Stereotactic radiosurgery versus whole brain radiotherapy in patients with intracranial metastatic disease and small-cell lung cancer: a systematic review and meta-analysis

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Summary

Background Patients with small-cell lung cancer (SCLC) are at high risk for intracranial metastatic disease (IMD). Although stereotactic radiosurgery (SRS) has supplanted whole brain radiotherapy (WBRT) as first-line treatment for IMD in most solid cancers, WBRT remains first-line treatment for IMD in patients with SCLC. We aimed to evaluate the efficacy of SRS in comparison with WBRT and assess treatment outcomes following SRS.

Methods In this systematic review and meta-analysis, we searched MEDLINE, Embase, CENTRAL, and grey literature sources for controlled trials and cohort studies published in English reporting on SRS for IMD treatment in patients with SCLC from inception to March 23, 2022. Studies were excluded that did not report on SRS for IMD secondary to SCLC. Summary data were extracted. The primary outcome was overall survival, presented as pooled hazard ratios (HR) through random-effects meta-analysis for studies comparing SRS with WBRT with or without SRS boost, and as medians for single-arm SRS studies. This study is registered with the Open Science Framework, DOI 10.17605/OSF.IO/8M4HC, and PROSPERO, CRD42021258197.

Findings Of 3823 identified records, 31 were eligible for inclusion; seven were included in the meta-analysis. Overall survival following SRS was longer than following WBRT with or without SRS boost (HR 0·85; 95% CI 0·75–0·97; n=7 studies; n=18 130 patients), or WBRT alone (0·77; 0·72–0·83; n=7 studies; n=16 961 patients), but not WBRT plus SRS boost (1·17, 0·78–1·75; n=4 studies; n=1167 patients). Using single-arm studies, pooled median overall survival from SRS was 8·99 months (95% CI 7·86–10·16; n=14 studies; n=1682 patients). Between-study heterogeneity was considerable when pooled among all comparative studies (I^2=71·9%).

Interpretation These results suggest survival outcomes are equitable following treatment with SRS compared with WBRT in patients with SCLC and IMD. Future prospective studies should focus on tumour burden and differences in local and distant intracranial progression between WBRT-treated and SRS-treated patients with SCLC.

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Introduction

Intracranial metastatic disease (IMD) is a serious and mortality-inducing complication in patients with cancer. Retrospective clinical series and autopsy studies have found that among patients with small-cell lung cancer (SCLC), as many as 40–60% develop IMD during the course of their disease.[1,2] Furthermore, population-based studies have shown that, compared with patients with non-small-cell lung cancer, patients with SCLC show a 1·3–2-times higher risk of developing IMD and a reduced median time to intracranial disease progression.[3,4] Historically, the estimated median overall survival of patients with IMD secondary to SCLC has been poor (between 4–6 months).[5–8] Given the high incidence of IMD, rapid progression of intracranial disease, and poor survival in this population, patients with limited-stage disease and good response to systemic treatment typically receive prophylactic cranial irradiation (PCI) after primary treatment, which has been shown to reduce IMD incidence and improve overall survival.[9–12] However, this practice has been called into question, suggesting that a change in the treatment for patients with IMD secondary to SCLC could be imminent.[13–15]

In the setting of most primary solid cancers, stereotactic radiosurgery (SRS) has emerged as the preferred first-line treatment modality for patients with limited IMD (≤4 brain metastases). Randomised controlled trials have shown that SRS is non-inferior to whole brain radiation therapy (WBRT) in terms of overall survival in patients with IMD, even though WBRT is often associated with superior intracranial control.[16–22] In addition, as SRS limits radiation exposure to healthy brain tissue, SRS is associated with less CNS toxicity and fewer cognitive side effects.[20,22] However, the prospective studies that have established the use of SRS over WBRT for treatment of IMD have historically excluded patients with SCLC.[17,20,21] Given the lack of prospective evidence otherwise, first-line management for IMD in patients with SCLC consists of WBRT, even in patients with limited metastatic disease.[23] Challenging this framework, the FIRE-SCLC

Research in context

Evidence before this study

Although stereotactic radiosurgery (SRS) has supplanted whole brain radiotherapy (WBRT) as first-line treatment for patients with limited brain metastases (≤4) in most solid malignancies, WBRT remains the preferred treatment in patients with small-cell lung cancer (SCLC). We searched PubMed for systematic reviews published from database inception until March 23, 2022, using search terms related to "small cell lung cancer", "brain metastases", and "radiosurgery", but did not retrieve any meta-analyses that comprehensively assessed survival and intracranial response outcomes following SRS in patients with intracranial metastatic disease secondary to SCLC.

