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Multi-institutional Analysis of Prognostic Factors and Outcomes After Hypofractionated Stereotactic Radiotherapy to the Resection Cavity in Patients With Brain Metastases

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IMPORTANCE For brain metastases, the combination of neurosurgical resection and postoperative hypofractionated stereotactic radiotherapy (HSRT) is an emerging therapeutic approach preferred to the prior practice of postoperative whole-brain radiotherapy. However, mature large-scale outcome data are lacking.

OBJECTIVE To evaluate outcomes and prognostic factors after HSRT to the resection cavity in patients with brain metastases.

DESIGN, SETTING, AND PARTICIPANTS An international, multi-institutional cohort study was performed in 558 patients with resected brain metastases and postoperative HSRT treated between December 1, 2003, and October 31, 2019, in 1 of 6 participating centers. Exclusion criteria were prior cranial radiotherapy (including whole-brain radiotherapy) and early termination of treatment.

EXPOSURES A median total dose of 30 Gy (range, 18-35 Gy) and a dose per fraction of 6 Gy (range, 5-10.7 Gy) were applied.

MAIN OUTCOMES AND MEASURES The primary end points were overall survival, local control (LC), and the analysis of prognostic factors associated with overall survival and LC. Secondary end points included distant intracranial failure, distant progression, and the incidence of neurologic toxicity.

RESULTS A total of 558 patients (mean [SD] age, 61 [0.50] years; 301 [53.9%] female) with 581 resected cavities were analyzed. The median follow-up was 12.3 months (interquartile range, 5.0-25.3 months). Overall survival was 65% at 1 year, 46% at 2 years, and 33% at 3 years, whereas LC was 84% at 1 year, 75% at 2 years, and 71% at 3 years. Radiation necrosis was present in 48 patients (8.6%) and leptomeningeal disease in 73 patients (13.1%). Neurologic toxic events according to the Common Terminology Criteria for Adverse Events grade 3 or higher occurred in 16 patients (2.8%) less than 6 months and 24 patients (4.1%) greater than 6 months after treatment. Multivariate analysis identified a Karnofsky Performance Status score of 80% or greater (hazard ratio [HR], 0.61; 95% CI, 0.46-0.82; $P < .001$), 22 to 33 days between resection and radiotherapy (HR, 1.50; 95% CI, 1.07-2.10; $P = .02$), and a controlled primary tumor (HR, 0.69; 95% CI, 0.52-0.90; $P = .007$) as prognostic factors associated with overall survival. For LC, a single brain metastasis (HR, 0.57; 95% CI, 0.35-0.93; $P = .03$) and a controlled primary tumor (HR, 0.59; 95% CI, 0.39-0.92; $P = .02$) were significant in the multivariate analysis.

CONCLUSIONS AND RELEVANCE To date, this cohort study includes one of the largest series of patients with brain metastases and postoperative HSRT and appears to confirm an excellent risk-benefit profile of local HSRT to the resection cavity. Additional studies will help determine radiation dose-volume parameters and provide a better understanding of synergistic effects with systemic and immunotherapies.

Invited Commentary

Supplemental content

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Local recurrence of brain metastases is a challenge in neuro-oncology. Because of peritumoral spread, even after complete neurosurgical resection,[1,2] the recurrence rate without any adjuvant radiotherapy is approximately 50%.[1,3] Improved diagnostics and increasing options in systemic treatment, including immunotherapy, have continuously increased survival in oncology, making local failure (LF) of bone metastases an urgent issue to address.

Historically, patients with bone metastases had poor outcomes and were offered whole-brain radiotherapy (WBRT) or best supportive care independently of the number of metastases present. Whole-brain radiotherapy is associated with neurocognitive decline, and a multi-institutional European Organisation for Research and Treatment of Cancer trial failed to demonstrate an overall survival (OS) benefit compared with surgery and observation alone or stereotactic radiosurgery (SRS).[1] An exploratory analysis[4] of the same trial found that local recurrence rates were similar between SRS and surgery. However, when stratified by interval, patients after surgery had a much higher risk of early local recurrence (0-3 months) compared with those undergoing SRS, although specifically, the likelihood of local recurrence was lower after 9 months in the surgery group.

This finding argues for more intensive local treatment, and increasing evidence supports local radiotherapy of the resection cavity of bone metastases.[3,5-9] Radiotherapy focused on the affected areas (ie, surgical bed) can minimize adverse effects by sparing healthy tissue and organs at risk.

