von Hoff, 2013 |
| Metastatic | Monotherapy | 5–6 months | <10% | Lambert, 2019 |
| Metastatic | Palliative care only | 2–4 months | <5% | Balaban, 2016 |

Abbreviations: FOLFIRINOX= 4-drug chemotherapy regimen containing folinic acid, fluorouracil, irinotecan, and oxaliplatin, LAPC= locally advanced pancreatic cancer

In resectable pancreatic cancer, surgery followed by adjuvant therapy has improved outcomes, with median OS increasing from around 23 months with gemcitabine alone to over 53 months with modified FOLFIRINOX, and 5-year survival rising from approximately 20% to 40% (Conroy et al., 2011; Oettle et al., 2013; Neoptolemos et al., 2017).

Survival outcomes in LAPC vary across studies. A phase III trial reported a median OS of 15.5 months in patients treated with either FOLFIRINOX or gemcitabine, with a slight PFS advantage for FOLFIRINOX (Ducreux et al., 2022). Neoadjuvant therapy followed by resection, which is possible in about 20% of patients, yields improved survival in selected patients (35.3 vs. 16.2 months) (Gemenetzis et al., 2019). Other reports describe median OS around 10 months, with chemotherapy and chemoradiotherapy providing only a modest additional benefit of approximately 2 months (Wang et al., 2023).

Recurrence after surgery is common, usually within 2 years and most often occurring locally around the pancreatic bed, the peritoneum, or as liver metastases, while extra-abdominal recurrence is rare and typically limited to the lung (Sinn et al., 2017; Conroy et al., 2018; Gemenetzis et al., 2019).

For metastatic disease, prognosis remains poor. Median OS is typically 3–6 months, though selected patients receiving combination therapy may reach 9–12 months, with 1-year survival rates of 35–48% (Conroy et al., 2011; Von Hoff et al., 2013; Sohal et al., 2020).

### 2.1.8 Clinical manifestations, complications, and symptom management

For >50% of patients, the intent of care is palliative from the time of diagnosis (Latenstein et al., 2020). This reflects not only the aggressive nature and typically late presentation of the disease but also the fact that many patients, who are often older and with significant comorbidities, are not suitable candidates for tumor-directed treatment. For those who initiate disease-modifying treatment, timely discontinuation is crucial, as chemotherapy close to the EOL can harm frail patients. The benefits of treatments in the late phase are typically marginal, while toxicity and adverse effects (AE) are more pronounced. As such, the treatment focus should shift toward symptom management and QoL, rather than life prolongation.

Pancreatic cancer imposes a considerable symptom burden throughout the disease course due to its retroperitoneal location, proximity to vital structures, aggressive biology, and metastatic potential, all of which severely impair QoL. Fatigue (86%), weight loss (85%), anorexia (83%), and abdominal pain (79%) are among the most frequent reported symptoms, and cancer-associated cachexia develops in over 80% of patients. Obstructive and systemic manifestations are

common, including biliary obstruction (65-90%) gastric outlet or duodenal obstruction (20-40%), thromboembolic events (5-41%), tumor-related bleeding (13%), depression (33-76%), and exocrine pancreatic insufficiency (25% in tumors of the pancreatic head). Clinical presentation varies according to tumor site and the presence of metastases, contributing to the symptoms (Kulaylat et al., 2017; Grossberg et al., 2020; Peixoto da Silva et al., 2020; Park et al., 2021; Mazur and Trna, 2023; Basturk et al., 2025).

Approximately 70% of tumors arise in the pancreatic head, often causing biliary obstruction and jaundice, dark urine, weight loss, fatigue, anorexia, and exocrine insufficiency. Tumors of the body or tail typically present with nonspecific abdominal or back pain and cachexia (Park et al., 2021). New-onset or worsening diabetes may be an early indicator, while acute pancreatitis can occasionally be the first manifestation (Park et al., 2021).

Pain is common and often progressive, managed with oral opioids or parenterally if needed (Conroy et al., 2023). Adjunct therapies, such as radiotherapy and percutaneous celiac plexus block, can improve analgesia and reduce opioid requirements, with response rates of 50–90% lasting up to a year (Conroy et al., 2023).

Cachexia is particularly prevalent in pancreatic cancer. It is a severe, multifactorial syndrome characterized by progressive loss of skeletal muscle mass and adipose tissue. Its development is driven by interrelated mechanisms involving systemic inflammation, metabolic disturbances, anorexia, and gastrointestinal impairment (Peixoto da Silva et al., 2020; Daley, 2025). Chemotherapy may worsen cachexia by activating pro-cachectic pathways and accelerating muscle catabolism, while pancreatic cancer-related insulin deficiency can further disrupt metabolism (Peixoto da Silva et al., 2020). Cachexia leads to functional decline, reduced QoL, and shorter survival (Peixoto da Silva et al., 2020; Daley, 2025). Although dietary counseling may offer support, nutritional interventions cannot reverse cachexia. ASCO does not recommend any specific pharmacological therapy as standard care, though progesterone analogues and short-term corticosteroids may be used for symptomatic relief (Roeland et al., 2020).

Fatigue is a frequent and burdensome symptom, impairing all aspects of QoL and potentially reducing survival. Inflammation is recognized as a central biological contributor to cancer-related fatigue (Bower, 2014; Thong et al., 2020). Treatment options include exercise, which is considered the most effective intervention, although evidence of benefit specifically in pancreatic cancer patients is still limited. The efficacy of pharmacological approaches, such as stimulants, short-course glucocorticoids, or hematopoietic agents in cases of anemia, remains uncertain (Bower, 2014; Grossberg et al., 2020; Thong et al., 2020).

Biliary obstruction is typically treated with ERCP and self-expandable metallic stents, which are preferred over plastic stents or percutaneous drainage due to fewer complications, lower costs, and shorter hospital stays (Conroy et al., 2023; Mazur and Trna, 2023).

Gastric outlet obstruction causes nausea, vomiting, and epigastric pain (Kulaylat et al., 2017; Conroy et al., 2023; Mazur and Trna, 2023). Management options include dietary modifications, analgesics, prokinetics and antiemetics, endoscopic enteric stenting, or surgical gastrojejunostomy, with enteric stents favored for faster recovery time (Conroy et al., 2023; Mazur and Trna, 2023).

Psychosocial distress is prevalent, with depression reported in 33–76% of patients. The incidence of depression and anxiety is higher in patients with cancer than in the general population, and those with pancreatic cancer are at particularly high risk. Notably, depressive symptoms often precede diagnosis, suggesting they are not merely a reaction to the devastating prognosis but may result from tumor-related changes, functioning as a paraneoplastic manifestation in some patients (Michoglou et al., 2023). Depression can also occur as a comorbidity of cognitive decline, which is also common in pancreatic cancer and requires appropriate psychological or psychiatric support, including antidepressant treatment when indicated (Grossberg et al., 2020; Cipora et al., 2023; Michoglou et al., 2023). Common clinical manifestations and their treatment strategies are listed in Table 2.

**Table 2.** Common clinical manifestations and their treatment strategies.

| Clinical manifestation | Management |
|---|---|
| **Pain** | Opioids; neuropathic pain agents; radiotherapy; celiac plexus block |
| **Biliary obstruction** | ERCP with stents, percutaneous biliary drainage |
| **Gastric outlet or duodenal obstruction** | Dietary changes; analgesics, prokinetics/antiemetics, endoscopic enteric stenting, or surgical gastrojejunostomy |
| **Cachexia** | Dietary counseling; progesterone analogues, short-term corticosteroids; pancreatic enzymes (if insufficiency) |
| **Fatigue** | Exercise; psychosocial support; pharmacological agents (psychostimulants, corticosteroids, hematopoietic agents) |
| **Depression** | Psychological support; antidepressants |

Abbreviations: ERCP= Endoscopic retrograde cholangiopancreatography

The heavy symptom burden of pancreatic cancer leads to a poor QoL (Carrato et al., 2015; Bauer et al., 2018; Yoo et al., 2022). Given the complex symptomatology and aggressive disease course, most patients benefit from multidisciplinary care and palliative management initiated at the time of diagnosis (Sohal et al., 2018; Safyan et al., 2024). Early symptom assessment and integration of PC can improve QoL,

reduce aggressive treatments near the EOL, and lower hospitalizations, thereby alleviating the overall healthcare burden (Basturk et al., 2025). A recent study showed a reduction in pain and fatigue in particular after referral to PC (Allende-Pérez S, 2025).

## 2.2 Palliative care

### 2.2.1 Definition, principles, and scope of palliative care

PC is widely recognized as a comprehensive approach supporting individuals with incurable illnesses, as well as their families. The WHO (2002) defines PC as an integrated and holistic approach that improves the QoL of patients and families facing life-threatening illnesses. It focuses on early identification, thorough assessment, and treatment of pain and other physical, psychological, social, and spiritual problems. It provides symptom relief, affirms life without aiming to hasten or delay death, and supports patients to live as fully as possible. It also supports families during illness and bereavement, uses a team-based approach, and is applicable early alongside life-prolonging treatments. The International Association for Hospice and Palliative Care (IAHPC) similarly describes PC as active, holistic care for people experiencing severe health-related suffering, particularly near the EOL, with the goal of improving QoL for both patients and their families (WHPCA, 2020; Radbruch et al., 2020). The National Consensus Project further emphasizes PC as patient- and family-centered care that optimizes QoL by anticipating, preventing, and addressing suffering across physical, cognitive, emotional, social, and spiritual domains, while promoting autonomy and informed decision-making through clear communication and accessible information (Ferrell et al., 2017). Across these definitions, PC is grounded in the principle that life is valued throughout its course and that dying is a natural process; therefore, PC interventions neither hasten nor postpone death (WHPCA, 2020.

According to ESMO, EOL care refers to PC provided when death is imminent (Cherny et al., 2003). A Delphi consensus by Schüttengruber et al. (2022) describes the EOL phase as characterized by progressive physical decline and worsening symptoms, such as pain or cognitive impairment. Timely recognition of this transition is essential to ensure appropriate EOL care, although its exact onset is often difficult to determine. In the literature, the timeframes used to define EOL vary widely, from the final days to up to the last two years before death (Stow et al., 2019). While PC includes care at the EOL, it is not limited to the final stages of illness and may and should be integrated alongside disease-directed therapies throughout the disease trajectory.

Supportive care comprises a broad and variably defined range of practices. While PC is a key component, supportive care extends beyond it (Berman et al., 2020). According to Multinational Association of Supportive Care (MASCC) it aims to prevent and manage the AE of cancer and its treatment across the disease trajectory. Medical societies uniformly recommend the term "patient-centered care" to describe a holistic, needs-based approach that includes, but is not limited to, supportive and palliative care (Ferrell et al., 2017; Jordan et al., 2018).

Building on this patient-centered approach, PC should be offered according to individual need rather than prognosis. The consensus definition, based on the Serious Health-Related Suffering (SHS) concept from the Lancet Commission on Palliative Care and Pain Relief, shifts focus from the disease to the person and emphasizes needs-based care across all settings, including both general and specialist PC (Sleeman et al., 2019; Radbruch et al., 2020). Care is typically delivered by interdisciplinary teams, ensuring coordinated support for both patients and caregivers while assisting families in coping with illness progression and bereavement (Ferrell et al., 2017; Jordan et al., 2018)

Over the last half-century, the role of PC has expanded markedly, transforming from a service reserved for the final days of life into a specialty that provides comprehensive support throughout the entire course of serious illness (Hui and Bruera, 2020). Studies show that limiting PC to EOL care overlooks significant benefits, as earlier integration can greatly improve outcomes for both patients and caregivers (Hui et al., 2018). Reflecting this, the WHO notes that PC should be introduced early alongside curative or life-prolonging therapies, with its role increasing as illness advances.

### 2.2.2 Need for palliative care

In Finland, the WHO estimates that around 30,000 individuals require PC annually at the EOL, with at least an equivalent number needing it earlier in the disease course. Altogether, this means that approximately 70,000–75,000 people require PC each year (Saarto et al., 2019; WHPCA, 2020).

Globally, 56.8 million people need PC annually, of whom 25.7 million are in the final year of life. With rising chronic illness and aging populations, serious health-related suffering amenable to PC is projected to increase by 87% by 2060 (WHPCA, 2020. In Europe, 9 million adults require PC annually (Garralda et al., 2025). Despite this growing need, access remains severely limited outside North America, Europe, and Australia, while 76% of the global demand is in low- and middle-income countries (Global Atlas of Palliative Care).

In Europe, as well as in the United States, approximately 40% of PC need is related to cancer (Garralda et al., 2025; WHPCA, 2020). While PC has traditionally

been associated with oncology, most global needs now arise from non-malignant diseases, underscoring that PC should not be restricted to any specific diagnosis (WHPCA, 2020).

### 2.2.3 Levels of palliative care

PC delivery is generally categorized into levels based on complexity and required expertise (Hui et al., 2018). In clinical practice, this is often described as generalist PC and specialist PC (SPC).

Generalist PC refers to basic assessment and management of common symptoms, communication, decision-making, and the identification of situations that warrant escalation to SPC services (Hui et al., 2018). Generalist PC should be provided throughout all parts of the healthcare system. Therefore, clinicians caring for seriously ill patients should have core competence in generalist PC (Greer et al., 2013). Oncologists can provide generalist PC for cancer patients, although relying solely on oncologists to manage all aspects of PC has limitations, including variable knowledge in supportive and PC and insufficient time to address the full range of patient needs (Hui et al., 2018).

SPC is delivered by interdisciplinary teams with advanced expertise in palliative medicine and is intended for patients with complex needs beyond the capacity of generalist care. SPC teams provide specialized symptom management, psychosocial and spiritual support, caregiver guidance, and assist in complex decision-making, including EOL care. They are well suited to collaborate closely with the primary or referring clinician (Greer et al., 2013; Hui et al., 2018). SPC is delivered through different complementary service models. Outpatient SPC clinics are most appropriate for patients with good to moderate PS and expected survival of months to years. These clinics, whether stand-alone, co-located, or embedded within oncology services, provide longitudinal follow-up and timely access to specialist support (Hui and Bruera, 2020). Inpatient SPC consultation teams assist hospitalized patients with acute symptoms and often poorer functional status by providing expert symptom management and coordinating discharge planning. Dedicated inpatient SPC units offer intensive care for patients with severe distress and complex needs, such as palliative sedation and complex symptom management (Hui and Bruera, 2020). Although opioid titration is not exclusively a specialist-level intervention, it is often managed by SPC teams in cases of difficult symptoms. If such units are unavailable, patients are typically managed on oncology wards. Community-based SPC and hospice services support patients with limited PS and short prognoses, focusing on EOL care, through home visits, equipment provision, and family support. Together these services create a coordinated continuum of care that spans the entire trajectory of serious illness (Greer et al., 2013; Hui and Bruera, 2020).

