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Systematic Review

Treatment Protocols and Outcomes of Intraoperative Radiotherapy for Brain Metastases: A Systematic Review

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Abstract

Objectives: Intraoperative radiotherapy (IORT) is the delivery of ionizing radiation to the tumor or tumor bed during surgery. It is being explored as a treatment modality for brain metastases (BrMs). We aimed to determine the safety and efficacy of IORT for BrMs by reviewing the current evidence.

Methods: We performed a systematic review of the online databases for studies on IORT for BrMs. Data on clinical features, treatment modalities, and outcomes were collected.

Results: Five studies (n=179) were included. Mean age was 60.4 years, 43% were women. The most common etiology of BrMs were lung, melanoma, breast, and renal cancer. Ninety-five patients underwent IORT with the Photon Radiosurgery System (PRS) while 84 were treated with the INTRABEAM system. Follow-up ranged from 5 days to 94 months. The most frequent complication was radiation necrosis. Local recurrence and distal progression were seen in 11-77% and 0-82%, respectively. The 6- and 12-month overall survival ranged from 60-86% and 34-73%, respectively.

Conclusion: The results of the systematic review on the safety and efficacy of IORT on BrMs were inconclusive, due to heterogeneity of the studies. Larger prospective studies are needed to determine the optimal dose, efficacy, and safety of IORT for BrMs.

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Intraoperative radiotherapy (IORT) is the delivery of ionizing radiation to the tumor or tumor bed during surgery while the targeted tissue is exposed.[1] In contrast to other radiation modalities such as whole brain radiotherapy (WBRT), external beam radiotherapy (EBRT), and stereotactic radiosurgery (SRS), IORT has the advantages of increased precision and minimal radiation exposure to adjacent normal tissues,[2] thereby minimizing side effects. Because IORT is administered at the time of surgery, there is also the theoretical advantage of preventing tumor cell repopulation by not giving them time to proliferate, as may be the case in post-operative radiotherapy (RT).[3,4] Patient satisfaction and convenience are also improved since the surgery and radiation are performed in the same sitting,[5] potentially decreasing the duration of treatment. Given these advantages, IORT has been used in a wide range of

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malignancies such as breast and colorectal cancer and soft tissue sarcomas.[1,6] With further investigations, the indications for IORT have expanded to include brain metastases (BrM).[7]

BrMs are the most common intracranial tumor in adults, affecting up to 30% of adult cancer patients.[8] Treatment options include surgical resection with adjuvant RT and cancer-specific medical therapy.[9] Historically, the prognosis has been dismal, with a median survival of 1 month without treatment, 4-6 months with adjuvant RT, and 7-8 months with adjuvant RT, modern systemic therapy (chemotherapy, targeted therapy), and supportive care.[9–11] In view of this, other modalities of radiation delivery have been investigated for BrMs, including IORT. In fact, IORT has been used for BrMs since the 1980s, but the techniques and protocols varied widely,[12,13] including electron IORT, high-dose-rate IORT, and low-energy or low-kilovolt (kV) IORT.[14] However, with the development of low-kV IORT and its uniform devices in the last two decades, it became possible to compare techniques, protocols, and outcomes.[15]

In this paper, we performed a systematic review to determine the treatment protocols and outcomes of patients with BrMs who were treated with IORT, focusing on studies that utilized low-kV IORT. This type of IORT is the one most commonly used in modern times, due to the rapid dose fall-off resulting in less radiation damage to the brain adjacent to the target.[6] It also does not require radiation shielding.[14] Moreover, the uniformity of the devices that deliver low-kV IORT afford some degree of comparison between studies.

Methods

We performed our systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Supplemental material).

Criteria for Considering Studies for Review

This review included studies that investigated the safety and efficacy of IORT for BrMs using a low-kV device. Only low-kV IORT was included because it is currently the one most widely used, and because its uniform devices allow comparison between studies. We have excluded studies where radiation sources were implanted in the tumor bed, since this is defined as interstitial brachytherapy rather than IORT.[15] We have also excluded studies that utilized electron beam IORT, as this has fallen out of favor due to logistics and sterility concerns.[16] Older studies that utilized high-dose-rate IORT were also excluded.

