Effect of implementing cancer patient pathways on timing of radiation therapy and survival for glioblastoma patients in Oslo, Norway

Master Student: **Divija Singireddy**

Supervisor: **Kirsten Kierulf Vieira**
LIS General Practice
Norabakken Lege- og Kiropraktorklinikk

Co-Supervisors:
Ibrahimu Mdala
Researcher, Department of General Practice
University of Oslo

Einar Vik-Mo
Neurosurgeon, Department of Neurosurgery
Oslo University Hospital

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Department of Community Medicine
Institute of Health and Society
Faculty of Medicine
University of Oslo, Norway

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List of Abbreviations

CNS- Central Nervous System

CPP – Cancer Patient Pathway

FLAIR- Fluid-attenuated inversion recovery

GBM - Glioblastoma

HR – Hazard Ratio

IFRT- Involved field RT.

IDH - Isocitrate dehydrogenase

MRI - Magnetic Resonance Imaging

OS – overall survival

OUH- Oslo University Hospital

RT- Radiation therapy

TMZ- Temozolomide

TTFields- Tumor treating fields

WBRT- Whole-brain RT

Abstract

Background

Glioblastoma (GBM) is an aggressive form of primary brain cancer, with a median survival rate of less than one year in unselected patient populations. Standard treatment for GBM includes surgery, chemotherapy, and radiation therapy (RT). In 2015, Norway implemented Cancer Patient Pathways (CPPs) to streamline the patient process for various types of cancer, aiming to provide predictability and reduce non-medical delays. While CPPs were not initially expected to impact patient outcomes, for rapidly progressing cancers like GBM, even minor delays in treatment initiation could affect prognosis. This study explores the effect of implementing CPPs on the time interval between GBM resection and the initiation of RT, as well as their potential impact on GBM patient survival.

Materials and Methods

This retrospective cohort study utilizes data from established databases at Oslo University Hospital's (OUH) Neurosurgical Department and Department of Oncology. The study encompasses 1,215 patients diagnosed with GBM between 2006 and 2019 who received RT, categorized into two groups: the pre-CPP group, spanning from 2006 to 2014 (n=731), and the post-CPP group, encompassing the years from 2016 to 2019 (n=397). The patients diagnosed in the year 2015 (n=86) were excluded. The patient population is stratified based on the time interval between surgery and the initiation of RT (≤4 weeks, 4.1-6 weeks, >6.1 weeks). The study employs Kaplan-Meier and Cox regression analyses to compare overall survival (OS) between these groups.

Results

In a cohort of 1,128 eligible patients for the CPP analysis, no significant survival difference was observed between the pre-CPP and post-CPP groups in unadjusted analysis ($p=0.060$). However, when adjusting for patient, tumor, and treatment factors, the post-CPP group had a significantly better outcome compared to the pre-CPP group ($p<0.001$). In addition, there was a significant higher fraction of patients, receiving RT within 4 weeks in the post-CPP group compared to the pre-CPP group ($p<0.001$).

In unadjusted analysis both standard and hypofractionated RT groups had improved outcomes post-CPP implementation ($p=0.017$ and $p<0.001$, respectively), as well as older

patients (p=0.001), and patients with multifocal tumors (p=0.004). Adjusted analysis of both pre- and post-CPP groups identified prognostic factors associated with better outcomes, including female gender (p=0.024), age ≤ 60 years (p<0.001), gross total resection (p<0.001), and standard RT dose (p<0.001). In the entire cohort (n=1215), including patients diagnosed with GBM in 2015, patients who started RT ≤4 weeks after surgery did not experience a survival benefit compared to those with a more delayed RT initiation at 4.1-6 weeks (p=0.641) and >6 weeks (p=0.359).

Conclusion

Patients with GBM had significantly improved survival after the introduction of CPPs when adjusting for patient, tumor, and treatment factors. However, the survival difference was not significant in unadjusted analysis. In addition, a significant higher proportion of patients received RT start within 4 weeks from surgery in the post-CPP group. However, the timing of RT start from surgery did not impact survival.

1 Introduction

This chapter will present the background of the project "Impact of Cancer Patient Pathway on Glioblastoma," which includes the problem statement and rationale of this study. This chapter also includes the overall research question, including the specific research questions and the project's main objectives.

1.1 Background

Cancer is characterized by abnormal and uncontrollable cell divisions that have the ability to infiltrate other parts of the body and destroy the normal functioning of organs. According to the World Health Organization (WHO), cancer is one of the leading causes of death worldwide, accounting for around 10 million deaths in 2020 (1). Cancer incidence rises due to genetic mutations from environmental and lifestyle factors.

Cancer mortality incidence has decreased in recent years due to early diagnosis and screening of specific cancer or pre-cancer before they have developed symptoms, as well as more effective treatment for specific cancer. So, cancer programs should be designed to reduce delays and barriers to diagnosis and, treatment. Palliative care is also essential to improve quality of life of patients and their caregivers.

Glioblastoma (GBM) is the most aggressive form of brain cancer (2). GBM patients are at increased risk for tumor-related and treatment-related complications (2). While radiation therapy (RT) remains a cornerstone on the management of GBM, a study performed by Stupp et al. showed that the addition of concomitant and adjuvant temozolomide (TMZ) chemotherapy improve the prognosis (3).

1.2 Statement of the Problem

Although the primary treatment of GBM is standardized, the optimal timing of RT start after surgery is still unknown. Numerous studies have been conducted to find the optimal timing of RT start and impact on outcome. However, there are conflicting results in the literature regarding the optimal timing of RT. Cancer Patient Pathways (CPP) are introduced in Norway in 2015, which are intended to contribute to expeditious investigation and start of the treatment without any unnecessary waiting. Studies in Norway report the effect of CPP on

various cancers like colorectal cancer, lung, breast, and prostate cancer (4). These studies focused on changes in waiting time for treatment rather than patient survival. Furthermore, no study has examined patient prognosis after implementing CPP for brain cancer in Norway. Thus, it is essential to address these research gaps by analyzing the data of GBM patients treated with RT provided from OUH in Norway.

1.3 Rationale

The GBM patients have a poor prognosis. Patients 70 years or younger in good general condition treated with standard radiochemotherapy have a median survival of approximately 15 months (5). Most GBM patients seek medical help at later stages due to clinical challenges in early cancer detection. The alkylating chemotherapy TMZ given in addition to RT has shown to improve the prognosis of GBM patients (3). The findings of this study can contribute to a broader understanding of the impact of the timing of RT for survival in GBM patients. Furthermore, this study will present the effect of CPP on GBM in Norway.

To date, no study has examined patient outcome after implementing CPP for brain cancer in Norway. Thus, we aim to address the research gaps by analyzing data from OUH in Norway. These findings can encourage further research to understand RT in GBM patients.

1.4 Research Questions

Research Question 1: Has the introduction of CPP for brain cancer reduced the interval between surgical resection and initiation of RT in GBM patients?

Research Question 2: Has a more rapid initiation of RT led to improved survival in GBM patients?

1.5. Objectives

a) To compare the intervals between surgical resection and RT of GBM patients before and after the CPP implementation in Norway.

b) To compare the changes in patient outcome of GBM patients before and after the CPP implementation in Norway

2 Literature Review

In this chapter, the literature on GBM and CPP is reviewed. It covers the burden of GBM in Norway, risk factors, clinical characteristics of the disease, treatment procedures, the effect of timing of RT on outcome, and CPP. This literature review provides essential knowledge about the effect of the timing of RT for GBM patients and identifies the research gaps. The internet databases like PubMed and Google Scholar were used. The additional relevant articles were found by following up on the reference list of other articles. The existing literature on CPP needs to be more extensive.

There were numerous studies on the timing of RT after surgery. However, there were no quantitative studies on the effect of CPP on the timing of RT after surgery and the clinical outcome in Norway. Hence, there needs to be more research regarding this concept. Thus, further research on this aspect of CPP and its effect on GBM patients is needed.

2.1 Epidemiology

Gliomas are primary brain tumors, and they are classified based on their cell of origin. These gliomas originate from glial cells or neural progenitors (5). The glioma tumors include astrocytic tumors (astrocytoma, anaplastic astrocytoma, and GBM), oligodendrogliomas, ependymomas, and mixed gliomas (6,7). GBM, a WHO grade IV glioma, was first identified in 1865 by German pathologist Dr. Rudolf Virchow (8). He was the first to describe gliomas pathologically, segregating them into groups we now recognize as low- and high-grade gliomas based on their cellularity and general contrast compared to normal brain tissue (9). The GBM, known initially as spongioblastoma multiforme, was renamed GBM by Bailey and Harvey in 1926 (10). The current nomenclature and diagnosis of gliomas are WHO classifications. WHO classifies gliomas into grades I to IV, which is based on malignancy level determined by the molecular and histopathological criteria. According to WHO, GBM is a grade IV glioma; it is the most aggressive, invasive, and undifferentiated type of tumor.

GBM is the most common primary central nervous system (CNS) tumor in adults. GBM accounts for approximately 80% of all brain-related malignancies (11). The GBM is a rare tumor with an annual incidence rate of 0.59 to 5 per 100,00 persons (12). According to the Cancer Registry of Norway, around 200 high-grade glioma cases are registered annually (13). GBM occurs in all age groups. However, the peak incidence is between 55 to 60 years (5).

The incidence rate of GBM has increased in recent years. The contributing factors for this increased incidence rate may include an aging population, increased ease of access to a diagnosis like neuroimaging. According to the Cancer Registry of Norway, the incidence of GBM is higher in males than in females (14)(15). GBM patients have a poor prognosis, with a median survival of approximately 15 months after diagnosis for selected group of patients who are below 70 years, however for unselected patients it is approximately 11-12 months and a 5-year survival rate of less than 5% (5,15).

2.2. Etiology

For most GBM the etiology is unknown. The only known risk factor of GBM is prior exposure to high-dose ionizing radiation (16). Other risk factors are rare genetic disorders like neurofibromatosis type 1 and 2, tuberous sclerosis, Turcot syndrome, and Li Fraumeni syndrome (5,13,16). In addition, some risk factors that may increase the chances of GBM are exposure to chemicals, such as organochlorides and alkylureas, combined with copper sulfates, petroleum, synthetic rubber, and vinyl chloride (5). Individual studies have also shown a possible role between the developing GBM and ovarian steroid hormones (5).
Environmental factors such as smoking, dietary risk factors, cell phones or electromagnetic field, severe head injury, occupational risk factors, and pesticide exposure have not shown any conclusive association with GBM (5,7,16). People suffering from infection and allergic diseases show a lower risk of gliomas (5).

2.3. Pathogenesis of GBM

GBM is most frequently located in the frontal lobe, followed by multiple lobes (overlapping tumors), temporal lobe and parietal lobe (17). GBM is rarely located in the cerebellum and in the spinal cord (17,18). Most of the gliomas occur as solitary tumors, but multicentric GBM can also occur. GBM can grow rapidly, within weeks to months, to significant contrast-enhancing mass. The histological features of GBM include marked hypercellularity, nuclear atypia, microvascular proliferation, and necrosis (19). The tumor shows palisading of tumor cells around necrotic foci, and studies indicate that the highly infiltrative nature of GBM may be due to the presence of cancer stem cells (19). One of the characteristic features of GBM is the variation in the gross appearance of the tumor from one region to the other (5). The necrosis in GBM causes the tumor to appear soft and yellow. In contrast, some tumor areas

are firm and white, and some regions may show marked cystic degeneration and hemorrhage (5).

The New WHO Classification of GBM 2021

WHO classified GBM as grade IV (1,20). GBM classification primarily relied on histology of tumor until the 5th edition of WHO classification of CNS tumors published in June 2021. This revised document enables the diagnosis of GBM to be made not only based on histology but also based on several molecular biomarkers (20).

The molecular biomarkers have gained importance in providing both ancillary and defining diagnostic information because of development of more advanced technologies. Therefore, the fifth edition of the WHO CNS classification incorporates numerous molecular changes with clinicopathologic utility. This method gives accurate classification of CNS neoplasms. Based on the recent WHO classification, the diagnosis of glioblastoma can include the presence of molecular markers such as, IDH-wildtype in combination with TERT promoter mutation, EGFR amplification, or +7/-10 copy number changes (20,21).

The IDH-mutant astrocytoma is graded as CNS WHO grade 2, 3, or 4 and considered a single type known as Astrocytoma, IDH mutant (21). IDH-mutant astrocytoma grade 4 is replacing the former term glioblastoma, IDH mutant, WHO grade 4. So, the term glioblastoma is no longer used to refer to IDH-mutant astrocytic grade 4 gliomas (20).

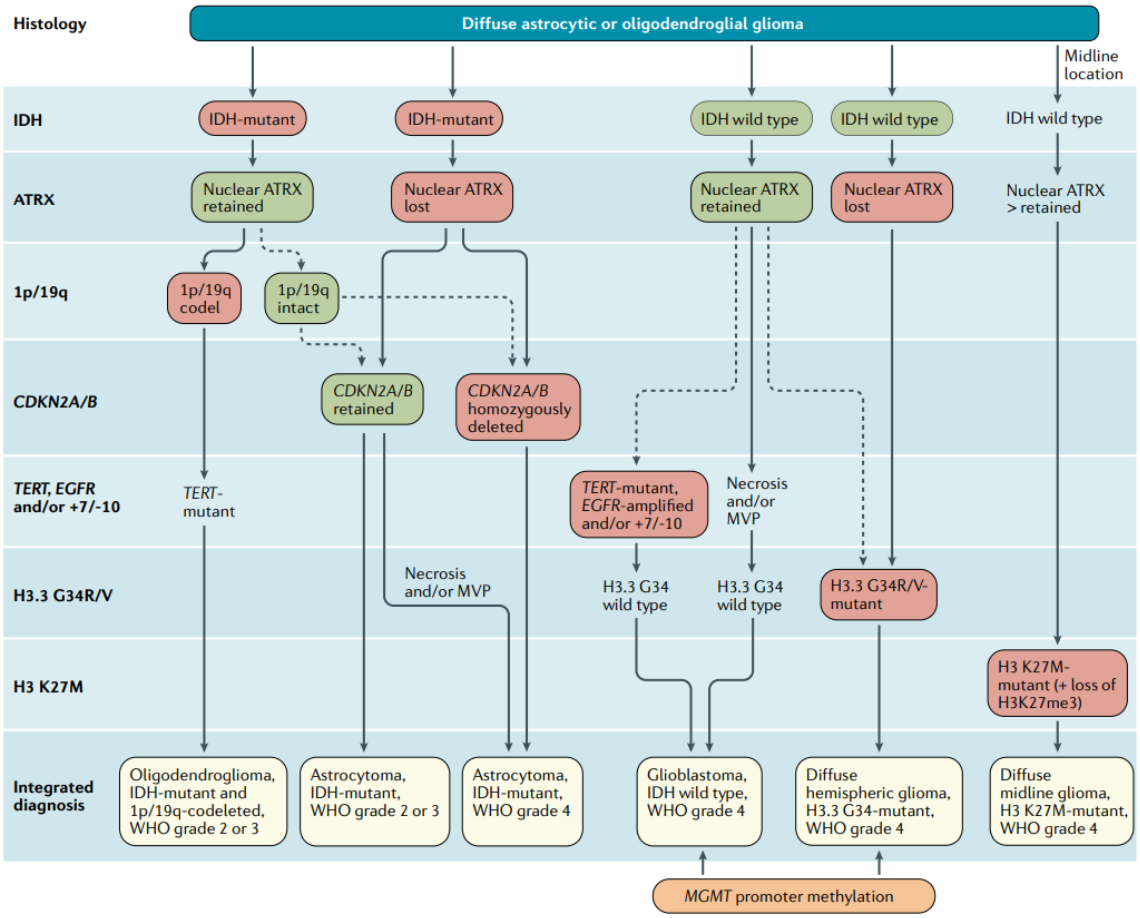

Figure 1: The immunohistochemistry assessment of tissue specimens with diffuse gliomas. The presence and absence of the diagnostically most relevant molecular alterations for each tumor type are highlighted in red and green boxes. The figure is adopted from Michael Weller et al. 2021

2.4 Clinical Presentation

The clinical history of GBM patients is short and ranges from 3-6 months. However, the clinical history spans several years if the tumor arises from a low-grade astrocytoma. The symptoms of GBM vary depending on the region of the brain which is affected by the tumor and the size of the tumor. Many symptoms are related to brain swelling and increased pressure in the brain (22).

Neurological functions are intricately tied to specific regions in the brain, and the manifestation of symptoms depends on the location of tumors and peritumoral edema. These can lead to diverse neurological signs, including epileptic seizures and heightened intracranial pressure (5,22,23). Increased intracranial pressure may present as headaches, nausea, drowsiness, and gait imbalance (5,23). Necrosis of brain tissue results in focal neural deficits and cognitive impairments (22). GBM in the temporal lobe causes hearing and visual issues,

while GBM in the frontal lobe can alter personality and cognitive functions (5,22). Large tumors contribute to gait imbalance and incontinence. Headaches are a prevalent feature in GBM, stemming from heightened intracranial pressure due to tumor growth and surrounding edema (5,22,23). Seizures, whether partial, complex partial, or generalized, are determined by the tumor's specific location.

2.5 Variants

Based on the 5th edition of the WHO classification of CNS tumors, there are three GBM histological variants (24).

- Giant cell glioblastoma
- Gliosarcoma
- Epithelioid glioblastoma

2.6 Diagnosis

GBM diagnosis is usually achieved by combining clinical features and characteristic radiological findings confirmed by histopathology and molecular pathology (20,25). However, during the early stages of GBM, the diagnosis is challenging because the tumor can cause atypical clinical and radiological presentations. GBMs are typically large tumors, often have thick, irregular enhancing margins and a central necrotic core, and may also contain hemorrhagic components (26).

Some of the tests and procedures used to diagnose GBM are:

Neurological exam

In this test, the doctor will check the patient`s muscle power, sensation, balance, reflexes, coordination, vision, hearing, and short-term memory. The doctor will examine the eyes to look for swelling caused by pressure on the optic nerve. The optic nerve connects the eyes and brain. This swelling is known as papilledema, and which requires immediate medical attention (27). Even though neurological examinations are inadequate for diagnosing, they might eliminate a brain tumor as the problem or point to more testing for a definitive

diagnosis. If the patient is suspected to have a brain tumor, he will be referred for medical imaging (radiology).

Imaging Tests

At present, sophisticated imaging techniques can pinpoint the location of brain tumors. These scan tests provide beneficial information, like the tumor location, whether it is pressing upon any areas, and how it might affect body functions controlled by specific brain parts. A trained radiologist performs the test and submits the report to the neurologist. The diagnostic tools are computed tomography (CT or CT scan), magnetic resonance imaging (MRI).

MRI

MRI is a safe and painless test that produces detailed brain images. Intraoperative MRI (iMRI) may also be applicable during surgery to guide tissue biopsies and tumor removal. In addition, magnetic resonance spectroscopy (MRS) is used to examine the chemical profiles of the tumors.

Conventional MRI: It is the gold standard imaging method to study glioma. Usually GBM has a distinct appearance compared to low-grade glioma or benign tumors. The center of the tumor contains dead cells (necrosis) surrounded by a rim of growing tumor cells, surrounded by swelling and edema.

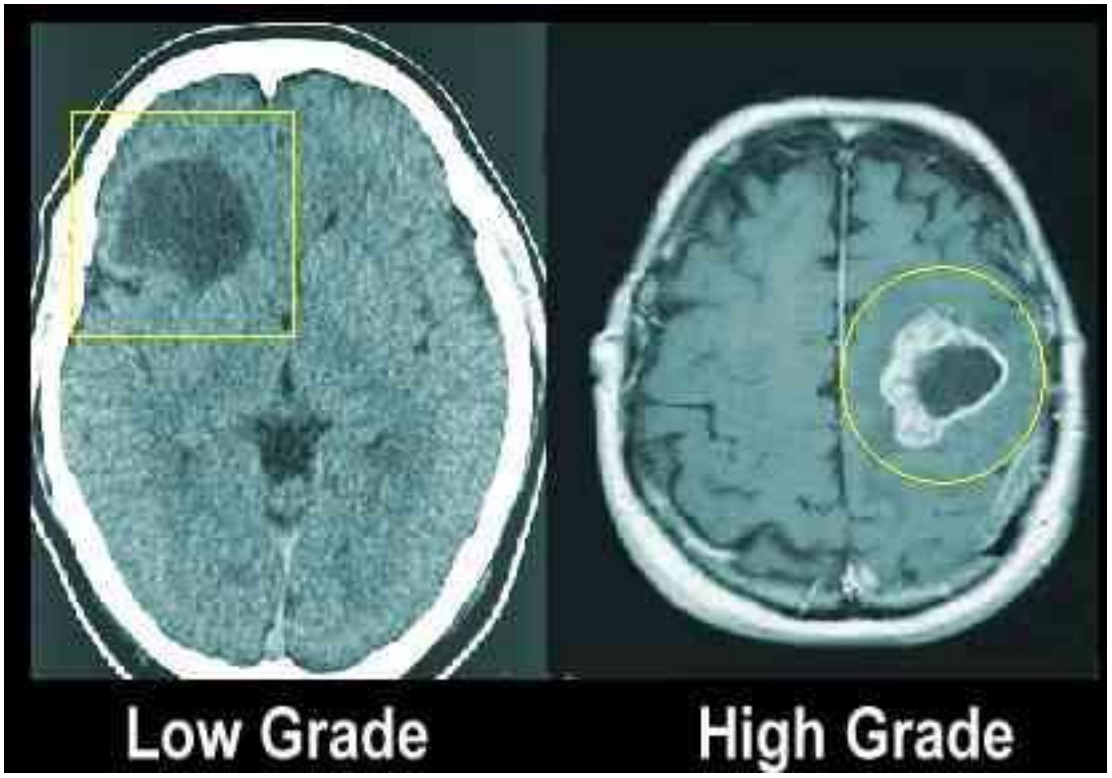

Figure 2: Differentiating low-grade from high-grade gliomas: Low-grade gliomas feature a central low-density area, while high-grade gliomas display central necrosis encircled by edema.

MRI Spectroscopy (MRS): This tool is based on MRI, which provides information on the chemical composition of the tumor. It works on the principle that certain chemicals are abundant in the normal brain, whereas choline is abundant in tumor (22). Here the individual resonance peaks represent metabolite concentrations from a specific region (28). The chemical structure of the metabolite contributes to the position and characteristics of the metabolic peak on the MRS spectra. In contrast, the metabolite concentration contributes to the area under the peak (28). The typical spectroscopic characteristics include (26).

