



Radiotherapy for brain metastases from small-cell lung cancer in distinct clinical indications and scenarios

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Contributions: (I) Conception and design: L Kepka; (II) Administrative support: None; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: None; (V) Data analysis and interpretation: None; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

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Abstract: Management of brain metastases (BM) from small-cell lung cancer (SCLC) is complex and not supported by a strong evidence from prospective clinical trials. Owing to the different clinical and pathological characteristics of SCLC, patients with this histology were not included in the prospective studies on the value of whole-brain radiotherapy (WBRT) and local surgical or ablative radiation treatment like stereotactic radiosurgery (SRS). Chemotherapy also represents a major part of the armamentarium against BM from SCLC due to the well-recognized chemoresponsiveness of this cancer and the frequent presentation of BM with extracranial progression. WBRT in combination with chemotherapy has long been a standard approach in this setting. However, data on the neurocognitive toxicity and the lack of documented impact on overall survival of WBRT in the management of BM from other solid tumors, as well as the increasing availability of the stereotactic radiotherapy technologies, has led to the increasing use of SRS with omission of WBRT also in SCLC. In the current review the use of different modalities of radiotherapy and ways of combining radiotherapy with chemotherapy for BM from SCLC will be presented for distinct clinical situations: presentation of BM synchronous with primary, metachronous presentation of BM—without previous prophylactic cranial irradiation (PCI) *vs.* after PCI, and asymptomatic BM found at the staging before PCI.

Keywords: Small-cell lung cancer (SCLC); brain metastases (BM); whole-brain radiotherapy (WBRT); stereotactic radiosurgery (SRS)

Submitted Sep 06, 2019. Accepted for publication Oct 14, 2019.

doi: 10.21037/jtd.2019.10.51

View this article at: <http://dx.doi.org/10.21037/jtd.2019.10.51>

Small-cell lung cancer (SCLC) is a rapidly progressing disease with a predilection for early metastasizing. The most common site of metastases is the brain; about 40–50% of patients develop brain metastases (BM) within 2 years from diagnosis (1). Radiotherapy plays a crucial role in the management of BM from SCLC. However, there are a number of distinct biological and clinical characteristics of SCLC that preclude the direct incorporation of the results of the studies on the treatment of BM from other solid tumors to the management of BM from SCLC. These are: the high aggressiveness of the disease with rapid micro- and macro-dissemination to the brain, the rare

occurrence without the presence of extracranial disease, chemo-sensitivity that incites the use of systemic treatment, the use of prophylactic cranial irradiation (PCI) as a part of the standard strategy for patients without BM, and a dismal disease course. The historical treatment of BM from SCLC was whole-brain radiotherapy (WBRT) alone or combined with chemotherapy (CHT). The outcome of such strategies was poor; median overall survival (OS) after WBRT was 3.0–4.7 months in both prospective and retrospective studies (2–5). However, a temporal trend towards a slight survival improvement in SCLC exists (6) and is also seen for patients with BM in recently published

population-based studies. In the cohort of 13,657 patients with BM from SCLC managed with WBRT in the USA between 2004 and 2013, a median OS of 8 months was demonstrated (7). In another study, also based on the data from the USA National Cancer Database (NCDB), 5,752 patients managed between 2010 and 2014 with WBRT for BM from SCLC had a median OS of 7 months (8). Thus, contemporarily treated patients probably had a slightly better, yet still disappointingly low survival chance.

Technological advances in radiotherapy, the neurocognitive toxicity of WBRT, the lack of impact of WBRT on survival in BM from other solid tumors led to the increased use of up-front stereotactic radiosurgery (SRS) with omission of WBRT also in SCLC (7). However, a high potential of SCLC for diffuse dissemination in the central nervous system (CNS), the impact of PCI on survival in the absence of overt BM (9,10), and the exclusion of SCLC patients from the trials on radiotherapy of BM (11-15) indicate that the optimal way of delivering radiotherapy (WBRT *vs.* SRS or both) for patients with BM from SCLC remains to be defined. In the current review we present some evidence and unresolved issues on the use of radiotherapy for patients with BM from SCLC in distinct clinical situations: (I) in newly diagnosed SCLC, (II) in asymptomatic BM, found at the staging before PCI, (III) at metachronous presentation—without previous PCI *vs.* after PCI. Each of these clinical situations will be also presented in the context of the suitability of the patient for the use of SRS, the role of WBRT, and the use of systemic treatment.

