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Interventional stereotactic radiotherapy (brachytherapy) for unresected brain metastases: Systematic review of outcome and toxicity

Mateusz Bilski [a,b,c,1], Federico Mastroleo [d,e], Łukasz Kuncman [f,g,*,2], Paul Rogowski [h], Stefano Durante [d,e], Costantino Putzu [d,e], Artur Chyrek [i,j], Giulia Marvaso [d,e], Bruno Fionda [k], Luca Tagliaferii [k,l], Jacek Fijuth [f,g], Andrea Vavassori [d,e], Ranjini Tolakanahalli [m], Barbara Alicja Jereczek- Fossa [d,e], Rupesh Kotecha [m]

[a] Department of Brachytherapy, Saint John's Cancer Center, Lublin, Poland
[b] Department of Radiotherapy, Medical University of Lublin, Lublin, Poland
[c] Department of Radiotherapy, Saint John's Cancer Center, Lublin, Poland
[d] Division of Radiation Oncology, European Institute of Oncology IRCCS, Milan 20141, Italy
[e] Department of Oncology and Hemato-Oncology, University of Milan, Milan, Italy
[f] Department of Radiotherapy, Medical University of Lodz, Poland
[g] Department of External Beam Radiotherapy, Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology, Poland
[h] Department of Radiation Oncology, University Hospital, LMU Munich, Marchioninistr. 15, Munich 81377, Germany
[i] Brachytherapy Department, Greater Poland Cancer Centre, Poznań, Poland
[j] Electroradiology Department, Poznan University of Medical Science, Poznań, Poland
[k] UOC Degenze di Radioterapia Oncologica, Dipartimento di Diagnostica per Immagini e Radioterapia Oncologica, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy
[l] Università Cattolica del Sacro Cuore, Rome, Italy
[m] Department of Radiation Oncology, Miami Cancer Institute, Baptist Health South Florida, Miami, FL, United States

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ABSTRACT

Background: Stereotactic brachytherapy (SBT) is an underutilized treatment for brain metastases. This systematic review evaluates SBT's clinical outcomes, toxicity, and procedural characteristics for intact brain metastases in radiation-naive and radiation-recurrent patients.

Methods: A systematic review was conducted following PRISMA guidelines and the PICOS framework. Studies published until June 30, 2024, were identified through searches of PubMed, Scopus, Web of Science, and Cochrane databases. Retrospective studies and prospective trials were included. Key extracted data included

List of abbreviations: **ASCO**, American Society of Clinical Oncology; **ASTRO**, American Society for Radiation Oncology; **BM**, Brain Metastases; **COMIRI**, Complexity Index of Interventional Radiotherapy; **CR**, Complete Response; **CRC**, Colorectal Cancer; **CSF**, Cerebrospinal Fluid; **CNS**, Central Nervous System; **CTCAE**, Common Terminology Criteria for Adverse Events; **CTV**, Clinical Target Volume; **CUP**, Cancer of Unknown Primary; **DCR**, Disease Control Rate; **DIC**, Distant Intracranial Control; **EBRT**, External Beam Radiotherapy; **EANO**, European Association of Neuro-Oncology; **EORTC**, European Organisation for Research and Treatment of Cancer; **ESMO**, European Society for Medical Oncology; **FSRS**, Fractionated Stereotactic Radiosurgery; **GI**, Gastrointestinal; **GTV**, Gross Tumor Volume; **IRT**, Interventional Radiotherapy Brachytherapy; **KPS**, Karnofsky Performance Status; **LC**, Local Control; **MRI**, Magnetic Resonance Imaging; **NSCLC**, Non-Small Cell Lung Cancer; **OAR**, Organs-At-Risk; **OMD**, Oligometastatic Disease; **ORR**, Objective Response Rate; **OS**, Overall Survival; **PD**, Progressive Disease; **PFS**, Progression-Free Survival; **PICOS**, Population, Intervention, Comparison, Outcome, and Study Design; **PR**, Partial Response; **QoL**, Quality of Life; **RANO**, Response Assessment in Neuro-Oncology; **RPA**, Recursive Partitioning Analysis; **RTOG**, Radiation Therapy Oncology Group; **SBRT**, Stereotactic Body Radiotherapy; **S-IRT**, Stereotactic Interventional Radiotherapy; **SCLC**, Small Cell Lung Cancer; **SD**, Stable Disease; **SRS**, Stereotactic Radiosurgery; **STaRT**, Stereotactic Tumor Radiosurgery Trial; **TAE**, Transarterial Embolization; **TPS**, Treatment Planning System; **WBRT**, Whole Brain Radiotherapy.

* Correspondence to: Department of External Beam Radiotherapy, Copernicus Memorial Hospital in Lodz Comprehensive Cancer Center and Traumatology, Pabianicka 62, Łódź PL 93-513, Poland.

E-mail addresses: bilskimat@gmail.com (M. Bilski), Federico.Mastroleo@ieo.it (F. Mastroleo), lukasz.kuncman@umed.lodz.pl (Ł. Kuncman), paul.rogowski@med.uni-muenchen.de (P. Rogowski), stefano.durante@ieo.it (S. Durante), costantino.putzu@ieo.it (C. Putzu), chyrek.artur@gmail.com (A. Chyrek), giulia.marvaso@ieo.it (G. Marvaso), bruno.fionda@policlinicogemelli.it (B. Fionda), luca.tagliaferri@policlinicogemelli.it (L. Tagliaferii), andrea.vavassori@ieo.it (A. Vavassori), RanjiniT@baptisthealth.net (R. Tolakanahalli), barbara.jereczek@ieo.it (B.A. Jereczek- Fossa).

[1] 0000-0002-4962-3028
[2] 0000-0003-3568-269X

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Oligometastatic disease
Stereotactic brachytherapy
Interstitial radiosurgery
Iodine-125
Cesium-131
Radiation source

patient characteristics, treatment protocols, local control (LC), distant-intracranial control (DIC), overall survival (OS), and procedure-related toxicity. The risk of bias was assessed using the Newcastle-Ottawa Scale.
Results: Eight retrospective single-center studies involving 427 patients and 456 metastases met inclusion criteria. Median patient age ranged from 47 to 60 years, with most having a Karnofsky Performance Status $\geq$ 70. SBT mostly demonstrated high 1-year LC rates (93.3 %–100 %) and a 1-year DIC from 52 % to 90 %. Median OS for radiation-naive patients ranged from 8 to 17 vs. 6–28.4 months for radio-recurrent patients, with RPA class 1 showing the best outcomes. Toxicity was minimal, with no reported fatal complications or significant late toxicity. Across all studies, I-125 seeds were utilized, with temporary implantation predominating, while permanent implantation involved higher doses, up to 150 Gy, and extended treatment durations. Postoperative morbidity within 30 days ranged from 0 % to 6.6 % across different studies. No G3/G4 acute toxicities were reported.
Conclusions: SBT is a highly effective and safe option for treating intact brain metastases, particularly in patients with large or radiation-recurrent lesions.

