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UTILIZATION OF PALLIATIVE CARE AND HEALTHCARE AT END-OF-LIFE BY PATIENTS WITH PRIMARY AND SECONDARY BRAIN TUMORS

Nelli-Sofia Nåhls

ACADEMIC DISSERTATION

To be presented, with the permission of the Faculty of Medicine of the University of Helsinki, for public examination in lecture room Ullanlinna, at Siltasairaala, Helsinki University hospital, on 6 June 2025, at 12 noon.

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To my family

Abstract

Background and objectives:

In cases of primary or secondary brain tumors, the prognosis is often poor, and patients often suffer substantial symptom burdens and frequently require hospitalization at the end of life (EOL). Although palliative care (PC) can alleviate suffering, it remains underutilized in neuro-oncology. This dissertation aims to assess how the timing of PC decisions—that is, decisions to terminate curative/life-prolonging anticancer treatments and to focus on PC—and the timing of specialist palliative care (SPC) contacts (early defined as >30 days before death, vs. late/no defined as ≤30 days or no decision or contact) are associated with EOL outcomes, including the utilization of healthcare resources and anticancer treatments at EOL and place of death.

Patients and methods:

Three retrospective studies were conducted as part of this dissertation study:

Study I: By examining 121 patients with malignant primary brain tumors treated at the Helsinki University Hospital Comprehensive Cancer Center, this study evaluated the association between the timing of PC decisions and emergency department visits, hospitalizations, and places of death.

Study II: Looking at 91 patients with brain metastases who received radiotherapy at Vaasa Central Hospital, this study examined the association between the timing of PC decisions and emergency department visits and hospitalizations, and the timing of radiotherapy administration.

Study III: Using a nationwide cohort of 373 adults who died from brain tumors in 2019, this study investigated whether the timing of the first SPC contact was associated with overall healthcare resource utilization and place of death.

The data were obtained from manual medical record reviews and national registers (Care Register, Kanta Services, and Causes of Death).

Results:

Study I: A PC decision was made in 78 percent of cases, with a median timing of 44 days before death. Early PC decisions were associated with fewer emergency department visits and hospitalizations at EOL, but no significant association was observed with place of death.

Study II: Overall survival was poor among patients with brain metastases (median 3.7 months) despite radiotherapy. In most cases, PC decisions were made late, but those with early PC decisions were hospitalized less often and had lower rates of in-hospital mortality.

Study III: Only 27 percent of the deceased brain tumor patients had SPC contact. Those with early SPC contact had significantly fewer hospitalizations in their last month (48% vs. 76%) and more often received EOL care in a long-term care facility or an SPC ward than in an acute care hospital.

Conclusions:

Early PC decisions and early SPC contact are associated with less utilization of acute care and lower in-hospital death rates. Despite these benefits, referral to PC in neuro-oncology is often delayed, which underscores the need for earlier integration of PC.

Keywords:

Palliative care, healthcare utilization, end-of-life care, place of death, brain tumor, brain metastasis

Tiivistelmä

Tausta ja tavoitteet:

Aivokasvainta sairastavilla potilailla on tyypillisesti huono ennuste, merkittävä oirekuorma ja he usein tarvitsevat sairaalahoitoa elämän loppuvaiheessa. Vaikka palliatiivinen hoito lievittää kärsimystä, sen integrointi neuro-onkologisten potilaiden hoitoon on puutteellista. Tässä väitöskirjassa tutkittiin, kuinka palliatiivisen hoitolinjan ajoitus – eli kuratiivisten tai elämän pidentämistä tavoittelevien syöpähoitojen lopettaminen ja siirtyminen palliatiiviseen hoitoon – sekä palliatiivisen hoidon kontaktien ajoitus (varhainen, yli 30 päivää ennen kuolemaa, vs. myöhäinen/ei ollenkaan, ≤30 päivää ennen kuolemaa) liittyvät elämän loppuvaiheen hoitoon, mukaan lukien terveydenhuollon resurssien käyttö, syöpähoitojen käyttö elämän loppuvaiheessa ja kuolinpaikkaan.

Potilaat ja menetelmät:

Väitöskirja koostuu kolmesta retrospektiivisestä tutkimuksesta:

Tutkimus I: Tutkimus sisälsi 121 pahanlaatuista aivokasvainta sairastavaa potilasta, joita hoidettiin Helsingin yliopistollisen keskussairaalan syöpäkeskuksessa. Tutkimuksessa selvitettiin palliatiivisten hoitolinjan ajoituksen ja päivystyskäyntien, sairaalaosastojaksojen sekä kuolinpaikan välistä yhteyttä.

Tutkimus II: Tutkimus sisälsi 91 potilasta, jotka saivat aivoetäpesäkkeiden vuoksi sädehoitoa Vaasan Keskussairaalan sädehoitoyksikössä. Tutkimuksessa selvitettiin palliatiivisten hoitolinjan ajoituksen yhteyttä päivystyskäynteihin, sairaalaosastojaksoihin sekä sädehoidon ajoitukseen.

Tutkimus III: Tutkimus sisälsi koko Suomessa vuonna 2019 aivokasvaimiin kuolleet aikuiset (n=373). Tutkimuksessa selvitettiin palliatiivisen hoidon kontaktin ajoituksen yhteyttä terveydenhuollon resurssien käyttöön ja kuolinpaikkaan.

Aineistot kerättiin manuaalisesti potilasasiakirjoista ja kansallisista rekistereitä (Terveydenhuollon hoitoilmoitusrekisteri, Kanta-palvelut ja Kuolinsyyrekisteri).

Tulokset:

Tutkimus I: Palliatiivinen hoitolinjaus tehtiin 78 %:lle potilaista, keskimäärin 44 päivää ennen kuolemaa. Varhain tehty palliatiivinen hoitolinja oli yhteydessä vähäisempiin päivystyskäynteihin ja sairaalaosastojaksojen määrään elämän loppuvaiheessa, vaikka merkittävää yhteyttä kuolinpaikkaan ei havaittu.

Tutkimus II: Aivoetäpesäkkeitä sairastavien syöpäpotilaiden kokonaiselossaoloaika oli lyhyt (keskimäärin 3,7 kuukautta) huolimatta saadusta sädehoidosta. Palliatiivinen hoitolinja tehtiin suurimmalla osalla potilaista myöhään. Potilailla, joille palliatiivinen hoitolinja tehtiin varhain, oli vähemmän sairaalaosastojaksoja ja alhaisempi sairaalakuolleisuus.

Tutkimus III: Vain 27 % aivokasvaimeen kuolleista potilaista oli palliatiivisen hoidon kontakti. Ne, joilla oli varhainen palliatiivisen hoidon kontakti, oli merkittävästi vähemmän sairaalaosastojaksoja viimeisen elinkuukauden aikana (48 % vs. 76 %). Lisäksi heidän elämän loppuvaiheen hoitonsa järjestettiin yleisemmin ympärivuorokautisen hoivan yksiköissä tai palliatiivisella vuodeosastolla sairaaloiden sijaan.

Johtopäätökset:

Varhainen palliatiivinen hoitolinjaus ja palliatiivisen hoidon kontakti liittyvät vähäisempään akuuttihoidon käyttöön ja alhaisempaan sairaalakuolleisuuteen. Tästä huolimatta palliatiivisen hoidon aloitus neuro-onkologiassa tapahtuu myöhään, mikä korostaa varhaisen integroidun palliatiivinen hoidon merkitystä tässä potilasryhmässä.

Avainsanat:
Palliatiivinen hoito, terveydenhuollon resurssit, terveydenhuolto, elämän loppuvaiheen hoito, kuolinpaikka, aivokasvain, aivoetäpesäke

List of abbreviations

ASCO	American Society of Clinical Oncology
CT	Computed tomography
EOL	End of life
ESMO	European Society for Medical Oncology
GBM	Glioblastoma multiforme
IDH	Isocitrate dehydrogenase
I.E.	id est, that is
MRI	Magnetic resonance imaging
NSCLC	Non-small cell lung cancer
OS	Overall survival
PC	Palliative care
QoL	Quality of life
SPC	Specialist palliative care
SRT	Stereotactic radiotherapy
WHO	World Health Organization
WBRT	Whole-brain radiotherapy

List of tables and figures

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List of original publications

This thesis is based on the following publications:

I	Nåhls NS, Leskelä RL, Saarto T, Hirvonen O, Anttonen A. Effect of palliative care decisions making on hospital service use at end-of-life in patients with malignant brain tumors: a retrospective study. BMC Palliat Care. 2023 Apr 10;22(1):39.
II	Nåhls NS, Anttonen A, Löyttyniemi E, Jekunen A, Akrén O, Saarto T. End-of-Life Care and Use of Hospital Resources in Radiotherapy-Treated Cancer Patients with Brain Metastases: A Single-Institution Retrospective Study. Palliative Medicine Reports. 2024;5:316-323.
III	Nåhls NS, Anttonen A, Nuutinen M, Saarto T, Carpén T. The impact of palliative care contact on the use of hospital resources at the end of life for brain tumor patients; a nationwide register-based cohort study. J Neurooncol. Published online January 20, 2025. doi:10.1007/s11060-025-04939-9

The publications are referred to in the text by their roman numerals.

1 Introduction

Palliative care (PC) is increasingly being recognized as a cornerstone of cancer treatment, as it aims to alleviate suffering and optimize quality of life (QoL) for individuals with life-threatening illnesses (World Health Organization [WHO], 2020). WHO estimates that globally, around 56 million people require PC each year, yet only about 14 percent actually receive it—largely those in higher-income regions such as Europe. Within Europe, cancer constitutes the single largest disease group in need of PC, and cancer patients represent approximately 40 percent of those who require PC (Connor et al. WHO Atlas 2020). However, despite this demand, resource gaps persist, especially in low- and middle-income countries (Arias-Casais et al. 2020; Clark et al. 2020; Lynch et al. 2013). In Finland, PC services are considered to be at a mid-level compared to other European countries, and although services have expanded, significant regional disparities remain (Arias-Casais et al. 2019; Saarto et al. 2019; Seppänen, 2024).

WHO recommends offering PC as early as possible to all individuals with life-threatening conditions (WHO, 2020), and major oncology societies—such as the American Society of Clinical Oncology (ASCO) and the European Society for Medical Oncology (ESMO)—specifically advise early integration of PC for patients with advanced cancers (Ferrell et al. 2017; Jordan et al. 2018).

Evidence from multiple systematic reviews and randomized controlled trials consistently shows that early PC improves QoL, reduces symptom burden, and enhances both patient and caregiver satisfaction (Chen et al. 2022; Haun et al. 2017; Kavalieratos et al. 2016; Temel et al. 2010; Vanbutsele et al. 2020; Zimmermann et al. 2014). Early PC can also reduce the need for aggressive treatments at the end of life (EOL), decrease hospital resource use, and encourage care in specialized palliative settings (Hui et al. 2014; Maltoni et al. 2016; Temel et al. 2010; Triplett et al. 2017).

Despite this consensus, many cancer patients—including those in Finland—continue to receive PC referrals late in the disease trajectory, limiting the potential benefits of early integration (Hirvonen et al. 2020; Hui et al. 2016; Hui et al., 2016; Iglesias-Santamaría, 2022, Sizoo et al. 2014). Within the broader cancer population, patients with primary or secondary brain tumors face particularly complex challenges. These include a rapidly progressing disease course and a range of symptoms such as seizures, headaches, fatigue, and neurological deficits (IJzerman-Korevaar et al. 2018; Koekkoek et al. 2023). Although primary malignant gliomas—especially glioblastoma multiforme (GBM)—are rare, brain metastases are up to ten times more common and often result from lung, breast, or melanoma primaries (Cagney et al. 2017; Ostrom et al. 2018; Ostrom et al. 2014). Ongoing advances in systemic and targeted treatments offer modest improvements to outcomes but can also complicate decisions regarding discontinuing therapy in the final stages of life (Kotecha et al. 2018; Valiente et al. 2018; van den Bent et al. 2023).

As a result, patients with brain tumors often visit emergency departments multiple times for acute or recurrent neurological symptoms, which leads to subsequent hospitalizations (Diamond et al. 2017; Wasilewski et al. 2017). Many also receive late-stage anticancer treatments even when they express a preference for dying at home (Cai et al. 2020; Lee et al. 2022; Pace et al. 2023). These trends highlight the urgent need for earlier, more comprehensive palliative approaches in neuro-oncology, and yet these services remain underutilized (Crooms et al. 2021; McDermott et al. 2020; Koekkoek et al. 2023; Walbert 2014, Walbert & Chasteen 2014).

Given these challenges, early, comprehensive PC is crucial for patients with primary and secondary brain tumors (Kang et al. 2021; Pace et al. 2017; Walbert & Pace 2016). Early integration enables proactive symptom management and timely psychosocial support and allows treatment decisions to be aligned with patients' wishes—especially before cognitive decline further complicates communication (Detering et al. 2010; Llewellyn et al. 2018). Nonetheless, many patients are still referred to PC services late in the disease course—or not at all—which leads to increased emergency department visits and inadequate EOL symptom control (Diamond et al. 2016; Hirvonen et al. 2020; Koekkoek et al. 2014).

This dissertation investigates how PC, particularly PC decisions and timing of specialized PC services, are associated with EOL healthcare utilization among patients with primary and secondary brain tumors.

2 Review of the literature

2.1 Characteristics of brain tumors and brain metastases

2.1.1 Incidence and classification

Malignant central nervous system tumors rank as the 19th most common type of cancer globally. According to 2020 estimates, the age-standardized incidence rate of these tumors is 3.5 per 100,000 people worldwide. In Europe, the incidence rates are higher, at 6.7 per 100,000 for males and 4.8 per 100,000 for females (Ferlay et al. 2020). In Finland, a total of 373 gliomas were diagnosed in 2022, with age-standardized incidence rates of 6.2 per 100,000 for males and 3.5 per 100,000 for females (Finnish Cancer Registry 2022).

Gliomas are the most prevalent primary intracranial tumors, comprising approximately 81 percent of all malignant brain tumors (Goodenberger et al. 2012; Ostrom et al. 2014). Despite their relatively low incidence, gliomas result in significant mortality and morbidity. Malignant GBM, the most common glioma histology, accounts for about 45 percent of gliomas and is the most aggressive form. The prognosis for GBM varies significantly, ranging from a few months to over a year (median survival 15 months), depending on the patient's age and treatment strategies (Keime-Guibert et al. 2007; Moroney et al. 2017; Ostrom et al. 2014; Stupp et al. 2005; Stupp et al. 2009).

In recent years, our understanding of the molecular underpinnings of primary central nervous system tumors has significantly improved, leading to a revised classification system that incorporates molecular characteristics. This update has enhanced diagnostic accuracy, influenced patient prognosis, and shaped treatment decisions (Louis et al. 2021; van den Bent et al. 2023). Age at diagnosis remains a critical prognostic factor (Miller et al. 2021). A crucial component of this molecular classification is the determination of isocitrate dehydrogenase (IDH) mutation status, which has significant implications for prognosis and therapy. According to the 2021 WHO classification of central nervous system tumors, gliomas are now primarily classified into IDH-mutant and IDH-wildtype categories. IDH-mutant gliomas typically have a more favorable prognosis and respond differently to therapy compared to IDH-wildtype tumors (Berger et al. 2022).