BM in synchronous presentation with initial diagnosis of SCLC

Brain imaging [magnetic resonance imaging (MRI) preferred over computerised tomography (CT)] is mandatory in the initial staging of SCLC, because of the frequency of BM in SCLC at presentation (about 15%) (1). Even if other distant metastases are detected at the initial work-up, brain imaging is still recommended with a view to avoiding an early neurological deterioration from untreated BM and to prevent complications during CHT delivery, as well as to properly select patients for PCI (16,17). The first-line treatment for such patients is CHT, due to the well-known chemo-sensitivity of SCLC and the need to start the treatment without delay in this very aggressive cancer in view of avoiding deterioration of performance status related to the systemic disease progression.

A question remains concerning the way of introduction of

brain radiotherapy in relation to CHT in such patients and the efficacy of CHT itself in the management of BM from SCLC. The use of CHT even for chemo-sensitive tumors has been questioned, because of the notion that the blood-brain barrier (BBB) is impenetrable/poorly penetrated by most drugs and therefore the brain is a pharmacological sanctuary site for microscopic tumors. However, it has been shown that cytotoxic agents may achieve a good penetration into the brain, because the BBB is damaged by BM, and there are clinical data confirming it (18). In the pooled data from five studies on 64 patients with synchronous BM, a 66% response rate (RR) was demonstrated (19). On the other side, the RR is usually lower in the brain than in the extracranial sites; in the study on 24 asymptomatic patients with BM from SCLC who received CHT with cyclophosphamide, doxorubicine, and vincristine, the RR was 27% in the brain and 73% outside the brain (20). There is only one randomized trial that compared CHT alone (teniposide) *vs.* teniposide + WBRT 30 Gy. In this trial, 120 patients with progression in the brain after or during first-line CHT were included. CHT alone led to a significantly shorter time to progression within the brain ($P=0.005$). RR were 57% and 22% for combined modality arm and CHT alone arm respectively, $P<0.001$. OS was not different in both arms (3). Additionally, a Cochrane Review evaluating a role of CHT for BM from SCLC found that there was insufficient evidence to indicate a survival advantage for CHT alone (21). Recently, it was demonstrated that the addition of atezolizumab [a humanized monoclonal anti-programmed death ligand 1 (PD-L1) antibody] to CHT (carboplatin + etoposide) in the first-line treatment of extensive-stage (ES) SCLC resulted in a significantly longer OS than CHT alone. In included patients with BM, no difference between the two groups was observed in OS or progression-free survival (PFS). However, patients with BM represented only 9% of the entire group. Thus, the firm conclusion about the role of immunotherapy in the management of BM from SCLC cannot be drawn (22). Certainly, further research is needed in this area. Nevertheless, the presented data (risk of rapid progression in the brain without the use of WBRT and lower RR in the brain) suggests that radiotherapy should be considered for asymptomatic patients after completion of CHT regardless of CHT response. However, we should be aware that strong evidence for such an approach is lacking. Recently, the USA NCDB-based study on 1615 elderly patients (≥ 75 years) with BM from SCLC showed that WBRT did not improve OS in patients who received CHT; median OS was 5.6 and

6.4 months with and without WBRT, respectively, $P=0.43$. In patients without CHT, median OS rates were 1.9 and 1.2 months with and without WBRT, respectively, $P<0.0001$ (23). These findings suggest that in a fragile population of elderly patients who are still able to receive CHT, an omission of WBRT may be considered.

In addition, there is a special case when SCLC histology is found unexpectedly in a brain tumor during a craniotomy without prior diagnosis of the lung primary of this histology. Obviously, the staging procedures in order to find the lung primary and the extracranial extensions of the disease should be launched before the therapeutic decision. When the lung primary is found, the management is not different than in the case of the unremoved BM diagnosed during an initial staging of SCLC, namely it is CHT followed by WBRT. SRS of the tumor bed is not yet a standard of care in SCLC, because of the increased risk of brain failure elsewhere. For this reason, the BM from SCLC were also not included in the clinical trials that compared the use of tumor bed SRS with the omission of WBRT (14,15).