Added value of this study

To our knowledge, this is the first systematic review and meta-analysis evaluating survival and intracranial response outcomes in patients with SCLC and brain metastases treated with SRS. This study determined that survival following SRS was longer compared with WBRT with or without SRS boost (HR 0·85; 95% CI 0·75–0·97; n=7 studies; n=18 130 patients). Pooled median survival from SRS was 8·99 months (95% CI 7·86–10·16; n=14 studies; n=1682 patients).

Implications of all the available evidence

Our findings suggest that SRS can achieve equitable survival compared with WBRT in patients with SCLC, challenging previous reservations regarding the use of SRS in these patients given the perceived risk of rapid intracranial progression. Given the retrospective nature of studies included in this systematic review and meta-analysis, prospective trials are needed to evaluate the effect of tumour burden, as well as local and distant intracranial tumour progression, on survival following treatment with SRS or WBRT.

study reported non-inferior overall survival—although with shorter time to CNS progression, as in other SRS settings—in a propensity score-matched analysis of patients with IMD receiving SRS or WBRT.[24] Evidence for SRS in patients with SCLC is limited to observational studies, which are frequently restricted by their small sample size and non-comparative reporting. To guide clinicians and inform trial design, we performed this systematic review and meta-analysis assessing survival outcomes between SRS and WBRT and summarising treatment outcomes following SRS in patients with IMD secondary to SCLC reported in controlled trials and cohort studies.

Methods

Study design

This systematic review and meta-analysis was conducted in accordance with the PRISMA guidelines and was preregistered in PROSPERO, CRD42021258197.[25] The complete protocol is available on Open Science Framework. This study did not use individual patient-level data.

For this **study protocol** see https://osf.io/8m4hc/

Search strategy and selection criteria

The literature search was conducted on March 23, 2022, in MEDLINE, Embase, and CENTRAL and grey literature sources using a combination of keywords and Medical Subject Headings (MeSH) terms related to the terms "small cell lung cancer", "brain metastases", and "radiosurgery". To ensure completeness, the MeSH term "radiotherapy", describing treatment administered in multiple sessions and often at lower intensities compared with SRS, was incorporated into the original search (appendix pp 2–3). Only articles and abstracts in English were considered due to resource constraints. Case reports, case series, commentaries, and review articles were excluded. Reference lists of identified review articles were scanned to ensure saturation and inclusion of key studies.

See Online for appendix

Eligible studies included adult patients (age ≥18 years) with SCLC who had a diagnosis of IMD and received SRS. Studies were eligible if they reported on first-line SRS or salvage SRS—ie, SRS following either therapeutic or palliative WBRT or PCI, in comparison with WBRT or WBRT plus SRS boost. Single-arm SRS studies were included post hoc, but before data extraction. Studies that did not report on patients receiving SRS for IMD secondary to SCLC were excluded.

Three reviewers (KG, AYL, APark) independently evaluated studies in duplicate by screening abstracts and full texts. Conflicts were resolved through discussion. Cohen's κ statistic was calculated to assess inter-rater reliability at both stages.

Data analysis

Three authors (KG, AYL, and APark) extracted study-level data in pairs using predetermined extraction forms, including study characteristics (author, country, design), patient characteristics (age, sex, smoking status, performance status), treatment characteristics (regimen and response), and survival (overall survival and progression-free survival). Disagreements were resolved through discussion. Only variables specific to IMD management in patients with SCLC were extracted. Study authors and investigators were not contacted due to resource constraints. The Newcastle-Ottawa Scale was used to assess the quality of evidence from cohort studies.[26]

The primary outcome was overall survival from the time of SRS, which was estimated as hazard ratios (HRs) and as medians for comparative and single-arm studies, respectively. Secondary outcomes were intracranial progression-free survival (collected as local and distant intracranial progression-free survival where available),

extracranial progression-free survival, overall progression-free survival, disease-free survival, adverse event rates, measures of neurocognitive function, and rate of, and time until, neurological cause of death. All outcomes were prespecified, collected, and reported; outcomes that are not shown in the manuscript (ie, extracranial progression-free survival, progression-free survival, and disease-free survival) were not reported in the included studies.

The primary analysis compared overall survival between SRS and WBRT with or without SRS boost. Secondary analyses assessed single-arm overall survival, single-arm local and distant intracranial control estimates, and single-arm intracranial progression-free survival, and compared intracranial progression-free survival between SRS and a comparator.