The study types considered were case series, retrospective cohort, case-control, and prospective clinical trials. The relevant outcomes included complications, toxicities, progression-free survival (PFS), and overall survival (OS). Only articles written in English were included.

Search Methods for Identification of Studies and Selection of Studies

Major scientific databases, namely Medline by Pubmed, CENTRAL by Cochrane, Scopus, EBSCOhost, and ClinicalTrials.gov were searched from inception until March 2021. Search strategies (detailed in Appendix) were developed and the following search strategy was used ["Intraoperative radiotherapy" or "intraoperative radiation therapy" or "intraoperative radiation" or "intraoperative photon" or "intraoperative electron" or "stereotactic interstitial radiosurgery" or "interstitial radiotherapy" or "electron IORT" or "IORT" or "IOERT"] AND [(brain or CNS or "central nervous system" or cerebral) and (mets or metasta*) or "metasta* brain tumor" or "metasta* brain neoplas*" or "neoplas* brain metasta*" or "secondary brain neoplas*"]. Handsearching of additional studies was performed by going through the references of included studies and relevant reviews.

Two study authors (JSGP and EMDC) independently searched the above databases to identify relevant articles using the search strategies developed. After duplicates were removed, the titles and abstracts of the remaining studies were assessed using predetermined screening criteria. Full-text articles meeting the criteria were retrieved and evaluated using predetermined eligibility criteria. Disagreements were solved with the contribution of two other investigators (ADY and KHDI) and via consensus. Finally, studies that satisfied the eligibility criteria were included in the qualitative analyses.

Data Collection and Analysis

Data from the included studies were extracted using standardized tables. The following information were collected: title, citation, setting, design, duration, and total population of patients in the study. Outcome data included IORT-related complications, time to progression, and survival. Mean, median, and percentages were used to summarize data.

Results

Literature Search

A total of 162 studies were identified from the electronic database search. After deduplication, 128 articles remained. We excluded 118 studies after assessing titles and abstracts, and an additional 5 articles after assessing full texts. Excluded studies were mainly physiologic laboratory studies, animal studies, and clinical studies that did not ful-

fill the inclusion criteria. Finally, 5 articles were subjected to eligibility criteria (Fig. 1).[17–21]

Study Characteristics, Descriptions, and Outcomes

Three retrospective cohort and two prospective studies were included in this review. The indication for surgery was left to the discretion of the neurosurgical team and followed standard-of-care practices during the time of publication of the studies. A total of 179 patients with BrM who underwent IORT were included in the 5 studies. The age ranged from 58 to 67 years old (mean 60.4), and 43% were women. The most common etiology of brain metastases were lung, melanoma, breast, and renal cancer. Two studies included only patients with single BrMs[18,19] while 3 studies included patients with multiple BrMs but did not specify the breakdown.[17,20,21] The size of the lesions ranged from 1.2 to 4.4 cm in diameter in 3 of the studies[20-22] but was not reported in the others. Only a tumor biopsy was performed in the two earlier studies,[17,18] while a maximal safe tumor resection was performed in the later 3 studies.[19–21]

Two types of low-kV IORT devices were used: the Photon Radiosurgery System (PRS, Photoelectron Corp., Inc., Lexington, MA, USA) and the INTRABEAM (Carl Zeiss Meditec AG, Oberkochen, Germany), which is a newer iteration of the PRS system and also includes the latter among its components.[22] The two earlier studies used the PRS[17,18] while the three most recent studies used the INTRABEAM system.[19–21] The radiation doses ranged from 10-20 Gy in the PRS studies,[17,18] and 14-30 Gy in the INTRABEAM.[19–21] The treatment duration ranged from 3.7-75 minutes for PRS and 8.4-25 minutes for INTRABEAM.[19-21,23] All the patients from the PRS group also underwent adjuvant WBRT.[17,18]