- Choline: increased
- Lactate: increased
- Lipids: increased
- NAA: decreased
- Myo-inositol: decreased

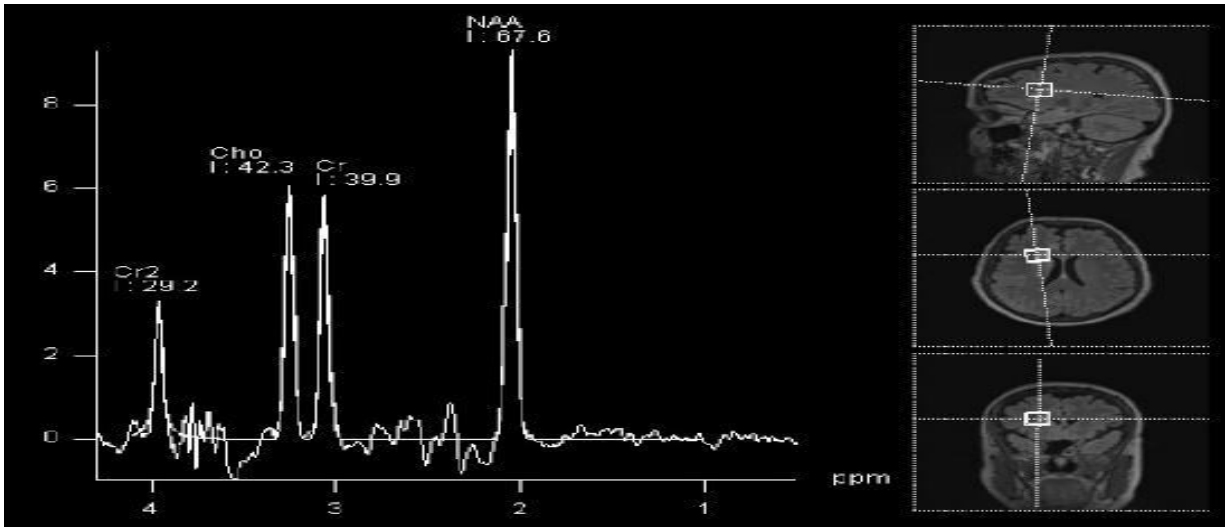

Figure 3: Comparing Normal and GBM Brain MRI Spectroscopy: NAA vs. Cho Peaks. Normal brain spectra feature NAA peaks, while GBM patients exhibit prominent Cho peaks. Sampled normal brain voxels are depicted on the right panel. Adapted from Vikram C P et al. 2023.

Functional MRI (fMRI): This is a helpful tool to find which parts of the brain are active or activated when the patient is asked to perform a specific task like talking or moving the arm or leg (22). By this, we can define which parts are damaged and would cause problems to patients during recovery. In addition, these fMRIs provide an essential adjunct during surgery for tumors in critical areas such as speech centers, motor cortex, or visual cortex (22). This fMRI shows the activated brain as a yellow/red signal.

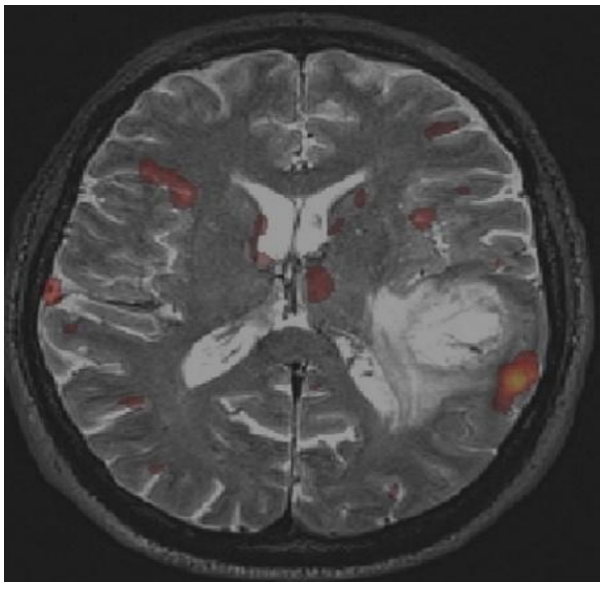

Figure 4: GBM tumor fMRI: Notable Activation in Language Region Near Tumor. Adapted from Vikram C P et al. 2023

The typical MRI sequence would include T1- weighted (pre- and post-gadolinium), T2-weighted, fluid-attenuated inversion recovery (FLAIR), T2*- weighted (or susceptibility-weighted imaging), and diffusion-weighted imaging sequence 1. In the T1-weighted image, the center of the lesion is hypointense due to necrosis (26,29,30). The brain edema surrounds the lesion; this edema appears hyperintense on T2-weighted and FLAIR (26,30). The Diffusion-weighted images (DWI) and apparent diffusion coefficients (ADC) for solid components there will be elevated signals which are expected (26,30). The perfusion-weighted imaging (PWI) reveals an increase in cerebral blood flow corresponding to neoangiogenesis and blood-brain barrier disruption (30). These diffusion/perfusion sequences are multimodal MRI techniques that provide information about the characteristics of the lesion (30).

A deeper understanding of the tumor properties is essential because it will affect tumor delineation. Generally, RT target volumes are determined based on the MRI reports.

CT SCAN

Typically, the initial imaging in the diagnostic process involves a CT scan. The CT scan can reveal soft tissue, a bone structure near the tumor, calcification, hemorrhage, and swelling. However, in GBM diagnosis, the CT scan may miss small tumors (26). The small low-grade glioma missed during the screening study may progress to GBM (31). The enhanced CT scans include significant enhancement of findings such as irregularity and inhomogeneity, possible ring enhancement, solid enhancement, and minor enhancement in diffuse forms (31). However, the CT scan may not depict all multifocal lesions and cannot diagnose cerebrospinal fluid spread (31). So, a CT scan can be helpful to patients who are unable to undergo MRI imaging.

2.7 Treatment

The ideal multimodal treatment for GBM includes maximal surgical resection, followed by RT plus concomitant and adjuvant TMZ chemotherapy. Still, most of the patients experience tumor recurrence with nearly universal mortality.

Surgery

Surgery is the primary treatment of malignant brain tumors. While performing the surgery, a wide spread of scenarios should be considered. Few of them are the medical conditions of the patient, the imaging reports and functional studies, neuropsychological evaluation, and the use of corticosteroids and antiepileptics. In this surgery, the primary goals are maximum resection without injuring the surrounding normal brain tissue, which is needed for normal neurological function, tissue specimen for pathological diagnosis, improving conditions for complementary treatments, delaying clinical worsening, and improving quality of life. Surgical resection is usually proposed to patients under 70 and should also be in good condition for surgery (30,32). In GBM, complete tumor removal is impossible because the migrating and infiltrating tumor cells invade the surrounding tissues. Tumors are often in eloquent areas of the brain, including areas that control speech, motor functions, and the senses (22,33). So, the good outcome of surgery is the patient-related, and the most essential treatment-related predictor is the extent of resection. The more extensive surgical resection is associated with longer life expectancy (33,34).

The prolonged survival can be achieved in those patients who undergo gross total resection followed by RT and TMZ. However, the most critical issue is the delicate balance between the aggressive removal of the tumor and the preservation of normal brain function. So, improvements in surgical and preoperative mapping techniques have enabled maximal safe surgical resection (33). In preoperative mapping, fMRI, and diffusion tensor imaging (DTI) are used, along with ultrasound, CT scans, and MRI with direct stimulation during surgery. This has allowed for multimodal neuronavigation and integration of patient-specific anatomic and functional data (33). The 5-aminolevulinic (5-ALA) dye for fluorescence guidance is more effective than the conventional neuronavigation-guided surgery to differentiate between a normal brain and a residual tumor (33). Some limitations of this novel technique include cost and the need for special equipment, operators, and surgery suites.

Radiation

After surgery, the patient waits for the craniotomy wound to heal to begin with RT. Before the 1960s, postoperative RT was limited to single-institution case series with RT less than or equal to 20 Gy (35). Later, the Montreal Neurology Institute reported the survival advantage where patients receive an average total dose of 50-60 Gy (36). Postoperative RT alone was the standard treatment alone until 2005. Later the standard of care for GBM changed when

the results of RT with concomitant TMZ followed by six courses of TMZ chemotherapy (known as the Stupp regimen) was more effective than RT alone (3).

Previously, whole-brain RT (WBRT) was used to treat newly diagnosed GBM, and multiple potential long-term complications of WBRT exist, including endocrinopathy, neurocognitive toxicity, and RT-induced leukoencephalopathy (35,37). This limitation of WBRT led the research to explore the use of involved field RT (IFRT), which reduces toxicity (33). This IFRT delivers external beam RT. Prior the RT the oncologist defines macroscopic tumor as Gross Target Volume. Further, an isotropic margin expansion from GTV generates the Clinical Target Volume to treat microscopic tumor. Historically a 2 cm margin from GTV to CTV was used based on the observation that, following RT, GBM recurs within 2cm of the original tumor site in 80-90% of cases (33,38,39). Lately, this margin is suggested to be reduced to 1.5 cm and rather to include the T2-FLAIR hyperintense signals suspect of tumor (39). Multiple studies confirmed that IFRT had a similar or slightly improved survival advantage over WBRT, with less tissue damage within the RT field (33,38).

The current standard of care regarding RT uses a three-dimensional conformal beam or intensity-modulated RT (40). After safe surgical resection, the RT is performed on the patients with the typical total dose is 60 Gy in 1.8-2 Gy fractions administered five days per week for six weeks (33,41). Even if the dose is escalated beyond 60 Gy, the results are increased toxicity without additional survival benefits (38). Other techniques can reduce toxicity to normal brain tissue and improve local control. Some are iodine-125 brachytherapy, radioimmunotherapy, stereotactic radiosurgery, and hyperfractionation. However, this has not resulted in a significant survival advantage for newly diagnosed GBM patients (33,38).

For patients above 70 years hypofractionated RT is commonly used (42). In such cases, RT is usually administered as a shorter course with a 40 Gy dosage in 15 daily fractions rather than 60 Gy over 6 weeks (42).

Despite surgery and RT with TMZ, the GBM carries a poor prognosis with a median survival of less than 2 years. The main reasons for these negative prognostic factors are increased necrosis, more significant enhancement, deep location, MGMT non-methylated, increased age, and lower pre-diagnosis functional status (26).

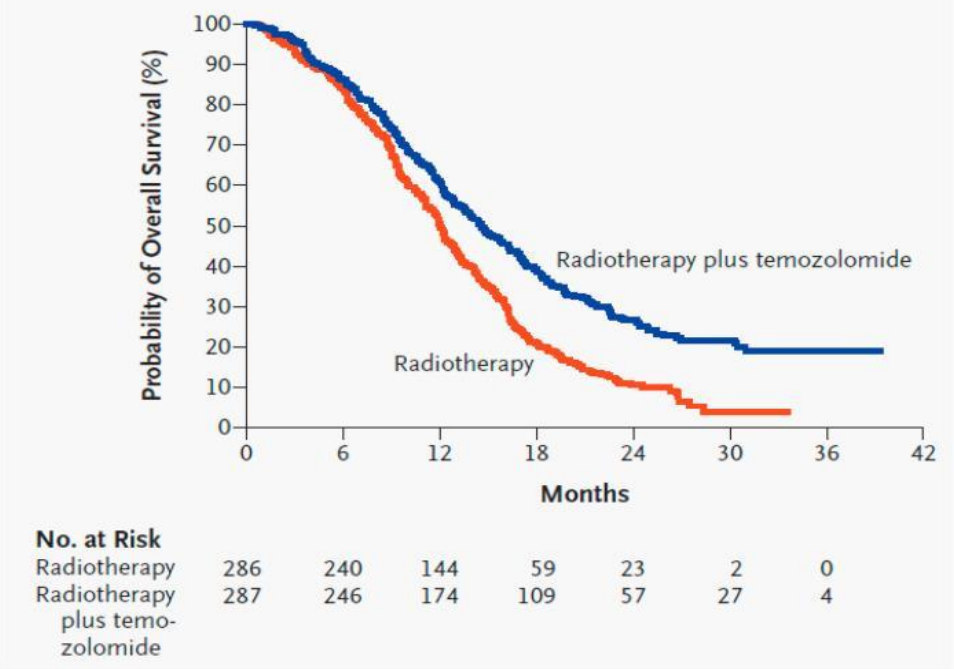

Figure 5: Kaplan-Meier overall survival of patients with RT and RT along with TMZ adapted from Fisher JP et al. 2021.

Chemotherapy

Chemotherapy is a cancer treatment where potent drugs kill rapidly dividing cancer cells. Presently, chemotherapy is used as a treatment for many cancers. These medications can be administered in the form of oral pills, injected into a vein, or, in specific circumstances, injected into the intrathecal space of the spine. GBMs are often comprised of several different types of cells. A chemotherapy drug might kill some of these cells while allowing others to grow unimpeded.

TMZ is the standard drug for GBM. This drug is administered every day during RT. The primary treatment is standardized, RT with concomitant TMZ. RT is typically given at a dose of 60 Gy in 30 fractions and concomitant TMZ 75 mg/m2/day for 6 weeks (33,41). After RT, the chemotherapy with six courses of adjuvant TMZ is administered after one month`s rest period. During chemotherapy, TMZ is dosed at 150 mg\m2 daily for 5 days for the first course, i.e., days 1-5 of 28 days (23,33,40). If clinical and biochemical tolerance is adequate, the dose is escalated to 200 mg\m2 for five consecutive days per month for the remainder of therapy (33,40). Generally, for elderly patients the RT dose of 40 Gy with concomitant and six to twelve adjuvant courses of TMZ will be given (40,42). A notable improvement in survival, particularly in MGMT-methylated tumors, is observed with this treatment approach for elderly patients (42).

Recurrent treatment is not standardized for GBM. For chemotherapy, TMZ re-challenge is the first choice if the elapsed time from adjuvant courses of TMZ is sufficient. Other chemotherapy drugs are carmustine, bevacizumab, and lomustine (41). Lomustine is hoped to help improve bevacizumab efficiency when administered together (41). Bevacizumab is used as a second-line treatment for recurrent GBM (41). However, Bevacizumab is not recommended in Norway as a treatment for recurrent GBM because studies do not show effect on OS.

Tumor Treating Fields therapy

Along with these drugs is a device called tumor-treating fields (TTFields) approved for GBM treatment in some countries. TTFields deliver low-intensity, intermediate-frequency altering electrical fields to tumor cells (22,33,41). TTFields interrupt cell division, causing apoptosis (33), and is used along the adjuvant courses of TMZ for adults with newly diagnosed GBM (33). A study on maintenance therapy with TTFields with adjuvant TMZ courses demonstrates a PFS of 7.1 months versus 4 months with TMZ alone (43). This treatment is currently not re-imbursed in Norway.

Disease Recurrence

Despite this standard care of therapy, around 70% of GBM patients experience disease progression within one year of diagnosis (33). Only 5% of patients survive 5 years after diagnosis (33). Re-resection is an option for selected patients. A dilemma after RT is whether the MRI changes are tumor recurrence, pseudo-progression or radiation necrosis (33). Molecular testing is also an option if available to identify possible molecular targets for treatment. Various studies show that a greater extent of resection at recurrence is associated with improved survival (44). Re-irradiation may be possible for some selected patients, but there is an increased risk of tissue necrosis of normal brain tissue.

Supportive Care

Supportive care, called palliative care, mainly focuses on relieving pain and other symptoms. This care also provides psychosocial support to the patients. The most common complications of GBM that may require supportive care are vasogenic brain edema, seizures, and venous thromboembolism (45). Recognition and management of these symptoms are essential to optimize the patient's quality of life and it is an advantage with palliative care in addition to standard neuro-oncological care and treatment.

3 Timing of RT

Adding RT to surgery will reduce the recurrence rate of GBM and improve the patient's OS. However, the fast-growing nature of GBM often manifests itself in rapid recurrence after the operation (46). Therefore, immediate treatment, especially RT, is expected. However, a delay of RT will give enough time to heal the wound caused by surgery and decrease the risk of post-surgery infection (46). In addition, this delay of RT will give time for the disappearance of brain edema caused by surgery, and also, the brain tissue displacement caused by edema will recover (46). Therefore, the timing of RT is critically important because it should balance the process of wound healing and the risk of tumor regeneration in the short term.

Multiple studies were conducted on the effect of RT timing and outcome on multiple types of cancers such as breast, lung, head, and neck. These studies demonstrate that delay in RT leads to high recurrence rates and worse outcomes. However, in the context of GBM, the relationship between RT timing and clinical outcome remains unclear. Multiple studies on RT timing and clinical outcome in GBM patients show conflicting results.
Some review studies examine the impact of time on initiating postoperative RT. These reviews are mentioned in my protocol for this thesis.

3.1 Delaying RT may worsen survival

Valduvieco et al. conducted a retrospective study on 107 patients suffering from GBM and who underwent complete tumor resection between 1994 and 2009 period (47). These patients were divided into two subgroups. One subgroup was treated with RT before 6 weeks, and another is treated after 6 weeks of tumor surgery (47). They received standard dosage of RT 60 Gy (47), and around 86% of patients received chemotherapy, receiving a standard protocol of concomitant and adjuvant TMZ from 2005. To determine the median OS, they implemented the Kaplan–Meier method and Cox regression model in the project. The results indicate that the patient may lose the survival advantage obtained with optimal surgery due to a delay in RT (47). This retrospective study had limitations with inclusion of patients with anaplastic astrocytoma and GBM and non-homogeneous doses of RT during the study period (47).

Viet Do et al. conducted a retrospective study on 182 patients suffering from grade III/IV gliomas from period 1979 -1995 (48). The patients were treated with RT with a median

dosage of 60 Gy over a median of 46 days after the surgery (48). This study implemented the Kaplan–Meier method to examine the effect of delay on the impact of RT. In addition, the Cox regression model was used while adjusting the variables like age, performance status, the extent of surgery, histological grades, and radiotherapy dose (48). The study observed that the risk of death increases by 2% each day of waiting for RT (48). This retrospective study´s limitations include possible selection bias, uncontrolled patient and tumor factors, physician treatment bias, and quality of the database record keeping (48). Also, the recruitment period is somewhat antiquated.

3.2 Delaying RT may improve survival

S.J Han et al. conducted a cohort study on 198 patients suffering from GBM between 2004 and 2010 (49). The study showed that a short delay in the start of chemoradiation therapy (CRT) administration (at 30–34 days) was predictive of prolonged OS and prolonged progression-free survival (PFS) compared to early initiation of CRT, that is, less than 30 days (49). The Cox regression model was used while adjusting the variables like treatment protocol, age, Karnofsky performance score KPS, and extent of resection (49). However, this cohort included patients undergoing both resective surgery and biopsy only. Patients receiving biopsies tend to have larger, non-operable tumors. When only undergoing a biopsy, these patients are often rushed to further RT – possibly introducing a bias of poor-prognosis patients in the "early-RT group." This is also the case in this study, where the number of patients undergoing biopsy was only 14 times higher in the early treated group than in the group that started RT at day 30-34 (49).

Inbar Zur et al. conducted a retrospective study on 465 patients diagnosed with high-grade glioma between 2005 and 2014 (50). They evaluated the association of the time gap between surgery and CRT with OS and PFS (50). This study conducted the survival rate test using univariate and multivariate analysis methods (50). For categorical variables such as the extent of surgery, RT interruption, steroid treatment, and gender, the Kaplan–Meier method was performed. In contrast, the Cox proportional hazard model was performed on variables like age, the extent of surgery, total RT dose (Gy), etc. (50). The comparative study was conducted between time-gaps < 4 weeks after surgery, between 4 and 6 weeks after surgery, and > 6 weeks after surgery (50). The study indicates a time gap of > 6 weeks was associated with better OS and PFS outcomes among newly diagnosed GBM patients (50). However, there are several limitations in this retrospective study, one of which is that the KPS score,

and performance status are not reported in many cases. There is also a lack of complete IDH and MGMT data and a lack of control for steroid treatment.

3.3 Delaying RT may not influence survival

Blumenthal et al. conducted a retrospective study on 1395 patients newly diagnosed with GBM and treated with RT and concurrent TMZ, followed by adjuvant TMZ (51). They investigated the OS rate using the Kaplan–Meier and Cox proportional hazard models (51). In addition, a comparison was made between early RT (> 4 weeks) and delayed RT (< 4 weeks) from the time of surgery (51). The study observed no significant difference in OS after adjusting for prognostic factors (51). This result varies from Blumenthal et al. previous report of the year 2009, which found that there was significantly improved survival in patients with newly diagnosed GBM when radiation was initiated more than 4 weeks from the time of surgery (52). This initial report was based on only radiation monotherapy, whereas the following report was based on patients who received both RT and TMZ (51).

4 Cancer Patient Pathway for GBM

The CPP is the patients journey from the initial suspicion of cancer through clinical investigation, patient diagnosis and treatment. Before implementation of CPP, the cancer diagnosis and treatment are complex in nature, and it may lead to unnecessary delays and regional disparities. Over the last two decades, several European countries have introduced programs to streamline cancer care, including the United Kingdom in 2001, the Spanish region of Catalonia in 2005, Denmark in 2007, and Sweden in 2015 (53–56).

4.1 CPP Norway

Influenced by the programs centered around CPPs, Norway published a national cancer plan in 2012 for the period 2013–2017 titled "Together against cancer," the core component of which was the introduction of CPPs (56). In 2015, CPPs were implemented in Norway to reduce unnecessary non-medical delays. The CPPs were first implemented for colorectal, lung, breast, and prostate cancer, with more types of cancer included in the following years (56). By the end of 2015, the Norwegian Directorate of Health had implemented 28 cancer-specific pathways, of which 26 are organ-specific pathways, one is for metastasis with unknown primary cancer, and the final covers diagnostic workup (53). In September 2015 the CPPs were extended to brain tumors.

The primary purpose of the CPPs was to "ensure that cancer patients experience a well-organized, comprehensive, and predictable course without unnecessary delays in assessment, diagnosis, treatment, and rehabilitation that are not medically justified" (53–55). CPP aimed to improve collaboration between general practitioners and hospitals in the health care system (57). To achieve this, the CPP set objective measures; each CPP has a specific set of maximum waiting times between receipt of the referral, the first consultation with a specialist, a clinical decision, and the start of treatment (4). Besides, the CPPs also cover initial treatment and successive monitoring and treatment, supportive care, and nursing (55,57).

4.2 CPP for GBM patients

The CPP for GBM patients represents a standardized route through which the patient follows through the diagnostic and treatment process. This pathway starts from the referral of a patient suspected of brain cancer to the start of investigation for clinical decision and

treatment. It provides a full-length program to patients with high-grade glioma. Low-grade glioma patients are also under a lifelong control system because these low-grade gliomas may develop into high-grade gliomas like GBM (55). This program for GBM is case-specific rather than general, so the course is provided based on the patient's condition. The program aims for the course to go without unnecessary delays and with close cooperation between all departments and specialists (54,55). The CPP is intended to give GBM patients and relatives predictability and security and is a national discipline-based standardized pathway.