Meta-analyses using random-effects models were performed to pool HR estimates for overall survival and intracranial progression-free survival. Given the heterogeneity in sample size of included studies, the restricted maximum likelihood estimator was used to estimate between-study heterogeneity.[27,28] Where summary survival and local, distant, or overall intracranial control estimates were not reported, Kaplan-Meier curves were digitised and summary estimates calculated using the method by Guyot and colleagues.[29,30] The extracted pseudo-individual patient data were used to generate summary overall survival and intracranial progression-free survival HRs with 95% CI for SRS versus a comparator. When assessing single-arm SRS outcomes, the method by Combescure and colleagues was used to generate pooled distribution-free survival as well as local and distant intracranial control curves.[29,31] We also estimated weighted median overall survival and intracranial progression-free survival according to treatment intent (ie, first-line, salvage, or any SRS) and survival timepoint definitions where reported, but without estimation of heterogeneity, due to under-reporting of measures of dispersion (ranges and IQR).[32] For any given analysis, all patients were included for whom the corresponding outcome was reported in a format amenable to pooling.

Post-hoc subgroup analyses stratifying by comparator type (WBRT or WBRT with SRS boost) and HR source (HR explicitly reported versus extracted from digitised Kaplan-Meier data) were performed for overall survival. A subgroup analysis by Agency for Healthcare Research and Quality rating was prespecified. Due to under-reporting, stratification or meta-regression by disease burden, patient age, or performance status were not performed. As a prespecified sensitivity analysis, summary estimates and I^2 values were compared when iteratively omitting studies one at a time as a leave-one-out assessment. Post-hoc sensitivity analyses were performed using propensity score-matched data and data from patients receiving first-line SRS without previous PCI.

Statistical heterogeneity was assessed using I^2, τ, and Q statistics, with I^2 values above 50% signifying high, and below 50% signifying low, between-study heterogeneity.[33] Effect analysis to identify potential sources of heterogeneity was performed based on outlier identification, leave-one-out analysis, and graphic display of study heterogeneity statistics.[34,35] Egger's tests and funnel plot inspection were performed to assess for publication bias.[36]

All statistical analyses were performed using the R (version 4.0.3). An α of 0·05 was considered statistically significant. All tests were two-sided.

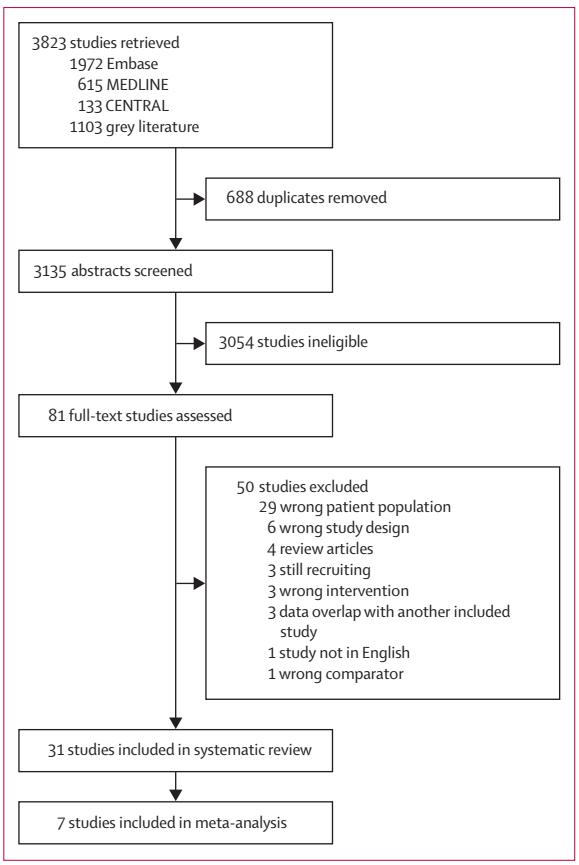

Figure 1: **Study selection**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

The literature search yielded 3823 records, from which 31 unique studies were identified that satisfied abstract and full-text eligibility criteria (figure 1).[5,24,37–65] The characteristics of all 31 studies are shown in the appendix (pp 4–7). All studies were retrospective. Nine studies compared treatment outcomes between WBRT and SRS,[5,24,58–64] of which seven reported data in formats amenable to meta-analysis.[5,24,58,59,62–64] One study reported