### 2.2.4 Access to palliative care

Access to PC is recognized as an essential component of primary health care and, moreover, is increasingly acknowledged as a fundamental human right (Garralda et al., 2025; Saarto et al., 2019; WHPCA, 2020; Radbruch et al., 2020). Although the availability of PC services is improving globally (Greer et al., 2013; Zimmermann et al., 2014; Hui and Bruera, 2020), they remain disproportionately concentrated in high-income countries, where access reaches 70% in primary care and 81% in home or community settings, whereas in low-income countries the corresponding figures drop to just 10% and 19%, respectively (WHPCA, 2020). Data from the first-ever global ranking of PC indicates that over half of the world's population resides in countries with inadequate services, highlighting persistent structural inequities in access and capacity (Tripodoro et al., 2025).

Despite global growth in PC services, only about 12% of need is met (WHPCA, 2020). Even in Europe, where PC is relatively advanced, access remains limited, and countries are at varying stages of integrating PC into their health system coverage (Garralda et al., 2025). Outside high-income regions, especially in low- and middle-income countries, PC remains severely underdeveloped, and access to PC is hindered by policy shortcomings, unequal funding, restricted access to essential medicines, particularly opioids, and challenges related to education, culture, and psychological factors (Garralda et al., 2025; WHPCA, 2020; Radbruch et al., 2020).

### 2.2.5 Timing and integration into cancer care

Both ESMO and ASCO recommend early integration of PC for all patients with advanced cancer, provided concurrently with disease-directed therapies (Ferrell et al., 2017; Jordan et al., 2018). Building on the principle that PC can be integrated at any stage of the disease trajectory (Kaasa et al., 2018), the concept of Early Integrated Palliative Care (EIPC) represents a paradigm shift in oncology and PC delivery, repositioning SPC support from a late-stage adjunct to a routine, concurrent element of standard care delivered alongside life-prolonging treatments. In this context, integrated palliative care (IPC) refers to SPC involvement initiated while patients are still receiving oncological treatment. Importantly, IPC reflects the timing of SPC contact rather than the timing of discontinuation of anticancer treatment. The definition of early referral is not standardized across studies and has been variously interpreted as a referral made within the last 1–3 months of life, or even up to 6 months before death. (Hui et al., 204; Michael et al., 2019; Robbins et al., 2019; Bevins et al., 2021; Gonzalez et al., 2023). Late referrals are considered a quality concern, and timely involvement of specialized PC is regarded as a benchmark of high-quality cancer care (Temel et al., 2010). Early PC functions as a form of preventive care (Hui et al., 2018) and is essential for achieving meaningful

improvements in QoL and EOL care (Temel et al., 2010; Greer et al., 2013; Zimmermann et al., 2014; Hui et al., 2016).

Despite this, a persistent gap remains between expectations and real-world practice. Referrals occur late, typically within the last 2 months of life, or not at all (Temel et al., 2010; Zimmermann et al., 2014; Bhulani et al., 2018; Michael et al., 2019; Bevins et al., 2021).

Regardless of the substantial symptom burden and aggressive disease course of pancreatic cancer, many patients do not receive PC (Bhulani et al., 2018; Bevins et al., 2021). In large cohort studies, only 6–52% of patients were referred to PC (Jang et al., 2015; Bhulani et al., 2018; Bevins et al., 2021; Gonzalez et al., 2023), rarely at the time of diagnosis. More recently, a study found that only 39% of patients with metastatic pancreatic cancer accessed PC, with a mean interval of 232 days from diagnosis to consultation and 121 days from PC consultation to death (O'Brien et al., 2025).

Many oncologists continue to refer primarily for uncontrolled symptoms or late in the disease course at the time of discharge planning (Greer et al., 2013; Hui et al., 2018). Consequently, the duration of PC before death is far shorter than recommended. A meta-analysis of 169 studies involving nearly 12 million patients found a median duration of only 18.9 days (Jordan et al., 2020), far below the 3–4 months generally considered needed for the full benefits of PC to be realized (Davis et al., 2015)

Early access is hindered by both systemic and attitudinal barriers. The absence of clear referral criteria leads to inconsistent and delayed involvement of PC (Hui et al., 2016). Capacity constraints, particularly the shortage of specialty-trained clinicians, limit the ability to provide ongoing support throughout the illness trajectory (Greer et al., 2013). Psychological barriers also play a role: some oncologists worry that PC referrals may distress patients, and the term palliative often carries negative associations, contributing to reluctance among both clinicians and patients (Greer et al., 2013; Jordan et al., 2018; Hui and Bruera, 2020)

Although guidelines recommend early SPC for all patients with advanced cancer, resource limitations support a more selective, needs-driven referral strategy, using standardized criteria rather than automatic referral alone (Jordan et al., 2018; Sohal et al., 2018).

In the absence of standardized criteria, referrals to palliative care are often variable and delayed, shaped by individual clinicians' perceptions rather than patient need. An international Delphi consensus study of 60 experts defined clear triggers for referral to outpatient specialist palliative cancer care, grouped into two categories: needs-based criteria, favored for identifying appropriate patients, and time-based criteria, which support early integration (Hui et al., 2016). **Needs-based criteria** prioritize the intensity and complexity of patient suffering. The consensus

panel identified nine core criteria, including severe physical or emotional symptoms, spiritual or existential distress, a request for hastened death, complex decision-making needs, neurological complications (e.g. delirium, brain or leptomeningeal metastases, spinal cord compression), and patient request. **Time-based criteria** remain relevant but are more limited. Two primary triggers were endorsed: (1) within 3 months of diagnosis of advanced/incurable cancer with an expected survival of ≤1 year, and (2) progressive disease despite second-line systemic therapy.

Hui et al. (2018) suggest that adopting structured, needs-based referral criteria alongside routine symptom and distress assessment would support earlier and more consistent identification of patients who require specialist input. Common tools to guide referral include the Edmonton Symptom Assessment System (ESAS), the Surprise Question ("Would you be surprised if the patient died in the next year?"), and PS measures such as ECOG. A decline in functioning, for example referral within 3 months of an advanced cancer diagnosis when the patient's ECOG PS is 2 (i.e. active for more than half the day and able to perform self-care, but unable to work), has been proposed as a practical indicator for referral (Hui et al., 2016). Such targeted strategies help to ensure that patients are referred at appropriate times and that PC resources are used effectively.

Given the poor prognosis of pancreatic cancer, EIPC is particularly important. For patients with metastatic disease, a comprehensive assessment of symptoms, psychological needs, and social support should occur ideally at the first clinical encounter, as it frequently reveals the need for formal PC involvement (Sohal et al., 2020). Early referral is recommended not only for metastatic disease but also for LAPC (Balaban et al., 2016). Despite robust evidence of benefit and inclusion in major clinical guidelines, EIPC remains underutilized, with only approximately 30% of pancreatic cancer patients receiving it in a timely manner (Michael et al., 2019; Bevins et al., 2021; Seow et al., 2021; Gonzalez et al., 2023).

In an Australian study of pancreatic cancer patients, the median interval from PC referral to death was 48 days (Michael et al., 2019). US Medicare data revealed that 72% of initial PC encounters for pancreatic cancer patients occurred within 30 days of death (Bevins et al., 2021), and in a cohort of elderly pancreatic cancer patients, one-third of consultations took place during the final week of life (Bhulani et al., 2018).

## 2.2.6 Impact of palliative care

### 2.2.6.1 Overview

Evidence indicates that early integration of PC can decrease hospital admissions and associated healthcare costs and is most effective when delivered by a

multidisciplinary team including, among others, physicians, nurses, and volunteers (Global Atlas of Palliative Care, 2020). Prior research has identified several markers of overly aggressive EOL care in advanced cancer—such as death in an acute-care hospital, receipt of chemotherapy within the last 30 (or 14) days of life, intensive care unit (ICU) admission within 30 days of death, multiple hospitalizations or emergency department (ED) visits in the final month, and more than 14 inpatient days during that period—which are widely regarded as indicators of potentially poor-quality EOL care (Earle et al., 2004; Ho et al., 2011). Building on this evidence, early PC involvement and advance care planning (ACP) have been shown to reduce such aggressive care patterns, enhance symptom control and patient satisfaction, and promote earlier referral to SPC services (Temel et al., 2010; Zimmermann et al., 2014; Maltoni, 2016; Vanbutsele et al., 2018).

EIPC has been shown to reduce aggressive EOL care, decrease hospitalization rates, and enhance QoL (Haun et al., 2017a; Huo et al., 2022). A recent systematic review and meta-analysis of 129 studies found that aggressive EOL care remains common globally, with approximately half of patients receiving at least one aggressive EOL intervention. However, regional variation was observed, and inconsistent metrics and limited data from low-income regions continue to constrain global assessment (Ma et al., 2024). By contrast, national data from Korea indicate a decline in aggressive EOL care among patients with advanced cancers, including pancreatic cancer (Kwon et al., 2024).

While aggressive EOL care indicators are commonly used as markers of poor-quality care, internationally recognized quality frameworks also emphasize positive indicators for high-quality EOL care. These include timely referral to PC, effective and regularly assessed symptom control, documented ACP, clear establishment of goals of care, alignment of treatment with patient preferences, death in the patient's preferred place (often at home), and support for the families (WHO, 2002, Henson et al., 2019, Radbruch et al., 2020).

Establishing goals of care early in the illness trajectory, together with ACP and timely recognition that a patient is nearing the EOL, is essential for delivering high-quality EOL care. Examples of randomized clinical trials evaluating the impact of IPC near the EOL are presented in Table 3, and examples of randomized trials concerning PC in pancreatic cancer are given in Table 4.

**Table 3.** Examples of randomized clinical trials evaluating the impact of integrated palliative care near the end of life.

| Authors | Number of participants | Cancer type | Primary endpoints | Intervention | Outcome |
|---|---|---|---|---|---|
| Brumley et al., 2007, US | 298 | Terminally ill patients | Patient satisfaction, use of medical services, site of death, costs of care | In-home PC vs. standard care | Better satisfaction with care, fewer ED visits and hospitalizations, more home deaths, lower costs |
| Bakitas et al., 2009, US | 322 | GI, lung, GU, breast | Patient-reported QoL (FACIT-Pal), symptom intensity (ESAS), and healthcare resource utilization | Nurse-provided systematic support vs. standard care | Better QoL and mood, no effect on symptom burden or healthcare use |
| Temel et al., 2010, US | 151 | Lung | Change in QoL at 12 weeks measured by the FACT-L Trial Outcome Index (TOI) | Early PC vs. Standard care | Better QoL and mood, less aggressive EOL care, increased survival |
| Tattersall et al., 2014 Australia | 120 | Newly detected metastatic cancer | QoL over time (McGill QoL total score) | Nurse-provided early PC vs. standard care | No difference in QoL, symptoms, place of death or use of chemotherapy |
| Greer et al., 2012, US | 151 | Lung | Chemotherapy use (number, type, timing, and frequency) and hospice referral | Early PC vs. standard care | No difference in number of chemotherapy regimens but treatment halted earlier, more and longer hospice stays |
| Zimmermann et al., 2014 Canada | 461 | Lung, GI, GU, breast, gyn | Change score for FACIT-Sp (spiritual wellbeing) scale at 3 months | Early systematic PC vs. standard care | Non-significant difference in the change score for FACIT-Sp at 3 months, better QoL at 4 months, better satisfaction with care |
| Bakitas et al., 2015, US | 207 | Advanced | QoL, symptom impact, mood, 1-year survival and resource use | Nurse-led early PC vs. delayed PC care | No difference in QoL, symptoms, mood or resource use, better 1-year OS |
| Maltoni et al., 2016, Italy | 207 | Pancreatic | Change in QoL at 12 weeks (FACT-Hepatobiliary Trial Outcome Index (TOI)) | Systematic early PC vs. early PC on-demand | Better QoL, higher hospice use, less chemotherapy use near EOL |
| McDonald et al., 2017, Canada | 182 | Lung, GI, GU, breast, gyn | Caregiver satisfaction with care (FAMCARE-19) and caregiver QoL (SF-36v2 and CQoL-C). | Early systematic PC vs. standard care with PC on-demand | Higher caregiver satisfaction with care, no difference in caregiver QoL |

| Authors | Number of participants | Cancer type | Primary endpoints | Intervention | Outcome |
|---|---|---|---|---|---|
| Vanbutsele et al., 2018, Belgium | 186 | Solid tumors | Change in global health status/QoL scale (EORTC QLQ C30) at 12 weeks. | Early systematic PC vs. standard care | Better QoL, no difference in OS |
| Scarpi et al., 2019, Italy | 186 | Gastric | Change in QoL at 12 weeks (FACT-Gastric Trial Outcome Index (TOI)) | Systematic early PC vs. early PC on-demand | No difference in QoL, mood, hospital service use, use or timeliness of hospice use, place of death or survival |
| Ferrel et al., 2021, US | 479 | Solid tumors | Psychological distress, symptom intensity and severity | Nurse-led early PC vs. standard care | Less psychological distress and emotional well-being, no survival gain |

Abbreviations: ED = emergency department; ESAS = Edmonton Symptom Assessment System; EOL = end of life; EORTC QLQ C30 = European Organisation fro Research and Treament of Cancer Quality of Life Questionnaire Core 30 items; FACT=Functional Assessment of Cancer Therapy ; FACIT-Pal = Functional Assessment of Chronic Illness Thearpy-Palliative Care; FACIT-Sp = Functional Assessment of Chronic Illness Therapy–Spiritual Well-Being; FAMCARE-19 = 19-item FAMCARE caregiver satisfaction with care scale; GI = gastrointestinal; GU = genitourinary; GYN = gynecological; OS = overall survival; PC = palliative care; ESAS), SF-36v2 = SF-36v2 Health Survey; CQoL-C = Caregiver Quality of Life Index-Cancer.