The above considerations were mainly dedicated to the treatment of asymptomatic or slightly symptomatic patients with BM. For symptomatic BM patients, a customary practice is to start treatment with radiation in order to improve the patient's condition before the start of CHT, because the response in the brain is more likely to occur with radiotherapy. However, such decisions should be taken jointly with a medical oncologist.

WBRT following CHT in asymptomatic patients remains the standard treatment of synchronous BM in newly diagnosed SCLC. There is no strong evidence for the use of SRS in this indication. However, the increasing tendency towards the use of SRS with omission of WBRT in BM from SCLC is observed (7). This issue is discussed in more details below.

Pre-PCI imaging for limited stage (LS) or ES SCLC

Results of meta-analyses confirmed that PCI reduces BM incidence and improves OS rates in both LS and ES SCLC (9,24). Taking into account the low percentage of patients with ES included in the meta-analysis [15% of patients in Auperin *et al.* meta-analysis (9)], and a short OS of ES SCLC patients with practically no long-term survivors, the use of PCI for this group was more debatable (25). For a long time, PCI was recommended only for LS SCLC patients after completion of (radio) CHT. Based

on the effectiveness and toxicity data, PCI at the dose of 25 Gy in 10 fractions has been recommended for LS SCLC patients who have a good response to CHT (26,27). The EORTC phase 3 trial demonstrated that also the ES SCLC patients who responded to the first-line CHT had improved survival with the use of PCI; 1-year OS rates were 27.1% and 13.3% in the PCI and non-PCI (control) group, respectively, $P=0.003$. Brain imaging was not a part of standard staging, neither at baseline, nor before PCI, unless symptoms suggestive of BM were present (10). Contrarily, in the Japanese trial that evaluated a value of PCI in ES SCLC patients, the MRI was required at baseline, before randomisation and every 3 months in the follow-up. This study confirmed that PCI reduces the risk of BM development without any survival benefit. There was even a non-significant trend for longer survival observed in patients who did not receive PCI (17).

Brain imaging has not always been a standard procedure before qualification for PCI in either LS or ES SCLC. NCCN guidelines recommend pre-PCI MRI for patients with response to initial therapy (28). Some prospective studies reported using MRI or CT scans, some did not require any imaging, and some did not mention any requirements for imaging (29,30). A recent survey conducted in the USA, demonstrated that up to 96% of 309 radiation oncologists performed pre-PCI MRI (31). The European practice differs in this regard; according to the recommendations, the brain imaging is not mandatory before PCI, at baseline in elsewhere confirmed ES, or during follow-up in the absence of symptoms (32). Recently, in the survey on the practice of PCI for ES SCLC, some European experts from both the European Society for Therapeutic Radiation Oncology (ESTRO) and the International Association for the Study on Lung Cancer (IASLC) highlighted that they perform PCI for ES SCLC patients, because the restrictions in reimbursement for MRI and problems with its availability prevent them from the omission of PCI that was proved to prolong OS in one randomized trial, in which patients had suboptimal brain imaging performed (10). However, with MRI surveillance, patients could avoid brain irradiation, unnecessary in some cases (33).

What evidence do we have for the value of performing MRI before qualification for PCI?

Against such an approach, there are some indications that patients who are free of BM at baseline and develop BM during a first line treatment, have a particularly poor

prognosis. The use of WBRT doses higher than usually prescribed for PCI did not reverse the poor prognosis of these patients in two case-series (34,35). Thus, the routine use of the pre-PCI MRI would not be supported. In one study, patients with initial diagnosis of LS SCLC had a baseline MRI performed. Complete responders who qualified for PCI after treatment completion had a second, pre-PCI MRI; 13 out of 40 (32.5%) patients harbored asymptomatic BM in the pre-PCI MRI. Despite higher WBRT doses, patients with pre-PCI detected BM had worse OS than those without BM in the pre-PCI MRI receiving standard PCI doses: 17% *vs.* 74% of 1-year OS rate, respectively, $P=0.0001$. Of note, the PCI was applied late in this study, between 4 and 10 months after diagnosis (34). Similar findings were presented at the IASLC World Conference on Lung Cancer in 2018. From 119 LS SCLC patients with a baseline brain MRI, referred for PCI after chemo-radiotherapy, 25 (21%) had BM on pre-PCI MRI, and 23 were asymptomatic. Patients with BM in pre-PCI MRI had significantly shorter OS than those without. The duration of chemo-radiotherapy (in excess of 4.5 months) was the only prognostic factor for the occurrence of the pre-PCI BM (35). What we learn from these studies is that we should avoid unnecessarily prolonging chemo-radiotherapy for SCLC and start PCI as quickly as possible after the end of the first-line treatment. A radiobiological modeling study supports this opinion. When PCI was delayed for over 60 days, significantly higher doses were necessary for reduction of the risk of BM from SCLC, which is consistent with a fast growth rate of the untreated subclinical BM (36).

