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Radiation Therapy in the Prevention of Brain Metastases

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Abstract

Brain metastases are common sequelae of many adult cancers accounting for more than 150,000 cases per year (NCI). It is a very devastating diagnosis. Patients with brain metastases experience a variety of symptoms with a wide range of neurological complications that can be very debilitating. The overall prognosis is guarded even with the most aggressive treatments. Traditionally, treatment of brain metastases involves surgery and radiation with the main focus on symptom palliation. However, there is a significant risk for decline in quality of life due to either treatment toxicities or irreversible symptoms caused by brain metastases despite best therapeutic efforts. An additional challenge after successful treatment is a great potential for reoccurrence of intracranial disease. Prevention of brain metastases therefore has been an important topic in oncology. Over the years, many approaches have been tried including systemic and local therapies. This article addresses the role of radiation and other therapies as strategies in the prevention of brain metastasis.

“Keywords Brain metastases. Prevention. ALL. Small cell lung cancer. Non-small cell lung cancer. Breast cancer. Neurocognitive dysfunction. Neuro-oncology”

Introduction

Brain metastases is one of the most common and devastating complication of many malignancies with reported overall incidence of 9%-17% [1]. Certain cancers have a much higher propensity for intracranial dissemination. It has been established that lung cancer, breast cancer, and melanoma are the most frequent to develop brain metastases, and account for 67%–80% of all cases [2].

It is believed the incidence of brain metastases is even higher than reported, based on autopsy studies [3]. Many experts anticipate that with more sensitive imaging techniques and more effective treatments that allow for longer survival of patients with cancer, the incidence of brain metastases will rise. For example a high resolution brain MRI with thin slices and double dose contrast allow for early detection of small, asymptomatic brain lesions. Longer survival allows for cancer to disseminate to the brain. In addition, many chemotherapies do not reliably cross the blood brain barrier to effectively treat disease.

Once brain metastases occur, the survival and quality of life can both be negatively impacted.The survival with brain metastasis for most patients remains poor. Even in young patients with the best performance status and controlled extra-cranial disease, the median survival was reported at approximately 7 months [4]. Symptoms of brain metastasis can include headache, nausea with emesis, mental status changes, seizures, neurologic and/or cognitive deficits. Although some patients are asymptomatic at diagnosis, mainly due to improvement in imaging technology allowing for early detection, once symptoms develop, they may be irreversible even with most advanced treatment techniques. Treatments of brain metastases themselves carry a risk for toxicities and can further impact quality of life.

Thus, prevention of brain metastasis has been of interest among oncologists, specifically, prophylactic cranial irradiation (PCI), that became a standard of practice in management of Small Cell Lung Cancer (SCLC). However, its importance in other cancers is less evident and has been debated, especially due to emergence of improved treatment approaches of brain metastases and with the development of new techniques to overcome toxicities of these therapies. Currently, several methodshave shown good promise at reducing neurocognitive toxicity of whole brain radiotherapy (WBRT), such as the use of Memantine and hippocampal avoidance techniques [5, 6].Researchers are also exploring factors such as pretreatment white matter changes detectable on MRI that can predict for cognitive decline following WBRT [7]. With such treatment innovations, the role of PCI can appear to be less important. Nevertheless, it is imperative to carefully assess the value of PCI in cancer management, especially due toits potential beneficial impact on survival and quality of life in carefully selected patients.

Brain Metastases Treatments

The standard treatment options for brain metastases depend on number of lesions, their locations and symptoms. Standard treatments include surgery followed by WBRT, or WBRT alone, or stereotactic radio surgery with or without WBRT. Currently, the management of detected brain metastases continues to evolve rapidly with emergence of new techniques. One such technique is the utilization of systemic therapies to address intracranial disease. Presently, systemic therapy alone or in addition to other more established treatment options is not considered a standard approach for brain metastases as previous studies were negative. Earlier studies showed limited utility of chemotherapy in themanagement of brain metastasis, which has been mainly attributed to their poor ability to cross the blood-brain barrier and exert therapeutic action intracranially. For example, the addition of Carboplatin or Temozolomide to WBRT failed to show improvement in overall survival in comparison to WBRTalone in randomized studies. However,

Temozolomide is one of the chemotherapy agents that crosses the blood-brain barrier, and when it was utilized WBRT,this showed improvement in progression free survival and radiologic response [8-10].

