Whole Brain Radiotherapy among Lung Cancer Patients

Lung cancer is the most common cancer causing brain metastases at the time of diagnosis and brain metastases can be found in up to 50% of patients with lung cancer. Brain metastases among lung cancer patients have, in general, been associated with serious symptoms and a short survival. However, local treatments of brain metastases have been developed over time in terms of refined neuroimaging, surgery, and radiotherapy. This allows patients to receive improved treatment with prolonged benefits and fewer side effects. In addition, there have been advances in systemic oncological therapies for lung cancer patients in recent years, and systemic treatment, including chemotherapy, targeted therapy, and immunotherapy, may prevent or delay brain metastases. Determining the appropriate treatment for patients with lung cancer and brain metastases, therefore, requires a clear understanding of the brain metastases, molecular characteristics, tumor histology, and the overall lung cancer prognosis.

1. Introduction

Overall survival from the date of diagnosis of brain metastases in lung cancer is short and varies from a few months up to just over one year in former studies [1]. Patients with brain metastases at the time of diagnosis have a median survival of 4–10 months [2]. The most favorable prognostic factors for lung cancer patients with brain metastases seem to be young age (under 50 years), good performance status (Karnofsky performance score between 90 and 100), absence of extracranial metastases, and a low number of brain metastases [3][4]. Moreover, patients with adenocarcinomas with positive epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) alterations show improved survival compared to those without these alterations [4][5]. Several scoring systems have been developed to prognosticate survival in patients with brain metastases and thus aid clinicians in treatment decisions regarding WBRT: Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) [6], graded prognostic assessment (GPA) [7], and diagnosis-specific GPA (Lung-molGPA score) that includes assessment of EGFR and ALK alterations in non-small cell lung cancer (NSCLC) [8][9]. These scoring systems provide useful tools for patients with good prognoses while avoiding overtreatment in patients with poor prognoses [10].

Patients with few and small size brain metastases due to lung cancer can be treated with surgery, sometimes followed by adjuvant radiotherapy, or with stereotactic radiotherapy [3][7][10]. Until recently, whole-brain radiotherapy (WBRT) was the primary treatment when aiming for symptom control for patients with poor prognosis, poor performance status, massive distribution of brain metastases, and uncontrolled spread of other distant metastases. However, the use of WBRT has decreased in recent years [3] for many reasons, including the development of other more localized treatments for brain metastases and due to a concern about late side effects due to WBRT. There are also better tools to select patients who will benefit from the WBRT and negative results from randomized trials [3][11][12][13]. Thus, it has been argued that patients with the more advanced disease, according to prognostic scores, should not be treated with WBRT [14]. Still, updated consensus guidelines are lacking [15] and treatment practices vary greatly in a European setting [16][17].

According to the Swedish national treatment guidelines, chemotherapy is the first treatment of choice for small cell lung cancer (SCLC) patients with brain metastases at diagnosis. Patients with NSCLC and solitary brain metastases should be discussed for the possibility of radical treatment with neurosurgery; otherwise, stereotactic radiotherapy (SRT) or radiosurgery with a gamma knife. Patients with multiple brain metastases from NSCLC should primarily be treated with steroids and thereafter be discussed for WBRT. Performance status and expected survival should be taken into account in treatment decisions regarding WBRT [18].

If WBRT is given to terminal patients, it affects the end-of-life period, including the patient's ability to choose health care level in this situation. Deaths in hospitals are common among cancer patients in Western countries, even though many of

them prefer their homes as the place for dying [19].

Palliative care is a specialized medical care for patients with incurable diseases and life-threatening illnesses [20]. Palliative care aims to maintain as high a quality of life (QoL) as possible and to relieve symptoms. The goal is not necessarily to prolong life neither to hasten death. As maintained, QoL is the goal, but the side effects of medical treatments and interventions should not outweigh the possible beneficial effects, and the focus should always remain on symptom relief. This must be considered when making treatment decisions regarding WBRT.

