Radiotherapy and Oncology 212 (2025) 111128

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Meta-analysis

Intraoperative radiotherapy for resectable brain metastases: a systematic review and meta-analysis

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ARTICLE INFO

Keywords:
Intraoperative radiotherapy
Brain metastasis
Stereotactic radiotherapy
Systematic review
Meta-analysis

ABSTRACT

Background: In recent years, intraoperative radiotherapy (IORT) with low-energy X-rays is emerging as an alternative to postoperative stereotactic radiotherapy (SRT) of the resection cavity in patients with resectable brain metastases (BMs).
Methods: We performed a systematic review of the MEDLINE, Embase, and Scopus databases, including all original articles on IORT for resectable BMs from 2015 to 2025. Data on safety, local control, and survival outcomes were collected.
Results: Ten records (5 prospective single-arm trials) were included, representing 261 patients (49 % lung primary) with a median follow-up (range) of 14 (0–79) months. 77 % of patients had a solitary BM at the time of surgery and IORT. The median applicator size was 2.0 cm and the median prescribed dose (range) 22.3 (20–30) Gy. The 1-year local control rate was 93 % and the 1-year distant brain control rate 48 %. Median overall survival was 19 months. Only 6 % of patients developed leptomeningeal disease and the cumulative rate of radiation necrosis was 2.6 % (grade 1 in 56 % of cases). The median time to next treatment beyond BM therapy (range) was 31 (1–136) days. This was significantly shorter compared to SRT control collectives.
Conclusions: IORT for patients with BMs has a favorable toxicity profile and yields excellent local control. A potential advantage is the rapid completion of interdisciplinary BM treatment, allowing a swift transition to subsequent cancer treatments. A planned registry and a prospective randomized phase 3 trial will establish the preferred radiotherapy modality in the context of resectable BMs.

Introduction

Brain metastases (BMs) are the most common malignant intracranial tumors in adults [1]. Depending on the primary tumor, they affect 10 to more than 30 % of cancer patients [1]. For symptomatic or large BMs, maximal surgical resection is a key component of treatment, offering immediate symptom relief and a potential survival benefit [2]. Without adjuvant radiotherapy, however, local recurrences within the resection

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https://doi.org/10.1016/j.radonc.2025.111128
Received 7 July 2025; Received in revised form 7 August 2025; Accepted 4 September 2025
Available online 8 September 2025

cavity are common, occurring in up to 50 % of patients [3,4]. Over the past few years, whole-brain radiotherapy (WBRT) has gradually been replaced by more precise approaches, namely stereotactic radiotherapy (SRT) of the resection cavity in one to several fractions, as the latter greatly reduces neurocognitive decline while preserving quality of life and providing equal local efficacy [5,6]. Despite these advantages, SRT increases the risk of developing radiation necrosis (RN), a radiogenic late effect that is notoriously difficult to diagnose and manage if symptomatic [7,8]. Furthermore, adjuvant radiotherapy is usually initiated after a postoperative interval of several weeks, to allow for surgical wound healing and clinical stabilization, thus increasing the overall BM treatment time [9].

Intraoperative radiotherapy (IORT) with low-energy (usually 50 kV) X-rays has emerged as an alternative strategy, delivering a single-fraction, high-dose radiation treatment directly into the resection cavity during surgery (Fig. 1a) [10]. This approach offers several advantages, including the immediate eradication of microscopic tumor cells (thus preventing early tumor repopulation), maximal healthy tissue sparing due to a steep dose gradient (Fig. 1b), and the potential to reduce delays in systemic therapy initiation, which is of particular interest in treatment-naive patients [10]. A previous systematic review by Pascual *et al.* in 2021 assessed five studies ($n = 179$) on IORT for BMs and reported inconclusive results due to the heterogeneity of included records [11]. Roughly half of the patients underwent IORT with a photon radiosurgery system (PRS), following biopsy of the BM only. All patients in the PRS studies also underwent adjuvant WBRT [11]. As local control (LC) is influenced by the extent of resection, the pooling of these results and a comparison with modern IORT approaches appears problematic [12].

In recent years, multiple trials have further explored the feasibility, safety, and efficacy of IORT for resectable BMs. Here, we aim to comprehensively assess the current evidence, including toxicity profiles, LC rates, survival outcomes, and comparisons with other adjuvant radiation modalities. By summarizing available data, this systematic review and *meta*-analysis seeks to elucidate the benefits and limitations of IORT for resectable BMs and highlight key knowledge gaps that warrant further investigation.

Materials and methods

Search strategy

Following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement, we performed a comprehensive literature search of the MEDLINE, Embase, and Scopus databases [13]. All available publications from the past ten years (i.e. from March 2015 until April 2025) matching the keywords "*intraoperative radiotherapy*", "*brain metastasis*", and relevant truncations were independently screened by two authors (CSD and JPL) based on title and abstract and without language restriction. Identified records were included if (1) they employed photon-based kilovoltage IORT of the surgical cavity following resection of a histologically confirmed BM and (2) reported efficacy at least in terms of LC. If a single center had multiple publications matching the inclusion criteria, only the largest, most recent cohort was selected in order to avoid double inclusion of patients. Similarly, if a report pooled data from multiple centers, it was excluded and, if available, only the respective monocentric publications were used. Case reports were also considered. Additional records were identified by cross-searching the already included articles' references. Furthermore, a free internet search was performed to identify relevant conference proceedings. Lastly, ClinicalTrials.gov was queried with the same keywords to further extend the search. The full process of literature research and selection is shown in Fig. 2.

