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Prophylactic cranial irradiation in extensive disease small cell lung cancer: An endless debate

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ABSTRACT

Extensive disease Small cell lung cancer (ED-SCLC) represents a very aggressive malignancy in which brain metastases (BM) are quite common. Clinical trials on prophylactic cranial irradiation (PCI) have showed a clear decrease in the risk of developing BM but conflicting results concerning a possible survival advantage. A landmark European Organisation for Research and Treatment of Cancer (EORTC) prospective trial, as well as multitude of retrospective series confirm survival benefit after PCI. Recently, a Japan Clinical Oncology Group (JCOG) study did not find such survival benefit, provided that non-irradiated patients are closely followed by MRI. Henceforth, the role of PCI in this population has been questioned, on the ground of the possible absence of survival benefit, leading to a gradual shift in oncology practice. We performed a review of the literature on the subject of PCI in ED-SCLC patients. We conclude that PCI could still play a crucial role in these patients, considering not only a possible survival benefit, but also alternative endpoints, such as improved local control, delay in the onset of symptomatic BM and lower toxicity of a prophylactic- rather than an eventual active-intent treatment. Individualized attitude should be discussed with patients, while addressing all arguments in favour and against PCI.

1. Introduction

Small-cell lung cancer (SCLC) represents nearly 13% of all newly diagnosed lung cancers. Most patients present with extensive disease (ED) and, without treatment, median overall survival (OS) remains poor, ranging from 2 to 4 months (Goldstraw et al., 2007). At diagnosis, at least 18% of SCLC patients already present BM, and the rate could increase up to 25% with more accurate brain imaging such as magnetic resonance imaging (MRI). Furthermore, the incidence of BM increases considerably during the course of the disease, reaching up to 80% in patients surviving 2 years after diagnosis (van Meerbeeck et al., 2011). The development of BM can be associated with severe neurological symptoms and significant impairment of health-related quality of life (QoL), with a median survival of less than 6 months. The blood-brain barrier is poorly penetrated by most of the anticancer drugs, making systemic treatment less effective in preventing such a complication. One landmark achievement to prevent the development of BM was the introduction of prophylactic cranial irradiation (PCI) more than 40 years ago (Jackson et al., 1977). Since the publication of a meta-analysis in 1999 (Auperin et al., 1999), PCI has been recommended as standard of care in SCLC patients responding to initial systemic treatment. This meta-analysis included 987 patients and the use of PCI resulted in an absolute increase in the 3-year OS rate of 5.4%, along with a significant decrease in BM incidence (from 58.6% to 33.3% after 3 years). Even though patients with ED constituted only 15% of the studied population, the majority having limited disease (LD), the observed benefit was similar in the two subgroups.

In 2007, the European Organisation for Research and Treatment of Cancer (EORTC) published the results of a trial studying the role of PCI specifically in ED-SCLC patients who had responded to chemotherapy (Slotman et al., 2007). PCI reduced the incidence of symptomatic BM, decreasing the cumulative risk at 1 year from 40.4% in the control group down to 14.6% in the PCI group and prolonged the 1-year OS (27% in PCI group versus 13% in the control arm, hazard ratio

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[HR] = 0.68, p = 0.003). This trial, alongside the previous meta-analysis, strengthened the role of PCI in the ED population and PCI became the standard of care in metastatic patients with its use being recommended in international guidelines (Rudin et al., 2015; Fruh et al., 2013). Notably, an analysis of patterns of care in the USA showed high adherence to guidelines; namely, 98% of radiation oncologists recommended PCI for patients with ED-SCLC (Jain et al., 2016).

Over the past years the role of PCI in ED-SCLC has been readdressed (Takahashi et al., 2017) and conflicting results, as far as OS is concerned, have been reported. Takahashi and colleagues ran a phase III trial where patients were randomised at the end of their standard first-line chemotherapy and in the absence of progression to PCI versus brain MRI monitoring. The study did not show any difference in terms of OS between the 2 arms, with a median OS of 11.6 months (in the PCI arm) versus 13.7 months (in the observation arm) (HR = 1.27; 95% confidence interval [CI] 0.96–1.68, p = 0.94). The study was interrupted early for probable futility and based on these findings, the role of PCI has been challenged and become controversial. International guidelines, such as Version 1.2019 National Comprehensive Cancer Network (NCCN) guidelines (Network NCC, 2019) suggest to consider PCI or MRI brain surveillance in ED-SCLC with complete or partial response to first line chemotherapy.

