Limited Cerebral Metastases in NSCLC: A Literature Review of SRS Versus Whole-brain Radiotherapy

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Abstract. Background/Aim: Brain metastases (BMs) are common in patients with non-small cell lung cancer (NSCLC). Whole-brain radiotherapy (WBRT) with or without corticosteroid use has historically been the first choice for most patients with BMs despite its negative impact on cognition and quality of life. However, stereotactic radiosurgery (SRS) has emerged as a safe and effective treatment and has been established for patients with limited, inoperable BMs. SRS and WBRT are either used separately or together, in an attempt to achieve the best possible local and distal control rates and even improve overall survival. A number of phase III trials have focused on answering the question which modality – SRS, WBRT or both – can achieve the best possible results. In this review, we present the existing data regarding the use of SRS compared with WBRT and their combination for NSCLC patients with limited, non-operable BMs. Materials and Methods: A literature review was performed in PubMed, Medline, and the Cochrane Library databases from 1995 up to 2021. Principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement were followed. Results: We identified seven randomised control trials (RCTs) that compared WBRT with WBRT plus SRS boost and four RCTs that compared SRS alone with SRS plus WBRT. Conclusion: Overall, addition of WBRT to SRS did not improve survival but had a positive effect on locoregional control.

Lung cancer is the leading cause of death among both men and women. According to data collected from the American Cancer Society, the National Cancer Institute’s (NCI) Surveillance, Epidemiology and End Results (SEER) program and the Centre’s for Disease Control and Prevention’s (CDCC) National Program of Cancer Registries (NPCR), in 2021 approximately 235,760 adults were diagnosed with lung cancer in the USA alone, with 131,880 dying from the disease (1). About 85% of lung cancers are non-small cell lung cancers (NSCLC) (2), with adenocarcinoma being the most common subtype. At initial diagnosis, approximately 10-20% of patients present with brain metastases (BM) (3) and up to 30% will develop BMs during the course of their illness (2, 4).

Historically, it has been considered that prognosis of NSCLC patients with BM at diagnosis is universally poor, spanning weeks or months (4). However, recent advances in systemic therapies and technologies, genomic profiling with the identification of molecules that can be directly targeted as well as the development of prognostic indices have shown that prognosis can vary greatly. Various treatment modalities

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Key Words: Cerebral metastases, radiotherapy, stereotactic radiosurgery, whole brain radiotherapy, non-small cell lung cancer, review.
have been utilised over the years for the treatment of BMs, with WBRT being the most commonly used- especially for poor prognosis patients or patients with multiple BMs - followed by steroid management, neurosurgery or even systemic therapy with chemotherapy or targeted treatments. For poor and intermediate prognosis NSCLC patients, even the use of WBRT has been questioned, as it did not show a survival benefit over best supportive care with steroids alone in the recent QUARTZ trial (5).

Stereotactic radiosurgery (SRS) is an irradiation technique, that allows the delivery of highly conformal, precisely localised doses while sparing the surrounding healthy brain tissue and adjacent structures (6). Delivery of SRS can be achieved via GammaKnife, CyberKnife or linear accelerator (LINAC) with either one or multiple isocentres (7). SRS has been gaining ground the last two decades, with or without WBRT or even as adjuvant treatment after surgical resection. Even though it is a more or less well-established treatment modality for certain patient groups, such as patients with limited number of BMs of relatively small size (1-4 metastases, <3 or 4 cm) not amenable to surgical resection (8), many trials in the recent 20 years have questioned its combination with WBRT. When combined with WBRT, does SRS improve survival or tumour control? Or can WBRT be safely omitted? Is cognitive function better preserved when SRS is used alone? Does combined treatment affect quality of life or performance status (PS) in a positive manner?

Our goal was to review the literature on the role of stereotactic radiosurgery with or without WBRT for NSCLC patients presenting with limited (up to 4) BMs not amenable to surgery.

Patient prognostic groups. The promising results of modern treatment approaches, such as SRS, led to the important question whether these are due to the treatment modality alone or can be attributed in part to patient selection. There have been several prognostic indices reported in the literature in an attempt to categorise patients with BMs in groups according to specific characteristics that can influence decision-making of patients and clinicians and treatment outcomes, such as survival (9-14).