**Table 4.** Examples of randomized trials concerning palliative care in pancreatic cancer**.**

| Authors | Number of patients | Primary endpoints | Definition of early PC, if applicable | Percentage of patients receiving PC | Main findings |
|---|---|---|---|---|---|
| Bhulani et al., 2019, US | 54,130 | Trends in PC utilization and its association with EOL healthcare utilization and costs | Not applicable; noted that only 11% received PC more than 12 weeks before death | 5.8% (increased from 1.4% in 2000 to 7.4% in 2009) | PC utilization increased but occurred mainly very close to death (70% in the last 30 days) and did not reduce healthcare use or costs |
| Bevins et al., 2021, US | 3166 | Association between early PC and healthcare utilization and costs | First PC encounter within 30 days from diagnosis | Early PC 28% | Early PC associated with fewer ED visits, lower costs |
| Jang et al., 2015, Canada | 5381 | Impact of PC on aggressive EOL care | Not applicable; analyzed PC consultation and visit intensity | 52.3% | Less use of hospital services (ICU admissions, ED visits, and hospitalizations), less use of chemotherapy near EOL |
| Lees et al., 2019, Canada | 365 | Association between SPC consultation timing and aggressive EOL care | PC within 8 weeks from diagnosis | 84.1% (58.9% early, 25.2% late) | Less aggressive EOL care, regardless of timing |

| Authors | Number of patients | Primary endpoints | Definition of early PC, if applicable | Percentage of patients receiving PC | Main findings |
|---|---|---|---|---|---|
| Michael et al., 2019, Australia | 278 | Indicators of aggressive EOL care in the last 30 days of life, timing of PC referral, and place of death | >90 days before death | Early PC 32.7% | Less hospital service use; no differences in ICU use, chemotherapy, or place of death |
| Adsersen et al., 2021, Denmark | 5851 | SPC admittance in relation to age and geographic region | Not explicitly defined by a specific time frame | 60% were admitted to SPC (increased from 44% in 2011 to 63% in 2018); 73% were referred | Admittance increased over time but median survival from admittance was only 35 days, admittance was higher for younger patients and varied by region |
| Gonzalez et al., 2023, US | 419 (out of 1458) | Impact of early vs. late PC referral on healthcare utilization. | PC within <30 days from diagnosis | 28.7% | No impact on healthcare service use after adjustment |
| Zhang et al., 2024, US | 2883 | Incidence of PC consultations and their association with aggressive EOL interventions | Not applicable; examined PC consutations in the last 6 months of life | 29.8% | PC consultation associated with more aggressive interventions near EOL |
| O'Brien et al., 2025 | 610 | Utilization of PC and impact on EOL care outcomes | Not applicable; noted median time from diagnosis to PC was 111 days. | 39.7% | PC involvement led to less use of chemotherapy, more hospice use and DNR orders, no survival benefit |

Abbreviations: ED = emergency department; EOL = end of life; DNR = Do not resuscitate; OS = overall survival; PC = palliative care

#### 2.2.6.2 Quality of life

Most randomized controlled trials show that integrating PC with standard oncology leads to superior QoL outcomes. The landmark trial by Temel et al. (2010) demonstrated significant improvements in both QoL and mood. Bakitas et al. (2009) found that nurse-provided telephone support enhanced QoL even though symptom burden remained unchanged, whereas other work has documented benefits in both domains (Kavalieratos et al., 2016). In some cases, effects appear gradually. A study observed no QoL improvements at 3 months, but significant gains by 4 months (Zimmermann et al., 2014). Further evidence supports these patterns. Maltoni et al. (2016) showed that systematic EIPC improved QoL compared with standard care. Similarly, a Belgian randomized trial reported significant improvements in overall QoL at both 12 and 18 weeks (Vanbutsele et al., 2018).

Beyond these clinical outcomes, early PC has also been associated with greater satisfaction with care among both patients and caregivers, likely reflecting improvements in communication, support, and overall care experience (Brumley et al., 2007; Zimmermann et al., 2014; J. McDonald et al., 2017). A recent pancreatic cancer study showed that referral to PC significantly improved symptom management, notably pain and fatigue, reinforcing the need for EIPC for better care (Allende-Pérez S, 2025).

Results across studies are not entirely consistent, as not all trials have reported positive findings, with some failing to observe differences in QoL or symptom burden (Tattersall et al., 2014; Bakitas et al., 2015; Scarpi et al., 2019). Nevertheless, given the profound symptom burden associated with pancreatic cancer, early PC is expected to meaningfully ease psychological distress and enhance overall QoL in this patient population (Chung et al., 2022; Kim et al., 2023).

#### 2.2.6.3 Hospital service utilization at the end of life

The impact of PC on hospital service utilization is generally characterized by a decrease in acute, aggressive, and costly interventions near the EOL, particularly when PC is integrated early in the disease course.

EIPC has in multiple studies been associated with fewer ED visits, hospitalizations, and ICU admissions, reflecting more effective proactive symptom management (Temel et al., 2010; Greer et al., 2012; Zimmermann et al., 2014; Vanbutsele et al., 2018).

Among pancreatic cancer patients, Bevins et al. (2021) reported that early PC, though provided to only 28% of patients, was associated with reduced ED visits. Similarly, Jang et al. (2015) demonstrated that both PC consultation and higher-intensity PC were linked to less aggressive care near death, including reduced likelihood of repeated hospital stays, ICU admissions, and ED visits.

Further supporting this pattern, Robbins et al. (2019) observed that in a large cohort of hospice decedents receiving PC, 84.5% were referred within 90 days of death. Although this was earlier than reported in many other studies, it was still considered late in the context of the study, and patients with late PC involvement were more likely to require ICU care in the last 6 months of life (56% vs. 19% among early enrollees). Home-based PC interventions have also shown reductions in both ED visits and hospital admissions (Brumley et al., 2007), and specialist PC consultations have been associated with a lower likelihood of aggressive EOL care indicators, though timing did not consistently modify these outcomes (Lees et al., 2019).

Evidence from other intervention models is mixed. For instance, one study reported that a nurse-led telephone intervention did not reduce acute care utilization

(Bakitas et al., 2009), and retrospective analyses of late PC referrals suggest that PC initiated very near death may not significantly decrease healthcare use (Bhulani et al., 2018). Gonzalez et al. (2023) observed fewer ED visits and hospital admissions among pancreatic cancer patients with early PC referrals. However, when recurrent events were accounted for, timing was no longer associated with overall healthcare utilization. Seemingly controversial findings have also been reported, showing that patients with a PC contact receive more aggressive EOL interventions (Zhang et al., 2024). The authors suggest that this likely reflects that patients being referred to PC often have greater symptom burden and more complex illness, and that many referrals occur extremely late, sometimes only days before death, limiting the ability of PC to reduce aggressive care.

Findings from Finnish studies support the benefits of early PC involvement. Hirvonen et al. (2020) observed fewer ED visits and hospitalizations among cancer patients with earlier PC decisions and SPC unit contact, while Haltia et al. (2023) reported similar reductions in hospital service use. This was also noted in patients with pancreatic cancer, where SPC recipients had fewer hospitalizations in a university hospital during the last 30 days of life (47% vs. 78% in the standard care group) (Rautakorpi et al., 2021).

#### 2.2.6.4 Anticancer therapies at the end of life

Earle et al. (2005) proposed that the use of anticancer therapies near the EOL should serve as a marker of overly aggressive care, recommending that fewer than 10% of patients receive systemic anticancer treatment in the last 14 days of life and that fewer than 2% initiate a new regimen in the final month. However, a systematic review showed that 24.4% of cancer patients received chemotherapy during the last 30 days of life, demonstrating the continued overuse of anticancer treatment at the EOL (Ma et al., 2024). Although anticancer therapies are often intended to alleviate symptoms and improve QoL in advanced cancer, evidence indicates that they do not improve QoL for patients with moderate or poor PS and may even worsen it for patients with good PS (Prigerson et al., 2015).

In pancreatic cancer, first- and second-line life-prolonging anticancer therapy is generally recommended for patients with sufficient functional status. Nevertheless, the proportion of patients receiving third-line chemotherapy continues to rise (Martín et al., 2018), despite limited evidence for its benefit and a lack of guideline support (Sohal et al., 2018; Conroy et al., 2023).

Several studies have examined the impact of PC on treatment intensity near the end of life. Maltoni et al. (2016) found that systematic early PC was associated with reduced use of anticancer therapy compared with on-demand early PC among patients with pancreatic cancer. PC consultation has also been linked to lower rates

of chemotherapy use near death in pancreatic cancer, and similar findings have been reported in other malignancies (Temel et al., 2010; Jang et al., 2015; O'Brien et al., 2025).

Across studies, the proportion of pancreatic cancer patients receiving anticancer therapy in the final month of life has ranged from 2–23% (Lees et al., 2019; Michael et al., 2019; Zhang et al., 2024). Research suggests that patients managed primarily by oncologists in their last month are more likely to receive late-stage chemotherapy, which can shorten the duration of PC involvement and increase the risk of treatment-related harm (Earle et al., 2008; Martín et al., 2018; Salazar et al., 2023; Gueiderikh et al., 2024).

#### 2.2.6.5 Place of death

Most cancer patients prefer home-based care and, when possible, to die at home (Gomes et al., 2013; Khan et al., 2014, Donkor et al., 2024). Evidence shows that home-based PC increases the probability of a home death and alleviates symptom burden, without worsening caregiver grief (Gomes et al., 2013). Nonetheless, a recent study found that 40.5% of patients continued to die in acute-care hospitals (Ma et al., 2024). Several studies demonstrate that integrating PC into the home setting enhances key EOL outcomes, and PC involvement supports more timely hospice transitions. Brumley et al. (2007) showed that patients receiving in-home PC were more likely to die at home and had fewer ED visits and hospital admissions.

In Finland, approximately 60% of all patients and up to 80% of cancer patients die in hospital, whereas death at home is considerably less common and occurs more frequently among patients with non-malignant diseases (26%) (Ahtiluoto et al., 2025). National quality recommendations state that the place of death should be guided by patient preferences. Currently, only 17% of all deaths occur at home, but this proportion could increase with strengthened home-based PC and readily available specialist support (Saarto et al., 2022).

Maltoni et al. (2016) reported that systematic early PC, compared with on-demand PC in patients with pancreatic cancer, increased the likelihood of hospice enrollment and longer hospice stays. Ma et al. (2024) further reinforced these findings by demonstrating that patients with PC consultations were more likely to be referred to hospice. Together, these findings underscore that early and structured PC not only aligns care with patients' preferences but also reduces acute medical interventions and promotes high-quality EOL care.

#### 2.2.6.6 Costs

Evidence shows that early PC is associated with lower healthcare costs (Hui et al., 2018). Seow et al. (2021) found that cancer decedents who received early PC—37% of the cohort—had significantly reduced costs in the last month of life, largely due to fewer hospitalizations.

Aggressive EOL care is strongly linked to higher expenditures: patients receiving chemotherapy in the final 2 weeks of life incur substantially greater costs (Cheung et al., 2015). Brumley et al. (2007) showed that in-home PC reduced both ED visits and hospital admissions, resulting in meaningful cost savings, while in pancreatic cancer, early PC has demonstrated similar effects, as Bevins et al. (2021) reported fewer ED visits and lower ED-related charges among early-PC patients.

Overall, access to PC consistently predicts lower healthcare costs, including in studies of pancreatic cancer patients in Finland (Rautakorpi et al., 2021)

#### 2.2.6.7 Survival benefit

Temel et al. (2010) demonstrated a survival advantage of roughly 2 months for patients with metastatic non-small-cell lung cancer receiving EIPC, even though they underwent less aggressive treatment near the EOL. This finding has often been interpreted to suggest that reduced treatment intensity may have contributed to improved survival by limiting treatment-related toxicity. Similarly, Bakitas et al. (2015) reported improved 1-year OS in the PC intervention group.

However, subsequent meta-analyses (Kavalieratos et al., 2016; Haun et al., 2017) have not confirmed a consistent survival benefit, suggesting that while PC improves QoL and reduces aggressive care, its effect on survival remains uncertain.

### 2.2.7 Palliative care in Finland

Finland is categorized as having a generalist level of PC development (Level 3b) according to a mapping system utilized in the Global Atlas of Palliative Care (WHPCA, 2020), reflecting widespread PC activity across regions, multiple funding sources, morphine availability, and a broad range of hospice and PC services. PC has advanced considerably since the 1980s, following the first national EOL care guidelines (1982) and the establishment of the country's first hospice (1988) (Garralda et al., 2025; Kontro, 2025).

Finland now has a well-developed network of SPC services, with 85 units nationwide (1.52 per 100,000 inhabitants), exceeding the European median. Although services cover most of the country, significant regional disparities persist, with Southern Finland better resourced than rural and remote areas. These gaps

contribute to many, particularly elderly patients, dying in hospitals rather than at home or in PC units (Forsius, 2020; Kontro, 2025).

National policies strongly support PC, even though Finland lacks dedicated PC legislation. PC is embedded in major policy frameworks, including the Cancer Plan and national recommendations for palliative and EOL care, and is part of primary care service obligations. To reduce inequities, national recommendations issued in 2019 called for integrating PC and EOL care across the entire health system, establishing coordinated PC service pathways within each healthcare district, and strengthening home-based services (Saarto et al., 2019). Building on this, the National Institute for Health and Welfare developed a quality recommendation to standardize care, identifying ten key quality areas—six covering the patient care pathway, from identifying palliative needs to bereavement support, and four addressing service organization and information transfer. It includes 50 quality criteria, although specific indicators still need refinement, and proposes a three-tier model for implementing PC in the new wellbeing services counties, aiming to guide consistent quality monitoring across all healthcare and social welfare units involved in EOL care (Saarto et al., 2022). Several of these criteria, such as timely identification of the PC phase, documentation of treatment goals, coordination of care, and systematic collection of patient-reported outcome measures (PROMs), are directly relevant to the outcomes examined in this thesis.

PC is provided within the public healthcare system, and nationally services are structured into three tiers: basic (A), special (B), and demanding special (C). B-level units provide specialist palliative and hospice care as their primary function, delivered by personnel with dedicated PC training, and form a coordinated regional network within each wellbeing services county. C-level units, located in university hospitals, represent the highest level of specialist care, managing the most complex cases and holding responsibility for research, education, and service development. Specialist services across these levels include outpatient clinics, hospital consultation teams, inpatient PC and EOL wards, four hospices, day hospitals, and expanding hospital-at-home programs. Hospital-at-home services are available in all wellbeing services counties and in approximately 73% of municipalities, covering about 92% of the population, though gaps remain in some rural areas (Garralda et al., 2025; Härkönen et al., 2024).

In Finland, PC is guided primarily by intent-of-care decisions rather than prognostic thresholds. A formal PC decision marks the documented transition from life-prolonging treatment to palliative intent, typically made by the responsible physician within a multidisciplinary framework and recorded using ICD-10 code Z51.5. Integrated PC may nevertheless be initiated earlier alongside cancer-directed therapy based on patient needs, independent of the timing of the formal decision.

Education in PC is well established: all medical schools include mandatory PC training, aligned with national curriculum recommendations, and all nursing programs follow a national PC competence framework. While palliative medicine is not an official specialty, physicians may obtain a Certification of Special Competence through the Finnish Medical Association after 2 years of clinical training and theoretical coursework (Garralda et al., 2025).

## 2.3 Assessment of symptoms and quality of life in pancreatic cancer

Due to the aggressive clinical course, high symptom burden, and intensive treatment demands, systematic assessment of symptoms and QoL is essential in pancreatic cancer. Preserving and improving QoL remains a central aspect of care (Lewis et al., 2018; Laquente et al., 2020), and such evaluations should be initiated early in the disease trajectory (Sohal et al., 2020).

### 2.3.1 Symptom and quality-of-life assessment

Patients with pancreatic cancer often experience a heavy symptom burden, including loss of appetite, weight loss, abdominal pain, fatigue, pruritus, and nausea, many of which are related to cancer-related cachexia or biliary obstruction and frequently lead to hospitalizations and interventions. As a result, QoL is typically poor or, at best, modest (Carrato et al., 2015; Bauer et al., 2018; Yoo et al., 2022). Both pancreatic cancer and its treatment can further impair physical, psychological, social, and sexual domains (Chung et al., 2022). Aside from chemotherapy-related AEs, patients also experience heightened psychological distress and reduced functional status due to poor nutrition, low muscle strength, and diminished independence (Witvliet-Van Nierop et al., 2017; Hubner et al., 2019; Chung et al., 2022).

QoL is a multidimensional concept reflecting individuals' subjective perceptions of their physical, psychological, and social well-being. In healthcare research, the focus is typically on health-related quality of life (HRQoL), which refers specifically to the impact of health status, illness, and treatment on physical, psychological, and social functioning, and can be evaluated using validated questionnaire. Assessing QoL is essential for both patients and clinicians when managing pancreatic cancer, as treatment decisions often require weighing modest survival gains against the preservation of patients' well-being and daily functioning. As a subjective outcome, QoL extends beyond symptom severity alone and captures how patients experience the broader impact of illness and treatment on their lives.