1. Introduction

External beam radiotherapy (EBRT), particularly stereotactic radiosurgery (SRS) and fractionated radiosurgery (FSRS) is a well-established treatment modality for intact brain metastases and for tumor bed irradiation after surgical resection (Redmond et al., 2021; Gondi et al., 2022). On the other hand, interventional radiotherapy (brachytherapy - IRT) is a well-known radiotherapy modality for treating many primary extracranial cancers but with historically limited application in the brain. Because of favorable dosimetric parameters, there is growing interest in its application in patients with oligometastatic disease (OMD), similar to SRS or stereotactic body radiotherapy (SBRT). Moreover, recent studies demonstrate more favorable dosimetry for brachytherapy plans than for SBRT, i.e., liver metastases (Bilski et al., 2024a, 2024b). As patients with metastatic disease generally live much longer than they did 10–20 years ago, it is crucial to consider that re-irradiation may need to be performed more often due to local recurrence, and therefore durable upfront treatment is advised. The development of new modalities and clinical trials is of great importance, especially in the reirradiation setting, according to consensus guidelines (Andratschke et al., 2022).

Even though stereotactic-IRT (S-IRT) for brain metastases was first used before 1990, it has not been adopted in any international guidelines (Vogelbaum et al., 2022; Le Rhun et al., 2021). Recently, favorable clinical outcomes with overall low toxicity rates were described after brachytherapy for recurrent glioblastoma patients (Xiang et al., 2024). A previously conducted systematic review for brachytherapy in brain metastases suggested excellent local control (LC) rates and quality of life (QoL), strengthening the need for future studies and a broader interest (The role of brachytherapy, 2020). Since January 2018 (end date of search for last systematic review), new studies, and prospective ones, with novel methods of brachytherapy application, have been conducted. Therefore, we aimed to perform the most updated systematic review with a slightly different focus, not only on radiation sources, as was done before, but also on evaluating the outcomes and toxicity of brachytherapy used for the intact tumor without surgical resection. We also aimed to compare outcomes in radiation-naive versus radiation recurrent patients.

2. Materials and methods

2.1. Study design

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency and rigor. We adhered to the Population, Intervention, Comparison, Outcome, and Study Design (PICOS) framework to define the research question and guide the search strategy. The primary objective was to identify studies investigating brachytherapy/ interventional radiotherapy to treat intact brain metastases without previous resection.

A comprehensive search was performed across four major databases: PubMed, Scopus, Web of Science, and Cochrane. To enhance the completeness of the review, additional relevant studies were identified through citation tracking of selected articles. The search was restricted to studies published up to June 30, 2024.

2.2. Search strategy

The search strategy incorporated a broad range of keywords, acronyms, and synonyms relevant to the topic. Terms such as "brachytherapy" or "interventional radiotherapy" were searched alongside "brain", "central nervous system (CNS)", and "intracranial" to capture studies involving brain metastases. Studies focusing on gliomas or meningiomas were expressly excluded to narrow the focus to secondary brain malignancies. The following full string was adapted for the different databases: ((brachytherapy OR interventional-radiotherapy)) AND ((brain OR "Central Nervous System" OR cns OR "Intracranial") AND ((metastasis OR metastases OR secondary)) AND NOT ((glio* OR meningioma)). All identified articles were imported into Rayyan's reference management tool, where duplicates were removed before screening.

2.3. Study selection

Three independent reviewers carried out the selection process in two stages. In the first stage, titles and abstracts were screened to exclude irrelevant studies. In the second stage, the full text of the remaining studies was reviewed to assess their eligibility based on the predefined inclusion and exclusion criteria. The screening and selection process was performed blinded to minimize the risk of bias.

Following PICOS criteria, we have included retrospective or prospective clinical trials with published results written in English (Table S1 in Supplementary Materials). We excluded studies without access to full-text, unclear, or unreported results, case reports, review articles, and study protocols.

2.4. Data extraction

Data extraction was carried out systematically, focusing on key characteristics and outcomes related to the clinical application of brachytherapy for brain metastases. The following data were extracted:

- Author, year of publication, and study type (retrospective/ prospective).
- Sample size, sex, age, and treatment details, including naive or radiation recurrent brachytherapy application, performance status, exclusion criteria, number of metastases, volume of metastases, type of primary, and follow-up time.
- Information on disease control outside the brain, ongoing systemic therapies used concurrently with brachytherapy.

- Radioisotope type, type of application, dose prescribed, dose constraints for organs-at-risk (OARs), dose rate and irradiation time, source activity, and dose specification.
- Response rates (complete (CR), partial (PR), stable (SD), progression (PD), LC, distant intracranial control (DIC), PFS, overall survival (OS), procedure-related complications, and radionecrosis rate.
- Acute and late toxicity, QoL, and neurocognitive function were reported.

2.5. Risk of bias assessment

The quality of the included studies was assessed using the Newcastle-Ottawa Scale (NOS) (Stang, 2010), which evaluates key factors such as selection, comparability, and outcome assessment. Studies receiving higher NOS scores were considered to have a lower risk of bias. In the absence of a non-exposed cohort, the JBI Critical Appraisal Checklist for Case Series was adopted. The results of RoB analysis are available in Table S2-S3 in Supplementary Material (Munn et al., 2019).

3. Results

A total of 1183 records were identified through database searches (Scopus: 523, Embase: 265, Medline: 207, and Web of Science: 188), with 374 duplicates removed prior to screening. After screening 809 records, 734 were excluded, leaving 75 reports sought for retrieval. An additional record was identified through citation searching, bringing the total number of reports sought for retrieval to 76. Of these, 75 were assessed for eligibility, and after excluding ineligible studies, 8 studies were included in the final review. Fig. 1 presents study design, while Fig. 2 illustrates the PRISMA flow diagram for the study selection process.

3.1. Risk of bias analysis

At the RoB analysis the majority of studies achieved moderate to high-quality ratings, minimizing the potential for significant bias (Table S2-S3 in Supplementary Materials)). Most studies demonstrated good representativeness of the exposed cohort and appropriate ascertainment of exposure. However, due to the absence of comparative cohort in 6 articles, variability was observed in the comparability domain. Outcome assessment was generally consistent, though certain studies did not report follow-up durations sufficiently, impacting their scores.

3.2. Studies characteristics

Our search strategy allowed us to include eight studies that provide a comprehensive overview of outcomes and toxicity following brachytherapy performed as a monotherapy without previous surgery (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c; Yang et al., 2022; He et al., 2023; Ostertag and Kreth, 1995; Bernstein et al., 1995). All the studies we selected were retrospective, single-center. Notably, two studies, one by Yang et al. and the other by He et al., were conducted after 2020 (Yang et al., 2022; He et al., 2023), four between 2010 and 2016 (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c), and two reports involved data from as early as 1995 (Ostertag and Kreth, 1995; Bernstein et al., 1995), showcasing a diverse range of research over time. Two studies compared the results of SBT with EBRT (Ruge et al., 2011a; Yang et al., 2022). One analysis evaluated the results of adding whole-brain radiation therapy (WBRT) to