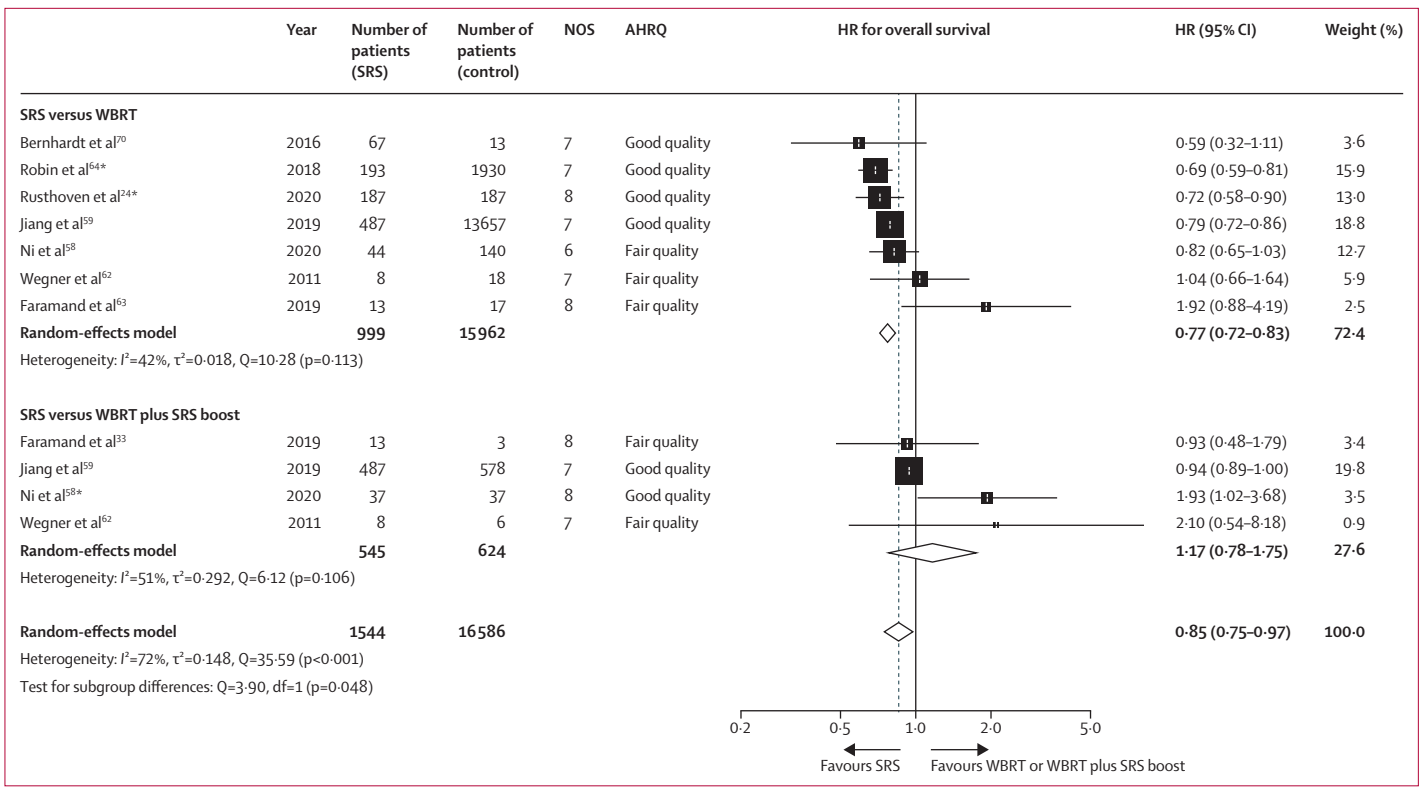

Figure 2: **Random-effects meta-analysis of SRS versus WBRT with or without SRS boost for the primary outcome of overall survival**
AHRQ=Agency for Health Research and Quality. HR=hazard ratio. NOS=Newcastle-Ottawa Scale. SRS=stereotactic radiosurgery. WBRT=whole brain radiotherapy. *These studies reported propensity score-matched data.