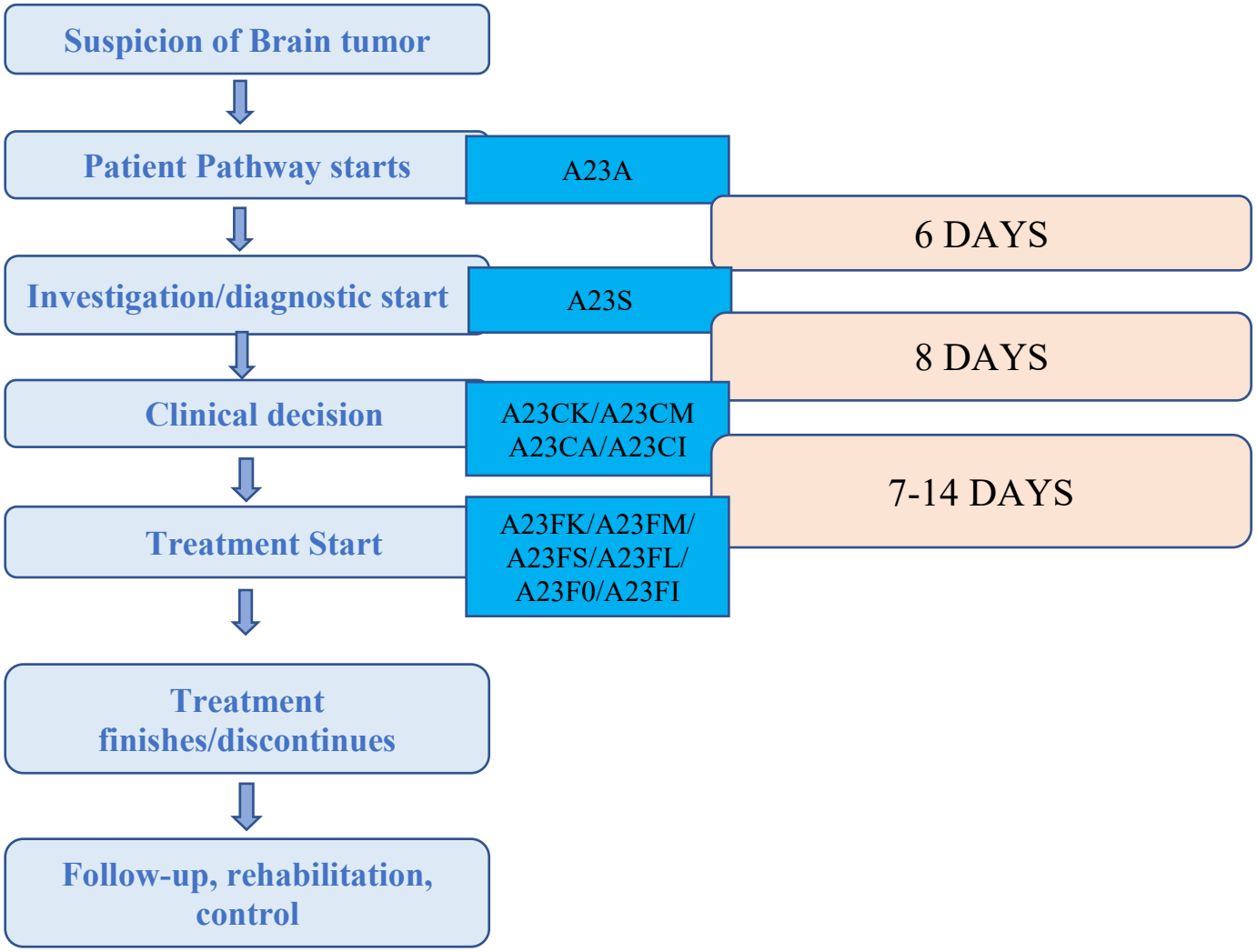

Figure 6: Flow chart of CPP treatment plan for brain tumor patients Adapted from Helsedirektoratet: Pakkeforløp for Hjernekreft. [Norwegian Directorate of Health: Cancer patient Pathway for brain cancer.]

National package procedures are normative procedures that describe the organization of investigation, treatment, follow-up, and communication with the patient and next of kin, as well as the placement of responsibilities and concrete progress times (54,55). These must be

based on national professional guidelines or national professional councils where they exist, alternatively on the best available knowledge and professional consensus (54,55).
This action program deals with diagnostics, treatment, and follow-up of high-grade diffuse gliomas (54). The action program for general brain tumors is

Diagnosis and treatment lead times

The pathway lead times is a stipulated maximum time based on calendar days the different phases in the process should take. The lead time for GBM is represented in Figure 6. The course times in the CPP for brain tumors are represented in Table 3. The goal is to ensure compliance with the overall target time in the pathway for 70% of the patients, but these target times are normative and not legally binding (58).

Progress coordination

Coordination of the patient process must ensure the process from the time the referral is received in the specialist health service to the start of the treatment or the completion of the packaging process, without unnecessary delay and with close cooperation between all departments and specialists involved (55). Therefore, all hospitals investigating and treating cancers must have process coordinators who will have close contact with patients and the agencies involved.

The multidisciplinary/interdisciplinary team (MDT)

The multidisciplinary (MDT) comprises a neurosurgeon, pathologist, radiologist, oncologist, neurologist, and course coordinator (55). This team assess patients with primary brain tumors. Other professional groups who will naturally participate in MDT in the CPP program are nurses, physiotherapists, occupational therapists, social workers, and neuropsychologists. The MDT meetings will discuss the patient's disease path, treatment procedures, and alternatives if required and ensure the patient receives quality treatment.

These instruments are used for implementing CPP for GBM, aiming to solve the problems like medically unjustified delays in assessment, diagnosis, treatment, and rehabilitation. In addition, these instruments are helpful for the patient to experience a well-organized, comprehensive, and predictable treatment course.

Table 1: The treatment course for GBM patients under CPP.

Course description		*Expiration time*
From referral received to first appearance investigative department		6 Calendar days
From the first appearance in the investigative department to the completed investigation		8 Calendar days
From completed examination to start treatment	Surgical treatment	7 Calendar days
From completed examination to start treatment	Medical treatment	14 Calendar days
From completed examination to start treatment	Radiation therapy	14 Calendar days
From referral received to start treatment	Surgical treatment	21 Calendar days
From referral received to start treatment	Medical treatment	28 Calendar days
From referral received to start treatment	Radiation therapy	28 Calendar days

Adapted from Helsedirektoratet: Pakkeforløp for Hjernekreft. [Norwegian Directorate of Health: Cancer Patient Pathway for Brain Cancer.]

4.3 Background for CPP

The main of CPP is to avoid unnecessary delays to improve the quality of life. The capacity of an organization defines the quality of diagnosis and treatment. The Norwegian Board of Health Supervision (NBHS) performed a risk analysis of cancer treatment in 2010 on the national level to identify the risk areas and bottlenecks in cancer treatment (59). The report mentioned the 16 most critical problem areas: diagnosis, primary treatment, interactions, and complications. These risk factors are mentioned in Table 4. In addition, they defined the severity level of these risk factors as a risk matrix. The most important risk factors are delays in diagnosis (59). This risk analysis contributed to the national debate. In 2011, the Ministry of Health and Care set a national goal of a maximum of 20 working days from referral to the start of cancer treatment (59). The NBHS risk analysis also identified poor information exchange and discontinuity in the treatment chain as significant hazards (59).

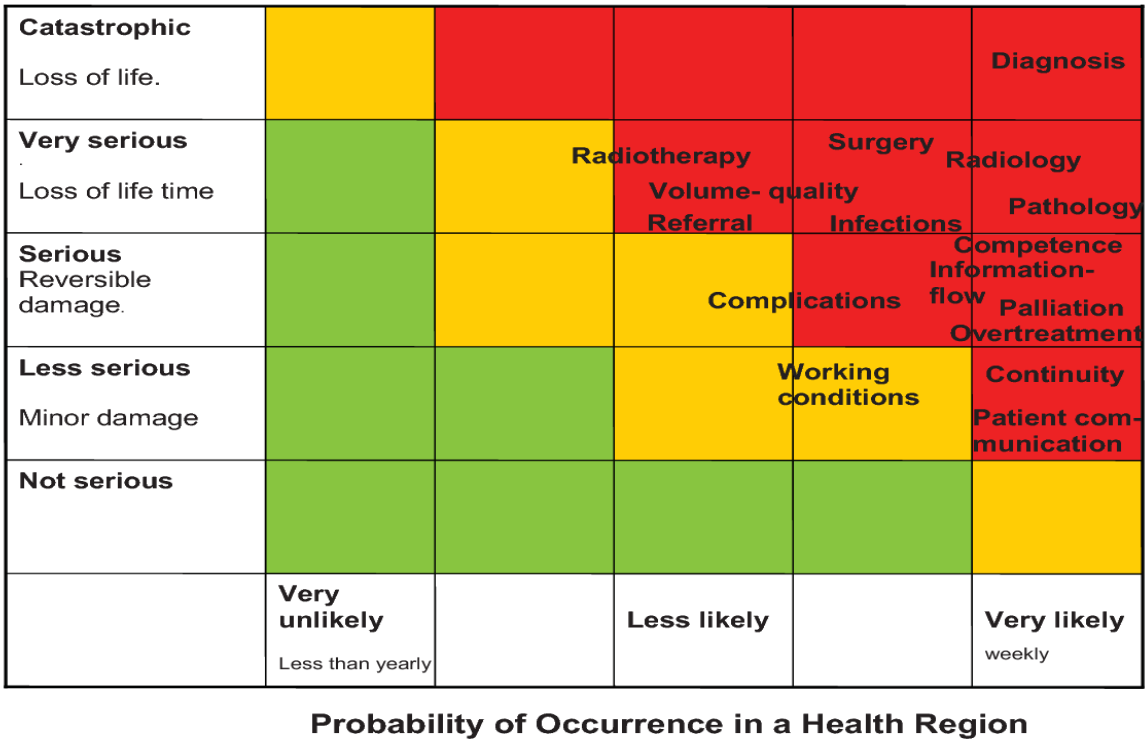

Figure 7: Risk Analysis Matrix from NBHS 2010 Report: 16 Top Hazards in Cancer Care Adopted from Risikobildet av norsk kreftbehandling

The above risk analysis matrix is from the NBHS report of 2010. The NBHS detected 16 top hazards in cancer care regarding consequence and likelihood. This figure's "red" category denotes unacceptably high risk, with intervention mandatory in a short time. The "Yellow" connotes medium risk, with intervention needed to avoid escalation to the red category. The Green boxes are partly elevated risk, where intervention is not needed. Here RT and complications overlap between yellow and red

Several studies were conducted on waiting time for treatment and patient outcomes for breast, colorectal, and lung cancer. The results showcased the differences in waiting times from diagnosis to treatment among different regions in Norway. To respond to these problems, Norway implemented the CPP program so that the whole country would have a similar program in all regions. The Norway treatment guidelines are available for 28 CPP programs. Therefore, by implementing the CPP program, the treatment is predictable and transparent.

The Norway treatment guidelines are followed for GBM, and radiotherapy should be followed immediately after surgery within 2 to 4 weeks.

4.4 CPP and waiting period for RT

In this master thesis study, we aimed to evaluate the effect of CPP implementation on RT timing and survival for GBM.

With the help of the CPP program, the RT treatment after surgery is accessed within 2-4 weeks, as recommended by guidelines. The standard time gap between surgery and RT, which is possible with the help of CPP, is crucial for this thesis so that we can understand the importance of the timing of RT for GBM and the survival outcome. This is not the case before the introduction of CPP.

Various studies are based on waiting times for surgery and RT and outcomes for GBM. However, there needs to be more clarity among the results, possibly due to the variation in periods between RT and surgery in various studies. After the CPP introduction, the waiting time is constant, and we will have more stable data. This retrospective data may provide a result that may showcase the effect of waiting time and RT on GBM patients. This thesis focuses only on OUH patients above 18 years of age diagnosed with GBM in the time period from 2006 to 2019.

5 Materials and Methods

5.1 Study Site Overview

Oslo, the capital city of Norway, is the focus of this study. This city, although the smallest in terms of area, holds the distinction of being the most populous in the country. Oslo is a well-developed urban center with a wealth of healthcare resources available to its residents. In 2019, the life expectancy of the population in Oslo was recorded at 81.3 years, reflecting the city's commitment to healthcare and well-being. Norway, as a whole, allocates approximately 10.5% of its national budget to the healthcare system, and Oslo plays a vital role in this allocation, ensuring the availability of healthcare services to its residents.

5.2 Oslo University Hospital

This healthcare institution emerged through the amalgamation of three esteemed University Hospitals in Oslo, Norway, namely Rikshospitalet, Ullevål, and Radiumhospitalet. Notably, OUH stands as the largest hospital organization in Europe, boasting a workforce of over 24,000 dedicated professionals. This institution also plays a pivotal role in the realm of medical research, contributing to approximately 60% of all medical research conducted in Norway's medical centers.

Furthermore, OUH is highly engaged in extensive international and national research collaborations, underlining its commitment to advancing medical knowledge and patient care (60). As a national reference hospital in Norway, OUH shoulders the significant responsibility of spearheading the introduction and development of cutting-edge medical examination techniques, innovative treatment methodologies, and rigorous patient follow-up protocols (61). This pivotal role underscores OUH's dedication to the advancement of healthcare practices and the well-being of patients.

5.3 Implementation of the Cancer Patient Pathway at OUH

In the case of Brain Cancer, OUH initiated the CPP program in September 2015, coinciding with the wider implementation of the program across various cancer types. OUH's medical department tailors the treatment approach for each GBM patient based on their clinical condition, with the ultimate aim of enhancing patient survival.

In adherence to the CPP program's principles, OUH ensures that patients receive timely treatment. Through the effective utilization of the CPP program, OUH consistently delivers RT to GBM patients within the specified timeframe following their surgical procedures ensuring strict adherence to clinical standards. This commitment to timely and organized care underscores OUH's dedication to optimizing patient outcomes and the overall quality of healthcare services.

5.4 Justification for Research Method Selection

Upon reviewing the existing literature (47–50,52), it became apparent that a retrospective cohort study represents an appropriate choice for researchers to investigate various treatment modalities, particularly to evaluate the efficacy of the timing of RT and its impact on patient outcomes in the context of GBM. The primary advantage of employing this method is its cost-effectiveness, as it relies on pre-existing data and medical records, thereby facilitating the acquisition of a substantial dataset spanning extended timeframes. By leveraging this approach, researchers can comprehensively assess a wide array of potential risk factors associated with GBM, shedding light on prognosis and survival rates for GBM patients.
Nonetheless, it is imperative to acknowledge potential disadvantages linked to retrospective cohort studies, notably concerns related to data accuracy and data completeness. These limitations can introduce variability into the study results. Furthermore, retrospective studies have limited control over data collection, which can affect the comprehensiveness of the dataset. For this particular research question, a prospective cohort study was not deemed suitable. Prospective cohort studies are typically time-consuming and creating a sufficiently large cohort for GBM would be impractical given the rarity of this condition and the extensive timeframes needed to generate conclusive results.

5.5 Research Design

This research was executed as a retrospective cohort study with a specific focus on GBM patients at OUH.

5.6 Patient Selection and Exclusion Criteria

The identification of patients diagnosed with GBM at OUH spanning from 2003 to 2019 was conducted through the Brain Tumor Registry at the Department of Neurosurgery. GBM diagnoses were histopathologically confirmed by the WHO classification relevant at the time of diagnosis (62).

Included in this study were patients aged 18 and above who had received partial brain RT following surgery at OUH's Neurological Department. RT, with or without concomitant TMZ, was administered in collaboration with the South-Eastern Health Authority, specifically, OUH, Innlandet Hospital, or Sørlandet Hospital. Given the implementation of the Stupp protocol in 2005, patient inclusion commenced from 2006 onwards, facilitating a more homogenous treatment group.

In adherence to the study's methodological rigor, specific exclusion criteria were applied:

Patients whose diagnoses were made outside the predefined time frame (2006 to 2019) were excluded to ensure the study's relevance and precision, aligning with the research objectives.

Patients who did not undergo RT, those who received TMZ monotherapy with or without subsequent RT (n=11), individuals with an unknown commencement date for RT (n=33), and those who received whole brain RT (n=2) were excluded from the analysis. Notably, the median OS for these excluded patients was 2 months.

Additionally, patients diagnosed in the year 2015 were also excluded from the study, despite falling within the designated time frame. This decision was made during the analysis due to the transitional nature of the year 2015, which marked the shift from Non-CPP to CPP. Such transitional periods may introduce data entry errors, missing information, or discrepancies, and therefore, excluding data from the year 2015 was intended to enhance data quality and accuracy.

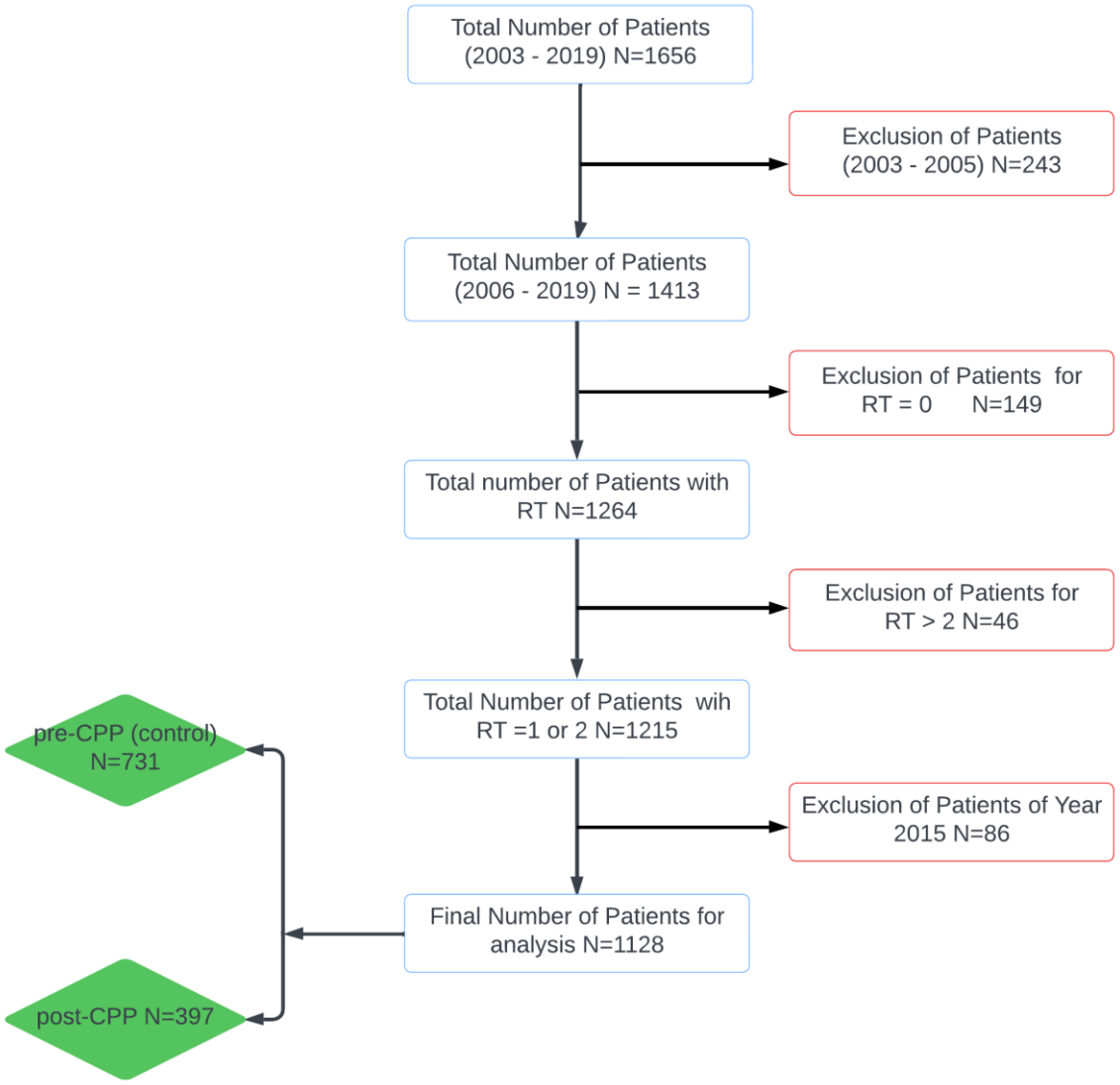

Figure 8: Patient Exclusion and Inclusion Flowchart, Stratification into Pre and Post-CPP Cohorts

5.7 Sample size

The flowchart presented above outlines the patient selection and exclusion criteria for this research analysis. A total of 1656 patients were initially identified in the Brain Tumor Registry for the period spanning from 2003 to 2019. However, patient inclusion commenced in 2006, aligning with the Stupp protocol, and excluded patients amounted to 149 who did not receive RT and 46 with incomplete data concerning the start date of RT, as well as those who had received total brain RT or TMZ monotherapy. An additional 86 patients from the transitional year 2015 were excluded due to potential data discrepancies. Consequently, the final patient cohort for this study comprised 1128 individuals. These patients were

categorized into two distinct groups: the pre-CPP group, consisting of 731 patients from 2006 to 2014, and the CPP group, comprising 397 patients from 2016 to 2019.

5.8 Data collection

Patient identification relied on the Brain Tumor Database at OUH, with data encompassing patient demographics (age, sex), tumor characteristics (localization), and primary diagnosis and treatment. The information was sourced from both the Internal quality registry and electronic patient records. Molecular genetic characteristics of the tumors like MGMT promoter methylation and IDH mutation status were largely unavailable for patients before 2015 and thus were not part of the dataset. Assessment of resection grade was conducted based on post-operative contrast-enhanced MRI scans and categorized as biopsy, gross total resection (GTR), or subtotal resection (STR). Notably, data concerning concomitant and adjuvant TMZ was only partially accessible and, as a result, was not collected for this study.

5.9 Ethics

The Regional Committee for Medical and Research Ethics approved this study. Exemption from the need to obtain informed consent from all included patients was granted. The data protection officer at OUH approved.

5.10 Statistical Analysis

The timing of RT within the spectrum of GBM treatment has garnered substantial attention and discussion. For GBM patients who have undergone surgical resection, the decision regarding when to commence RT carries significant implications for treatment effectiveness, disease management, and patient well-being. In this segment, we delve into the statistical analysis conducted to explore the research question concerning the timing of RT and its influence on OS within the framework of the CPP program.

Our research endeavors to investigate the impact of the CPP program on the timing of RT following surgery for GBM patients in Norway. Additionally, we assess survival outcomes both before and after the introduction of CPP, considering the timing of RT. To achieve this objective, we analyzed a retrospective cohort study encompassing GBM patients who underwent surgical interventions as part of their comprehensive treatment regimen. Our study encompasses GBM cases across all stages and involves three distinct surgical techniques. Our

overarching aim is to provide a robust, evidence-based evaluation of whether the CPP program has a discernible effect on the timing of RT and OS among GBM patients.

The datasets were analyzed using Stata version 17 (StataCorp LLC, Texas, USA). The collected data was securely stored in a sensitive data server (TSD).

5.10.1Analysis population

In our analyses, all registered patients were included, regardless of whether they were exposed to or complied with the CPP guidelines. This approach is commonly referred to as "intention-to-treat" (ITT). We chose to analyze our data using the ITT principle because it allows for accurate and unbiased inferences regarding the effectiveness of the CPP. In other words, it enables us to consistently interpret the effectiveness of the CPP.
Conversely, conducting Per-Protocol (PP) analyses would have involved focusing only on patients who strictly adhered to the CPP guidelines. However, such an approach could have introduced a higher risk of bias into our analysis. Therefore, we made the decision not to base our data analysis on the PP principle.