Data collection and analysis

Following their inclusion, manuscripts, supplements, and trial protocols (where available) were fully assessed and relevant data summarized independently by two authors (CSD and JPL). Information on demographics, disease and treatment characteristics, safety (especially the cumulative incidence of RN), efficacy (in terms of LC, distant brain control [DBC], overall survival [OS], and leptomeningeal disease [LMD]), additional patient-relevant outcomes (e.g. time to systemic treatment onset or in-hospital time), and (where available) comparison with other adjuvant radiation modalities were extracted. Data were pooled and median and range were calculated where applicable. For pooled data without the availability of individual data sets, weighted medians were calculated, taking the respective sample size of considered trials into account. Studies where certain data were not reported were censored from the respective analyses.

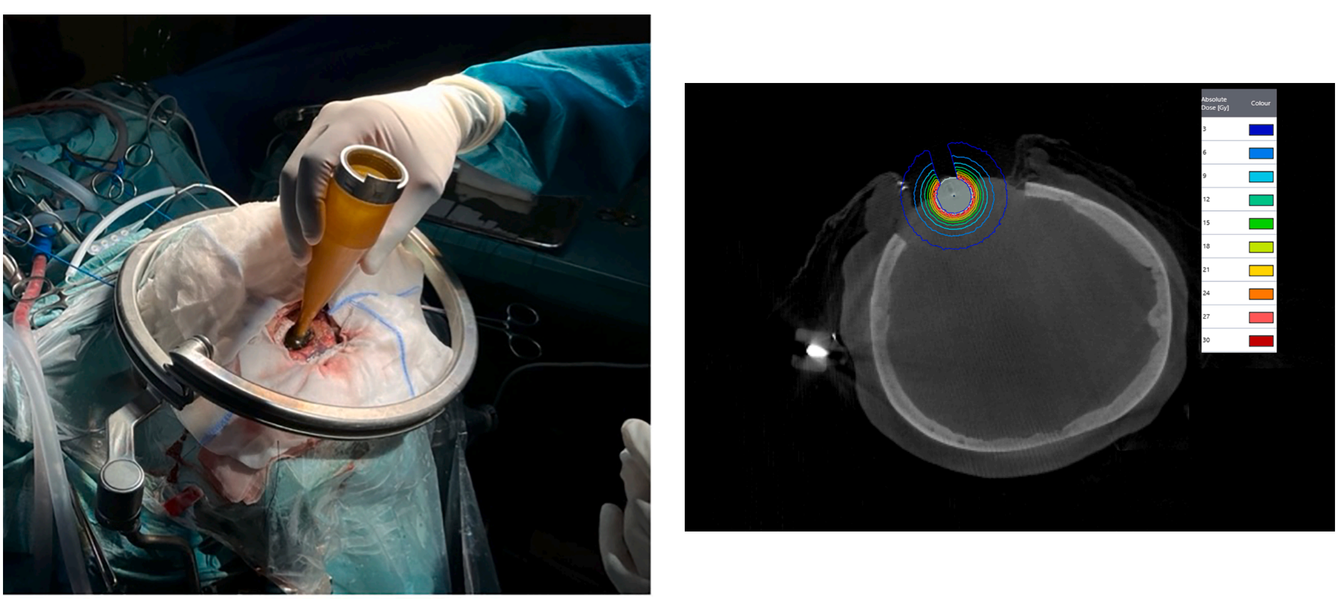

Fig. 1. (a) Intraoperative radiotherapy with low-energy (50 kV) X-rays delivers a single-fraction, high-dose radiation treatment to the surface of a spherical polyetherimide applicator, positioned directly into the resection cavity, following gross total resection of a brain metastasis. **(b)** Exemplary post-hoc calculation of dose distribution within the surgical resection cavity (30 Gy prescribed to the surface of a 2.0-cm applicator), depicting the characteristic steep dose gradient allowing for maximal healthy tissue sparing.

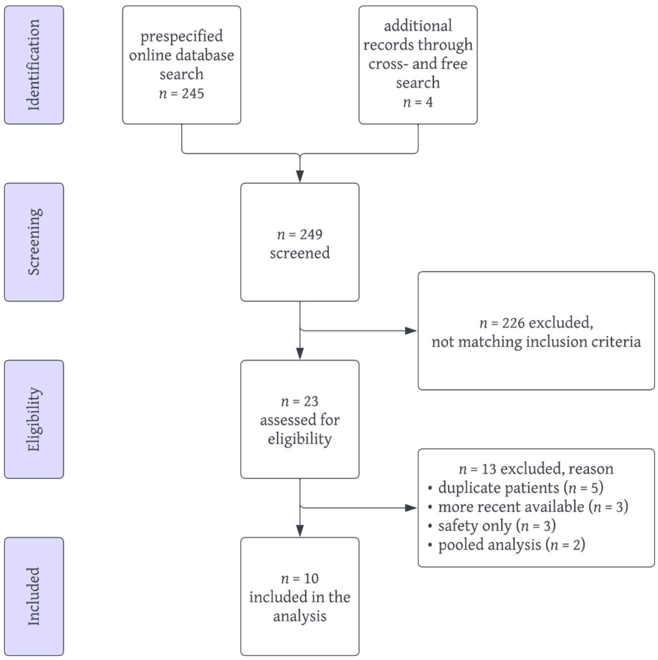

Fig. 2. Flowchart of literature research and selection following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. [13].