Two of these have been widely used by researchers, the RTOG Recursive Partitioning Analysis (RPA) (9, 10) and the Graded Prognostic Assessment (GPA) (11-13). The RPA, mainly based on patients treated with WBRT in the RTOG database (1979-1993), was published in 1997 by Gaspar et al. (9). Table I presents patient characteristics that define each class and the median survival for the three classes. However, there are several downsides of the RPA. The patients from who the data were extracted from, were treated with WBRT, making the validity of this tool questionable. Additionally, the vast majority of patients were generally classified as intermediate risk. Finally, it is an all-diagnosis prognostic index, developed in a time before immunotherapy or targeted therapies were established (15). We should note, however, that it has been validated for several diagnoses, including breast and NSCLC (16). The GPA was later developed, identifying significant diagnosis- specific (DS-GPA) prognostic factors in an updated era (1985-2007) (11). The GPA was developed using data from 1960 patients treated with WBRT +/- radiosensitizers +/- SRS included in prospective clinical trials in the RTOG database. Later, it was validated (12) and refined based on a second retrospective analysis of more than 4200 patients with BMs treated with surgery/WBRT/SRS and diagnosis – specific prognostic indices were developed (Table I: RTOG RPA prognostic classes; Table II: DS-GPA for NSCLC) (13). In the modern era, where molecular profiling has changed the landscape of NSCLC, a further refined GPA, the LungmolGPA, has been especially developed for NSCLC patients, integrating driver mutations such as those in epidermal grown factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) (14). It can be said that the identification of prognostic factors for patients with BMs is ongoing with researchers underlining the number of BMs, use of systemic therapy, and status of extracranial disease as the most commonly associated with survival and intracranial progression (17).

Materials and Methods

Data collection. A comprehensive search was performed in PubMed, Medline, and the Cochrane Library databases from 1995 up to 2021. We followed the principles outlined in the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) statement (Figure 1) (18). The search terms: “stereotactic radiosurgery”, “brain metastases” and “non-small cell lung cancer”, both free text and truncated, along with their synonyms. Furthermore, randomised trials and meta-analyses written in English language, and published in peer reviewed journals were included. We should note that most published randomised clinical trials that study the use of SRS in the management of patients with BMs, include patients with various primary cancers (radiosensitive cancers such as small-cell lung cancer are excluded) and are not specific for NSCLC patients, even though they represent the vast majority of the recruited patients in all included studies. Additionally, not all prognostic indices used in these studies to stratify patients into risk groups and help guide estimated prognosis have found histology to be statistically significant for outcome prediction (e.g., RPA). Therefore, we included all trials that study the use of SRS in the management of patients with BMs, even though we focus on data for NSCLC patients.

The participants were patients at least 18 years old with 1-4 BMs up to 4 cm in diameter with a Karnofsky performance status (KPS) >70. Non-small cell lung cancer patients should represent the majority of the recruited patients in each study.

The interventions included: SRS vs. SRS plus WBRT; WBRT vs. WBRT plus SRS, where SRS means any high dose of focal RT delivered by GammaKnife, CyberKnife or LINAC. The outcomes evaluated were: overall survival, local tumour control, distal tumour control, cognitive decline, quality of life (QoL), functional independence.
Based on the above, we reviewed 7 randomised trials and 2 meta-
analyses on the use of SRS vs. SRS combined with WBRT (Table
III and Table IV). With regards to the use of WBRT vs. WBRT in
combination with SRS, we reviewed 4 randomised clinical studies
which focused mainly on conclusions regarding survival and local
tumour control.

Results

WBRT alone versus WBRT with stereotactic radiosurgery
“boost” for single or multiple BMs. WBRT with or without
steroid use has been the standard of care for the management
of BMs for decades (19). With the development of SRS and
its safe use in the management of intracranial lesions
including BMs, two important questions remained to be
answered: whether SRS can be used as an adjunct to WBRT
to improve local tumour control and whether it impacts on
survival. The randomised controlled trials that exist up to
now aimed to answer exactly that.