There is an ongoing discussion on the best treatment approach for postoperative surgical cavities. The main differences, aside from the dose concept, are contouring and expansion to cover microscopic disease. Critics argue that local radiotherapy to the resection cavity is associated with a higher risk of leptomeningeal disease (LMD), that large cavities are at risk for earlier recurrence, and small safety margins applied with SRS contribute to a higher risk of LF. For SRS, most centers do not include an additional safety margin; for hypofractionated stereotactic radiotherapy (HSRT), a safety margin of 2 to 5 mm is added.[6,7,10,11]

To date, it is inconclusive whether HSRT or SRS is best for cavity radiotherapy; most trials applied SRS, and local recurrence rates seem relatively high: Mahajan et al[3] and Brown et al,[5] investigating SRS to the resection cavity, reported lower local control (LC) rates (72%[3] and 60%,[5] respectively at 12 months). Recently, Shi et al[12] reported an excellent LC of 93% in a large SRS cohort. In SRS, commonly, no or very small safety margins are applied to minimize toxic effects, which in turn potentially explain the higher rates of LF. On the contrary, for HSRT, 2 studies[13,14] found high LC rates of 93% and 87% at 1 year, and Traylor et al[15] reported LC rates of 91% at 6 months and 85% at 18 months. The meta-analysis by Lehrer et al[16] investigated 4 treatment groups: SRS vs HSRT for large bone metastases in definitive and postoperative settings. For 405 patients with HSRT treated with heterogenous fractionation regimens, the 1-year LC was 87%, whereas in the SRS group of 183 patients, it was 68%. No significant difference between groups was seen. A retrospective study by Susko et al[17] analyzed recurrences after SRS following published guidelines. They found that a dural safety margin should be considered for SRS and might improve LC. The Technical University of Munich cohort found that HSRT could lead to enhanced LC and that toxicity rates are low and acceptable; neurocognitive decline may be prevented compared with WBRT.[7,18]

In the current study, we assembled a large, international, high-volume, multicenter study group evaluating the effect of HSRT to the resection cavity; all centers have demonstrated expertise in the management of brain tumors. A special aim was to evaluate LC, OS, and the alleged risk for LMD. The data were generated from the largest series of bone metastases treated with HSRT and provide a strong argument for postoperative resection cavity radiotherapy, which could change guidelines and practices in many centers.

Key Points

Question What are the outcomes and prognostic factors after hypofractionated stereotactic radiotherapy to the resection cavity of patients with brain metastases?

Findings In this cohort study of 558 patients, overall survival was 65% at 1 year, 46% at 2 years, and 33% at 3 years, and local control was 84% at 1 year, 75% at 2 years, and 71% at 3 years. Prognostic factors associated with overall survival were a Karnofsky Performance Status score of 80% or greater, 22 to 33 days between resection and radiotherapy, and a controlled primary tumor, whereas prognostic factors associated with local control were a target volume of 23 mL or less, a single brain metastasis, and a controlled primary tumor.

Meaning The results of this study suggest that hypofractionated stereotactic radiotherapy has a favorable risk-benefit profile and, compared with whole-brain radiotherapy, a low risk of treatment-related adverse effects.

Methods

Patients

In this cohort study, patients with resected bone metastases were treated with postoperative HSRT between December 1, 2003, and October 31, 2019. Data from 558 patients with 581 cavities were retrospectively collected and pooled from 6 international centers. Exclusion criteria included prior cranial radiotherapy (including WBRT), more than 100 days between resection and radiotherapy, and early termination of the radiation course. Patient characteristics are given in **Table 1**. The Medical Faculty of the Technical University of Munich Ethics Commission approved this study. Informed consent was waived by the ethics committee. All data were deidentified. The researchers at each institution obtained individual institutional review board approval and data-sharing agreements. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for cohort studies.

Treatment

All patients were treated with HSRT after resection of 1 bone metastasis, and 23 patients received multiple treatment courses

Table 1. Patient Characteristics

Characteristic	Finding[a]
Sex	
Male	257 (46.1)
Female	301 (53.9)
Age at radiotherapy, mean (SD), y	61 (0.50)
Primary tumor diagnosis	
NSCLC (adenocarcinoma)	163 (28.1)
NSCLC (nonadenocarcinoma)	29 (5.0)
SCLC	2 (0.3)
Melanoma	89 (15.3)
RCC	47 (8.1)
Breast cancer	98 (16.9)
Gastrointestinal tumor	65 (11.2)
Other	88 (15.1)
KPS score at radiotherapy (%)	
≥90	226 (38.9)
80	168 (28.9)
70	77 (13.3)
60	28 (4.8)
≤50	11 (1.9)
Unknown	71 (12.2)
No. of cranial metastases	
1	373 (64.2)
2-3	180 (31.0)
≥4	28 (4.8)
Extracranial metastases	
Yes	283 (48.7)
No	262 (45.1)
Unknown	36 (6.2)
Resection status	
Complete gross total resection	455 (78.3)
Incomplete subtotal resection	126 (21.7)
RPA score	
1	94 (16.2)
2	345 (59.4)
3	39 (6.7)
Unknown	103 (17.7)
GPA score	
0-1.0	67 (11.5)
1.5-2.0	175 (30.1)
2.5-3.0	211 (36.3)
3.5-4.0	55 (9.5)
Unknown	73 (12.6)
Time from resection to radiotherapy, median (IQR), d	34 (26-42)
Time from resection to radiotherapy, d[b]	
0-21	78 (13.4)
22-33	196 (33.7)
≥34	307 (52.8)
PTV, median (IQR), mL	23.9 (13.5-36.3)
CV, median (IQR), mL	10.9 (5.9-19.9)
D_{mean} (PTV), median (IQR), Gy	30.3 (27.1-34.9)
D_{max} (PTV), median (IQR), Gy	32.9 (29.8-36.6)
$D_{98\%}$ (PTV), median (IQR), Gy	26.5 (23.8-33.8)