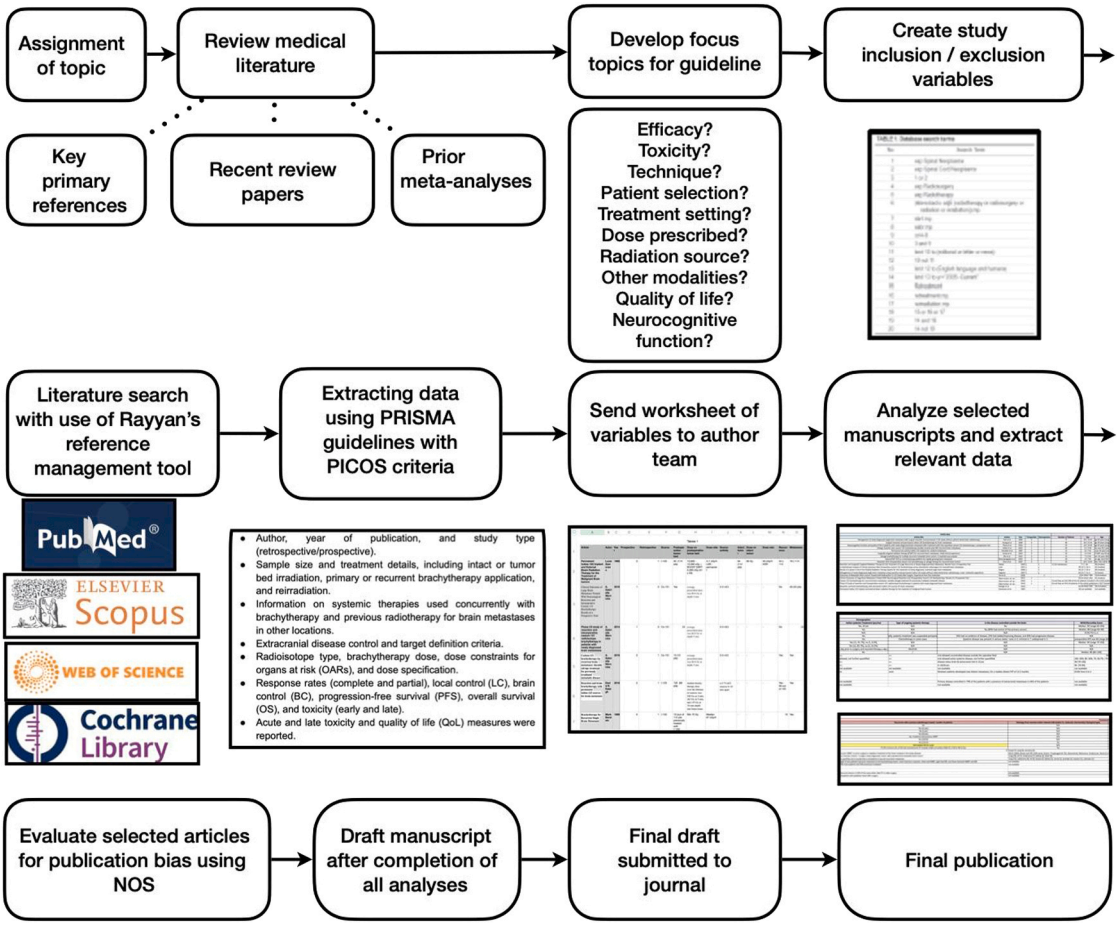

Fig. 1. Summary flow chart of steps taken during systematic review preparation.

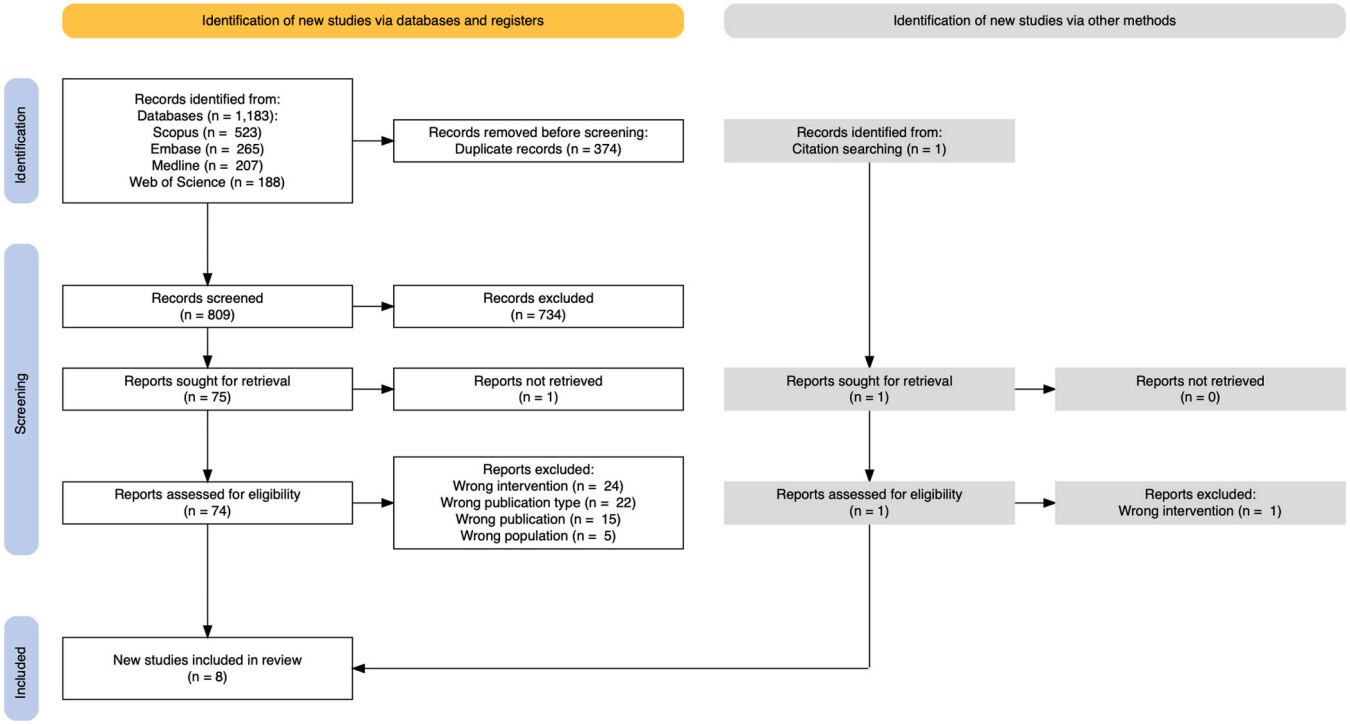

Fig. 2. PRISMA flow diagram detailing the study selection process.

SBT (Ostertag and Kreth, 1995). The results of 427 patients with more than 456 metastases treated were described. The proportion of sex was almost equal, with 45.7 % females. Usually, patients in the middle age, with median age ranging from 47 to 60.3 years, were included. Most studies qualified the patients with Karnofsky Performance Status (KPS) at least 60–70 and estimated patient survival at least 3 months. Patients with 1–3 brain metastases were qualified, preferably with controlled extracranial disease (Ruge et al., 2011a, 2011b; He et al., 2023; Ostertag and Kreth, 1995). Most studies included intracranial radiation-naive patients (292 patients, 68.4 %) (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011c; Yang et al., 2022; Ostertag and Kreth, 1995). Three reports included patients with radiation recurrent and radiation-naive metastases (Ruge et al., 2011a, 2011c; Ostertag and Kreth, 1995). The other three reports focus on the outcomes and toxicity of radiation recurrent metastases (Ruge et al., 2011b; He et al., 2023; Bernstein et al., 1995). There was no precise information about ongoing systemic therapy in all but two studies (Yang et al., 2022; Bernstein et al., 1995). Berenstein et al. did not allow for systemic therapy treatment, and in the study of Yang et al., 89.8 % of patients could have been under active systemic therapy. All studies also applied SBT for more extensive brain metastases up to 6 cm. Metastases volume had a high range from 0.2 up to even 99 cc in older series (Ruge et al., 2011a, 2011b, 2011c; Yang et al., 2022; He et al., 2023; Ostertag and Kreth, 1995; Bernstein et al., 1995). Metastases from different primaries were included with the most frequent non-small-cell lung cancer (NSCLC), which was present in 181 (42.4 %) of included patients. Breast cancer and kidney cancer were the second and third dominant primary tumor histologies, including 67 (15.6 %) and 49 (11.5 %) patients, respectively. Only Osertag et al. mentioned that the exclusion criteria were small cell lung cancer, lymphoma, or germ cell tumor histology (Ostertag and Kreth, 1995). Ruge et al., in their three studies, used an additional RTOG score with division on classes 1, 2, and 3 for patients' performance status characteristics (Ruge et al., 2011a, 2011b, 2011c) (Table 1).