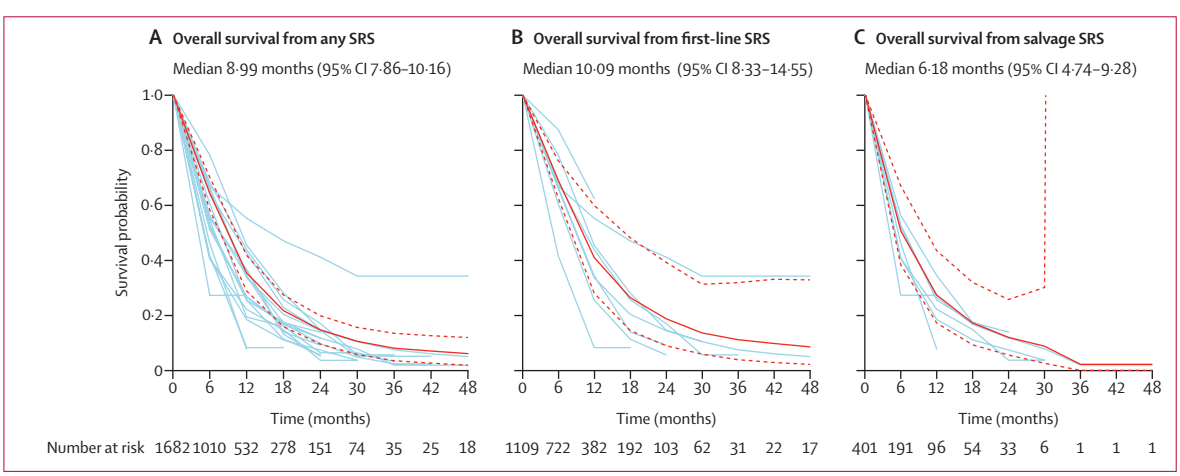

Figure 3: **Pooled summary overall survival curves of patients treated with SRS from the time of any SRS (A), first-line SRS (B), and salvage SRS (C)**
Blue lines represent overall survival curves for individual studies. Solid red lines represent summary survival curves with 95% CIs (dashed red lines). SRS=stereotactic radiosurgery.

on outcomes in patients who previously received PCI,[5] whereas the remaining six excluded patients with a history of PCI. Median follow-up ranged from 4·0 to 54·8 months. Median time to IMD development from SCLC diagnosis ranged from 5·10 to 14·00 months (n=8 studies). Two studies compared overall survival between SRS and WBRT in formats not amenable to meta-analysis (appendix p 8). Among the nine studies that reported adverse events, five reported radiation necrosis or radiation injury occurring in 4% to 33% of patients treated with SRS (appendix p 9); however, scarce and inconsistent reporting prohibited analysis of safety outcomes (ie, adverse events, neurocognitive decline, and rate and time to neurologic cause of death).

In the meta-analysis, SRS was associated with longer survival compared with WBRT with or without SRS boost (HR 0·85 [95% CI 0·75–0·97], n=18 130 patients; figure 2, appendix p 10). Subgroup analysis showed that SRS was associated with longer survival than WBRT alone (0·77 [0·72–0·83], n=16 961 patients), but not WBRT with SRS boost (1·17 [0·78–1·75], n=1167 patients; post-hoc analysis). The HR differences observed comparing SRS to WBRT alone or SRS to WBRT with SRS boost were not statistically significant by subgroup analysis (p=0·048). In post-hoc sensitivity analyses of propensity score-matched cohorts, SRS was associated with longer overall survival compared with WBRT (0·70 [0·61–0·80], n=2497 patients; appendix pp 11–12). A sensitivity analysis of studies reporting on patients without prior PCI who received first-line SRS or WBRT with or without SRS boost did not find differences in overall survival with SRS (0·87 [0·76–1·01], n=18 050 patients).

To better estimate overall survival following SRS, we constructed pooled summary survival curves from pseudo-individual patient data from the 18 studies where this data were available.[5,24,40,42,46–49,51,53,54,58,59,63–66] 14 studies reported overall survival (median 8·99 months [95% CI 7·86–10·16]; n=14 studies; n=1682 patients) from SRS administration[5,24,37–39,42,46,48,50,53–55,58,62,64] (figure 3), whereas three studies reported survival from the time of SCLC diagnosis[44,53,59] (appendix p 13). Weighted median overall survival estimates from time of first-line, salvage, any SRS, and other index dates are shown in the table.

Few studies reported on extracranial and intracranial disease burden (appendix pp 2, 14). Of four studies[58,59,61,64] that described extracranial disease burden, three reported that a higher proportion of patients treated with WBRT than SRS presented with extracranial disease,[58,59,64] of which two performed propensity score matching to account for this difference.[58,64] Two studies reported that SRS-treated patients presented with fewer intracranial lesions than WBRT-treated patients and performed propensity score matching to control for this (appendix p 12).[24,58]

Single-arm SRS local and distant intracranial control estimates were pooled from reporting studies (figure 4, appendix pp 15–16). Local intracranial control rates at 6 months were 81% (95% CI 67–99) and at 12 months 78% (61–98).[44,48,53,55,62] Distant intracranial control rates at 6 months were 66% (50–86) and at 12 months 58% (46–75).[37,38,40,42,44,48,55] We were unable to calculate local and distant intracranial disease progression between SRS and WBRT with or without SRS boost due to lack of data.

Intracranial progression-free survival was not different between SRS and WBRT (HR 0·99 [95% CI 0·81–1·20], n=2 studies; n=492 patients without previous PCI; appendix p 17).[24,58] Weighted single-arm estimates for median intracranial progression-free survival from first-line, salvage, and any SRS were 4·92 months (95% CI 4·92–6·10, n=808 patients),[24,46,49,56,58] 6·80 months (6·80-9·80, n=24 patients),[44,49] and 4·92 months (4·92-5·68, n=832 patients),[24,41,46,49,56,58] respectively. Additional intracranial progression-free survival estimates are reported in the appendix (pp 15–19).