In a single institution study published by Kondziolka et
al. in 1999 (20), patients with 2 to 4 BMs up to a maximum
of 25 mm were randomised to receive 30 Gy of WBRT in 12
fractions or WBRT plus SRS. The primary outcome was
local tumour control. The study was stopped at an interim
evaluation at 60% accrual with only 27 patients randomised
(14 patients in the WBRT alone group and 13 patients in the
combined therapy group), as the analysis revealed a local
failure rate of 100% at one year in the WBRT alone group
compared to 8% in the WBRT plus radiosurgery group.
Median time to local failure after WBRT alone was 6 months
(95%CI=3.2-8.5) in comparison to 36 months (95%CI=15.6-
57) after combined modality management. The median time
to any brain failure, meaning progression of initial brain
tumour or development of new one, was also significantly
longer in the WBRT plus SRS group (34 months compared
to 5 months in the WBRT group). However, there was no
survival benefit in the stereotactic radiosurgery boost group.
Histologic type had no effect on survival, nor did number of
BMs (2, 3 or 4). This study did not report any cognitive
outcomes.

The Radiation Therapy Oncology Group (RTOG) 9508 trial
(21) was a large multi-institutional randomised study, which
randomised 333 patients with 1 to 3 BMs with a maximum
diameter of 4 cm for the largest lesion and a KPS of more than
70% to receive either WBRT (n=164), or WBRT plus
radiosurgery boost (n=167). Patients were stratified by number
of metastases (single versus 2-3), extent of extracranial disease
(absent versus present) and RPA groups for BMs, in order to
ensure intergroup homogeneity (21). Primary outcome was
overall survival, which did not differ between groups in general.
However, WBRT plus radiosurgery provided a survival benefit

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**Table I. Radiation Therapy Oncology Group (RTOG) recursive
partitioning analysis (RPA) prognostic classes.**

<table>
<thead>
<tr>
<th>RPA class</th>
<th>Description</th>
<th>Median survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>KPS≥70 and Age &gt;65 and Controlled primary tumour and No extracranial metastases</td>
<td>7.1</td>
</tr>
<tr>
<td>II</td>
<td>KPS≥70 and one more of the following: Age≥65 Uncontrolled primary tumour Presence of extracranial metastases</td>
<td>4.2</td>
</tr>
<tr>
<td>III</td>
<td>KPS &lt;70</td>
<td>2.3</td>
</tr>
</tbody>
</table>

KPS: Karnofsky performance status.

**Table II. Details of the graded prognostic assessment (GPA) for non-small cell lung cancer (NSCLC).**

<table>
<thead>
<tr>
<th>GPA score</th>
<th>Age</th>
<th>KPS</th>
<th>No. of brain metastases</th>
<th>Extracranial metastases</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>&gt;60</td>
<td>&lt;70</td>
<td>&gt;3</td>
<td>Present</td>
</tr>
<tr>
<td>0.5</td>
<td>50-60</td>
<td>70-80</td>
<td>2-3</td>
<td>Absent</td>
</tr>
<tr>
<td>1.0</td>
<td>&lt;50</td>
<td>90-100</td>
<td>1</td>
<td>Absent</td>
</tr>
</tbody>
</table>

KPS: Karnofsky performance status.
Table III. Selected trials evaluating the role of stereotactic radiosurgery (SRS) ± whole brain radiotherapy (WBRT) for patients with limited brain metastases.