Interestingly, although consolidation radiotherapy to the initial thoracic site in ED-SCLC has not been shown to improve OS (Gore et al., 2017) international guidelines suggest the use of this treatment modality, whereas PCI still remains a matter of debate.

The aim of the present review is to critically analyze prospective trials and retrospective series reporting results in terms of intracranial control and OS in ED-SCLC patients with the intention of clarifying the role and finding a possible place for the use of PCI in this setting.

2. Materials and methods

An extensive review of the literature has been performed between April 2018 and August 2019 throughout *PubMed.* Articles reporting on “PCI in ED-SCLC” and “metastatic SCLC” have been identified and analyzed. In order to avoid studies in which patients were treated with non-standard radiotherapy (RT) doses or non-platinum containing systemic treatment, only publications after 2000 have been considered. The following keywords have been entered to identify potential articles: ((small AND cell AND lung AND cancer) OR SCLC) AND (extensive OR ED OR metastatic OR stage 4) AND (PCI OR (prophylactic AND cranial AND irradiation)). We found and screened 690 articles. These were screened by relevancy. Review articles, commentaries, case reports and abstracts have been excluded. Studies targeting LD-SCLC or reporting on patients treated with concomitant therapy (systemic treatment and/or thoracic RT), and reports without clear comparison between PCI treated patients and observed population were excluded. The final reference list, based on originality and relevance to the broad scope of this review, contained 8 full-text articles, including prospective and retrospective trials that were included in the qualitative synthesis. Quantitative analysis was done on the final list of 6 articles. The flowchart is presented in Fig. 1.

3. Results

We have identified and included 6 studies in the review, 2 prospective (Slotman et al., 2007; Takahashi et al., 2017) and 4 retrospective (Sharma et al., 2018; Bang et al., 2018; Chen et al., 2016; Nicholls et al., 2016). All the retrospective series favor PCI in terms of OS and intracranial control. The 2 prospective trials report conflicting results with regards to OS, while both favor PCI in terms of local control.

Radiation treatment dose and fractionation vary slightly between the series (total PCI dose ranges from 24 to 30 Gy), with 25 Gy in 10 fractions being the most common schedule (Table 1).

Brain screening for BM at diagnosis was always performed in both prospective and retrospective trials with the exception of one prospective study (Slotman et al., 2007) where screening for BM was performed only in 29% of patients. MRI was the preferred imaging modality. Computed tomography (CT) scan instead of MRI was used in a minority of cases and mostly due to MRI contraindication (pacemakers, artificial implants, etc). Only in one prospective study brain imaging was systematically performed after systemic treatment and before PCI (Takahashi et al., 2017). In two studies there was no standardized protocol and only a few patients had brain imaging, either CT or MRI (Bang et al., 2018; Nicholls et al., 2016). Information regarding brain imaging modalities before PCI is missing in two studies (Sharma et al., 2018; Chen et al., 2016).

Median follow up across studies was 23 months (range, 9–36).

3.1. Retrospective studies

Within the retrospective studies, the largest one (Sharma et al., 2018) used the American National Cancer Database and evaluated a total of 4257 SCLC metastatic patients (3784 not receiving PCI and 473 receiving PCI). In this large cohort, patients treated between 2010 and 2012 with chemotherapy for ED-SCLC and without BM have been analyzed. After propensity score matching on factors associated with receipt of PCI and OS, results in the overall cohort favored PCI with improved median survival (13.9 vs 11.1 months; p < 0.001), 1-year probability of survival (61.2% vs 44%, p < 0.001) and 2-year probability of survival (19.8% vs 11.5%, p < 0.001). The benefit was confirmed even after excluding patients with less than 6 months or with less than 9 months survival (median survival for patients surviving at least 6 months: 14% vs 11%; median survival for patients surviving at least 9 months: 15% vs 13%; p < 0.001).