Although the etiology of brain tumors is not fully understood, both hereditary and environmental factors have been explored. Most cases appear to be sporadic, with mutations primarily arising from endogenous factors rather than exogenous exposures (Claus et al. 2022). External risk factors, such as radiation therapy or exposure to ionizing radiation (e.g., computed tomography (CT) scans) to the head or face, have been linked to an increased risk of brain tumors in a dose-dependent manner (Hauptmann et al. 2023).

In contrast, brain metastases are up to ten times more common than primary malignant brain tumors (Ostrom et al. 2018). These metastatic lesions occur in 10–40 percent of patients with advanced cancers (Cagney et al. 2017; Lamba et al. 2021), affecting a substantial patient population. Their incidence has risen over time, partly due to advances in imaging techniques and oncological treatments (Nayak et al. 2012). However, there are no comprehensive studies on their prevalence and prognosis, making accurate estimates challenging. Older population-based studies have estimated the incidence of brain metastases to be around 3.4 cases per 100,000 people. Based on hospital admission data, the age-adjusted incidence of brain metastases was 14 patients per 100,000 people in 2006 (Fogelholm et al. 1984; Smedby et al. 2009).

The incidence of brain metastases varies according to the primary cancer type, with breast cancer, lung cancer, melanoma, and kidney cancer being the most common sources (Berghoff et al. 2016; Cagney et al. 2017). The molecular subtypes of the primary cancer can also influence the likelihood of developing brain metastases. For instance, the highest incidence is observed in non-small cell lung cancer (NSCLC) with epithelial growth factor receptor mutations, BRCA1-, triple-negative- and HER2+ breast cancer, and melanoma with BRAF mutations (Kuksis et al. 2021; Tabor et al. 2023).

Patients with brain metastases constitute a heterogeneous group, and like primary malignant brain tumors, these metastatic lesions are associated with significant morbidity and mortality. Treatment of brain metastases is complicated by the blood-brain barrier, which impedes the delivery of traditional chemotherapeutic agents to the tumor site (Muldoon et al. 2007).

The timing of brain metastasis occurrence can vary; it may occur concurrently with the primary cancer diagnosis, presenting as initial symptoms of metastasis (Cagney et al. 2017; Füreder et al. 2018), or it may develop later as the primary cancer progresses. A descriptive statistical analysis found that 27 percent of patients had synchronous brain metastases at the time of primary cancer detection, with lung cancer being the most common primary site. For those with metachronous brain metastases, the median time from cancer diagnosis to metastasis occurrence was 24 months (Berghoff et al. 2016). Most patients exhibit symptoms at the time of brain metastasis diagnosis (Steindl et al. 2019).

2.1.2 Prognosis

Despite significant advances in treatment modalities, the prognosis for malignant brain tumors, particularly gliomas, and brain metastases remains modest overall. However, it is essential to understand that these conditions are heterogenous, as a subset of patients may experience longer survival times than the general trends suggest.

GBM, a WHO Grade 4 tumor, is among the most aggressive forms of brain cancer, with a median survival time of approximately 12–15 months (Stupp et al. 2009; Wen et al. 2008). Nonetheless, some patients with GBM survive significantly longer, and exploring the factors that contribute to this long-term survival, such as molecular markers like MGMT promoter methylation status (Hegi et al. 2005), could provide valuable insights. Prognosis is influenced by various factors, including the extent of surgical resection, the use of adjuvant chemotherapy—in which more extensive resections, combined with effective chemotherapy, improve outcomes (Ahmadloo et al. 2013)—performance status, the presence of multifocal tumors, and age. Younger patients, and those with a single tumor site, generally fare better (Patil et al. 2012; Wang et al. 2018). Elderly patients with GBM in particular have a poorer prognosis: A randomized Phase III trial indicated that patients over the age of 70 have a median survival of four months even with supportive care alone, which extends to seven months when radiotherapy is added (Keime-Guibert et al. 2007). This underscores the importance of age-appropriate treatment strategies. Among brain tumors, anaplastic gliomas (WHO Grade 3) have a relatively better prognosis than GBM, with median survival ranging from two to five years (Wen et al. 2008).

Studies have shown that, in certain cancer types, patients receiving PC live longer than those who do not receive PC (Allende et al. 2024; Temel et al. 2010). These findings have increased interest in the potential survival benefits of PC, particularly when integrated early in the disease course. Nevertheless, evidence remains mixed across cancer types and clinical contexts. In GBM, for example, some studies suggest that PC may not improve survival and could even be associated with shorter survival (Pando et al. 2023), whereas others report that early PC consultations are linked to prolonged survival (Crooms et al. 2023). It would be valuable to explore the potential reasons for these conflicting findings, such as differences in study designs, patient populations, or the timing and nature of PC interventions. Moreover, although PC may not always increase survival, it has consistently shown to improve QoL, which is a crucial consideration for patients with advanced cancers (Maltoni et al. 2016; Temel et al. 2010, Zimmermann et al. 2014).

The prognosis of brain metastases varies significantly depending on the primary cancer's histology. Patients with brain metastases from cancers such as prostate cancer, bronchoalveolar carcinoma, and breast cancer, typically have longer survival times than those with metastases from other primary sites (Cagney et al. 2017). Subtypes such as HER2-positive breast cancer benefit from targeted therapies (Ivanova et al. 2023), which could potentially improve prognosis.

The first-line treatment choice for brain metastases considerably affects survival outcomes. Chemotherapy is associated with the longest median overall survival (OS) (10 months), followed by neurosurgical resection (8 months), stereotactic radiotherapy (SRT) (6 months), and whole-brain radiotherapy (WBRT) (5 months) The best supportive care alone results in the shortest median survival (0 months) (Berghoff et al. 2016). Similar results have been reported in Finland, where the prognosis of patients treated for intracranial metastases with WBRT was modest, with median survival of 4 months depending on age, performance status, and the presence of extracranial disease (Sundstrom et al. 1998). Recent studies highlight that patients treated by SRT tend to live longer than those who receive WBRT (Karlsson et al. 2024; Karlsson et al. 2021). However, it is important to note that these treatment modalities may have various risks and side effects, which may impact QoL and treatment decisions.

Several other factors influence the prognosis of patients with brain metastases, including age, performance status (Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1/ Karnofsky performance status of ≤70), number of brain metastases, presence of extracranial metastasis, and the availability of small molecule-targeted therapies (Karlsson et al. 2021; Zhou et al. 2020). Younger age and good performance status are generally associated with better survival outcomes, and the absence of extracranial disease is a favorable prognostic factor (Id Said et al. 2023; Sperduto et al. 2020). Symptoms at diagnosis significantly influence the survival rates of brain metastasis patients, with symptomatic patients tending to have a shorter survival than asymptomatic patients (Steindl et al. 2019; Steindl et al. 2020). The effect of these variables on prognosis was found in a study of patients with NSCLC and an ECOG performance status of 2 or above, which made them unsuitable for surgery or SRT. These patients had a prognosis of only 1.2–1.9 months with WBRT (Karlsson et al. 2024).

However, continued research and individualized treatment plans are essential for enhancing QoL and survival rates. The treatment of brain metastases has evolved over the last 30 years, shifting toward less neurosurgical intervention, more radiotherapy, and more systemic therapy. These changes have improved prognosis: A retrospective analysis of a heterogeneous population of patients with brain metastases showed an increase in median OS from five months to seven months, comparing cohorts from earlier (late 1980s–1990s) and more recent (2010s) treatment eras (Steindl et al. 2022).

It is worth noting that emerging targeted therapies and immunotherapies, particularly for certain primary tumor types such as melanoma and lung cancer (Goldberg SB et al. 2016; Margolin et al. 2012), could potentially improve the prognosis of brain metastases. Additionally, the potential synergistic effects of combining different treatment modalities (e.g., surgery, radiotherapy, and systemic therapy) on brain metastases prognosis (Patel et al. 2017) could be explored further.

Although the general trends of the factors affecting the prognosis of patients with primary and secondary brain tumors are known, it is important to consider the heterogeneity of the diseases and patient-specific differences.

2.1.3 Clinical presentation, diagnosis, and treatments

Brain tumors and brain metastases are severe neurological conditions that can significantly impact a patient's QoL and survival. Brain tumors can affect individuals across various age groups, and the mean age of diagnosis varies, depending on the tumor grade. Low-grade tumors (Grade I and II) typically present at a younger age, with mean ages of 39 and 46, respectively. In contrast, high-grade tumors (Grade III and IV) are usually diagnosed at older ages, with mean ages of 56 and 64 (Rasmussen et al. 2017).

The clinical presentation of brain tumors can vary widely, depending on the tumor type, location, and stage, with symptoms manifesting either at diagnosis or as the disease progresses. A systematic review identified the ten most common symptoms among patients with glioma: seizures (37%), cognitive deficits (36%), drowsiness (35%), dysphagia (30%), headache (27%), confusion (27%), aphasia (24%), motor deficits (21%), fatigue (20%), and dyspnea (20%) (IJzerman-Korevaar et al. 2018). It is important to note that high-grade tumors are more frequently associated with headaches, cognitive changes, and focal deficits, while seizures are more common in patients with low-grade gliomas (Rasmussen et al. 2017).

Magnetic resonance imaging (MRI) is the primary imaging modality for diagnosing and monitoring brain tumors (Sabeghi et al. 2024). MRI provides detailed images that are crucial for accurately assessing tumor size, location, and progression, and thus facilitates the planning of appropriate treatment strategies.

The standard treatment for GBM, a highly aggressive brain tumor, involves chemoradiotherapy followed by adjuvant chemotherapy (Stupp et al. 2005). This multimodal approach has been shown to improve survival outcomes to a greater extent than either modality alone (Joo et al. 2015). Supportive medications, such as steroids and anti-epileptic drugs, also play a vital role in managing symptoms and enhancing the QoL of patients with primary and secondary brain tumors (Bénit & Vecht et al. 2016; Moon et al. 2021; Rudà et al. 2020).

The incidence of brain metastases, which occur when cancer spreads to the brain from a primary tumor site elsewhere in the body, varies according to the patient's age at diagnosis and the primary cancer type. For example, the highest incidence has been observed among patients diagnosed with primary breast cancer between the age of 20 and 39, primary lung cancer between 40 and 49, and primary melanoma, kidney, or colorectal cancer between the age of 50 and 59 (Barnholtz-Sloan et al. 2004).

Contrast-enhanced MRI is recommended for the diagnosis of brain metastases (Sze et al. 1990). In some cases, brain metastases may be detected asymptomatically during routine staging of the primary cancer (Berghoff et al. 2016). However, one of the most distressing symptoms for patients with both primary and secondary brain tumors are epileptic seizures, particularly as the disease progresses toward EOL. Managing these seizures can be challenging due to factors such as swallowing difficulties and impaired consciousness (Koekkoek et al. 2014; Sizoo et al. 2014). Effective symptom management is crucial for maintaining the QoL of these patients.

The choice of treatment for brain metastases is made on a patient-by-patient basis, considering the patient's general condition and the extent of the disease. Treatment options include surgical treatment, SRT, WBRT and systemic therapy (Vogelbaum et al. 2022). In cases of advanced or recurrent brain metastases, the situation is reassessed, and in certain situations, for example, SRT may be given, even if the patient has previously received WBRT (Caballero et al. 2012). For patients who are more fragile at the time of diagnosis of brain metastases and who are not candidates for surgery or SRT, symptomatic treatment may also be an alternative to WBRT (Mulvenna et al. 2016).

Brain tumors and brain metastases are complex conditions, and their diagnosis and treatment require a multidisciplinary approach. According to the ESMO guidelines for high-grade gliomas, patients should be evaluated, and the treatment plan determined by a specialized multidisciplinary team, including neurosurgeons, oncologists, as well as expert neuropathologists and neuroradiologists. This comprehensive approach is essential for individualized patient care and optimal clinical outcomes (Stupp et al. 2014).

2.2 Palliative care

2.2.1 Definition

According to the WHO (WHO, 2020), PC is an approach that aims to improve the QoL of patients facing life-threatening illnesses, as well as their families. It involves the prevention and alleviation of suffering through early identification, careful assessment, and treatment of physical, psychosocial, and spiritual problems. Similarly, the International Association for Hospice and Palliative Care (IAHPC, 2024) defines PC as active, holistic care for individuals of all ages experiencing serious health-related suffering due to severe illnesses—particularly near the EOL—with the goal of enhancing the well-being of patients, their families, and caregivers.

EOL care is a component of PC that focuses on the care of patients in their final days, weeks, or months of life. The ESMO Clinical Practice Guideline defines EOL care as "care for people with advanced disease once they have reached a point of rapid physical decline, typically the last few weeks or months before an inevitable death as a natural result of a disease" (Crawford et al., ESMO Clinical Practice Guidelines 2021; ESMO 2023). However, it is important to note that the definition and timing of EOL can vary in different guidelines, studies, and healthcare settings, and may be determined by patient-specific factors and clinical assessments rather than by a fixed timeline. This dissertation defines the EOL stage on the basis of the ESMO guidelines.

Hospice care represents a further specialized form of PC, specifically for patients estimated to have six months or less to live. The focus is on ensuring peace, comfort, and dignity through comprehensive medical, psychological, and spiritual support, also extending care to family members (National Hospice and Palliative Care Organization, 2022; Connor et al., WHO Atlas 2020; WHO, 2020).

Although PC is often associated with EOL care, the concept of "early integrated PC" emphasizes its integration alongside disease-specific, life-prolonging treatments from the time of diagnosis (Ferrell et al. 2017). This approach aims to provide comprehensive care throughout the disease trajectory, addressing the physical, emotional, and psychosocial needs of the patient from the onset of serious illness, rather than only during the final stages of life. Table 1 presents the definitions of the key PC terms.

Table 1 Definitions of key palliative care terms

Term	Definition	Reference
Palliative care	An approach that improves the quality of life of patients and families facing life-threatening illness	WHO, 2020
	Active holistic care of individuals across all ages with serious health-related suffering due to severe illness, especially of those near the end of life. It aims to improve the quality of life of patients, their families and their caregivers	IAHPC, 2024
End-of-life	The final stage of life, typically the last weeks or months before death	ESMO, 2023
	Care given to people who are near the end of life and have stopped	National Cancer Institute

Term	Definition	Reference
	treatment to cure or control their disease	
	Life-limiting disease with irreversible decline and expected survival of months or less	Hui et., 2014 Concepts and definitions for "actively dying," "end of life," "terminally ill," "terminal care," and "transition of care": a systematic review
Hospice care	Specialized palliative care for patients with a life expectancy of less than six months	National Hospice and Palliative Care Organization, 2022
	Hospice care is end-of-life care provided by health professionals and volunteers. They give medical, psychological and spiritual support	Connor et al., WHO Atlas 2020
Early integrated palliative care	Integration of palliative care into disease-specific, life-prolonging treatments from diagnosis	Ferrell et al. 2017
General palliative care	Basic palliative care provided by healthcare professionals (e.g., primary care physicians, general nurses) who are not PC specialists. It includes symptom management, communication, and coordination of care.	Ferrell et al. 2017 Mathews et al. 2021 WHO 2016
Specialized palliative care	Palliative care provided by a multidisciplinary team with specific expertise and training in palliative medicine	Ferrell et al. 2017 Mathews et al. 2021 WHO 2016
Hospital-at-home	A service model that delivers hospital-level palliative care in the patient's home, often involving visits from specialized healthcare providers	Pöyhiä et al. 2018

2.2.2 Needs for and access to global palliative care

An estimated 60 million individuals die each year worldwide, and recent WHO figures suggest that over 56 million might benefit from PC interventions, particularly in the advanced stages of their illness (WHO, 2023). Of these, approximately 25.7 million may require support during their final year of life. However, only around 14 percent ultimately receive such services. Studies indicate that the majority of this 14 percent reside in high-income regions, primarily in Europe, where PC services are relatively well established (WHO, 2020). In Europe, cancer patients appear to constitute around 40 percent of those needing PC, making them the largest single disease group requiring such support. Similarly, in the United States, cancer accounts for approximately 40 percent of PC needs, which suggests a similar pattern in other high-income countries (Connor et al., WHO Atlas 2020).

