Review Article

Prophylactic cranial irradiation (PCI) or magnetic resonance imaging (MRI) monitoring in limited small cell lung cancer: is it a question?

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Abstract: Brain metastases are a major problem in the management of small cell lung cancer (SCLC) with an incidence rising to 50% at 2 years. Prophylactic cranial irradiation (PCI) has shown through randomized trials and meta-analysis to decrease the incidence of brain metastases by 25% leading to a 5% survival benefit at 3 years for patients in complete response to the initial therapy. The major concern with PCI is the risk of inducing neurologic symptoms, especially cognitive functions, and an impaired quality of life. In extensive disease SCLC, an active surveillance with magnetic resonance imaging (MRI) has questioned the value of routine PCI challenging its use for limited disease. In this paper, we will review some main limitations of the different randomized trials, the impact of new technologies and the data available on the possibility to omit (or not) PCI for limited disease.

Keywords: Small cell lung cancer (SCLC); prophylactic cranial irradiation (PCI); magnetic resonance imaging (MRI)

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Neurological disorders represent a major challenge in the management of small cell lung cancer (SCLC). In an old series including 641 patients, 189 (29.5%) had at least one neurologic disorder either at the time of presentation or during the subsequent clinical course of the disease. The total number of neurologic disorders was 210, including brain metastases (75.7%), epidural metastases (11.0%), meningeal carcinomatosis (6.7%) and intramedullary metastases (2.4%) (1). Clearly, brain metastases are a major issue with an incidence as high as 50 % at 2 years (2). The brain was considered a sanctuary site due to the blood brain barrier and the limited access for most available drugs. Following the experience in the management of leukemia, Heine Hansen introduced in 1973 the concept of prophylactic cranial irradiation (PCI) for SCLC (3). The goal was to prevent brain metastases, avoiding the possible neurological complications and ultimately improving survival. PCI was tested through a series of randomized trials which showed very early that PCI decreased the incidence of brain metastases but they all failed to show a survival benefit probably due to the limited number of patients included in those trials. The response was provided by the analysis of Auperin *et al.* who included the individual data of 987 patients from seven randomized trials (2). This meta-analysis demonstrated a 25% reduction in brain metastases leading to a 5% survival benefit at 3 years for patients considered in complete response to the initial therapy. Most of these patients had a limited disease (85%). A more recent meta-analysis including 1983 patients from 16 randomized trials showed a similar survival benefit of 4.4%, especially among patients with a complete response. However, there was no correlation with the disease extent,

i.e., limited *vs.* extensive (4). An interesting observation was reported by Arriagada *et al.*: in trials comparing PCI (24 Gy in 8 fractions) to no PCI, at 5 years the rate of brain metastases was 37% *vs.* 59%, respectively, but the interesting figure was the number of patients with only a relapse in the brain, 20 *vs.* 43 %, leading to a 3% survival benefit in favor of PCI (5). This outlines the competing events, brain metastases being only one issue besides control of the primary tumor and extra-cerebral metastatic sites.

Today, PCI is recommended for patients in complete remission after systemic treatment for limited or even disseminated disease (6). In a recent survey amongst US radiation oncologist, 98% will recommend PCI but only after a brain magnetic resonance imaging (MRI) in the initial staging (7). In another survey including 295 responses, 35% from the United States and Europe and mainly including radiation (45%) and medical (43%) oncologists, the picture is a little more contrasted: 88% and 50% would recommend PCI to a 50- and 70-year-old patient, respectively. In contrast, this is not the case in Japan where less than 15% of patients have a PCI (8). Should all patients receive PCI, this question is also raised among elderly patients, especially as in the experience of the MD Anderson no survival benefit was observed for patients older than 70 (9)

So, what is the reason to reopen today the debate on the usefulness of PCI? The goals of PCI are to reduce the incidence of brain metastases, avoiding central nervous system (CNS) symptoms and improving survival being clearly achieved according to the trials and meta-analysis. Therefore, we should first look at the design and limitations of those randomized trials: there was a wide range of radiation schedules (from 8 Gy in one fraction to 40 Gy in 20 fractions), the timing of PCI, the definition of a complete response was based on a chest X-ray, and most trials did not include a brain imaging at the staging, before the PCI or during the follow-up of the patients.

Regarding the issue of the radiation schedule, a large-scale trial has compared 25 to 36 Gy but failed to show any benefit from a higher radiation dose neither on the incidence of brain metastases (which remained high, around 35% at 3 years) nor on survival (10). This confirms the results of a pooled analysis of patients included in four phase II and III trials from the North Cancer Center treatment group: for limited disease 25 Gy in 10 fractions was associated with significantly better survival compared with 30 Gy in 15 fractions (11). So, 25 Gy in 10 fractions is now the recommended radiation schedule.