5.10.2 Variables

In this analysis, the selection and inclusion of variables are pivotal in comprehending and modeling the timing of RT and time-to-event death, significantly influencing the study's validity and interpretability. The following variables have been incorporated in this study to construct models that estimate the timing of RT before and after CPP implementation, as well as to understand and model the OS for these two groups:

Gender: This variable characterizes the patients' gender.
Age at Diagnosis: This variable is patients' age in years at the time of the initial GBM diagnosis and is categorized into three groups: ≤60 years, 60-70 years, and >70 years.
Type of Surgery: This variable indicates the type of surgery performed on the GBM patient. The analysis encompasses three types of surgeries: GTR (Gross Total Resection), STR (Subtotal Resection), and biopsy.
Lobe: This variable indicates the specific lobe of the brain where the tumor is located (tumor location) and is categorized into solitary tumors and multifocality tumors.
Side: Denotes the side of the brain where the tumor is situated (tumor location).

Treatment: This variable describes the treatment received by the patient after surgery, encompassing radiation with or without TMZ. It also incorporates the dosage of radiation administered to the GBM patient. The Standard RT dosage of 48-60 Gy, and the hypofractionated RT dosage is 30-40 Gy.

Timing of RT: This variable characterizes the commencement of RT after surgery and is categorized into three intervals: ≤4 weeks, 4.1-6 weeks, and >6 weeks.

Patient Status: This variable indicates the patient's status as either deceased or alive. The death date considered for this analysis is 27 April 2023.

These variables collectively serve as the foundation for this analysis, facilitating the creation of predictive models and a comprehensive understanding of the timing of RT and patient outcomes in the context of CPP implementation."

5.10.3 Descriptive statistics of patient characteristic data

Patient's characteristics data were compared between the two groups using descriptive statistics. Descriptive statistics in the form of counts and percentages were used to describe categorical variables with the chi-square test used to evaluate associations among them. To assess the difference in the timing of RT after surgery between the pre-CPP and post-CPP groups, a chi-square test was employed.

5.10.4 Time-to-event data

Survival was defined as time from primary surgery to death of any cause or censoring (April 27th, 2023). In the context of cancer research, it is not uncommon for some patients to still be alive at the end of the follow-up period. For those patients who remained alive beyond the last follow-up date at the conclusion of the study, we anticipated that the event of interest (death) might eventually transpire. This type of censoring, known as right censoring. Given that our pre-CPP group consisted of all the reported deaths prior to the CPP, we did not need to consider other forms of censoring, such as left censoring or interval censoring.

5.10.5 Analysis of time-to-event data

We employed two probability functions to analyze our time-to-death data: the survival (survivor) function and the hazard function. The survival probability was defined as the likelihood that a cancer patient would survive to a specified future time from their registration in the CPP. In contrast, the hazard function represented the probability that a patient, who was still alive at a particular time "t," would die at that time. Essentially, it conveyed the conditional probability of a patient dying at time "t," given that the patient had survived up to that point.

For survival analysis in this study of GBM cancer, we utilized both non-parametric methods: Kaplan-Meier plots and the log-rank test and semi-parametric regression model, Cox proportional hazards.

Non-parametric tests

Kaplan-Meier test

The Kaplan-Meier analysis quantified the duration of survival from specific data points until the occurrence of death or other significant events (63). It utilized the Kaplan-Meier survivor curve, a graphical representation that depicted the evolution of survival probability over time, to summarize the data and estimate key parameters such as the median survival time. The computation of survival probability took into consideration various event times, especially instances of subject mortality after their entry into the trial, which might transpire at different time intervals. Even when some subjects remained alive at the study's conclusion, the Kaplan-Meier analysis could accommodate these scenarios. The cumulative probability at a specific time interval was derived by multiplying the survival probabilities from all preceding intervals, adhering to the principles of probability multiplication.

The median survival time, marking the point at which the total probability of survival reached 0.50, was calculated. These estimates were visually conveyed through a graph that presented estimated survival probabilities or survival percentages on the Y-axis, while the X-axis represented the time elapsed since entry into the study. This chart featured both horizontal and vertical lines, facilitating the comparison of two survival curves. Variations in these curves, whether horizontal or vertical, indicated differences in the survival experiences of distinct groups. Vertical gaps suggested that at a specific time, one group had a larger proportion of surviving subjects, while horizontal gaps indicated that it took longer for one group to reach a particular fraction of deaths.

To compare the median survival times between the pre-CPP group and the post-CPP group, the log-rank test shall be used.

Log-rank test

The comparison of median survival times between the pre-CPP group and the post-CPP group was conducted using the log-rank test. This test was a statistical method employed to assess and compare the survival distributions of the two sample groups. It belonged to the

category of nonparametric tests, which rendered it suitable for right-skewed or censored data. The log-rank test was widely utilized to evaluate the effectiveness of a new treatment in comparison to the pre-CPP group when the primary outcome was the time to an event, as was the case in our study, where the event of interest was death.

Semi-parametric

To model our data and evaluate the impact of various factors (covariates) on patient survival, we applied the Cox proportional hazards (PH) model to our research. We operated under the assumption that the survival times of the patients were independent of each other and that the censoring type was right censoring. Crucially, we postulated that the hazard in any group was a constant multiple of the risk in another group. This was known as the proportionality assumption, which we verified through the Schoenfeld residual test.

Cox-proportional hazard regression

Cox proportional hazards regression is a statistical method designed to explore the influence of multiple variables on the timing of a specific event, in our case, mortality. Our study focuses on mortality, making it a Cox regression for survival analysis. The Cox regression yields more accurate survival probabilities and cumulative hazard estimates compared to the Kaplan-Meier function. Notably, the Cox proportional hazards regression can accommodate both quantitative and categorical predictor variables, whereas Kaplan-Meier curves and log-rank tests are primarily suitable for categorical predictor variables.

The Cox regression model allows us to investigate how certain factors affect the rate of a particular event, such as death, occurring at a specific time. This rate is known as the hazard rate, represented by the hazard function h(t). The hazard function signifies the risk of experiencing an event (in this case, death) at a time "t" and can be estimated as:

$$h(t) = h0(t) \times \exp(b1 \times 1 + b2 \times 2 + \cdots + \text{bp} \times p)$$

Here, "t" signifies the survival time, while h(t) represents the hazard function influenced by a set of "p" covariates (x1, x2, …, Xp). The coefficients b1, b2, …, bp measure the impact of these covariates. The baseline hazard is referred to as h0.

The Cox regression model is essentially a multiple linear regression of the natural logarithm of the hazard on the variables xi, with the baseline hazard acting as an "intercept" term that

varies over time (64). The quantities exp(bi) are termed hazard ratios (HR), and their values are interpreted as follows:

- HR = 1 indicates no effect.
- HR < 1 indicates a reduction in hazard.
- HR > 1 indicates an increase in hazard, implying a negative association with survival duration.

The p-value is defined as the probability, under the null hypothesis (assumption of no effect or difference), of obtaining a result equal to or more extreme than the observed result (65). In our analysis, p-values less than 0.05 were considered statistically significant.

6 Results

6.1 Characteristics of Patients, Tumors, and Treatment for whole cohort

In this study, a total of 1128 patients who met the inclusion criteria Table 2 were analyzed. Among these patients, the majority were male, accounting for 669 individuals (59.3%). The proportion of patients under the age of 60 was notably higher, with 484 cases (42.9%). Tumor localization revealed a higher frequency in the right hemisphere, comprising of 563 patients (49.9%), followed by the left hemisphere with 531 cases (47.0%). Tumor was located in the midline with 12 patients (1.1%) and bilaterally with 23 patients (2.0%). The most frequent tumor location was in the frontal lobe, representing 383 patients (33.9%). Multifocal tumors were present in 100 patients (8.9%). Surgical interventions consisted of gross total resection (GTR) in 329 patients (29.2%), and subtotal resection (STR) in 684 patients (60.6%), while only biopsy was performed in 115 patients (10.2%).

The majority, comprising 892 individuals (79.1%), underwent the conventional standard RT regimen, characterized by doses within the range of 48 to 60 Gy. In contrast, a minority of 236 patients (20.9%) received hypofractionated RT, where doses fell within the spectrum of 30 to 40 Gy.

The timing of RT initiation post-surgery was stratified into three intervals ≤4 weeks, 4.1-6 weeks, and >6 weeks. Notably, a substantial portion of patients, specifically 543 cases (48.1%), received RT treatment within the initial four weeks following their surgical procedures.

6.2 Characteristics of Patients, Tumors, and Treatment in-between pre and post-CPP

The study cohort was divided into two distinct groups based on the period of diagnosis (Table 2). The pre-CPP group, comprising patients diagnosed between 2006 and 2014, accounted for 731 individuals (60.2% of the total sample), while the post-CPP group included patients diagnosed between 2016 and 2019, totaling 397 individuals (32.7% of the sample). Most of the patients in both treatment groups were male, 426/731 (59.6%) pre-CPP and 233/397 (58.7%) post-CPP. Patients under 60 years of age were more numerous in both groups, with 311/731, (42.5%) in pre-CPP and 173/397 (43.5%) in post-CPP, respectively. In both pre-CPP and post-CPP groups, most tumors were in the right hemisphere, accounting for 363/731, (49.6%) and 201/397 (50.6%), respectively. The most common tumor location was the frontal lobe, with 250/731 (34.2%) in pre-CPP and 133/397 (33.5%) in post-CPP, followed by the temporal lobe with 205/731 (28%) in pre-CPP and 110/397 (27.7%) in post-

CPP. Multifocal tumors were less frequent, representing only 67/731 (9.2%) in pre-CPP and 33/397 (8.3%) in post-CPP.

In both treatment groups STR was most frequent with 466 out of 731 patients (63.7%) in the pre-CPP group, and 206 out of 397 patients (51.8%) in the post-CPP group. Conversely, biopsy was a less frequent, albeit it was slightly more common in the post-CPP group, accounting for 57 out of 397 patients (14.3%), as compared to 58 out of 731 patients (7.9%) in the pre-CPP group.

It is worth noting that a significant majority of patients in both the pre-CPP and post-CPP groups received the standard RT regimen, involving doses within the range of 48-60 Gy, with 614 out of 731 patients (83.9%) and 278 out of 397 patients (70%), respectively. In contrast, a minority of patients, comprising 16% (117 out of 731 patients) in the pre-CPP group and 30% (119 out of 397 patients) in the post-CPP group, underwent hypofractionated RT, with doses ranging from 30 to 40 Gy.

Table 2: Characteristics of the patients stratified by treatment group (N = 1128)

	Total (N = 1128)	Pre-CPP (n = 731)	Post-CPP (n = 397)
Gender			
Female	459 (40.7)	295 (40.4)	164 (41.3)
Male	669 (59.3)	436 (59.6)	233 (58.7)
Age (in years)			
< 60	484 (42.9)	311 (42.5)	173 (43.6)
60 - 69	388 (34.4)	278 (38.0)	110 (27.7)
≥ 70	256 (22.7)	142 (19.4)	114 (28.7)
Tumor location			
Right	563 (49.9)	363 (49.6)	201 (50.6)
Left	530 (47.0)	342 (46.8)	187 (47.1)
Midline	12 (1.1)	10 (1.4)	2 (0.5)
Bilateral	23 (2.1)	16 (2.2)	7 (1.8)
Tumor focality			
Frontal	382 (33.9)	250 (34.2)	132 (33.3)
Parietal	196 (17.4)	119 (16.3)	77 (19.4)
Temporal	315 (27.9)	205 (28.0)	110 (27.7)
Occipital	90 (8.0)	62 (8.5)	28 (7.0)
Insula	18 (1.6)	11 (1.5)	7 (1.8)
Corpus Callosum	27 (2.4)	17 (2.3)	10 (2.5)
Multifocal (2 or more)	100 (8.9)	67 (9.2)	33 (8.3)
Type of Surgery			
GTR	329 (29.2)	195 (26.7)	134 (33.8)
STR	684 (60.6)	478 (65.4)	206 (51.9)
Biopsy	115 (10.2)	58 (7.9)	57 (14.3)
Timing of RT			
≤ 4 weeks	543 (48.1)	285 (39.0)	258 (65.0)
4.1-6 weeks	433 (38.4)	307 (42.0)	126 (31.7)
> 6 weeks	152 (13.5)	139 (19.0)	13 (3.3)
Radiotherapy			
48-60 Gy	892 (79.1)	614 (84.0)	278 (70.0)
30-40 Gy	236 (20.9)	117 (16.0)	119 (30.0)

Significant p-values highlighted in bold. Abbreviations: GTR, gross total resection; STR, Subtotal resection; Gy, gray

6.3 Analysis of Survival for whole patient cohort

The median OS for the study cohort was calculated to be 12.9 months. Both unadjusted and adjusted, has been provided in Table 3 for reference. Notably, the adjusted analysis unveiled the identification of several statistically significant favorable prognostic factors. These factors encompassed female sex, patients under the age of 60 years, the application of gross total resection (GTR) as a surgical approach, and the utilization of higher RT doses.

Table 3: Unadjusted and adjusted analysis of patient cohort comprising pre- and post-CPP groups (n=1128)

	Unadjusted		Adjusted	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age in years (ref: < 60)				
60 – 69	1.52 (1.32, 1.74)	**< 0.001**	1.51 (1.31, 1.73)	**< 0.001**
≥ 70	2.29 (1.96, 2.69)	**< 0.001**	1.46 (1.18, 1.80)	**< 0.001**
Gender (ref: Female)				
Male	1.16 (1.03, 1.31)	**0.015**	1.15 (1.02, 1.30)	**0.024**
Type of Surgery (ref: GTR)				
STR	1.60 (1.39, 1.83)	**<0.001**	1.58 (1.38, 1.82)	**<0.001**
Biopsy	2.37 (1.91, 2.95)	**<0.001**	1.84 (1.46, 2.32)	**<0.001**
Timing of RT (ref: <4 weeks)				
4-6 weeks	1.04 (0.91, 1.18)	0.56	1.02 (0.89, 1.16)	0.793
> 6 weeks	1.07 (0.89, 1.29)	0.45	1.04 (0.86, 1.25)	0.690
Tumor Location (ref: right)				
Left	0.96 (0.85, 1.08)	0.481	1.01 (0.90, 1.14)	0.859
Midline	0.97 (0.55, 1.72)	0.917	0.95 (0.53, 1.69)	0.856
Bilateral	1.67 (1.10, 2.54)	**0.016**	1.24 (0.80, 1.91)	0.340
Tumorfocality (ref: Solitary)				
Multifocal (2 or more)	1.42 (1.15, 1.75)	**<0.001**	1.23 (0.99, 1.53)	0.065
Radiotherapy (ref: 48-60 Gy)				
30-40 Gy	2.73 (2.35, 3.16)	**<0.001**	2.22 (1.81, 2.72)	**<0.001**

Significant p-values highlighted in bold. Abbreviations: OS, overall survival; CI, confidence interval; GTR, gross total resection; STR, Subtotal resection; Gy, gray

6.4 Impact of cancer patient pathway on timing of RT

Analysis revealed that in the pre-CPP group, the median interval between surgery and the initiation of RT was 31 days, as opposed to the post-CPP group, where the median time was reduced to 27 days (Table 4).

Table 4: Comparison of Postoperative Radiation Therapy Timing between Pre-CPP and Post-CPP Groups

Groups	Median time (25^{th}, 75^{th}) (in days)	Mean	Standard Deviation
Pre-CPP	31 (26, 39)	34.93	13.03
Post-CPP	27 (22, 31)	28.10	9.84

The timing of RT administration following surgery was categorized into three distinct intervals: ≤4 weeks, 4.1-6.0 weeks, and >6 weeks. Significantly, a higher proportion of patients in the post-CPP group, representing 258 out of 397 patients (65.0%), received RT within the first four weeks post-surgery, in contrast to 285 out of 731 patients (39.0%) in the pre-CPP group (Table 2). This discrepancy in timing was found to be statistically significant ($p<0.001$). Moreover, the proportion of patients receiving RT within the 4.1-6.0 week and >

6-week intervals was markedly higher in the pre-CPP implementation phase as compared to the post-CPP phase, with both differences being statistically significant ($p<0.001$). These findings underscore the notable impact of CPP implementation on the interval between surgery and RT.

6.5 Impact of cancer patient pathway on survival

The median OS within the pre-CPP group was 12.3 months, while the post-CPP group exhibited a median OS of 13.7 months (Table 5). This difference, however, was not found to be statistically significant ($p=0.060$) (Table 6 and Figure 9). Among the older patients, aged 70 years or older, the pre-CPP group displayed a median OS of 8.3 months, contrasting with 11.0 months observed in the post-CPP group. Notably, an unadjusted analysis revealed a significant survival difference favoring the post-CPP group (HR 0.66, 95% CI 0.51-0.85, $p=0.001$), as depicted in Table 6 and Figure 10. In contrast, among younger patients, there was no significant difference in survival between the pre- and post-CPP groups.

Furthermore, significant differences in survival were identified in unadjusted analysis both for patients receiving standard and hypofractionated RT ($p=0.017$ and $p<0.001$, respectively). Further details can be found in Table 6 and Figures 11 and 12.

Patients diagnosed with multifocal disease demonstrated distinct median OS durations, with a median OS of 12.1 months observed in the post-CPP group and 8.6 months in the pre-CPP group. Notably, an unadjusted analysis revealed a significant difference in survival, with a HR of 0.52 and a 95% confidence interval (CI) ranging from 0.33 to 0.81 ($p=0.010$). Further details can be found in Table 6.

In analysis when adjusting pre- and post-CPP groups for patient, tumor, and treatment factors, the patients in the post-CPP group had significantly better outcome than patients in the pre-CPP group; HR 0.74, 95% CI 0.65-0.85, $p<0.001$.

Table 5: Median survival time in months stratified by treatment group (N = 1128)

	Overall (1128)	Pre-CPP (731)	Post-CPP (397)
	Median OS (25th, 75th)	Median OS (25th, 75th)	Median OS (25th, 75th)
Overall survival	12.9	12.3	13.7
Gender			
Female	13.2 (8.0, 24.5)	12.4 (7.5, 23.1)	14.2 (8.8, 29.3)
Male	12.8 (8.2, 19.2)	12.1 (7.9, 18.9)	13.5 (8.9, 19.9)
Age group (years)			
<60	15.6 (10.2, 28.8)	15.4 (10.1, 27.6)	16.3 (10.4, 31.6)
60-69	12.6 (7.5, 19.2)	11.8 (7.1, 19.1)	14.4 (9.9, 19.9)
≥70	9.1 (5.5, 13.5)	8.2 (5.1, 11.9)	11 (6.6, 15.9)
Tumor Location			
Right	13.0 (8.1, 21.4)	12.1 (7.9, 20.8)	14.0 (8.7, 21.4)
Left	12.9 (8.4, 20.2)	12.8 (8.0, 19.1)	13.3 (9.0, 23.1)
Midline	13.7 (4.7, 22.5)	10.4 (4.7, 22.5)	13.7 (13.7, 32.5)
Bilateral	9.1 (3.2, 16.1)	8.0 (3.2, 12.6)	13.0 (7.5, 16.8)
Tumor focality			
Solitary	13.4 (8.4, 21.2)	12.9 (8.2, 20.3)	13.9 (8.8, 22.1)
Multifocal (2 or more)	9.2 (5.5, 13.5)	8.6 (4.6, 12.3)	12.1 (9.1, 22.2)
Type of surgery			
GTR	16.4 (11.2, 30.3)	15.8 (10.5, 29.4)	17.3 (12.4, 30.9)
STR	12.1 (7.9, 18.5)	11.7 (7.3, 18.2)	13.2 (8.9, 20.7)
Biopsy	8.3 (4.6, 13.3)	6.6 (4.6, 13.4)	8.4 (4.8, 12.9)
Timing of RT			
< 4 weeks	13.4 (8.5, 21.6)	12.4 (8.1, 21.3)	14.3 (9.2, 22.1)
4.1-6 weeks	12.5 (8.2, 19.6)	12.1 (7.9, 19)	13.3 (8.8, 24.1)
> 6 weeks	12.3 (6.7, 19.5)	12.7 (6.9, 19.9)	7.5 (6.1, 13.0)
Radiotherapy			
48-60 Gy	14.7 (9.8, 24.1)	14 (8.9, 23.1)	15.6 (11.3, 28.4)
30-40 Gy	7.3 (4.1, 11.7)	5.9 (3.8, 8.9)	9.7 (5, 13.6)

Table 6: Unadjusted Analysis: Pre-CPP vs. Post-CPP Comparison

Characteristics	Unadjusted analysis	
	Hazard ratio (95% CI)	P-value
ref: pre-CPP		
Post-CPP	0.88 (0.78, 1.00)	0.060
Age in years		
<60	0.95 (0.78, 1.16)	0.610
60-69	0.86 (0.69, 1.10)	0.188
≥70	0.66 (0.51, 0.85)	**0.001**
Gender		
Female	0.85 (0.70, 1.04)	0.120
Male	0.91 (0.77, 1.07)	0.257
Surgical resection		
GTR	0.94 (0.75, 1.20)	0.618
STR	0.85 (0.72, 1.01)	0.065
Biopsy	0.99 (0.68, 1.43)	0.943
Tumorfocality		
solitary	0.93 (0.82, 1.06)	0.300
Multifocal (2 or more)	0.52 (0.33, 0.81)	**0.004**
Radiotherapy		
48-60 Gy	0.84 (0.72, 0.97)	**0.017**
30-40 Gy	0.52 (0.40, 0.67)	**<0.001**

Significant *p*-values highlighted in bold. Pre-Cancer Patient Pathway group used as reference. All patients included in the pre- and post-Cancer Patient Pathway groups. Gross total resection deemed by surgeon, but no available postoperative MRI. Abbreviations: OS, overall survival; CI, confidence interval; GTR, gross total resection