Performance of the pre-PCI MRI is supported by the results of the above mentioned Japanese randomized trial that challenged the routine use of PCI for ES SCLC and supported the use of the MRI brain surveillance and early salvage radiation for overt BM (17). A lesson taken from this trial is that BM identified early in the context of MRI surveillance (not as in the above case-series, with patients for whom the delay in the start of PCI led to the development of overt BM), may be salvaged without negative impact on survival. It is also pointed out that the omission of PCI with a strict MRI surveillance may spare a subset of patients from brain irradiation and neurocognitive sequelae and the at-least-temporary worsening of a quality of life related to it; 42% of ES SCLC patients from this trial did not require brain radiation until death.

Pre-PCI MRI is also a pre-requisite for the PCI with hippocampal avoidance (HA), for the accurate delineation of the HA zone. The HA is one of the strategies used to

reduce neurotoxicity in PCI and WBRT. The rationale for this approach is that the proliferating neuronal progenitor cells in the subgranular zone of the hippocampus play an essential role in memory function and the use of new radiation technologies, such as the IMRT technique, may spare this structure from the detrimental cognitive effects of radiation by minimizing a dose given to this region. Two prospective trials demonstrated a short-term (at 4–6 months) improvement of neurocognitive function with HA in WBRT for BM (37,38). Some reports supported the safety of HA, demonstrating a risk of failure in the HA zone for SCLC patients to be less than 5% (35,39). In contrast, other studies reported a risk of failure of more than 10% in the HA zone with HA in PCI for SCLC (40,41). The safety of such an approach remains to be confirmed by prospective trials, but in the meantime, when performing HA-WBRT for PCI or overt BM we need reliable imaging, i.e., a high-quality MRI performed for HA planning according to recommendations (42).

Concluding, pre-PCI MRI is recommended, because for the patients treated in a timely and optimal way, early salvage WBRT may be not inferior to PCI, as showed by the prospective data from one trial in ES SCLC (17). Also, it may serve for radiotherapy planning purposes.

Metachronous presentation of BM in SCLC

Metachronous presentation is meant as the occurrence of BM after the first-line treatment for SCLC. The time of occurrence of BM in relation to the diagnosis of the primary (synchronous *vs.* metachronous BM) is considered as a prognostic factor for OS. Patients presenting with metachronous BM had worse OS compared with patients presenting with synchronous BM (43,44). This is related to the very limited therapeutic arsenal after first-line CHT. Median survival after second-line CHT varies between 3 and 6 months in clinical trials (45). Additionally, BM in SCLC occur very rarely as a sole event, as demonstrated by the EORTC phase II trial, in which the very slow accrual of patients with brain-only metastases led to the premature closure of the study, before the required number of patients was reached (2). The extracranial disease progression is also a well-recognized adverse prognostic factor in BM, including SCLC (46,47). Thus, a management of metachronous BM in SCLC represents a complex therapeutic problem. Additionally, the management becomes challenging if BM occur after previous PCI. We will discuss the treatment strategies for the metachronous

BM with regard to the prior use, or not, of PCI.

Metachronous BM that occur without prior use of PCI

Owing to the poor prognosis of these patients and the lack of clear guidelines for the management of brain relapse in SCLC patients, the decisions are individual in each case. All the available treatment options, such as a second line CHT, radiotherapy alone, and radiotherapy combined with CHT have limited therapeutic potential. Taking into account the generally poor treatment outcome, in some more unfavorable cases, an active oncological treatment like CHT or any form of radiation should be weighed against supportive therapy with steroids alone.