More recently a publication from Ontario (Bang et al., 2018) reports results of 155 patients with ED-SCLC without baseline BM. Authors found a statistically significant difference in OS (HR 0.55; 95% CI 0.39–0.77; p = 0.0005) and time to BM (HR 0.40; 95% CI 0.23–0.66; p = 0.0004) with the use of PCI. Median survival for the PCI and non-PCI groups was 13.5 and 8.5 months, respectively. Furthermore, the authors found a significant increase in 1 and 2-year OS in the PCI group (HR 0.41; 95% CI 0.29–0.57; p < .0001). The median time to develop BM was also found to be longer in the PCI group (23.8 months vs 10.2 months) with an HR of 0.36 (95% CI 0.21–0.60; p < .0001). A survival difference with PCI was observed in both patients that received post-chemotherapy brain imaging (HR 0.55; 95% CI 0.35-0.88; p = 0.012) and those who did not (HR 0.48; 95% CI 0.29–0.77; p = 0.0025).

Furthermore Chen et al. (Chen et al., 2016) reviewed 204 ED-SCLC patients who had any response after 4–6 cycles of chemotherapy. PCI was performed in 45 patients (22.1%) and the remaining 159 (77.9%) were observed. PCI significantly prolonged median OS (16.5 vs 12.6 months [HR 0.63, 95% CI 0.41–0.96; p = 0.033]). Also, the risk of developing BM was lower in the PCI group (HR 0.48; 95% CI 0.30–0.76; p = 0.001), with 1-year incidence of BM of 17.1% vs 55.9% in the PCI and control group, respectively. PCI was a favorable independent predictor for OS in multivariate analysis. In this trial, brain imaging was mandatory prior to initial treatment.

Nicholls et al (Nicholls et al., 2016) reported their institutional experience and analyzed retrospectively patients with SCLC (both ED and LD) treated between January 2008 and December 2013. Of the 129 ED patient population, 13% received PCI. Median OS in the ED-SCLC cohort receiving PCI was 13.6 months compared to 5.6 months in patients not receiving such treatment (p < 0.001).

3.2. Prospective studies

At present, there are only two prospective trials available. The first one is the EORTC study published in 2007 by Slotman et al (Slotman et al., 2007). The primary endpoint of the trial was the time to

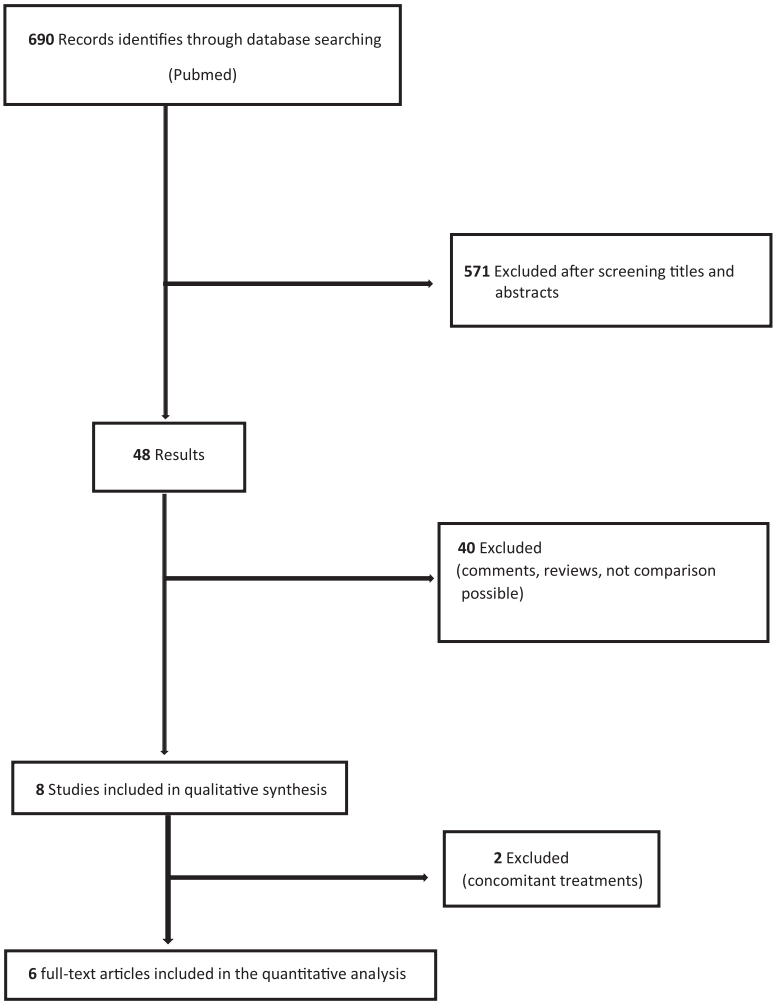

Fig. 1. Flow Chart of trials selected for the reviews.