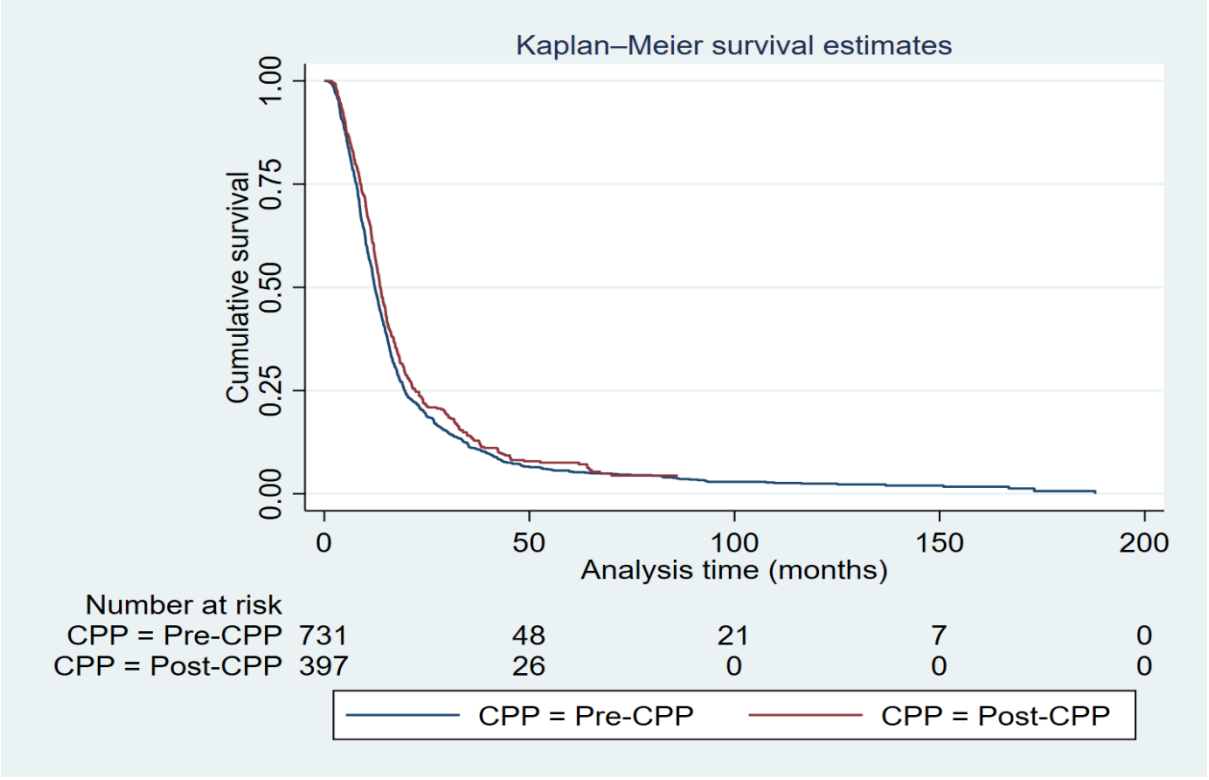

Figure 9: Kaplan-Meier survival curve for GBM since time of diagnosis by pre-CPP and post-CPP. (P=0.060)

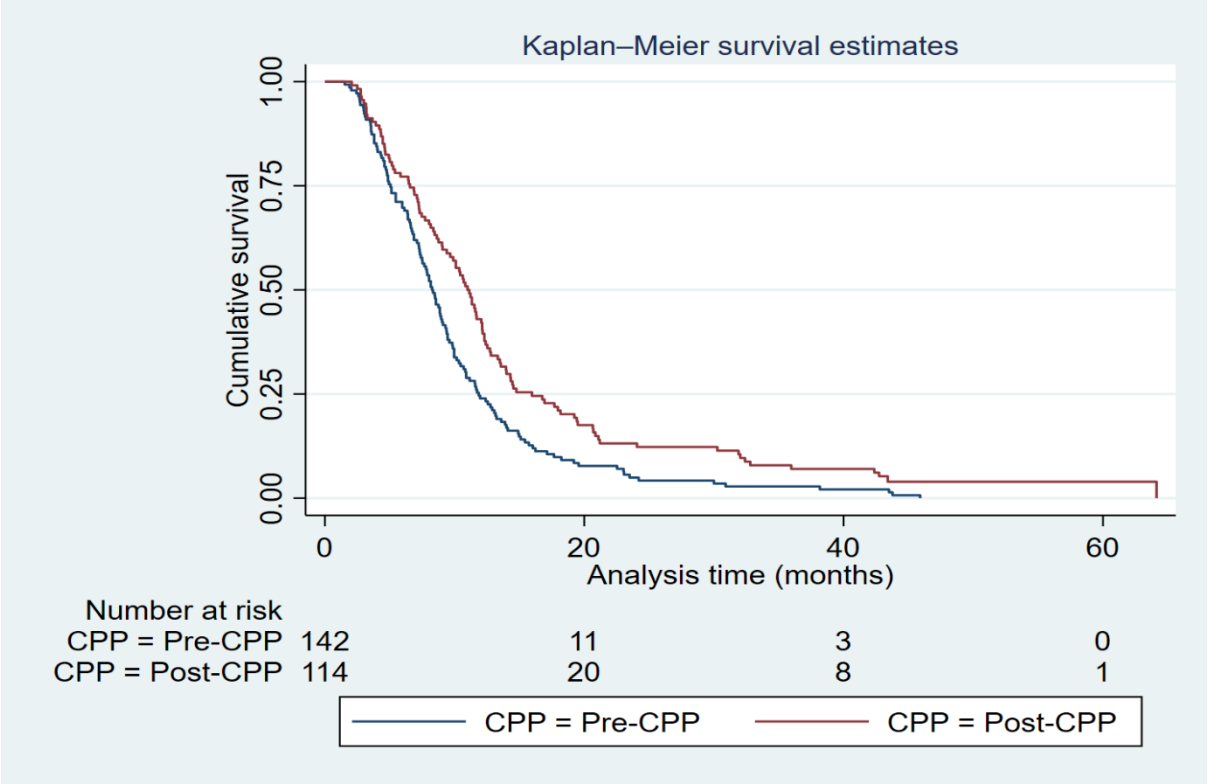

Figure 10: Kaplan-Meier survival curve for GBM by Age Group (≥70 years) Pre and Post-CPP (P = 0.001)

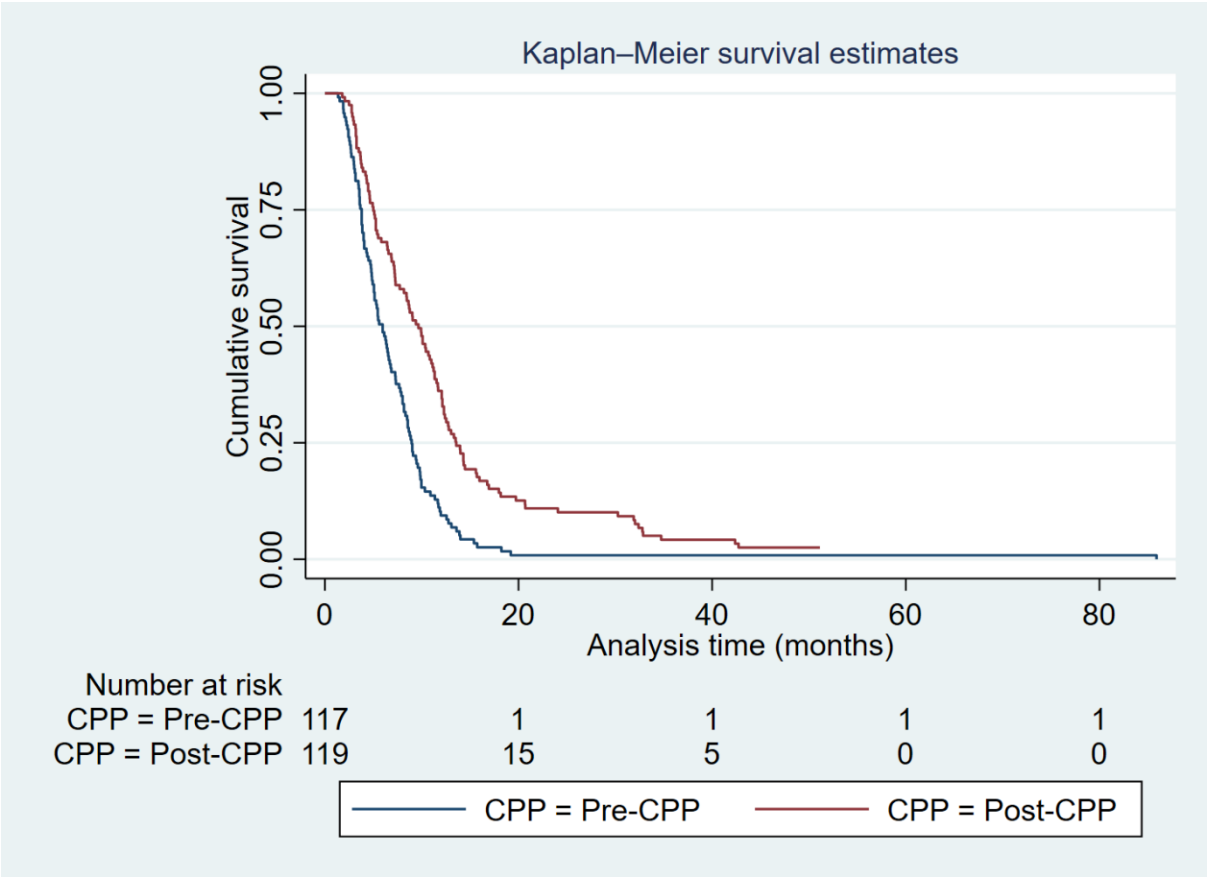

Figure 11: Kaplan-Meier survival curve for GBM by hypofractionated RT (30-40Gy) Pre and Post-CPP. (P<0.001)

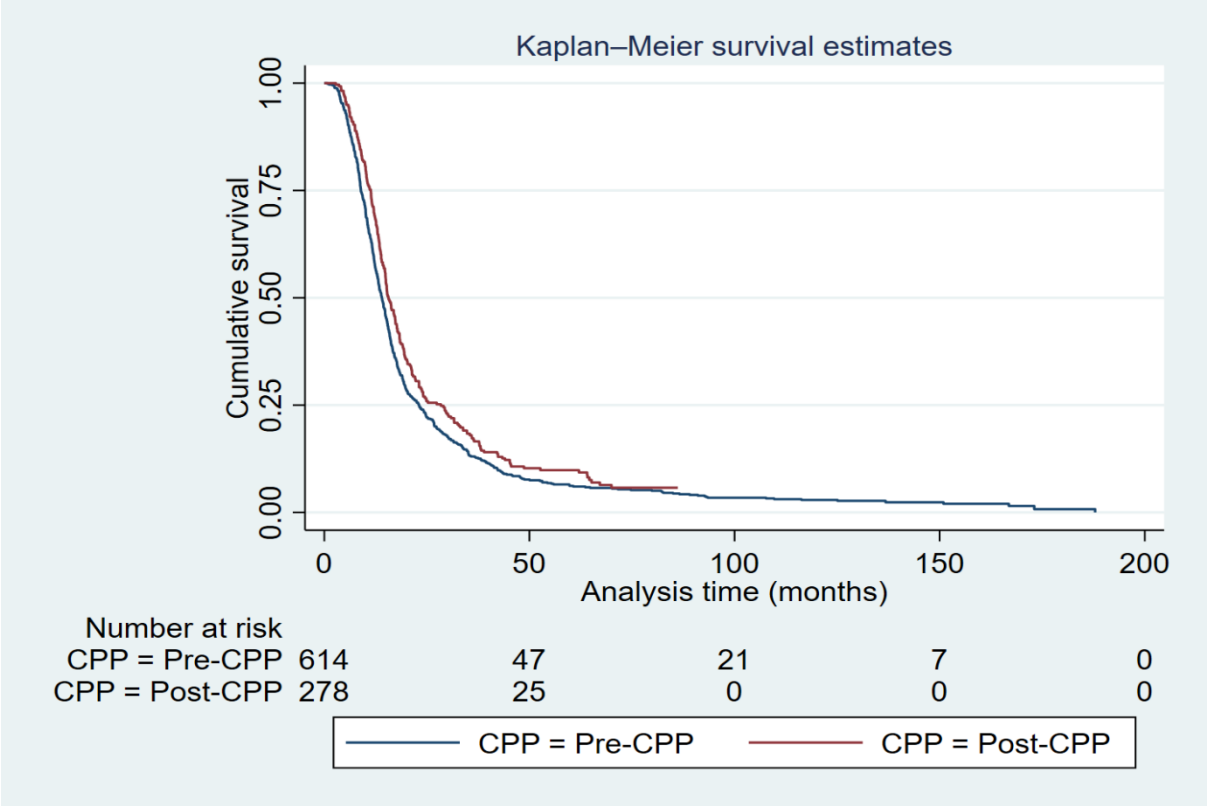

Figure 12: Kaplan-Meier survival curve for GBM by standard RT (48 - 60Gy) Pre and Post-CPP. (P=0.017)

6.6 Impact of time to radiation start on survival

This analysis encompassed all patients, including those diagnosed in the year 2015, resulting in a total sample size of 1215 individuals. The timing of RT initiation following surgery varied among these patients, with the majority (n=605, 49.8%) commencing RT within four weeks of their surgical procedures. Additionally, 37.5% of patients (n=456) initiated RT between 4.1 and 6 weeks post-surgery, while 12.7% (n=154) embarked on RT after a delay exceeding six weeks, as outlined in Table 7.

The group that initiated RT within four weeks from surgery served as the reference, revealing the most extended median OS at 13.3 months. In comparison, the median OS was slightly reduced to 12.5 months in the 4.1-6 weeks group (HR 1.03, 95% CI 0.91-1.17; p=0.641), and further decreased to 12.2 months in the >6 weeks group (HR 1.09, 95% CI 0.91-1.30; p=0.359). Importantly, the statistical analysis did not identify a significant difference in survival outcomes among these timing groups (Table 7)

Table 7: Timing of Radiotherapy After Surgery and Characteristic Distribution

Characteristics	≤4weeks		4.1-6 weeks				>6 weeks			
	N%	Median OS	N%	Median OS	Unadjusted analysis		N%	Median OS	Unadjusted analysis	
					Hazard Ratio (HR)	P-value			Hazard Ratio (HR)	P-value
Patients (1215)	605 (100)	13.3	455 (100)	12.5	1.03 (0.91, 1.17)	0.641	154 (100)	12.2	1.09 (0.91, 1.30)	0.359
Gender										
Female	238(39.3)	13.0	196 (43.1)	13.8	0.87 (0.71, 1.06)	0.157	55 (64.3)	12.3	1.05 (0.78, 1.42)	0.357
Male	367 (60.7)	13.5	259 (56.9)	11.8	1.21 (1.03, 1.42)	**0.023**	99 (64.3)	12.2	1.11 (0.89, 1.39)	0.751
Age in years										
<60	270 (44.6)	15.7	179 (39.3)	15.6	0.94 (0.77, 1.14)	0.505	67 (43.5)	15.6	0.95 (0.72, 1.25)	0.699
60-69	197 (32.6)	13.5	180 (39.6)	11.9	1.16 (0.94, 1.42)	0.158	48 (31.2)	12.2	1.20 (0.87, 1.65)	0.269
≥70	138 (22.8)	10.0	96 (21.1)	8.8	0.97 (0.75, 1.27)	0.837	39 (25.3)	7.3	1.36 (0.95, 1.94)	0.094
Surgical resection										
GTR	184 (30.4)	17.5	144 (31.7)	16.3	1.03 (0.82, 1.29)	0.826	30 (19.5)	13.0	1.24 (0.83, 1.85)	0.301
STR	347 (57.4)	12.8	265 (58.2)	11.5	1.10 (0.94, 1.30)	0.236	114(74.0)	12.3	1.06 (0.86, 1.31)	0.597
Biopsy	74 (12.2)	8.0	46 (10.1)	7.2	0.83 (0.57, 1.21)	0.337	10 (6.5)	7.2	0.64 (0.31, 1.29)	0.211
Tumor focality										
Solitary	545 (90.1)	13.9	413 (90.8)	13.1	1.04 (0.91, 1.18)	0.582	145(94.2)	12.7	1.08 (0.90, 1.30)	0.403
Multifocal	60 (9.9)	9.1	42 (9.2)	9.4	0.99 (0.66, 1.49)	0.960	9 (5.8)	9.8	1.54 (0.76, 3.15)	0.234
Radiotherapy										
48-60 Gy	470 (77.7)	15.1	369 (81.1)	13.8	1.07 (0.93, 1.23)	0.360	123(79.9)	14.0	1.10 (0.90, 1.35)	0.337
30-40 Gy	135 (22.3)	7.3	86 (18.9)	6.8	1.00 (0.76, 1.31)	0.988	31 (20.1)	6.5	1.16 (0.78, 1.73)	0.454
CPP										
Pre-CPP	285 (47.1)	12.4	303 (66.4)	12.1	1.02 (0.87, 1.20)	0.816	139(90.3)	12.7	1.00 (0.82, 1.23)	0.973
Post-CPP	258 (42.6)	14.3	126 (27.6)	13.3	1.01 (0.81, 1.26)	0.927	13 (8.4)	7.5	1.27 (0.71, 2.26)	0.426

Radiotherapy starts within 4 weeks used as reference. All patients from 2006 till 2019 are included. Gross total resection deemed by surgeon, but no available postoperative MRI. Abbreviations: GTR, gross total resection; STR, subtotal resection; Gy, gray; CPP, cancer patient pathway.

7 Discussion

Efforts to improve the prognosis of patients with GBM have been extensive. Improving survival and quality of life for GBM patients depends on using the best available treatment methods. The matter of the timing of RT initiation and its implications for GBM patient survival has been a longstanding subject of debate, with numerous published studies addressing survival outcomes in relation to RT timing. Over the last few decades, the implementation of comprehensive treatment strategies, including surgery, RT, and chemotherapy, has effectively prolonged the survival of GBM patients, with median survival of approximately 15 months (66).

In the context of this study, our primary objective was to investigate the influence of a dedicated CPP on the timing of RT and the OS of GBM patients. However, we concurrently investigated the significance of the timing of RT for the entire patient cohort. This exploration aimed to elucidate the role of RT timing within the standardized treatment regimen for individuals with GBM.

In this study, a central finding is that the introduction of CPP for GBM did not impact survival in unadjusted analysis ($p=0.060$), however, in adjusted analysis it was highly significant ($p<0.001$). Whereas, coming to the timing of RT between pre- and post-CPP there is no significant alterations in RT. However, 65% of patients receiving the RT within 4 weeks in post-CPP compared to 39% in pre-CPP and this difference was significant ($p<0.001$).

This study has several strengths. This retrospective cohort study includes extensive data spanning from 2006 to 2019, encompassing a diverse patient population. The careful inclusion of GBM patients minimizes the potential for selection bias such as sampling bias (specific subgroups are overrepresented), healthy volunteer bias (long-term survivors are included in the study, it may not account for patients with poor outcomes), thereby enhancing the trustworthiness of the study's findings. Another strength of this study is the Norwegian patients have been treated uniformly since TMZ was introduced.

This study exhibits a number of constraints that merit attention. This is typical in retrospective studies, there exists the possibility of patient selection bias. Nevertheless, this bias is likely of minimal concern given the study's inclusion of a large, comprehensive, and consecutive patient cohort. Particularly, we lack specific information regarding the proportion of patients who were enrolled in the CPP. All patients diagnosed after the CPP

implementation are classified in the post-CPP group, regardless of their inclusion in the CPP. However, it is important to highlight that a significantly higher percentage of patients received RT within four weeks of surgery after the CPP implementation. Additionally, the introduction of CPP may have potentially advanced the timing of diagnosis, introducing a lead-time bias (67). Another limitation is the lack of information regarding IDH and MGMT status; however, in this extensive dataset, this limitation may not be particularly relevant. Similarly, the inclusion of patients with a now-past diagnosis of IDH-mutated GBM is not applicable, as no such patients were included from 2020 onwards (21). The study's limited knowledge of concomitant and adjuvant TMZ use represents another constraint.

The impact of the time interval between surgery and the commencement of RT has been a topic of investigation in numerous retrospective studies of GBM patients. In this study, we conducted a comparative analysis between the pre-CPP and post-CPP groups to evaluate the influence of the timing of RT following surgery on patient survival. In unadjusted analysis the implementation of CPP did not result in a significant impact on survival outcomes (HR 0.88, 95% CI 0.78-1.00; p=0.060). However, adjusted for patient, tumor, and treatment factors, the CPP implementation had a highly significant impact on survival (HR 0.74, 95% CI 0.65-0.85; p<0.001).

The analysis of age differences between the pre-CPP and post-CPP periods reveals notable variations. Elderly patients, aged over 70 years, experienced significantly improved OS in the post-CPP period, with a median OS of 11 months, compared to 8.2 months in the pre-CPP era (p=0.001). Similarly, patients with multifocal tumors exhibited a significant survival advantage in the post-CPP period, with a median OS of 12.1 months, compared to 8.6 months in the pre-CPP phase (p=0.004). Furthermore, patients who received standard RT and hypofractionated RT demonstrated significant better OS post-CPP period (p=0.017 and p<0.001, respectively). It is worth noting, however, that while the data suggests an impact of CPP on survival, possible confounders can be lead-time bias (67,68) and a potentially more aggressive treatment approach in elderly patients. The latter aspect especially relevant in light of a 2017 study indicating that the addition of TMZ to short-course RT resulted in extended survival compared to short-course RT alone (42).

In this study, we observed no significant differences in survival among the groups commencing RT within ≤4 weeks, 4.1-6 weeks, or >6 weeks post-surgery. Previous reports,

such as Valduvieco et al. (47), Viet Do et al. (48), have suggested that an early initiation of RT is associated with improved outcomes, while others have proposed that a desire to expedite the treatment for patients with unfavorable prognostic factors may introduce bias. On the other hand, reports have indicated that delaying RT after surgery could lead to better outcomes, as seen in S.J Han et al. (49). However, delaying RT, even for patients with favorable prognostic factors, may also introduce bias in favor of those receiving delayed RT. Several prior studies have yielded results consistent with our findings. For instance, Blumenthal et al. (51) analyzed the RTOG database and reported on 1395 patients, finding no significant difference in OS when RT was administered within <4 weeks, 4.1-6 weeks, or >6 weeks (51). Similarly, Magrowski et al. (69) conducted a retrospective analysis of 346 GBM patients who underwent surgical treatment and received RT with concomitant TMZ (69). The regression analysis in the latter study showed that the time interval had not statistically impact on OS.

In this study the adjusted analysis for CPP showed a significant impact on OS ($p<0.001$). However, this impact may not be the result of timing of RT. The analysis indicates that the RT≤ 4 weeks does not provide a survival benefit compared to a more delayed RT initiation Table 7. This indicates that the improved survival may not be related to RT at all. A possible explanation for the significant better outcome after CPP implementation in adjusted analysis can be a more aggressive treatment approach in elderly patients, since the fraction of patients 70 years or older increased from 19.4% in the pre-CPP era to 28.7% in the post-CPP era. In addition, a higher fraction of patients received hypofractionated RT post-CPP compared to pre-CPP (30.0% versus 16%).

this analysis supports existing literature suggesting that the timing of RT, within the studied timespan, may not be a critical factor in determining survival outcomes. The comparison of RT timing before and after CPP implementation, as well as for the entire cohort, contributes to the broader understanding of the multifaceted factors influencing GBM treatment outcomes.

The analysis showed that over the period from 2016 to 2019, the waiting time for RT following GBM surgery marginally decreased to 27 days. However, when contrasted with the pre-CPP era, specifically the period from 2006 to 2014, during which the waiting period was 31 days, this change did not attain statistical significance. Notably, an examination of the data across three distinct periods (≤4 weeks, 4.1-6 weeks, and >6 weeks) both before and after

CPP implementation revealed significant differences. Following the introduction of CPP, a considerably higher proportion of patients initiated RT within four weeks post-surgery compared to the pre-CPP period (65.0% versus 39.0%, respectively; $p<0.001$). On the other hand, substantial differences were also noted in the timing of RT initiation between the pre-CPP and post-CPP periods, for intervals of 4.1-6 weeks and more than six weeks post-surgery ($p<0.001$ and $p<0.001$, respectively). This observed increase in patients receiving RT within four weeks post-surgery may be considered a favorable impact of the implementation of CPP guidelines.