Yet, a disproportionate share of global PC needs—around 75 percent—is concentrated in low- and middle-income countries. In these settings, access to PC remains critically limited due to factors such as weak healthcare systems, economic constraints, limited training opportunities, and restricted access to essential medications such as opioids. Cultural attitudes and stigma related to EOL care may also impede the development of comprehensive palliative services (Connor et al., WHO Atlas 2020; Mathew-Geevarughese et al. 2019).

In high-income countries, including those in Europe, the United States, Australia, and New Zealand, PC has advanced notably over the past few decades, particularly for cancer patients (Connor et al. WHO Atlas 2020). Both the ASCO and the ESMO emphasize early integrated PC for patients with advanced cancers. Nevertheless, referrals of cancer patients to PC services frequently occur late in the disease trajectory, which may limit the full benefits of early integration (Ferrell et al. 2017; Hausner et al. 2021; Hui et al. 2014; Jordan et al. 2018; Pace et al. 2017; Kaasa et al. 2018; Salins et al. 2020). Despite growing recognition of its importance, the broader implementation of PC remains limited—even in high-income countries. According to the WHO Atlas, key barriers include inadequate funding models, lack of reimbursement systems, and insufficient investment in workforce training and service infrastructure (Connor et al. WHO Atlas 2020).

Integrating PC more broadly into healthcare systems involves further challenges. These include the need for standardized referral criteria (Hui et al. 2016), comprehensive professional training, and consistent guidelines to ensure uniformity in QoL outcomes (den Herder-van der Eerden et al. 2018). These difficulties are compounded by limited political commitment, inadequate healthcare infrastructure, economic constraints, and cultural attitudes toward EOL care—especially in low- and middle-income countries, where the need for PC is the most acute (Connor et al. WHO Atlas 2020; Mathew-Geevarughese et al. 2019).

2.2.2.1 Finland

According to WHO estimates, approximately 75,000 individuals annually require PC in Finland, with cancer patients comprising around 40 percent of this total (Connor et al., WHO Atlas 2020; WHO 2020; Saarto et al. 2019). Although in Finland, PC has traditionally focused on cancer patients, individuals with advanced non-malignant chronic illnesses also represent a growing proportion of those receiving PC (Saarto et al. 2019).

The development of PC in Finland has been guided by recommendations from the Ministry of Social Affairs and Health, which in turn have been influenced by Norway's integrated PC model (Kaasa et al. 2007; Saarto et al. 2019). In recent years, both the availability and quality of PC has progressed significantly. By 2024, 75 percent of health and welfare regions (wellbeing services counties) had established specialized PC centers, compared to just 25 percent in 2018. Additionally, hospital-at-home services, which covered only 36 percent of the population in 2018, now reach 96 percent (Seppänen, 2024).

Nevertheless, certain challenges persist. A 2019 study from Helsinki University Hospital Comprehensive Cancer Center found that although 82 percent of cancer patients who had died in 2014 had a documented PC decision in their last year of life, one-third of these decisions had been made late in the disease trajectory. Furthermore, not all patients with a PC decision had visited a specialized PC unit. However, the earlier the decision had been made, the more likely it was that the patients had visited such a unit (Hirvonen et al. 2019). Another study by Haltia et al. (2023) indicated that 37 percent of cancer patients treated in Finnish University Hospital Cancer Centers in 2013–2014 visited a palliative outpatient unit in the last year of life, with the median of 112 days before death. Similarly, Rautakorpi et al. (2021) reported that among 378 patients with pancreatic cancer treated in Turku University Hospital, 20 percent had had contact with the PC unit near EOL. These findings suggest that around one-third of cancer patients had accessed specialized PC—and in many cases, relatively early. Since then, although the overall availability of palliative services has increased, regional variations remain a concern, which highlights the need for continued efforts to ensure equitable access nationwide (Seppänen, 2024).

2.2.3 Timing of palliative care in cancer care

Determining the optimal timing for PC referral presents a complex challenge. Although WHO generally recommends early integration of PC for patients with life-threatening illnesses, practical implementation can be hindered by prognostic uncertainty and common misconceptions. Clinicians often overestimate survival, which can delay timely referrals (Hui, 2015). Moreover, the perception that PC is exclusively associated with EOL care remains a significant barrier to its earlier integration, as stigma and misconceptions persist even after positive experiences of PC (Zimmermann et al. 2016).

The definition of “early” PC varies across studies and guidelines. Some researchers define early integration as starting PC at the time of advanced cancer diagnosis, alongside disease-specific life-prolonging treatments (Temel et al. 2010). Others consider PC as early if it is received during the last three months of life (Hui et al. 2014) or after cancer treatments have failed (Rugno et al. 2014). Systematic reviews have also noted these discrepancies, emphasizing the importance of reaching a consensus for the effective guidance of clinical practice (Haun et al. 2017; Kavalieratos D et al. 2016).

To address this variability, Hui et al. (2016) proposed evidence-based referral criteria for outpatient PC in The Lancet Oncology journal. These criteria can be categorized as follows:

Symptom-based criteria: Severe physical symptoms (e.g., pain, dyspnea), severe emotional symptoms (e.g., depression, anxiety), and spiritual or existential crises.

Condition-specific criteria: Delirium, spinal cord compression, and brain or leptomeningeal metastases.

Time-based criteria: Referral within three months of diagnosis for advanced cancer patients with a median survival of one year or less, or of the disease progresses despite second-line therapy.

Decision-making and planning: Need for assistance with advance care planning, complex decision-making, or at the explicit request for PC involvement by the patient.

The ASCO guidelines recommend initiating PC within eight weeks of an advanced cancer diagnosis (Ferrell et al. 2017). However, the applicability of this recommendation varies, particularly for certain malignancies such as primary brain tumors, which often carry a poor prognosis even in the absence of metastases (Hui et al. 2016). In neuro-oncology, the timing of PC referrals may require additional disease-specific considerations to address rapid disease progression, cognitive impairment, and functional decline. (Pace et al. 2017; Sizoo et al. 2010; Walbert 2014)

Evidence from systematic reviews indicates that structured, multidisciplinary models—often led by specialist teams—may facilitate earlier PC integration (Haun et al. 2017; Kavalieratos et al. 2016). In contrast, on-demand models, in which PC is primarily provided in response to acute symptoms or crises, can result in diminished benefits (Maltoni et al. 2016). The Lancet Oncology Commission has emphasized the need for policy changes and standardized education to support effective implementation of early integrated PC (Kaasa et al. 2018).

WHO has also recognized PC as a core component of healthcare, urging its inclusion throughout the continuum of care. The 67th World Health Assembly resolution (2014) called for its integration into national health systems, reinforcing the importance of early referrals to optimize patient outcomes (WHO, 2014).

2.2.3.1 Early integrated palliative care

Early integrated PC refers to introducing PC concurrently with disease-directed oncological treatment. Its goal is to address not only physical symptoms but also psychological, social, and existential needs early in the disease trajectory, thereby improving both the quality of care and overall QoL of patients and their families. Multiple early integrated PC models have been evaluated, with systematic, multidisciplinary approaches demonstrating the most robust evidence of benefit (Chelazzi & Ripamonti, 2020; Haun et al. 2017; Huo et al. 2021). Research has also highlighted the importance of aligning early integrated PC with personalized cancer therapies to optimize patient-centered outcomes (Petrillo et al. 2023).

Systematic models—often involving regular, structured meetings with PC physicians, nurses, social workers, and other specialists—have shown significant improvements in patient-reported outcomes and healthcare utilization. For example, Temel et al. (2010) demonstrated that early integrated PC in metastatic NSCLC was associated with reduced aggressive EOL measures, fewer depressive symptoms, and a survival benefit. Similarly, Maltoni et al. (2016) reported that systematic models, compared to an on-demand model, promoted better QoL and more appropriate hospice use, while reducing the likelihood of chemotherapy in the last 30 days of life. Importantly, these approaches aim to embed palliative services within standard oncology care, rather than treating them as an adjunct.

Nurse-led coordination models, as examined by Bakitas et al. (2009, 2015), focus on proactive symptom management and care coordination. While the 2009 study showed notable improvements in QoL and mood, the subsequent 2015 study, which utilized telephone-based consultations, did not yield significant changes in QoL metrics—though it did correlate with improved one-year survival.

Hybrid models, such as that evaluated by Vanbutsele et al. (2020), combine nurse-led interventions with periodic physician consultations to balance resource constraints with comprehensive care delivery. Meanwhile, rehabilitation-oriented frameworks, like that described by Nottelmann et al. (2021), integrate palliative rehabilitation to improve the physical and psychological well-being of patients with newly diagnosed advanced cancer.

Despite these positive outcomes, not all trials have shown consistent benefits. Scarp et al. (2019) found no significant differences in QoL or hospice utilization from early integrated PC and standard care plus on-demand early PC for patients with advanced gastric cancer. This may be due to “contamination”, as a substantial proportion (43%) of the control group had also received PC interventions. Groenveld et al. (2017) similarly observed a limited impact on a heterogeneous advanced cancer population, in which most patients had received only a single consultation and telephone follow-up—around 50 percent of the patients in the early PC group had two or more face-to-face contacts. In malignant pleural mesothelioma, Brims et al. (2019) reported no significant improvements in QoL or psychological distress despite regular consultations over 24 weeks, underscoring the importance of disease-specific and patient-centered tailoring of early integrated PC interventions.

Systematic reviews, meta-analyses, and randomized controlled trials (Haun et al. 2017; Huo et al. 2021; Maltoni et al. 2016; Temel et al. 2010; Zimmermann et al. 2014) consistently affirm the benefits of integrating PC early in the cancer trajectory, including improved patient-centered outcomes, reduced symptom burden, and, in some cases, even extended survival. However, effective implementation depends on multiple factors such as disease type, timing, multidisciplinary collaboration, and patient/caregiver engagement. As Petrillo et al. (2023) emphasize, early integration of PC into personalized cancer care can enhance the alignment between targeted therapies and supportive services, ensuring that each patient's evolving clinical needs and preferences remain central. In addition to these findings, a range of randomized controlled trials have evaluated early integrated PC interventions in oncology. Table 2 summarizes the key studies and their outcomes.

2.2.3.2 Current practice

Despite growing consensus on the benefits of early PC, actual referral practices vary considerably worldwide, and many patients still receive palliative consultations late in their disease trajectory. A systematic review and meta-analysis by Jordan et al. (2020) reported that, in routine international practice, the median duration from the initiation of PC to death was 18.9 days, which shows how short the PC phase can be for many patients. For instance, in Spain, only approximately 50 percent of advanced cancer patients are referred to PC units at all, and 8.4 percent die within just 72 hours of referral (Iglesias-Santamaría et al. 2022). In contrast, a Finnish study reported a median of 112 days between the first PC appointment and death (Haltia et al. 2023). Similarly, a study on high-grade glioma patients found that the median time between PC referral and death was 10.7 weeks (Harrison et al. 2021).

In the United States, hospital-based PC programs are now available in roughly 90 percent of large hospitals (300+ beds) (Dumanovsky et al. 2016). However, many patients still only receive referrals during the final weeks or months of their lives (Humphreys & Harman et al. 2014; Kozlov et al. 2015). A study specifically examining primary malignant brain tumors found that 22.5 percent of hospice-enrolled patients were referred during the last seven days of life, and that these patients were significantly more likely to be severely debilitated upon admission

(Diamond et al. 2016). Similarly, a study of brain metastases patients found that only 48 percent attended a PC consultation during their lifetime, with 35 percent receiving their first PC consultation during their last month of life. The median time from oncologic appointment to PC referral was 2.8 months, whereas the median duration from initial PC consultation to death was only 1.6 months, illustrating a persistent delay in palliative integration. (McDermott et al. 2020) European data, such as those from the EAPC Atlas (Arias-Casais et al. 2019), reveal considerable differences between countries in both the availability and timing of PC services.

Recent studies from Mainland China further underscore these challenges. Gu et al. (2020) found that among patients with advanced NSCLC, the median interval between PC referral and death was only 41 days, and that over half of them received PC for less than one percent of their total disease course. Similarly, Wang et al. (2018) reviewed 54 studies and concluded that while the concept of PC is widely recognized, systematic screening and timely referral mechanisms remain largely absent in Mainland China. A study focusing on brain metastases from lung cancer reported a wide range in the time from PC center admission to death, from 2 to 196 days, with a mean of 42.6 days (Yamanaka et al. 2011).

In low- and middle-income countries, structural challenges—including limited numbers of trained personnel, economic constraints, and restricted access to essential medications—further delay timely PC integration (Connor et al., WHO Atlas 2020).