Abbreviations: CV, cavity volume; D_{max}, maximum dose; D_{mean}, mean dose; $D_{98\%}$, dose of 98% of volume; GPA, graded prognostic assessment[19]; IQR, interquartile range; KPS, Karnofsky Performance Status; NSCLC, non–small cell lung carcinoma; PTV, planning target volume; RCC, renal cell carcinoma; RPA, recursive partitioning analysis[20]; SCLC, small cell lung carcinoma.

[a] Data are presented as number (percentage) of patients unless otherwise indicated.

[b] Groups according to Scharl et al.[21]

for further bone metastases. The median total dose was 30 Gy (range, 18-35 Gy), and the dose per fraction was 6 Gy (range, 5-10.7 Gy). eTable 1 in the Supplement gives the dose schemes used with equivalent dose in 2 Gy and biologically equivalent dose using a tumor α/β of 10 (BED_{10}). Treatment planning and aftercare followed the individual institutions' procedures. The cavity volume was defined as the resection bed. Additional margins may have been added to determine the clinical target volume, and further margins to the clinical target volume resulted in the planning target volume (PTV). Postoperative magnetic resonance imaging (MRI) was recommended for treatment planning at all institutions mainly because of the changes in cavity volume over time and the potential risk of local recurrence before the initiation of radiotherapy.

Radiation-induced brain necrosis and LMD were determined after surgery and histopathologic examination or on MRI by an interdisciplinary board. Resection status was determined by postoperative imaging (MRI: n = 554; computed tomography: n = 23; unknown: n = 4).

Statistical Analysis

Primary end points were OS, LC (based on time to LF of the treated metastases), and the analysis of associated prognostic factors. Secondary end points included distant intracranial failure (DICF, defined as the growth of new or not-treated bone metastases), distant progression (DP, defined as the growth of extracranial metastases or tumor), and the incidence of neurologic toxic effects. Survival analyses were based on Kaplan-Meier estimates with log-rank tests and the Cox proportional hazards regression model. The probability of LF before death was determined by competing risk analysis.

Outcomes were calculated from the last day of radiotherapy until the event, last follow-up, or death, whichever came first. For patients treated with multiple courses, we used the first treatment for OS, DICF, and DP. Local control was determined per metastases treated (n = 581). Follow-up time since resection was calculated for all patients as the observation from the last day of radiotherapy to the last follow-up. The Kaplan-Meier and Cox proportional hazards regression models automatically right censor patients for outcome analysis at the last follow-up time point at which we know that the event did not

Table 2. Proportion of Patients Surviving at Several Time Points for LC, DICF, DP, OS, and LMD According to Kaplan-Meier Estimates

	Patients surviving or free of event, %						
Outcome	3 mo	5 mo	8 mo	10 mo	1 y	2 y	3 y
LC	97	94	89	87	84	75	71
DICF	82	74	61	58	54	42	35
DP	85	79	72	67	63	45	39
OS	93	86	77	72	65	46	33
LMD	96	93	90	89	87	84	82

Abbreviations: DICF, distant intracranial failure; DP, distant progression; LC, local control; LMD, leptomeningeal disease; OS, overall survival.

occur. For testing prognostic factors associated with OS and LC, patients with a missing value were excluded.

Statistical calculations were performed using SPSS software, version 25 (IBM Inc) and R Statistics (R Foundation for Statistical Computing). A 2-sided $P < .05$ was considered statistically significant.

Results

Outcomes

A total of 558 patients (mean [SD] age, 61 [0.50] years; 301 [53.9%] female) with 581 resected cavities were analyzed. Median observation time was 12.3 months (interquartile range [IQR], 5.0-25.3 months) for all patients and 19.7 months (IQR, 8.6-37.9 months) for surviving patients only. Of the 240 patients alive at the time of this analysis (43.0%), 131 (54.6%) had no recent follow-up within the last 18 months.