All data were managed using Microsoft Excel version 16 (Microsoft, Redmond, WA, USA) and data analysis was performed with GraphPad Prism version 10 (GraphPad Software, San Diego, CA, USA) and *R* version 3.3.2 (x86_64-pc-linux-gnu, *R* Foundation for Statistical Computing, Vienna, Austria). Figures and graphs were created using GraphPad Prism and Adobe Illustrator 2023 (Adobe Inc., Mountain View, CA, USA).

Results

Of 248 records initially identified, 10 were included in the final analysis: 5 prospective trials (all single-arm), 1 observational cohort, 3 retrospective, and 1 case report (Fig. 2). Two phase 2 trials only reported preliminary results in the form of a conference abstract. Overall, 273 IORT treatments in 261 patients were identified. Of these, 52.4 % were female and the median age was 61 years. The median preoperative Karnofsky performance score (KPS) was 80 % and the median diagnosis-specific graded prognostic assessment (DS-GPA) 2. The most common primary tumor entity was lung cancer (49 %), followed by melanoma and breast cancer. 77 % of patients had a solitary BM at the time of IORT. The median follow-up across all trials was 14 months, ranging from 0–79 months within individual reports. Treatment and follow-up protocols were very similar between included studies with standard post-operative contrast-enhanced magnetic resonance imaging (MRI) performed at least every 3 months, enabling assessment of BM response and progression according to the Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria. Minor study-specific differences are detailed in Supplementary Table 1. Additionally, advanced sequences such as perfusion measurements to differentiate between RN and local BM recurrence were used in the majority of trials (Supplementary Table 1). Trial and patient characteristics are described in Table 1.

All patients were treated with an INTRABEAM device (Carl Zeiss Meditec, Oberkochen, Germany) using nominal 50 kV photons in all cases. The median spherical applicator size was 2.0 cm with a median prescribed dose (range) to the applicator surface of 22.3 (20–30) Gy. The median crude IORT delivery times ranged from 12–18 across all trials. Depending on applicator size and prescribed dose, this ranged from 6–49 min for individual patients. Further IORT characteristics are provided in Table 2.

All included trials reported the cumulative incidence of RN over the prespecified follow-up times (Fig. 3a). Overall, the weighted median RN rate was 2.6 %, ranging from 0–20 % within individual cohorts (excluding the single case report). The weighted median grade ≥ 2 RN

Table 1
Summary of included record ($n = 10$) and patient ($n = 261$) characteristics, in chronological order.

No.	First author (year)	Country	Type / Design	BMs (*n*)	Female (%)	Median age (yr)	Median KPS (%)	Median DS-GPA	Solitary BM (%)	Histology (top 3; %)	Median follow-up (range) (mo)
1	Weil (2015) [36]	USA	prospective single-arm	23	43.5	61	80	2.0	100	lung (35), GU (26), breast (22)	na (60–na)
2	Vargo (2018) [37]	USA	retrospective	7	na	67	na	na	na	lung (71), na, na	6.2 (3.6–8.8)
3	Foro (2021) [38]	Spain	prospective single-arm phase 2 (abstract only)	7	14.3	61 *	na	na	na	lung (57), na, na	na
4	Diehl (2023) [39]	Germany	retrospective	18	55.6	56	90	2.5	50	lung (33), melanoma (22), GU (17)	10.8 (0–39)
5	Guedes de Castro (2023) [40]	Brazil	prospective single-arm phase 2	10	50.0	58	na	2.5	40	lung (40), melanoma (20), breast (20)	11.2 (8.2–22.7)
6	Layer (2023) [41]	Germany	observational cohort	35	54.3	63	80	2.0	57	lung (60), melanoma (11), kidney (11)	10.4 (0.5–24.5)
7	Aninditha (2024) [26]	Germany	case report	1	100.0	42	na	na	100	lung (100)	33.0 (na)
8	Kahl (2024) [42]	Germany	retrospective	117	52.4	65	na	na	na	lung (43), melanoma (14), breast (11)	14.0 (0–79)
9	Macià i Garau (2024) [18]	Spain	prospective single-arm phase 2 (abstract only)	20	40.0	59	90	2.5	90	lung (45), melanoma (15), breast (15)	29.4 (1–40)
10	Brehmer (2025) [19]	Germany	prospective single-arm phase 2	35	45.7	64	80	na	77	lung (69), GI (9), GU (9)	25.7 (0.8–64.5)

no. = number; BMs = brain metastases; na = not available; yr = years; KPS = Karnofsky performance score; DS-GPA = diagnosis-specific graded prognostic assessment; GU = genitourinary; GI = gastrointestinal; mo = months. * Mean instead of median.

Table 2
Summary of technical IORT characteristics.