Table 2 Randomized controlled trials evaluating early integrated palliative care in oncology

Authors	**Year**	**Number of patients, country**	**Palliative care intervention model**	**Study population**	**Main findings**
Physician-led interventions					
Temel et al.	2010	151, USA	Systematic, multiprofessional team, monthly meetings in outpatient setting Control group: Standard oncology care	Newly diagnosed metastatic non-small-cell lung cancer	Early palliative care improved quality of life, reduced aggressive care at end of life, reduced hospitalizations (53.6% vs. 36.7% in the last month of life), reduced depression, and potentially increased survival
Greer et al.	2012				Early palliative care halved the odds of receiving chemotherapy during the last 60 days of life, extended the interval between the last dose of intravenous chemotherapy and death (64 vs. 41 days), and increased enrollment in hospice care for longer than 1 week
Pirl et al.	2012				Early palliative care associated with greater improvement in depression

Authors	**Year**	**Number of patients, country**	**Palliative care intervention model**	**Study population**	**Main findings**
Zimmermann et al.	2014	461, Canada	Systematic, multiprofessional team, monthly meetings in outpatient setting and 24-h on-call service Control group: Standard oncology care	Adults with advanced, mixed cancer diagnoses, EGOG 0-2, estimated survival of 6–24 months	Early palliative care was associated with improved quality of life and satisfaction with care
Maltoni et al.	2016	186, Italy	Systematic, multiprofessional team, meetings in outpatient setting every 2–4 weeks (97 patients) and on-demand consultations (89 patients) Control group: Standard oncology care plus on-demand early palliative care	Metastatic or locally advanced pancreatic cancer	Systematic palliative care improved quality of life more significantly than on-demand care. Timeliness and use of hospice care were more appropriate in the systematic group. Fewer patients underwent chemotherapy in the last 30 days of life
Temel et al.	2017	350, USA	Systematic, multiprofessional team, monthly meetings in	Metastatic lung or non-colorectal	Early integrated palliative care improved quality of life and depression in week 24. Intervention

Authors	Year	Number of patients, country	Palliative care intervention model	Study population	Main findings
			outpatient setting with physician or nurse Control group: Standard care	gastrointestinal cancer	effects varied according to cancer type
El-Jawahri et al.	2017	275, USA		Caregivers of patients with metastatic lung or non-colorectal gastrointestinal cancer	Early integrated palliative care reduced caregivers’ distress and depression symptoms at 12 weeks
Groenveld et al.	2017	297, Denmark	Systematic, multiprofessional team, 8 weeks follow-up in outpatient setting Control group: Standard care	Advanced cancer, included central nervous system cancers	Early specialized palliative care had no effect on change in patients’ primary need, no difference in survival
Vanbutsele et al.	2018	186, Belgium	Systematic, multiprofessional team, monthly meetings with	Adults with advanced solid cancer	Early, systematic integration of palliative care in oncology improved quality of life

Authors	**Year**	**Number of patients, country**	**Palliative care intervention model**	**Study population**	**Main findings**
Vanbutsele et al.	2020		nurse in outpatient setting and physician consultations if necessary Control group: Standard oncology care		Significantly better global health status and quality of life at 1, 3, and 6 months
Brims et al.	2019	174, UK and Australia	Systematic, monthly meetings with physician for at least 24 weeks Control group: Standard care	Malignant pleural mesothelioma	No difference in health-related quality of life, depression/anxiety or survival
Franciosi et al.	2019	281, Italy	Systematic, multiprofessional team, meeting every 2–3 weeks with physician or nurse for 24 weeks in outpatient setting Control group: Standard oncology care, palliative care visit if requested	Advanced non-small cell lung, gastric, pancreatic and biliary tract cancer patients	No difference in quality of life
Scarpi et al.	2019	179, Italy	Systematic, palliative care physician meetings within 2 weeks of enrollment and	Adults with locally advanced or	No differences in quality of life, mood, depression, anxiety, use of health services, chemotherapy in

Authors	Year	Number of patients, country	Palliative care intervention model	Study population	Main findings
			every 2–4 weeks thereafter until death. Control group: Standard oncology care plus on-demand early palliative care	metastatic gastric cancer	the last days of life, number and timeliness of hospice care activations, place of death, or survival
Slama et al.	2022	126, Czech Republic	Systematic, consultation with palliative care physician every 6–8 weeks Control group: Standard oncology care	Newly-diagnosed advanced cancer	No impact on quality of life, anxiety or survival
Temel et al.	2020	391, USA	Systematic, multiprofessional team, monthly meetings in outpatient setting with physician or nurse Control group: Standard oncology care	Advanced lung or non-colorectal gastrointestinal cancer	No difference in quality of life, depression or anxiety
Eychmüller et al.	2021	150, Switzerland	Systematic, multiprofessional team, single intervention performed by a physician and a nurse	Adults with advanced, mixed cancer diagnoses	No improvement in patient distress, health-related quality of life or survival

Authors	Year	Number of patients, country	Palliative care intervention model	Study population	Main findings
			Control group: Standard oncology care		
Nottelmann et al.	2021	279, Denmark	12-week intervention offered by a specialized palliative care team with two mandatory consultations and the opportunity to participate in an interdisciplinary group program that encompassed elements of rehabilitation Control group: Standard oncology care	Newly-diagnosed advanced cancer patients	Early integrated palliative rehabilitation improved the quality of life and patients in this group benefited significantly from help with their chosen primary problem
Patil et al.	2021	180, India	Systematic, multiprofessional team, monthly follow-up for 3 months in outpatient setting Control group: Standard oncology care	Adult patients with squamous cell carcinoma of the head and neck region	No improvement in quality of life or survival

Authors	**Year**	**Number of patients, country**	**Palliative care intervention model**	**Study population**	**Main findings**
Chen et al.	2022	120, China	Systematic, multiprofessional team, monthly follow-up for at least 24 weeks in outpatient setting Control group: Standard oncology care	Newly-diagnosed non-small cell carcinoma patients	Improvement in quality of life, depression symptoms and better nutritional status
Adenis et al.	2024	470, France	Systematic, five meetings with physicians every month in outpatient setting Control group: Standard oncology care	Adult patients with metastatic upper gastrointestinal cancer	No improvement in survival
Allende et al.	2024	146, Mexico	Systematic, multiprofessional team, meeting every other treatment session in outpatient setting Control group: Standard oncology care	Advanced non-small cell lung cancer	No difference in quality of life, depression or anxiety. Improved survival
Kang et al.	2024	144, South Korea	Systematic, multiprofessional team, telephone coaching every	Adults with advanced,	Improvement in quality of life and overall health status at 18 weeks, no improvement at 12 or 24 weeks,

Authors	**Year**	**Number of patients, country**	**Palliative care intervention model**	**Study population**	**Main findings**
			week for the first 12 weeks, then every other week Control group: Standard oncology care	mixed cancer diagnoses	significant improvement in self-management or coping skills
Nurse-led interventions					
Bakitas et al.	2009	322, USA	Nurse-led, 4 times a week, after which monthly meeting with nurse Control group: Standard care	Adults with advanced cancer	Early integrated palliative care improved quality of life and mood, no difference in symptom intensity scores or healthcare resource use
Tattersall, et al.	2014	120, Australia	Nurse-led, monthly phone calls Control group: Standard oncology care	Newly detected incurable metastatic cancer	No difference in quality of life, symptoms, place of death, or number of chemotherapy sessions received
Bakitas et al.	2015	207, USA	Nurse-led, in-person palliative consultation followed by structured phone calls (once per week for six weeks) and monthly follow-ups. The early intervention group received this care within 30–60 days	Adults with advanced cancer	No difference in quality of life, symptoms, or mood at 3 months. Better overall survival at 1 year. No impact on hospital days, emergency room visits, chemotherapy in last 14 days, or home deaths

Authors	Year	Number of patients, country	Palliative care intervention model	Study population	Main findings
			of being informed of an advanced cancer diagnosis. Control group: Received the same intervention, but with a 3-month delay after enrollment		
McCorkle et al.	2015	146, USA	Nurse-led, 10-week intervention (visits and phone calls once a week) + staff training Control group: Standard care	Patients with newly-diagnosed late-stage cancer	No difference in patient-reported outcomes
Ferrell et al.	2021	479, USA	Nurse-led, two teaching sessions Control group: Standard care	Patients with solid tumors in Phase 1 Studies	Improved psychological distress and emotional well-being. No improvement in survival
Schenker et al.	2021	672, USA	Nurse-led, three-monthly visits with nurse in outpatients setting Control group: Standard care	Adult patients with metastatic solid tumors	No difference in quality of life, symptom burden or mood symptoms

Authors	**Year**	**Number of patients, country**	**Palliative care intervention model**	**Study population**	**Main findings**
Reinke et al.	2022	151, USA	Nurse-led, phone calls Control group: Standard care	Newly-diagnosed lung cancer patients	No improvement in quality of life or satisfaction with care
Matsumoto et al.	2024	204, Japan	Nurse-led, comprised comprehensive needs assessments, counseling, and service coordination by advanced-level nurses Control group: Standard care	Patients with advanced lung cancer	No improvement in depression, anxiety or survival

Key messages from the above randomized controlled trials:

Physician-led multidisciplinary interventions generally resulted in improved patient outcomes, especially in advanced lung cancer and mixed cancer populations, showing enhanced QOL, reduced depressive symptoms, and more appropriate EOL care. However, effects varied significantly depending on cancer type and intensity of follow-up.

Nurse-led interventions demonstrated inconsistent or limited effects on QOL and survival, suggesting physician-led, multidisciplinary care may be more beneficial for patients with advanced cancers.

Randomized controlled trials evaluating early integrated PC are relatively recent, with most studies published within the last decade, underscoring that evidence on the efficacy of these interventions is still developing and evolving.

2.2.4 Palliative care decision and anticancer treatments at the end of life

As outlined by The Lancet Oncology Commission on Palliative Care and Oncology Integration (Kaasa et al. 2018), cancer treatment typically proceeds along multiple "lines" of therapy. The early lines focus on controlling the disease and prolonging survival, but the later lines often become less effective and more burdensome. At this stage, a PC decision—to terminate life-prolonging anticancer treatments—prioritizes QoL and aligns care with patient preferences.

This transition is usually facilitated by a multidisciplinary team, consisting of physicians, nurses, and social workers, which develops a personalized care plan that addresses symptom control and psychosocial well-being (Fernando & Hughes, 2019). However, accurately predicting survival and determining the optimal timing of PC remains challenging (Hui, 2015). To help reduce aggressive EOL treatments, Earle CC et al. (2005) proposed benchmarks indicating that chemotherapy should be given to a maximum of ten percent of patients during their last 14 days of life, and that a new regimen should be initiated for a maximum of two percent during their last 30 days of life.

Despite these recommendations, chemotherapy at EOL remains widespread. Late-stage use of anticancer therapies can lead to increased hospital visits and admissions to intensive care unit (Matsumoto et al. 2023; Näppä et al. 2011; Wright et al. 2014), which often prevent patients being able to die in their preferred setting, such as at home or in hospice care. For example, in the United States, Earle et al. (2004) found that 15.7 percent of patients with advanced solid tumors received chemotherapy during the last two weeks of their lives. Similar patterns have been observed in Europe (Iglesias-Santamaría et al. 2022). Data from Finland further illuminate current practices: Rautakorpi et al. (2017) retrospectively analyzed 11,250 cancer patients and found that 35.3 percent received intravenous chemotherapy during their last three months of life. Notably, in the final month, approximately one-third of patients aged under 50 received intravenous chemotherapy, in comparison to only one-tenth of those aged over 80. Such aggressive use of chemotherapy at EOL is linked to lower QoL and a diminished likelihood of patients being able to die in their preferred settings (Wright et al. 2014).

2.2.5 Palliative care for patients with primary or secondary brain tumors

Patients with brain tumors—whether primary or metastatic—face a unique constellation of challenges that require comprehensive, individualized PC. They commonly experience significant neurological deficits (such as motor weakness, seizures, headaches, and fatigue), which substantially impair daily functioning and overall QoL (Liu et al. 2009; Moore et al. 2013; Taphoorn et al. 2010). High rates of depression, anxiety, and cognitive decline further complicate the clinical picture (Mainio et al. 2005; Mainio et al. 2006; Talacchi et al. 2011). For individuals with brain metastases, the coexistence of intracranial and systemic disease-related symptoms makes the situation even more difficult (Arvold et al. 2016; Berghoff et al. 2016). Supportive care, including early PC interventions, is essential for maintaining symptom control and optimizing patient well-being in this population (Pace et al. 2010). Early PC can offer proactive symptom management, facilitate advance care planning, and align treatments with patient preferences, its ultimate aim being to enhance both QoL and patient autonomy (Pace et al. 2017; Walbert and Pace, 2016).

Despite clear clinical need, brain tumor patients' access to PC is not guaranteed. For example, an Australian study found that malignant glioma patients with a high symptom burden were more likely to receive PC—and those who did were more likely to be able to die at home (Sundararajan et al. 2014). However, a retrospective analysis in the United States indicated that only a small fraction of critically ill patients with brain metastases received PC in the earlier stages: Reported figures have ranged from as low as 3.2 percent in 2005 to 28.5 percent in 2014 (Rubens et al. 2020). A survey of German neuro-oncological centers further highlighted that only about 30 percent of centers offer PC services early in the diagnostic process (Lawson McLean et al. 2024).

Timely integration is especially critical in neuro-oncology, in which rapid cognitive decline—as seen in conditions such as GBM—can preclude effective symptom management and complicate decision-making. Early PC enables better alignment with patients' wishes and more effective management of complex symptoms. Nonetheless, studies indicate that only 37 percent of GBM patients have early palliative consultations (Hemminger et al. 2017). The factors that deter early integration include the unpredictable disease trajectory, a lack of consensus on referral criteria, and persistent cultural stigma that associates PC solely with EOL care (Byrne et al. 2022; Zimmermann et al. 2016). Addressing these obstacles through education, standardized referral guidelines, and multidisciplinary collaboration is essential to optimize care for this vulnerable group.

In the context of aggressive treatments, observational cohort data indicate that many brain tumor patients continue to receive (chemo)radiotherapy at EOL (Pace et al. 2023). For instance, one single-center report on GBM patients showed that approximately 17 percent underwent chemotherapy and nine percent radiotherapy in their final month (Kuchinad et al. 2017). Similarly, a separate analysis of brain metastases patients identified that nine percent received radiotherapy during the last 30 days of their lives, with one percent treated in their final two weeks (Jung et al. 2013).

Although these findings may not be fully generalizable to all settings, they illustrate that a notable subset of neuro-oncology patients persist with active cancer therapies in their last weeks of life. Palliative radiotherapy—commonly administered as WBRT in ≤5 fractions—often remains key for symptom control, but its benefits must be weighed against its potential side effects, particularly in the case of patients with poor performance status, whose overall benefit might be limited (Chee et al. 2022; Davis et al. 2023; Nieder et al. 2015; Wu et al. 2019).

2.3 Effects of palliative care

PC has shown to have multiple benefits for cancer patients, such as improved symptom management, enhanced QoL, and potentially lower healthcare costs and resource use (Hui et al. 2014; Kavalieratos et al. 2016; May et al. 2018; Temel et al. 2010). Emerging evidence suggests similar advantages for patients with brain tumors (Crooms et al. 2020; Wu et al. 2022). A recent population-based register study by Lindskog et al. (2022) in Sweden, which included patients with brain tumors, highlighted that acute healthcare utilization at EOL—commonly driven by uncontrolled symptoms or urgent clinical situations—could potentially be mitigated by timely PC interventions.

2.3.1 Anticancer treatments at the end of life

Studies have consistently shown that early PC referral is associated with less chemotherapy during the final months of life. For instance, Woldie et al. (2022) demonstrated that early PC referral significantly lowered the probability of chemotherapy administration during the last 30 days of life. Similarly, Lammers et al. (2019) observed that early PC correlated with reduced chemotherapy intensity among patients with advanced lung cancer, while a nationwide analysis from Japan by Sano et al. (2017) found that PC consultations decreased inpatient chemotherapy use among elderly cancer patients.