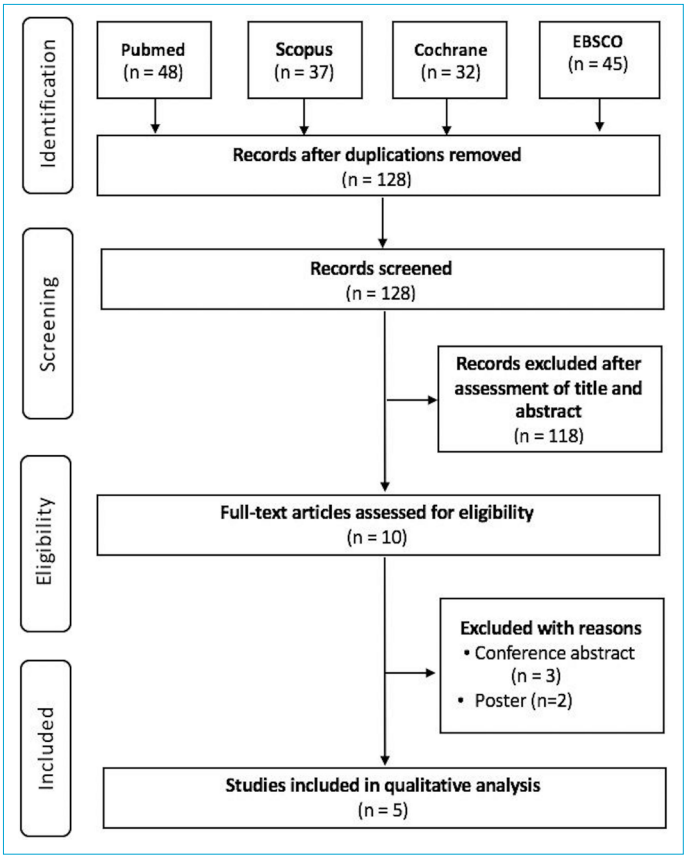

Figure 1. PRISMA Diagram.

In the PRS group (n=95), the follow-up ranged from 5 days to 94 months, with a median of 5.8 months. Radiation necrosis was seen in 5.4% of patients, and other complications included seizures, transient neurologic deficits, post-operative hemorrhage, lesion edema, and leukoencephalopathy. One study[18] reported RTOG graded complications[23] but did not specify details. Local recurrence was seen in 19-77%[17,18] and distal progression in 82%,[16] and the mean time to progression was 4.7 to 7.3 months.[18] Salvage therapy in the form of WBRT, SRS, resection of tumor or radiation necrosis, cyst aspiration, and chemotherapy were instituted for the patients with tumor progression.[17,18] The 6- and 12-month OS were 60-63% and 34-34.3%, respectively.[17,18]

For the INTRABEAM group (n=84), the median follow-up for two of the studies was 6.7 months,[20,21] while one study followed up their patients until mortality.17 The complications reported were radiation necrosis in 0-7%[19–21] and hematoma in 4%.[19] Local recurrence and distal progression were seen in 11-30% and 0-42%, respectively,[19–21] and the mean time to progression was 8.8 to 16.6 months.[19–21] Salvage therapy included WBRT, SRS, EBRT, and resection of tumor recurrence or radiation necrosis.[19–21] The OS was reported as 86% at 6.2 months[18] and 73% at 12 months.[19] A summary of the studies included in the review can be seen in Table 1.

Discussion

IORT for BrMs has been investigated since the 1980s.[12] Most of the early series were from Japan, and involved mixed populations of patients with malignant brain tumors.[24–26] Until recently, the methods and devices used for IORT on BrMs varied, and no consensus was formed.[7, 15] When uniform devices became available, particularly with the advent of low-kV IORT, it became possible to compare techniques, protocols, and outcomes.[17,18,27] In addition, low-kV IORT is characterized by a rapid dose fall-off resulting in less damage to adjacent normal tissue, improving the safety of the procedure.[1–3] In this paper, we reviewed the efficacy and safety profile of low-kV IORT for BrMs.