development of symptomatic BM, while secondary endpoints were survival, QoL, toxic effects, and treatment costs. Cumulative risk of developing symptomatic BM within 1 year was 14.6% in the PCI group, compared to 40.4% in the control arm. Although OS was a secondary endpoint of the study, patients in the PCI group showed longer OS, with a median survival of 6.7 months compared to 5.4 months ($p = 0.003$). In this study, brain imaging was not mandatory before enrolment and not routinely performed during follow-up (unless patients presented symptoms suggestive of BM).

The second prospective trail was run by the Japan Clinical Oncology Group (JCOG) readdressing the role of PCI in ED-SCLC (Takahashi et al., 2017). In this phase III trial, patients were randomised to PCI or observation with active MRI monitoring. Conversely from the EORTC trial, the primary endpoint was OS, while time to BM was among secondary endpoints. This study did not demonstrate any difference in median OS between patients receiving PCI (11.6 months) and those assigned to the observation arm (13.7 months) (HR 1.27; 95% CI 0.96–1.68, $p = 0.94$]. However, the cumulative incidence of BM at 6, 12 and 18 months was lower in the PCI group compared to the observation group (15%, 32.9% and 40.1% vs 46.2%, 59% and 63% respectively, Gray's $p < 0{\cdot}0001$).

In the current literature, reports on QoL and adverse events (AE) are inconsistent and reported only in three publications (Takahashi et al., 2017; Chen et al., 2016; Slotman et al., 2009). In the EORTC trial (Slotman et al., 2007, 2009), there was no statistically significant difference in global health status between the two groups from baseline to 9 months ($p = 0.10$). Most common side effects in the PCI group were hair loss and fatigue, that were significantly higher compared to control arm ($p < 0.001$). No significant differences were found between the study groups in role functioning ($p = 0.17$), cognitive functioning ($p = 0.07$) or emotional functioning ($p = 0.18$). In the JCOG trial (Takahashi et al., 2017), Mini-mental state examination (MMSE) scores were assessed at baseline, after 6 and 12 months, without significant differences between the two groups. Toxicity scores of grade 3 or higher were similar between the irradiated or observed group. The most frequent grade 3 AE were anorexia (5% in the PCI group vs 2% in the observation cohort), malaise (3% in the PCI group vs 1% in the observation cohort) and muscle weakness (1% in the PCI group vs 5% in the observation cohort). Impact on QoL was not addressed in this trial. Chen et al. (2016) report acute and late AE in the irradiated population. Grade 3 or worse acute toxicities were overall low (2.2% grade 3 headache, no grade 4 acute side effect, and no grade 3 or 4 late effects). The most frequent grade 2 acute side effect was headache (6.7%) and nausea or vomiting (4.4%).

4. Discussion

Due to the considerable likelihood to develop BM and the clinically relevant consequences that this event implies, the prevention of BM is of paramount importance in patients with SCLC. Consensus has been reached in the setting of LD-SCLC, where, according to international guidelines (Rudin et al., 2015; Fruh et al., 2013), PCI is part of standard treatment, providing a benefit in terms of survival and local control. However, in the ED-SCLC, the indication to deliver PCI is not

Table 1
Principal Characteristics of Trials Included in the review.