The use of CHT in this setting is not a first-choice treatment, in contrast to the BM simultaneous to the newly diagnosed primary. It is conditioned by a number of factors, such as the site and extent of progression (brain only *vs.* brain and extracranial site with consideration of the extent of extracranial disease), previous response to CHT, previous tolerance of CHT, the time interval from the last line of CHT, and performance status. In the *Cochrane Database Syst Rev*, a value of CHT for BM from SCLC based on three randomized trials including 192 patients was evaluated. No sufficient evidence to indicate a survival advantage for CHT use was found (21). Only one trial compared CHT with no CHT; 33 patients, including 28 with metachronous presentation, were randomized to WBRT alone *vs.* WBRT plus topotecan. No significant difference in survival was found between these two groups (48). Despite the lack of evidence that CHT improves brain tumor control and OS in these patients, CHT is given especially if there is also an extracranial disease progression, patients are in good performance status and are able to tolerate CHT, previous response and tolerance of CHT were good enough, and also if the time interval from the last CHT is sufficiently long and/or available CHT options exist. This is based on the recognized chemo-responsiveness of SCLC.

Although a high RR in the brain after CHT for SCLC is recognized (19), both prospective and retrospective data show improved PFS and brain control with the addition of WBRT to CHT (3,49). WBRT is usually given sequentially to CHT, unless the patient has bothersome symptoms related to the brain progression. In one small prospective study on 39 patients, sequential and concomitant (radio) CHT schedules (teniposide plus cisplatin with WBRT) were compared. No difference in OS and RR for either

combination was demonstrated. The concomitant arm was revealed to be more toxic (50). The use of WBRT in BM from SCLC is not based on the results of randomized trials. There is also a concern about the neurotoxicity of such an approach. As mentioned above, in the population-based study including 1,615 patients older than 74 years, the addition of WBRT to CHT did not improve OS. Thus, it cannot be excluded that asymptomatic patients may be treated with CHT alone. This approach may be preferential in fragile populations, susceptible to neurotoxicity—such as, for example, elderly patients.

Patients with BM in RTOG RPA (the Radiation Therapy Oncology Group, Recursive Partitional Analysis) class 3, that is, with poor performance status [Karnofsky performance status (KPS) <70] had a median OS about two months (4,5,46). With such a short survival, the benefit of any active oncological treatment, including WBRT is doubtful. In 538 patients with BM from NSCLC unsuitable for resection or SRS, who were randomly assigned to WBRT and best supportive care (steroids) or best supportive care alone, the WBRT did not improve OS, quality of life, and reduction of the dose of steroids (51). One prospective trial that also included patients with SCLC histology aimed to determine whether WBRT had any benefit in terms of symptom palliation in 91 patients with KPS <70. All patients received WBRT and were asked to complete a questionnaire about their symptoms before and 1 month after WBRT. One month after WBRT, 53% of patients from this group had died or were not able to respond to the survey questions because of further deterioration of performance and/or neurological status. In the remaining 47% of patients, the intensity of symptoms of the disease significantly increased after WBRT (52). These results challenge the value of WBRT; steroids only are a reasonable option that should be proposed for such patients.

Metachronous BM that occur after prior use of PCI

PCI reduces the incidence of BM by about 50%, however the risk of BM is not eliminated with the PCI use. The extracranial disease progression, which is a frequent event in LS SCLC and practically inevitable in ES SCLC, becomes a source of subsequent seeding into the CNS and this pattern of progression cannot be prevented by the PCI use. The results of meta-analysis and prospective trials indicate that the risk of brain relapse after PCI varies between 15 and 33%, and in most studies, it is closer to about 30% than 15% (9,10,17,24). The 3-year BM rate after PCI was 33%

vs. 59% without PCI in a meta-analysis of seven randomized trials that compared treatment with and without PCI in LS SCLC and ES SCLC (9). In the EORTC trial on PCI in ES SCLC, the 1-year risk of symptomatic BM after PCI was 15% *vs.* 40% without PCI (10). In the trial that compared treatment with and without PCI with staging and strict surveillance with brain MRI in ES SCLC patients only, the 1-year (mainly asymptomatic) BM rate was as high as 33% with PCI *vs.* 59% in patients without PCI. This high rate of detection of BM seen in this study was mainly attributable to the strict surveillance with brain MRI performed every 3 months (17).