The limited results of systemic drugs have been also attributed to potential cancer cell resistance to these agents if they were utilized previously in the management of extracranial disease. However, the emergence of new systemic targeted agents hasrenewedinterest to utilize systemic therapy for brain metastases. Epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors, such as Erlotinib andGefitinib,haverecently shown promisein the treatment of brain metastases in select group of patients with Non-Small Cell Lung Cancer (NSCLC), especially ifEGFR mutation is present [11]. Another EGFR/Her-2 tyrosine kinase inhibitor Lapatinib appears effective in Her-2positive breast cancer patients with brain metastases based on two phase II clinical trials [12, 13].Patients with Her-2 positive breast cancer post WBRT or gamma knife receiving Lapatinib alone achieved 6% central nervous system (CNS) objective response rate defined as>50% volumetric reduction of CNS lesions assessed by MRI, in the absence of increasing steroid use [13]. An exploratory analysis revealed 21% of patients in the Lapatinib monotherapy group achieved a 20% or greater CNS tumor volume reduction. When Lapatinib was combined with Capecitabine,40% of patients achieved a 20% or greater CNS tumor volume reduction. Tumor volume reductions correlated with improvement in neurologic symptoms and progression free survival (PFS) [13]. Studies have also shown that Lapatinib in combination with chemotherapy can decrease the rate of CNS relapse as a primary site from 6% to about 1-2% [14, 15]. The Radiation Therapy Oncology Group (RTOG) 1119 is evaluating complete response (CR) rate in the brain at 12 weeks post WBRT as determined by MRI scan of the brain, with the addition of Lapatinib to WBRT compared to WBRT alone in women with Her-2 positive breast cancer that metastasized to the brain [16]. Other promising targeted systemic agents includeBRAF inhibitors (Dabrafenib and Vemurafenib), multi-kinase angiogenesis inhibitors (Sorafenib, Sunitinib, Pazopanib, and Vandetanib), ALK/c-MET (Crizotinib) and ALK/IGF-1 (Ceritinib) inhibitors [17].

Despite advances in management of brain metastases, radiation therapy remains a crucial treatment modality. There are two types of radiation therapy techniques that are utilized in the treatment of brain lesions, stereotactic radio surgery (SRS) and WBRT. Both have advantages and disadvantages.

The idea behind the SRS is to deliver ablative doses of radiation to a precise target in the brain. Thus, radio surgery treats the lesion while significantly minimizing gradiation exposure to the remainder of the brain. It has been shown in phase III trial that SRS alone as compared to SRS plus WBRT results in less cognitive deterioration at 3 months. In the absence of a difference in overall survival, these findings suggested that for patients with 1 to 3 brain metastases SRS alone may be a preferred strategy [18]. This approach is currently considered a standard of care for limited number of brain metastases. One disadvantage of SRS is that untreated brain remains at high risk for developing new metastases. It has been estimated that on average 70% of patients treated with radio surgery will develop new brain metastases within the first year of surveillance[19].

Another radiation technique in the management of brain metastases is WBRT. Although it treats all brain lesions and addresses areas with potential micrometastases, it also exposes the whole brain to radiation. Generally, WBRT is well tolerated with limited side effects, the majority of which resolve overtime. However, one of the most feared long term toxicities of WBRT is neurocognitive dysfunction. This side effect is less pronounced in adult patients than in children, although patients aged >60 years appear to be more susceptible than younger adults to cognitive impairment after radiation [20].It is not well understood why some patients decline while others do not or why some patients decline more than others. Previous research has shown a clear relationship between treatment-

specific variables and the degree of brain injury following radiation therapy. Higher total radiation dose, higher dose per fraction, and increased brain volume irradiated have all been associated with greater radiation-induced brain injury [21]. The degree of neurocognitive dysfunction can vary widely.