3.3. Treatment planning and prescribed dose characteristics

In all of the selected studies, I-125 seeds were used. Most studies applied temporary seed implantation (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c; Ostertag and Kreth, 1995; Bernstein et al., 1995). A permanent type of application was used in two reports (Yang et al., 2022; He et al., 2023). The variety of dose levels was informative, with 50 Gy prescribed on the tumor surface in four reports (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c) and 60 Gy in one (Ostertag and Kreth, 1995). Osertag et al., in one of their split cohorts, added 40 Gy administered in 2 Gy fractions with EBRT. In the permanent type of applications, higher doses were applied; Bernstein et al. used 70 Gy, Yang et al. used a median dose of 93.5 Gy (80−120), and He et al. with a dose rate of 7.7 Gy/h applied a median of 150 Gy (120−165). Ruge et al., in their three reports, mentioned that implants were removed after 35–42 days (Ruge et al., 2011a, 2011b, 2011c). Yang et al. described the irradiation time of about 6–8 months (Yang et al., 2022). Source activities for the temporary type of implantation were from 0.1 cGy/min (Ruge et al., 2011a, 2011b, 2011c) to 10–15 cGy/h (Romagna et al., 2016; Bernstein et al., 1995). Source activity for the temporary application of Ruge et al. was 4.2–24.5 mCi (Ruge et al., 2011b). Bernstein et al., in their temporary seed application, used 20–40 mCi source activity (Bernstein et al., 1995). In the permanent type of application, most modern series 0.7–0.8 mCi were applied (Yang et al., 2022; He et al., 2023). The dose was commonly specified on the tumor surface (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c; Ostertag and Kreth, 1995; Bernstein et al., 1995). Only one report mentioned dose constraints applied to OaRs. In Yang et al., the brainstem was the only OaR with a maximum tolerated dose of 79.6 Gy (Yang et al., 2022). (Table 2).

3.4. Response and outcomes evaluation

Five reports evaluated the response achieved after SBT (Ruge et al., 2011a, 2011b, 2011c; He et al., 2023; Ostertag and Kreth, 1995). The Macdonald criteria (Macdonald et al., 1990) were utilized for assessing the response, LC, and DIC in studies conducted by Ruge et al (Ruge et al.,

Table 1
Basic characteristics of included studies for intact brain metastases stereotactic interventional radiotherapy application.

Author and year	Ruge et al. (11) 2011	Romagna et al. (12) 2016	Ruge et al. (13) 2011	Ruge et al. (14) 2010	Yang et al. (15) 2022	He et al. (16) 2023	Ostertag et al. (17) 1995	Bernestein et al. (18) 1995
Study type	Retrospective, single-center, S-IRT vs. SRS	Retrospective, single-center	Retrospective, single-center	Retrospective, single-center	Retrospective, single-center S-IRT vs. EBRT	Retrospective, single-center	Retrospective, single-center a) S-IRT + WBRT, b) S-IRT for naive metastases, c) S-IRT for recurrent metastases,	Retrospective, single-center
Exclusion criteria	KPS< 60 and/ or estimated survival < 3 months	a) De novo - more than one metastasis, Salvage - more than 2 metastases, b) KPS < 70 and estimated survival < 3 months	a) KPS < 60 and estimated survival < 3 months, b) uncontrolled systemic disease	a) KPS < 60 and estimated survival < 3 months, b) uncontrolled systemic disease	a) BMs involved the bilateral cerebral hemisphere, b) the number of BMs was more than three, c) intratumoral hemorrhage	a) KPS< 40, b) PLT < 50 × 109/ l, c) INR> 1.5, d) APTT> 2xnormal	a) non-spherical, b) > 4 cm, d) SCLC, lymphoma, germ cell tumors	a) > 1 metastasis, b) KPS < 70, c) unstable extracranial disease
No of patients	77	43	27	90	59	28	93, a) 38, b) 34, c) 21	10
No of metastases treated	77	43	27	90	> 59	38	112	10
Volume of treated metastases (cc)	9.1 (1.2–35.5)	3.4 (0.2–9.9), de novo - 4.1, salvage - 2.3	8.1 (2.3–22.5)	0.5–14 cc- 70 (77.8 %), > 14cc- 20 (22.2 %)	Diameter- 3 cm (1.5–5)	Diameter- 3.4 cm (1.9–6.0)	13 + - 15.6, Diameter- 1.5 cm + - 0.54	36.4 (12.1–99)
Sex	35 F, 42 M	14 F, 29 M	12 F, 15 M	42 F, 48 M	29 F, 30 M	12 F, 16 M	44 F, 49 M	7 F, 3 M
Age (median)	58 (17−80)	60.3	53 (17–71)	59 (17−80)	29 < 60 yrs; 30 ≥ 60 yrs	59 (36−76)	47–58 (depending on group)	57.5 (35−66)
Type of primary cancer	kidney- 10 (13 %), breast- 16 (20.8 %), NSCLC- 20 (26 %), melanoma- 7 (9.1 %), CRC- 6 (7.8 %), CUP- 6 (7.8 %), other- 12 (15.6 %)	lung −17 (39.5 %), breast- 11 (25.6 %), GI- 3 (6.9 %), skin- 5 (11.6 %), prostate- 1 (2.3 %), kidney- 3 (6.9 %), uterus- 1 (2.3 %), ovary- 1 (2.3 %), musculoskeletal system- 1 (2.3 %)	breast - 11 (40.7 %), NSCLC- 5 (14.8 %), melanoma- 3 (11.1 %), CRC- 3 (11.1 %), kidney- 1 (3.7 %), CUP- 1 (7.4 %), esophagus- 1 (3.8 %), other- 2 (7.4 %)	kidney−12 (13.3 %), breast- 17 (18.9 %), NSCLC- 27 (30 %), melanoma- 8 (8.9 %), colorectal- 7 (7.8 %), CUP- 6 (6.7 %), other- 13 (14.4 %)	NSCLC- 59 (100 %)	lung−13 (46.4 %), GI- 7 (25 %), breast- 3 (10.7 %), kidney- 2 (7.1 %), sarcoma- 2 (7.1 %), skin−1 (3.57 %)	NSCLC- 31 (33.3 %), melanoma - 18 (19.4 %), GI- 8 (8.6 %), breast- 8 (8.6 %), kidney- 21 (22.6 %), thyroid- 2 (2.2 %), uterus/ovarian- 3 (3.2 %), CUP- 2 (2.2 %)	lung- 9 (90 %), breast- 1 (10 %)
Radiation naive/ Radiation recurrent	Naive- 77 (100 %)	Naive- 20 (46.5 %), Recurrent- 23 (53.5 %)	Recurrent- 100 %	Naive- 64 (71.2 %), Recurrent- 26 (28.8 %)	Naive- 59 (100 %)	Recurrent- 28 (100 %)	Naive - 72 (77.4 %), Recurrent - 21 (22.6 %)	Recurrent- (100 %)
Active systemic treatment and type	NR	NR	NR	NR	Yes- 53 (89.8 %),	NR	NR	No
Disease control outside the brain	77 (100 %)	60 %, de novo - 45 %, Salvage - 74 %	Stable systemic disease- 19 (70.4 %), no signs of systemic disease- 8 (29.6 %)	49 (54.4 %)	NR	28 (100 %)	NR	10 (100 %)
WHO/ Karnofsky Score	70 (60−90)	de novo: 90, salvage: 80	70 (60–90)	70 (60−90)	< 90–43; ≥ 90–16	60 (40−90)	70–80	At least 70
RTOG score	RPA class 1–22 (28.6 %), RPA class 2–40 (58.4 %),	NR	RPA class 1–12 (44.4 %), RPA class 2–12 (44.4 %),	RPA class 1–34 (37.8 %), RPA class 2–49 (54.4 %),	NR	NR	NR	NR