Re-irradiation of the brain that has previously received about 30 Gy with PCI is challenging because of the risk of neurotoxicity. The incidence of cognitive decline is volume dependent, especially when using large doses per fraction as in palliative settings (53). SRS appears a very appealing strategy in the previously irradiated region. The increased availability of SRS and improvements in the technology make this technique easily accessible. SRS is increasingly employed even for patients with multiple BM. It was demonstrated in a large randomized trial on 1,194 patients that SRS without WBRT in patients with 5–10 BM from solid tumors including SCLC was not inferior in terms of OS to that in patients with 2–4 BM (54). However, the possibility of using SRS depends not only on the number of BM but, most of all, of the volume of respective lesions and the total volume of the BM. The above-mentioned study that demonstrated non-inferiority of the outcome of SRS for 5–10 BM compared to 2–4 BM enrolled patients with one to ten BM with a maximum diameter of the largest tumor <3 cm, and total volume of all BM ≤15 mL. Even if in one study, the criteria of inclusion in the SRS were extended to BM with the largest diameter of 5 cm and a maximum number of 10, still 60% of 32 patients who experienced recurrence within the brain after PCI were unsuitable for SRS (55). Thus, a question arises about safety of using WBRT in such patients. It is reasonable to presume that their short life expectancy counted in weeks or months at best makes a risk of late neurotoxicity of WBRT unlikely, though there are very limited data on this. Bernhardt *et al.* (56) reported on 76 patients reirradiated after a PCI with a dose of 30 Gy in 15 fractions and with a median time between PCI and reirradiation of 14 months (range, 4–42 months). Repeat WBRT was given to 66 (88%) of them with the doses of 20–30 Gy in 10–15 fractions. Median OS after repeat WBRT was 3 months (range: 0–12 months); about 40% of symptomatic patients

improved after reirradiation. Notably, no serious, grade >2 toxicity was observed in these patients. These results support our assumption that WBRT with moderate doses may be beneficial for these many patients who are not candidates for SRS after prior PCI.

However, for patients suitable for SRS, the minimal invasiveness and ease of the use of SRS make the SRS a preferred salvage method after prior PCI for patients with a better prognosis, *i.e.*, life expectancy >3 months. Thirteen patients with one to four BM from the above-mentioned series of 76 patients reirradiated after PCI received SRS with 18–24 Gy. Their median OS was 5 months; data on local and distant control in the brain were not provided. There was no radionecrosis reported in this group (56). Other reports on the outcome and safety of SRS for BM delivered after PCI include also the cases with prior WBRT for overt BM (57–62). In these series, median OS of patients after SRS ranged from 3 to 9 months. However, we should be aware that a selection bias in such retrospective series seriously impacts the results. Additionally, the local control after SRS for BM from SCLC was lower than for BM from other solid tumors. One-year local control rates were lower than 70% in evaluated patients (57–62), whilst in prospective trials on SRS with the exclusion of SCLC histology, these rates were of 70–90% (12,13). Distant brain control (<60%) was also lower than that reported in prospective trials on SRS alone for non-SCLC histology (57–62). Nevertheless, the average patient with BM after PCI differs considerably from the patients participating in clinical trials on the use of ablative techniques for BM. For the former, very limited therapeutic options exist and his prognosis is ultimately fatal. If life expectancy exceeds 3 months and the technical possibilities for the use of SRS exist, we may proceed with SRS. WBRT at moderate doses is feasible for patients unsuitable for SRS or symptomatic patients with limited life expectancy (<3 months) regardless of the technical possibilities of using SRS. For patients with poor performance status, we should consider supportive care only.

SRS vs. WBRT for newly diagnosed BM in SCLC

Whilst locally ablative treatments without WBRT are the standard of care for patients with 1–4 BM from solid tumors other than SCLC, the evidence for their use in SCLC is weak. The use of SRS for relapses after PCI or prior WBRT for overt BM in suitable cases is recommended, however, the upfront SRS for limited BM from SCLC is not a