Impact of brain imaging

Brain imaging was not part of the initial staging in many trials and this has a direct impact on the reported incidence of brain metastases: in the absence of brain imaging PCI reduces the incidence of brain metastases from 53% to 40% and in case of a brain imaging from 33% to 10% (12). We should point out that in these studies brain imaging was done by CT or nuclear imaging. Nowadays MRI is available and its introduction has increased the detection of brain metastases from 10% to 24% (13). However, in a recent published trial conducted between 2008 and 2013 baseline imaging of the brain was still done by CT scan in 79% of the 449 patients (14). Furthermore, patients detected with brain metastases through CT had symptoms while they were asymptomatic in case of MRI. Therefore, the proportion of patients eligible for PCI is lower in the MRI era. Another problem is the delay between the initial staging and the time of the PCI: in a series of 40 patients treated by chemoradiotherapy for a limited disease, an MRI repeated before the PCI showed 13 patients (33%) to have developed brain metastases of whom 11 were fully asymptomatic (15).

Side effects of PCI

Another concern with PCI, as it is whole brain radiotherapy (WBRT), is the risk of acute and late toxicities: hair loss, fatigue, hearing impairment, dementia, leukoencephalopathy… Already in 1985, Bruce Johnson reviewed 20 long-term survivors, alive and free of cancer 2.4 to 10.6 years after the initial treatment; 15 (75%) had neurological late effects with also an abnormal CT scan (16). Several risk factors were identified including the dose per fraction above 3 Gy, and the administration of concurrent chemotherapy including methotrexate used in the past. However, the major problem was the absence of a baseline evaluation. Indeed, different studies have also tested the patients before PCI. In a study of the MD Anderson, 97% of the 30 patients evaluated before PCI presented abnormalities in the cognitive functions, mainly alteration of verbal memory, frontal function and fine coordination; the intellectual capacity, the language and the visual perception were preserved (17). The concern with PCI is the risk of (further) altering those cognitive functions leading to an impaired quality of life. The RTOG has evaluated patients before and 6 and 12 months after PCI using the Hopkins

Verbal Learning Test-Revised (HVLT-R) test from Harvard and the self-reported cognitive functioning tests of the European Organisation for the Research and Treatment of Cancer (EORTC): a three-fold decrease was observed both at 6 and 12 months after PCI (18).

In order to handle these important side effects, one might think of two solutions. The first solution can be to omit PCI and to only treat the metastases when they appear, alternatively new radiotherapy techniques have been developed in order to safely spare the critical zones in the brain out of the high dose zones.

WBRT *vs.* radiosurgery (RS) for brain relapses

When considering PCI avoidance, we also need to look at the treatment available for a brain relapse. In the past and still today, the classical approach of such metastases is WBRT with mainly a palliative goal, many patients dying with progressive CNS disease regardless of the radiation schedule used, including 20 Gy in 5 fractions to 30 Gy in 10 fractions (19). In a large series, median survival after WBRT was 17 months for patients in recursive partitioning analysis (RPA) class I; 7 months in class II; and 3 months in class III (20). Important prognostic factors were the performance status (PS), metachronous disease and initial response to chemotherapy. Nevertheless, survival not only depends on the brain disease but also on the extracranial progression: in a study of Gerdan *et al.* the 6-month survival rate dropped from 52% in the absence of extracranial disease to 0% when 3 or more organs are affected (21). RS is now largely available and is becoming more and more popular in the treatment of brain metastases. RS may allow avoiding toxicity risks and might be more efficacious: in a randomized trial, patients were operated followed by either WBRT or RS limited to the surgical cavity; there was less cognitive deterioration after RS (22). RS is now also used for brain metastases from SCLC: this is a very effective local treatment to control the disease but many patients will develop new brain metastases. As an example, one large series included 70 consecutive patients with brain metastases either after surgery, PCI or WBRT who were treated with RS between 2009 and 2015. Only three patients had an intracranial progression and 9 developed a meningeal carcinomatosis but 40 patients required repeated brain treatment. Indeed, at 12 months the rate of distant intracranial recurrence was 47% (23).