<table>
<thead>
<tr>
<th>Trial (Ref)</th>
<th>Year</th>
<th>No. of patients</th>
<th>Patient characteristics</th>
<th>Primary endpoint</th>
<th>LC</th>
<th>OS</th>
<th>Neurocognitive outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aoyama (25)</td>
<td>2006</td>
<td>132</td>
<td>1-4 BMs, KPS≥70, lesion diameter &lt; 3 cm</td>
<td>OS</td>
<td>1 yr 72.5% vs. 88.7% (p=0.002)</td>
<td>1 yr 28.4% vs. 38.5% (p=0.42)</td>
<td>No difference (MMSE used)</td>
</tr>
<tr>
<td>Aoyama (27)</td>
<td>2015</td>
<td>88</td>
<td>1-4 metastases, NSCLC pts</td>
<td>OS</td>
<td>-</td>
<td>DS-GPA≥2.5:10.6 vs. 16.7 m (p=0.04), DS-GPA &lt;2: 6.5 vs. 4.75 m (p=0.86)</td>
<td>No difference (MMSE used)</td>
</tr>
<tr>
<td>Chang (28)</td>
<td>2009</td>
<td>58</td>
<td>1-3 BMs, RPA class I and II</td>
<td>Neurocognitive function (measured by HVLT-R)</td>
<td>1 yr: 67% vs. 100% (p=0.012)</td>
<td>15.2 vs. 5.7 m</td>
<td>Mean probability of decline 52% vs. 24%</td>
</tr>
<tr>
<td>Kocher (31)</td>
<td>2011</td>
<td>359</td>
<td>1-3 BMs, WHO status≤2</td>
<td>Functional independence (WHO≤2)</td>
<td>2 yr: 69% vs. 81% (p=0.04)</td>
<td>10.9 vs. 10.7 m (p=0.89)</td>
<td>No difference 10.0 vs. 9.5 m</td>
</tr>
<tr>
<td>Brown (29)</td>
<td>2016</td>
<td>213</td>
<td>1-3 BMs, ECOG≤2, diameter &lt; 3 cm</td>
<td>Cognitive decline</td>
<td>3 m 75.3% vs. 93.7% (p&lt;0.001)</td>
<td>10.4 vs. 7.4 m (p=0.92)</td>
<td>Less deterioration in SRS + WBRT arm, as measured by 7 different test incl. HVLT-R</td>
</tr>
<tr>
<td>Churilla</td>
<td>2017</td>
<td>126 NSCLC</td>
<td>1-3 BMs, NSCLC pts</td>
<td>Cognitive decline</td>
<td>-</td>
<td>DS-GPA ≥2.5: 17.9 vs. 11.3 m (p=0.63), DS-GPA &lt;2: 6.6 vs. 3.7 m (p=0.85)</td>
<td>-</td>
</tr>
<tr>
<td>Churilla</td>
<td>2017</td>
<td>329 of whom</td>
<td>1-3 BMs, WHO≤2, patients with stable extracranial disease only</td>
<td>OS according to DS-GPA score (favourable vs. unfavourable) and OS in patients with controlled extracranial disease with addition of WBRT</td>
<td>-</td>
<td>No difference in survival with addition of WBRT with increased intracranial control in all pts.</td>
<td>-</td>
</tr>
</tbody>
</table>

LC: Local control; OS: overall survival; BM: bone metastasis; MMSE: mini-mental state examination; HVLT-R: Hopkins verbal learning test – revised.

to patients with a single metastasis (6.5 versus 4.9 months, p=0.0393) and patients that were RPA class I (Table I) (11.6 versus 9.6 months). It is of note that patients with NSCLC had longer survival in the radiosurgery arm compared to the control group in multivariate analysis (5.9 months versus 3.9 months).

KPS score and steroid use at 6 months and local control at one year (82% vs. 71%, p=0.01) were improved in the SRS patient group. No difference in mental status was noted between the WBRT alone and the WBRT plus SRS group.

In the secondary analysis of the RTOG 9508 trial published in 2014 (22), Sperduto et al. poststratified patients according to the Graded Prognostic Assessment (GPA) score (Table II). In this analysis, 252 of the 331 patients from the original RTOG 9508 study were evaluated. Almost 84% of those were lung cancer patients. In this study, no survival advantage was observed for patients treated with WBRT and SRS compared with those treated with WBRT alone for all patients (1-3 BMs). However, there was an advantage for patients with a good prognosis treated with both modalities, meaning a GPA score of 3.5-4 regardless of the number of metastases. Specifically, median survival time for the combined group was 21.0 months versus 10.3 months in the WBRT alone group.

El Gantery et al. (23) performed a single institution randomised controlled trial which randomised 60 patients with 1-3 BMs with a maximum diameter of 4 cm on contrast - enhanced MRI and KPS of more than 70% into three
groups: WBRT plus SRS, WBRT alone and SRS alone. The study reported an improvement in local control in the WBRT plus SRS group, with the median LC of 10 months for the WBRT+SRS group compared to 6 months for the SRS alone group and 5 months for the WBRT alone group ($p=0.04$). There was no difference in overall survival between the three groups. However, subgroup analysis showed that WBRT + SRS provided a survival benefit to patients whose largest BMs was 3 cm in diameter (23) (15 months versus 8 months versus 5 months for WBRT+SRS versus SRS versus WBRT respectively) and to those with controlled primary (median survival 12 months versus 8 months versus 5.5 months for WBRT + SRS versus SRS alone versus WBRT alone, respectively).