Role of prophylactic cranial irradiation in Acute Lymphoblastic Leukemia (ALL)

Prophylactic cranial irradiation (PCI) arose as a modality for addressing micrometastatic CNS disease in childhood leukemia [22].Early ALL studies established that patients with high risk features had poor survival rates of 15% even after initial complete remission. Such limited survival rate was attributed to high rate of disease recurrence in the CNS [23- 25]. The emergence of prophylactic approaches for disease dissemination into the CNS dramatically reduced the incidence of CNS failures and improved cure rates [24]. It has been reported that CNS failure rates can be as high as 42% to 100% without any CNS-therapy. PCI alone can reduce the rate of CNS relapse to 4% [26]. In studies using intrathecal chemotherapy prophylaxis alone the CNS relapse rate ranged from 3% to 42%, as compared to 3% to 15% when both PCI and intrathecal therapy were used together [27]. Similar results have been also seenin adults. The GMALL study reported that CNS irradiation (24 Gy) with intensive intrathecal therapy resulted in only 1/45 patients experiencing CNS relapse (2%) [28].

PCI has been used as part of standard therapy for 2–20% of patients with ALL without CNS involvement but with high risk factors such as young age at diagnosis, T cell phenotype, WBC greater than 50,000 or 100,000, extrame dullary disease, presence of Philadelphia chromosome, and poor response to induction therapy [29, 30].However, due to concerns of radiation induced long term side effects such as neuropsychological deficits, mood disturbances, short stature in children, endocrinopathies and secondary malignancies, the dose of PCI has been progressively reduced from 24 Gy to 18 Gy, and to 12 Gy in some protocols.

More recently, prophylactic approaches without PCI became preferable [31-33].A number of studies demonstrated that with more intense chemotherapy regimens utilizing systemic high dose methotrexate and intrathecal methotrexate the CNS relapse rate remained low despite omission of PCI. The Berlin-Frankfurt-Munster (NHL-BFM) 95trial showed that CNS-negative patients with stage III-IV Lymphoblastic leukemia with sufficient early response who did not receive PCI had one isolated and two combined CNS relapses with five-year DFS rate of 88%, which was comparable to historical control of 91% in NHL-BFM90/86 [34]. Children's Leukemia Group (CLG) reported based on their prospective trial that even for patients with CNS involvement at diagnosis the EFS and OS rate at 6years was 77.5% and 86% respectively without radiation. In this trial only two patients (1.8%) had an isolated CNS relapse[35]. MDACC reported that with combination of high-dose systemic chemotherapy and appropriate intrathecal chemotherapy without PCI the relapse rate is only 3% [36].

It is now widely accepted that ALL can be managed without PCI. Approaches aimed to reduce side effects of WBRT that have been investigated in other cancers have not been attempted in ALL patients. The use of hippocampal sparing technique have not been applied to PCI in the setting of ALL out of concern for sparing cerebrosipinal fluid that could harbor tumor cells. The use of drugs to lessen neurocognitive decline, like Memantine, have also not been explored in this patient population, however, clinical trials should be considered.

Role of PCI in Small Cell Lung Cancer

Multiple similarities between ALL and Small Cell Lung Cancer (SCLC) exist. These include sensitivity to chemotherapy and radiation, rapid disease progression, high rate of CNS involvement and CNS failure rate (60% at 2 years post diagnosis), as well as poor prognosis upon relapse [37]. These similarities led to the consideration of using PCI in SCLC patients, which has been proven to be very effective not

only in preventing brain metastases, but also in improving survival. PCI became a standard of care in the management of SCLC patients.

Initial clinical trials done in 1970s and 1980s showed mixed results. Statistically significant reduction in the rate of CNS failure was demonstrated in 6 out of 9 trials. None of these trials reported improvement in overall survival. Criticisms of these trials include a very heterogeneous patient population and poor brain imaging modalities. The doses of PCI varied substantially in these trials, including 8 Gy x 1, 20 Gy in 5 fractions, 24 Gy in 8 fractions, 25 Gy in 10 fractions, 30 in 10 fractions and 40 in 20 fractions.

Cranial Irradiation Overview Collaborative Group performed a meta-analysis including 7 randomized phase III studies. These meta-analyses demonstrated that utilization of PCI at varying dose fractionation schedules in patients with initial limited disease (LD) SCLC who had shown a complete systemic disease response led to a 50%reduction
in the incidence of brain metastases, with an absolute 5% (15.3% observation vs 20.7% PCI) increase in overall survival [38].A systematic review by Meert et al performed a similar analysis on 12 studies and showed similar results. PCI significantly decreased the incidence of brain metastases and improved survival in patients achieving a complete response (CR) after chemotherapy with hazard ratio [HR] of 0.48 (95% CI 0.39–0.60) for incidence of brain metastases, and HR of 0.82 (95% CI 0.71-0.96) for survival. However, when patients with less than a CR to chemotherapy were included in this analysis, the benefit of PCI on survival became non-significant (HR 0.94, 0.87–1.02) [39].