Trial	Nr pt (tot.)	Median age (y)	Design	Median follow up (mth)	Brain imaging Before PCI	PCI dose	Primary Endpoint	Secondary Endpoint	Main efficacy results	Main safety results
Slotman B. et al. 2007	**286**	62	Multicenter Phase III RCT	9	no	20-30 Gy	Time to Symptomatic Brain MTS	OS, QoL, AE, treatment costs	Lower risk of symptomatic brain MTS (hazard ratio, 0.27; 95% confidence interval [CI], 0.16 - 0.44; P < 0.001). 1-year survival rate: 27.1% in the irradiation group vs. 13.3% in the control group.	Common acute side effects with irradiation: headache, nausea / vomiting, fatigue or lethargy. No clinically significant effect on global health status.
Takahashi T. et al. 2017	**224**	69	Multicenter Phase III RCT	11.5	Yes	25 Gy	OS	Time to BM, PFS, AE, neurocognitive function	Median OS: 11.6 months in the irradiation group vs. 13.7 months in the control group (hazard ratio 1.27, 95% CI 0.96-1.68; p = 0.094).	Most frequent severe adverse events at 3 months were anorexia (6% in the irradiation group vs 2% in the observation group), malaise (3% vs < 1%), and muscle weakness in a lower limb (< 1% vs 5%).
Nicholls L. et al. 2016	**129**	65	Retrospective	7.6	Not consistent	25 Gy	OS PCI use Pt.demogr	N/A	Median OS in LS-SCLC patients: 18.8 months in irradiated pts vs. 8.2 months in control group (P < 0.001). Median OS in ES-SCLC: 13.6 months in irradiated pts vs. 5.6 months in control group (P < 0.001).	Not available
Chen Y.et al. 2016	**204**	58	Retrospective	11.2	N/A	25 Gy	OS Risk for BM	N/A	Median OS: 16.5 months with PCI vs. 12.6 months with control (hazard ratio 0.63; 95 % CI 0.41 - 0.96; p = 0.033).	Acute and chronic adverse effects were generally low grade and well tolerated in patients receiving PCI.
Sharma S. et al. 2018	**4257**		Retrospective	30	N/A	> 20 Gy - < 30 Gy	OS	N/A	Whole series: OS with PCI longer than control (hazard ratio 0.66; 95% CI 0.60-0.74; P < .0001). Propensity score-matched cohorts: median OS 13.9 months PCI vs. 11.1 months control; P < .0001).	Not available
Bang A.et al. 2018	**155**	66	Retrospective	*	Not consistent	25 Gy	OS Postchemotherapy brain imaging	N/A	OS better with PCI (HR 0.55; 95% CI: 0.39-0.77; P = 0.0005) Median OS: 13.5 months with PCI vs. 8.5 months with control.	Not available

Gy: Gray; OS, overall survival; QoL, quality of flife; AE, adverse events; N/A, not available.
* not specified but minimum follow up: 36 mths.

universally established. So far, on the basis of the results from the EORTC trial (Slotman et al., 2007), most guidelines (Rudin et al., 2015; Fruh et al., 2013) recommended PCI for ED-SCLC patients who achieved at least a partial response. However, after the publication of the JCOG trial (Takahashi et al., 2017), PCI in this setting has become more controversial due to the uncertainty of OS benefits and practice has been shifting. For example in the recent Impower 133 trial (Horn et al., 2018) comparing chemotherapy plus Atezolizumab versus chemotherapy alone in ED-SCLC patients, PCI was optional and only 10% of the centers opted for it.

The EORTC study (Slotman et al., 2007) was the cornerstone and first randomized trial. It showed that PCI reduces the risk to develop symptomatic BM by two to three-folds and prolongs OS with 1-year OS reaching 30% in the treated population versus 13% in the non-PCI group. Key criticism to the EORTC trial is that patients were not systematically screened for BM (unless symptoms suggested so). This pragmatic approach may have led to treating with PCI some patients that already had BM, and this could imply that the OS improvement could have been due to the treatment of existing disease, and not to a true prophylactic effect. However, according to Hochstenbag et al. (2000), the proportion of patients with asymptomatic BM detected by follow-up MRI is rather small, about 15%, and we argue that it seems unlikely that this small proportion can justify the observed OS benefit.