Additionally, Hoerger et al. (2018) showed that patients whose treatment decisions were discussed more frequently were less likely to initiate further anticancer therapies, a finding echoed by Mack et al. (2012), who noted that EOL discussions correlated with less aggressive care. A retrospective study by Hirvonen et al. (2019) at the Helsinki University Hospital Comprehensive Cancer Center revealed that an early PC decision was associated with significantly lower rates of systemic cancer treatment and radiotherapy in the final month of life. More recently, Zhang et al. (2025) reported that PC consultations reduced aggressive interventions among patients with metastatic breast cancer, and Le et al. (2024) found that aggressive anticancer treatments near EOL were more common among patients without PC referrals. In line with these findings, Nieder et al. (2016), who examined the impact of early palliative interventions on patients with NSCLC, found that those who received early PC were the least likely to receive active anticancer treatment in their last month of life.

Consistent with these findings, early integrated PC randomized controlled trials (Greer et al. 2010; Maltoni et al. 2016; Temel et al. 2010) have documented a lower likelihood of receiving aggressive anticancer therapy at EOL. However, it should be noted that only a few studies assessing this outcome were randomized controlled trials, while the majority of evidence is based on observational or retrospective cohort studies. For a summary of key studies demonstrating the benefits of PC in EOL anticancer treatments, see Table 3.

Table 3 Benefits of palliative care in end-of-life anticancer treatments: Key studies and findings

Study	**Year**	**Study design**	**Population**	**Key findings**
Greer et al. Temel et al.	2010	Randomized controlled trial (USA)	151 patients with metastatic non-small-cell lung cancer	Less aggressive care at the end of life
Mack et al.	2012	Prospective cohort study (USA)	1,231 patients with stage IV lung or colorectal cancer	End-of-life discussions were associated with less chemotherapy near death
Maltoni et al.	2016	Randomized controlled trial (Italy)	207 patients with metastatic or locally advanced inoperable pancreatic cancer	Fewer patients underwent chemotherapy in their last 30 days of life

Study	**Year**	**Study design**	**Population**	**Key findings**
Sano et al.	2017	Nationwide administrative database analysis (Japan)	26,012 patients with advanced cancer	Palliative care consultation was associated with less chemotherapy
Hoerger et al.	2018	Prospective study (USA)	171 patients with newly-diagnosed advanced lung or non-colorectal gastrointestinal cancer	Patients whose treatment decisions were discussed more frequently less often initiated further chemotherapy
Hirvonen et al.	2019	Retrospective cohort study (Finland)	993 outpatient adult cancer decedents at a single university hospital	An early palliative care decision was associated with lower rates of systemic treatment (1% vs. 38%) or radiotherapy (22% vs. 31%) in the last month of life
Lammers et al.	2019	Retrospective national cohort study (USA)	23,566 patients with advanced lung cancer	Early palliative care was linked to reduced chemotherapy intensity
Woldie et al.	2022	Single-center retrospective cohort study (Canada)	681 cancer patients who died between 2016 and 2018	Early palliative care referral significantly reduced chemotherapy in the final 30 days of life
Le et al.	2024	Retrospective study (Austria)	685 patients with a solid tumor	Aggressive anticancer treatments near end of life were more common among patients with no palliative care referrals

Study	Year	Study design	Population	Key findings
Zhang et al.	2025	Retrospective cohort study (USA)	2,615 patients with metastatic breast cancer	Palliative care consultations reduced chemotherapy in the last 60 days of life

2.3.2 Use of hospital resources at the end of life

Many patients still receive hospice referrals during their last week of life and often require acute hospital care in their final month (Arvold et al. 2014; Diamond et al. 2016; Pace et al. 2023). In response to these challenges, PC interventions have had a significant impact on hospital resource utilization at EOL. A systematic review and meta-analysis by Kavalieratos et al. (2016) revealed that PC interventions can reduce healthcare usage among patients with life-limiting illnesses. Similarly, a large cohort study by Obermeyer et al. (2014) from the United States, focusing on patients with poor-prognosis cancer, found that hospice care substantially decreased hospitalizations, intensive care unit admissions, and invasive procedures in the final stages of life.

Focusing specifically on brain tumor patients, Pace et al. (2014) documented a considerable reduction in rehospitalization rates when home-based PC was provided. Additionally, Hui et al. (2014) reported that patients introduced to PC more than three months before death experienced fewer emergency department visits, hospital admissions, and in-hospital deaths in their last 30 days. Extending this timeframe, Seow et al. (2022) showed that early PC (6–12 months before death) reduced overall healthcare costs, largely owing to fewer hospitalizations near EOL.

In a large Ontario cohort, Barbera et al. (2006) found that cancer patients who received a PC assessment near EOL were significantly less likely to require intensive care unit admissions or emergency department visits, underscoring PC's potential to reduce the use of hospital resources.

In Finland, Haltia et al. (2023) evaluated the effect of palliative outpatient units and found a significant decrease in hospital resource utilization among cancer patients receiving specialized outpatient PC.

Hirvonen et al. (2020) also emphasized that patients who received PC decisions earlier and visited the PC unit had fewer emergency department visits and inpatient stays than patients who did not receive a PC decision. Similarly, Rautakorpi et al. (2021) highlighted the role of contact with the PC unit in minimizing unnecessary emergency department visits and hospitalizations among pancreatic cancer patients. Jang et al. (2015) demonstrated that PC consultations significantly decreased the use of aggressive EOL treatments, leading to more appropriate use of hospital resources. Bevins (2021) in turn found that palliative interventions effectively reduced the need for hospital services and the utilization of aggressive EOL care, further optimizing hospital resource utilization. Table 4 provides an overview of these and other key findings on how PC impacts hospital resource use.

Table 4 Impact of palliative care on hospital resource utilization

Study	**Year**	**Study design**	**Patient population**	**Key findings**
Barbera et al.	2006	Population-based retrospective study (Canada)	21,323 patients with cancer	Patients receiving a palliative care assessment near the end of life were significantly less likely to require intensive care unit admissions or emergency department visits
Obermeyer et al.	2014	Retrospective cohort study (USA)	36,330 patients with poor-prognosis cancer	Hospice patients had fewer hospitalizations, intensive care unit admissions, and invasive procedures at the end of life
Pace et al.	2014	Prospective observational study (Italy)	848 patients with brain tumor	Reduction in rates of rehospitalization visit for patients receiving home-based palliative care
Jang et al.	2015	Retrospective cohort study (USA)	5,381 patients with pancreatic cancer	Less intensive care unit admissions, multiple emergency department visits, and multiple hospitalizations for patients with palliative care consultations

Study	Year	Study design	Patient population	Key findings
Hirvonen et al.	2020	Retrospective cohort study (Finland)	992 cancer patients	An earlier palliative care decision was linked to fewer emergency department visits and inpatient days
Bevins et al.	2021	Retrospective cohort study (USA)	3,166 patients with pancreatic cancer	Palliative interventions reduced emergency department visits and intensive care unit admissions
Haltia et al.	2023	Retrospective cohort study (Finland)	2,007 cancer patients	Significant decrease in emergency department visits and hospitalizations among those who visited palliative care unit

2.3.2.1 Home-based palliative care services

Home-based PC services provide important support for patients with advanced illnesses, such as cancer and brain tumors, in the comfort of their home environment. A Cochrane review by Gomes et al. (2013) reported that home-based PC can reduce the symptom burden of patients with advanced illnesses. Another Cochrane review by Shepperd et al. (2016) showed that EOL hospital-at-home interventions increased the likelihood of being able to die at home.

Building on this, a randomized controlled trial by Brumley R et al. (2007,) found that in-home PC, comparable to hospital-at-home services, increased the likelihood of patients being able to die at home, improved patients' satisfaction with care, reduced both emergency department visits and hospitalizations, and lowered overall care costs for patients with terminal illnesses. International studies from Italy, India, and the United States have further demonstrated that home-based palliative services can reduce hospital stays, allowing patients to remain at home for longer (Riolfi et al. 2014; Yeager et al. 2016; Wang et al. 2019). Pace et al. (2012) reported that home care lowered hospital admissions and was cost-effective for brain tumor patients in particular. Even patients with complex neurological symptoms can benefit from comprehensive home care, including palliative sedation and multifaceted symptom management (Pace et al. 2009; Pompili et al. 2014).

A systematic review by Nordly et al. (2016) highlighted that 44–90 percent of patients receiving specialized PC at home ultimately died at home, suggesting that home-based interventions can help meet patients' EOL preferences. Additionally, a Canadian study by Seow et al. (2014) found that patients who frequently utilized homecare services were less likely to use emergency departments or be hospitalized at EOL, indicating that comprehensive home-based PC may not only improve continuity of care but also reduce overall healthcare expenditures. In Finland, a nationwide hospital-at-home network provides specialized home-based care, with PC being one of its main functions. The network covers nearly the entire population and represents a key component of EOL care services (Ohvanainen et al. 2021).

2.3.2.2 Palliative care outpatient clinic

A PC outpatient clinic is a specialized setting that provides comprehensive, multidisciplinary support to patients with life-limiting illnesses on an outpatient basis (Hui, 2019). According to a 2020 review by Hui and colleagues on models of PC delivery, outpatient clinics are a cornerstone for delivering early, integrated palliative services to cancer patients, offering expert symptom control, psychosocial and emotional support, and care coordination.

Research highlights the benefits of outpatient PC for individuals with advanced cancer. A Canadian study by Follwell et al. (2009) found that early PC consultations in a dedicated outpatient clinic significantly improved symptom burden and satisfaction among patients with metastatic cancer. Similarly, Singer AE et al. (2016), in a review focusing on patients with advanced illness, mainly cancer, concluded that outpatient PC services are associated with better patient and caregiver outcomes and fewer hospital admissions near EOL.

As noted in earlier, multiple randomized controlled trials evaluating early integrated PC—often implemented in outpatient clinics—demonstrate significant improvements in QoL, symptom control, and patient satisfaction (Chen et al. 2022; Maltoni et al. 2016; Temel et al. 2010; Temel et al. 2017; Vanbutsele et al. 2020; Zimmermann et al. 2014). Beyond these randomized controlled trial findings, a Finnish study by Haltia et al. (2023) demonstrated that patients who accessed a dedicated PC outpatient clinic had a median interval of 112 days between their first visit and death. Earlier engagement with these services was associated with significantly lower use of acute hospital resources. In a German retrospective chart review of oncology outpatients, Bükki et al. (2013) identified high PC needs and frequent aggressive interventions, highlighting the potential value of specialized outpatient PC for reducing treatment intensity and better address EOL symptoms.

A review by Crooms et al. (2020) underscored that regular outpatient follow-up of brain tumor patients enables proactive symptom management (e.g., for seizures or headaches), individualized counseling, and family support—components that may not be as readily addressed in sporadic inpatient settings.

2.3.2.3 Palliative care consultation team

A PC consultation team is a multidisciplinary group of healthcare professionals who provide specialized PC advice and support to other clinical teams and their patients. These teams can function in both inpatient (hospital-based) and outpatient settings, tailoring their services to the nature of the disease and the specific needs of each patient (Hui et al. 2018; Hui et al. 2020).

Many international studies underscore the benefits of such consultation teams in improving outcomes for patients with life-limiting illnesses. A systematic review by Scott et al. (2020) found that these teams enhanced symptom management and QoL while potentially reducing healthcare costs. Likewise, Rabow et al. (2004) demonstrated in a controlled trial that outpatient palliative consultations led to reductions in dyspnea, anxiety, and spiritual distress, in addition to fewer urgent care visits. Morrison et al. (2011) also indicated that hospital-based consultation teams can significantly lower overall costs by fostering timely goals of care discussions and diminishing the use of high-intensity interventions at EOL. Rosenberg et al. (2020) also noted increased hospice utilization under palliative consultation.

Canadian research by Lees et al. (2019) highlighted how PC consultation teams effectively reduce aggressive interventions near EOL. More broadly, a systematic review and meta-analysis by Gaertner et al. (2017) found that PC interventions, including consultation teams, were associated with improved QoL for cancer patients, though the magnitude of this benefit varied.

Another randomized controlled trial by Gade et al. (2008) confirmed that inpatient consultation significantly reduced intensive care unit admissions and improved patient satisfaction. Additional evidence from South Korea, reported by Suh et al. (2024), shows that early PC consultation correlates with less aggressive EOL care and a longer duration of hospice use. Furthermore, Crooms et al. (2023) reported that earlier referrals to a palliative consultation team were linked to extended survival among patients with high-grade glioma. These different PC service models—home care, outpatient clinics and consultation teams—seem to have an impact on patient care. Table 5 summarizes the studies that support each model's effectiveness.

Table 5 Effectiveness of palliative care service models for cancer patients

Reference	Year	Study design (Country)	Patient population	Key findings
Hospital at home (In-home palliative care)				
Brumley R et al.	2007	Randomized controlled trial (USA)	298 terminally ill patients	Less emergency department visits and hospitalizations Improved satisfaction with care

Reference	**Year**	**Study design (Country)**	**Patient population**	**Key findings**
				Increased the likelihood of being able to die at home
Pace et al.	2012	Prospective observational study (Italy)	143 patients with primary brain tumor	Less hospital admissions Demonstrated cost-effectiveness of home-based interventions
Riolfi et al.	2014	Retrospective cohort study (Italy)	402 patients with cancer	Fewer hospital stays Extended time at home More likely to be able to die at home
Seow et al.	2014	Retrospective cohort study (Canada)	6,218 patients with emergency department visits or hospitalizations (80% with cancer)	Fewer emergency department visits Reduced hospitalizations Lower costs
Yeager et al.	2016	Retrospective analysis (India)	746 patients with chronic illness	Reduced hospital utilization
Wang et al.	2019	Retrospective cohort study (USA)	54,751 decedents who had at least one hospitalization in the 12 months before dying	Less need for hospital admissions
Bojesson et al.	2024	Randomized controlled trial (Sweden)	118 patients with advanced gastrointestinal cancer	Improved quality of life
Reference	**Year**	**Study design (Country)**	**Patient population**	**Key findings**
Outpatient clinic				
Follwell et al.	2009	Prospective study (Canada)	150 patients with metastatic cancer	Reduced symptom burden and higher patient satisfaction

Reference	**Year**	**Study design (Country)**	**Patient population**	**Key findings**
Temel et al.	2010	Randomized controlled trial (USA)	151 patients with metastatic non-small cell lung carcinoma	Improved quality of life, fewer depressive symptoms, and a survival benefit
Bükki et al.	2013	Retrospective chart review (Germany)	96 patients with advanced tumors	Reduced treatment intensity and better-addressed end-of-life symptoms
Zimmermann et al.	2014	Randomized controlled trial (Canada)	461 patients with advanced cancer	Improved satisfaction with care Improved quality of life
Maltoni et al.	2016	Randomized controlled trial (Italy)	207 patients with metastatic or locally advanced inoperable pancreatic cancer	Improved quality of life, more appropriate hospice use, less aggressive end-of-life treatments
Vanbutsele et al.	2020	Randomized controlled trial (Belgium)	186 patients with advanced solid cancer	Better patient-reported outcomes and quality of life measures
Chen et al.	2022	Randomized controlled trial (China)	120 patients with newly-diagnosed non-small cell carcinoma	Improved quality of life, less depression, and better nutritional status
Haltia el al.	2023	Retrospective study (Finland)	2007 cancer patients	Fewer emergency department visits and hospitalizations
Reference	**Year**	**Study design (Country)**	**Patient population**	**Key findings**
Consultation team				

Reference	**Year**	**Study design (Country)**	**Patient population**	**Key findings**
Rabow et al.	2004	Controlled trial (USA)	90 outpatient patients with chronic illness	Reduced dyspnea, anxiety, spiritual distress Fewer urgent care visits
Gade et al.	2008	Randomized controlled trial (USA)	517 patients with life-limiting illnesses	Fewer intensive care unit admissions Higher patient satisfaction than with usual care
Morrison et al.	2011	Retrospective analysis (USA)	2,061 hospitalized patients	Reduced overall costs by limiting high-intensity end-of-life interventions Increased hospice referrals
Lees et al.	2019	Retrospective cohort study (Canada)	365 patients with unresectable pancreatic cancer	Fewer aggressive interventions near end of life, with timely consultation
Rosenberg et al.	2020	Retrospective cohort study (USA)	90 patients with high-grade gliomas	Increased hospice utilization
Crooms et al.	2023	Retrospective study (USA)	621 patients with high-grade gliomas	Earlier palliative care referral extended survival
Suh et al.	2024	Prospective observational (South Korea)	205 patients with glioblastoma	Early palliative care consultation correlated with less aggressive end-of-life care and longer hospice use

2.3.3 Place of death

The place in which a patient spends their final days is central in EOL care and often reflects patient preferences and the quality of care they have received. Research consistently shows that most cancer patients prefer to die at home or in a hospice setting rather than in a hospital (Donkor et al. 2024; Fereidouni et. al., 2021; Gomes et al. 2012; Nilsson et al. 2017; Tang, 2003).