Based on the above analyses PCI has been recommended for patients with LD SCLC who achieved a CR to chemotherapy. However, it is important to realize that in earlier studies the assessment of disease response was done with chest X-ray alone, which is a far less sensitive modality in comparison to a CT scan of the chest. It is possible that many patients in these older studies who benefited from PCI had less than a CR. Thus, PCI is currently recommended for all patients with any response to chemotherapy as long as patients have a good performance status.

The incidence of brain metastases in LD SCLC post-surgery varies by stage, with 3 year rates reported as 6.5%-9.7% in stage I disease, 18.5-25.4% in stage II disease, and 28.8-35.4% in stage III disease [40, 41].PCI has not been studied prospectively in this group of patients possibly due to difficulty conducting such studies because of rarity of such clinical cases. Nevertheless, at least one retrospective study found that utilization of PCI in patients with LD SCLC who underwent surgery reduces the incidence of brain metastases and improves survival [42]. Thus, PCI in this patient population should be strongly considered, especially in patients with stage II and III disease.

In patients with extensive disease (ED)SCLC, PCI has also shown benefit in terms of prevention of brain metastases and survival. Auperin's meta-analyses included a proportion of patients with ED SCLC, and as discussed earlier, patients who achieved a CR to chemotherapy had lower rates of brain metastases and a better survival when PCI was utilized. Based on this data PCI has been recommended to patients with ED SCLC with CR after chemotherapy.

Slotman and colleagues within the European Organisation for Research and
Treatment of Cancer (EORTC) further investigated in a phase III trial the role of PCI in patients with ED SCLC who had partial response (PR) or CR to chemotherapy [43]. The cumulative risk of symptomatic brain metastases at 1-year was significantly reduced in PCI group as compared to without PCI (14.6 % vs 40.4%), and the 1-year survival rate was also superior (27.1% in the PCI group and 13.3% in the control group).
This study utilized various doses of PCI ranging from 20-30 Gy with the fraction sizes ranging from 2.5-4.0 Gy. Brian imaging prior to PCI was not performed routinely, unless patient had symptoms. Based on the results of this trial, the

recommendation of PCI was extended to patients with ED SCLC who achieve PR or CR.

However, the application of PCI in the setting of ED SCLC continues to be debated. The Japanese phase III trial failed to show a survival advantage in patients with ED SCLC and negative initial MRI of the brain who received PCI (25 Gy in 10 fractions) [44].This trial was stopped prematurely after initial interim analysis showed futility of PCI. Median survival was 10.1 months in the PCI group versus 15.11 months without PCI (p=0.091).Conversely, this trial did demonstrate a significant reduction in cumulative risk at 1-year of developing symptomatic and asymptomatic brain metastasis (32. 2% in the PCI group compared with 58.0%). Brain metastases in this trial were detected early and subsequently treated. In the control group, about two-thirds of patients were diagnosed with brain metastases, and 80% of these patients received radiotherapy. The final results of this trial with longer follow up is underway.

Role of PCI in Non-Small Cell Lung Cancer

The overall incidence of brain metastases in NSCLC is about 30%, ranging from 17-54%[45-50]. Brain metastases occur in 15% to 40% of cases as a first site of recurrence [45-51].This incidence depends on the disease stage. In patients with stage I-II disease, treated surgically, the 5-yearactuarial risk of developing brain metastases has been estimated at around 10% or less [52, 53]. In Stage III disease, the incidence of brain metastases has been reported at around 30% or more [46]. In patients with disease progression, concurrent brain failure was reported at around 25% [47]. In one study it was reported that brain failure occurred less than 6 months after completion of curative therapies [47].