The JCOG study (Takahashi et al., 2017) found in the first analysis based on 163 patients no benefit in terms of OS with a median survival of 10.1 months in the PCI group compared with 15.1 months in the control group ($p = 0.091$). This finding led to the premature termination of the trial for probable futility. At the final analysis, with a longer follow-up of almost 12 months, the difference in median survival was less important (2 months difference vs 5 observed in the first analysis), leading the Authors to conclude that prophylactic cranial irradiation is not essential for patients with ED-SCLC if they are regularly assessed by MRI during follow-up, and treated for BM when encountered. Unlike the EORTC trial (Slotman et al., 2007), all patients had brain MRI before the enrolment, as well as during follow-up every 3 months for the first year, and every 6 months thereafter.

These results raise two important considerations. First, routine brain MRI imaging follow-up every 3 months would come with a considerable socioeconomic impact, which would not easily be applicable in clinical practice in many countries. Second, when comparing 1-year OS between the two trials, patients enrolled in the JCOG (Takahashi et al., 2017) had a much better survival in both the PCI arm and the control arm than in the EORTC trial (Slotman et al., 2007) (53.6% vs 13.3% in the non-PCI arm, 48.4% vs 27.1% in the PCI arm). This may be partially explained by different genetics between Asian and Caucasian populations (Zhou and Christiani, 2011), but also by a possible selection bias. Indeed, the proportion of patients who were offered second-line chemotherapy was higher in the JCOG (Takahashi et al., 2017) compared to the EORTC (Slotman et al., 2007) trial: within the JCOG (Takahashi et al., 2017), 40 patients in the observation arm (36%) and 29 patients in the PCI group (26%) were offered fourth-line chemotherapy. This is quite an exceptional event in SCLC patients and one might argue that it does not reflect daily practice.

As the unexpected results of the JCOG trial casted considerable confusion into the field, the topic of PCI indication in ED-SCLC became rapidly one of the most vigorously discussed areas in thoracic oncology. Several groups published independently letters, reviews and meta-analyses, with almost an unequivocal conclusion of some survival benefit derived from PCI, opposing the recent change of guidelines (Eze et al., 2019; Le Pechoux et al., 2017; Manapov et al., 2018).

A systematic review and meta-analysis published by Maeng and colleagues (Maeng et al., 2018) used OS as primary endpoint. They queried databases for primary and secondary analyses of prospective data only, with no exclusion based on publication year or systemic treatment employment. Of 6 analysed papers, only two of which being primary analyses, i.e. the EORTC and JCOG trials, and due to some auto-reported limitations of third-level patient pooling, this meta-analysis did not find an OS benefit of PCI (HR = 0.82; 95%, CI: 0.60, 1.11; $p = 0.19$). However, the PCI group had a significant advantage in 1-year survival (37.1% versus 27.1%; HR = 0.87; 95% CI: 0.80–0.95; $p = 0.002$), progression-free survival (PFS) (HR = 0.83; 95% CI: 0.70–0.98; $p = 0.03$) and decreased risk of BM (HR = 0.34; 95% CI: 0.23–0.50; $p < 0.001$) compared to the non-PCI group.

Another meta-analysis by Ge and colleagues (Ge et al., 2018) was recently published, showing that PCI significantly improved OS (HR = 0.57; 95%, CI: 0.47-0.69; $p < 0.001$) and reduced BM incidence (RR = 0.47, 95%CI: 0.33, 0.69; $p < 0.01$). However, this study had many flaws: an extremely heterogeneous population, different PCI doses, and PCI timings.

Development of symptomatic BM is responsible for significant morbidity, including hospitalization, and a median survival of only 4–6 months (Felletti et al., 1985; Lee et al., 2006; Gregor et al., 1997). The EORTC and JCOG trials (Slotman et al., 2007; Takahashi et al., 2017) have shown that PCI significantly reduces the incidence of BM by two- to three-folds. In the Japanese trial (Takahashi et al., 2017) the cumulative incidence of BM at all timepoints was significantly higher in the observation arm. In this group, 83% of patients (compared to 46% in the PCI arm) needed cranial radiotherapy. Also in the EORTC trial, cranial irradiation was ultimately offered to 59% of patients with symptomatic BM in the non-PCI cohort vs 8.3% in the PCI cohort (Slotman et al., 2007). Interestingly, LD-SCLC patients who develop BM have worse prognosis than those with locoregional recurrence (3-year OS, 6% vs 38%, $P < 0.001$). Moreover, among patients with BM, those who had received PCI had again significantly better prognosis (3-year OS, 17% vs 0%, $P = 0.005$) and had less BM (more than 5 BM 12% vs. 68%, $P < 0.001$), potentially permitting eventual salvage stereotactic radiosurgery (SRS), exclusively after PCI (Nakamura et al., 2018).