**Stereotactic radiosurgery alone versus WBRT and stereotactic radiosurgery for single or multiple BMs.** WBRT is known to have a late adverse effect on cognition, which is more prominent in patients with controlled or absent extracranial disease (24). Based on this, a longstanding debate exists whether WBRT is the best treatment option for patients with a limited number of BMs in terms of survival.

### Table IV. Selected trials evaluating the role of whole brain radiotherapy (WBRT) ± stereotactic radiosurgery (SRS) for patients with limited brain metastases

<table>
<thead>
<tr>
<th>Trial (Ref)</th>
<th>Year</th>
<th>No. of patients</th>
<th>Patient characteristics</th>
<th>Primary endpoint</th>
<th>LC</th>
<th>OS</th>
<th>Neurocognitive outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kondziolka (20)</td>
<td>1999</td>
<td>27</td>
<td>2-4 BMs up to 25 mm, KPS≥70</td>
<td>LC</td>
<td>1 yr: 100% vs. 8%</td>
<td>No difference between arms. No effect on survival from histologic type.</td>
<td>-</td>
</tr>
<tr>
<td>Andrews (RTOG 9508) (21)</td>
<td>2004</td>
<td>331</td>
<td>1-3 BMs up to 40 mm largest, KPS≥70</td>
<td>OS</td>
<td>1 yr: 71% vs. 82% ($p=0.01$)</td>
<td>No difference overall; improved survival for single brain metastasis in WBRT+SRS group 6.5 vs. 4.9 m ($p=0.0393$), improved survival in RPA class I and “favourable” histology such as NSCLC. No survival advantage overall; advantage for patients with a GPA of 3.5-4.0 treated with both modalities, regardless of the number of the metastases (median survival 21 m versus 10.3 m in the WBRT alone group)</td>
<td>-</td>
</tr>
<tr>
<td>Sperduto (secondary analysis RTOG 9508) (22)</td>
<td>2014</td>
<td>252 of whom 211 NSCLC</td>
<td></td>
<td></td>
<td></td>
<td>No survival advantage overall; advantage for patients with a GPA of 3.5-4.0 treated with both modalities, regardless of the number of the metastases (median survival 21 m versus 10.3 m in the WBRT alone group)</td>
<td>-</td>
</tr>
<tr>
<td>El Gantery (23)</td>
<td>2014</td>
<td>60</td>
<td>1-3 BMs up to 4 cm largest, KPS≥70</td>
<td>LC</td>
<td>19% vs. 42.9% vs. 22.2% ($p=0.04$). Better median LC for single BM.</td>
<td>No difference in median/6 m/12 m survival. Significant difference in controlled primary patients (5.5 vs. 12 vs. 8 m, $p=0.027$). Better median survival for single BM.</td>
<td>-</td>
</tr>
</tbody>
</table>

LC: Local control; OS: overall survival; BM: bone metastasis; MMSE: mini-mental state examination; HVLT-R: Hopkins verbal learning test – revised.
or neurological function or whether SRS can be used instead in selected patients.

The first randomised controlled trial that attempted to answer the question was the JROSG-99-1 by Aoyama et al. in 2006 (25). This RCT randomised 132 patients (88 were NSCLC patients) with 1 to 4 BMs with a diameter of up to 3 cm to receive SRS alone or SRS plus WBRT. Brain tumour recurrence rate was 46.8% in the WBRT + SRS group compared to 76.4% in the SRS group. Salvage brain treatment was more frequently required in the SRS alone group. There was no difference in survival and neurological functional outcome as assessed by Mini-Mental State Examination (MMSE) between the two groups, even though a hint of better preservation of neurological function at 12 months was observed in the WBRT plus SRS group compared to the SRS alone group (76% versus 59%). In a separate publication, Aoyama reported the cognitive outcomes of the study. The authors reported an average duration until deterioration of 16.5 months in the WBRT plus SRS arm compared with 7.5 months in the SRS alone arm (p=0.05) (26). This was attributed to the better tumour control provided by WBRT, which plays a crucial role with regards to cognition.