standard of care. The different biological behavior of SCLC prevented inclusion of these patients into most trials on local treatment of BM. The safety and potential benefit of such an approach remains to be confirmed in a prospective trial. However, the data on the futility of WBRT with respect to OS in BM from other solid tumors and the detrimental neurocognitive effect of WBRT, as well as the advancement in technologies and increasing availability of stereotactic techniques led to the growing use of upfront SRS for BM from SCLC. In one study, the availability of on-site SRS was the strongest factor related to the use of SRS for treatment of BM from solid tumors; 40% of patients who received WBRT had SRS when they were treated in a hospital that had on-site SRS technology, whilst only 3% of patients who received WBRT at a hospital without this technology had SRS, $P < 0.01$ (63). Indeed, one population-based study demonstrated a positive trend in the use of SRS in 14,722 patients with BM from SCLC identified from the US NCDB covering the period of 2004–2013; the increase of the SRS use from 2.7% in 2004 to 4.3% in 2013 was observed. Although availability and socio-economic factors mainly influenced the use of SRS for these patients, the OS of patients receiving SRS was significantly superior to that of patients receiving WBRT only, the median OS rates were 10.0 *vs.* 8.0 *vs.* 9.3 for SRS, WBRT and WBRT plus SRS, respectively, $P < 0.001$. The OS differences favored the SRS group also following propensity score matching, $P = 0.001$ (7). Another study based on the US NCDB data included 5,952 BM SCLC patients and covered the period from 2010 to 2014. Upfront SRS was associated with superior OS than WBRT alone; median OS for 200 patients who had SRS was 10.8 *vs.* 7.1 months for 5,752 WBRT patients, $P < 0.001$. These results were also confirmed in the propensity score matching analysis. Obviously, a small number of patients treated with SRS in these two studies, and a risk of undetected selection bias does not assert the value of the upfront SRS for these patients. Noteworthy, the OS of 7–8 months for patients in WBRT cohort was also higher than this reported in historical series (2–5). This may indicate that OS rates after SRS of about 3–9 months reported in case series would not be different if WBRT or other non-ablative radiotherapy techniques were used (56–62). However, the OS rates observed in the registry datasets suggest that upfront SRS may be appropriate for some SCLC patients. Patients with limited numbers of BM from SCLC may differ in their prognosis from patients with multiple BM. SCLC that occurs with single or oligo-BM may have more favorable prognosis than poly-metastatic

brain disease at its onset. Thus, a more aggressive local approach would be beneficial for such patients. In the retrospective analysis of 52 patients who received WBRT for single BM SCLC, the use of surgery in combination with WBRT was related to improved survival compared with WBRT alone, with median OS of 19 and 5 months, respectively, $P = 0.03$ (64). On the prognostic scale for BM from lung cancer, based on the results of 1,833 NSCLC and 281 SCLC patients, the number of BM (1 *vs.* 2–3 *vs.* >3) reached prognostic significance. When patients with SCLC were analyzed separately, the number of BM was also significantly prognostic for survival and is included in the diagnosis-specific prognostic scale of BM from both NSCLC and SCLC (47).

The value of the upfront SRS, the safety of omission of WBRT for patients with a limited number of BM in SCLC should be evaluated in further prospective clinical trials. The ENCEPHALON trial registered in the clinicaltrials.gov website (NCT03297788) is recruiting a planned number of 56 patients at the Heidelberg University Hospital. Patients with up to 10 BM from SCLC are randomized into the SRS of all lesions *vs.* WBRT. The primary endpoint of the study is neurocognitive function. The intracranial control, OS, quality of life and toxicity are secondary endpoints (65). More such studies are needed to accumulate the evidence regarding which patients with BM from SCLC can be safely managed with ablative techniques with omission of WBRT.

Acknowledgments

Funding: None.

Footnote

Provenance and Peer Review: This article was commissioned by the Guest Editor (Lucyna Kepka) for the series “Radiotherapy for Brain Metastases from Lung Cancer” published in *Journal of Thoracic Disease*. The article has undergone external peer review.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/jtd.2019.10.51>). The series “Radiotherapy for Brain Metastases from Lung Cancer” was commissioned by the editorial office without any funding or sponsorship. LK served as the unpaid Guest Editor of the series and serves as an unpaid editorial board member of *Journal of Thoracic Disease* from Aug 2018 to Jul 2020. The other authors have

no other conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Cite this article as: Kepka L, Socha J, Sas-Korczynska B. Radiotherapy for brain metastases from small-cell lung cancer in distinct clinical indications and scenarios. *J Thorac Dis* 2021;13(5):3269-3278. doi: 10.21037/jtd.2019.10.51