The results from retrospective series are in line with these findings. Chen et al (Chen et al., 2016) found a significantly increased BM-free survival ($p = 0.002$) with 1-year incidence of BM of 17% vs 56% in the PCI and non-PCI group, respectively. The median time for the development of BM was also found to be longer in the PCI group (23.8 months vs 10.2 months) by the Ontario study (Bang et al., 2018).

Although the CALGB 30504 study (Salama et al., 2016) was not included in our final list because of the presence of a possible confounding factor (i.e. the use of an anti-angiogenic tyrosine kinase inhibitor), we find it is worth taking into consideration the post-hoc unplanned analysis. This trial was a phase II randomized trial of sunitinib vs placebo in ED-SCLC patients responding to platinum-based chemotherapy. Brain imaging was required at pre-enrollment. PCI was delivered at the discretion of the treating physician. Results showed a trend for improved PFS and OS in patients receiving PCI and sunitinib, with a considerable rate of central nervous system progression in the non-PCI group (27% vs 12%, $p = 0.05$).

Hence, the burden of brain failure is relevant and must be considered, for both the patient's QoL that deteriorates with such an event (Le Rhun et al., 2015) and the balance of cost/benefit.

Over the past decade, concerns regarding the possible decline of the neurocognitive functions (NCF) in patients treated with PCI have surfaced. However, there is no robust data to demonstrate any difference in NCF with or without PCI (Grosshans et al., 2008). In a review by Tallet et al. (2012) on NCF in patients receiving whole-brain radiotherapy (WBRT), either administered as a PCI or as a therapeutic treatment for BM, most studies showed a very low incidence of NCF impairment at one year in the setting of PCI. More recently a randomized phase III trial assessing the role of PCI in stage III Non-Small Cell Lung Cancer (Ruysscher et al., 2018) showed that PCI significantly decreases the proportion of patients who develop symptomatic BM and significantly increases the time to develop symptomatic BM at the cost of slightly increased low grade toxicity (grade 1 and 2 memory impairment in 26 of 88 patients and cognitive disturbance in 16 of 86 patients). QoL decreased in the treated population only 3 months after

Table 2
Individual patient-centred arguments in the debate of PCI indication.

Against PCI	Favoring PCI
No OS benefit	Reduction in BM rate
Potential risk of NCF impairment	Rigorous and expensive MRI-based follow-up required
Risk of futility if progression elsewhere	Possibility of HA to imporve NCF
Possibility of rescue WBRT upon BM detection	Diminished QoL with appearance of symptomatic BM

As currently the choice of PCI is left at clinician's and patient's discretion, a thorough discussion of all possible consequences of the final decision is essential. Hereby we provide a comprehensive list of topics that should be discussed leading to a well-informed patient decision. OS - overall survival, NCF - neurocognitive function, QoL - quality of life, BM - brain metastases, HA - hippocampal avoidance, WBRT - whole brain radiotherapy.

PCI and was similar to the observation arm thereafter (median follow up of 48.5 months). MMSE was the only parameter assessed within the Japanese trial (Takahashi et al., 2017), and it did not show any difference between the two arms after 12 and 24 months. Furthermore, most patients possibly already have abnormal neuropsychology testing after chemotherapy and before PCI, stressing also the importance to assess the possible contribution of chemotherapy on NCF. QoL was tested in the EORTC trial (Slotman et al., 2007) and the impact of irradiation on functioning scales was moderate.

Multiple studies have demonstrated that NCF is associated with the generation of new neurons within the hippocampus. Therefore, preservation of this particularly sensitive area could further lower the risk of NCF impairment (Gui et al., 2019; Kim et al., 2018). The incidence of BM in the hippocampal region is low and the safety of hippocampal avoidance (HA) PCI in the setting of SCLC has been proven (Kundapur et al., 2015). A phase II trial confirmed that conformal avoidance of the hippocampal dentate gyrus using intensity-modulated radiotherapy (IMRT) during WBRT is associated with a better preservation of memory and QoL (Gondi et al., 2014).