### 2.3.2 Patient-reported outcomes of quality of end-of-life care

Historically, patient evaluation was primarily conducted by physicians, focusing mainly on PS and AEs. The physician-rated Karnofsky Performance Scale laid the groundwork for later tools, though proxy measures have limited value. Patient-reported measures of symptoms and QoL capture the patient's perspective directly, without physician interpretation. They are now widely recognized as providing the most accurate assessment and, when included in studies, offer a more complete evaluation of treatment outcomes (Ferrell et al., 1995; Tushoski-Alemán et al., 2024).

PROMs help to identify specific areas requiring intervention. QoL assessments reveal physical, emotional, and functional challenges, guiding supportive strategies such as symptom management, rehabilitation for physical impairment, and psychosocial support (Witvliet-Van Nierop et al., 2017; Macarulla et al., 2020). Longitudinal QoL data further enable the evaluation of treatment effectiveness and provide valuable insights into patients' experiences (Macarulla et al., 2020).

Patients with pancreatic cancer generally report poorer QoL than those with other cancers, reflecting a substantial burden and unmet needs (Chung et al., 2022). A review of 36 studies found consistent impairments across all domains of life, with psychological distress having the most substantial impact (Bauer et al., 2018).

Clinicians often underestimate both the frequency and severity of patients' symptoms, with discrepancies becoming more evident as symptom burden increases (Xiao et al., 2013). In the absence of robust QoL data, clinicians' understanding of treatment impact remains incomplete, potentially leading to decisions misaligned with patients' values and treatment goals (Tushoski-Alemán et al., 2024). QoL questionnaires support care across the disease trajectory, from diagnosis to the PC phase, by facilitating symptom monitoring, guiding treatment decisions, and promoting holistic patient management.

### 2.3.3 Quality-of-life patient-reported outcome measures

Symptom assessment tools measure the presence and severity of individual symptoms, whereas QoL instruments assess the broader impact of illness and treatment on functioning and overall well-being. Although QoL questionnaires often include symptom scales, they also evaluate functional, emotional, and social domains, offering a more comprehensive assessment of patient experience. Several validated instruments are available to assess QoL in cancer patients. The European Organisation for Research and Treatment of Cancer (EORTC) has developed a range of symptom assessment questionnaires designed to evaluate physical, emotional, and social functioning. These tools have been widely applied in clinical studies to capture disease- and treatment-related effects on patient well-being (Kristensen et al., 2016;

Laquente et al., 2020). Commonly used PROMs in pancreatic cancer trials are listed in Table 5.

**Table 5.** Commonly used patient-reported outcome measures.

| **PROM** | |
|---|---|
| EORTC QLQ-C30 | 30-item core cancer QoL instrument assessing global QoL, functional domains (physical, role, emotional, cognitive, and social), and multiple symptoms; highly validated and widely used in cancer trials (Aaronson *et al.*, 1993; Laquente *et al.*, 2020; Macarulla *et al.*, 2020; Tushoski-Alemán *et al.*, 2024). |
| EORTC-PAN26 | 26-item pancreatic cancer-specific module, used with QLQ-C30; allows patients to provide additional symptom and QoL information; captures disease-specific symptoms, treatment side effects, and emotional concerns; multi-item symptom scales (pain, digestive problems, bowel changes, hepatic symptoms, body image, satisfaction with care, and sexuality) and several single-item measures (Fitzsimmons *et al.*, 1999). |
| QLQ-C15-PAL | 15-item shortened version of the QLQ-C30 for palliative care patients; assesses key symptoms and overall QoL (Groenvold *et al.*, 2006). |
| FACT-G | 28-item general cancer QoL measure (physical, functional, social, and emotional); can be supplemented with disease-specific modules, (e.g. FACT-Pancreatic Cancer and FACT-Hepatobiliary) (Pallis and Mouzas, 2000; Tushoski-Alemán *et al.*, 2024). |
| ESAS | Brief symptom assessment tool covering nine core symptoms (pain, fatigue, nausea, appetite, depression, anxiety, drowsiness, dyspnea, well-being); widely used oncology and palliative care (Hui and Bruera, 2017). |
| EQ-5D | Generic 5-item health status measure (mobility, self-care, usual activities, pain/discomfort, anxiety/depression) plus a Visual Analog Scale (VAS); often used in economic evaluations (Rabin and De Charro, 2001). |
| Other PROMs used in pancreatic cancer trials | SF-36: Generic QoL questionnaire measuring multiple dimensions of health status and well-being.<br><br>Rotterdam Symptom Check List (RSCL): Assesses psychological and physical distress in cancer patients.<br><br>Functional Liver Index-Cancer (FLIC): 22-item tool.<br><br>Gastrointestinal Quality of Life Index (GIQLI): Health-related QoL across physical, mental, digestion, and defecation domains (Pallis and Mouzas, 2000; Witvliet-Van Nierop *et al.*, 2017; Macarulla *et al.*, 2020; Tushoski-Alemán *et al.*, 2024). |

Abbreviations: EORTC QLQ = European Organisation for Research and Treatment of Cancer Quality of Life Core Questionnaire; FACT-G = Functional Assessment of Cancer Therapy–General; EQ-5D = EuroQol 5-Dimension; ESAS = Edmonton Symptom Assessment System

### 2.3.4 Electronic patient-reported outcomes

Electronic Patient-Reported Outcomes (ePROs) involve patients directly reporting measurements about their health status, utilizing digital health technologies, with patients completing surveys on tablets, smartphones, or computers.

There is growing interest in using ePROs in cancer and PC. Studies show that their integration can improve patient outcomes and care processes. These systems enable timely interventions by quickly detecting significant changes in a patient's health or QoL, with alert messages commonly sent to healthcare professionals for severe or worsening symptoms (Karamanidou et al., 2020; Basch et al., 2022). Patients using electronic reporting have experienced better QoL, fewer ED visits and hospitalizations, and even improved survival, highlighting the clinical benefits of systematic patient self-reporting in cancer care (Basch et al., 2016, 2017, 2022, Denis et al., 2019). Notably, the 2022 Basch study included patients with metastatic pancreatic cancer among the study population.

### 2.3.5 Limitations of quality-of-life questionnaires in pancreatic cancer

The assessment of QoL in pancreatic cancer patients is not without challenges. There is currently no universally accepted ideal instrument for assessing QoL in pancreatic cancer patients, and the usage of the available questionnaires is not standardized, complicating comparisons across studies (Tushoski-Alemán et al., 2024).

QoL assessment is further limited by methodological and patient-related factors. High attrition and missing data due to disease progression, treatment toxicity, or death introduce survivor bias, often overestimating QoL outcomes (Kristensen et al., 2016; Hubner et al., 2019; Laquente et al., 2020; Tushoski-Alemán et al., 2024). Variability in assessment timing, frequency, and reporting further hinders comparability, and many studies omit survey completion rates, predefined hypotheses, or clinical relevance, with QoL often treated as a secondary endpoint (Kristensen et al., 2016; Bauer et al., 2018; Tushoski-Alemán et al., 2024).

Patient-related factors, like the physical and emotional burden of aggressive disease, can reduce compliance with questionnaires (Tushoski-Alemán et al., 2024). Furthermore, psychological adaptation, referred to as response shift, can lead patients to report improved QoL over time, not due to genuine improvement, but because of adjusted internal standards, and perceptions of well-being, masking declines in QoL (Ilie et al., 2019). Finally, general tools like the QLQ-C30 may overlook disease-specific symptoms and concerns, whereas pancreatic cancer-specific instruments such as the QLQ-PAN26 lack standardized interpretation thresholds (Bauer et al., 2018; Ilie et al., 2019; Macarulla et al., 2020).

Challenges of ePROMs include missing data bias, similar to paper PROMs, due to patient dropout or death (Basch et al., 2016), potential changes in responses when converting paper to electronic formats, incomplete validation across platforms (Pérez-Alfonso and Sánchez-Martínez, 2021), and nurses experiencing fatigue from high volumes of symptom alerts (Basch et al., 2022). Addressing these issues can guide future research.

### 2.3.6 Indicators of quality of end-of-life care

In addition to patient-reported perceptions of QoL, more objective indicators can be considered. Earle et al. have proposed measures of poor-quality EOL care, including initiating a new anticancer therapy within the last month of life, continuing ongoing treatment until the final 2 weeks, and frequent healthcare utilization near death, such as multiple ED visits, multiple hospital admissions, or intensive care during the final 15–30 days of life. These measures, along with metrics on hospice use and death in an acute-care institution, were evaluated to determine "empirical benchmarking standards" and assess statistical properties for use as performance measures for EOL cancer care (Earle et al., 2003; Earle et al., 2005). Such indicators are widely applied because they capture potentially avoidable high-intensity care and can be reliably derived from administrative data. Although they do not directly measure patient-reported QoL, they reflect care patterns often associated with reduced comfort and limited alignment with patient preferences. However, as registry-based measures, they exclude subjective dimensions, such as symptom burden, thereby providing only a partial assessment of EOL care quality.

# 3 Aims

The overall aim of this thesis was to assess EOL care in pancreatic cancer, including the role of QoL questionnaires in clinical practice and the impact of PC timing on EOL care. Given the poor prognosis and high symptom burden of pancreatic cancer, understanding how the timing of PC decisions and access to SPC services influence care trajectories is crucial for improving EOL care.

More specifically, the aims of the individual studies were:

- Study I: To evaluate the timing of PC decisions in relation to hospital service use and anticancer treatments, referral to SPC services, do-not-resuscitate (DNR) decisions, and place of death in pancreatic cancer patients.
- Study II: To assess the association between the timing of PC decisions and healthcare utilization during the past 30 days of life, including ED visits, hospitalizations, and anticancer treatments close to death, and to assess the extent of EIPC in clinical practice.
- Study III: To evaluate the feasibility and clinical utility of three EORTC QoL questionnaires (QLQ-C30, QLQ-C15-PAL, and QLQ-PAN26) in pancreatic cancer patients, and to describe patient-reported symptoms and QoL during follow-up.

# 4 Patients and Methods

## 4.1 Study design

The research process was initiated with the prospective Study III, which focused on the feasibility and clinical use of PROMs in patients with pancreatic cancer. During the recruitment phase of Study III, Study I was conducted as a retrospective analysis of EOL care patterns. The findings from Study I subsequently informed the design and analytical focus of Study II, which further examined PC decision-making and healthcare utilization in a later cohort.

## 4.2 Patients

This thesis consists of three studies on pancreatic cancer patients treated in Finland: two retrospective registry-based studies (Studies I and II) and one prospective cohort study (Study III).

### 4.2.1 Studies I and II

Studies I and II were conducted at the Department of Oncology, Helsinki University Hospital (HUH). The Study I cohort was derived from a larger dataset of 2,737 cancer patients treated 2013-2014 (Hirvonen et al., 2019, 2020). From this dataset, adult patients with pancreatic cancer (ICD-10 code C25) who had been treated in 2013-2014 and deceased by the end of 2014 were identified, resulting in a study population of 221 patients.

Similarly, the cohort in Study II originated from a broader dataset of 3,744 cancer patients treated in 2017–2018 at the same institution (Anttonen et al., 2025). Adult patients with pancreatic cancer (ICD-10 code C25) who had died by the end of 2018 were included (n=476). After excluding those who died before April 1, 2017 (n=36) to allow for a minimum three-month look-back period prior to death, the final cohort comprised 440 patients.

### 4.2.2 Study III

Study III was a prospective single-center cohort study conducted at Turku University Hospital. All adult outpatients with a newly diagnosed pancreatic cancer—based on clinical, radiological, or pathological findings—referred to the Department of Oncology were invited to participate. Recruitment took place between November 2019 and July 2022 and was conducted by the investigator with assistance from outpatient clinic staff during routine outpatient visits. Eligibility required that patients were in sufficient general condition to complete the questionnaires independently or with assistance. The only exclusion criterion was poor health status that made participation unfeasible, as assessed by the patient, clinician, or nurse. Inclusion further required sufficient proficiency in Finnish or Swedish. The number of excluded patients was not recorded. Written informed consent was obtained from all participants before study entry. The recruitment target was 75–100 patients over a 2-year period; 54 patients were ultimately enrolled, with follow-up extending until April 2023.

## 4.3 Methods

### 4.3.1 Definition and timing of palliative care decision

The PC decision was defined as the point when life-prolonging anticancer treatment was withheld or discontinued and the intent of care shifted to palliation. The PC phase was defined as the period from the PC decision to death. In Studies I and II, the timing of the PC decision was categorized as:

1. Early PC decision: >30 days before death
2. Late/no PC decision: ≤30 days before death or not made at all

The 30-day threshold is consistent with established EOL quality indicators and facilitates comparison with previous Finnish and international studies (Hirvonen et al., 2020; Zhang et al., 2024; Lees et al., 2019).

In Study II, the referral was defined as EIPC if the first visit to the Cancer Center's Outpatient PC unit occurred during ongoing oncological treatment.

### 4.3.2 Studies I and II

Both retrospective studies used hospital registries as data sources. In Finland, patient records are electronic and systematically documented. Extracted data included patient demographics, ICD-10 diagnoses, systemic and radiation therapy, outpatient

visits, ED visits, and hospitalizations. All data were retrieved in a structured format and exported directly, with the following exceptions:

For Study I, referrals to home care, primary care wards, hospice care, and home hospital care were manually retrieved. Additional data, including PC decisions, DNR orders, and reasons for treatment termination were manually retrieved from medical records. The cause, date, and place of death were obtained from death certificates.

For Study II, the date of the PC decision was identified either from ICD-10 diagnosis Z51.5 (palliative care) or, when absent, from free-text entries in the medical records (keywords: *palliative*, *end-of-life care*). In Finland, the transition to palliative intent is formally documented using ICD-10 code Z51.5, which provides a reliable marker for the timing of a recorded PC decision and is expected to capture all patients with a formally documented decision.

### 4.3.3 Study III

Study III focused on patient-reported outcomes. QoL and pancreatic cancer-related symptoms were measured, and participants completed two paper-based QoL questionnaires from the EORTC.

The questionnaires were:

- QLQ-C30: the core questionnaire assessing global QoL, two global health/QoL items, five functional scales, three symptom scales, and six single-item scales.
- QLQ-PAN26: a pancreatic cancer-specific module that complements the QLQ-C30, focusing on disease-related symptoms, treatment side effects, and psychosocial concerns. While a Finnish version exists, it has not yet been validated.

QLQ-C15-PAL, a shortened version of the QLQ-C30, developed for PC cancer patients was not administered separately. Its corresponding items were derived from the QLQ-C30 for analysis.

Questionnaires were administered at baseline (diagnosis), and at 2 and 4 months. Background information (living situation, occupation, smoking, alcohol, pain medication use) was also collected. Patient permission was sought to access electronic records, which were used to supplement survey data with information on treatments (surgery, chemotherapy, chemoradiation), contact with the SPC unit and timing of the formal PC decision, medication use, and survival.