(*continued on next page*)

Table 1 (*continued*)

Author and year	Ruge et al. (11) 2011	Romagna et al. (12) 2016	Ruge et al. (13) 2011	Ruge et al. (14) 2010	Yang et al. (15) 2022	He et al. (16) 2023	Ostertag et al. (17) 1995	Bernestein et al. (18) 1995
	RPA class 3–10 (13 %)		RPA class 3–3 (11.1 %)	RPA class 3–7 (7.8 %)				
Follow-up time (months)	NR	De novo- 15 (4–60), Salvage- 19.7 (9–49)	44.7 (31.1–79.2)	8.8 + /- 18.8	NR	14.2 (5.2–46.5)	19	0.5–81

S-IRT- stereotactic interventional radiotherapy, NR- not reported, RTOG- Radiation Therapy Oncology Group, RPA- Recursive Partitioning Analysis scale, WHO -World Health Organization, CUP- Cancer of Unknown Primary, CRC- colorectal cancer, NSCLC- non-small cell lung cancer, GI- gastrointestinal cancers, F- female, M- male, KPS- Karnofsky Performance Status, BMs- brain metastases, INR- the international normalized ratio, APTT- activated partial thromboplastin time, PLT- platelet count, SCLC- small cell lung cancer, SRS- stereotactic radiosurgery, WBRT- whole brain radiotherapy.

Table 2
Basic characteristics of dose, type of implantation, and other physical parameters for included studies.

Author	Ruge et al. (11)	Romagna et al. (12)	Ruge et al. (13)	Ruge et al. (14)	Yang et al. (15)	He et al. (16)	Ostertag et al. (17)	Bernstein et al. (18)
Radioisotope and type of implantation	I−125 seeds, temporary	I−125 seeds, temporary	I−125 seeds, temporary	I−125 seeds, temporary	I−125 seeds, permanent	I−125 seeds, permanent	I−125 seeds temporary	I−125 seeds, temporary
Dose rate and irradiation time	0.1 cGy/min, 42 days	< 15 cGy/h	0.1 cGy/min, 42 days	175–150 cGy/d (0.1 cGy/min), 35–42 days	NR	7.7 cGy/h	10 cGy/h	Median 67 cGy/h
Reference dose	50 Gy	50 Gy	50 Gy	50 Gy	93.5 Gy (80−120)	150 Gy (120−165)	a) 60 Gy (S-IRT) + 40 Gy (df 2 Gy) (WBRT), b) 60 Gy, c) 60 Gy	70 Gy
Source activity	NR	NR	4.2–24.5 mCi	NR	0.7 mCi	0.8 mCi	NR	20–40 mCi
Dose specification	tumor surface	tumor surface	tumor surface	tumor surface	NR	NR	tumor surface	tumor surface

NR- not reported, S-IRT- stereotactic interventional radiotherapy, WBRT- whole brain radiotherapy

2011a, 2011b, 2011c). Progression was so defined as an increase of 25 % in the pretreated volume on contrast-enhanced T1-weighted MRI scans. He et al. assessed the response based on RANO neuro-oncology criteria (He et al., 2023; Wen et al., 2010). Objective response rates (ORRs) varied across older series, ranging from 69.2 % to 82 % (Ruge et al., 2011a, 2011b, 2011c). In the most recent study, He et al. reported a high ORR of 91.3 %, with an even higher disease control rate (DCR) of 95.7 % (He et al., 2023). The incidence of progressive disease was between 0 % and 5 % among patients (Ruge et al., 2011a, 2011b, 2011c; Ostertag and Kreth, 1995; Bernstein et al., 1995). One-year LC rates across nearly all series ranged from 93.3 % to 100 % (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c; He et al., 2023; Ostertag and Kreth, 1995). In two studies investigating salvage SBT following prior radiation therapy, LC rates were recorded at 60 % and 65 % (Romagna et al., 2016; Bernstein et al., 1995). One-year DIC rates varied from 52 % to 90 % (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c; He et al., 2023; Ostertag and Kreth, 1995; Bernstein et al., 1995). Overall PFS was reported only in the study by Yang et al., showing rates of 76.3 % at 6 months and 40.7 % at 1 year post-SBT (Yang et al., 2022). The median OS time, calculated from the SBT procedure for radiation-naive patients, ranged from 8 to 17 months. RPA class 1 patients experienced the best outcomes, reaching a median of 18.1 months (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011c; Yang et al., 2022; Ostertag and Kreth, 1995). For patients with radiation-recurrent tumors, OS varied widely, from 6 months to as much as 28.4 months for RPA class 1 (Romagna et al., 2016; Ruge et al., 2011b, 2011c; He et al., 2023; Ostertag and Kreth, 1995; Bernstein et al., 1995). Most series employed salvage local therapies such as SRS, subsequent SBT, or surgery, which were applied to between 4.62 % and 30.2 % of patients (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c; Ostertag and Kreth, 1995; Bernstein et al., 1995)(Table 3).

3.5. Profile of procedure-related complications, toxicity, and quality of life with neurocognitive functioning

No fatal complications or procedure-related severe complications were reported in the reviewed series. Even the two patient deaths due to pulmonary embolism, as described by Bernstein et al., occurred 2 and 13 weeks after the procedure, which makes it challenging to attribute them solely to irradiation technique, vs the needed surgery itself (Bernstein et al., 1995). Yang et al. and He et al. each reported only two minor hemorrhages or instances of transient bleeding during their procedures (Yang et al., 2022; He et al., 2023). Postoperative morbidity within 30 days, which included superficial wound infections, cerebrospinal fistulas, and transient hemiparesis, ranged from 0 % to 6.6 % across different studies. Symptomatic radionecrosis was noted in only two patients, as reported by Bernstein et al., in their cohort of patients with radiorecurrent tumors (Bernstein et al., 1995). Three studies indicated that G1/G2 acute edema was present in 4.6–25.4 % of patients, which was transient (Romagna et al., 2016; Yang et al., 2022; He et al., 2023). No G3 or G4 acute toxicities were reported; however, two cases of G3 edema, which were transient, resolved after 7–14 days of treatment with corticosteroids and mannitol (He et al., 2023). There were no late toxicities directly associated with the SBT. Two patients whose radiation-recurrent tumors were situated in the motor cortex experienced permanent worsening of preexisting motor weakness (Bernstein et al., 1995). Four reports evaluated neurocognitive function and the KPS after SBT. They highlighted that 79–97 % of treated patients showed improved or stable performance, instilling optimism regarding the procedure's benefits (Ruge et al., 2011a, 2011b, 2011c; Ostertag and Kreth, 1995)(Table 4).

Table 3
Summary of Response Rates, Local Control, Distant Intracranial Control, Progression-Free Survival, Overall Survival, and Salvage Therapies.