Presently, there is an ongoing multicentre phase III trial comparing standard PCI versus PCI with HA in SLCL patients, which may ultimately establish the role of HA in reducing radiation-induced NCF decline (Rodríguez de Dios et al., 2018).

Moreover, in a recent attempt to further reduce NCF, a phase III was conducted to study the role of WBRT plus Memantine (a medication used to treat moderate to severe dementia) with or without HA in patients with BM. Results suggest an improvement in patient-reported symptoms and better preservation of NCF in the HA arm, while achieving similar intracranial control (Gondi et al., 2019).

Increased neurological side effects may be associated also with patient age. Although clinical data support the efficacy of PCI even in elderly patients, it seems to be associated with a slightly more frequent adverse effects in elderly (Maeng et al., 2018). Moreover, older patients often carry a worse performance status as well as a higher rate of comorbidities, affecting their baseline survival, which might cast doubts over the PCI necessity. Accordingly, PCI is much less performed in such patients despite no age limit in treatment guidelines (Damhuis et al., 2018). However, in a recent consensus of the European Society for Therapeutic Radiation Oncology (ESTRO) and the International Association for the Study of Lung Cancer (IASLC), experts supported PCI in fit elderly patients (Putora et al., 2019).

To comment on PCI doses and schedules, wide variations have been seen among studies with doses ranging from 20 to 30 Gy resulting in different biologically equivalent doses (up to 39 Gy with an α/β of 10 Gy). Nowadays the standard is 25 Gy in 10 fractions. A higher dose does not translate into higher local control rates, and is associated with a possible negative impact on NCF (Le Pechoux et al., 2009).

If BM occur after PCI, rescue brain radiotherapy can still be proposed. Bernhardt and colleagues found that cranial re-irradiation by both WBRT and SRS is feasible and relatively effective in symptom palliation with mild toxicity. Of note, SRS was not inferior to WBRT in this scenario and led to borderline better median survival (Bernhardt et al., 2016). Similar results were more recently obtained by Suzuki et al., who retrospectively analyzed different treatment modalities in patients with BM occurrence/recurrence after PCI or WBRT. Patients treated with SRS had the most favorable OS, whereas those undergoing repeat WBRT had worse outcomes than those salvaged with chemotherapy alone (Suzuki et al., 2018).

In both of these studies favoring SRS over WBRT, there is a probable selection bias in favor of patients with lower BM burden in the SRS group. In any case, survival rates after BM occurrence are usually counted in weeks rather than years and patient performance status seems the most favorable OS, whereas those undergoing repeat WBRT had worse outcomes than those salvaged with chemotherapy alone (Suzuki et al., 2018).

In both of these studies favoring SRS over WBRT, there is a probable selection bias in favor of patients with lower BM burden in the SRS group. In any case, survival rates after BM occurrence are usually counted in weeks rather than years and patient performance status seems to be the determining factor. Retreatment toxicity likely does not play a great role in overall outcome; however toxicity is possibly reduced if SRS is used for BM control after PCI (Rodríguez de Dios et al., 2018; Gondi et al., 2019).

Finally, presently, there are no specific risk stratification factors allowing to identify a sub-population of ED-SCLC patients at lower or higher risk of developing BM and clinical management algorithms currently are the same for the bulk of these patients. It is likely that some tumor-inherent determinants that constitute a tropism towards cranial metastasizing may be identified in the near future.

At present time, we emphasize the need for individualized clinical decision-making along with patient's choice. Patients should be presented with a detailed explanation of possible outcomes, pros and cons of PCI and of its omission. We provide a simple example of topics that should be discussed with the patients (Table 2).

5. Conclusions

Our review has highlighted the reduced incidence of BM with PCI in ED-SCLC patients who respond to first-line platinum-based chemotherapy. Thus, when considering omitting PCI, the risk of BM, its impact on QoL, and subsequent need for salvage treatment should be openly discussed with the patient. Furthermore, concerns about NCF decline could be curtailed given the availability of IMRT with HA techniques.

Declaration of Competing Interest

None.

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