No.	First author (year)	Device	Median applicator size (cm)	Median prescription dose to applicator surface (Gy)	Dose range (Gy)	Median delivery time (min)	Delivery time range (min)
1	Weil (2015) [36]	INTRABEAM	na	14.0 (2 mm) *	all	15.9 ***	8.4–25
2	Vargo (2018) [37]	INTRABEAM	na	30.0	all	na	na
3	Foro (2021) [38]	INTRABEAM	na	20.0	all	na	na
4	Diehl (2023) [39]	INTRABEAM	2.0	20.0	16–30	12.0	5.5–22.7
5	Guedes de Castro (2023) [40]	INTRABEAM	2.0	18.0 (1 mm) **	all	14.0	8–20
6	Layer (2023) [41]	INTRABEAM	2.5	30.0	16–30	18.2	6.9–49
7	Aninditha (2024) [26]	INTRABEAM	2.0	30.0	na	16.0	na
8	Kahl (2024) [42]	INTRABEAM	2.0	20.0	13.4–30	15.2	6–28.2
9	Macià i Garau (2024) [18]	INTRABEAM	2.0	22.3	20.1–24	16.5	8.1–39.3
10	Brehmer (2025) [19]	INTRABEAM	2.0	30.0	all	16.9	8.4–41

no. = number; na = not available; Gy = Gray. * This is equal to 21.1 Gy on the applicator surface (0 mm) for a 2.0-cm applicator. ** This is equal to 22.2 Gy on the applicator surface (0 mm) for a 2.0-cm applicator. *** Mean instead of median.

rate was 0.9 % and ranged from 0–11.1 %. In terms of RN severity, asymptomatic Common Terminology Criteria for Adverse Events (CTCAE) grade 1 RN was most common (56.2 % of RN cases), while 12.5 % of patients with RN suffered from grade 2 and 31.3 % had a grade 3 event. No grade 4 or 5 RN events were reported in any of the cohorts. Time to RN onset was reported by seven studies and ranged from 1.5–24 months.

The median postoperative 30-day mortality rate, included in five trials, was 5 % and ranged from 0–8 %. In a secondary safety analysis, Hamed *et al.* performed a comparative matched-pair analysis of perioperative adverse events between IORT and postoperative SRT that did not reveal significant differences between both modalities [14]. A single trial reported a non-significant difference in postoperative corticosteroid intake between IORT and SRT patients (8 days in both groups) [15]. Additional safety features are reported in Table 3.

The weighted median overall 1-year LC rate (1yLCR) was 92.9 % (range 84.2–100 %) and the overall 1-year DBC rate (1yDBCR) 47.9 % (range 13–100 %). The median OS was 19.4 months and ranged from 0.5–197 months for individual patients, translating into a 1-year OS rate (1yOSR) of 57.7 % (range 57.7–100 %). The overall LMD rate was 5.7 %, ranging from 0–13.3 %. Salvage WBRT was performed in 15.6 % of patients (range 0–26.1 %) over the course of follow-up. Efficacy of IORT is summarized in Fig. 3b and Table 4.

Time to next treatment (TTNT) was reported in five trials, with a weighted median (range) of 31 (1–136) days. Three groups compared TTNT in IORT patients with a cohort of patients undergoing postoperative SRT (n = 229 in the pooled control collective). All found a significant difference favoring IORT, with mean absolute differences of 16, 33, and 12 days, respectively. Weighted median time to discharge after surgery, reported in four trials, was 6 days. Comparing with postoperative SRT patients across two trials (n = 111), the time spent hospitalized was significantly lower following IORT. The total in-hospital time for BM treatment was significantly shorter after IORT, as described in one trial. Results are summarized in Fig. 3c and Table 5.

Discussion

While the first reports on IORT date back to the early 1900s, technical advancements have led to a revived interest in recent years, positioning kilovoltage IORT as a viable treatment option for resectable BMs [16,17]. In this systematic review and *meta*-analysis, we comprehensively summarize all currently available clinical reports, highlighting low-energy IORT as an emerging alternative to adjuvant SRT of the resection cavity.

A safe and precise execution of IORT warrants certain requirements. Dejonckheere *et al.* reported that of 95 BM patients screened, IORT was feasible in 84 cases (88 %) and ultimately performed in 64 (67 %) [15]. Similarly, Macià i Garau *et al.* reported a feasibility rate of 69 %, while this was 81 % in Brehmer *et al.* [18,19]. An inconclusive frozen section was the most common reason for not performing IORT in all three trials reporting on this aspect. Furthermore, gross total resection of the BM is important, as this was shown to be predictive of LC in a pooled series by Cifarelli *et al.* (n = 54) [12]. Additionally, IORT requires a somewhat spherical surgical cavity to prevent air gaps and a sufficient distance to surrounding organs at risk (OARs) such as brainstem and optic chiasm.