While the introduction of the CPP lead to a noteworthy improvement in the proportion of patients receiving RT within four weeks of surgery (Table 2 and 4). Norway initiated CPPs in 2015, establishing standardized patient pathways aligned with the national guidelines for cancer diagnosis and treatment. The primary objective of CPPs is to expedite patient assessments and treatment initiation, thereby reducing waiting times and ensuring equal access to the publicly reimbursed national healthcare system for all citizens, regardless of patient characteristics, tumor type, geographic location, or socioeconomic status (70). The results demonstrate that CPP implementation led to a noteworthy improvement in the proportion of patients receiving RT within four weeks of surgery, highlighting the positive impact of standardizing patient pathways.

8 Conclusion

In conclusion, we found that survival was increased after the introduction of the CPP when adjusted for patient, tumor, and treatment factors. In addition, the implementation of CPP did lead to a noteworthy improvement in the proportion of patients receiving RT within four weeks of surgery. The post-CPP group exhibited a significant increase in the number of patients receiving RT within 4 weeks after surgery compared to the pre-CPP period. However, patients who started RT ≤4 weeks after surgery did not experience a survival benefit compared to those with a more delayed RT initiation.

9 Reference list

1. IARC WHO classification of tumour.

2. Riblet NBV, Schlosser EM, Snide JA, Ronan L, Thorley K, Davis M, et al. A clinical care pathway to improve the acute care of patients with glioma. Neuro-Oncol Pract. 2016 Sep 1;3(3):145–53.

3. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJB, et al. Radiotherapy plus Concomitant and Adjuvant Temozolomide for Glioblastoma. N Engl J Med. 2005 Mar 10;352(10):987–96.

4. Nilssen Y, Brustugun OT, Tandberg Eriksen M, Gulbrandsen J, Skaaheim Haug E, Naume B, et al. Decreasing waiting time for treatment before and during implementation of cancer patient pathways in Norway. Cancer Epidemiol. 2019 Aug; 61:59–69.

5. Hanif F, Muzaffar K, Perveen K, Malhi SM, Simjee SU. Glioblastoma Multiforme: A Review of its Epidemiology and Pathogenesis through Clinical Presentation and Treatment. Asian Pac J Cancer Prev APJCP. 2017 Jan 1;18(1):3–9.

6. Schwartzbaum JA, Fisher JL, Aldape KD, Wrensch M. Epidemiology and molecular pathology of glioma. Nat Clin Pract Neurol. 2006 Sep;2(9):494–503.

7. Agnihotri S, Burrell KE, Wolf A, Jalali S, Hawkins C, Rutka JT, et al. Glioblastoma, a Brief Review of History, Molecular Genetics, Animal Models and Novel Therapeutic Strategies. Arch Immunol Ther Exp (Warsz). 2013 Feb;61(1):25–41.

8. Stoyanov GSt, Dzhenkov DL. On the Concepts and History of Glioblastoma Multiforme - Morphology, Genetics and Epigenetics. Folia Med (Plovdiv). 2018 Mar 1;60(1):48–66.

9. DeAngelis LM, Mellinghoff IK. Virchow 2011 or How to ID(*H*) Human Glioblastoma. J Clin Oncol. 2011 Dec 1;29(34):4473–4.

10. Book Review A Classification of the Tumors of the Glioma Group On A Histogenetic Basis With a Correlated Study of Prognosis . By Percival Bailey and Harvey Cushing. Philadelphia, London and Montreal: J. B. Lippincott Co. 175 pages. Boston Med Surg J. 1926 Jun 24;194(25):1202–3.

11. Ostrom QT, Cioffi G, Gittleman H, Patil N, Waite K, Kruchko C, et al. CBTRUS Statistical Report: Primary Brain and Other Central Nervous System Tumors Diagnosed in the United States in 2012–2016. Neuro-Oncol. 2019 Nov 1;21(Supplement_5):v1–100.

12. Grech N, Dalli T, Mizzi S, Meilak L, Calleja N, Zrinzo A. Rising Incidence of Glioblastoma Multiforme in a Well-Defined Population. Cureus. 2020 May 19;12(5):e8195.

13. B. Johannesen T. Cancer Registry of Norway: Malignant Brain Tumors in Adults. (2011). Available from: https://www.kreftregisteret.no/en/General/News/Malignant-Brain-Tumors-in-Adults/#:~:text=Around%20200%20Norwegians%20over%20the,survival%20per%20200 8%20i s%206.1%25.

14. Cancer Registry of Norway.

15. Stanley S S. Novel Treatment Strategies for Glioblastoma—A Summary. 2021 Nov 22;13(22). Available from: https://www.mdpi.com/2072-6694/13/22/5868

16. Ohgaki H. Epidemiology of Brain Tumors. In: Verma M, editor. Cancer Epidemiology [Internet]. Totowa, NJ: Humana Press; 2009 [cited 2023 Mar 15]. p. 323–42. (Walker JM, editor. Methods in Molecular Biology; vol. 472). Available from: http://link.springer.com/10.1007/978-1-60327-492-0_14

17. Tamimi AF, Juweid M. Epidemiology and Outcome of Glioblastoma. In: De Vleeschouwer S, editor. Glioblastoma [Internet]. Brisbane (AU): Codon Publications; 2017 [cited 2023 Mar 15]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK470003/

18. Engelhard HH, Villano JL, Porter KR, Stewart AK, Barua M, Barker FG, et al. Clinical presentation, histology, and treatment in 430 patients with primary tumors of the spinal cord, spinal meninges, or cauda equina: Clinical article. J Neurosurg Spine. 2010 Jul;13(1):67–77.

19. D'Alessio A, Proietti G, Sica G, Scicchitano BM. Pathological and Molecular Features of Glioblastoma and Its Peritumoral Tissue. Cancers. 2019 Apr 3;11(4):469.

20. Weller M, Van Den Bent M, Preusser M, Le Rhun E, Tonn JC, Minniti G, et al. EANO guidelines on the diagnosis and treatment of diffuse gliomas of adulthood. Nat Rev Clin Oncol. 2021 Mar;18(3):170–86.

21. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, et al. The 2021 WHO Classification of Tumors of the Central Nervous System: a summary. Neuro-Oncol. 2021 Aug 2;23(8):1231–51.

22. Vikram c P. AANS Glioblastoma Multiforme [Internet]. Available from: https://www.aans.org/en/Patients/Neurosurgical-Conditions-and-Treatments/Glioblastoma-Multiforme

23. Hansen AL, Desai SM, Cooper AN, Steinbach MA, Gosselin K, Wanebo JE. The clinical progression of patients with glioblastoma. Interdiscip Neurosurg. 2023 Jun;32:101756.

24. Organisation mondiale de la santé, Centre international de recherche sur le cancer, editors. Central nervous system tumours. 5th ed. Lyon: International agency for research on cancer; 2021. (World health organization classification of tumours).

25. Sa'adeh I, Saadh MJ. Multifocal glioblastoma multiform with "encephalitis-like presentation" : a case report. Egypt J Radiol Nucl Med. 2021 Dec;52(1):33.

26. Gaillard F. Glioblastoma, IDH-wildtype. In: Radiopaedia.org [Internet]. Radiopaedia.org; 2008 [cited 2023 Mar 25]. Available from: http://radiopaedia.org/articles/4910

27. Gliomas. John Hopkins Med [Internet]. Available from: https://www.hopkinsmedicine.org/health/conditions-and-

diseases/gliomas#:~:text=A%20neurological%20exam%3A%20This%20exam,the%20eyes%20to%20the%20brain.

28. Laino ME, Young R, Beal K, Haque S, Mazaheri Y, Corrias G, et al. Magnetic resonance spectroscopic imaging in gliomas: clinical diagnosis and radiotherapy planning. BJR Open. 2020;2(1):20190026.

29. Dumba M, Fry A, Shelton J, Booth TC, Jones B, Shuaib H, et al. Imaging in patients with glioblastoma: A national cohort study. Neuro-Oncol Pract. 2022 Nov 15;9(6):487–95.

30. Gilard V, Tebani A, Dabaj I, Laquerrière A, Fontanilles M, Derrey S, et al. Diagnosis and Management of Glioblastoma: A Comprehensive Perspective. J Pers Med. 2021 Apr 1;11(4):258.

31. Lobera A. Medscape: Glioblastoma (Multiforme) Imaging. 2022 Jun; Available from: https://emedicine.medscape.com/article/340870-overview#a1

32. Chambless LB, Kistka HM, Parker SL, Hassam-Malani L, McGirt MJ, Thompson RC. The relative value of postoperative versus preoperative Karnofsky Performance Scale scores as a predictor of survival after surgical resection of glioblastoma multiforme. J Neurooncol. 2015 Jan;121(2):359–64.

33. Davis ME. Glioblastoma: Overview of Disease and Treatment. Clin J Oncol Nurs. 2016 Oct 1;20(5 Suppl):S2-8.

34. Kuhnt D, Becker A, Ganslandt O, Bauer M, Buchfelder M, Nimsky C. Correlation of the extent of tumor volume resection and patient survival in surgery of glioblastoma multiforme with high-field intraoperative MRI guidance. Neuro-Oncol. 2011 Dec 1;13(12):1339–48.

35. Parsa A, Raizer J, editors. Current Understanding and Treatment of Gliomas. 1st ed. 2015. Cham: Springer International Publishing : Imprint: Springer; 2015. 1 p. (Cancer Treatment and Research).

36. Uihlein A, Colby MY, Layton DD, Parsons WR, Garter TL. Comparison of Surgery and Surgery Plus Irradiation in the Treatment of Supratentorial Gliomas. Acta Radiol. 1966 Jan;5(1):67–78.

37. Barani IJ, Larson DA. Radiation Therapy of Glioblastoma. In: Raizer J, Parsa A, editors. Current Understanding and Treatment of Gliomas [Internet]. Cham: Springer International Publishing; 2015 [cited 2023 Mar 29]. p. 49–73. (Cancer Treatment and Research; vol. 163). Available from: https://link.springer.com/10.1007/978-3-319-12048-5_4

38. Chao KSC, Perez CA, Brady LW, Marinetti T. Management of adult central nervous system tumors. Radiation oncology: Management decisions. 3rd ed. 146–191 p.

39. Niyazi M, Andratschke N, Bendszus M, Chalmers AJ, Erridge SC, Galldiks N, et al. ESTRO-EANO guideline on target delineation and radiotherapy details for glioblastoma. Radiother Oncol. 2023 Jul;184:109663.

40. Fernandes C, Costa A, Osório L, Lago RC, Linhares P, Carvalho B, et al. Current Standards of Care in Glioblastoma Therapy. In: De Vleeschouwer S, editor. Glioblastoma

[Internet]. Brisbane (AU): Codon Publications; 2017 [cited 2023 Mar 4]. Available from: http://www.ncbi.nlm.nih.gov/books/NBK469987/

41. Fisher JP, Adamson DC. Current FDA-Approved Therapies for High-Grade Malignant Gliomas. Biomedicines. 2021 Mar 22;9(3):324.

42. Perry JR, Laperriere N, O'Callaghan CJ, Brandes AA, Menten J, Phillips C, et al. Short-Course Radiation plus Temozolomide in Elderly Patients with Glioblastoma. N Engl J Med. 2017 Mar 16;376(11):1027–37.

43. Stupp R, Taillibert S, Kanner AA, Kesari S, Steinberg DM, Toms SA, et al. Maintenance Therapy With Tumor-Treating Fields Plus Temozolomide vs Temozolomide Alone for Glioblastoma: A Randomized Clinical Trial. JAMA. 2015 Dec 15;314(23):2535.

44. Bloch O, Han SJ, Cha S, Sun MZ, Aghi MK, McDermott MW, et al. Impact of extent of resection for recurrent glioblastoma on overall survival: Clinical article. J Neurosurg. 2012 Dec;117(6):1032–8.

45. Jeffrey N B. Glioblastoma Treatment & Management. Medscape [Internet]. 2023 Mar; Available from: https://emedicine.medscape.com/article/283252-treatment

46. Li S, Guo F, Wang X, Zeng J, Hong J. Timing of radiotherapy in glioblastoma based on IMRT and STUPP chemo-radiation: may be no need to rush. Clin Transl Oncol. 2022 Jun 26;24(11):2146–54.

47. Valduvieco I, Verger E, Bruna J, Caral L, Pujol T, Ribalta T, et al. Impact of radiotherapy delay on survival in glioblastoma. Clin Transl Oncol. 2013 Apr;15(4):278–82.

48. Do V, Gebski V, Barton MB. The effect of waiting for radiotherapy for grade III/IV gliomas. Radiother Oncol. 2000 Nov;57(2):131–6.

49. Han SJ, Rutledge WC, Molinaro AM, Chang SM, Clarke JL, Prados MD, et al. The Effect of Timing of Concurrent Chemoradiation in Patients With Newly Diagnosed Glioblastoma. Neurosurgery. 2015 Aug;77(2):248–53.

50. Zur I, Tzuk-Shina T, Guriel M, Eran A, Kaidar-Person O. Survival impact of the time gap between surgery and chemo-radiotherapy in Glioblastoma patients. Sci Rep. 2020 Jun 12;10(1):9595.

51. Blumenthal DT, Won M, Mehta MP, Gilbert MR, Brown PD, Bokstein F, et al. Short delay in initiation of radiotherapy for patients with glioblastoma-effect of concurrent chemotherapy: a secondary analysis from the NRG Oncology/Radiation Therapy Oncology Group database. Neuro-Oncol. 2018 Jun 18;20(7):966–74.

52. Blumenthal DT, Won M, Mehta MP, Curran WJ, Souhami L, Michalski JM, et al. Short Delay in Initiation of Radiotherapy May Not Affect Outcome of Patients With Glioblastoma: A Secondary Analysis From the Radiation Therapy Oncology Group Database. J Clin Oncol. 2009 Feb 10;27(5):733–9.

53. Helsenorge: Cancer patient pathways. Available from: https://www.helsenorge.no/en/sykdom/kreft/cancer-patient-pathways/

54. Helsedirektoratet: Diffuse høygradige gliomer hos voksne - handlingsprogram. Available from: https://www.helsedirektoratet.no/retningslinjer/diffuse-hoygradige-gliomer-hos-voksne-handlingsprogram/innledning

55. Helsedirektoratet: Pakkeforløp for Hjernekreft. Available from: https://www.helsedirektoratet.no/nasjonale-forlop/hjernekreft/introduksjon-til-pakkeforlop-for-hjernekreft

56. Nilssen Y, Brustugun OT, Eriksen MT, Haug ES, Naume B, Møller B. Patient and tumour characteristics associated with inclusion in Cancer patient pathways in Norway in 2015–2016. BMC Cancer. 2020 Dec;20(1):488.

57. Espetvedt S. Cancer Clinical Pathways in Norway [Internet]. Available from: https://cancercentrum.se/globalassets/vara-uppdrag/forskning/nordic-collaboration/2019/1.nostatus-report-on-cancer-patient-pathways-cpp-in-the-nordic-countries.pdf

58. Solbjør M, Sand K, Ervik B, Melby L. Patient experiences of waiting times in standardised cancer patient pathways in Norway - a qualitative interview study. BMC Health Serv Res. 2021 Jul 5;21(1):651.

59. Risikobildet av norsk kreftbehandling [Internet]. Available from: https://www.helsetilsynet.no/globalassets/opplastinger/Publikasjoner/rapporter2010/helsetilsynetrapport4_2010.pdf/

60. Utvalgt arbeidssted:Oslo universitetssykehus HF. Tidsskr Den Nor Legeforening. 2014;134(18):1786–1786.

61. Forside. Oslo Univ.

62. Louis DN, Ohgaki H, Wiestler OD, Cavenee WK, Burger PC, Jouvet A, et al. The 2007 WHO Classification of Tumours of the Central Nervous System. Acta Neuropathol (Berl). 2007 Aug;114(2):97–109.

63. Kishore J, Goel M, Khanna P. Understanding survival analysis: Kaplan-Meier estimate. Int J Ayurveda Res. 2010;1(4):274.

64. Cox Proportional-hazards Model. STHDA [Internet]. Available from: http://www.sthda.com/english/wiki/cox-proportional-hazards-model

65. Dahiru T. P - value, a true test of statistical significance? A cautionary note. Ann Ib Postgrad Med. 2008 Jun;6(1):21–6.

66. Villabona R. How surgery, radiotherapy and chemotherapy each contribute to the outcome of treatment for adult patients with Glioblastoma? Medicas UIS [Internet]. Available from: http://www.scielo.org.co/scielo.php?script=sci_arttext&pid=S0121-03192012000300005

67. Facciorusso A, Ferrusquía J, Muscatiello N. Lead time bias in estimating survival outcomes. Gut. 2016 Mar;65(3):538–9.

68. Jensen H, Vedsted P. Exploration of the possible effect on survival of lead-time associated with implementation of cancer patient pathways among symptomatic first-time cancer patients in Denmark. Cancer Epidemiol. 2017 Aug;49:195–201.

69. Magrowski Ł, Nowicka E, Masri O, Tukiendorf A, Tarnawski R, Miszczyk M. The survival impact of significant delays between surgery and radiochemotherapy in glioblastoma patients: A retrospective analysis from a large tertiary center. J Clin Neurosci. 2021 Aug;90:39–47.

70. Olsen F, Jacobsen BK, Heuch I, Tveit KM, Balteskard L. Equitable access to cancer patient pathways in Norway – a national registry-based study. BMC Health Serv Res. 2021 Dec;21(1):1272.

10 Appendices

10.1 REK approval

REK
REGIONALE KOMITEER FOR MEDISINSK OG HELSEFAGLIG FORSKNINGSETIKK

Region:	Saksbehandler:	E-post:	Telefon:	Vår dato:	Vår referanse:
REK sør-øst C	Johanne Holmen	rek-sorost@medisin.uio.no	22855260	13.04.2023	592740

Petter Brandal
Prosjektsøknad: Effekt av implementering av pakkeforløp for høygradige gliomer
Søknadsnummer: 592740 **Forskningsansvarlig institusjon**: Oslo universitetssykehus HF

Prosjektsøknad: Endring godkjennes med vilkår

Søkers beskrivelse

Glioblastom er en aggressiv form for hjernekreft. Median overlevelse for alle pasienter med glioblastom uselektert er ca. ett år. For undergruppen av pasienter som er under 70 år, har god allmenntilstand og som får standard behandling er median overlevelse på knappe 15 måneder. Standard primærbehandling er en kombinasjon av kirurgi, strålebehandling og cellegift. Prosjektets formål er å undersøke effekten av implementering av pakkeforløp for høygradige gliomer i Helse Sør-Øst.

Vi viser til søknad om forhåndsgodkjenning av ovennevnte forskningsprosjekt. Søknaden ble behandlet av Regional komité for medisinsk og helsefaglig forskningsetikk (REK sørøst C) i møtet 16.03.2023. Vurderingen er gjort med hjemmel i helseforskningsloven (hfl.) § 10.

REKs vurdering

Dette er et nytt vedtak som erstatter tidligere utsendt godkjenningsvedtak, datert 30.03.2023 som inneholdt en feil innlimt tekst på slutten som skapte uklarhet.
Det ble i 2015 implementert et pakkeforløp ved behandling av glioblastom. For å vurdere effekten av pakkeforløpet, både tids- og kostnadseffektiv, er det valgt å retrospektivt identifisere pasienter og innhente opplysninger fra elektronisk pasientjournal. Det søkes om dispensasjon fra taushetsplikt og samtykke for avdøde pasienter. Pasienter i live kan identifiseres og bes om aktivt samtykke, men det er ønskelig med fritak for samtykke for samtlige deltakere for å unngå skjevhet i gruppene.
Komiteen vurderer prosjektet som viktig for å evaluere effekten av pakkeforløpet. Studien skal måle effekt på overlevelse og faller derfor innenfor helseforskningslovens virkeområde, som omfatter prosjekter med det formål å skaffe ny kunnskap om helse og sykdom, selv om studien har klare likhetstrekk med kvalitetssikring.
Komiteen oppfatter at søker primært ber om fritak fra samtykke-kravet/ dispensasjon for taushetsplikt for alle deltakerne. Komiteen har vurdert dette premisset og er enig i søkers begrunnelse. Dette fordi de fleste av de gjenlevende som kunne avgitt samtykke vil være i en relativt nylig diagnostisert gruppe. Hvis denne gruppen blir lavt representert, vil det bli en skjevhet mellom gruppene før og etter implementering av pakkeforløp. Dette kan føre til en uriktig fremstilling av resultatene.

Vurderingen av om det kan gis dispensasjon fra taushetsplikt for tilgjengeliggjøring, sammenstilling og bruk av helseopplysninger ved gjennomføringen av prosjektet er gjort med hjemmel helsepersonelloven § 29, første ledd, jf. forskrift av 27. mai 2021 nr. 1725 om overføring av myndighet til den regionale komiteen for medisinsk og helsefaglig forskningsetikk.
For dispensasjon fra taushetsplikten vurderes følgende vilkår:

1. Det er vanskelig eller umulig å innhente samtykke,
2. opplysningene brukes til et uttrykkelig angitt formål som er innenfor registerets formål,3. det er godtgjort at behandlingen vil ha rettslig grunnlag etter personvernforordningen artikkel 6 og 9,
4. det er gjort rede for tekniske og organisatoriske tiltak som skal settes i verk for å ivareta informasjonssikkerheten,
5. det er begrunnet at omfanget og detaljnivået på opplysningene som relevante og nødvendige for å oppnå formålet med studien,
6. behandlingen av opplysningene er av vesentlig interesse for samfunnet, og
7. tilgjengeliggjøringen av opplysningene er ubetenkelig ut fra etiske, medisinske og helsefaglige hensyn.

Komiteen vurderer at vilkårene for å innvilge dispensasjon fra taushetsplikten er oppfylt og godkjenner tilgjengeliggjøring av helseopplysninger for å gjennomføre prosjektet som beskrevet.
Videre gis det fritak fra krav om samtykke for både levende og døde deltakere da det vurderes som viktig for gjennomføringen av prosjektet at de ulike pasientgruppene blir korrekt representert.
Komiteen setter som vilkår for godkjenningen at PVO går igjennom prosjektets protokoll og sikrer at personvern, databehandling og datasikkerhet er tilstrekkelig ivaretatt og i henhold til personvernregelverket.

Vedtak

Med hjemmel i helseforskningsloven § 10 godkjennes prosjektet med vilkår.
I tillegg til vilkår som fremgår av dette vedtaket, er godkjenningen gitt under forutsetning av at prosjektet gjennomføres slik det er beskrevet i søknad og protokoll, og de bestemmelser som følger av helseforskningsloven med forskrifter.
Med hjemmel i helsepersonelloven § 29, første ledd, godkjenner komiteen tilgjengeliggjøring, sammenstilling og bruk av helseopplysninger i gjennomføringen av forskningsprosjektet, uten hinder av taushetsplikt etter helsepersonelloven § 21.
Komiteens avgjørelse var enstemmig.
Prosjektet er godkjent til 31.03.2025
Etter prosjektslutt skal opplysningene oppbevares i 5 år for dokumentasjonshensyn. Enhver tilgang til prosjektdataene skal da være knyttet til behovet for etterkontroll.