Unlike SCLC, the role of PCI has not been established as the standard of care in NSCLC. In NCSLC there are two approaches employed in dealing with intracranial failure. A more commonly utilized approach is treatment of brain metastases at the time of detection. A less commonly employed strategy is prevention of CNS failure. There are several local therapies can be offered to treat brain metastases, including surgery, whole brain radiation, stereotactic radio surgery, or their combination. Another currently evolving treatment of brain metastases in patients with ALK or EGFR mutations is the use of tyrosine kinase inhibitors such as Erlotinib and Gefitinib. These agents are unique among systemic therapies because they have some ability to penetrate intracranially through the blood-brain barrier and have shown intracranial efficacy [54-58]. They are typically well tolerated and there is a growing interest in using them alone in patients with EGFR mutations to treat detected brain metastases without additional therapies. Another evolving interest is to use tyrosine kinase inhibitors such as Erlotinib and Gefitinib as chemoprevention of brain metastases in patients with EGFR mutated disease.

Patients without ALK or EGFR mutations represent the majority of patients with NSCLC [59]. For these patients PCI remains a potentially intriguing strategy in preventing disease occurrence in the CNS, however, its impact on survival remains unclear.

Several older studies have shown PCI reduces the rate of brain metastases and prolongs median time to development of brain metastases. Cox et al. [60] had shown that the addition of PCI decreased the incidence of brain metastases from13% to 6% (P=0.038) in all non-small cell histologies. Umsawasdi et al. [61] showed an additional statistically significant drop in CNS metastases from 27% in the observation group to 4% in the treatment group (P=0.002) with a corresponding increase in CNS metastases free survival.

A notable non randomized study involved 75 patients with locally advanced (LA) NSCLC that were treated with induction chemotherapy, preoperative chemo radiation, and surgery. PCI was introduced into the treatment regimen secondary to an observed high CNS failure rate. PCI reduced the rate of CNS metastases as the first site of relapse from 30% to 8% in 4 years of follow up(P=0.005) and decreased the rate of

overall brain relapse from 54% to 13% (P<0.0001) [62].

The criticism of PCI based on older studies has been that PCI had no effect on overall survival. Additionally, in the first RTOG trial that assessed PCI in patients with NSCLC, the reduction of brain metastases in the PCI arm did not reach statistical significance in comparison to arm not receiving PCI (9% vs19%; p=0.10) [63].However, a subgroup analysis of patients with resected tumors, showed that no patients in the PCI group developed brain metastases as compared to 25% of patients in the non-PCI group (p=0.06).

Due to the heterogeneous patient population that was included in the older studies, it was difficult to draw conclusions regarding a survival benefit from PCI. The RTOG attempted to conduct a phase III trial (RTOG 0214) to evaluate the role of PCI in patients with stage IIIA-IIIB NSCLC who did not show disease progression following treatment with surgery and/or radiotherapy with or without chemotherapy. Unfortunately, this trial closed early due to poor accrual. A total of 356 patients were accrued out of a targeted 1056. The PCI dose used in this trial was 30 Gy in 15 fractions. Similar to previous trials, PCI significantly reduced the rates of brain metastases at 1 year (7.7% vs 18.0%; p=0.004), however, 1-year overall survival did not differ between groups (75.6% vs 76.9%; p=0.86), and there was no difference in1-year disease-free survival (56.4% vs 51.2%; p=0.11) [64].A randomized phase III trial from China compared PCI with observation in patients with resected stage IIIA–N2 NSCLC and high risk of cerebral metastases after adjuvant chemotherapy [65]. The primary end point was disease-free survival (DFS). The secondary end points included the incidence of brain metastases, overall survival (OS), toxicity, and quality of life. This trial also closed early due to poor accrual. 156 patients (81 to PCI group and 75 to control group) were accrued and analyzed. PCI dose was 30 Gy in 10 fractions. DFS was significantly better in the PCI group, with a median DFS of 28.5 months versus 21.2 months [hazard ratio (HR), 0.67; 95% confidence interval (CI) 0.46–0.98; P = 0.037]. Decrease risk of brain metastases was associated with PCI (the actuarial 5-year brain metastases rate, 20.3% versus 49.9%; HR, 0.28; 95% CI 0.14–0.57; P < 0.001). The OS did not reach statistical difference. The median OS was 31.2 months in the PCI group and 27.4 months in the control group (HR, 0.81; 95% CI 0.56–1.16; P = 0.310). Toxicities from PCI were mild and included headache, nausea/vomiting and fatigue.