After a median follow-up time of 14 months, data demonstrate an excellent 1yLCR of 93 % following IORT. Landmark trials on the use of postoperative single-fraction SRT report very similar results, e.g. a 1yLCR of 91 % in Brown *et al.* (n = 98 patients; 12–20 Gy in a single fraction) [5,20]. Evidently, lesion volume is an important determinant of LC. Mahajan *et al.* report a drastically declining 1yLCR for single-fraction SRT with increasing BM size: more than half of patients with a BM diameter > 2.5 cm had experienced local failure after 1 year [20]. Large multicenter cohorts using fractionated SRT report a 1yLCR of 84 % (n = 581 resection cavities; median total dose of 30 Gy in 5 fractions) [21]. Early results of preoperative SRT trials demonstrate similar LC as in IORT, e.g. at 91 % after a median follow-up time of 14.7 months as described by Agrawal *et al.* (n = 48 patients, 12–18 Gy in a single fraction) [22].

The here observed 3 % risk of RN is in line with reports using other modalities: 4 % after postoperative single-fraction SRT (grade 2 or worse only), 9 % after fractionated SRT, and 8 % after preoperative SRT [5,21,22]. Importantly, more than half of the RN events observed in the reported IORT cohorts were asymptomatic (grade 1). The considerably low risk of RN despite a significantly higher dose prescription to the cavity surface may result from the maximal healthy brain tissue sparing due to the steep dose gradient (Fig. 1b). Equally, the high surface dose may provide an explanation for the excellent LC, particularly in large BMs.

In patients with BMs undergoing resection, adjuvant SRT should not be delayed for too long in order to prevent early recurrence. In a series of 21 consecutive patients, Shah *et al.* observed evidence of tumor progression within the resection cavity in half of patients, while withholding SRT for more than 40 days postoperatively more than doubled the risk of local failure [9,23]. Opposingly, IORT offers immediate eradication of microscopic residual disease, thus preventing early repopulation [24]. However, delaying adjuvant SRT for at least three weeks post-surgery has been associated with improved outcome, since too early SRT might interfere with surgical wound healing [9,21]. There is currently no evidence pointing towards an increased perioperative risk nor impaired outcome following IORT for BMs. On the contrary, IORT has demonstrated its utility in highly sensitive clinical scenarios including awake craniotomy, BM treatment during pregnancy, or after resection of motor-eloquent BMs [25–28].

Particularly from a patient perspective, the rapid completion of interdisciplinary BM treatment is an important advantage of IORT, as