Technique and Dose of IORT for BrMs

Two types of low-kV IORT devices were used: the PRS and

Table 1. Summary of included studies in the review

	Curry[17] 2005	Pantazis[18] 2009	Weil[19] 2015	Vargo[20] 2018	Cifarelli[21] 2019
Country	USA	Germany	USA	Germany, USA	Germany, USA
Study design	Retrospective cohort	Prospective	Prospective	Retrospective cohort	Retrospective cohort
Sample size	60	35	23	7	54
Mean age	58	59	61.2	60	64
% Female	42%	31%	44%	NR	56%
Tumor type	Lung 55%, melanoma 25%, renal 8%, esophageal 3%, breast 3%, colon 2%, Merkle cell 2%, MFH 2%	NSCLC 57%, renal 11%, SCL 3%, melanoma 3%, breast 3%, ovarian 3%, CRC 3%, testicular 3%	NSCLC 30%, breast 26%, renal 9%, bladder 9%, melanoma 9%, leiomyosarcoma 4%, prostate 4%, esophageal 4%, CRC 4%	NSCLC 71%, endometrial CA NR	NSCLC 43%, breast 15%, melanoma 15%, renal 4%, GI 7%, gynecologic 4%, other 9%
Surgery done	Biopsy	Biopsy	Resection	Resection	Resection
IORT Details					
Type	Photon Radiosurgery System	Photon Radiosurgery System	Zeiss INTRA BEAM	Zeiss INTRA BEAM	Zeiss INTRA BEAM
Dose (Gy)	10-20 (mean 16)	10-20 (mean 18)	14	30	20-30 (median 30)
Delivery time (minutes)	3.7-75 (mean 19.4)	4.4-28.7 (mean 14.2)	8.4–25 (mean 15.9)	NR	12.1-22.3 (mean 16.8)
Outcomes					
Median KPS					
Pre-treatment	90	80	80	NR	NR
Post-treatment	80	70	90	NR	NR
Radiation necrosis	5%	5.7%	1.3%	0	7%
Seizures	7%	11%	NR	NR	NR
Transient neurologic deficits	5%	NR	NR	NR	NR
Hemorrhage	3%	11%	4%	NR	NR
Lesion edema	0	29%	NR	NR	NR
Leukoencephalopathy	0	6%	NR	NR	NR
Local control	81%	82.3%	69.6%	86%	88%
Progression					
Local	19%	36% at 6 mos, 77% at 12 mos, 33% at 24 mos 82%	30%	14%	11% at 12 mos
Distal	NR		22%	0	42% at12 mos
Mean time to progression (months)					
Local	NR	7.3	9	8.8	NR
Distal	NR	4.7	16.6	NR	NR
Salvage therapy					
WBRT	100%	100%	26%	NR	2%
SRS	-	23%	30%		2%
EBRT	-	-	4%		-
Resection of recurrence	7%	6%	9%		6%
Resection of RN	5%	-	9%		-
Re-biopsy	2%	-	-		-
Stereotactic cyst aspiration	-	6%	-		-
Chemotherapy	-	3%	-		-

Table 1. CONT.

	Curry[17] 2005	Pantazis[18] 2009	Weil[19] 2015	Vargo[20] 2018	Cifarelli[21] 2019
Overall survival	63% at 6 mos, 50% at 8 mos, 34% at 12 mos	60% at 6 mos, 34.3% at 12 mos	36 mos (median)	86% at 6.2 mos	73% at 12 mos
Follow-up	5 days to 31 mos (median 6 mos)	10 days to 94.2 mos (median 5.6 mos)	NR*	median 6.2 mos	3.4 to 15.3 mos (median 7.2 mos)

*follow-up until death; CRC: colorectal; EBRT: external beam radiotherapy; GI: gastrointestinal; KPS: Karnofsky Performance Status; MFH: malignant fibrous histiocytoma; MOS: months; NR: not reported; NSCLC: Non-small cell lung cancer; RN: radiation necrosis; RT radiation therapy; SLC: small cell lung; CA, SRS: stereotactic radiosurgery; WBRT; whole brain radiotherapy.

the INTRABEAM. In brief, the PRS is a miniature portable x-ray device that has a cylindrical probe as an applicator.[15] It is used during tumor biopsy of BrMs, wherein the PRS is applied through the biopsy tract and the radiation dose is given.[17,18,28] The INTRABEAM is a device which incorporates a PRS system into a larger applicator and has a control console.[22] The applicator used in brain IORT is spherical in shape, which allows it to be placed inside tumor resection cavities rather than biopsy tracts.[19,21,22] Both these systems use holders to keep the device in place while administering the radiation dose.[17,19]