Scoring followed EORTC guidelines, with scores transformed to a 0–100 scale. Higher scores indicated better functioning and QoL, while higher symptom scores

reflected greater burden. In the PAN26 module, higher scores denoted greater symptom severity, except for healthcare satisfaction, where higher scores represented better satisfaction.

Overall QoL and global health status were derived from items 29 and 30 of the EORTC QLQ-C30. These items are scored on a 1–7 scale and linearly transformed to a 0–100 scale according to the EORTC scoring manual, with higher scores indicating better perceived QoL and health status.

Usability was evaluated by examining completion rates, missing data patterns, internal consistency, and the clinical interpretability of questionnaire results. No formal assessment of clinician- or patient-reported usability or impact on clinical decision-making was conducted.

## 4.4 Statistical analyses

Studies I and II were retrospective, registry-based studies, while Study III was conducted prospectively.

All three studies used descriptive statistics to characterize the study population, including means, medians, interquartile ranges, frequencies, and percentages. Group comparisons were carried out using one-way ANOVA for continuous variables and Fisher's exact test or Pearson's chi-squared test for categorical variables. When the distribution of continuous variables was not normally distributed, the Mann-Whitney U test was applied. In Studies I and II, time-to-event analyses included only patients with a recorded date of PC decision. Study II additionally employed logistic regression to identify factors independently associated with ED visits and hospitalizations during the last 30 days of life. In Study III, questionnaire scoring and analyses were conducted in accordance with EORTC guidelines. Internal consistency was assessed using Cronbach's alpha, and associations between scales were examined using Pearson correlation coefficients. Longitudinal analyses were not performed due to substantial non-random missing data primarily related to clinical deterioration or death.

The statistical analyses in Studies I and II were performed with IBM SPSS Statistics Version 29 (IBM Corp., Armonk, NY, USA). Study III was analyzed with SAS software, Version 9.4 for Windows (SAS Institute Inc., Cary, NC, USA). A p value $<0.05$ was considered statistically significant across all three studies.

## 4.5 Ethical considerations

All studies included in this dissertation were conducted in accordance with the principles of the Declaration of Helsinki.

The registry-based studies (Studies I and II) included only deceased patients and involved no patient interventions. All data were anonymized, handled with strict attention to data privacy, and stored according to the General Data Protection Regulation (GDPR). Permission for the retrospective registry-based studies was granted by the authorities of Helsinki University Hospital. According to Finnish regulations, ethics committee approval is not required for retrospective registry-based studies (Act on the Secondary Use of Social and Health Information [522/2019]).

The prospective cohort study (Study III) was approved by the Ethics Committee of the Wellbeing Services County of Southwest Finland, Turku University Hospital (ETMK 43/2019). Permission was also obtained from Turku University Hospital. Written informed consent was obtained from all patients prior to participation.

# 5 Results

## 5.1 Studies I and II

### 5.1.1 Patient characteristics

Study I included 221 patients with pancreatic cancer, with a median age at death of 69 years (range 62–76), and a balanced sex distribution. Study II included 440 patients, with a median age at death of 72 years (range 29–93 years), and 53% were men. Patient characteristics available in both Studies I and II are summarized in Table 6.

**Table 6.** Patient characteristics in Studies I and II. Modified from Studies I and II.

| | Study I | Study II |
|---|---|---|
| Number of patients | 221 | 440 |
| Median age | 69 | 72 |
| Males | 50% | 53% |
| PC at any point | 88% | 87% |
| >30 days prior to death | 56% | 53% |
| ≤30 days prior to death | 32% | 34% |
| No PC decision | 12% | 13% |

Abbreviation: PC= palliative care

### 5.1.2 Treatment patterns (Study I)

At diagnosis, 52% of patients presented with distant metastases, and 12% were considered primarily operable. Curative-intent therapy was provided for 9%, life-prolonging treatments for 61%, and 35% were managed solely with palliative intent. Clinical and treatment-related characteristics are summarized in Table 7.

**Table 7.** Clinical and treatment-related characteristics in Study I. Modified from Study I.

| | n (%) |
|---|---|
| **Operability at diagnosis** | |
| Primarily operable | 26 (12%) |
| Primarily inoperable, no metastases | 77 (35%) |
| Distant metastases | 114 (52%) |
| **Primary treatment intent** | |
| Curative | 19 (9%) |
| Life-prolonging | 135 (61%) |
| Palliative | 78 (35%) |
| **Chemotherapy use** | |
| Any systemic chemotherapy[a] | 155 (70%) |
| Adjuvant or neoadjuvant chemotherapy | 36 (16%) |
| Non-curative chemotherapy | 143 (65%) |
| 1 line | 87 (39%) |
| 2 lines | 43 (19%) |
| 3 lines | 13 (6%) |
| During the last month of life | 20 (9%) |
| During the last 2 weeks of life | 8 (4%) |
| No systemic anticancer treatment | 78 (35%) |

[a] Categories are not mutually exclusive; patients may have received both adjuvant and non-curative chemotherapy.

### 5.1.3 Anticancer treatment

In Study I, 65% initiated systemic anticancer treatment, while 35% did not receive any disease-modifying therapy. The median duration of life-prolonging therapy was 5.4 months. Treatment discontinuation was most often due to disease progression (49%), followed by clinical deterioration (27%) and treatment toxicity (8%). Chemotherapy near death was relatively infrequent, administered to 9% during the last month and 4% in the last 2 weeks of life.

In Study II, 8% of the whole cohort and 18% of patients with late/no PC decision received chemotherapy in the last month ($p<0.001$). Patients with a late/no PC decision continued anticancer therapy significantly closer to death (median 43 vs. 115 days, $p<0.001$). In the study cohort, 4% received radiotherapy in the last month of life.

### 5.1.4 Palliative care decisions

In Study I, a PC decision was recorded for 88% of the cohort, with a median timing of 2 months prior to death. Nevertheless, 32% of patients had a late (≤30 days before death) PC decision and 12% had no PC decision at all. Older individuals more often received an earlier PC decision (61% vs. 48%, p=0.052).

In Study II, PC decisions were documented for 87% (n=384), with a median of 45 days before death. For the whole cohort, early PC decisions (>30 days before death) occurred in 53%, late decisions in 34%, and 13% had no recorded PC decision. The median duration of the palliative care phase was substantially longer in the early decision group (79 vs. 13 days, p<0.001). The timing of the PC decision in relation to death is shown in Figure 2.

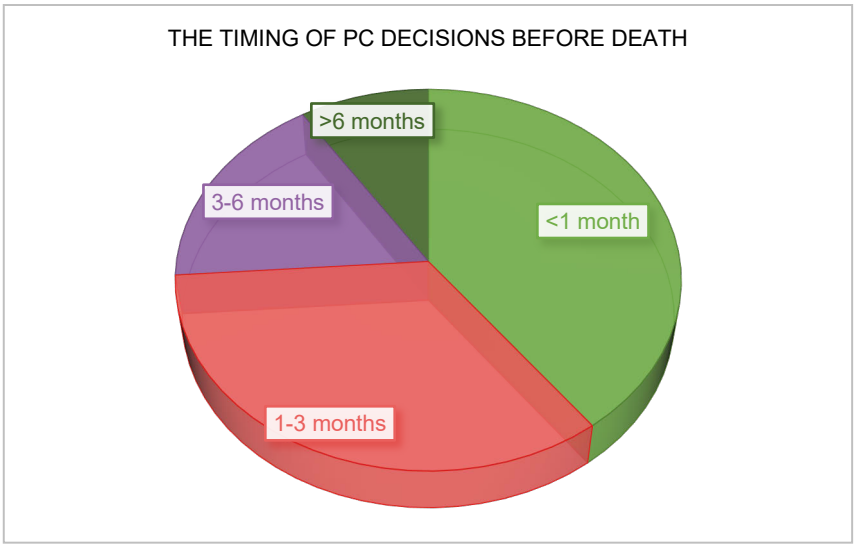


**Figure 2.** Timing of the PC decision in relation to death in Study II. Modified from Study II.

### 5.1.5 Specialist palliative care contact

In Study I, nearly half of the cohort (49%) had at least one visit to the SPC Unit, typically 2.4 months prior to death. In Study II, SPC visits occurred in 73%, with earlier and more frequent visits among those with early PC decisions (3.6 vs. 1 month before death, p<0.001).

### 5.1.6 Do-not-resuscitate orders, Study I

A DNR order was present for 40% of patients. These directives were usually issued within the last 2 weeks of life. In 67%, the order was made by someone other than the treating oncologist.

### 5.1.7 Early integrated palliative care, Study II

EIPC, defined as SPC contact during ongoing anticancer treatment, occurred in 36% of the cohort, typically at a median of 112 days before death, and was associated with a markedly prolonged PC phase (85 vs. 15 days, $p<0.001$). Patients receiving both EIPC and an early PC decision experienced a substantially extended palliative period of approximately 3 months, with their initial contact with the PC unit occurring a median of 6 months before death.

### 5.1.8 Healthcare utilization at the end of life

In Study I, 42% of patients were admitted to a secondary or tertiary hospital, and 38% visited the ED without admission during the final month of life. In the last 2 weeks, 29% required hospitalization, and 26% had ED visits. Patients with early PC decisions had markedly lower overall use of hospital services, with 32% requiring hospital-based care in the last month compared with 68% in the late/no decision group. Late or absent PC decisions were associated with significantly more hospital ED visits (0.75 vs. 0.32 per patient, $p<0.001$) and longer inpatient stays (6.1 vs. 2.3 nights, $p<0.001$) compared to those with early decisions. The same pattern was observed in patients who received chemotherapy, as early PC decisions were linked to substantially lower hospital use in the last month of life (24% vs. 50%, $p=0.001$).

In Study II, delayed or absent PC decisions were linked to increased healthcare utilization: patients experienced nearly twice as many ED visits (61% vs. 27%, $p<0.001$) and roughly threefold more hospitalizations (59% vs. 20%, $p<0.001$) during the last month of life. Median inpatient stay was longer for patients with late/no decision (7 vs. 4 days, $p<0.001$). Service use in the groups with early and late or no PC decision during the last month of life in Studies I and II is shown in Figure 3.

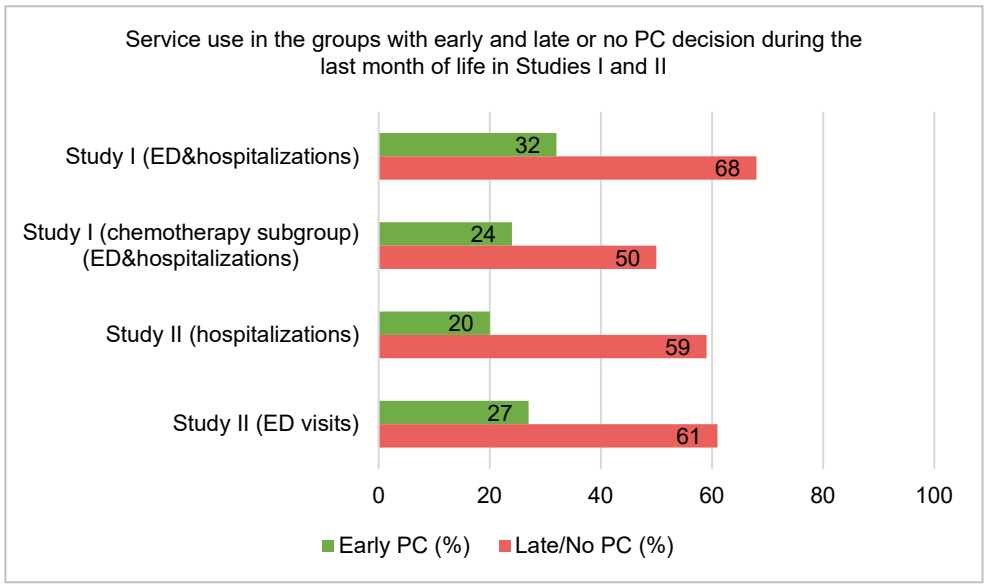


**Figure 3.** Service use in the groups with early and late or no PC decision during the last month of life in Studies I and II. Abbreviations: PC= palliative care, ED= emergency department.

### 5.1.9 Place of death, Study I

The majority of patients (41%) died in primary care hospitals, 31% in hospice or hospital-based SPC wards, 17% at home or in nursing homes, and 10% in tertiary or secondary hospitals. A late or absent PC decision was linked to a higher proportion of hospital deaths (64% vs. 36%) and fewer deaths in hospice or SPC wards (42% vs. 58%), though this difference did not reach statistical significance (p=0.25).

### 5.1.10 Impact of palliative care timing

Across both studies, early PC decisions were consistently associated with lower-intensity EOL care. Patients had fewer ED visits, fewer hospitalizations, shorter inpatient stays, and less chemotherapy near death. In Study I, early decisions also showed a trend toward more deaths in hospice or at home, rather than in hospital. In Study II, contact with the SPC unit during ongoing anticancer treatment (operationalized as EIPC) provided additional benefit, further reducing aggressive EOL care and substantially extending the duration of the PC phase. In both studies, late or missing PC decisions were associated with substantially greater acute healthcare use.

## 5.2 Study III

### 5.2.1 Patient characteristics

The cohort included 54 patients with pancreatic cancer, with a median age of 70 years (range 51–80), with an equal distribution of men and women. Twenty percent had primarily operable tumors and 41% presented with distant metastases at diagnosis. Life-prolonging anticancer therapy was administered to 72% of patients, whereas 20% received no systemic anticancer therapy, with palliative intent from the outset. A PC decision was documented for 76% of patients, and 70% had contact with a palliative care physician at some point, at a median of 6.1 months from diagnosis and 1.7 months before death. Surgical patients received a PC decision less often (27%). Only 31% had a PC contact at the initiation of anticancer therapy. Follow-up was from November 2019 to April 2023.

### 5.2.2 Quality-of-life questionnaires

Three EORTC questionnaires were used: QLQ-C30, QLQ-C15-PAL, and QLQ-PAN26. Correlations between the questionnaires were high ($r \geq 0.76–0.96$, $p < 0.0001$), indicating consistency between general, palliative, and pancreatic cancer-specific items. Missing data increased over time due to patient mortality, limiting the use of conventional repeated-measures models.

### 5.2.3 Reported Symptoms and quality of life during follow-up

Among participants with available follow-up data, no significant changes were observed in experienced overall QoL or general health, which both remained stable throughout follow-up, irrespective of the number of anticancer therapy lines received. Figures 4 and 5 illustrate the reported overall QoL and general health at three assessment time points. Percentages are calculated among respondents at each time point. Attrition over time and unanswered individual items resulted in varying numbers of missing responses across questions.