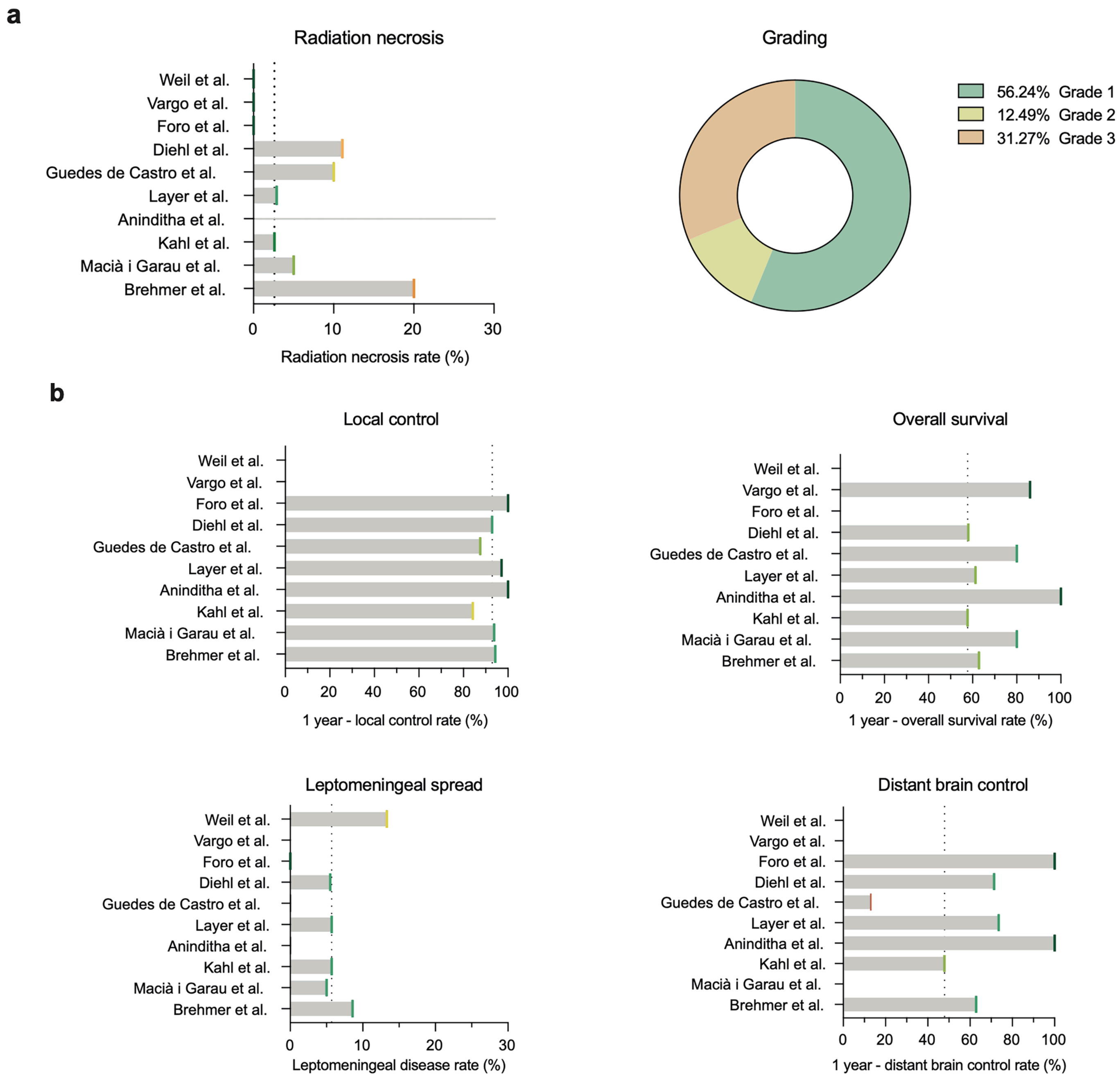

Fig. 3. Comparison of the main outcomes of the included reports. **(a)** Left: Forest plot showing the respective radiation necrosis rates (%) for the included trials as indicated on the y-axis. The dotted line indicates the cumulative weighted median. Color-coding represents ranking of the respective trial within all included series. Right: Composition of grading of observed radiation necrosis events for all included reports. **(b)** Forest plots illustrating the major clinical endpoints 1-year local control rate, 1-year overall survival rate, leptomeningeal disease rate, and 1-year distant brain control rate (%) for the included trials as indicated on the y-axis. The dotted line indicates the cumulative weighted median. Color-coding represents ranking of the respective trial within all included series. **(c)** Graphical representation of patient-centered outcomes, as in (b). * indicates a significant benefit for intraoperative radiotherapy in comparison with postoperative stereotactic radiotherapy reported in the respective trial for that endpoint.

consequently, patients can (re)initiate systemic therapy in a timely manner. More than 75 % of the included patients had a solitary BM receiving IORT, thus not requiring sequential definitive SRT for additional BMs. Importantly, in some cohorts, up to half of the patients did not have a previously known primary at the time of BM surgery and where thus otherwise treatment-naive, requiring urgent attention to extracranial disease [19]. There are numerous reasons why the (re) initiation of systemic treatment might be delayed in patients undergoing postoperative SRT, e.g. incomplete staging, conflicting appointments, SRT-related side effects, unfavorable combination of SRT and the planned systemic treatment (e.g. BRAF/MEK inhibitors in melanoma patients), or patient decision against simultaneous treatments [29]. In trials comparing IORT patients with an SRT control collective, TTNT was anywhere from 2–5 weeks shorter [15,19,30]. Of note, adequate timing and sequence of systemic therapy and radiotherapy predicts OS in patients with BMs [31]. In a subset of IORT patients receiving immunotherapy, the early initiation of systemic treatment was associated with a trend towards improved DBC and OS [32]. While this indicates a

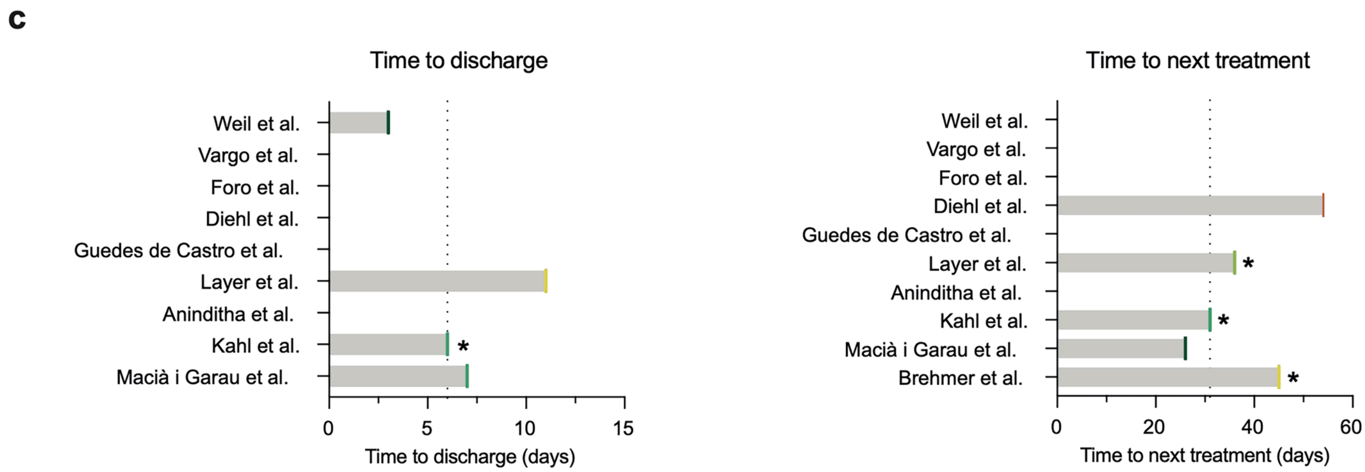

Fig. 3. (*continued*).

Table 3
Summary of safety features in reporting trials.