Local control was 94% at 5 months, 84% at 1 year, 75% at 2 years, and 71% at 3 years (the median was not reached). Ninety-six of the 581 cases (16.5%) had a local recurrence. The probability of LF was 3% at 3 months, 5% at 5 months, 9% at 8 months, 11% at 10 months, 13% at 1 year, 17% at 2 years, and 19% at 3 years (**Table 2**). The median DICF was 14.7 months (95% CI, 10.8-18.5 months), and the median DP was 19.6 months (95% CI, 16.2-23.0 months).

At the time of analysis, 318 patients (57.0%) had died. Median OS was 21.2 months (95% CI, 18.1-24.2 months). Table 2 provides more-detailed data on outcomes. Overall survival and LC are displayed in **Figure 1**D, **Figure 2**D, and eTable 2 in the Supplement according to primary diagnosis and in eTable 3 in the Supplement according to participating centers.

Clinical radionecrosis was observed in 48 patients (8.6%). It was classified as Common Terminology Criteria for Adverse Events grade 1 in 42 cases (87.5%) and as grades 2 and 3 in 3 cases (6.3%) and confirmed by MRI (n = 39) or biopsy (n = 9). Median time to occurrence of radionecrosis was 13.1 months (IQR, 6.7-18.4 months).

During follow-up, 73 patients (13.1%) developed LMD, with a median time to occurrence of 5.8 months (IQR, 2.6-10.4 months). The LMD-free rates were 87% at 1 year, 84% at 2 years, and 82% at 3 years. The development of LMD was not identified by histologic analysis (χ^2 test, $P = .93$) or BED_{10} dose (<48 vs ≥48 Gy) (χ^2 test, $P = .79$). However, patients with larger PTVs were at higher risk for LMD (χ^2 test, $P = .04$).

Neurologic Common Terminology Criteria for Adverse Events toxic effects of grade 3 or higher were seen in 16 cases (2.8%) in the first 6 months after treatment and in 24 cases (4.1%) after that.

Prognostic Factors Associated With OS and LC

Univariate analyses identified a Karnofsky Performance Status (KPS) score of 80% or greater, 22 to 33 days between resection and radiotherapy, a complete resection, the absence of extracranial metastases, and a controlled primary tumor as prognostic factors associated with OS (**Table 3** and Figure 2). The graded prognostic assessment (GPA) and recursive partitioning analysis (RPA) scores were statistically significant as well. In the multivariate analysis, KPS score of 80% or greater (hazard ratio [HR], 0.61; 95% CI, 0.46-0.82; $P < .001$), 22 to 33 days between resection and radiotherapy (HR, 1.50; 95% CI, 1.07-2.10; $P = .02$), and a controlled primary tumor (HR, 0.69; 95% CI, 0.52-0.90; $P = .007$) were associated with increased OS.