Both of these phase III trials confirmed that PCI reduced the rate of brain metastases in high risk patients. The Chinese study was also able to demonstrate improvement in DFS with PCI. However, both studies were under powered and failed to improve OS. Patients on RTOG 0214 study were evaluated for neuro cognitive function (NCF)with Mini-Mental Status Examination (MMSE), Activities of Daily Living Scale (ADLS), and Hopkins Verbal Learning Test (HVLT), as well as quality of life (QOL) was assessed with the European Organization for Research and Treatment of Cancer (EORTC) core tool (QOL Questionnaire-QLQC30) and brain module (QLQBN20) [66]. Authors concluded that there were no statistically significant differences at 1 year between PCI and observation noted in any component of the EORTC-QLQC30 or QLQBN20 (P> .05), although a trend for greater decline in patient-reported cognitive functioning with PCI was noted. There were no significant differences in MMSE (P = .60) or ADLS (P = .88). However, for HVLT, there was greater decline in immediate recall (P = .03) and delayed recall (P = .008) in the PCI arm at 1 year.

SEER population-based analysis of 17 852 patients treated from 1988 to 1997 for stage III NSCLC of which 326 (1.8%) received PCI, did not suggest OS benefit from PCI (HR 1.04, 95% CI 0.93–1.16) [67]. There have been reports of detrimental effects of PCI on OS. Chinese researchers recently published a systematic review with meta-analysis that investigated the role of brain metastases and overall survival (OS) in patients with NSCLC [68]. Based on 12 trials (6 RCTs and 6 non-RCTs) involving 1,718 NSCLC patients, this systematic review concluded that while PCI reduced the risk of

brain metastases (OR = 0.30, 95% [CI]: 0.21–0.43, p = 0.00001), it may impose a detrimental effect on OS. HRs for OS favored non-PCI (HR = 1.19, 95% [CI]: 1.06–1.33, p = 0.004), without evidence of heterogeneity between the studies. Thus, due to lack of data supporting survival benefit from PCI, it is currently not considered a standard treatment for LA-NSCLC [69, 70].

Role of PCI in Breast Cancer

Breast cancer is another malignancy with high risk of brain metastases. There are several risk factors identified that predict for greater risk of developing brain metastases. These factors include HER-2 (HER-2+) over expression, basal epithelial phenotype also known as triple-negative breast cancer (TNBC), uncontrolled systemic disease and young age at diagnosis. [71-74].

The overall risk of brain metastasis in breast cancer patients has been reported as 5%. In newly diagnosed HER-2+ patients this risk on average is 9%, based on stage: in stage I–III the risk is 1%–3%, and in stage IV it is 25%–35%[72, 75]. A similar picture is observed in patients with TNBC. Stage I–III TNBC patients have a 6% chance of developing CNS metastases, while patients with stage IV TNBC have 40%–45% risk of brain metastases [73]. Many of these patients will succumb to intracranial as opposed to extracranial disease [76-79].

The success of HER-2 Neu inhibitors (Trastuzumab) at controlling and eradicating systemic disease unfortunately has limited effect intracranially. Patients treated with Her-2 Neu inhibitors still have a high incidence of brain metastases [75-77, 80]. This is attributed to poor ability of such systemic agents to cross the blood–brain barrier [71]. Improvements in systemic therapies has increased survival of patients with breast cancer, putting patients at higher risk of developing CNS metastases [73].

Therefore, several groups of breast cancer patients have high enough risk of developing brain metastases to consider preventative therapies. Unfortunately, such strategies have not been well established. In one study, 24 breast cancer patients were prospectively enrolled in a complex metastatic protocol. Ten patients received PCI and three of these patients survived long enough to experience significant cognitive decline [81]. Another recently published phase III trial that investigated the role of PCI in patients treated with Trastuzumab for metastatic breast cancer showed negative results. 51 patients were randomized at 1:1 ratio to no PCI (n=26) or PCI (n=25). PCI was delivered6 weeks after study entry. Cognitive function was assessed prospectively. The cumulative incidence of CNS metastases at 2 years was 32.4% (standard error 9.8%) on the control arm and 21.0% (standard error 8.6%) on the PCI arm; the associated hazard ratio was 0.57 (95% confidence interval 0.18-1.74; p= 0.32). There was no evidence of cognitive dysfunction in PCI patients.

It is difficult to draw a definitive conclusion about PCI in breast cancer patients based on these small studies. Furthermore, the studies are needed to identify the population of patients with breast cancer that would benefit most from PCI, to establish the optimaltiming of delivery, and whether PCI should be delivered with targeted systemic agents that may alsooffer CNS control [82].