Opplysningene er i denne perioden ikke tilgjengelig for videre forskning. Prosjektleder og forskningsansvarlig institusjon er ansvarlig for at opplysningene oppbevares indirekte personidentifiserbart i denne perioden, dvs. atskilt i en nøkkel- og en datafil. Etter endt periode for oppbevaring for dokumentasjonshensyn skal opplysningene slettes eller bearbeides til anonyme data. Vi gjør oppmerksom på at anonymisering er mer omfattende

enn å slette koblingsnøkkelen. For mer informasjon om anonymisering, se Datatilsynets veileder Anonymisering av Personopplysninger (2015).

Vi gjør samtidig oppmerksom på at det også må foreligge et behandlingsgrunnlag etter personvernforordningen. Dette må forankres i egen institusjon.

Sluttmelding

Prosjektleder skal sende sluttmelding til REK på eget skjema via REK-portalen senest 6 måneder etter sluttdato 31.03.2025, jf. helseforskningsloven § 12. Dersom prosjektet ikke starter opp eller gjennomføres meldes dette også via skjemaet for sluttmelding.

Søknad om endring

Dersom man ønsker å foreta vesentlige endringer i formål, metode, tidsløp eller organisering må prosjektleder sende søknad om endring via portalen på eget skjema til REK, jf. helseforskningsloven § 11.

Klageadgang

Du kan klage på REKs vedtak, jf. forvaltningsloven § 28 flg. Klagen sendes på eget skjema via REK portalen. Klagefristen er tre uker fra du mottar dette brevet. Dersom REK opprettholder vedtaket, sender REK klagen videre til Den nasjonale forskningsetiske komité for medisin og helsefag (NEM) for endelig vurdering, jf. forskningsetikkloven § 10 og helseforskningsloven § 10.

Med vennlig hilsen

Erik Fosse Prof.,
PhD.
Leder REK sør-øst C

Johanne Holmen Seniorrådgiver
Kopi til:

Oslo universitetssykehus HF

10.2 PVO from OUH

Oslo universitetssykehus HF

Postadresse:
Postboks 4950
Nydalen 0424 Oslo

Sentralbord:
02770

Org.nr:
NO 993 467 049
MVA

w
w
w.oslo-universitetssykehus.no

UTTALELSE HELSEFORSKNINGSPROSJEKT

-

Til: Petter Brandal

Fra: Stab Forskning, innovasjon og utvikling (FIU)
Forskningsrådgivning og personvern

Saksbehandler: Elsa Roland

Dato: 24.04.2023

Sak: 23/08097

«Effekt av implementering av pakkeforløp for høygradige gliomer»

Prosjektleder: Petter Brandal

Formål: Prosjektets formål er å undersøke effekten av implementering av pakkeforløp for høygradige gliomer i Helse Sør-Øst.

Oslo universitetssykehus er data- og forskningsansvarlig virksomhet.

Studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nr. 592740), med hjemmel i helseforskningsloven § 10.

Studien har lovlig grunnlag for behandling av person- og helseopplysninger i GDPR art. 6 nr. 1 e) og art. 9 nr. 2 j). Det er gitt vedtak om dispensasjon fra REK etter helsepersonelloven § 29 og uten hinder av taushetsplikt etter helsepersonelloven § 21.

Den dataansvarlige skal sikre at personvernombudet på riktig måte og i rett tid involveres i alle spørsmål som gjelder vern av personopplysninger, jf. artikkel 38. Artikkel 30 pålegger OUS å føre oversikt over hvilke behandlinger av personopplysninger virksomheten har. Behandling av personopplysninger meldes derfor til sykehusets personvernombud.

Databehandlingen tilfredsstiller forutsetningene for melding etter forordning (EU) nr. 2016/679 (generell personvernforordning) artikkel 30.

Data i behandles samsvar med sykehusets retningslinjer, jf. foreliggende tillatelser. Prosjektleder er ansvarlig for at gjennomføringen av prosjektet er i tråd med forskningsinstruksen (http://ehandbok.ous-hf.no/document/60) og forskningsprosedyren (http://ehandbok.ous-hf.no/document/61).

1. Databehandlingen skjer i samsvar med og innenfor det formål som er oppgitt i meldeskjema.
2. Data lagres som oppgitt i meldeskjema og i samsvar med sykehusets retningslinjer.
3. Oppslag i journal med formål å identifisere potensielle deltagere til studien gjøres av ansatte ved sykehuset som har selvstendig lovlig grunnlag for oppslaget. Se eHåndbok - Grunnlag for oppslag i journal (ous-hf.no)
4. Vesentlige endringer i prosjektet skal meldes iht. Retningslinje om endringsmelding i medisinsk og helsefaglig forskning (http://ehandbok.ous-hf.no/document/13300)
5. Den dataansvarlige har fylt ut egenerklæring for DPIA. Det anses ikke påkrevd full DPIA jf. generell personvernforordning artikkel 35.

Ytterligere informasjon og veiledning finnes på nettsidene til regional forskningsstøtte (https://forskerstotte.no/) eller rett en henvendelse til: godkjenning@ous-hf.no

Med hilsen

Elsa Roland
Spesialrådgiver

Forskningsrådgivning og personvern
Oslo Universitetssykehus HF

10.3 PVO from Innlandet

Sykehuset Innlandet HF

Hanne Blakstad
hanbla@ous-hf.no
Radiumhospitalet, Oslo universitetssykehus
Petter Brandal

Personvernombudet i Sykehuset Innlandet HF
personvernombud@sykehuset-innlandet.no

Vår ref.: 27193591 Brumunddal, 01.11.2023

PERSONVERNOMBUDETS VURDERING I SAK 27193591 EFFEKT AV IMPLEMENTERING AV PAKKEFORLØP FOR HØYGRADIGE GLIOMER

Viser til innsendt melding til personvernombudet, og tilhørende saksdokumentasjon. Med hjemmel i forordning (EU) nr. 2016/679 (generell personvernforordning) artikkel 37, er det oppnevnt personvernombud ved Sykehuset Innlandet (SI). Den dataansvarlige skal sikre at personvernombudet på riktig måte og i rett tid involveres i alle spørsmål som gjelder vern av personopplysninger, jf. artikkel 38. Artikkel 30 pålegger SI å føre oversikt over hvilke behandlinger av personopplysninger virksomheten har. Behandling av personopplysninger er derfor meldt til personvernombudet.

Sammendrag av personvernombudets vurdering
Saken **tilrådes,** forutsatt at vilkårene nederst i dokumentet er oppfylt.

Om saken – prosjektansvarliges beskrivelse

Formål
Glioblastom er en aggressiv form for hjernekreft. Median overlevelse for alle pasienter med glioblastom uselektert er ca. ett år. For undergruppen av pasienter som er under 70 år, har god allmenntilstand og som får standard behandling er median overlevelse på knappe 15 måneder. Standard primærbehandling er en kombinasjon av kirurgi, strålebehandling og cellegift. Prosjektets formål er å undersøke effekten av implementering av pakkeforløp for høygradige gliomer i Helse Sør-Øst.

Hvem er de registrerte?
Pasienter

Kilde
Brain power database, en tumor cerebri kvalitetsdatabase ved Oslo universitetssykehus
medinsight

Annet
K:/ sensitiv mappe OUS server

Annen lagring av koblingsnøkler

Medinsight/Brain power

Datoer
Oppstart
8/5/2023

Avslutning
31/3/2025

Personvernombudets vurdering
Den innmeldte saken er et Helseforskningsprosjekt, forskningsansvarlig og dataansvarlig institusjon er OUS. Prosjektets formål er å undersøke effekten av implementering av pakkeforløp for høygradige gliomer i Helse Sør-Øst.

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Studien er godkjent av Regional komité for medisinsk og helsefaglig forskningsetikk (REK nr. 592740), med hjemmel i helseforskningsloven § 10.

Behandlingsgrunnlag
Behandlingsgrunnlaget er GDPR artikkel 6.1.e allmennhetens interesse og nummer 6.3, samt artikkel 9.2.j arkiv, forskning og statistikk.

Supplerende lovgrunnlag er personopplysningsloven §§8 og 9. Det vises for øvrig til etisk vurdering og forhåndsgodkjenning av REK. Det er gitt vedtak om dispensasjon fra REK etter helsepersonelloven § 29 og uten hinder av taushetsplikt etter helsepersonelloven § 21.

Behandlingen av opplysninger **tilrådes.**

Vilkår:

- Behandlingen av personopplysninger gjennomføres som beskrevet i melding, øvrig dokumentasjon, aktuelle godkjenninger og behandlingsgrunnlag
- Ved vesentlige endringer sendes det endringsmelding til personvernombudet.
- Behandlingen av personopplysninger er i henhold til gjeldende prinsipper og krav til informasjonssikkerhet hos dataansvarlig som er OUS
- Kryssliste som kobler avidentifiserte data med personopplysninger, lagres i samsvar med gjeldende retningslinjer
- Oppslag i journal:
    - Gjøres av ansatt som har selvstendig lovlig grunnlag for oppslaget (Prosedyre 44555)
    - Påse at riktig tilgang brukes. Forskere skal bruke forskertilgang (Prosedyre 46207)
    - Eksterne forskere må ha en avtale med aktuelt fagmiljø i SI for bistand. Ved spørsmål kontakt forskningsavdelingen (Se ellers prosedyre 49419)
- Publisering forutsettes å skje uten at deltagerne kan gjenkjennes, hverken direkte eller indirekte

Som en del av virksomhetsstyringen i SI, kan det bli gjennomført kontroll av etterlevelsen av vilkårene over.

Dette dokumentet er lagret i Public 360, og er ikke unntatt offentlighet. Saken er registrert i protokoll over behandlingsaktiviteter i SI, i henhold til personvernforordningens artikkel 30.

Eventuelle spørsmål eller senere henvendelser om saken, må merkes med saksnummeret øverst i dokumentet.

Vennlig hilsen

Birgit Hovde
Konstituert personvernombud i SI

10.4 PVO from Sørlandet

SØRLANDET SYKEHUS

Petter Brandal, OUS

Vår dato	Vår referanse
18.juni 2023	23/05302
Deres dato	Deres referanse

Godkjenning av forskningsprosjekt

Det vises til søknad om godkjenning av forskningsprosjekt

Effekt av implementering av pakkeforløp for høygradige gliomer

med Oslo Universitetssykehus som forskningsansvarlig institusjon.

Det søkes om journaltilgang til SSHFs pasienter som er operert for høygradige gliomer.

Prosjektet faller innunder helseforskningsloven og er forhåndsgodkjent av REK (592740). REK har gitt dispensasjon fra taushetsplikten for oppslag i pasientrjounalen.

Prosjektet har vært vurdert av SSHFs personvernombud som har tilrådd prosjektet

Prosjektet har vært vurdert av SSHFs informasjonssikkerhetsleder som har tilrådd prosjektet.

For journaltilgang ved SSHF må det opprettes et 0% stillingsforhold ved forskningsseksjonen, og det må gis DIPS tilgang samt at nødvendige dokumenter (taushetserklæring, sikkerhetsinstruks) må signeres. Ta kontakt med tonje.sti@sshf.no for hjelp med det praktiske.

Prosjektet er godkjent.

Med vennlig hilsen

Øyvind Holme
Forskningssjef
Sørlandet sykehus HF

10.5 Data and Materials

Table 8: Table of 16 risk factors by NBHS 2010 report

Hazards	Examples of Hazards	Addressed by 2013
Diagnosis and primary treatment		
1. Diagnostic delay	Several examples of more than 3 months' delay from referral to start of cancer treatment	Yes
2. Radiology	Insufficient radiological service (due to persistent bottlenecks)	Yes
3. Pathology	Wrong pathological diagnosis or limitations in diagnostic panel (tissue markers)	Yes
4. Surgery	Failure in surgical treatment (performance of procedures)	Yes
5. Volume and quality	Overly low patient volumes in some trusts (< 5–10 patients a year)	Yes
Interactions		
6. Information exchange	Failure in information exchange/coordination between actors in the care process There is no main national information portal which is complete and regularly updated (recommendations, clinical guidelines).	No
7. Referral	Referrals are lost or delayed in all parts of the treatment chain.	Yes
8. Communication	Failure in patient communication and lack of involvement of patients and their relatives	Yes
9. Overtreatment	The limits of treatment are stretched in advanced cancer cases. Difficult talks about stopping treatment are left to another actor in the care chain.	Yes
10. Discontinuity	Failures of continuity in the treatment chain, particularly too many oncologists involved with the same patient over a short time span	Yes
11. Palliation	Failure in palliative care, particularly for patients in terminal stages in the community health care system	Yes
12. Competence	Failure in transferring competence between actors in hospitals and community health care. Limited recruiting and education of oncology health personnel	Yes
13. Working environment	Burnout of health personnel and unsatisfactory working environment reduces the quality/quantity of services delivered.	No
Complications		
14. Complications	Lack of any national overview and surveillance of serious complications	No
15. Infections	Failure in infection prevention and treatment of serious infections	No
16. Radiotherapy	Long-term complications after radiotherapy are underdiagnosed or detected too late.	No

This table is from NBHS of 2010 report. In this table they mentioned 16 risk factors for bad outcomes of cancer in Norway.

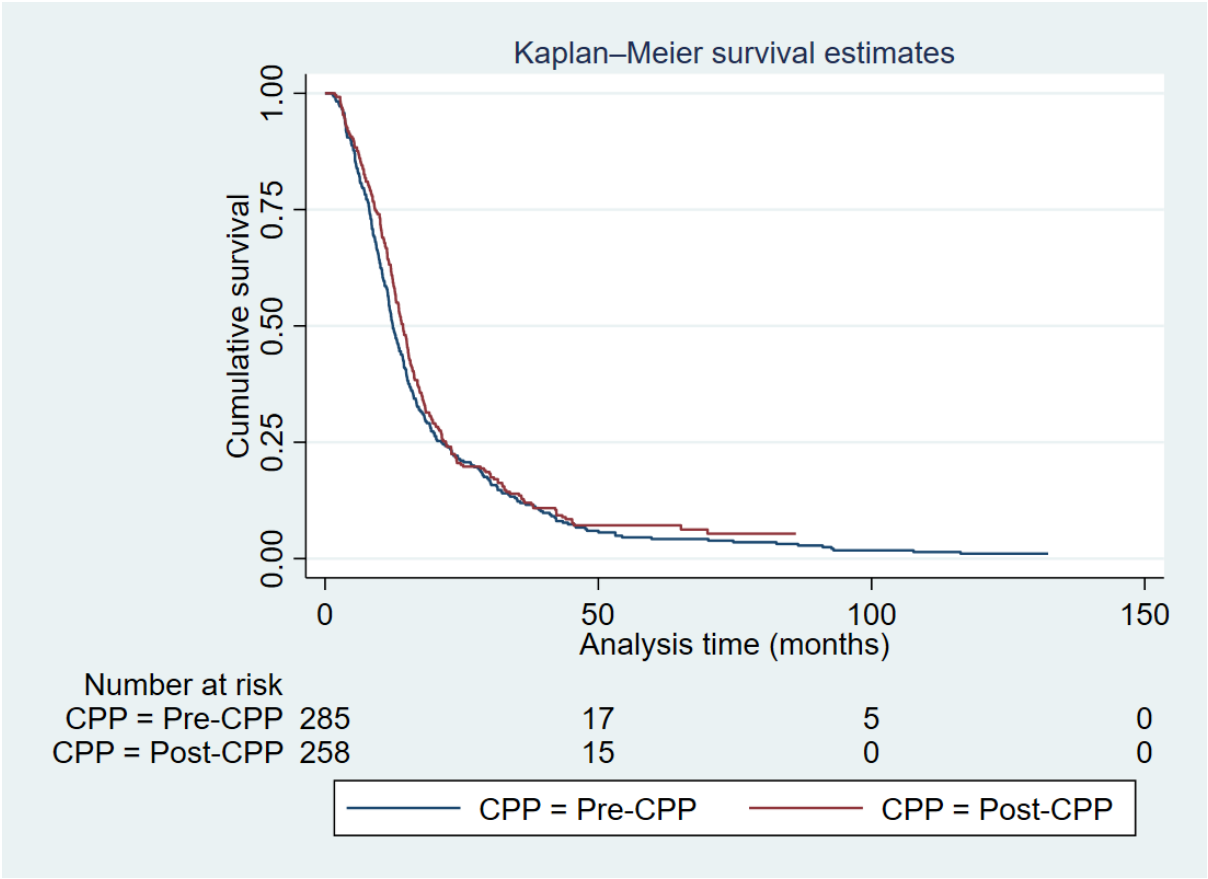

Figure 13: Kaplan-Meier survival curve for GBM by timing of RT (≤4 weeks) Pre and Post-CPP (P >0.05)

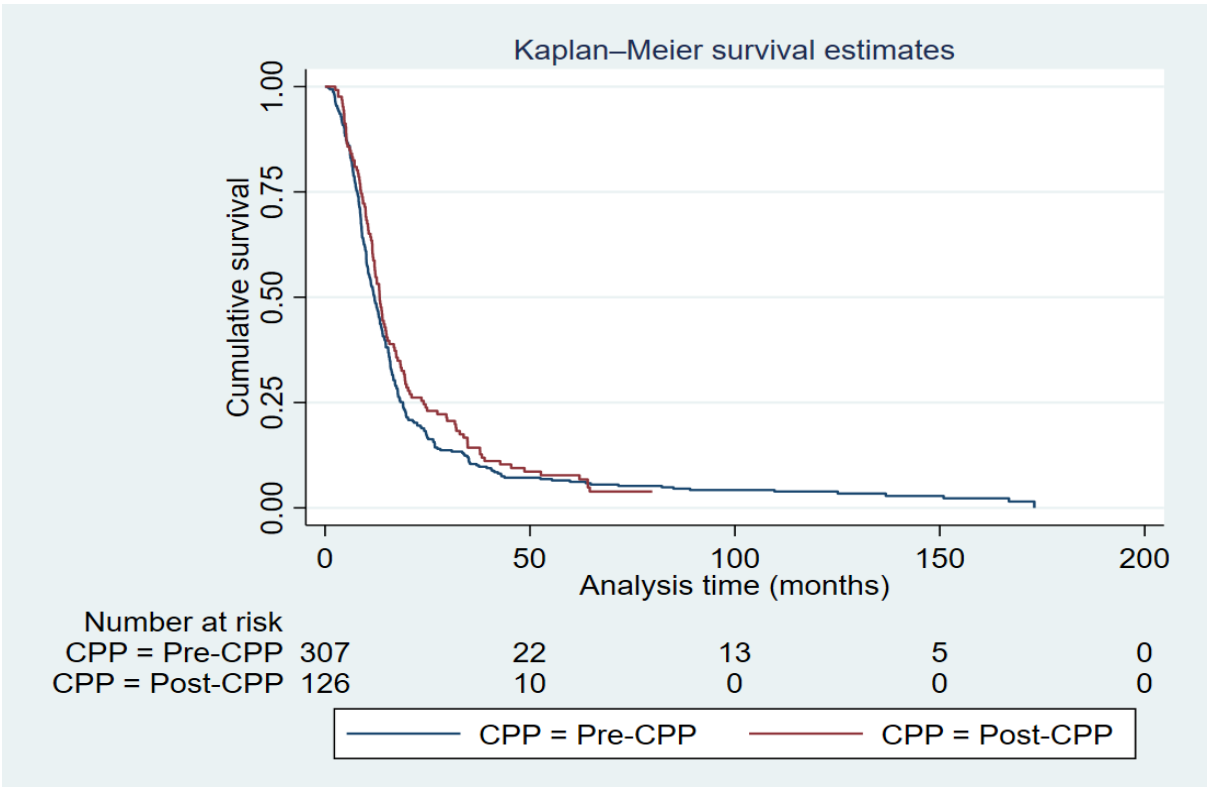

Figure 14: Kaplan-Meier survival curve for GBM by timing of RT (4.1-6 weeks) Pre and Post-CPP (P >0.05)

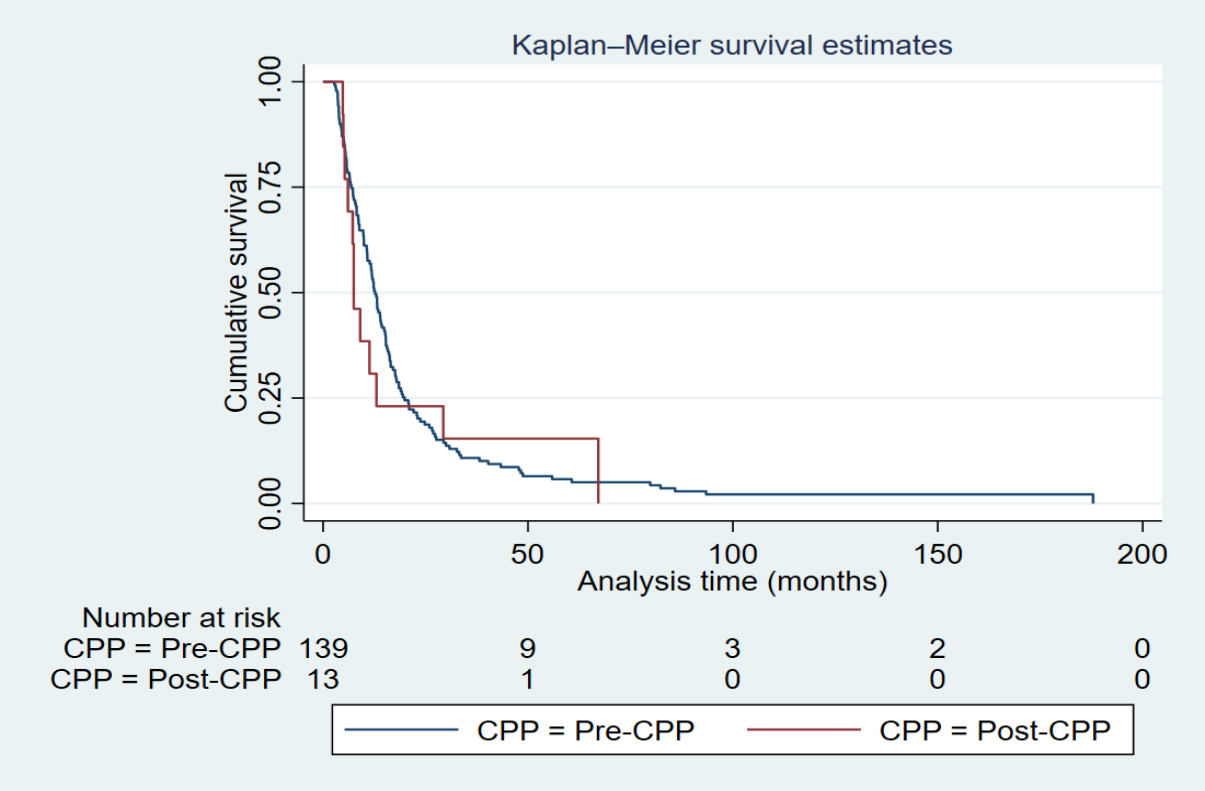

Figure 15: Kaplan-Meier survival curve for GBM by timing of RT (>6 weeks) Pre and Post-CPP (P >0.05)