Author	Ruge et al. (11)	Romagna et al. (12)	Ruge et al. (13)	Ruge et al. (14)	Yang et al. (15)	He et al. (16)	Ostertag et al. (17)	Bernstein et al. (18)
Response rates (MRI)	CR - 5 (7.7 %), PR - 40 (61.5 %), SD - 19 (29.2 %), PD - 1 (1.1 %)	NR	CR - 4 (22.2 %), PR - 9 (50.0 %), SD - 4 (22.2 %), PD - 1 (5.55 %)	CR - 5 (7.7 %), PR - 40 (61.5 %), SD - 19 (29.2 %), PD - 1 (1.54 %)	NR	ORR- 91.3 %, DCR- 95.7 %	ORR- 76 (82 %), SD- 17 (18 %), PD- 0 (0 %)	NR
Local control (LC)	1- year- 94.6 %	1-year- upfront S-IRT vs. salvage S-IRT - 94 % vs. 65 %	1-year- 93.3 %	1-year- 94.6 %	NR	at the end of follow-up −96.43 %	at the end of follow-up- 100 % but 8 (8.6 %) reimplantation to 100 Gy total	at the end of follow-up- 60 %
Distant intracranial control (DIC)	1- year- 53.6 %	1-year- upfront S-IRT vs. salvage S-IRT - 87 % vs. 57 %	1-year- 54.5 %	1-year- 53.6 %	NR	at the end of follow-up - 71.43 %	at the end of follow-up - 52 %	at the end of follow-up- 90 %
Progression-free survival (PFS) (months)- from S-IRT	NR	NR	NR	NR	6-month- 76.3 %, 12-month- 40.7 %	NR	NR	NR
Overall Survival (OS) (months)- from S-IRT	8.0 (5.5–10.6), RPA class 1–18.1 (5.3–30.8), RPA class 2–6.8 (5.0–8.7), RPA class 3–4.3 (2.6–6.1)	De novo - 13 months, Salvage - 28.4 months	14.8, RPA class 1–24.2, RPA class 2–4.0, RPA class 3–8.0	8.5 (0.2–18.1) RPA class 1–18.1, RPA class 2–6.9, RPA class 3–4.4	12-month- 67.7 %, 24-month- 27.1 %	14.1 (10.6–17.6), 1-year- 57.1 %	a) 17, b) 15, c) 6	11.5 months, 1-year- 50 %, 3-year- 20 %
Salvage local therapies	20 (25.9 %)	13 (30.2 %)	1 (5.55 %)	3 (4.62 %)	NR	NR	18 (19.3 %), reimplantation to 100 Gy total- 8 (8.6 %), WBRT- 10 (10.7 %)	1 (10 %)

CR- complete remission, PR- partial response, SD- stabilization of the disease, PD- progression of the disease, ORR- objective response rate, DCR- disease control rate, NR- not reported, S-IRT- stereotactic interventional radiotherapy, RPA- recursive partitioning analysis scale, WBRT- whole brain radiotherapy

Table 4
Toxicities profile with quality of life characteristics.

Author	Ruge et al. (11)	Romagna et al. (12)	Ruge et al. (13)	Ruge et al. (14)	Yang et al. (15)	He et al. (16)	Ostertag et al. (17)	Bernstein et al. (18)
The scale used for toxicity assessment	RTOG/EORTC (CTCAE v3.0)	RTOG/EORTC	RTOG/EORTC (CTCAE v3.0)	NR	NR	RTOG/EORTC (CTCAE v4.0)	NR	NR
Procedure-related complications	Postoperative 30-day morbidity - 2 (2.5 %) (superficial wound infection, CSF fistula)	0 %	Postoperative 30-day morbidity - 2 (6.6 %) (superficial wound infection and surgical revision, transient aphasia)	Postoperative 30-day morbidity- 2 (3.3 %) (superficial wound infection, CSF fistula)	No fetal complications, bleeding during the procedure - 2 (3.39 %)	2 (7.1 %) small hemorrhages (1 subdural, 1 intra-parenchymal)	Postoperative 30-day morbidity- 2 (2 %) (2 transient hemiparesis due to edema and small hematoma)	0 %
Symptomatic radionecrosis rate	0 %	0 %	0 %	0 %	0 %	0 %	0 %	2 patients
Acute toxicity	G 3/4–0 %	G1/2 - upfront S-IRT vs. salvage S-IRT- 0 (0 %) vs. 2 (4.6 %) (edema)	G3/4–0 %	NR	G1/2 edema - 15 (25.4 %)	G2 edema- 3 (10.7 %), G3 edema- 2 (7.15 %)	NR	NR
Late toxicity	0 %	0 %	0 %	NR	NR	NR	NR	NR
Quality of life/ Neurocognitive function	KPS and neurological status- stable or improved- 97 %	NR	KPS and neurological status- stable or improved- 17 (94.4 %)	KPS and neurological status- stable or improved- 63 (95.5 %)	NR	NR	Improved or stable performance status- 73 (79 %)	NR

S-IRT- stereotactic interventional radiotherapy, NR- not reported, RTOG- Radiation Therapy Oncology Group, EORTC- European Organisation for Research and Treatment of Cancer, CTCAE- Common Terminology Criteria for Adverse Events, CSF- cerebrospinal fluid, KPS- Karnofsky Performance Status.

4. Discussion

Our systematic review included 8 studies and 427 patients with 456 unresected brain metastases. Stereotactic interventional radiotherapy (brachytherapy), also known as interstitial radiosurgery, has been used for intact metastasis or after resection for tumor bed irradiation with

good outcomes and a favorable toxicity profile (Kutuk et al., 2023, 2024). It is more frequently selected for the second scenario as it is generally not as complicated as for intact tumors, as shown by search results for this systematic review. As high manual skills and the labor-intensive nature of the procedure limited its use, the application techniques have evolved, making this type of radiation therapy more accessible to a broader range of clinicians treating brain metastases.

The procedure can be classified as "very complex" according to the complexity index of interventional radiotherapy (brachytherapy) implants (COMIRI) scale (Fionda et al., 2024). Older reports relied primarily on the temporary placement of radiation sources within the metastases, which were removed after 35–42 days (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c; Ostertag and Kreth, 1995). Recent studies, however, present another method of application for which I-125 sources placed permanently in the tumor are used (Ruge et al., 2011c; Yang et al., 2022). Given the source activity of 0.7–0.8 mCi, the irradiation time is 6–8 months. Yang et al. described a technique during which a treatment planning system (TPS) is used to navigate implantation. Patients were placed on vacua directly on the CT scanner. After skull drilling sites were selected, flat needles were used to implant radiation sources. In the latest available analysis, He et al. presented the possibility of using a more straightforward surgical procedure with 3D templates for 125-I seed implantation (He et al., 2023). This technique can be further conjugated with MR imaging to guide seed implantation. In their report, high-speed twist drills of a diameter of 1.9 mm were used to create application holes. What is essential is that MRI-compatible 18-gauge ball-tipped needles were used. A non-coplanar, individualized 3D plate with an accuracy of 0.1 mm was used to facilitate the insertion of the sources. In this study, 5 mm was added to the gross tumor volume (GTV) to create a clinical target volume (CTV) assuming subclinical spread of metastatic lesions. The 3D plate consisted of a base plate component and interchangeable components for positioning, performing the navicert, and performing the insertion. Implantation of radioactive sources was performed based on a pre-plane made before application. Pre- and post-operative dosimetric analysis was performed to evaluate D90, V100, and conformity index (CI). There were no statistically significant differences for both plans.