In the two studies that utilized PRS for BrMs, only a stereotactic tumor biopsy was performed rather than a resection, followed by IORT using doses ranging from 10-20 Gy (mean 16 and 17.3 Gy).[17,18] Curry et al. used 18 Gy on lesions 2 cm or less and 15 Gy on lesions greater than 2 cm, with a 2 mm margin beyond the tumor in both cases.[17] Meanwhile, Pantazis et al. gave a dose of 18 Gy to 32 patients and 15 Gy to 3.[18] These doses were obtained from previous pioneering work using PRS,[28,29] and were comparable to the doses given during SRS, wherein the maximum tolerated doses for lesions <2, 2.1 to 3, and 3.1 to 4 cm were 24, 18, and 15 Gy, respectively.[30] The rate of dose decline in PRS is 1/r3 which results in a 30% dose reduction per millimeter.[31] This creates a steep dose falloff and allows the treatment of lesions greater than 3 cm.[17]

In the INTRABEAM group, surgical resection of the BrM was performed, followed by IORT using 14 to 30 Gy.[19–21] In their series, Weil and colleagues reported that 14 Gy may not be sufficient, since their series exhibited a local recurrence rate of 30%.[19] Building on this work, the studies by Vargo and Cifarelli used higher doses of 20-30 Gy.[18-19] This was also recommended by Giordano et al., who reported that a radiation dose as high as 40 Gy (range 20-40 Gy) was safe and effective during IORT for glioblastoma.[32,33]

The use of a higher dose in IORT is radiobiologically favorable since it creates more lethal DNA lesions in tumor cells.[34] It would also result in a higher dose in the adjacent tissue which may harbor microscopic residual disease.[20,22] However, high radiation doses pose a risk to normal brain tissue, but the steep dose falloff of IORT mitigates this risk.[1] The main organs at risk in BrM surgery are the adjacent cortex, with a dose restriction of 10 Gy for less than 10 cc of brain, as well as the optic apparatus and brainstem if they are in close proximity, with dose restrictions of 10-12 Gy.[35] The proximity to the brainstem may be a reason why posterior fossa tumors were excluded in most of the studies in the review,[18,19,21] and constituted only the minority in the few series where they are included.[17,20]

The duration of treatment in IORT ranged from 3.7 to 75 minutes (mean 16.6 minutes), which was comparable to other RT modalities with intraoperative applications, such as brachytherapy and linear accelerator (LINAC) EBRT.[17–21] However, the additional surgery for removal of implanted material in brachytherapy and the transport time to a LINAC suite increased the treatment time and risk.[36,37]

Outcomes of IORT Studies on BrMs

The most frequently reported complication was radiation necrosis, which occurred in 0-7% of patients and was reported in 4 of the 5 studies.[17–21] This was comparable to the incidence of radiation necrosis seen in WBRT and SRS for BrMs.[38–40] Other complications included seizures, edema, and neurologic deficits,[17–19] which makes it difficult to determine if the complication was due to the surgery or the IORT. Direct local radiation effects were minimal, since the applicator was in close proximity to the target tissue and because it was possible to retract the skin and normal tissues in real time during the procedure.[1,6] No IORT-related mortalities were reported.

Functional outcomes such as KPS were also assessed. The post-treatment KPS ranged from 70 to 90,[17–19] which was favorable compared to WBRT.[41] This was likely due to the use of a low-kV machine whose radiation dose coverage is

limited to a short distance from the applicator, sparing adjacent normal tissue.[22,42]

Local recurrence was reported in 11-77%, and distal progression in 0-82%. All the studies except one administered IORT to patients with both solitary and multiple BrMs, and the broad range of the recurrence rate reflected the heterogeneity of the treatment population. Since IORT is a form of local therapy, distal disease progression is not the main target and can be expected as part of the natural history of the disease.[1,43] The mean time to progression improved upon the natural history of BrMs,[43] but this effect cannot be attributed to IORT alone since patients also underwent surgery and adjuvant therapy. Salvage therapy was instituted upon tumor recurrence or progression, according to the standard of care.[17–21]