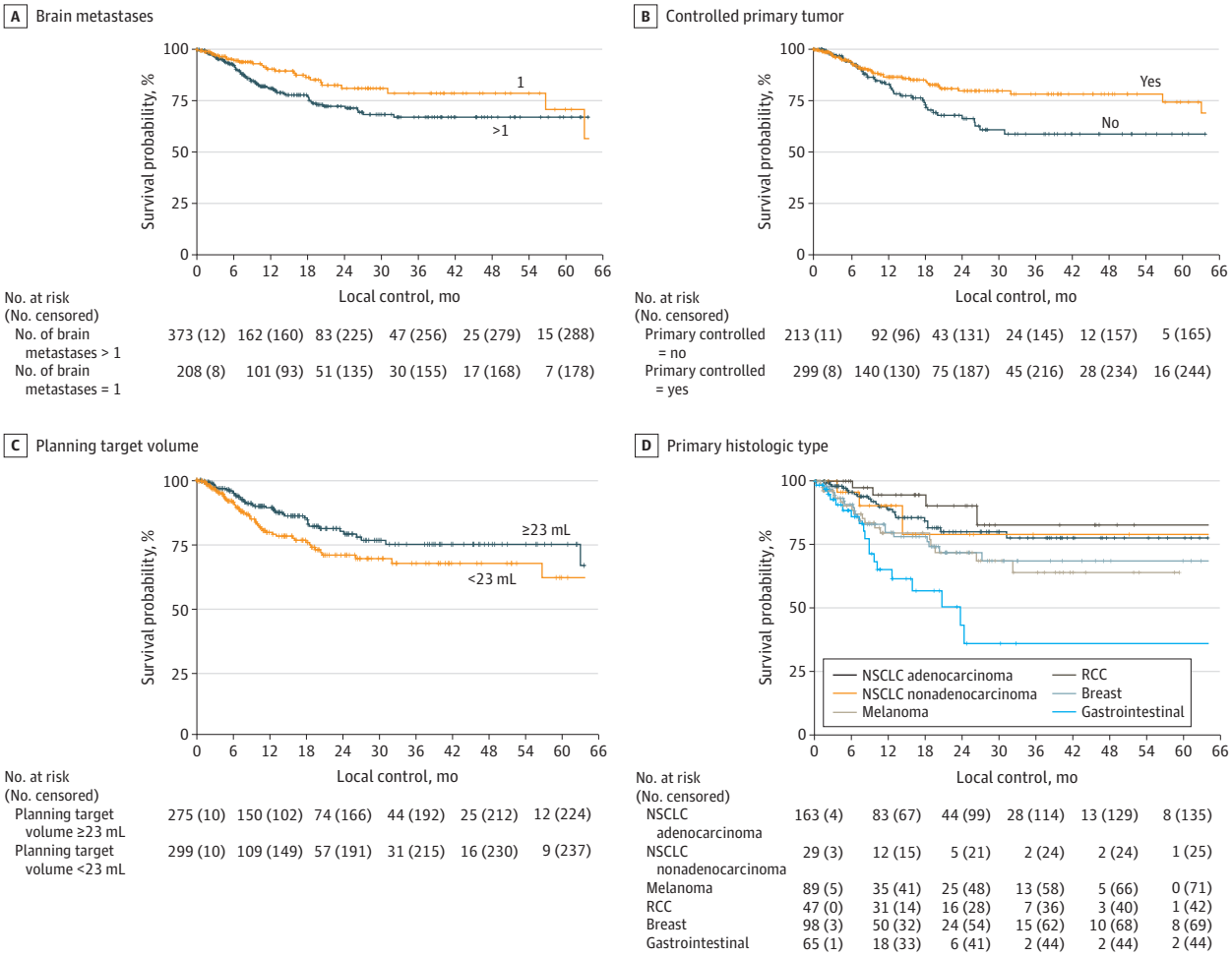
For LC, a PTV of 23 mL or less (hazard ratio [HR], 1.54; 95% CI, 1.02-2.32; $P = .04$), a single brain metastasis at the time of radiotherapy (HR, 0.61; 95% CI, 0.39-0.96; $P = .03$), and a controlled primary tumor (HR, 0.59; 95% CI, 0.39-0.91; $P = .02$) were significant in the univariate analysis. In the multivariate analysis, a single bone metastasis (HR, 0.57; 95% CI, 0.35-0.93; $P = .03$) and a controlled primary tumor (HR, 0.59; 95% CI, 0.39-0.92; $P = .02$) remained significant. For DICF, the absence of extracranial metastases (HR, 1.35; 95% CI, 1.05-1.73; $P = .02$), a single brain metastasis (HR, 1.58; 95% CI, 1.24-2.03; $P < .001$), and a controlled primary tumor (HR, 0.64; 95% CI, 0.50-0.83; $P = .001$) were significant in the univariate analysis. A single brain metastasis (HR, 1.48; 95% CI, 1.13-1.92; $P = .004$) and a controlled primary tumor (HR, 0.71; 95% CI, 0.54-0.92; $P = .001$) remained significant in the multivariate analysis (Table 3 and Figure 1).

Discussion

The current study assessed outcomes after postoperative HSRT of patients with resected bone metastases in a multicenter, international consortium. Local control was 84% at 1 year and 71% at 3 years. The rate of treatment-related necrosis was 8.6%, and the rate of leptomeningeal spread was 13.1%. Prognostic factors associated with OS were a KPS score of 80% or greater, 22 to 33 days between resection and radiotherapy, complete resection, absence of extracranial metastases, single bone metastasis, and a controlled primary tumor. Local control was associated with a PTV of 23 mL or less, a single bone metastasis, and a controlled primary tumor.

Given the infiltrating nature of bone metastases, a strong argument for local radiotherapy of the resection cavity has been raised in the past.[22] This argument is supported by the facts that remnant cells are left even after macroscopic total resection, the known benefit of high local doses regarding LC, and the risk of neurocognitive decline and lack of OS benefit associated with WBRT. Several centers started local treatment concepts,[12,23-25] and evidence is continuously increasing. How-