General anesthesia for the implantation procedure was a standard method (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011b, 2011c; Yang et al., 2022; He et al., 2023; Ostertag and Kreth, 1995; Bernstein et al., 1995). Only Bernstein et al. (1995) reported that the procedure was performed under local anesthesia. The average hospitalization time for the implantation procedure was short, 3–5 days (Romagna et al., 2016; Ruge et al., 2011b; Ostertag and Kreth, 1995; Bernstein et al., 1995). In most reports, dexamethasone was used on the day of the procedure and, on average, for 3 days more (Romagna et al., 2016). The temporarily implanted seed was removed under local anesthesia after 42 days (Ruge et al., 2011a, 2011b, 2011c).

Another critical issue is the fact that in many clinical scenarios, it is recommended to perform a repeat biopsy, especially in situations where there is a suspicion of recurrence of a tumor already previously irradiated, a lack of primary diagnosis, or a long period until the appearance of brain metastases of more than 2–3 years after the end of therapy of the primary tumor. In all these situations, the decision to perform a biopsy is made by a multidisciplinary team, further promoting SBT because, in such a situation, surgical intervention occurs anyway. This collaborative approach ensures that the most appropriate and effective treatment is chosen for each patient. Another vital aspect to consider is the size of the metastasis. Patients with large metastases, i.e., $>$ 14 cm3 and $>$ 3–4 cm, were specially qualified for the SBT procedure, where data on the results of SRS or FSRS are still scarce, and there is no solid scientific evidence for such a procedure. In addition, it should be taken into account that when using stereotactic radiotherapy from the outer half, for tumors $>$ 2.5 cm, toxicity and the percentage of symptomatic radionecrosis can reach 14–18.5 % (Ruge et al., 2011b; Van Schie et al., 2024). Radionecrosis could be indistinguishable from tumor progression on conventional imaging, creating a significant diagnostic challenge (Mayo et al., 2024). For SBT and the risk of symptomatic radionecrosis, dose rate might be the most crucial factor. The old series described a rate similar to external beam stereotactic radiotherapy of about 14 %, but 50 Gy in 4–5 days was applied, corresponding to dose rates of 40–50 cGy/h (Prados et al., 1989). In the newer series, for temporary application, lower dose rates of 6.2 cGy/h and 50 Gy were administered in 35–42 days, leading to no reports of radiation necrosis (Ruge et al., 2011a; Romagna et al., 2016; Ruge et al., 2011c). Similarly, Osertag et al. recommended not exceeding the dose rate of 10 cGy/h and reported no radiation necrosis even if the population of patients had previously been irradiated within the exact location (Ostertag and Kreth, 1995). Only Bernstein et al. described two cases of symptomatic radiation necrosis. Still, it has to be considered that all patients in his series were previously irradiated and permanent implantation with a dose rate of 67 cGy/h, source activity of 20–40 mCi, and dose of 70 Gy were prescribed (Bernstein et al., 1995). In the most modern series, with permanent implantation, median doses of 93.5 Gy and 150 Gy were prescribed (Romagna et al., 2016; Ruge et al., 2011b). With longer treatment times, low dose rates of about 7.7 cGy/h were applied, and no symptomatic radiation necrosis events or other acute toxicity was described (Yang et al., 2022; He et al., 2023). Radionecrosis management includes the use of corticosteroids, which act as modulators of the inflammatory changes, reducing cerebral edema and showing complete response in approximately 50 % of patients and partial response in 33 %. Bevacizumab could be employed in corticosteroid-refractory cases and surgical excision could be evaluated in case of no response to medical therapy (Sayan et al., 2020; Zhuang et al., 2019).

The application procedure was remarkably safe in the illustrated series, with no fatal complications or significant late toxicity reported. The rates of 30-day morbidity were meager, ranging from 0 % to 6.6 %. Most importantly, most patients presented improved or stable performance status and/or neurological functioning, underscoring the safety and positive outcomes of the procedure. The absence of dose–volume parameters for organs-at-risk (OARs) in the analyzed studies (with the exception of one) highlights the need for EQD2-based conversion using established dose constraints from SRS and underscores this area as a priority for future prospective studies.

The definition of complete remission after SBT can be evaluated by modified McDonald criteria because of the frequently observed presence of residual traces of contrast enhancement around the implant seeds resulting from treatment-induced local blood-brain barrier disruption (Ruge et al., 2011c). In most modern series, RANO neuro-oncology criteria were selected for responsive evaluation (He et al., 2023). High ORRs were achieved in most of the series, indicating high local efficacy of this type of management in patients undergoing prior irradiation. The one-year rate of distant intracranial control exceeded 50 % in all included studies. Only one study indicated the use of systemic treatment in 90 % of the included patients (Yang et al., 2022). The role of systemic therapy in the context of SBT is to address any systemic disease that may be present in addition to brain metastases, providing a more comprehensive patient care approach. Unfortunately, it was not stated which systemic treatment was used, and all included patients had a diagnosis of lung cancer. SBT could play a potential role in the multimodal management of the oligometastatic setting, as might enhance treatment outcomes when associated with systemic therapies. Its high dose conformality could potentially preserve immune function, compared to EBRT, limiting the depletion of radiosensitive lymphoid cells. However, present evidences are limited and further studies are warranted (Serre et al., 2025).

The outcomes, including OS, were favorable in most of the series. The factors that significantly improved survival were KPS$\geq$ 70, stable systemic disease, RPA class 1, and a prolonged ($>$12 months) interval between initial diagnosis and SBT (Ruge et al., 2011a, 2011b, 2011c). Better local response was present when tumor volume was $\leq$ 14 cc (Ruge et al., 2011a, 2011b, 2011c). Osertag et al. showed that better

results after SBT can be achieved in a group of patients with KPS $\geq$ 70, solitary brain metastasis, absence of metastases outside the brain, and at least a 12-month time interval between primary diagnosis and brain metastasis occurrence (Ostertag and Kreth, 1995). A remarkably high median OS of 28.4 months was also reached in radio-recurrent metastasis (Romagna et al., 2016). The modern reports involving stereotactic external beam radiotherapy for radiorecurrent brain metastases describe a high median OS of 25 months, LC of 67 %, and radionecrosis rates of 12 % (Touati et al., 2023). In other multi-institutional analysis, 1-year and 2-year LC were 79 % and 72 %, respectively. Radiation necrosis was detected in 20 % of cases, and symptomatic radiation necrosis was detected in 7 % of treated patients. The cumulative maximum dose from both stereotactic treatments of $\geq$ 40 Gy was also predictive for increased RN (Kowalchuk et al., 2022).

Only three retrospective reports compare the results of EBRT with SBT (Ruge et al., 2011a; Yang et al., 2022; Ostertag and Kreth, 1995). Yang et al. showed better 6-month PFS favoring permanent SBT in a median dose of 93.5 Gy vs. a median EBRT dose of 41.3 Gy, 76.3 % vs. 51.5 % (Romagna et al., 2016; Yang et al., 2022). However, there was no statistically significant difference regarding 1-year PFS 1-and 2-year OS, but it has to be considered that the median tumor diameter for SBT was 3 cm versus 2 cm in the EBRT arm. Evaluation of results of SBT with the dose of 60 Gy with SBT+ WBRT (40 Gy in 2 Gy fractions) showed no significant difference in OS, which was 15 months and 17 months, respectively (Ostertag and Kreth, 1995). Similarly, Ruge et al., when comparing the outcomes of SRS with SBT, showed no significant difference regarding OS (Ruge et al., 2011a). Doses of 18–22 Gy were prescribed to SRS and 50 Gy for SBT. However, careful consideration should be posed since patients who qualified for SBT had worse performance status, larger tumors $>$ 3 cm, and metastasis volume $>$ 14cc than in the subgroup receiving SRS. These limited comparative data might introduce potential selection bias that must be acknowledged. Future studies should employ propensity score matching or stratified analyses adjusting for tumor volume, histology, and prior radiation exposure to provide more balanced comparisons between these treatment modalities and better clarify the benefits of SBT compared to conventional approaches.