Region Stockholm in Sweden had a population of 2,377,081 in 2019 [21]. The health care system in Sweden is funded with taxes and Karolinska University hospital is a tertiary healthcare center in the region providing for medical oncology, neurosurgery, and radiotherapy. The region has an expanded network of advanced palliative home care units for cancer patients as well as several specialized palliative wards.

The lung cancer incidence in Sweden has increased by 30% in the last 15 years [18], although Sweden has a very low prevalence of smokers [22]. In 2020, 4325 patients were diagnosed with lung cancer in Sweden [23][24], approximately 1000 of these new cases were from the Stockholm region [25]. In Sweden, the expected relative 5-year survival rate after diagnosis is 20% (17% in men, 24% in women) [26]. In a recent Swedish cohort study on lung cancer patients (*n* = 3562) with access to advanced palliative care, 52% of the patients had at least one hospital admission during the last month of life, and 20% of patients died in hospital [27].

2. Current Insights

In the present single-center population-based cohort study of all lung cancer patients with metastases to the brain treated with WBRT, the overall median survival was short, 2.4 months from the start of treatment with WBRT. One in five patients in this cohort, more women than men, were not able to return home again after treatment with WBRT. The prognosis for lung cancer patients with brain metastases is generally poor. In this research, the researchers did not have the opportunity to compare with patients who did not receive WBRT for brain metastasis, so the researchers cannot draw any conclusions regarding the efficacy of the treatment.

However, the short survival time is in line with results from a recent study on SRT and WBRT in a Norwegian cohort covering the period from 2006 to 2018, where the median overall survival in the WBRT-group was 3.0 months [28].

The researchers observed, as expected, a strong association between poor PS WHO score and short survival. Lung cancer patients with PS WHO score 3–4 had a median overall survival of only 1.0 months. The odds of not coming home after treatment with WBRT were affected by PS and the health care level one week before treatment with WBRT and by gender. The odds of not coming home again were higher for women than for men and the difference was statistically significant. The odds of not coming home again were also affected by marital status; patients living alone or with children living at home ran a higher risk of prolonged stay in hospital or palliative wards.

Patients with small and few metastases to the brain can be treated with neurosurgery, sometimes with adjuvant radiation therapy afterward or with stereotactic radiotherapy [3]. Stereotactic radiosurgery is recommended for patients who cannot go into neurosurgery, with at most 4–5 brain metastases (Less than 3 cm in diameter) and with no or only a few symptoms. These developments of more local treatments in combination with guidelines advocating best supportive care over WBRT in patients with a survival time of fewer than 3 months changed treatment practice at the Karolinska University hospital already early in the 2010′s, resulting in a decrease in the use of WBRT as single treatment over time during the researchers' studied time period, from 175 2011–2013 to 88 2014–2016. In 2016, the QUARTZ study was published [13]. This was a randomized trial addressing the efficacy of best supportive care alone versus WBRT together with best supportive care in patients with NSCLC. The results concluded that WBRT can be omitted and that patients can be treated with the best supportive care alone, without an important reduction in either overall survival or QoL. These results may have further affected the use of WBRT and reduced the WBRT-treated patients observed in the researchers' cohort, with only 25 patients treated in 2017–2019 due to a change in treatment practice at the Karolinska University Hospital. This is in line with another study on a similar Stockholm cohort from the same time period that showed a reduction in the use of all radiotherapy in lung and pancreatic cancer patients in Stockholm in the last 30 days of life when comparing 2017 and 2010 [29]. Unfortunately, the selected group of patients in the present research treated with WBRT in the latter time period did not have a significantly better survival compared to earlier time periods. From these real-life data, the researchers can conclude that the selection of patients for WBRT emphasizing PS and introducing scoring systems in the clinic did not result in better survival over time. However, while one-quarter of patients in the earlier time periods (2008–2010, 2011–2013) did not come home after treatment, only 14 and 12% of patients did not come home in 2014–2016 and