For cancer patients in general, the place of death can vary widely, and is influenced by factors such as cancer type and stage, availability of support services, and the involvement of PC. A retrospective cohort study in Finland by Hirvonen et al. (2020) found that the duration of the PC period significantly influenced the place of death for cancer patients. Patients who received a PC decision earlier were more likely to die in primary care wards, whereas those without PC decision tended to die in secondary/tertiary care hospitals.

The impact of PC on the place of death has been demonstrated in several studies. A Cochrane review by Gomes et al. (2013) found that home-based PC more than doubled the odds of being able to die at home for cancer patients. Additional evidence from Oluyase (2021) demonstrates that the integration of home-based PC services significantly increases the number of home deaths. Furthermore, Poulose et al. (2013) demonstrated that early referral (≥30 days before death) to a PC team was associated with a higher probability of being able to die at home or in an inpatient hospice facility than dying in a hospital.

The place of death seems to vary between patients with primary and secondary brain tumors. A higher proportion of patients with secondary brain tumors (24%) pass away in hospital settings than those with primary brain tumors (16%) (Shenker et al. 2022). The integration of PC services has had a significant impact on the place of death for these patients (Sundararajan et al. 2014). Pompili et al. (2014) found that 53 percent of GBM patients receiving home care died at home and 13 percent at a hospital. This trend is further supported by Pace et al. (2014), who reported that among brain tumor patients receiving home care, 61 percent died at home, 22 percent died in a hospital, and 17 percent died in a hospice. Kelly (2022) also found that comprehensive home-based PC reduced hospital deaths and increased hospice deaths. However, as with many studies in this area, the majority of the evidence is based on retrospective cohort designs. Table 6 presents a concise overview of the key studies linking PC interventions to place of death.

Table 6 Impact of palliative care on cancer patients' place of death

Reference	**Year**	**Study design (Country)**	**Patient population**	**Key findings related on place of death**
Poulose et al.	2013	Retrospective cohort (Singapore)	842 critically ill patients (86% of cancer patients)	Earlier referral was associated with higher probability of being able to die at home or in an inpatient hospice than dying in hospital
Pompili et al.	2014	Observational study (Italy)	197 patients with glioblastoma multiforme	Home palliative care enabled 53% to die at home, whereas 34% died in hospice care, and only 13% died in hospital.
Pace et. al.	2014	Observational study (Italy)	848 patients with brain tumor	Neuro-oncological home care enabled 61% to die at home, whereas 22% died in hospital, and 17% in a hospice
Sundararajan et al.	2014	Retrospective cohort study (Australia)	678 patients with malignant glioma patients	Patients receiving palliative care were 1.7 times more likely to be able to die outside hospital
Hirvonen et al.	2020	Retrospective cohort study (Finland)	992 cancer patients	Earlier palliative care decisions increased the likelihood of dying in primary care wards instead of secondary/tertiary hospitals
Kelly et al.	2022	Retrospective cohort study (Ireland)	4,103 patients with cancer	Less hospital deaths and more hospice deaths

3 Aims

The aim of this dissertation is to investigate how the timing of a PC decision—the decision to terminate curative/life-prolonging anticancer treatments—and to focus on PC and SPC service—the first documented contact with SPC services—were associated with the use of healthcare resources at EOL by patients with primary or secondary brain tumors.

The more specific aims were:

Study I: To evaluate how the timing of a PC decision was associated with (1) acute hospital resource utilization (emergency department visits, hospitalizations) and (2) the use of anticancer treatments at EOL among patients with primary malignant brain tumors treated at Helsinki University Hospital.

Study II: To examine the association between the timing of a PC decision and (1) emergency department visit, (2) hospitalizations, and (3) the utilization of radiotherapy at EOL among patients with brain metastases who had received radiotherapy.

Study III: To investigate the association between the timing of the first SPC contact and (1) healthcare resource utilization and (2) place of death among a nationwide cohort of patients with brain tumors who died in 2019.

4 Patients and methods

4.1 Patients

This dissertation examines three separate retrospective study populations (Studies I, II, and III) of patients diagnosed with primary (Studies I and III) or secondary (Study II) brain tumors. Studies I and II were single-institution analyses, whereas Study III was conducted on a nationwide level in Finland. Table 7 and Table 8 present summaries of these study populations.

4.1.1 Study I and III populations (primary brain tumors)

Study I used data from a retrospective registry-based project at the Helsinki University Hospital Comprehensive Cancer Center. Patients with malignant brain tumors (ICD-10 codes C71.1–71.9, including Grade II–IV gliomas) who were treated between 1993 and 2014 and died between 2013 and 2014 were identified from a larger cohort of adult cancer decedents (n=2737). Pediatric patients (<18 years) were excluded, resulting in a final sample of 121 adult patients.

Study III investigated all adult patients (≥18 years) in Finland with a primary brain tumor (ICD-10 codes C71.0–71.9) listed as the cause of death in 2019. This investigation was part of a larger national register survey (n=38,540) by the Finnish Institute for Health and Welfare (THL), which extracted data on non-communicable life-limiting diseases from the Causes of Death Register (Statistics Finland) and the National Care Register, including Kanta Services. After excluding individuals who had died outside Finland, 373 patients with an underlying brain tumor as their cause of death were included in the study.

4.1.2 Study II population (brain metastases)

Study II evaluated patients with brain metastases (ICD-10 codes C79.30–79.49) who received radiotherapy at Vaasa Central Hospital between 2011 and 2021 and had died by November 2021. Thirteen patients who were assessed but did not receive radiotherapy were excluded, leaving 91 patients in the final study population.

Table 7 Overview of study populations (Part I)

	Study I	**Study II**	**Study III**
Data source	Helsinki University Hospital Comprehensive Cancer Center	Vaasa Central Hospital	Nationwide, Finland
Study population	Patients with malignant brain tumors (ICD-10: C71.1–71.9) died in 2013–2014	Patients with brain metastases (ICD-10: C79.30–79.49) treated with radiotherapy in 2011–2021 and deceased by November 2021	Patients with malignant brain tumors (ICD-10: C71.0–71.9) who died in 2019
Number of participants	121	91	373
Main inclusion criteria	Histologically/ imaging-confirmed malignant brain tumor	Radiotherapy-treated brain metastases	Brain tumor as underlying cause of death
Exclusion criteria	Pediatric (<18-year-old) patients	Patients who did not receive radiotherapy	Death outside Finland

4.2 Methods

4.2.1 Definitions of early and late/no palliative care decision and contact

The timing of a PC decision was defined as the date on which a clinician had explicitly documented a decision to terminate curative or life-prolonging anticancer treatments and to focus on PC. This decision was classified as “early” if it occurred more than 30 days before death. In contrast, decisions made during the 30 days before death or not made at all were classified as “late/no” PC decision. (Study I and II)

An SPC contact was defined as the first recorded contact with SPC services. SPC was classified as early if this contact occurred more than 30 days before death and late/no contact if it took place during these 30 days or did not occur at all. (Study III)

4.2.2 Study I and III (primary brain tumors)

In **Study I,** data were collected from the Helsinki University Hospital Comprehensive Cancer Center through a systematic search of electronic medical records and manual review of the period from initial diagnosis to death. The collected information consisted of patient demographics (age, sex), tumor histology (GBM vs. other), details of oncological treatments (surgical resection, chemotherapy, radiotherapy, and lines of systemic treatments and re-irradiations), do-not-resuscitate orders (and who made them), psychosocial support visits, PC unit visits, and emergency department visits and hospitalizations—particularly in the final month of life. The date of the PC decision was identified from the documentation, indicating termination of curative or life-prolonging anticancer treatments and a focus on PC. Patients were classified as having an early or late/no PC decision on the basis of this date. Date and place of death (home, hospice, hospital setting or nursing home) were noted.

Study III used national-level registry data (Causes of Death Register, National Care Register, and Kanta Services), covering 1 January 2018 to 31 December 2019. These registries, which are standardized and regulated by Finnish healthcare authorities, mandate data submission from both public and private healthcare providers. The linked dataset provided each patient's age; sex; ICD-10 diagnosis code Z51.5; primary, secondary, and tertiary care admissions; length of inpatient stays; outpatient clinic contacts; social services contacts; emergency department contacts, and SPC contacts (including outpatient clinic contacts, hospital-at-home services, SPC wards, hospices or dedicated palliative consultation). Data on place of death (home, hospital, long-term care facility, SPC ward) were also collected. Data on home care contacts, PC unit visits, and hospital at home services association with place of death were collected. Place of death was reported as the SPC ward if the patient was receiving SPC on the day of their death. Healthcare resource utilization in the final six months and last month of life was examined across primary, secondary, and tertiary care settings, focusing on emergency department contacts and hospitalizations. For the purposes of Study III, we combined secondary and tertiary care data and refer to it collectively as "secondary care" throughout the study.

4.2.3 Study II (brain metastases)

Information on age, gender, ECOG performance status, primary cancer type, number of brain metastases, extracranial organ metastases, radiotherapy and radiotherapy fractionation, and systemic therapy after radiotherapy were manually collected from medical records. Reasons for visiting the emergency department in the last month of life were also manually collected from patient records and categorized as deterioration in overall clinical health, pain, neurological symptoms, infection, dyspnea, embolism, and other reasons. In determining key time points, the date of brain metastases diagnosis was defined as the date of the earliest CT or MRI scans confirming metastatic lesions, whereas the start of radiotherapy corresponded to the actual day on which treatment commenced. The PC decision date was determined from medical records as the date on which life-prolonging treatments were terminated to focus on PC, and the date of death was verified from death certificates. The timing of the PC decision—categorized as early versus late/no—was recorded. Emergency department visits (with the reasons for these visits) and hospitalizations during the last month of life, along with details on whether radiotherapy was given in the final 30 or 14 days before death were also noted.

Table 8 Overview of study populations (Part II)

	Study I	**Study II**	**Study III**
Palliative care measure	Palliative care decision	Palliative care decision	Specialist palliative care contact
Timing definitions	Early: >30 days before death; Late/No: ≤30 days before death or no decision/contact	Early: >30 days before death; Late/No: ≤30 days before death or no decision/contact	Early: >30 days before death; Late/No: ≤30 days before death or no decision/contact
Primary outcomes	Use of hospital resources (emergency department visits/hospitalizations) Place of death	Emergency department visits (reasons, frequency) Hospitalizations Radiotherapy near the end of life	Healthcare use in final six months and last month of life (emergency department contacts, hospitalizations) Place of death Utilization of specialist palliative care services

4.3 Statistical analyses

In all three studies, the population was subdivided into groups on the basis of the timing of the PC decision or SPC contact (early vs. late), and various clinical and care-related variables were analyzed accordingly. All three studies used descriptive statistics—such as means, medians, ranges, number of incidences, and percentages—to describe the patient and disease characteristics and the EOL care patterns. The specific methods varied slightly:

Study I used Microsoft Excel (version 2108) to conduct chi-squared tests (χ^2) to compare the categorical variables. To ensure an expected size of at least five for each group, the place of death was categorized as either “specialized” or “general”. OS was calculated from the date of pathologic diagnosis to the date of death, and survival following the PC decision was calculated from the date of the decision to the date of death.

Study II used IBM SPSS Statistics (version 28, IBM Corp, Armonk, NY, USA) for Pearson’s chi-squared and Fisher’s exact tests to compare the categorical variables. OS was defined as the time in months from the radiographic diagnosis of brain metastases to the date of death. Kaplan–Meier analysis was performed to determine the median OS along with its 95% confidence interval.

Study III used IBM SPSS Statistics (version 29, IBM Corp, Armonk, NY, USA). The patients were classified on the basis of the timing of their first SPC contact. Pearson’s chi-squared or Fisher’s exact tests were used for categorical variables (e.g., emergency department contacts, hospitalizations). Because hospital days were unevenly distributed, the Mann–Whitney test was applied to compare the lengths of stay of the groups.

In all three studies, a threshold of **$p<0.05$** denoted statistical significance.

4.4 Ethical considerations

This dissertation adhered to the ethical principles outlined in the Helsinki Declaration and the guidelines and regulations set by the respective institutions involved.

All the three register-based retrospective studies of this dissertation involved deceased patients, and no interventions were performed on them or their relatives.

To ensure ethical conduct, several measures were taken:

The data were processed pseudonymously, and all personal identifiers were removed to protect patient privacy and maintain confidentiality. To preserve anonymity, groups of less than five patients were not reported.

The studies were conducted with the required approval and permission of the relevant authorities:

Study I: Approval was obtained from the authorities of the Helsinki University Central Hospital and permission from the coordinating ethical committee of the Helsinki and Uusimaa district.

Study II: Approved by the Medical Director of the Vaasa Central Hospital.

Study III: Conducted as part of the Project on Quality Information on Palliative Care and End-of-life Care, approved by the Finnish Institute for Health and Welfare (THL) and Findata.

As all the patients were deceased before data collection began, obtaining informed consent was not feasible or necessary for these retrospective studies. Strict protocols were followed to ensure the secure handling and storage of sensitive data and minimize the risk of breaches or unauthorized access to the data.

5 Results

5.1 Association between palliative care decisions and hospital service utilization at the end of life by patients with malignant brain tumors: A retrospective single institute study (Study I)

The study population consisted of 121 adult patients with malignant brain tumors. Their median age at diagnosis was 62 (range: 26–89 years). Men slightly outnumbered women (61% vs. 39%). GBM was the most frequent histology (76%). Table 9 summarizes these baseline characteristics.