There is a growing interest in using Cesium-131 sources for brain applications, which are currently being tested in prospective randomized controlled trials such as STaRT, ROADS, and TRLS-07 (Kutuk et al., 2023; Weinberg, 2021; Odia et al., 2022; Moss et al., 2021). The Cesium-131 radiation source has a half-life of 9.7 days, which is more than six times shorter than that of Iodine-125 (59.4 days) (Garcia et al., 2024). Additionally, the dose rate for Cesium-131 is more favorable, at 0.342 Gy/h compared to 0.069 Gy/h for Iodine-125. This allows for a faster dose delivery and provides a radiobiological advantage (Odia et al., 2022).

The short irradiation time enables the administration of more than 90 % of the dose within one month, making this treatment convenient and cost-effective (Palmisciano et al., 2023). However, all available data regarding outcomes after Cesium-131-based brain brachytherapy are limited to the postoperative setting. There are currently no reports evaluating the efficacy of the Cesium-131 source in direct applications, highlighting a potential area for further research regarding using radionuclide sources in cases without tumor resection.

5. Conclusions

There is no prospective trial that directly compares Stereotactic Radiosurgery (SRS) with Stereotactic interventional radiotherapy (brachytherapy) (S-IRT) for unresected brain metastases. Nevertheless, given the very favorable outcomes, low morbidity, and positive results observed in patients with larger tumors and/or those who have experienced recurrences after previous radiotherapy, S-IRT should be considered more frequently in specialized centers. Multidisciplinary team management is essential for this type of procedure.

Declaration of Competing Interest

The authors- Mateusz Bilski, Federico Mastroleo, Łukasz Kuncman, Paul Rogowski, Stefano Durante, Costantino Putzu, Artur Chyrek, Giulia Marvaso, Bruno Fionda, Luca Tagliaferii, Jacek Fijuth, Andrea Vavassori, Barbara Alicja Jereczek- Fossa declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.critrevonc.2025.104777.

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Mateusz Bilski MD PhD Is a board-certified radiation oncologist and Deputy Chief of Brachytherapy Department, Saint John's Cancer Center of Lublin, Poland. He also works in the Clinics of Radiotherapy at the Medical University of Lublin. His research background and clinical interests have primarily focused on the treatment of patients with male and female urogenital systems, central nervous systems, liver, lung, and skin cancers. His special interests include metastasis-directed therapy (MDT) delivered through stereotactic radiotherapy (SBRT/SRS) and interventional radiotherapy (brachytherapy) in patients with oligometastatic disease. In his daily clinical and scientific work, he particularly appreciates the possibilities of combining external beam radiotherapy (EBRT) and interventional radiotherapy (brachytherapy) in different clinical settings.

Federico Mastroleo MD, PhD is a Radiation Oncologist at the European Institute of Oncology, Milan, Italy and a PhD student at the University of Milan, Italy.

Łukasz Kuncman MD, PhD. Dr. Łukasz Kuncman is a radiation oncologist and Assistant Professor at the Medical University of Łódź. He also serves as Deputy Head of the Department of External Beam Radiotherapy at Copernicus Memorial Hospital in Łódź. His clinical and research interests focus on stereotactic radiotherapy, integration of radiotherapy with systemic treatments, and personalized approaches in thoracic oncology.

Paul Rogowski MD Is a senior radiation oncologist at the Department of Radiation Therapy at LMU Medical Center since 2022. His clinical and scientific focus includes urological and gastrointestinal tumors. He also works in brachytherapy.

Stefano Durante is a Radiation Oncologist at the European Institute of Oncology, Milan, Italy.

Costantino Putzu is a Resident in Radiation Oncology at the European Institute of Oncology, Milan, Italy and University of Milan, Italy.

Artur Chyrek, MD, Ph.D. Radio-oncologist specialized in interventional radiotherapy (brachytherapy). Head of the Permanent Implants Laboratory at the Greater Poland Cancer Center and Assistant at the Poznań University of Medical Sciences. His main research interests include modern brachytherapy techniques, treatment outcomes, and the application of augmented reality in interventional radiotherapy.

Giulia Marvaso MD, PhD is a Radiation Oncologist at the European Institute of Oncology, Milan, Italy and an Assistant Professor at the University of Milan, Italy.

Bruno Fionda, MD. Has been working at the Gemelli ART (Advanced Radiation Therapy) at the Fondazione Policlinico Universitario Agostino Gemelli IRCCS in Rome. His clinical expertise includes both interventional and external beam radiotherapy. With substantial experience in research initiatives, he has contributed to various national and international conferences through presentations and has authored several publications in relevant scientific journals. His key research endeavors primarily on head and neck, skin and eye tumors.

Luca Tagliaferii, MD, PhD, currently works at the Gemelli ART (Advanced Radiation Therapy) Center of the Gemelli University Hospital of Rome. His clinical interests focus primarily on interventional and metabolic radiotherapy. He has experience in research projects and has discussed numerous presentations at international conferences and published in renowned journals. His main research projects involve the diagnosis, treatment, and prognostic analysis of head and neck, skin, thyroid, and urologic cancers.

Jacek Fijuth MD, PhD. Prof. Jacek Fijuth is a radiation oncologist and Head of the Department of Radiotherapy at the Medical University of Łódź, Łódź, Poland, and the Department of External Beam Radiotherapy at Copernicus Memorial Hospital, Comprehensive Cancer Center and Traumatology, Łódź, Poland. His clinical and academic work focuses on radiotherapy education, treatment optimization, and multidisciplinary cancer care.

Andrea Vavassori. is a Radiation Oncologist at the European Institute of Oncology, Milan, Italy.

Ranjini Tolakanahalli, PhD, DABR, is a board-certified medical physicist serving as Director of Photon Physics in the Department of Radiation Oncology at Miami Cancer Institute, Baptist Health South Florida. She also serves as an Assistant Professor in the Department of Radiation Oncology at Florida International University's Herbert Wertheim College of Medicine. Her recent research focuses on evaluating imaging techniques, developing optimization algorithms for stereotactic radiosurgery, advancing central nervous system brachytherapy, exploring theranostics, and automating radiotherapy workflows.

Barbara Alicja Jereczek- Fossa, MD, PhD. is the Head of the Radiation Oncology Division at the European Institute of Oncology, Milan, Italy and Full Professor at the University of Milan, Italy.

Rupesh Kotecha, M.D., is a board-certified radiation oncologist and Chief of Radiosurgery in the Department of Radiation Oncology and Director of the Central Nervous

System (CNS) Metastasis program at Miami Cancer Institute. He is a professor in the departments of radiation oncology and translational medicine at the FIU Herbert Wertheim College of Medicine and an adjunct faculty in the Department of Radiation Oncology at Memorial Sloan Kettering Cancer Center. His research background and clinical interests have primarily focused on the treatment of patients with stereotactic radiotherapy, including CyberKnife, LINAC-based, ZAP-X and GammaKnife radiosurgery. He also specializes in advanced radiation therapy treatment techniques, including re-irradiation, proton beam radiotherapy, and MR-guided radiation therapy.