The funnel plot for overall survival showed no asymmetry by visual inspection or Egger's test, suggesting no publication bias (appendix p 20). Results from evaluation of risk of bias are reported in the appendix (pp 21–22).

Between-study heterogeneity was considerable when pooled among all studies (I^2=71·9% [95% CI 48·3–84·7]). Stratification by WBRT comparators showed one source of this heterogeneity, as estimates were reduced in WBRT (I^2=42%) and WBRT with SRS boost (I^2=51%) comparator subgroups. Subgroup analyses by HR source and Agency for Healthcare Research and Quality rating did not reveal further sources of heterogeneity (data not shown). Effect analysis was performed to identify individual studies that contributed disproportionately to

	Overall survival definition timepoint	Number of studies	Number of patients	Median overall survival (95% CI)
Any data[5,24,37–39,41–58,61,62,64,65]	SRS or NR	27	2015	6·74 (6·74–8·66)
Any data[5,24,37–39,41–46,48,50,52,54–57,62,64,65]	SRS	21	1633	8·04 (6·74–8·66)
First line[24,38,46,49,50,52,55,56,58,61,62,64]	SRS or NR	12	1157	8·66 (8·66–11·10)
First line[24,38,46,50,52,55,56,62]	SRS	8	882	8·66 (8·04–8·66)
Salvage[5,39,41–45,47,49–53,55,65]	SRS or NR	15	645	6·20 (5·80–6·29)
Salvage[5,39,41–45,50,52,55,65]	SRS	11	517	6·20 (5·80–6·58)
Any data[41,44,45,54,59,63]	SCLC diagnosis	6	704	10·50 (10·50–21·90)
Salvage[41,44,45]	SCLC diagnosis	3	86	24·80 (12·00–29·30)
Any data[39,41,45,54,60]	IMD diagnosis	5	144	14·30 (11·00–18·10)
Salvage[39,41,45,60]	IMD diagnosis	4	103	16·90 (13·70–18·10)

IMD=intracranial metastatic disease. NR=not reported. SCLC=small-cell lung cancer. SRS=stereotactic radiosurgery.

Table: **Weighted median overall survival estimates in months by treatment intent**

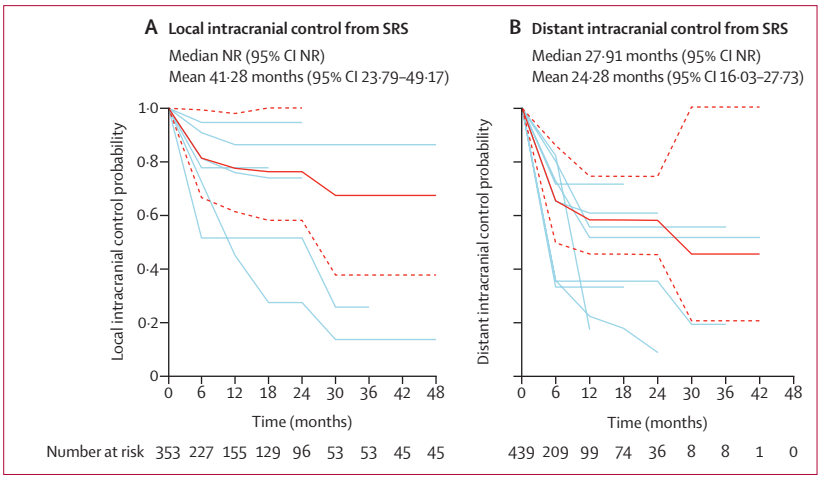

Figure 4: **Pooled summary local intracranial (A) and distant intracranial (B) control estimates of patients treated with SRS from the time of SRS treatment regardless of treatment intent**
Blue lines represent the control curves for individual studies. Solid red lines represent the summary control curves with 95% CIs (dashed red lines). NR=not reached.

between-study heterogeneity, but none was identified (appendix pp 23–24).

Discussion

This study found no significant reduction in overall survival associated with SRS compared with WBRT with or without SRS boost, as well as SRS compared with WBRT alone. These results mirror findings of non-inferiority of SRS compared with WBRT from landmark trials that established the use of SRS in patients with limited brain metastases (≤4) and excluded patients with SCLC.[17,20,21,67] Despite the depth and breadth of SRS literature in other malignancies, this is, to our knowledge, the first systematic review and meta-analysis to assess survival and intracranial response outcomes following SRS in patients with IMD secondary to SCLC.