Extensive disease SCLC

PCI has also been proposed for extensive disease SCLC: in a meta-analysis of 14 clinical studies including 1,221 patients treated with PCI and with 5,074 patients in the control group, PCI reduced the incidence of brain metastases but also prolong survival (24). Nevertheless, a recent phase III trial has challenged this point of view and opened the debate on the place of PCI both for extensive and limited disease. This Japanese phase III trial randomized patients between PCI and no PCI after any response to the initial chemotherapy but only when a new MRI showed no brain metastases. The PCI schedule was 25 Gy in 10 fractions. The no PCI arm included an active surveillance with an MRI every 3 months. PCI reduced the incidence of brain metastases but without any benefit in term of survival and this was also observed for patients with a complete response to the initial treatment (25,26). The median survival in these 163 patients was even lower in the PCI arm (11.6 months) than in the control group (13.7 months). In contrast, the EORTC trial who also randomized PCI *vs.* no PCI for patients with any response to chemotherapy observed a reduction of the incidence of symptomatic brain metastases at 1 year from 40% to 16% and a statistically significant survival benefit from 13% to 27% (27). The PCI dose most commonly used was 20 Gy in 5 fractions but varied with 25 or 30 Gy in 10 fractions. So, what are the main differences between those trials? First, the EORTC trial did not include a brain imaging in the staging or at the time of PCI, it was only performed in presence of symptoms. In the Japanese trial, 64 out of 77 patients (83%) with brain metastases, even when asymptomatic, received radiotherapy and in the EORTC trial 35 out of the 59 patients (59%) were treated for a symptomatic brain disease. Furthermore, the Japanese trial often used RS. So, the main differences are an earlier diagnosis and a more aggressive approach in case of disease progression by the Japanese colleagues. We should also notice the clear difference in median survival between the two trials: between 11 and 13 months for the Japanese trial *vs.* 6 months for the European trial; reflecting a different patient population and probably also a very selected group of patients.

Limited disease SCLC

Do we have data in case of limited disease? There are

several reports but always with a very limited number of patients. In the series of Ozawa *et al.*, patients had MRI just before PCI: 29 patients received PCI and 95 not (28). At 2 years the incidence of brain metastases was respectively 45.5% and 30.8% in the group with and without PCI; without any difference in survival. In the non-PCI group 25 patients (26%) developed brain metastases of whom 17 (18%) relapsed only at the brain. All were treated with RS. In the series of Sakaguchi *et al.*, 60 patients with an almost complete response after chemoradiotherapy were just followed and only 13 (22%) developed brain metastases; treated by WBRT the ultimately cause of death was brain progression (29). However, the most common site of relapse was still locally, i.e., the lung. In the series of Mamesaya *et al.*, no difference was observed in terms of 3-year survival after PCI (60 patients) *vs.* no PCI (20 patients), the incidence of brain metastases being respectively 28% and 40% (30). In contrast, Giuliani *et al.* observed a higher number of patients without brain failure at 3 years and a better survival after PCI compared to the observation arm, respectively 40% *vs.* 28%. This series included 127 patients with PCI and 80 without (31). The key question is the selection of patients: those are retrospective studies and patients included in the no-PCI arm may have been selected by old age, poor PS or patient refusal.

Another interesting question is the role of PCI for surgically resected patients minimizing the risk of local progression. The current guidelines recommend adjuvant chemotherapy and PCI for early stage SCLC. The risk of brain metastases is related to the extent of the primary lung disease: in the largest series, the rates of brain metastases were respectively 13.6%, 22.4% and 27.8% for pathological stage I, II and III. PCI did not reduce brain relapse for stage I and a survival impact was only seen for stage III (32).

Hippocampus sparing radiotherapy

Finally, one might wonder whether it is possible to decrease the potential brain toxicity induced by PCI. The neurocognitive function highly depends on the sparing of the hippocampus area: doses above 7 Gy may alter the neurocognitive functions. Most of the brain metastases in case of non-small cell lung cancer (NSCLC) are located at distance from this area: amongst 1,133 brain metastases less than 100 (9%) were located within 1 cm from this area (33). Using modern radiation techniques, it is possible to deliver a dose of 25 Gy to the brain while keeping the dose to the hippocampus below 7 Gy. Randomized trials are on-going to show the safety and efficacy of sparing hippocampal sparing PCI. On the one hand, safety is certainly a concern. In contrast to Gondi *et al.* for NSCLC, the rate of hippocampal metastasis may be higher in SCLC: Korkmaz *et al.* observed a hippocampal metastasis rate of 32% in a series of 44 patients (34). On the other hand, some small published series have shown a clear potential benefit: Redmond *et al.* followed 20 patients without any decline in memory using the HVLT-R delayed recall and only two patients developed metastases in the under-dosed regions but both had additionally other brain metastases (35). On-going randomized trials may also give some additional information on the MRI.

Conclusions

Today, the question whether MRI monitoring and surveillance can be an alternative to PCI for patients with limited disease remains unanswered. There is no randomized trial comparing MRI surveillance *vs.* PCI using a hippocampus sparing approach but some series suggesting the feasibility of such an approach challenge the PCI dogma. Quality of life and an economic analysis should be part of a phase III trial. However, there is also a major problem due to the limited MRI resources in many countries. In the absence of a clear cut answer, PCI may still be proposed to patients but only after a clear explanation of benefits and risks while avoiding patients at high risk such as old patients and patients in poor condition.

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