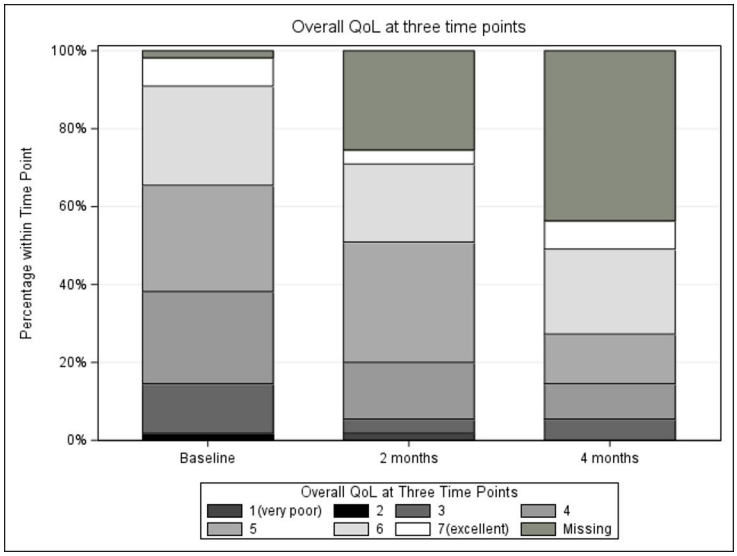


**Figure 4.** Overall quality of life at three time points. Reproduced from original publication III.

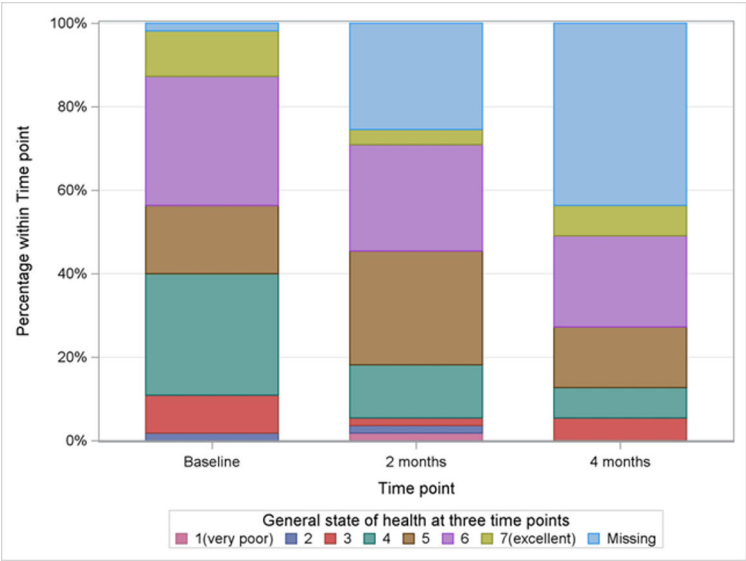


**Figure 5.** General state of health at three time points. Reproduced from original publication III, supplementary material.

The most frequently reported concern was worry about future health, with 52–65% of patients experiencing it as moderate or severe during the study. Figure 6 illustrates the percentage of patients experiencing moderate or severe worry about future health at three time points.

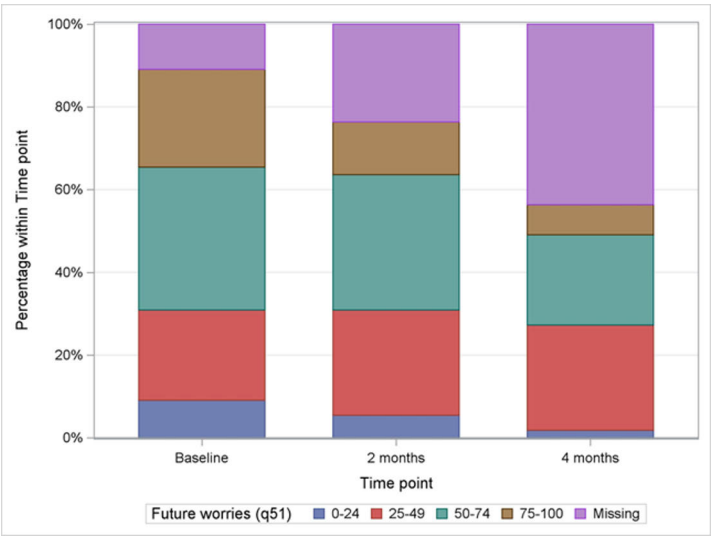


**Figure 6.** Percentage of patients experiencing moderate or severe worry about future health at three different time points. Reproduced from original publication III, supplementary material.

Moderate or severe symptoms included flatulence, worry about low weight, fatigue, abdominal discomfort, and pain, with only minor changes over time. These are summarized in Table 8, showing also the declining number of patients answering the questionnaires. Disturbing AE from anticancer therapy were reported in only 11–22% of patients. Most patients (88–91%) reported satisfaction with support from healthcare professionals.

**Table 8.** Most common moderate or severe symptoms reported by patients. Modified from Study III.

| | Baseline | 2 months | 4 months |
|---|---|---|---|
| **Worry about future health** | 65%, n=49 | 60%, n=42 | 52%, n=31 |
| **Flatulence** | 39%, n=54 | 36%, n=42 | 40%, n=30 |
| **Worry about low weight** | 31%, n=54 | 19%, n=42 | 16%, n=31 |
| **Fatigue** | 35%, n=54 | 27%, n=41 | 16%, n=31 |
| **Abdominal discomfort** | 32%, n=53 | 17%, n=42 | 13%, n=31 |
| **Pain** | 25%, n=52 | 12%, n=42 | 9%, n=32 |
| **Pain interference with daily activities** | 20%, n=54 | 7%, n=41 | 7%, n=31 |

Abbreviation: n = number of patients answering the question

Survival was more than twice as long for patients receiving at least one line of anticancer therapy, whereas patients receiving only PC had a median survival of 2.1 months. Regular opioid use at diagnosis did not affect survival outcomes. Attrition was substantial, with 80% of patients dying during follow-up.

# 6 Discussion

## 6.1 Healthcare resource use in relation to the timing and initiation of palliative care (Studies I and II)

### 6.1.1 Overview

These two retrospective studies examined the timing and impact of PC decisions and referrals in patients with pancreatic cancer treated at a tertiary Finnish cancer center. The definition of early or timely PC in pancreatic cancer varies widely in the literature, ranging from PC initiated within 30 days of diagnosis to referrals made 30–90 days before death (Michael et al., 2019; Bevins et al., 2021; Gonzalez et al., 2023). In the studies of this dissertation, a 30-day threshold was used to define early PC, reflecting a marker of timely PC, as shorter intervals are unlikely to allow patients and caregivers to benefit fully from PC. This threshold has also been applied in several previous studies (Poulose et al., 2013; Blackhall et al., 2016; Hirvonen et al., 2020).

Both studies demonstrated that delayed or absent PC decisions were associated with increased use of acute hospital services during the final month of life, whereas early PC decisions were linked with less aggressive EOL care and greater access to SPC services. Given the known short median survival of approximately 1 year and the limited efficacy of systemic therapies, timely and structured integration of PC is essential for optimizing patient-centered care in pancreatic cancer. Such integration should extend beyond simple concurrent involvement to coordinated multidisciplinary collaboration and shared decision-making. Comparison of the 2013-2014 and 2017-2018 cohorts allows assessment of temporal changes in PC practices, revealing both improvement in SPC access and persistent gaps in early integration. Repeating the study in a later cohort was particularly informative, as EIPC had been introduced between the two periods. This provided an opportunity to evaluate the extent to which guideline recommendations were adopted in clinical practice and whether this was reflected in measurable changes in PC access and EOL care patterns.

### 6.1.2 Timing and referrals to palliative care

Across both studies, PC decisions and SPC referrals frequently occurred late. In Study I, 88% of patients had a PC decision made a median of 2 months before death, and only about half accessed the PC Unit, typically after discontinuation of life-prolonging anticancer treatments. In Study II, 87% of patients had a documented PC decision (median 1.5 months before death), and 73% had SPC contact, representing an improvement compared with Study I (49%). These findings align with earlier Finnish data. In a tertiary hospital cancer center cohort, based on the same institutional dataset, 82% of decedents had a recorded PC decision, and 37% visited the SPC unit (Hirvonen et al., 2020). In another national study of 2,000 cancer patients, 75% had a PC decision, although only approximately one-third had an outpatient SPC visit (Haltia et al., 2023). Similarly, in a more recent analysis from our research group, we reported that 57% of cancer patients had at least one visit to an outpatient PC clinic, indicating gradual improvement in access to specialist services (Anttonen et al., 2025).

Despite this progress and although EIPC had formally been introduced, only one-third of patients in Study II received SPC during ongoing anticancer therapy (median 3.7 months before death), and just 22% received PC in line with guideline recommendations for advanced cancers (Ferrell et al., 2017; Jordan et al., 2018). Similarly, Anttonen et al. (2025) reported that one-third of the visits (32.2%) to the SCP unit occurred during ongoing disease-modifying therapies.

In both Studies I and II, PC decisions and SPC referrals were closely linked to treatment termination rather than being initiated proactively. In Study II, the median interval between treatment cessation and PC initiation was approximately 1 month, suggesting a delayed transition to the PC phase. The present data do not allow determination of why many patients were referred late or not at all. Apart from older age, no clear patient-related predictors of referral timing were identified. It is possible that referral patterns were influenced by physician-related factors, such as individual attitudes toward PC, perceived patient readiness, prognostic uncertainty, or time constraints. Organizational factors, including resource limitations or unclear referral criteria, may also have contributed. These factors were not captured in the current datasets and would require prospective evaluation.

Similar patterns of late referral to the PC unit, often occurring only after anticancer therapy has been discontinued, have been reported both in elderly patients with pancreatic cancer and nationally among cancer patients (Haltia et al., 2023), as well as internationally (Bhulani et al., 2018). In Denmark, comparable results showed that although 60% of pancreatic cancer patients had contact with SPC, the duration of involvement was short, limiting the potential benefit and reflecting incomplete implementation of EIPC (Adsersen et al., 2021). In another study, Michael et al. (2019) reported a median interval of only 48 days between referral and

death, further illustrating the narrow window in which patients receive SPC. Notably, early PC decisions increased both the likelihood and timeliness of SPC referral, emphasizing the synergistic value of proactive decision-making and early engagement with specialist services.

### 6.1.3 Anticancer treatments at the end of life

Across both cohorts, few patients received anticancer treatment near the EOL, reflecting adherence to guidelines discouraging aggressive therapy in late-stage pancreatic cancer. In Study I, chemotherapy was discontinued a median of 2.4 months before death, with fewer than 10% receiving therapy during the last month. Study II reported a similar proportion (8%), consistent with previously reported ranges of 2–23% (Zhang et al.,2024; Lees et al., 2019; Michael et al., 2019). In Study I, treatment discontinuation was most commonly due to disease progression and declining PS, although toxicity and patient preference also played a role.

Delayed or absent PC decisions were linked to anticancer therapy being continued much closer to death. Moreover, although anticancer treatment was typically halted weeks before a formal PC decision, referral to the SPC unit often coincided with the last administered treatment, while the actual decision to forgo disease-modifying therapy was made later, possibly at the next scheduled treatment visit. The interrelation between the timing of the PC decision and access to the PC unit has previously been demonstrated by Hirvonen et al. (2019), who showed that late PC decisions were associated with continuation of anticancer treatments close to death and limited access to PC services.

Previous studies have shown that late referrals to PC are associated with prolonged aggressive treatment, sometimes until the final weeks or days of life (Barth et al., 2020; Haltia et al., 2023).

### 6.1.4 Do-not-resuscitate orders (Study I)

Timely DNR documentation is a critical component of ACP, associated with improved QoL and less aggressive care near death (Garrido et al., 2015; Cui et al., 2021). PC involvement can facilitate these discussions, ensuring that patient preferences are recognized and implemented appropriately (Ma et al., 2019). In our study (Study I), 40% of patients had documented DNR orders, which was higher than in previous reports (18–20%) (Temel et al., 2010; McDonald et al., 2017b), yet these were often issued late and by clinicians other than the primary oncologist. A recent study of pancreatic cancer patients found that those who received a PC consultation were significantly more likely to have a DNR order (83.3% vs. 44.5%) (O'Brien et al., 2025).

### 6.1.5 Utilization of healthcare services

Both studies consistently showed that delayed or absent PC decisions were linked with a greater need for acute hospital services in the last month of life. In Study I, early PC decisions were associated with a 50% reduction in hospital service use, while in Study II, patients with late or no PC decision had approximately twice as many ED visits and three times more hospitalizations compared to those who had early decisions.

Similar observations have been reported in prior studies, where early PC initiation (≥30–90 days before death) reduced ED visits and hospitalizations among pancreatic cancer patients (Michael et al., 2019; Bevins et al., 2021; Gonzalez et al., 2023). In Finnish studies concerning cancer patients, similar patterns have been observed. Contact with the PC unit has been associated with fewer ED visits and inpatient days (Haltia et al., 2023). At the institutional level, Hirvonen et al. (2020) reported that patients without a PC decision had the highest number of ED visits and inpatient days, whereas those with both a documented PC decision and a PC unit appointment had the lowest use of acute services. Moreover, earlier PC decisions increased the likelihood of having an appointment at the PC unit (Hirvonen et al., 2020). In a related analysis from the same research group, in which the present author participated, Anttonen et al. (2025), found that any SPC outpatient visit, integrated or not, decreased the likelihood of hospitalization in the final month of life.

Hospitalizations are often triggered by complications such as pain, infections, nausea, biliary obstruction, or ascites (Michael et al., 2019). Proactive and integrated PC can anticipate and manage such complications or symptoms in outpatient or home settings, reducing patient distress and alleviating pressure on acute-care services.

The PC decision in this study was used as a structural marker of transition to palliative intent. While this documentation reflects an important shift in care planning within the Finnish system, it does not in itself confirm improvements in symptom control, communication, or holistic care at the bedside. No patient-reported or qualitative process indicators were available to verify how the documented decision translated into clinical practice. The associations observed therefore reflect system-level care patterns rather than direct measures of care quality.

### 6.1.6 Place of death (Study I)

Only about 10% of patients died in tertiary hospitals, suggesting limited overtreatment near death. However, patients with late or absent PC decisions were twice as likely to die in hospital settings compared with those with early decisions. This is in line with a Finnish study of cancer decedents, which also noted that a missing formal PC decision was linked to a higher likelihood of death at

secondary/tertiary hospitals (Hirvonen et al., 2020). Early PC decisions were associated with a higher likelihood of death in SPC units, consistent with evidence that PC increases hospice admissions and duration of stay (Maltoni et al., 2016).

Increased acute hospital use near the EOL may partly reflect underlying disease severity rather than solely differences in PC integration. Patients with poorer PS, higher symptom burden, or more complications may require more frequent hospital-based interventions irrespective of the timing of a PC decision. Data on symptom intensity, functional status, and comorbidity were not available in the retrospective cohorts, and residual confounding by disease severity cannot be excluded. Therefore, the observed associations should be interpreted cautiously.

Home deaths were rare, likely reflecting both the severity of disease and the tertiary hospital setting, which tends to manage patients receiving anticancer treatment and may underrepresent the frailest and oldest individuals who are primarily cared for in community settings.

### 6.1.7 Comparison of Studies I and II

Direct comparison of Studies I (2013–2014) and II (2017–2018) suggests partial improvement in PC access over time. While the proportion of patients with a documented PC decision remained similar (88% vs. 87%) and the timing of the decision did not substantially shift, access to SPC increased markedly from 49% to 73%. However, PC decisions and referrals in both cohorts remained closely linked to treatment discontinuation, indicating that integration continued to be largely reactive rather than needs-based. The association between delayed PC decisions and increased acute hospital utilization was consistent across both time periods, underscoring the strength of the findings.