Figure 1. Kaplan-Meier Estimates of Local Control



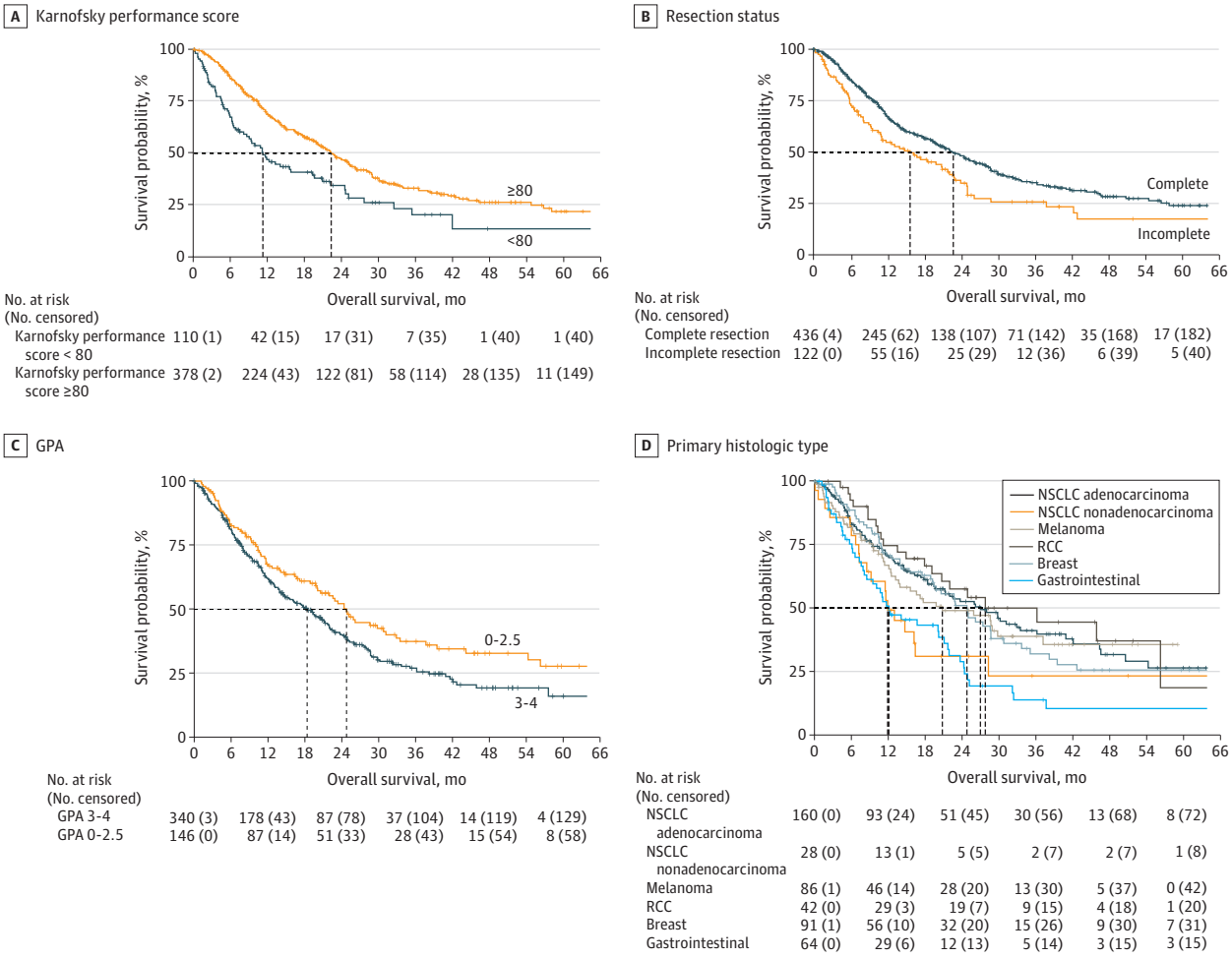
NSCLC indicates non–small cell lung cancer.

ever, results from large randomized clinical trials comparing SRS and HSRT regimens are missing. The recruiting phase 3 trial from the Alliance for Clinical Trials in Oncology[26] performed by the National Cancer Institute and the Mayo Clinic, comparing the radiotherapy concepts, will provide first results in 2025.

Previous studies[27-29] have evaluated the role of margins around the resection cavity. Specifically, Choi et al[27] and Gui et al[28] found superior LC with a 2-mm radial expansion around the resection cavity. In patients treated without expansion, the LF was 16% at 12 months, whereas in the group treated with a margin, 3.4% developed LF. Histologic subtypes did not influence outcomes. No-margin concepts are generally used with SRS, offering fast and noninvasive treatment. However, regardless of the treatment concept, all stringently require recent MRI because resection cavities can change substantially over time.[29]

Furthermore, at the Technical University of Munich, investigators found that the timing for local radiotherapy after resection is essential for outcomes and that cavity changes after surgery must be monitored closely by computed tomography and MRI for treatment planning.[18,21] Importantly, enough time for wound healing must be diligently weighed against a quick start to minimize the risk of local recurrence before radiotherapy initiation. Therefore, considering the risk of local recurrence, the timely performance of radiotherapy is essential. In addition, Jarvis et al[29] found that the risk of recurrence increases over time, which again argues for additional MRI if treatment is scheduled later after surgery. If local recurrence is present, some centers prescribe higher doses. For example, Bilger et al[30] reported that 35 Gy (5 Gy/d; BED_{10}, 52.5 Gy) is applied in patients with macroscopic tumor after surgery compared with 30 Gy (5 Gy/d; BED_{10}, 45 Gy) in patients without residual tumor. To date, no evidence indicates that higher doses are required for residual tumors, and most centers do not determine the dose based on residual disease.[7,25] In the current multicenter analysis, we could not find an influence of BED_{10} doses on OS or LC. However, especially in patients with local recurrences or radioresistant histologic tumor types, the presence of a macroscopic tumor and potential benefits of higher doses regarding radiotherapy effects are apparent; therefore, any of these factors might have to be evaluated within prospective clinical trials.