In most solid malignancies, SRS is recommended for patients with limited intracranial disease and well controlled systemic disease, but remains under investigation for patients with multiple brain metastases.[68,69] Intracranial and extracranial disease burden affect treatment choice and patient prognosis. For example, in the study by Ni and colleagues, a higher proportion of patients presented with extracranial disease in the WBRT-treated cohort (53 [38%] of 140 WBRT-only patients and six [14%] of 44 SRS patients), whereas patients who received SRS had a lower number of brain metastases (ie, 1–3 lesions; 39 [89%] of 44 SRS patients *vs* 34 [24%] of 140 WBRT-only patients).[58] Given the heterogeneity in our pooled cohort in terms of disease burden, performance status, and number of intracranial lesions, our results should not be understood to imply superior survival in all patients with IMD due to SCLC who were treated with SRS instead of WBRT. However, even with differences in intracranial and extracranial disease burden, our findings suggest that patients with SCLC could benefit from SRS, and thus expose a need to re-examine the current framework for IMD treatment in patients with SCLC. Careful patient selection might improve outcomes in patients with SCLC and IMD.

Despite advances in treatment, IMD diagnosis in patients with SCLC remains associated with poor survival, ranging between 4 and 6 months.[6–8,70] Our single-arm analysis challenges this idea. Pooled survival data from our study indicate that, in the first-line setting, median survival following SRS could be as high 10·1 months. These estimates were supported by an orthogonal approach where we pooled median survival estimates, suggesting a summary median survival of 8·7 months following first-line SRS, which compares favourably to historical median overall survival estimates of 6 months following WBRT in patients with extensive stage SCLC.[70] In other cancers, overall survival estimates following SRS have been reported between 7 and 12 months.[17–21] This extended overall survival, even in the presence of IMD, might be attributable to advances in systemic therapies, including immunotherapies, which play an increasingly important role for the systemic management of patients with SCLC.[71] As in other malignancies, immunotherapies might positively influence the effect of SRS on overall survival and intracranial progression or, conversely, increase IMD incidence as life expectancies, and consequently time for IMD development, increase.[72–74] Our single-arm results do not clarify whether SRS alone is sufficient to maintain survival given the high propensity for IMD progression observed in patients with SCLC. Prospective series are required to investigate the impact of advances in systemic therapies in synergy with SRS.

Although concerns regarding rapid IMD progression in patients with SCLC remain, intracranial progression-free survival was found not to differ between patients treated with SRS or WBRT in our study. This finding contrasts with current literature from other cancers that suggest improved intracranial disease control with WBRT, even in the absence of survival benefits.[22] Of note, our weighted estimate for median intracranial progression-free survival following SRS was shorter than previously reported for WBRT.[70] Pooled estimates for intracranial control rates at 12 months were 78% for local intracranial progression, and 58% for distant intracranial progression. These results are comparable with findings from trials in other solid malignancies reporting intracranial control rates ranging from 67% to 73% for local intracranial progression, and 36 to 45% for distant intracranial progression.[17,20,21] These conflicting findings could be attributable to the substantial effect of prognostic factors, including number of lesions treated, Recursive Partitioning Analysis score, presence of synchronous IMD, response to chemotherapy, receipt of PCI, extracranial disease, and adverse events related to radiotherapy, which we were unable to examine in the present analysis due to the absence of data.[70] Intracranial control rates must be interpreted in the context of these prognostic factors and survival.

Our study highlights the paucity of SRS data available in patients with SCLC and IMD. A survey of radiation oncologists in the USA showed that although many would consider employing SRS for patients with SCLC and limited brain metastases, rapid intracranial progression and the absence of high-level data remain major concerns.[75] We were able to identify nine studies that compared SRS with WBRT with or without SRS boost, all of which were retrospective. This highlights the need for prospective SRS evidence in an era marked by rapid advances in systemic and targeted treatments.

One of the prevailing advantages of SRS over WBRT is the reduced risk of neurocognitive sequelae following SRS treatment, which has been shown in other malignancies and has driven preferential use of SRS over WBRT.[18,20] In patients with SCLC, the benefits of sparing healthy brain tissue with SRS must be weighed against the risk of neurocognitive decline secondary to intracranial progression. None of the studies that compared SRS directly with WBRT with or without SRS

boost reported long-term neurocognitive function or radiotherapy-related adverse events. Neurocognitive decline following WBRT can be detected as early as 2 months following treatment, and previous reports have found a statistically significant reduction in cognitive deterioration 3–4 months after treatment with SRS alone compared with WBRT with SRS boost.[16,18,20] Our findings indicate that at least a subset of patients with SCLC survive sufficiently long following SRS treatment to benefit from reduced neurotoxicity. In addition to the shorter treatment schedule that could enhance patient comfort, our findings underline that prospective studies are necessary to clarify this assumption.