In 2015, a secondary analysis of the JROSG-99-1 trial was published (27). From the original 132 patients, 88 with NSCLC were included and post-stratified by the diagnosis-specific Graded Prognostic Assessment (DS-GPA). It was observed that in patients with a favourable prognosis (DS-GPA of 2.5-4) the addition of WBRT to SRS provides an overall survival benefit. In the combined modality group, median survival was 16.7 months as opposed to 10.6 months in the SRS alone group (p=0.04). This benefit was not observed in the poor prognosis group. In terms of brain tumour recurrence, omission of WBRT increased BTR at the initial and distal brain sites, with the effect being more obvious in the favorable prognosis group. This resulted in more frequent use of salvage treatment. The authors did not report any difference in cognitive function when patients were classified by DS-GPA score, as measured by the Japanese version of the MMSE, even though data were not available for all patients.

Chang et al. reported the results of another randomised controlled trial from MD Anderson in 2009 (28). The researchers started by proposing that cognitive functions, such as learning and memory of patients (as measured by the Hopkins Verbal Learning Test - Revised) who receive SRS plus WBRT is worse than those of patients who undergo SRS alone. The primary endpoint required 90 patients; however, after accrual of 58 patients (55% were NSCLC patients) with 1 to 3 newly diagnosed BMs classified as RPA class I or II, the trial was stopped early. This was due to a very high probability (96%) of cognitive decline at 4 months of patients in the SRS plus WBRT arm (mean probability of decline of 52% versus 24% for the SRS alone arm). Similarly with the Aoyama study (25), higher rates of local and distal brain tumour recurrence were reported in the WBRT plus SRS group. The 1-year freedom from CNS recurrence was 27% for SRS alone and 73% for SRS plus WBRT (p=0.0003). Median and overall survival were higher for the SRS alone arm than for the SRS plus WBRT arm (15.2 versus 7 months, 63% versus 21% respectively, p=0.03). Based on these results, the authors recommended SRS with close follow-up for patients with limited BMs.

The NCCTG N0574 trial by Brown et al. (29) was a much larger randomised clinical trial of 213 patients with 1-3 BMs who were randomised to receive SRS alone or SRS plus WBRT. NSCLC patients represented again the largest group with 146 patients of 213 overall. Just like the Chang study, the trial’s primary endpoint was cognitive deterioration, defined as a decline of greater than 1 standard deviation from baseline in any of 7 cognitive tests at 3 months. The results showed that there was less cognitive decline at 3 months (64% vs. 92%), as well as better QoL after SRS alone. Time to intracranial failure was significantly shorter in the SRS alone group. The tumour control rates were studied at 3, 6, and 12-months for both local and distal recurrence. There was an absence of difference in median overall survival, therefore the authors suggest that for patients with 1 to 3 BMs amenable to SRS, SRS alone is probably the preferred strategy.

A secondary analysis of this study was reported in 2017 (30), which examined 126 NSCLC patients from the original Brown study, who were post-stratified according to the DS-GPA scores for NSCLC. The researchers evaluated overall survival according to receipt of WBRT and DS-GPA score using two separate cut-off points (≥2.0 vs. <2.0 and ≥2.5 vs. <2.5). The post-hoc analysis showed that there was no significant difference in overall survival between DS-GPA groups (p=0.53). It did, however, confirm that the brain tumour recurrence-free survival was significantly longer in patients receiving WBRT compared to the SRS alone group (median BTR free survival 21.6 months vs. 7.4 months, p<0.001) and this benefit was universal in all favorable and unfavorable prognosis patients.

Kocher et al. published the results of the EORTC 22952 – 26001 trial (31), a large trial that consisted of 359 patients with 1-3 metastases with stable solid tumours, comparing adjuvant WBRT with observation after surgery or SRS. The NSCLC patients represented more than 50% of the sample. No difference in OS was observed with or without WBRT. After SRS, at 2 years, WBRT reduced the probability of relapse both at initial and new sites. As far as the primary endpoint is concerned, median survival time with functional independence (defined as median time to WHO performance status of 2) was 10 months in the observation group and 9.5 months in the WBRT group (p=0.71). The authors conclude that even though adjuvant WBRT reduced the risk of
A summary of the text is as follows:

intracranial recurrence, it improves neither OS nor functional independence. The health-related quality of life (HRQoL) results of the above study were reported a year later (32). QoL was assessed by the validated European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire C30 and Brain Cancer Module. Overall, patients that were randomised in the observation group had better HRQoL scores, with the differences between arms being statistically significant in the early follow up period.