Table 9 Patient characteristics (Study I)

Characteristics	**Value**
Number of patients	121
Age, median (range)	62 years (26–89)
Age <65 years	77 (64%)
Age ≥65 years	44 (36%)
Sex	74 (61%) men 47 (39%) women
Glioblastoma multiforme	92 (76%)
Other histologies	Astrocytoma, oligoastrocytoma, oligodendroglioma (24%)

5.1.1 Treatment patterns

Most patients (89%) underwent surgical resection, while nine percent only had a biopsy taken. A small proportion (5%) received no oncological treatment. Table 10 presents the treatments administered, including systemic therapy lines and re-irradiation rates.

Table 10 Treatments received by 121 patients with malignant brain tumors

Treatment modality	**Number (%) of patients**
Surgical intervention	
Resection	108 (89%)
Biopsy only	11 (9%)
Primary treatment with curative intent	105 (87%)
Palliative radiotherapy only	10 (8%)
No oncological treatment	6 (5%)
Systemic anticancer treatment after primary treatment	
First-line	28 (23%)
Second-line	21 (17%)
Third-line or more	14 (12%)
Re-irradiation (≥1 repeat radiation course)	44 (36%)

5.1.2 Timing of palliative care decision

A documented PC decision was found for 78 percent (n=95) of patients. Of these, 54 percent (n=51) were categorized as early and 46 percent (n=44) as late PC decisions. The median time from the PC decision to death was 44 days overall (range 1-293 days)—38 days for GBM and 71 days for other histologies.

Early PC decisions correlated with fewer anticancer interventions near EOL. In the last 60 days of life, only 56 percent of early PC decision patients underwent anticancer treatment, in comparison to 84 percent in the late/no PC decision group ($p<0.001$). Age, diagnosis (GBM vs. other), and number of treatment lines did not correlate with the timing of the PC decision.

5.1.3 Utilization of end-of-life care

Overall, 31 percent (n=38) of the patients had visited the emergency department at least once in the last month of their lives, mostly for neurological symptoms (48% of emergency department visits). Figure 1 shows the reasons for these emergency department visits.

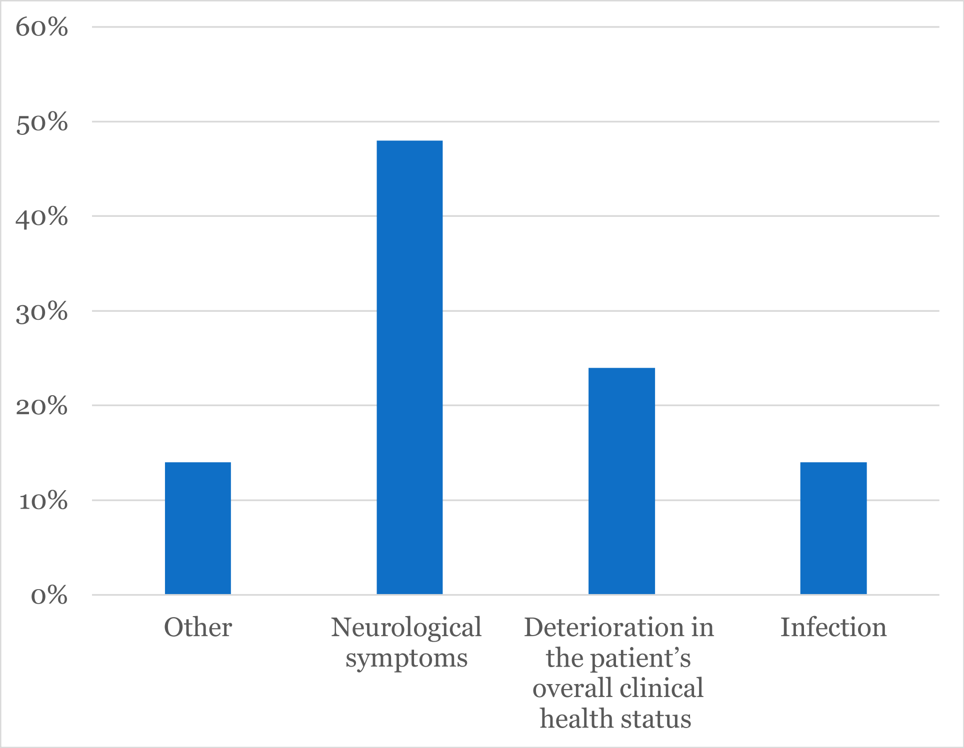

Figure 1 Reasons for emergency department visits in last month of life

Among those with an early PC decision, only four percent had emergency department visits in the last month, compared to 42 percent in the late/no decision group (p<0.001). Hospital admissions followed a similar pattern: No early PC decision patients were hospitalized at the university hospital in the final month, whereas 35 percent of late/no-decision patients were admitted (p<0.001). Figure 2 summarizes these EOL resource utilization findings.

Among those hospitalized, 51 percent died during their final admission, with neurological deterioration being the principal cause of emergency department visits leading to admission. Despite the differences in acute-care utilization, place of death did not significantly differ in terms of the PC decision timing. A small proportion (6%) died at home, but the vast majority (74%) died in hospital settings.

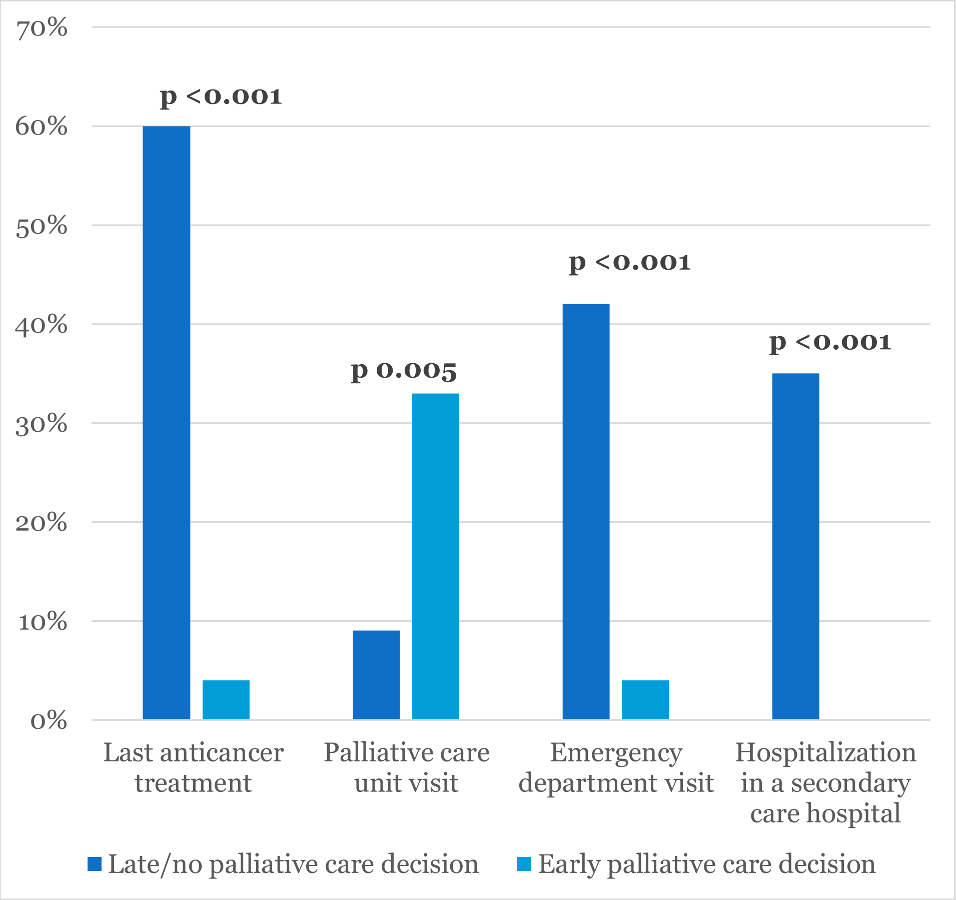

Figure 2 Comparison of anticancer treatments, palliative care unit visits, emergency department visits, and hospital admissions in last month of life of early and late/no palliative care decision groups

5.2 End-of-life care and use of hospital resources among radiotherapy-treated cancer patients with brain metastases: A single-institution retrospective study (Study II)

The population of Study II consisted of 91 adult patients with brain metastases. The median age was (range 23–91 years), 59 percent were male, and 64 percent had an ECOG performance status of ≥2. Lung cancer was the most common primary cancer type (24%), followed by breast cancer (12%) and melanoma (12%). Over half (52%) presented with ≥4 intracranial lesions, and 65 percent had metastases in ≥2 extracranial organs. Most patients (93%) received WBRT, predominantly 30 Gy in ten fractions (72%) or 20 Gy in five fractions (21%). Table 11 summarizes these baseline demographics and tumor characteristics.

5.2.1 Palliative care decision

A documented PC decision was found for 87 percent of patients (n=79). Among these, 41 percent (n=32) had an early decision (>30 days before death), while the remainder (n=47) had a late decision (≤30 days) or none at all.

Table 11 Patient characteristics (Modified from Study II)

Patient characteristics (n=91)			
	Patients n (%)	No PC decision or PC decision ≤30 days before death, n=59 (%)	PC decision >30 days before death, n=32 (%)
Age (mean)	67 years	67 years	67 years
Male	54 (59)	38 (64)	16 (50)
ECOG Performance status			
0–1	33 (36)	22 (37)	11 (34)
2	37 (41)	21 (36)	16 (50.0)
3	21 (23)	16 (27)	5 (16)
Primary tumor type			
Other tumors	28 (31)	17 (29)	11 (34)
Non-small cell lung cancer	22 (24)	16 (27)	6 (19)
Breast cancer	11 (12)	6 (10)	5 (16)
Melanoma	11 (12)	7 (12)	4 (13)
No histological diagnosis	11 (12)	8 (14)	3 (9)

Patient characteristics (n=91)			
Small cell lung cancer	8 (9)	5 (8)	3 (9)
Number of brain metastases			
1–3	44 (48)	28 (47)	16 (50)
≥4	47 (52)	31 (53)	16 (50)
Number of involved extracranial organs			
0	11 (12)	7 (12)	4 (13)
1–2	47 (52)	30 (51)	17 (53)
≥3	33 (36)	22 (37)	11 (34)
WBRT regimen			
20 Gy in 5 fractions	19 (21)	12 (20)	7 (22)
30 Gy in 10 fractions	66 (72)	43 (73)	23 (72)
Stereotactic radiotherapy	6 (7)	4 (7)	2 (6)
Radiotherapy for recurrent metastases	6 (7)	3 (5)	3 (9)
Systemic treatment after radiotherapy	33 (36)	21 (35)	12 (37)

5.2.2 Key time intervals

As Table 12 shows, the median time from brain-metastasis diagnosis to radiotherapy initiation was similar in both groups. However, patients in the early decision group experienced significantly longer intervals between the start of radiotherapy and death and between the PC decision and death.

Table 12 Key time intervals by timing of palliative care decision

Time interval	**Early palliative care decision**	**Late/no palliative care decision**
Between diagnosis of brain metastases and start of radiotherapy (days)	19 (1–182)	17 (5–167)
Between start of radiotherapy and death (days)	236 (36–1862)	54 (17–1002)
Between palliative care decision and death (days)	79 (31–621)	10 (1–27)
Overall survival after diagnosis of brain metastases (days)	255 (44–1864)	75 (29–1047)

5.2.3 Utilization of healthcare at the end of life

Patients with an early PC decision were significantly less likely to be hospitalized (p=0.005) or die during a hospital stay (p=0.047) at the central hospital, as shown in Table 13. These patients were more also likely to visit a PC unit (p<0.001) than those with a late/no PC decision.

Table 13 Healthcare utilization in the last month of life

Central hospital service utilization during the last 30 days of life	**Early palliative care decision (%)**	**Late/no palliative care decision, n (%)**	**p-value**
Emergency department visits	41%	53%	0.277
Hospitalizations	22%	53%	0.005

Central hospital service utilization during the last 30 days of life	**Early palliative care decision (%)**	**Late/no palliative care decision, n (%)**	**p-value**
Died during hospitalization period	9%	27%	0.047
Palliative care unit visits	38%	8%	<0.001

5.3 Association between specialist palliative care and use of healthcare resources at the end of life by brain tumor patients: A nationwide study (Study III)

The study population comprised 373 adult patients who died from brain tumors in Finland in 2019. The mean age was 68 (range 18–94 years), and 58 percent (n=216) were male. An ICD-10 diagnosis code for PC (Z51.5) was documented for 161 patients (43%). Only 27 percent (n=102) SPC contact. Of these 102 patients, 81 (22% of total) had early contact (>30 days before death; Group I) but 21 (6% of total) had late contact (≤30 days). The remaining 271 (73%) patients had no SPC contact at all (Group II). Table 14 summarizes these baseline variables and group allocations.

In Group I, the median time from first SPC contact to death was 138 days (range 33–708 days), while in Group II, for patients with SPC contact, this was 17 days (range 0–27 days) (p<0.001). A significantly larger fraction of Group I had an ICD-10 code of Z51.5 (68% vs. 36%, p<0.001).

5.3.1 Use of social and healthcare services

Overall, 38 percent of the patients (n=142) had had at least one emergency department contact in their last 30 days. No significant difference was found between Group I (35%) and Group II (39%, p=0.463). Major contrasts emerged in tertiary outpatient visits: 28 percent in Group I vs. 53 percent in Group II (p<0.001). Hospitalizations followed a similar trend: 48 percent in Group I vs. 76 percent in Group II (p<0.001), as shown in Table 14. Patients with early SPC contact more frequently used specialized palliative services, including hospital-at-home services (33% vs. 2%, p<0.001) and PC outpatient clinics (16% vs. 4%, p<0.001).

Table 14 Utilization of hospital resources in last month of life, by timing of first specialist palliative care contact (Modified from Study III)

Patients N=373	**All**	**Group I Early SPC contact (n=81)**	**Group II Late or no SPC contact (n=292)**	**P-value**
Emergency department visits	142 (38%)	28 (35%)	114 (39%)	0.463
Outpatient clinic visits				
Tertiary/Secondary care	179 (48%)	23 (28%)	156 (53%)	<0.001
Primary healthcare	243 (65%)	48 (59%)	195 (67%)	0.209
Hospitalizations				
All hospitalizations	262 (70%)	39 (48%)	223 (76%)	<0.001
Tertiary/Secondary care	115 (31%)	8 (10%)	107 (37%)	<0.001
Primary healthcare	209 (56%)	35 (43%)	174 (60%)	0.009
Specialist palliative care				
Palliative care outpatient unit	24 (6%)	13 (16%)	11 (4%)	<0.001

Patients N=373	All	Group I Early SPC contact (n=81)	Group II Late or no SPC contact (n=292)	P-value
Hospital-at-home service	34 (9%)	27 (33%)	7 (2%)	<0.001
Special palliative care ward	29 (8%)	22 (27%)	7 (2%)	<0.001
Social services	62 (17%)	21 (26%)	41 (14%)	0.011
Home care	128 (34%)	39 (48%)	89 (31%)	0.003

5.3.2 Place of death

Early SPC contact also correlated with fewer in-hospital deaths (51% vs. 80%, p<0.001). Group I patients more often died in long-term care facilities (18% vs. 7%, p=0.002) or an SPC ward (21% vs. 2%, p<0.001). There was no significant difference between the frequency of home deaths of the groups. Table 15 shows the distribution of place of death across the two groups.