## 6.2 Patient-reported quality of life (Study III)

### 6.2.1 Overview

QoL in pancreatic cancer patients is severely impaired due to the disease's aggressiveness, treatment burden, and associated physical and emotional symptoms (Hubner et al., 2019; Alexander et al., 2022; Tushoski-Alemán et al., 2024). Given that these patients report worse QoL than those with other cancers (Macarulla et al., 2020; Chung et al., 2022) and the short life expectancy in this population, careful assessment of QoL is essential to address this burden and unmet need (Anota et al., 2015; Hubner et al., 2019; Sohal et al., 2020).

QoL data can help patients and clinicians choose treatment strategies that align with patient priorities, particularly in advanced disease settings. Study III aimed to

evaluate the feasibility and clinical utility of three QoL questionnaires in patients with pancreatic cancer and to describe patient-reported symptoms and QoL over a four-month period. Even though PROMs are increasingly recognized as valuable tools for capturing patients' symptoms, the optimal way to integrate PROMs into clinical practice remains unclear, and no consensus has been reached on the most appropriate instrument for assessing QoL (Tushoski-Alemán et al., 2024).

Demographic characteristics and OS in our cohort were consistent with prior reports (Carrato et al., 2015; Laquente et al., 2020; Amin et al., 2022; Yoo et al., 2022), suggesting that the cohort broadly resembled previously described pancreatic cancer populations in terms of age and survival. However, representativeness is limited by the small sample size, selective participation, and substantial attrition.

### 6.2.2 Utility and quality-of-life questionnaires

Although ESAS has been used routinely in our clinic, it has not been formally validated in Finland. In addition, it serves primarily as a symptom screening tool rather than a comprehensive QoL instrument. Study III therefore focused on internationally validated EORTC questionnaires: the QLQ-C30 and its abbreviated version, the QLQ-C15-PAL, together with the pancreatic cancer specific module QLQ-PAN26. While the Finnish translation of the QLQ-PAN26 has not undergone formal psychometric validation, it has been internationally validated and translated according to standardized EORTC procedures. The objective of Study III was not to perform full validation, but to assess the feasibility and practical applicability of the questionnaires in routine care and to describe symptom burden over a four-month follow-up period in a real-world cohort.

All three questionnaires provided largely overlapping information. While the QLQ-C15-PAL is a shortened version of the QLQ-C30, its brevity makes it more feasible for routine clinical use. The QLQ-PAN26, although not a stand-alone instrument, adds value by capturing pancreatic cancer-specific symptoms. Similarly, a systematic review noted that although the EORTC QLQ-C30 is among the most used instruments and captures many factors influencing patients' QoL, the addition of the QLQ-PAN26 may enhance assessment accuracy by addressing disease-specific symptoms, AE, and emotional issues unique to pancreatic cancer (Tushoski-Alemán et al., 2024).

In this study, questionnaires were assessed primarily from the investigator's perspective within a clinical setting. No structured assessment of patient-reported usability or of the direct influence of questionnaire results on treatment decisions was conducted. The primary utility of these tools in this context appears to be in their ability to provide a structured overview of symptom burden and patient concerns, thereby supporting clinical dialogue and individualized symptom management.

However, the study design does not permit conclusions regarding their direct influence on treatment modifications or clinical outcomes.

### 6.2.3 Feasibility of the study

Assessing QoL in pancreatic cancer is particularly challenging due to the disease's aggressiveness and methodological limitations in gathering and interpreting PROMs in a population with high morbidity and mortality. Our study reflected these challenges: recruitment was difficult, as many patients declined enrollment or withdrew due to clinical deterioration. Consequently, the study cohort was skewed toward more well individuals, and attrition during follow-up further selected for those who remained clinically stable. These selective completion rates mirror prior reports of aggressive disease, where high attrition and terminal missingness commonly produce survival selection bias and inflate QoL results, as patients with worsening symptoms often withdraw while those feeling better continue, leading to overestimated results (Tang ST, 2002; Coste et al., 2013; Tushoski-Alemán et al., 2024). Because the primary aim was to examine feasibility and practical applicability rather than to compare subgroups, the limited sample size does not invalidate the descriptive analyses. However, the skewed cohort restricts generalizability, and the findings apply primarily to patients well enough to complete questionnaires in an outpatient oncology setting. Furthermore, no significant changes in QoL were observed over time. Given the high attrition, the limited number of repeated assessments, and the relatively long two-month interval between measurements, the study design does not allow robust conclusions regarding symptom trajectories or the detection of potentially rapid deterioration. Furthermore, although individual-level longitudinal data were analysed, no consistent or clinically meaningful changes were identified. Given the small and progressively selected cohort and the absence of major changes, presentation of individual trajectories was not considered to add meaningful interpretive value.

### 6.2.4 Symptom burden and quality of life

While previous studies have reported severe symptom burden (Yoo et al., 2022), symptom control, including pain management, was generally adequate for this cohort. However, patients with the highest symptom burden may have discontinued follow-up, since, as noted above, patients experiencing greater symptom burden are more likely to drop out, while those with less severe symptoms remain. Variations in the timing and completion of QoL assessments may also bias the results, as well as the so-called response shift, where patients adapt to their changed circumstances

and report better outcomes over time (Witvliet-Van Nierop et al., 2017; Ilie et al., 2019).

Worry about future health was a major concern, understandable given the aggressive disease trajectory. Concurrent COVID-19 social restrictions may also have affected this. Anticancer treatment may stabilize or improve QoL (Laquente et al., 2020; Yoo et al., 2022; Conroy et al., 2023). However, evidence remains limited, and a review found that only a minority of prospective studies have shown sustained QoL improvement over time (Kristensen et al., 2016). In our cohort, no significant changes in QoL were observed over the 4-month follow-up, partly due to patient dropout and variable participation, as discussed earlier.

We collected QoL data to assess its role in symptom management and clinical decision-making. In this cohort, the questionnaires did not predict imminent death or survival, but identified patients' most pressing symptoms and concerns, facilitating individualized dialogue and care planning. Clinical decision-making in advanced pancreatic cancer is inherently multifactorial and guided by PS, clinical examination, laboratory and radiological findings, treatment tolerance, and patient preferences. PROMs should therefore be regarded as complementary tools that enhance structured symptom assessment and patient-centered communication rather than as independent decision-making instruments. Their primary value may lie in systematically capturing patient's perspective. While previous studies indicate that QoL measures can also provide prognostic information and be used for shared decision-making (Montazeri, 2009; Ediebah et al., 2018; MacKay et al., 2020), the present study supports their role primarily as facilitators of structured clinical dialogue rather than predictors of outcomes.

Randomized trials have demonstrated that systematic electronic symptom reporting, by using web-based platforms or automated telephone systems with clinician alerts, can significantly improve outcomes in patients with advanced or metastatic cancer. These interventions have been associated with better symptom control, fewer ED visits and hospitalizations, and in some settings even prolonged survival (Basch et al., 2016, 2017, 2022; Denis et al., 2019). The observed benefits are thought to arise from earlier detection of symptom deterioration, more timely clinical responses, and greater patient engagement in care. In addition to survival benefits, digital symptom monitoring has been shown to improve HRQoL and maintain physical functioning. Patients also report a greater sense of control over their treatment experience. Among these studies, the PRO-TECT trial (Basch et al., 2022) included patients with pancreatic cancer.

In the present study, questionnaires were administered in paper format at predefined intervals, and no real-time alert system was implemented. Consequently, the benefits reported in ePROM trials cannot be directly extrapolated to this cohort. In a disease characterized by rapid clinical deterioration, more structured and

potentially more frequent electronic symptom monitoring may be particularly relevant for enabling earlier PC integration and reducing unplanned acute care utilization.

### 6.2.5 Integration of palliative care

EIPC was not yet standard at the study site during data collection. During the study, 70% of patients had contact with the Palliative Care Unit at least once, and one-third met a physician at the initiation of anticancer therapy, suggesting early integration in some cases. During the time of the study, most pancreatic cancer patients met a nurse specialist from the SPC team early in the disease trajectory. This is in line with evidence that nurse-led or early PC interventions can improve QoL and facilitate better symptom management (Bakitas et al., 2009; Chung et al., 2022). Evidence from other advanced cancers indicates that earlier PC involvement may reduce high-intensity EOL care and hospital use (Temel et al., 2010; Maltoni et al., 2016; Vanbutsele et al., 2018), findings that are highly relevant in pancreatic cancer.

### 6.2.6 Synthesis of findings across Studies I–III

Studies I-II demonstrated that delayed or absent PC decisions were common and consistently associated with higher health care utilization during the last month of life. Early PC decisions were associated with earlier and more frequent access to SPC and less aggressive EOL care. PC decision-making and SPC referrals were closely linked to termination of anticancer treatment, indicating that integration often occurred late and reactively rather than based on systematic needs assessment.

Study III complements these findings by showing that structured PROMs are feasible in routine outpatient care and can identify key symptoms and patient concerns in pancreatic cancer. Although longitudinal monitoring was limited by non-random attrition, PROMs provided meaningful information at individual time points and supported structured clinical dialogue.

Together, the three studies suggest that delayed palliative integration in pancreatic cancer reflects structural and behavioral patterns within oncology care. The combined findings suggest that lack of structured needs assessment may contribute to delayed recognition of palliative needs and consequently to late PC decision-making.

## 6.3 Strengths and limitations

The main limitations of Studies I and II relate to their retrospective design, single-center setting, and reliance on hospital medical records, which may underestimate

PC delivered outside tertiary care. In addition, the data were partly dated, and patterns of care may have evolved since the study period. However, systematic early PC integration remains uncommon in many settings, making the findings relevant. Because the studies were retrospective and relied on registry-based electronic records, QoL data were not available, as PROMs were not routinely documented during the study periods. Thus, assessment was limited to registry-based structural and utilization indicators rather than bedside symptoms.

By including only deceased patients, complete data on EOL utilization was ensured. However, this design excludes patients who survived beyond the study period and may introduce selection bias when interpreting care trajectories. A further methodological consideration concerns the categorization of PC timing (>30 days vs. ≤30 days before death or none). Patients with shorter survival are inherently more likely to fall into the late/no-PC group, and they may also have more aggressive disease, higher symptom burden, and greater healthcare needs. This creates potential internal bias (confounding by prognosis), particularly when examining associations with hospital use and treatment intensity. Although demographic factors were examined, residual confounding by disease severity, PS, and symptom burden cannot be excluded. Information on cancer stage at diagnosis and timing of treatment initiation was not available in structured form, further limiting adjustment for disease trajectory. The study design did not allow adjustment for these variables, and the findings should therefore be interpreted as associations rather than causal effects.

Strengths of Studies I and II include comprehensive real-world data covering all pancreatic cancer patients treated at the institution during defined periods, reliable documentation of hospital utilization, and the opportunity to compare two time points before and after institutional implementation of EIPC principles.

Study III was limited by small sample size, recruitment challenges, and substantial attrition due to rapid deterioration. The absence of a screening log and systemic documentation of reasons for non-participation restricts assessment of recruitment bias and external validity. Only limited background variables were collected. A standardized baseline dataset (i.e. the EAPC Basic Dataset) was not applied, and PS was not recorded, which limits characterization of the study population and impairs assessment of generalizability. The cohort therefore primarily represents outpatients with sufficient functional capacity to complete questionnaires, rather than the full spectrum of pancreatic cancer patients.

A further limitation is that QLQ-C15-PAL was not independently completed by the patients but instead derived from QLQ-C30 responses, since responses may be influenced by instrument length, item order, and contextual effects from preceding questions. Therefore, extracting QLQ-C15-PAL items from the longer QLQ-C30 may not fully reflect how the shorter instrument would perform if administered separately. This approach inherently produces overlapping data and limits

independent comparison between instruments. In addition, QLQ-PAN26 is designed as a supplementary module and should not be interpreted as a stand-alone instrument. These methodological aspects restrict conclusions regarding comparative instrument performance. While the feasibility of structured PROM collection in outpatient pancreatic cancer care was demonstrated, this is not a novel finding. Rather, the contribution of Study III lies in describing practical implementation challenges and symptom patterns in this specific high-morbidity population. The study did not formally evaluate the impact of PROMs on clinical decision-making. High attrition and survival-related missingness further limit conclusions regarding longitudinal symptom trajectories. Consequently, findings regarding QoL stability over time should be interpreted cautiously.

Consistent with prior studies, further improvements, such as standardized assessments, reduced attrition, systematic PS collection, and better handling of missing data, are needed to enhance the validity of QoL research in pancreatic cancer (Tushoski-Alemán et al., 2024; Coste; Tang et al., 2021).

## 6.4 Clinical relevance of the findings

Pancreatic cancer is characterized by short survival and high symptom burden, making timely PC integration particularly important. The present findings show that PC decisions were often made late and frequently coincided with discontinuation of anticancer treatment. This pattern was associated with greater use of acute hospital services at the EOL. Several factors may contribute to these patterns. Referral to SPC appeared to occur primarily when disease-modifying therapy was stopped, suggesting that PC was often viewed as a late-stage transition rather than concurrent supportive care. Prognostic uncertainty, therapeutic optimism, institutional treatment culture, limited referral triggers, and constrained SPC resources may all contribute. In addition, rapid clinical deterioration may shorten the window for proactive involvement.

From a clinical perspective, earlier and structured identification of PC needs, through standardized referral criteria, routine symptom assessment, and proactive goal-of-care discussions, may reduce high-intensity hospital-based care and improve patient-centered trajectories. Integration of PROMs into routine practice, particularly in electronic formats with automated alerts, may support earlier recognition of unmet needs.

## 6.5 Future considerations

PC should be incorporated into the care pathway of all patients with advanced pancreatic cancer from an early stage. The present findings indicate that referral

practices remain largely reactive and closely linked to treatment cessation. More structured, needs-based referral pathways are therefore warranted. Embedding a PC specialist within the multidisciplinary team at predefined clinical milestones, such as the initiation of second-line therapy, during complex decision-making, or when conducting ACP, could facilitate earlier and more consistent integration. However, the optimal timing and model for integrating PC in pancreatic cancer still require further prospective evaluation. Although some patients in Study II were classified as having received IPC, PC contact concurrent with ongoing anticancer treatment often occurred late and did not represent true early integration. Additional research focused on true EIPC in pancreatic cancer patients is therefore needed, particularly given differences in definitions and implementation across studies.

Cost-effectiveness of EOL care represents another important area for future work. Acute hospital care in the final weeks of life is resource-intensive and often misaligned with patient preferences. Hospital visits may impose a substantial burden on frail patients and reduce time spent at home with family. Evaluating the economic impact of EOL care would complement the findings of this dissertation and help guide policy and resource allocation.

Further research is also needed to better understand QoL outcomes and patient preferences regarding EOL care. These aspects are best captured through prospective designs or through the implementation of more structured symptom and QoL assessments in routine practice, though such studies often face challenges such as small cohorts and selection bias toward patients who are well enough to participate. Routine PROM implementation should include sufficiently frequent assessments to detect escalating symptoms in a timely manner. In Study III, the two-month interval between measurements was likely too long to capture rapid clinical changes typical of pancreatic cancer.