Several trials are ongoing to compare SRS and WBRT in patients with SCLC and IMD. The ENCEPHALON trial (NCT03297788) is a phase 2 randomised study designed to investigate the effect of SRS compared with WBRT for treatment of ten or fewer brain metastases measuring overall survival, intracranial progression, and neurocognitive decline. Another phase 3 trial (NCT04804644) has been designed to compare SRS and WBRT with hippocampal avoidance for ten or fewer brain metastases with neurocognitive decline as the primary endpoint, and overall survival and other neurocognitive outcomes as secondary endpoints. Additionally, two single-arm phase 2 trials (NCT03391362 and NCT04516070) to investigate overall survival, quality of life, and cognitive function following SRS in patients with IMD and SCLC are currently recruiting. These trials could play a crucial part in clarifying the role of SRS in patients with SCLC and IMD.

Our study has several limitations. First, all studies included in this review were retrospective and, therefore, susceptible to selection bias. As suggested by differences in intracranial and extracranial disease burden between cohorts treated with SRS and WBRT, it is possible that patients with more favourable survival prognoses and limited metastatic burden were selected for SRS treatment, which could have inflated summary estimates for overall survival and other outcomes. Additionally, most studies excluded patients with previous PCI, hindering our ability to generalise our findings to patients who have received this standard-of-care treatment. Furthermore, pooled studies might differ in demographic and clinicopathological characteristics. Nonetheless, we pooled survival data from over 1600 patients in single-arm SRS studies, which represents, to our knowledge, the largest assembled cohort of patients with SCLC with IMD investigated for survival outcomes. Second, due to limited data availability, we were unable to investigate the number and size of brain metastases treated or the time to development of IMD—these are significant shortcoming, as metastatic burden and timing of brain metastases are strong predictors of survival that contribute to treatment selection and can affect summary effect measures for overall survival. However, our subgroup analysis of propensity score-matched cohorts was performed to address metastatic burden, although no reporting of IMD timing precluded analysis of this covariate. Due to limited data availability, we were also unable to comment on receipt and response to chemotherapy, which is associated with systemic disease control and overall survival. Third, several key outcomes that inform the comparison of SRS to WBRT were underreported. Poor rates of local and distant intracranial control have historically driven preference for WBRT over SRS in patients with SCLC and IMD, but these were not adequately reported for meta-analysis. Considering reported advantages of WBRT over SRS, future prospective trials need to determine whether SRS does not have a negative effect on survival outcomes in this cohort at high risk for IMD. Fourth, only articles published in English were considered for inclusion, introducing selection bias and decreasing the generalisability of our findings to other settings. Last, several of our analyses pooled single-arm outcome estimates, which lend precision to prognostication with SRS, but must be interpreted with caution when used for comparison.

In summary, to our knowledge, this is the first meta-analysis to examine survival and intracranial response outcomes following SRS in patients with SCLC and IMD, representing the largest cohort of patients with SCLC and IMD treated with SRS. Our findings suggest no significant disadvantage in outcomes following SRS compared with WBRT in this cohort. Future prospective controlled trials are needed to investigate the impact of IMD burden and differences in intracranial control between WBRT and SRS in this historically excluded population.

Contributors

KG, AWE, and SD conceived and designed the study. KG, AYL, and APark independently assessed studies for possible inclusion and collected the data. KG analysed the data with results checked and verified by AWE and AYL. KG drafted the initial manuscript with input from AYL. All authors had access to the data reported in this study, critically revised the report for important intellectual content, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. The corresponding author had full access to all of the data and the final responsibility to submit for publication.

Declaration of interests

BHL declares institution grants from AstraZeneca and Pfizer; and honoraria and support for travel or attending meetings from AstraZeneca. AS reports institution grants from Elekta AB and Varian; honoraria from (Medical Advisory Group and CNS Teaching Faculty), Elekta (Gamma Knife Icon) and Elekta AB, BrainLab, AstraZeneca, Medtronic Kyphon, Accuray, Merck, Abbvie, and Roche; support for attending meetings or travel from Elekta, Varian, and BrainLab; and acting as board member with International Stereotactic Radiosurgery Society (ISRS), co-chair of AO Spine Knowledge Forum Tumor, and member of Elekta MR Linac Research Consortium, Elekta Spine, Oligometastases and Linac Based ISRS Consortia; and sitting on the advisory board with VieCure. SD received royalties from Oxford University Press; acts as a consultant for, and has received speaker fees from, Medexus; reports support for travel and accommodation from the Congress of Neurological Surgeons and the American Association of Neurological Surgeons; participated on a data safety monitoring board or advisory board for the Subcortical Surgery Group and XPan Medical; is the provincial lead Provincial Lead for CNS Cancers, Ontario Health, Cancer Care Ontario; and reports a research grant from Alkermes. All other authors declare no competing interests.

Data sharing
Extracted data are available upon request to the corresponding author.

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