No.	First author (year)	RN rate (%)	G2 + RN rate (%)	RN severity	RN timing (mo)	30-day mortality rate (%)	Other
1	Weil (2015) [36]	0.0 *	0.0 *	nr	na	na	4 % bleeding
2	Vargo (2018) [37]	0.0	0.0	nr	nr	na	na
3	Foro (2021) [38]	0.0	0.0	nr	nr	na	no complications so far
4	Diehl (2023) [39]	11.1	11.1	all G3	5.0–12.0	na	11.1 % G3 wound infection ***, 5.5 % G2 CSF fistula
5	Guedes de Castro (2023) [40]	10.0	0.0	all G1	10.0	na	no dehiscence
6	Layer (2023) [41]	2.9	2.9	all G2	18.7	8.0 **	11 % PAE **
7	Aninditha (2024) [26]	100.0	0.0	all G1	24.0	0.0	wound hematoma
8	Kahl (2024) [42]	2.6	0.9	67 % G1, 33 % G3	2.7–17.6	5.3	5.1 % bleeding, 3.4 % hygroma, 3.4 % wound infection
9	Macià i Garau (2024) [18]	5.0	5.0	all G3	1.5	5.0	none
10	Brehmer (2025) [19]	20.0	5.6	72 % G1, 14 % G2, 14 % G3	2.8–21.4	2.9	no G4/G5, 28.6 % postoperative seizures ****

no. = number; RN = radiation necrosis; G2+ = grade ≥ 2; nr = not reached; G = grade; mo = months; na = not available; CSF = cerebrospinal fluid; PAE = perioperative adverse event. * 13.3 % development of G3 RN after salvage SRS (excluded from the analysis). ** Reported by Hamed *et al.* [14] *** All patients had received both intraoperative radiotherapy and adjuvant postoperative stereotactic radiotherapy of the same resection cavity. **** Mainly if surgery was performed in eloquent zones.

Table 4
Summary of clinical efficacy of intraoperative radiotherapy (IORT).

No.	First author (year)	1yLCR (%)	LCR (%)	DBPR (%)	1yDBCR (%)	Median OS (mo)	Range	1yOSR (%)	LMDR (%)	1yLMDR (%)
1	Weil (2015) [36]	na	69.6	78.3	na	36.0	4–197	na	13.3	na
2	Vargo (2018) [37]	na	86.0	na	na	na	na	86.0 ***	na	na
3	Foro (2021)38	100.0	100.0	0.0	100.0	na	na	na	0.0	0.0
4	Diehl (2023) [39]	92.9	na	na	71.4	22.8 *	0–39	58.0	5.5	na
5	Guedes de Castro (2023) [40]	87.5	na	na	13.0	nr	nr	80.0	0.0	nr
6	Layer (2023) [41]	97.1	na	29.4	73.5	17.5	0.5–nr	61.3	5.7	na
7	Aninditha (2024) [26]	100.0	100.0	0.0	100.0	nr	nr	100.0	0.0	nr
8	Kahl (2024) [42]	84.2	90.5	38.1	47.9	18.2	0.5–79	57.7	5.7	10.4
9	Macià i Garau (2024) [18]	93.8	na	43.8	na	na	na	80.0	5.0	na
10	Brehmer (2025) [19]	94.3	94.3	42.9	62.9	37.4	28.9–46.9 **	na	8.6	na

no. = number; 1yLCR = 1-year local control rate; na = not available; DBPR = distant brain progression rate; 1yDBCR = 1-year distant brain control rate; OS = overall survival; nr = not reached; 1yOSR = 1-year overall survival rate; LMDR = leptomeningeal disease rate; 1yLMDR = 1-year leptomeningeal disease rate. * Mean instead of median. ** 95 % confidence interval instead of range. *** Reported after 6.2 months of follow-up.

potential benefit of combining IORT with systemic treatment, the limited availability of detailed data precluded an assessment within the current study. The true clinical benefit of shorter TTNT with IORT in comparison with SRT remain to be elucidated, particularly in patient populations with multiple BMs.

IORT renders a complex postoperative target volume delineation obsolete. The dynamic anatomy of the resection cavity implies that recent repeat brain imaging is crucial for SRT planning, to prevent a geographic miss (similar to glioma) [33,34]. This increases both economic costs and patient burden, which is of particular importance in areas with limited resources and access. On the other hand, SRT not only allows for complex beam modulation, but also provides precise reproducibility of dose distribution. This is of particular importance in patients with critical OAR exposure and the necessity of subsequent SRT. A

Table 5
Summary of other patient-relevant outcomes.

No.	First author (year)	Mean (range) TTNT (d)	Median (range) time to discharge (d)	Median (range) corticosteroid intake (d)
1	Weil (2015) [36]	na	3 (2–10)	14 (7–21)
4	Diehl (2023) [39]	for 27.8 % ≤ 15 d, overall 54 (10–132)	na	na
6	Layer (2023) [41]	36 (9–94) for 62 IORT patients vs. 52 (11–126) for 52 SRT patients (s) *	11 for 62 IORT patients vs. 12 for 52 SRT patients (ns) *	8 for 62 IORT patients vs. 8 for 52 SRT patients (ns) *
8	Kahl (2024) [42]	31 (1–136) 32 ± 28 for 40 IORT patients vs. 65 ± 54 for 59 SRT patients (s) **	6 (2–41) 10 ± 7 for 40 IORT patients vs. 20 ± 9 for 59 SRT patients (s) **	na
9	Macià i Garau (2024) [18]	26 (17–54)	7 (4–28)	na
10	Brehmer (2025) [19]	45 (35–55) vs. 57 (49–64) for 118 SRT patients (s)	na	na

no. = number; TTNT = time to next treatment; d = days; na = not available; IORT = intraoperative radiotherapy; vs. = versus; SRT = stereotactic radiotherapy; (s) = significant; (ns) = not significant. * Reported by Dejonckheere *et al.* [15] ** Reported by Krauss *et al.* [30].