Digital symptom monitoring tools may facilitate earlier detection of clinical deterioration and allow for more timely and targeted symptom management, potentially enhancing the quality of symptom control throughout the disease trajectory. A needs-based electronic questionnaire system with automated alerts to clinical staff could enable more timely interventions, reduce unnecessary hospital use, and support earlier SPC consultation and more individualized, responsive care.

# 7 Conclusions

Studies I and II collectively demonstrate the importance of timely PC decision-making in pancreatic cancer. Despite the aggressive disease course and well-documented benefits of early PC involvement, nearly half of the patients entered the PC phase only in the last month of life or lacked a formal PC decision altogether. This delay was consistently associated with higher healthcare utilization at the EOL, including more ED visits, more hospitalizations, and the continuation of anticancer treatments closer to death. Earlier initiation of the PC phase was associated with earlier and more frequent SPC involvement and was linked with less aggressive EOL care. Although SPC access improved over time, referrals still occurred late for many patients, limiting their potential benefit. These findings highlight the need for systematic early integration of PC, ideally alongside ongoing anticancer therapy, to reduce avoidable hospital use, optimize symptom management, and promote dignified, patient-centered care at the EOL.

Study III reflected the short survival typical of this population, resulting in substantial attrition during follow-up. PROMs did not demonstrate prognostic value in this cohort but were useful for highlighting key symptoms and supporting individualized clinical dialogue at the time of assessment. The QLQ-C15-PAL offered an adequate overview of patient well-being, while the QLQ-PAN26 added pancreatic cancer-specific symptom insight. However, the long intervals between assessments and dropout limited evaluation of symptom trajectories. Regular and sufficiently frequent symptom assessment is essential for documenting change and guiding timely interventions. PROMs remain important for tailoring care and enhancing patient-clinician communication.

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# List of Figures, Tables and Appendices

## Figures



## Tables



## Appendices

# Appendices

**Appendix 1.** Background Data Form, Study III.

TAUSTATIETOLOMAKE

1. Asutteko
    a. yksin
    b. perheen kanssa
        i. puoliso
        ii. lapsi/lapsia
            1. syntymävuodet
        iii. vanhemmat
        iv. muu

2. Ammattinne on:

3. Mitä kipulääkkeitä käytätte, lääkkeen nimi vahvuus ja annosmäärä?
    a. säännöllisesti
    b. tarvittaessa

4. Tupakoitteko?
    a. kyllä
        i. montako vuotta
        ii. miten monta savuketta vuorokaudessa?
    b. ei

5. Alkoholinkäyttö
    a. Kuinka usein juotte olutta, viiniä tai muita alkoholijuomia? Huomioikaa myös ne kerrat, jolloin nautitte vain pieniä määriä, esim. pullon keskiolutta tai tilkan viiniä.
        i. en koskaan

ii. noin kerran kuussa tai harvemmin
iii. 2-4 kertaa kuussa
iv. 2-3 kertaa viikossa
v. 4 kertaa viikossa tai useammin

b. Kuinka monta annosta alkoholia yleensä olette ottanut niinä päivinä, jolloin käytitte alkoholia?
   i. 1-2 annosta
   ii. 3-4 annosta
   iii. 5-6 annosta
   iv. 7-9 annosta
   v. 10 annosta tai enemmän

c. Kuinka usein olette juonut kerralla kuusi tai useampia annoksia?
   i. en koskaan
   ii. harvemmin kuin kerran kuussa
   iii. kerran kuussa
   iv. kerran viikossa
   v. päivittäin tai lähes päivittäin

**Appendix 2.** EORTC Questionnaires of Study III.

FINNISH

## EORTC QLQ-C30 (version 3.0.)

Selvitämme kyselyssämme joitakin teitä ja terveyttänne koskevia asioita. Pyydämme teitä vastaamaan itse kaikkiin kysymyksiin ympyröimällä parhaiten sopivan numeron. Tässä kyselyssä ei ole "oikeita" eikä "vääriä" vastauksia. Pidämme antamanne tiedot ehdottoman luottamuksellisina.

Täyttäkää tähän nimikirjaimenne: ⌊_⌋⌊_⌋⌊_⌋

Syntymäaika (päivä, kk, vuosi): ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

Kyselyn täyttöpäivä (päivä, kk, vuosi): 31 ⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋⌊_⌋

| | | Ei lainkaan | Vähän | Melko paljon | Hyvin paljon |
|---|---|---|---|---|---|
| 1. | Tuntuvatko rasittavat työt kuten painavan ostoskassin tai matkalaukun kantaminen teistä työläältä? | 1 | 2 | 3 | 4 |
| 2. | Tuntuvatko pitkät kävelymatkat työläiltä? | 1 | 2 | 3 | 4 |
| 3. | Tuntuvatko lyhyet kävelymatkat kotinne ulkopuolella työläiltä? | 1 | 2 | 3 | 4 |
| 4. | Pitääkö teidän pysytellä levossa tai istumassa päivän mittaan? | 1 | 2 | 3 | 4 |
| 5. | Tarvitsetteko apua ruokaillessanne, pukeutuessanne, peseytyessänne tai WC:n käytössä? | 1 | 2 | 3 | 4 |

| **Kuluneella viikolla:** | | Ei lainkaan | Vähän | Melko paljon | Hyvin paljon |
|---|---|---|---|---|---|
| 6. | Oliko teillä vaikeuksia suoriutua työstänne tai muista päivittäisistä toimistanne? | 1 | 2 | 3 | 4 |
| 7. | Oliko teillä rajoituksia harrastus- tai muissa vapaa-ajan toiminnoissanne? | 1 | 2 | 3 | 4 |
| 8. | Oliko teillä hengenahdistusta? | 1 | 2 | 3 | 4 |
| 9. | Oliko kipuja? | 1 | 2 | 3 | 4 |
| 10. | Tunsitteko levontarvetta? | 1 | 2 | 3 | 4 |
| 11. | Oliko unettomuutta? | 1 | 2 | 3 | 4 |
| 12. | Tunsitteko heikotusta? | 1 | 2 | 3 | 4 |
| 13. | Oliko ruokahaluttomuutta? | 1 | 2 | 3 | 4 |
| 14. | Oliko pahoinvointia? | 1 | 2 | 3 | 4 |
| 15. | Oksensitteko? | 1 | 2 | 3 | 4 |
| 16. | Oliko ummetusta? | 1 | 2 | 3 | 4 |

Jatkuu seuraavalle sivulle

FINNISH

| **Kuluneella viikolla:** | **Ei lainkaan** | **Vähän** | **Melko paljon** | **Hyvin paljon** |
|---|---|---|---|---|
| 17. Oliko ripulia? | 1 | 2 | 3 | 4 |
| 18. Olitteko väsynyt? | 1 | 2 | 3 | 4 |
| 19. Häiritsikö kipu päivittäisiä toimianne? | 1 | 2 | 3 | 4 |
| 20. Oliko teillä keskittymisvaikeuksia esim. sanomalehteä lukiessanne tai televisiota katsellessanne? | 1 | 2 | 3 | 4 |
| 21. Olitteko jännittynyt? | 1 | 2 | 3 | 4 |
| 22. Olitteko huolestunut? | 1 | 2 | 3 | 4 |
| 23. Olitteko ärtynyt? | 1 | 2 | 3 | 4 |
| 24. Olitteko masentunut? | 1 | 2 | 3 | 4 |
| 25. Oliko teidän vaikea muistaa asioita? | 1 | 2 | 3 | 4 |
| 26. Häiritsikö hoito tai fyysinen kuntonne perhe-elämäänne? | 1 | 2 | 3 | 4 |
| 27. Häiritsikö hoito tai fyysinen kuntonne sosiaalista kanssakäymistä? | 1 | 2 | 3 | 4 |
| 28. Aiheuttaako fyysinen kuntonne tai hoito taloudellisia vaikeuksia? | 1 | 2 | 3 | 4 |

**Vastatkaa seuraaviin kysymyksiin ympyröimällä numerosarjasta 1-7 teihin parhaiten sopiva vaihtoehto**

29. Millainen yleinen terveydentilanne oli kuluneella viikolla?

1 2 3 4 5 6 7

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30. Millainen yleinen elämänne laatu oli kuluneella viikolla?

1 2 3 4 5 6 7

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## EORTC QLQ - PAN26

Potilaat kertovat joskus, että heillä on seuraavia oireita tai ongelmia. Olkaa hyvä ja ilmoittakaa, missä määrin teillä on ollut näitä oireita tai ongelmia viimeisen viikon aikana. Vastatkaa ympyröimällä se numero, joka parhaiten sopii teihin.

| **Kuluneella viikolla:** | **Ei/en lainkaan** | **Vähän** | **Melko paljon** | **Hyvin paljon** |
|---|---|---|---|---|
| 31. Onko teillä ollut vaivoja vatsan alueella? | 1 | 2 | 3 | 4 |
| 32. Onko teillä ollut turvotuksen tunnetta vatsassa? | 1 | 2 | 3 | 4 |
| 33. Onko teillä ollut selkäkipua? | 1 | 2 | 3 | 4 |
| 34. Onko teillä ollut kipua öisin? | 1 | 2 | 3 | 4 |
| 35. Ovatko tietyt asennot tuntuneet teistä epämiellyttäviltä (esim. makuuasento)? | 1 | 2 | 3 | 4 |
| 36. Onko teidän täytynyt rajoittaa tiettyjen ruokien syömistä sairautenne tai siihen liittyvien hoitojen vuoksi? | 1 | 2 | 3 | 4 |
| 37. Onko teidän täytynyt syödä pienempiä annoksia sairautenne tai siihen liittyvien hoitojen vuoksi? | 1 | 2 | 3 | 4 |
| 38. Maistuiko ruoka ja juoma erilaiselta kuin ennen? | 1 | 2 | 3 | 4 |
| 39. Onko teillä ollut ruoansulatusvaivoja? | 1 | 2 | 3 | 4 |
| 40. Onko teillä ollut ilmavaivoja? | 1 | 2 | 3 | 4 |
| 41. Oletteko ollut huolissanne painonne alhaisuuden vuoksi? | 1 | 2 | 3 | 4 |
| 42. Ovatko käsivartenne ja jalkanne tuntuneet heikoilta? | 1 | 2 | 3 | 4 |
| 43. Onko suunne ollut kuiva? | 1 | 2 | 3 | 4 |
| 44. Onko teillä ollut kutinaa? | 1 | 2 | 3 | 4 |
| 45. Kuinka keltainen ihonne on ollut? | 1 | 2 | 3 | 4 |
| 46. Onko suolentoimintanne ollut säännöllistä? | 1 | 2 | 3 | 4 |
| 47. Oletteko tunteneet äkillistä, pakottavaa tarvetta ulostaa? | 1 | 2 | 3 | 4 |
| 48. Oletteko tuntenut itsenne ruumiillisesti vähemmän viehättäväksi sairautenne tai saamanne hoidon takia? | 1 | 2 | 3 | 4 |

Jatkuu seuraavalle sivulle

FINNISH

| **Kuluneella viikolla:** | **Ei/en lainkaan** | **Vähän** | **Melko paljon** | **Hyvin paljon** |
|---|---|---|---|---|
| 49. Oletteko tyytymätön vartaloonne? | 1 | 2 | 3 | 4 |
| 50. Kuinka paljon olette kärsinyt hoitonne sivuvaikutuksista? | 1 | 2 | 3 | 4 |
| 51. Oletteko huolissanne tulevasta terveydentilastanne? | 1 | 2 | 3 | 4 |
| 52. Onko teidän täytynyt rajoittaa tulevien tapahtumien suunnittelua (esim. ystävien tapaamista)? | 1 | 2 | 3 | 4 |
| 53. Oletteko saaneet asianmukaista tukea teitä hoitaneilta terveydenhuollon ammattilaisilta? | 1 | 2 | 3 | 4 |
| 54. Oletteko saaneet asianmukaista tietoa terveydentilastanne ja hoidoista? | 1 | 2 | 3 | 4 |
| 55. Onko kiinnostuksenne seksiin vähentynyt? | 1 | 2 | 3 | 4 |
| 56. Tuottaako seksi vähemmän nautintoa? | 1 | 2 | 3 | 4 |

FINNISH

**EORTC QLQ-C15-PAL (version 1)**

Selvitämme kyselyssämme joitakin teitä ja terveyttänne koskevia asioita. Pyydämme teitä vastaamaan itse kaikkiin kysymyksiin ympyröimällä parhaiten sopiva numero. Tässä kyselyssä ei ole "oikeita" eikä "vääriä" vastauksia. Pidämme antamanne tiedot ehdottoman luottamuksellisina.

Täyttäkää tähän nimikirjaimenne: |_|_|_|_|
Syntymäaika (päivä, kk, vuosi): |_|_|_|_|_|_|_|_|
Kyselyn täyttöpäivä (päivä, kk, vuosi): |_|_|_|_|_|_|_|_|

| | | Ei lainkaan | Vähän | Melko paljon | Hyvin paljon |
|---|---|---|---|---|---|
| 1. | Tuntuvatko lyhyet kävelymatkat kotinne ulkopuolella työläiltä? | 1 | 2 | 3 | 4 |
| 2. | Pitääkö teidän pysytellä maaten tai istumassa päivän mittaan? | 1 | 2 | 3 | 4 |
| 3. | Tarvitsetteko apua ruokaillessanne, pukeutuessanne, peseytyessänne tai WC:n käytössä? | 1 | 2 | 3 | 4 |

| **Kuluneella viikolla:** | | Ei lainkaan | Vähän | Melko paljon | Hyvin paljon |
|---|---|---|---|---|---|
| 4. | Oliko teillä hengenahdistusta? | 1 | 2 | 3 | 4 |
| 5. | Oliko kipuja? | 1 | 2 | 3 | 4 |
| 6. | Oliko unettomuutta? | 1 | 2 | 3 | 4 |
| 7. | Tunsitteko heikotusta? | 1 | 2 | 3 | 4 |
| 8. | Oliko ruokahaluttomuutta? | 1 | 2 | 3 | 4 |
| 9. | Oliko pahoinvointia? | 1 | 2 | 3 | 4 |

Jatkuu seuraavalle sivulle

FINNISH

| **Kuluneella viikolla:** | **Ei lainkaan** | **Vähän** | **Melko paljon** | **Hyvin paljon** |
|---|---|---|---|---|
| 10. Oliko ummetusta? | 1 | 2 | 3 | 4 |
| 11. Olitteko väsynyt? | 1 | 2 | 3 | 4 |
| 12. Häiritsikö kipu päivittäisiä toimianne? | 1 | 2 | 3 | 4 |
| 13. Olitteko jännittynyt? | 1 | 2 | 3 | 4 |
| 14. Olitteko masentunut? | 1 | 2 | 3 | 4 |

**Vastatkaa seuraavaan kysymykseen ympyröimällä numerosarjasta 1-7 teihin parhaiten sopiva vaihtoehto**

15. Millainen yleinen elämänne laatu oli kuluneella viikolla?

1 2 3 4 5 6 7

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TURUN
YLIOPISTO
UNIVERSITY
OF TURKU

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