Effects of PCI on Neurocognitive Function/Quality of Life

Even though the benefit of PCI has been well described in clinical trials for select patients, PCI remains underutilized due to concerns of its effects on neurocognitive function (NCF) and quality of life (QOL). Even in patients with SCLC, PCI can be often omitted either due to clinicians' hesitancy to offer it [83] or patients refusal [84]. One retrospective study reported that up to 40% of patients with limited disease may refuse PCI [84].

Although the concern for PCI induced neurocognitive decline and its negative impact on QOL is valid, its magnitude is potentially overestimated, especially in the context of

neurocognitive decline induced by metastases. Evaluation of PCI effects on brain function and QOL is often difficult because of multiple other factors, including patient specific variables, chemotherapy, radiation dose differences and cancer itself [85-89].

Earlier studies that reported detrimental effect of PCI on neurocognitive function were small, retrospective, and did not report pretreatment baseline [90]. However, it is known that age, chronic cigarette smoking, paraneoplastic syndromes, undiagnosed micrometastases, depression and anxiety can induce neurocognitive decline [86]. Thus, pretreatment neurocognitive evaluation necessary to establish a baseline. Furthermore, careful consideration should be given to older age at the time of treatment and the presence of cardiovascular co-morbidities when assessing radiation induced cognitive deterioration. These factors are thought to predict for poorer neurological outcomes [91, 92].

Modern PCI toxicity data comes from long-term follow-up of randomized studies that assessed quality of life, general health status, and neurological functions. Patient reported outcomes were evaluated via validated questionnaires. Some trials also used neurological and neurocognitive testing [66, 93-96]. In two large randomized trials, PCI in patients with LDSCLC had no significant effects on neurological function. These studies also reported that baseline assessment was abnormal in 40–60% of patients[93, 94].

Recent RTOG studies assessed PCI effects on neurocognitive function utilizing several specific tests such as Mini-Mental State Examination (MMSE), Hopkins Verbal Learning Test (HVLT), Controlled Oral Word Association, and others [97-99]. RTOG 0212 reported an association between higher-dose PCI and increased chronic neurological toxicity, but this was not specifically associated with greater decline in HVLT score [97].Logistic regression analysis showed increasing age to be the most significant predictor of chronic neurotoxicity ($p=0.005$). An EORTC trial [95] that investigated PCI in EDSCLC showed significantly decreased quality of life in the PCI group at 6 weeks, which became non-significant at 3 months. These can be attributed to acute and sub acute effects of radiation that usually resolve by 3 months post treatment.QOL assessments from RTOG 0214 evaluating PCI in LA NSCLC showed that while there was no decline in global cognitive function (MMSE) or quality of life between PCI and observational groups, there was a significant decline in memory as measured by the HVLT in the PCI group [66].

Pooled analysis of RTOG 0212 and RTOG 0214 [100] reported that patients treated with PCI had a more than three-fold higher risk of self-reported neurocognitive decline at 6 months (odds ratio [OR] 3.60, 95% CI 2.34–6.37; $p<0.0001$) and 12 months (OR 3.44, 1.84–6.44; $p<0.0001$) compared with observation group. Decline in HVLT recall score at 6 and 12 months was also associated with PCI treatment.

Therefore, PCI can have both positive and negative outcomes. On one hand PCI can prevent the cognitive effects of brain metastases, however, on the other hand PCI may negatively impact NCF and QOL. Optimization of the therapeutic ratio of PCI is the current area of research. Based on WBRT studies, it has been hypothesized that radiation-induced injury to proliferating neuronal progenitor cells in the sub granular zone of the hippocampi may be responsible for the radiation induced NCF decline, thus, avoiding the hippocampal region of the brain may ameliorate the NCF side effects [101, 102]. It should be noted that brain metastases in the hippocampal region seem rare, 4-5%[103, 104].

A small phase II RTOG study (RTOG 0933) evaluated hippocampal avoidance whole brain radiation therapy (HA-WBRT) delivered with intensity-modulated radiotherapy (IMRT) in the treatment of patients with metastatic disease to the brain. This trial has shown that HA-WBRT was associated with the preservation of memory and quality of life compared with historical series. The mean relative decline in HVLT-Revised distant recall score from baseline to 4 months was 7% in HA-WBRT compared with

30% in historical series [5]. There has been a growing interest in applying hippocampal sparing technique with PCI. Currently, at least 3 phase III trials are investigating this approach in patents with SCLC: Netherlands and Belgium (NCT01797159), Spain (NCT01780675), and in North America led by NRG Oncology (formerly RTOG; NCT02635009). A German phase III trial will be investigating the effect of hippocampal-sparing PCI on survival in patients with LA-NSCLC (NCT02341170).