workflow for image-guided IORT has been proposed, which enables real-time treatment planning inside the operating room [35]. This might, however, significantly increase the operation time, while in a series by Cifarelli *et al.*, conventional IORT already consumed about one-tenth of total anesthetic time [27]. A report by Krauss *et al.* did not observe increased lengths of surgery if IORT was performed or not [28]. Whether this result is biased by surgically more demanding BMs in the non-IORT group is unclear.

Following an increase in clinical reports in very recent years, this is the first comprehensive summary exclusively focusing on kilovoltage IORT in the context of resectable BMs. Several previous reports have pooled IORT cohorts from multiple centers, however, generated a limited sample size only or investigated specific clinical scenarios [12,32]. However, this systematic review is not without limitations. Inherently, data on certain secondary endpoints of interest (eg, LMD) were only reported by a minority of trials and should therefore be considered carefully. The very similar follow-up regimens as well as a comparable definition of most endpoints between the included reports allowed for the pooling of results. The RN rates should, however, be interpreted with caution, as somewhat diverse definitions were used. Hence, particularly grade 1 RN reporting was heterogenous. In general, results of RN rates are more comparable between individual cohorts when only grade ≥ 2 RN is considered, as newly-onset symptoms are less open to interpretation. Despite providing valuable pooled information on important endpoints, parameters influencing toxicity or outcome could not be evaluated, as this would require the availability of individual participant data. Therefore, important questions such as the optimal IORT prescription dose or individual factors predisposing to RN remain elusive at this time. Furthermore, information on the exact nature and number of cycles of subsequent systemic treatment was generally lacking. This could, however, have influenced the outcomes reported here. Perspectively, a multicenter registry of European IORT centers is set to address these important issues through the reporting of homogeneous and qualitative results. Finally, a prospective randomized phase 3 trial, currently in preparation, will determine the differences between IORT and postoperative adjuvant SRT, in terms of tolerability, efficacy, as well as impact on neurocognition and quality of life.

Conclusion

This is the first systematic review and *meta*-analysis on kilovoltage IORT for resectable BMs highlighting IORT as a viable treatment option with high local control rates and a favorable toxicity profile. Further advantages over established radiotherapy modalities include the expedited completion of interdisciplinary BM treatment thus facilitating a seamless transition to subsequent therapies. Prospective trials are warranted to address remaining questions and further clarify the role of IORT in this setting.

Data sharing statement: No new data were generated during the preparation of this manuscript.

Data availability

No new data were generated during the preparation of this manuscript.

CRediT authorship contribution statement

Cas S. Dejonckheere: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Matthias Schneider:** Writing – review & editing. **Anna-Laura Potthoff:** Writing – review & editing. **Motaz Hamed:** Writing – review & editing. **Davide Scafa:** Writing – review & editing. **Thomas Zeyen:** Writing – review & editing. **Lea L. Friker:** Writing – review & editing. **Molina Grimmer:** Writing – review & editing. **Fabian Kugel:** Writing – review & editing. **Stephan Garbe:** Writing – review & editing. **Alexander Radbruch:** Writing – review & editing. **Hartmut Vatter:** Writing – review & editing. **Frank A. Giordano:** Writing – review & editing. **Ulrich Herrlinger:** Writing – review & editing. **Eleni Gkika:** Writing – review & editing. **Gustavo R. Sarria:** Investigation. **Julian P. Layer:** Investigation.

Funding

The authors declare that no funds, grants, or other support were received during the preparation of this manuscript.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: CSD reports honoraria from Carl Zeiss Meditec AG, unrelated to this work. FAG reports travel expenses, stocks, and honoraria from TME Pharma AG; research grants and travel expenses from ELEKTA AB; grants, research grants, travel expenses, and honoraria from Carl Zeiss Meditec AG; grants, research grants, travel expenses, and honoraria from OncoMANGETx, Inc.; travel expenses and research grants from Varian Medical Systems, Inc.; travel expenses and/or honoraria from Bristol-Myers Squibb, Cureteq AG, Roche Pharma AG, MSD Sharp and Dohme GmbH, Siemens Healthineers AG, Varian Medical Systems, Inc., and AstraZeneca GmbH; non-financial support from Oncare GmbH and Opasca GmbH; patent US10857388B2 together with Carl Zeiss Meditec AG, and patent EP4119191A1 with the University of Heidelberg, all unrelated to this work. JPL reports travel expenses and honoraria from Carl Zeiss Meditec AG; travel expenses and stocks from TME Pharma AG; honoraria and clinical advisory board membership from OncoMAGNETx, Inc.; stocks and honoraria from Siemens Healthineers AG; and stocks from Bayer and BioNTech, all unrelated to this work. The remaining authors report no conflict of interest related to this work.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2025.111128.

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