2017–2019, respectively. The researchers' data nevertheless suggest that the researchers need to be better at using existing tools to select patients that will benefit from treatment or possibly that the ones currently in use today are difficult to implement in the clinic and that easier tools, therefore, need to be explored. However, for a patient with good performance status and disease under control outside the CNS, WBRT may very well be beneficial. The goals for treatment with WBRT are symptom relief and reduced need for steroids, as well as an increase in life expectancy. Patients with fewer symptoms may have less need for palliative care during a period after treatment with WBRT. Theoretically, the benefits of radiotherapy, in general, may first be experienced after a few days or after up to a few weeks after the treatment with WBRT. In light of this delayed effect of WBRT for symptom control of the disease, the researchers' results support that patients with poor performance status and that have a short, expected survival may benefit more from refraining from WBRT than from the treatment, well in line with previous studies and real-life experiences [28][30].

Existing scoring systems to predict the prognosis for patients with brain metastases, such as Radiation Therapy Oncology Group (RTOG) recursive partitioning analysis (RPA) [6], graded prognostic assessment (GPA) [7], and diagnosis-specific GPA (Lung-molGPA score) would have been possible to use in this cohort of lung cancer patients. They have not been used systematically, more in occasional cases. More widespread use of these scoring systems would probably have spared some patients' treatment with WBRT.

Health care level after treatment with WBRT is expected to differ by patient characteristics and survival, but also by external factors such as family situation and access to specialized palliative home care. In the Stockholm area, the access to specialized palliative home care is high. Therefore, the researchers found it surprising to note that as many as 20% of all patients in the cohort were not able to come home again from the hospital after treatment with WBRT. For many lung cancer patients who received WBRT in the present research, the best supportive care and a dialogue addressing both the patient's and the family's aim for care at the end-of-life situation would have been preferable. Toxic side effects due to treatment with WBRT could be avoided and time spent in hospital for the patients due to treatment would then be saved. Deaths in hospitals are common among cancer patients in western counties, even though their own homes are the most preferred place for dying, as shown in a small Swedish study from 2019 [31]. In this retrospective research of 456 deceased patients, they collected data from the medical records of the patients who were admitted to one of the specialized palliative home care units in the Stockholm region in 2017. Data on several variables were collected from the medical files, such as age, diagnosis, marital status, actual, and preferred place of death. In the cohort, 154 patients (34%) had preferred the place of death in the medical files, 116 (75%) had expressed ending their life in their own homes, and 38 (25%) in a specialized palliative ward. Of the patients who had expressed a preferred place of death, 80% (n = 123) had their wish fulfilled, and there were no differences between men and women. In another Swedish review article from 2017, Nilsson et al. conducted a systematic review of 23 papers that studied the patient's wishes in the end-of-life situation and found a preference for home deaths in 59.9% (39.7–100%) of these studies. The preferred place of death and the actual death place among these studies were significantly different (p < 0.05) [19]. In the present resesarch, the researchers found that cohabitating lung cancer patients with no children at living home were discharged from the hospital more often than lung cancer patients in other family situations. These patients may have a strong wish to go home and be discharged from the hospital and may thus have a higher ability to communicate their wishes together with their families. The researchers' findings suggest some overtreatment of WBRT for terminally ill lung cancer patients with brain metastases during the studied time period. The results encourage the use of validated scoring systems, such as the diagnosis-specific GPA (Lung-molGPA score), to help the clinician predict the prognosis and choose the most optimal strategies together with the patients. Many of the patients probably did not gain a better QoL due to the treatment and may have spent the last time in the hospital or traveling to the radiotherapy department for daily treatments. For these palliative patients, dialogues about the patient's wishes for health care during the terminal period should consequently occur.

There is, of course, also a health economical aspect of using health care and treatments on patients that will not be beneficial to them.

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