Figure 2. Kaplan-Meier Estimates of Overall Survival



GPA indicates graded prognostic assessment; NSCLC, non–small cell lung cancer; RCC, renal cell carcinoma.

This study investigated the known prognostic factors associated with OS on the basis of RPA and GPA scores. Both had a significant association with OS in our cohort. A controlled primary tumor, as 1 factor of the RPA score, was also significant for LC and DICF. A controlled primary tumor might be associated with an overall controlled or less aggressive disease, which could explain the association with LC.

In this cohort, the incidence of LMD was 13.1%, which might be explained by extensive pretreatment diagnostics in the large university-based, high-volume centers to rule out LMD at early stages. Our low rates could be compared with the rate of a recent retrospective analysis by Nguyen et al[31] with a 1-year LMD rate of 12%. In addition, the prospective trial by Mahajan et al[3] found an LMD rate of 28.0% in 63 patients treated with SRS. Brown et al[5] reported a rate of 7.2% in the SRS treatment arm, including 98 patients.

There are ongoing discussions of whether SRS or HSRT is superior for resection cavity radiotherapy in patients with bone metastases. Two prospective trials[3,5] found a favorable toxicity profile for SRS. Brown et al[5] reported a decline in cognitive function associated with WBRT and not with SRS and no difference in OS. However, LC was not suboptimal, arguing for larger margins and/or fractionated treatments. Almost in parallel, Mahajan et al[3] published the results of a randomized clinical trial that found that SRS of the surgical cavity in patients who had complete resection of 1, 2, or 3 bone metastases significantly lowers local recurrence compared with observation only, without WBRT. Taking into consideration the results of those 2 randomized trials[3,5] and all data from retrospective series, local radiotherapy of the resection cavity can be considered a standard option and appears to be superior to close observation. In addition, WBRT offers a benefit of locoregional control, with an increased risk of neurocognitive decline; therefore, the clinical benefit is arguable.[32]

Lehrer et al[16] reviewed 24 trials on SRS and HSRT and found that, with fractionated concepts, the risk of radiation necrosis could be mitigated and the risk of LC at 1 year can be reduced. This finding and all data combined argue for at least 2-mm safety margins, which are safely applied only in a fractionated setting. Controversy about the inclusion of the surgical corridor and meningeal resection margins remains, and the practice is highly center specific.[17,23,32] Considering the risk-

Table 3. UVA and MVA of Prognostic Factors Associated With LC, DICF, and OS[a]

Factor	LC (UVA)		LC (MVA)		DICF (UVA)		DICF (MVA)		OS (UVA)		OS (MVA)	
	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at radiotherapy[b]	1.00 (0.98-1.02)	.99	NA	NA	1.00 (0.99-1.01)	.92	NA	NA	1.01 (1.00-1.02)	.06	NA	NA
PTV[b]	1.01 (1.00-1.01)	.19	NA	NA	1.00 (1.00-1.01)	.65	NA	NA	1.00 (1.00-1.01)	.35	NA	NA
PTV (<23 vs ≥23 mL)	1.54 (1.02-2.32)	.04	1.43 (0.93-2.22)	.11	1.11 (0.87-1.42)	.40	NA	NA	1.22 (0.98-1.53)	.08	NA	NA
CV[b]	1.01 (0.99-1.03)	.41	NA	NA	1.00 (0.99-1.02)	.80	NA	NA	1.00 (0.99-1.01)	.93	NA	NA
KPS score (<80% vs ≥80%)	0.95 (0.55-1.66)	.86	NA	NA	0.94 (0.67-1.32)	.57	NA	NA	0.58 (0.44-0.76)	<.001	0.61 (0.46-0.82)	.001
Time from resection to radiotherapy[b]	1.00 (0.98-1.01)	.64	NA	NA	1.00 (0.99-1.01)	.89	NA	NA	0.99 (0.99-1.00)	.10	NA	NA
Time from section to radiotherapy (0-21 vs 22-33 d)	0.74 (0.37-1.46)	.38	NA	NA	0.91 (0.60-1.38)	.65	NA	NA	1.50 (1.08-2.10)	.02	1.50 (1.07-2.10)	.02
Time from resection to radiotherapy (22-33 vs 34 d)	1.26 (0.79-1.99)	.33	NA	NA	0.99 (0.76-1.29)	.93	NA	NA	1.08 (0.84-1.38)	.56	NA	NA
Resection status (complete vs incomplete)	1.51 (0.95-2.39)	.08	NA	NA	1.15 (0.85-1.55)	.37	NA	NA	1.43 (1.11-1.85)	.007	1.19 (0.89-1.59)	.33
RPA (1 vs 2)	0.56 (0.31-1.01)	.06	NA	NA	0.64 (0.44-0.91)	.02	NA	NA	0.45 (0.31-0.64)	<.001	NA	NA
RPA (2 vs 3)	1.82 (0.57-5.86)	.32	NA	NA	1.51 (0.77-2.96)	.23	NA	NA	0.57 (0.38-0.86)	.008	NA	NA
GPA (0-2.5 vs 3-4)	1.01 (0.65-1.58)	.95	NA	NA	0.84 (0.63-1.12)	.23	NA	NA	1.73 (0.56-0.94)	.02	NA	NA
Extracranial metastases (yes vs no)	1.15 (0.76-1.73)	.52	NA	NA	1.35 (1.05-1.73)	.02	1.23 (0.94-1.62)	.13	1.30 (1.04-1.64)	.02	1.19 (0.90-1.58)	.21
No. of all brain metastases (1 vs >1)	0.61 (0.39-0.96)	.03	0.57 (0.35-0.93)	.03	1.58 (1.24-2.03)	<.001	1.48 (1.13-1.92)	.004	1.00 (0.79-1.26)	.99	NA	NA
Controlled primary tumor (yes vs no)	0.59 (0.39-0.91)	.02	0.59 (0.39-0.92)	.02	0.64 (0.50-0.83)	.001	0.71 (0.54-0.92)	.01	0.74 (0.58-0.95)	.02	0.69 (0.52-0.90)	.007
BED_{10} (<48 vs ≥48 Gy)	1.50 (0.86-2.60)	.15	NA	NA	1.04 (0.77-1.39)	.82	NA	NA	1.11 (0.84-1.47)	.45	NA	NA