Table 15 Participants' place of death, by timing of first specialist palliative care contact

Patients N=373	All	Group I Early SPC contact (n=81)	Group II Late/no SPC contact (n=292)	P-value
Place of death				<0.001
Home	41 (11%)	8 (10%)	33 (11%)	0.717
Hospital	273 (73%)	41 (51%)	232 (80%)	<0.001

Patients N=373	All	Group I Early SPC contact (n=81)	Group II Late/no SPC contact (n=292)	P-value
Long-term care facility	36 (10%)	15 (18%)	21 (7%)	0.002
Specialist palliative care ward	23 (6%)	17 (21%)	6 (2%)	<0.001

5.3.2.1 Hospital-at-home services

Patients who received hospital-at-home services more often died at home, in long-term care, or in an SPC ward than in hospitals, in comparison to those who did not receive hospital-at-home services (38% vs. 77% for hospital deaths). These findings are summarized in Table 16, which illustrates how hospital-at-home services influence the distribution of patients' place of death.

Table 16 Distribution of place of death by hospital-at-home service usage

Patients N=373	All	Hospital-at-home service (n=34)	No hospital-at-home service (n=339)	P-value
Place of death				<0.001
Home	41 (11%)	10 (29%)	31 (9%)	0.004
Hospital	273 (73%)	13 (38%)	260 (77%)	<0.001
Long-term care facility	36 (10%)	5 (15%)	31 (9%)	<0.001
Specialist palliative care ward	23 (6%)	6 (18%)	17 (5%)	0.295

6 Discussion

6.1 Effect of palliative care decision (Study I) and specialist palliative care contact (Study III) on patients with brain tumors

The findings of **Studies I** and **III** underscore the complexities of caring for patients with malignant brain tumors and indicate that earlier integration of PC—whether through a timely PC decision or an early SPC contact—may help reduce utilization of healthcare services, particularly acute hospital services, and facilitate more appropriate EOL care.

Most patients with primary brain tumors—mainly GBM—receive intensive therapies, including surgery, radiotherapy, and systemic treatments, even in the final stages of the disease. While these approaches follow established international guidelines (Stupp et al. 2014; Sulman et al. 2017) and median survival times are consistent with published data (Korja et al. 2019; Stupp et al. 2009), the proportion of patients persisting with multiple lines of anticancer therapy until the last few weeks of their lives exceeded that observed elsewhere (Kuchinad et al. 2017; Hemminger et al. 2017). Notably, only five percent of the patients in our cohort received no treatment at diagnosis—a figure considerably lower than those documented in previous studies (Rusthoven et al. 2016). As the disease advanced, a mere 25 percent transitioned to PC without further oncological interventions, which is in contrast to the substantial fraction of patients in the other two series (39.5% and 42%, respectively) who had no further radiotherapy or systemic therapy (van Linde et al. 2017; Shi et al. 2018). This aggressive treatment paradigm persisted into the final stages of life, with 31 percent of patients receiving anticancer therapy during their last month and 17 percent during their last two weeks—exceeding the respective approximately 17 percent and six percent reported for late-life chemotherapy in other GBM cohorts (Kuchinad et al. 2017; Hemminger et al. 2017) (**Study I**).

Although a PC decision was eventually made for 78 percent of the brain tumor patients treated at the Helsinki University Hospital Cancer Center (**Study I**)—a proportion consistent with earlier Finnish cancer data (Haltia et al. 2023; Hirvonen et al. 2019)—the median interval from that decision to death was only 44 days, signifying a relatively late transition to symptom-focused care. This delayed timing contradicts guidelines advocating earlier palliative integration, especially in cases of diseases with heavy symptom burdens (Ferrell et al. 2017; Bakitas et al. 2015). The nationwide data in **Study III** similarly showed that SPC contacts were uncommon, occurring in only 27 percent of decedents with brain tumors. When such contacts did occur, however, they were initiated a median of 76 days before death, highlighting the potential for substantial supportive interventions once PC is pursued. According to the literature, PC is still relatively rare in neuro-oncology worldwide. Hemminger et al. (2017) reported that 37 percent of GBM patients attended palliative consultations.

PC unit attendance also remained low in the populations of **Studies I and III**, revealing a broader trend of underutilized or delayed specialized palliative services for brain tumor patients (Haltia et al. 2023). In the single-institution University hospital population (Study I), only 18 percent visited a PC unit, whereas in the nationwide population (Study III), only six percent did so in their last month of life

The symptom burden of malignant brain tumors provides an additional rationale for earlier PC. Patients experience escalating neurological deficits, fatigue, headaches, and, in the last days, significant alterations in their consciousness (Pace et al. 2009; Thier et al., 2016; Walbert & Khan 2014). **Study I** documented that many participants had repeated hospital admissions for symptom control, echoing a broader body of literature describing high acute-care usage, particularly in GBM (Diamond et al. 2017; Kuchinad et al. 2017). Likewise, **Study III** showed that 70 percent of decedents had had an inpatient stay in their final month, accompanied by a notable proportion needing emergency department visits (38%), a pattern consistent with the intense healthcare needs of individuals facing advanced neurological decline.

Despite the overall aggressive treatment patterns, both studies suggest that PC decision or PC contact, once initiated, can modify certain EOL measures. In **Study I**, patients whose PC decision was made more than 30 days before death had fewer hospital admissions and emergency department visits—an observation consistent with previous studies showing that patients who receive earlier or more integrated PC interventions tend to use less acute care (Brumley et al. 2007; Temel et al. 2010). Yet the observed differences in survival might reflect selection bias, given that even an “early” decision was still during the last weeks of the patient’s life. Meanwhile, **Study III** revealed that patients with early SPC contact were more likely to shift their EOL care from secondary outpatient clinics to SPC settings, such as inpatient SPC wards or hospital-at-home services. This realignment was associated with fewer hospitalizations in the last month of life—a finding consistent with broader oncology literature that shows that earlier SPC referral can reduce emergency admissions and hospitalizations (Hui et al. 2014; Triplett et al. 2017).

Place of death emerged as another key outcome. While the timing of the PC decision in **Study I** did not substantially influence whether or not patients died at home, **Study III** showed that early SPC contact was associated with more deaths in a long-term care facility or an SPC ward than in an acute hospital. However, neither study found an increase in home deaths, and this finding conflicts with some studies in other cancer populations, which have associated early PC with an increased likelihood of being able to die at home (Gomes et al. 2013). The unique challenges posed by neurological symptoms in brain tumor patients may contribute to this difference, perhaps making more hospital-level support necessary, and home death less feasible.

Notably, hospital-at-home services correlated with fewer transitions near EOL, enabling some patients to remain at home or in long-term care. This suggests that hospital-at-home services may play a crucial role in fulfilling patients' wishes regarding place of death and reducing burdensome transitions at EOL.

6.2 Effect of palliative care decision on patients with brain metastases (Study II)

A real-life retrospective study provides valuable insights into the aggressive nature of both the disease and treatments administered near EOL in patients with brain metastases who have received radiotherapy. Despite radiotherapy, the overall prognosis remained poor, with a median OS of only 3.7 months from the time at which metastatic lesions were first detected. This figure is generally lower than the survival times reported for other cohorts, which have ranged from several months to over a year, depending on tumor histology, primary cancer subtype, and the availability of targeted systemic therapies (Darlix et al. 2019; Sperduto et al. 2017; Corti et al. 2022; Yousefi et al. 2017). On the other hand, a Finnish study with a comparable patient population reported similar survival outcomes (Sundström et al. 1998). In our population, the underlying diagnoses were heterogeneous, resulting in median survival times varying from 6.3 months in melanoma cases to 5.5 months in breast cancer cases and 3.9 months in NSCLC cancer cases, which was the most common primary cancer.

Choice of treatment also influenced survival. The majority of patients underwent WBRT—commonly prescribed as 30 Gy in 3 Gy fractions—whereas only seven percent received SRT. Notably, treatment often continued until very late in the disease trajectory, as evidenced by 32 percent of patients receiving radiotherapy in the final 30 days of their lives, a higher proportion than that reported in some other studies (Ryoo et al. 2017). More than half of our study population had advanced diseases in multiple extracranial organs alongside four or more brain metastases, emphasizing the complexity of the required care. Surgical intervention—known to prolong survival in select cases (Moravan et al. 2020; Paek et al. 2005)—was uncommon here, which likely contributed to the overall limited survival.

Against this background, our study underscores the fact that the PC decision was often delayed, with a median interval of only 18 days between decision and death—frequently after radiotherapy had ended. Consequently, it rarely influenced key treatment choices, such as whether to initiate or continue WBRT. Still, about one-third of patients had an earlier decision (>30 days before death) and lived substantially longer (median 8.5 months) than those with a late or no decision (2.5

months). Even in the early group, however, many decisions were made during the last three months of life, suggesting possible selection bias—patients who survived longer were probably better positioned to obtain an earlier decision. The approximately six-month OS gap between the early and late/no decision groups, despite only a few weeks' difference in timing, implies that other factors may also account for the survival advantage.

Nevertheless, once initiated, the PC decision appears to have significantly influenced EOL resource utilization. Our findings support those of Temel et al. (2010), who demonstrated that patients who had received early PC had not only experienced improved QoL but had also had fewer hospital admissions and other aggressive interventions near their deaths. Similarly, Triplett et al. (2017) found that patients who had attended PC consultations had had fewer hospital admissions and less intensive treatments near their deaths. These parallels highlight the fact that, even when a PC decision occurs later than is ideal, it may still temper aggressive EOL treatment approaches, alleviate some of the acute-care burden, and enhance the overall coordination of services.

Importantly, the patient characteristics of the early and late PC decision groups did not differ significantly, suggesting that the timing of PC may be one of the key factors that shape EOL experiences. Once initiated however, the PC decision was associated with meaningful improvements in EOL care. Patients had lower rates of hospitalization and died in an acute-care environment less often. The findings of this study highlight the potential benefits of early PC involvement for patients with brain metastases who are undergoing radiotherapy.

6.3 Study limitations

One main limitation of all three studies is their retrospective design, which precluded the collection of patient-reported outcomes, such as QoL measures or detailed symptom scores. This gap is especially relevant in PC, in which patient well-being is paramount. Nonetheless, retrospective studies can provide valuable insights into real-life clinical practices and resource utilization patterns over an extended period—insights that may be difficult to obtain in prospective trials with narrower windows for data collection. By examining medical records and national care registries, these studies furnish a comprehensive understanding of patient trajectories, including how and when PC decisions and contacts are deployed in practice.

Studies I and II used manual data extraction from a single academic institution's medical records, allowing for a detailed exploration of the entire care pathway from brain tumor (primary or secondary) diagnosis to death. Although this approach allowed detailed data collection on oncological treatments, symptom presentation, and hospital resource usage, as it was confined to a single site it may have failed to capture any care received in other facilities. Moreover, the small size of the cohorts—especially in **Study II**—inevitably raises concerns about selection bias and poor generalizability, and about potentially missing or inconsistently applied diagnosis codes for brain metastases.

Study III, in contrast, benefited from national registry data and encompassed patients across multiple levels of care (primary, secondary, and tertiary) throughout Finland. This broad scope provided a larger dataset, giving a more comprehensive picture of EOL service use.

Despite these limitations, the present dissertation study has unique strengths. Retrospective studies permit the identification of real-world challenges in service provision and can illustrate where PC is (or is not) integrated into oncology workflows. By combining smaller, more detailed single-institution datasets (**Studies I and II**) and a comprehensive national registry (**Study III**), these investigations shed light on how current practices are utilized across different scales of data collection. They also underline the potential value of earlier palliative engagement for reducing aggressive EOL measures.

In summary, although they lacked QoL data and broader symptom assessments, these retrospective analyses enabled large-scale, long-term observations of healthcare utilization and EOL care, and offer actionable insights for clinical practice.

6.4 Future considerations

PC is a patient-centered approach that aims to improve the QoL of individuals facing life-threatening illnesses and their families. By focusing on early identification, appropriate treatment, and effective management of physical and psychosocial distress, it offers security, comfort, and support in the final stages of disease. This holistic method is especially relevant in neuro-oncology, in which many primary and secondary brain tumors remain incurable. In addition to extending survival, the goal is to maintain and enhance patients' daily functioning and overall well-being (Walbert 2014; Koekkoek et al. 2023). Yet, the optimal timing and method for integrating PC into the continuum of neuro-oncological treatment remain insufficiently defined, which emphasizes the need for more in-depth research.

Future efforts could benefit from prospective, multi-center studies that evaluate how PC decisions and SPC contact function across different healthcare systems. Such research might reveal the most effective stage at which PC should be introduced—whether at the time of diagnosis of advanced disease, at the onset of neurological decline, or at some other crucial moment. Identifying this timeline would be invaluable for tailoring supportive measures to meet patient and caregiver needs. Further study of the optimal management of chemotherapy and radiotherapy, particularly in EOL scenarios, is also warranted. Understanding how these treatments affect symptom control, QoL, and overall outcomes will help refine protocols for when to continue, de-escalate, or discontinue treatment.

Although PC's benefits for enhancing patient and caregiver well-being are well documented, cost-effectiveness remains an important area for future research to examine. Comprehensive economic evaluations could explore the long-term value of palliative interventions, such as reductions in hospital admissions, fewer intensive care unit stays, and better symptom management (May et al. 2018). These findings could reinforce the importance of strategic investments in palliative teams and in outpatient and home-based care models. Highlighting economic benefits may also encourage broader adoption of integrated PC pathways.

Further research is essential for clarifying the timing and scope of PC in neuro-oncology, exploring the role of chemotherapy and radiotherapy in advanced disease, and for strengthening the evidence base of its cost-effectiveness. Future investigations will promote more personalized, effective treatment strategies that acknowledge not only clinical outcomes but also the QoL challenges faced by patients with brain tumors and their families.

7 Summary and conclusions

Studies I and **III** demonstrated that early PC involvement—whether defined as a PC decision or SPC contact—was associated with a reduced acute-care burden among patients with malignant brain tumors. Patients in these early groups had fewer emergency department visits, fewer hospitalizations in their last month of life, and were less likely to receive aggressive anticancer treatments near the EOL. In **Study III**, early SPC contact was also associated with a lower proportion of in-hospital deaths and a higher likelihood of receiving care in long-term care or specialized palliative settings.

Study II highlighted the poor prognosis often associated with brain metastases and found that early PC decisions were associated with fewer hospitalizations and lower likelihood of in-hospital death. However, there was no significant difference in emergency department visit rates between early and late/no PC decision groups. Importantly, patients with earlier PC decisions were less likely to receive radiotherapy during the last month of life.

In sum, these insights from **Studies I, II, and III** emphasize the crucial role of timely PC engagement—including early PC decisions and early SPC contact—in optimizing the management of advanced neuro-oncological disease, reducing burdensome acute-care utilization, and better aligning treatment pathways with patient-centered goals.

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