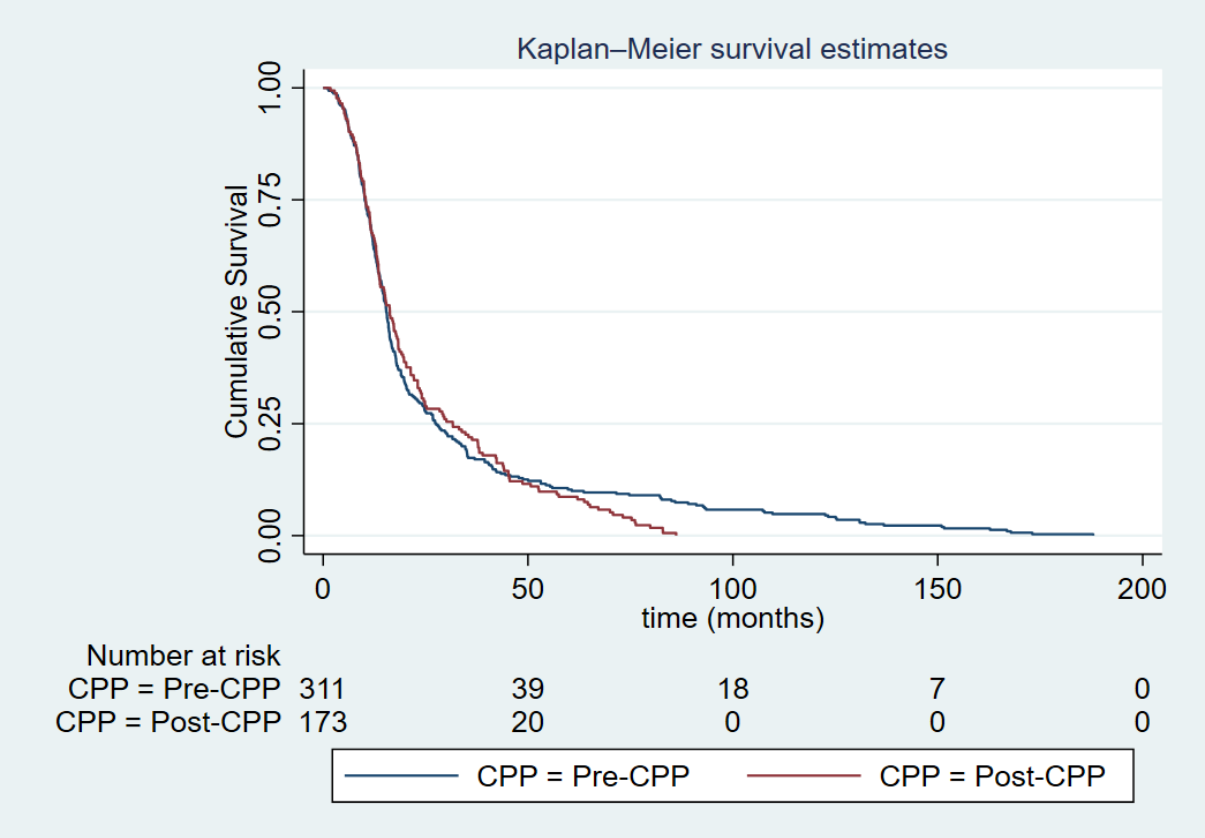

Figure 16: Kaplan-Meier survival curve for GBM by age group (<60 years) Pre and Post-CPP (P >0.05)

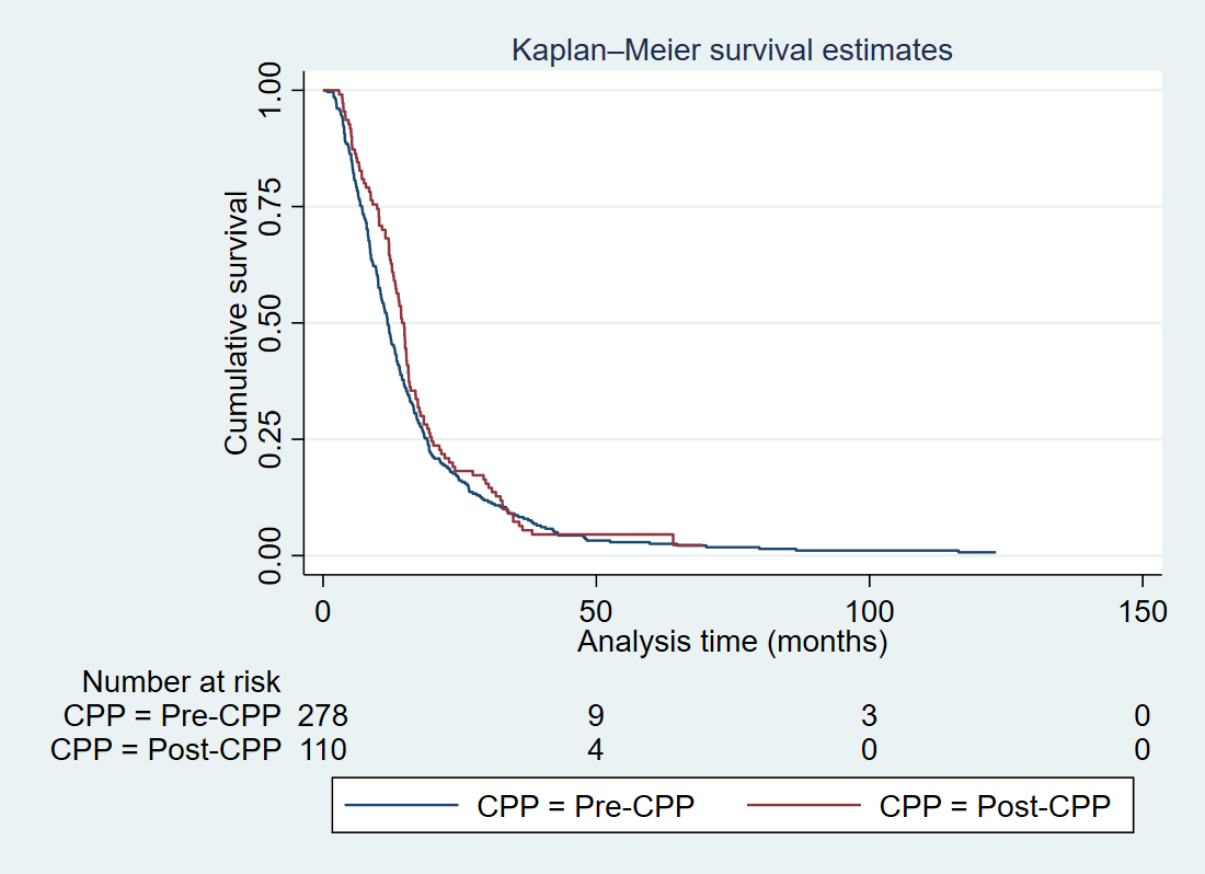

Figure 17: Kaplan-Meier survival curve for GBM by age group (60-69 years) Pre and Post-CPP (P >0.05)

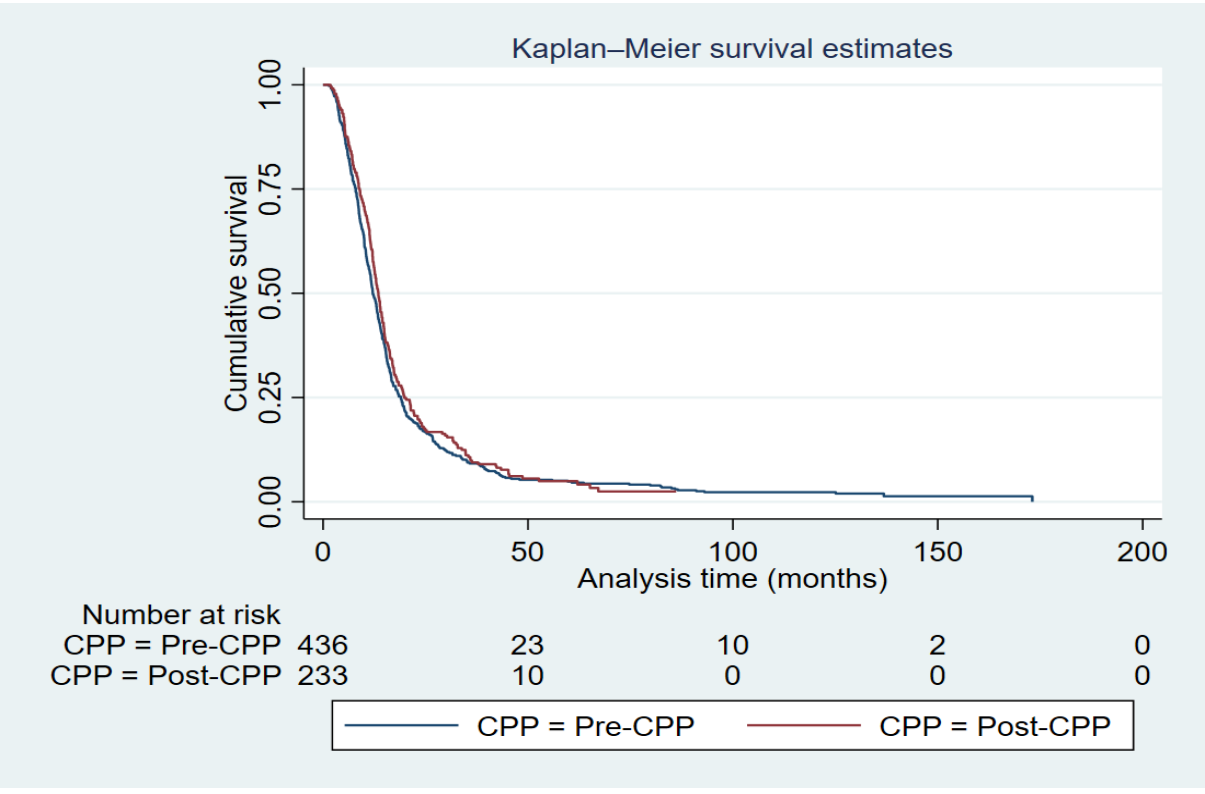

Figure 18: Kaplan-Meier survival curve for GBM by gender (Male) Pre and Post-CPP (P >0.05)

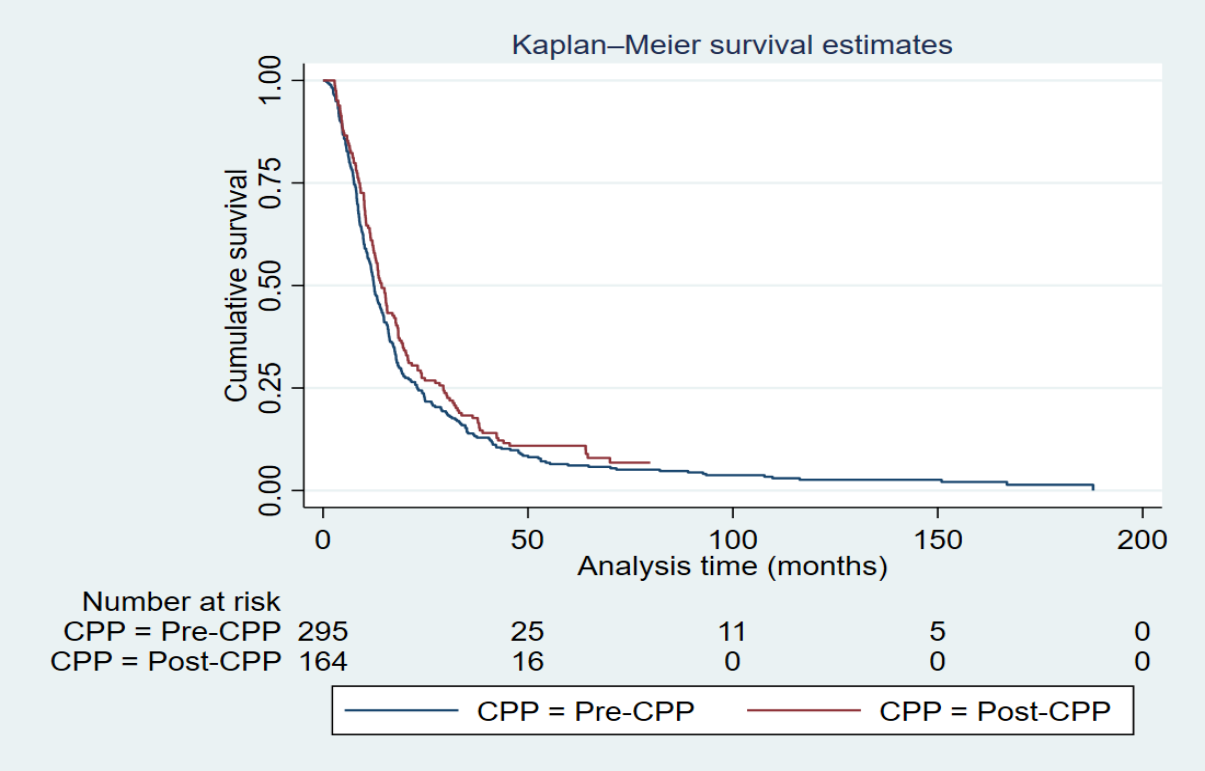

Figure 19: Kaplan-Meier survival curve for GBM by gender (Female) Pre and Post-CPP (P >0.05)

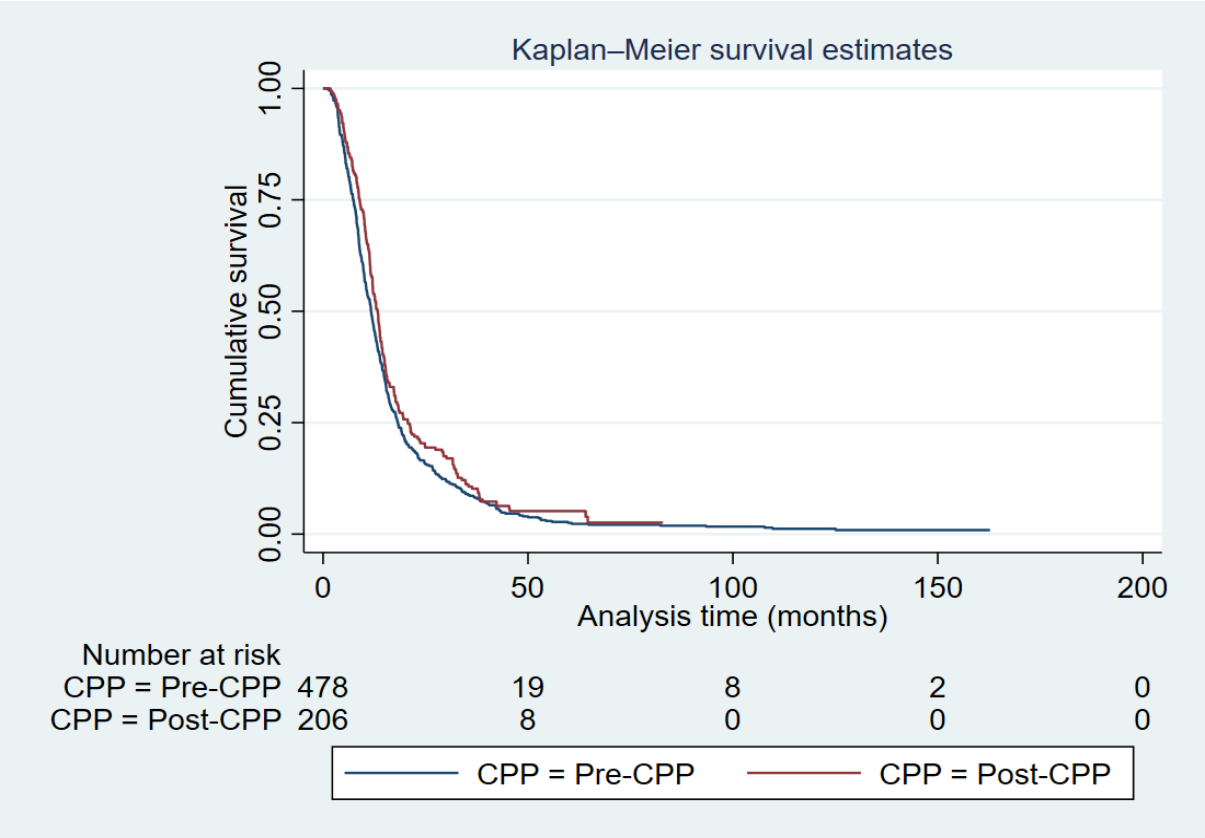

Figure 20: Kaplan-Meier survival curve for GBM by surgery (STR) Pre and Post-CPP (P >0.05)

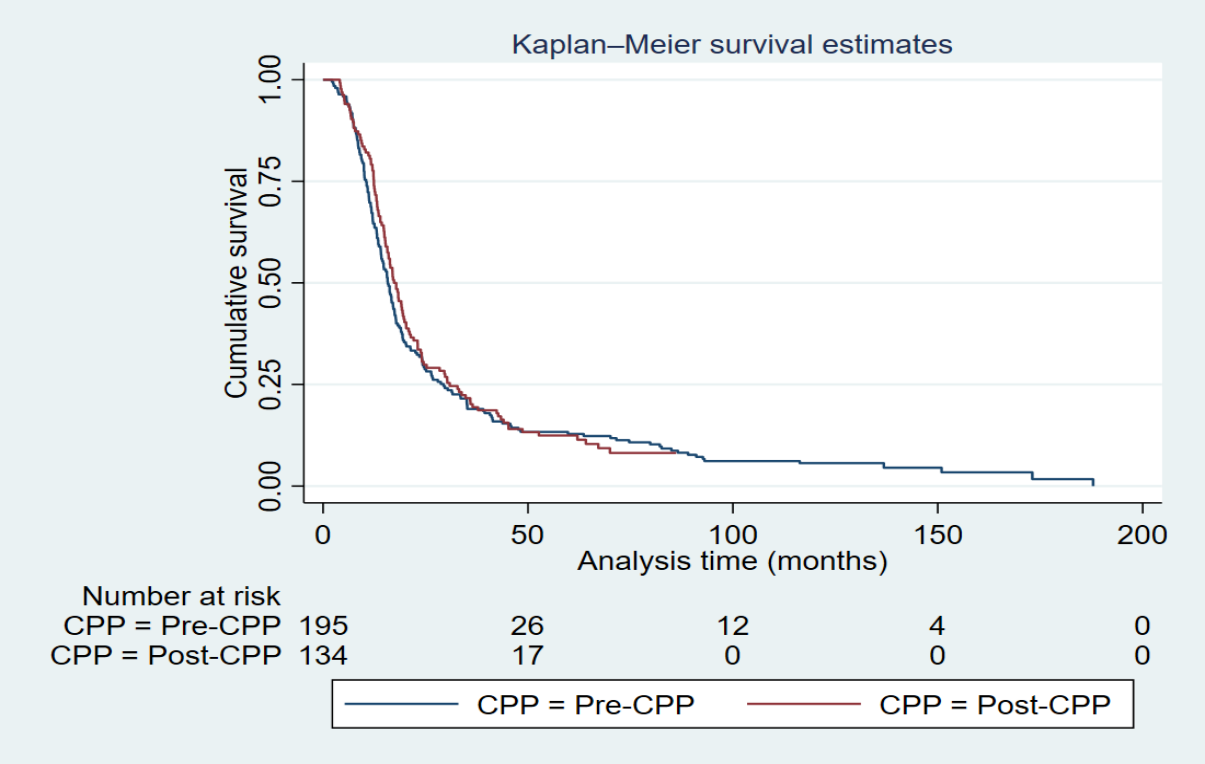

Figure 21: Kaplan-Meier survival curve for GBM by surgery (GTR) Pre and Post-CPP (P >0.05)

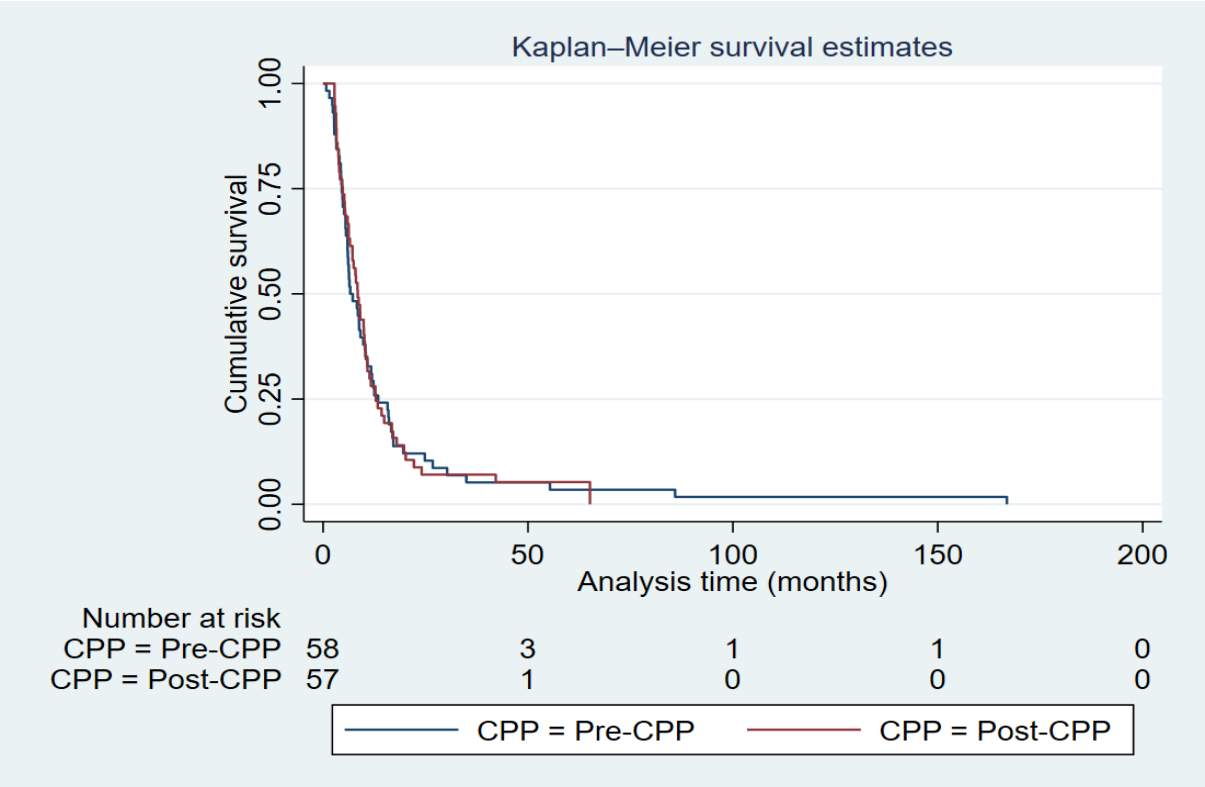

Figure 22: Kaplan-Meier survival curve for GBM by surgery (Biopsy) Pre and Post-CPP (P >0.05)