Abbreviations: CV, cavity volume; BED_{10}, biologically equivalent dose using a tumor α/β of 10; DICF, distant intracranial failure; GPA, graded prognostic assessment; HR, hazard ratio; KPS, Karnofsky Performance Status; LC, local control; MVA, multivariate analysis; NA, not applicable; OS, overall survival; PTV, planning target volume; RPA, recursive partitioning analysis; UVA, univariate analysis.

[a] Clinically relevant covariates and potential prognostic factors obtained from UVA were used in the multivariable model, except the combined RPA and GPA scores, because they already include the covariates-controlled primary and extracranial metastases.

[b] Continuous variable.

benefit profile of SRS, the finding strongly argues for fractionated concepts for which larger volumes, potentially including surgical tracts, might be associated with a more beneficial risk-benefit profile.[24]

The current large, multi-institutional analysis adds highly relevant data to the literature. Although the work by Lehrer et al[16] is a meta-analysis of published studies, the current work presents original data from high-volume international centers; specifically, the data suggest that the risk of LMD is very low and support the benefit of fractionated concepts with safety margins because LC compares favorably with previously published data sets.

Limitations

This study has some limitations. The retrospective, multicenter nature of the study is the reason for incomplete data, particularly regarding toxic effects, and center-specific contouring guidelines. However, because of the large number of patients, it is most likely that this effect will be eliminated. Moreover, the cohort has mixed histologic tumor subtypes; however, it represents a real-life scenario and, therefore, probably represents the best data available to answer the clinical questions.

We know from previous research that primary tumors, such as melanoma or renal cell carcinoma, are associated with a relative radiation resistance. Thus, the benefit of the higher single doses to the resection cavity is obvious. One might also argue for a further increased total dose; however, LC control data from this series mitigate this argument. In patients with breast cancer, dose prescription might depend on molecular subtypes, which currently do not influence the indication for local radiotherapy after bone metastasis resection.

Consequently, the data provide a group of mixed histologic tumor subtypes and outcomes, which might be differentiated in future trials. First attempts can be investigated in Figure 1D, Figure 2D, and eTable 2 in the Supplement. So far, the works from Sperduto et al[33-36] that report histologic subtype-specific scores have also reported that the underlying primary tumor must be taken into account in patients with bone metastases. The aim of the current work is to give a broad overview of the largest cohort of brain cavities ever reported and serve as a basis for clinical recommendations and decision-making.

Conclusions

This international, multicenter cohort study suggests that local HSRT to the resection cavity has a favorable risk-benefit profile. Compared with published SRS data, LC is favorable and argues for HSRT compared with SRS in this clinical situation. The risk of treatment-related adverse effects is low. Regular clinical follow-up should include MRI to catch locoregional progression. The risk of LMD also argues for tight imaging follow-ups to allow for early salvage treatment. Therefore, the current data represent valuable information for all radiation oncologists and oncologists involved in treatment decisions. Further prospective trials will define optimal dose-volume recommendations and prescription parameters based on the underlying primary tumor.

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