The secondary analysis of the EORTC 22952 – 26001 trial (33) reanalysed initial data to assess the impact of WBRT on survival of patients with controlled systemic disease or favorable prognosis (n=175). A separate analysis was done for NSCLC patients for whom GPA data was available. The authors concluded that there is no significant survival benefit with addition of WBRT among NSCLC patients with favorable GPA scores or controlled extracranial disease.

The data from three of the above studies, the JROSG - 11, the Chang et al., and the EORTC 22952 – 26001 trial were used by Sahgal et al. in an individual patient data meta-analysis (34). After analysis of 364 patient data, the authors concluded that patients 50 years old and younger who underwent SRS alone had improved survival compared to their age-matched cohort treated with SRS plus WBRT (10 months vs. 8.2 months, p=0.04). Also, in the same age group patients treated with SRS alone had no increased risk of new brain lesions compared to their age-matched cohort treated with SRS plus WBRT. Addition of WBRT reduced the risk of local tumour failure for all age groups. As a conclusion, the authors recommend SRS alone as the preferred treatment for patients aged 50 years old or less.

Another meta-analysis by Qie et al. (35), assessed SRS alone vs. SRS plus WBRT in NSCLC patients with up to 4 BMs stratified by the graded prognostic assessment. Addition of WBRT failed to improve OS in the 2 subgroups studied, unfavorable (GPA<2) and favorable (≥2.0), BTR-free time was longer with the use of WBRT in both groups and, as expected, salvage brain treatment was more frequent in the SRS alone group. No difference in grade 3 and 4 toxicities was demonstrated.

Discussion

Even though there has been a plethora of trials in the last two decades regarding the use of SRS in patients with limited BMs, especially ones comparing SRS with WBRT and the combination of the two, the number of RCTs limited to NSCLC patients is small. This is probably because in the era of molecular testing in NSCLC patients, studies are focused on targeted therapies (36), which are beyond the scope of this review.

Overall, as a first conclusion it can be said that addition of SRS to WBRT does not generally improve overall survival but adds significantly to local control of limited BMs. All studies reviewed here, report better local tumour control rates with the result being most prominent in the Kondziolka et al. study, where patient accrual was terminated early due to a local control failure rate of 100% with WBRT alone compared to 8% in the WBRT plus SRS arm (p=0.0016). The trial also reported a significantly longer time to any brain failure, even distant (34 vs. 5 months, p=0.002) (20). Andrews et al. a much larger study with a sample of 331 patients, also reported improved local control in the combined treatment group (82% vs. 71%, p=0.01), even though the MRI scans at the 3-month follow-up were deficient for 117 patients (21). El Gantery et al., in their small single institution randomised study, confirmed the same outcome, reporting a median LC of 10 months, which was a significant improvement to the 6 months in the SRS alone arm and the 5 months in the WBRT alone arm (23).

As far as overall survival is concerned, no benefit was demonstrated on the whole; however, two studies, Andrews and El Gantery, did show survival benefits on subgroup analysis (21, 23). The large multi-institution Andrews’ study showed that SRS boost as an adjunct to WBRT provides a survival advantage in patients with single, unresectable BMs (6.5 months) as compared to WBRT alone (4.9 months) (21). We should note that patients with one BM were included and analysed only in this trial. Additionally, the researchers showed a survival advantage for RPA class I patients treated with combination of SRS and WBRT. In multivariate analysis, NSCLC cancer patients also had longer survival compared to the control group. Sperduto et al. in a secondary analysis of the RTOG 9508 study, studied mainly the NSCLC patients included in the original trial in terms of OS when post-stratified for GPA scores. A survival advantage was not observed for patients treated with SRS plus WBRT compared to WBRT alone for all patients with 1-3 BMs but remained for good prognosis patients (GPA 3.5-4.0) as in the initial study (21 months vs. 10.3 months) (22).

Unfortunately, functional outcomes, including cognitive performance, and quality of life were not adequately reported in these trials. Only Andrews (21) et al. included performance measurements, as assessed by KPS score before and 6 months post-treatment. KPS was stable or improved in 43% of patients in the combined treatment arm versus 23% in the WBRT alone arm. QoL was not objectively measured but was assessed by reporting the need for steroid use at 6 months post-treatment. There was a statistically significant reduction in steroid use by 6 months in the combined treatment group and in reality, most patients had stopped use completely by 3 months. Overall, it can be concluded that cognitive outcomes and QoL have not been thoroughly assessed, even though they are important measures of treatment efficacy (36). Although it looks like there is a trend of better performance status after WBRT plus SRS compared
to WBRT alone, this needs to be further investigated, especially in long-term survivors.