Hippocampal avoidance is not the only technique that can potentially improve therapeutic ratio of PCI. A few neuro protective agents were investigated in studies with WBRT, and the interest to utilize these in PCI is emerging. One promising neuroprotective agent is Memantine. RTOG 0614 examined the use of Memantine with WBRT in patients with known brain metastases from lung cancer [6]. In this study, patients treated with Memantine during and after WBRT had better cognitive function preservation over time. Memantine specifically delayed time to cognitive decline and reduced decline in memory, executive function, and processing speed. There was no statistically significant difference among Memantine and placebo groups for decline in HVLT-Revised distant recall score. Memantine was very well tolerated by patients in this trial. The use of Memantine in PCI has not been assessed yet. It has been proposed that Lithium might lessen memory problems caused by PCI, and it is currently investigated in a phase I/II study in patients with SCLC undergoing PCI (NCT01553916).

Conclusions

Prophylactic radiotherapy has a clearly defined role in select group of patients. PCI is currently considered a standard of care for patients with SCLC who obtained a good response to initial therapies. However, PCI as a strategy to prevent brain metastases has been underutilized, even in patients with SCLC. In one study it was reported that 40% of patients with SCLC suitable for PCI do not receive it [84]. This underutilization of PCI stems from concerns of its effects on NCF and QOL.

Significant negative impact of PCI on these functions was initially observed in children with acute leukemias, where PCI has been now successfully replaced by high dose systemic Methotrexate and intrathecal Methotrexate. However, effects of PCI on NCF and QOL in adult population is less clear. Clinical trials that investigated these effects seem to be heterogeneous and without consensus regarding the best assessment tool. In addition, other factors that may negatively impact NCF and QOL, such as chemotherapy, depression and anxiety, and disease progression itself are not accounted for. Thus, it is hard to draw definitive conclusions from these studies, although, it is generally accepted that PCI will have some negative effects on NCF. It is also not well understood whether PCI induced NCF decline has significant impact on QOL. Studies that specifically assessed QOL did not control for radiation induced acute and subacute effects. These side effects can impact QOL post radiation, however, it is important to recognize that these effects are transient and can resolve within a short period of time. This may explain why QOL reported in PCI versus observation groups at 3 months was significantly worse than at 6 months post radiation therapy.

Besides negative effects on NCF and QOL, another criticism of PCI has been its lack of survival benefit, with exception of ALL. Initial studies in SCLC were underpowered to show survival benefit. However, recently published meta-analyses and systematic reviews, showed a clear beneficial impact of PCI on survival in both LD-SCLC and ED-SCLC. Attempts to investigate PCI's impact on survival in NSCLC have been disappointing due to surprisingly poor accrual into these studies resulting in their early closure. Utility of PCI in high risk breast cancer patients is poorly understood, and robust efforts to investigate this further have not been made. There are only a few small trials that evaluated PCI in breast cancer patients that failed to show any benefit, potentially due to being underpowered.

The techniques and modalities of brain metastases prophylaxis continue to evolve.

Efforts have been made recently to improve PCI's therapeutic ratio in patients with SCLC. Drawing from the experience with HA-WBRT, there are currently 3 phase III trials underway investigating hippocampal sparing technique with PCI. Additional studies that evaluate neuroprotective agents such as Memantine and Lithium should be highly encouraged. There is a rapidly growing interest of using targeted agents (Erlotinib, Gefitinib, Lapatinib, Dabrafenib, Sorafenib,Sunitinib, Pazopanib, Vandetanib, and others) as drug therapy for preventing metastases in patients with select gene mutations (EGFR, ALK etc) and these also warrant further investigation. The horizon of brain metastases prophylaxis is rapidly changing and new therapies are emerging. The accrual of patients to currently open clinical trials evaluating prophylactic measures and novel treatment techniques is vital to answer these questions. Clinicians will need to gain a better understanding of which group of patients will benefit most from thesetherapies.

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