A crucial question regarding patients with limited BMs is whether addition of WBRT to SRS provides any benefit in terms of survival, distal control, and what impact it might have on cognition. Again, most studies were not specific to NSCLC patients, apart from the secondary analysis of the JROSG-11 and the Churilla et al. study. Results from these RCTs agree that addition of WBRT to SRS improves local and distal control and prolongs time to salvage treatment. Overall, no improvement in survival was noted. However, a secondary analysis of the Aoyama trial (27), reported better OS in patients with DS-GPA score of 2.5-4.0 (16.7 vs. 10.6 months). The authors attributed this to the difference in BTR rates between prognostic groups, as the preventive effect of WBRT on BTR was more obvious in the favorable prognosis group. Sahgal et al. in their meta-analysis of pooled data from three studies identified age as a prognostic factor for both OS and distant tumour control. Patients ≥50 years old treated with SRS alone had significantly lower mortality, despite similar rates of distant failure in patients >50 years old, who had reduced rates of distant failure with addition of WBRT, but no improved survival (34).

Cognitive outcomes have been the primary or secondary endpoint of RCTs studying the effect of adding WBRT to SRS for the treatment of BMs. It is however of note, that not all studies have used validated and reliable cognitive instruments in order to determine the impact of WBRT on cognition. Aoyama et al. (25, 26) assessed cognition optionally as a secondary endpoint by using MMSE, which is a reliable assessment tool for dementia but there are conflicting opinions regarding its use in patients with BMs. They concluded that addition of WBRT contributed to a significant improvement of time to cognitive deterioration, most likely by protecting from early tumour recurrence. However, closer examination of the data reveals that patients treated with WBRT continue to deteriorate in the long-term (>24 months), as opposed to the SRS alone long-term survivors who seem to deteriorate early and then reach a plateau. Chang et al. (28) used the validated and more reliable too HVLT-R to assess cognitive outcomes. They concluded that cognitive functions of memory and learning at 4 months were much more likely to be impaired in the SRS plus WBRT group, even though one might argue that the 4-month point was a bit too early to draw definitive conclusions. These results are in alignment with results of the NCCTG N0574 study by Brown et al. (29).

Functional independence and QoL are very important factors when deciding on treatment modalities. The EORTC 22952 – 26001 study, which compared adjuvant WBRT with observation after neurosurgery or SRS, did not report increased functional independence on the WHO PS scale despite better intracranial control. Similarly, Aoyama reported no significant difference in preservation of KPS score ≥70 at 1 year between arms (34% in the WBRT plus SRS group vs. 27% in the SRS alone group). However, the NCCTG N0754 trial reported better QoL, as assessed by Functional Assessment of Cancer Therapy (FACT) scale (37, 38). In the HRQoL analysis of the EORTC study, Soffietti et al. found that patients who did not receive WBRT had better QoL scores (32). It has been assumed that closer follow-up of patients treated with WBRT allows early detection of failure or new metastases before they become symptomatic (39). Therefore, salvage therapies can be used in a timely manner, allowing patients to preserve their functional independence (40). Better QoL outcomes in the SRS alone group could be due to significant early side-effects from WBRT, but conclusions are difficult to draw, as this parameter has not been reliably reported in most of the aforementioned studies.

As a whole it can be concluded, that even though WBRT provides a significant benefit by protecting from intracranial failure, radiation induced toxicity should not be overlooked especially for long term survivors. A possible strategy could be to ensure that WBRT is delivered with modern techniques that minimise the side effects associated with this modality, always ensuring a balance between treatment benefit and cost-effectiveness. The phase II trial RTOG 0933 (41) and the phase III NRG - CC001 (42) have both evaluated the role of hippocampal sparing techniques with or without pharmacological protection and have both reported better cognitive function and patient-reported symptoms. In conclusion, a valid recommendation would be to treat NSCLC patients with unresectable limited BMs with SRS alone and follow a strict follow-up protocol in order to identify brain recurrence as early as possible, in order for salvage WBRT to be used.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

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