The reported survival rates in the reviewed studies varied considerably, with a range of a few months to 5 years.[17–21] In comparison, the reported median PFS and OS in adjuvant WBRT, EBRT, and SRS studies were 4.6, 11.4, and 7.6 months, and 10.9, 11.1, and 18 months, respectively.[9,44,45] The survival rates of the patients who underwent IORT with PRS (34-34.3% at 12 months)[17,18] differed from those who had INTRABEAM treatment (73% at 12 months).[19] This may be attributed to the surgical strategy employed, wherein the tumors in the PRS group were biopsied and the ones in the INTRABEAM group were excised.[17,21] Two of the studies found that the extent of resection was associated with improved survival rates,[19,21] consistent with the findings of landmark studies on BrMs.[11]

Future Directions

The dearth of published literature on IORT for BrMs reflects the novelty of the technology as well as the lack of experience regarding its use. Large, prospective, multicenter trials would be needed to definitively determine the efficacy and safety of IORT for BrMs. At present, there are four ongoing studies on IORT for BrMs listed in a clinical trials website (clinicaltrials.gov), and one group of researchers have just presented the initial results of their prospective study on 30 Gy IORT in resected BrMs (INTRAMET).[46]

Limitations

Our study has several limitations. First, we were constrained by the inherent limitations of a systematic review. Second, we only included research studies using low-kV IORT. Third, the sample size of the included studies were small. Fourth, there was a great deal of heterogeneity in the study population (different cancer types, single versus multiple metastases), surgical intervention (biopsy versus resection), IORT treatment details (equipment, dose), use of adjuvant treatment in addition to IORT, length of follow-up, and methods of reporting the outcome, which made it difficult to compare the results with other studies. Fifth, it was difficult to determine if some of the complications were due to the surgery or the IORT, confounding the safety evaluation.

Conclusion

The results of the systematic review on the efficacy and safety of IORT on BrMs are inconclusive, due to the heterogeneity of the study population and treatment protocols, as well as the presence of confounding factors. Larger prospective studies are needed to determine the optimal dose, efficacy, and safety of IORT for BrMs.

Disclosures

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Supplemental Material A. PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Title page
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Page 1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Page 3
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Page 3
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	N/A
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	Page 4
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Page 5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Page 1, Supplement B
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Page 4
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Page 4
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	Page 5
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Page 5
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	Page 5
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I2) for each meta-analysis.	N/A
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	Page 11
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	N/A
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Page 6
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Page 6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	N/A
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	N/A
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	N/A
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	N/A
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	N/A
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	Page 8-11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	Page 11

Supplemental Material A. CONT.

Section/topic	#	Checklist item	Reported on page #
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	Page 8-11
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	Page 12

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(7): e1000097. doi:10.1371/journal.pmed1000097

For more information, visit: www.prisma-statement.org.

Supplemental Material B. Search strategy used in identifying articles from major scientific databases

Table 1. Search terms and items found in MEDLINE by Pubmed

Search Terms	Items Found
1. "Intraoperative radiotherapy" or "intraoperative radiation therapy" or "intraoperative radiation" or "intraoperative photon" or "intraoperative electron" or "intraoperative brachytherapy" or "stereotactic interstitial radiosurgery" or "interstitial radiotherapy" or "electron IORT" or "IORT" or "IOERT"	4.218
2. (brain or CNS or "central nervous system" or cerebral) and (mets or metasta*) or "metasta* brain tumor" or "metasta* brain neoplas*" or "neoplas* brain metasta*" or "secondary brain neoplas*" or "Brain Neoplasms/secondary"[Mesh]	43.205
3. #1 and #2	48

Table 2. Search terms and items found in Scopus

Search Terms	Items Found
1. "Intraoperative radiotherapy" or "intraoperative radiation therapy" or "intraoperative radiation" or "intraoperative photon" or "intraoperative electron" or "intraoperative brachytherapy" or "stereotactic interstitial radiosurgery" or "interstitial radiotherapy" or "IORT"	13.262
2. (brain or CNS or "central nervous system" or cerebral) and (mets or metasta*) or "metasta* brain tumor" or "metasta* brain neoplas*" or "neoplas* brain metasta*" or "secondary brain neoplas*"	371.501
3. "Case series" or "prospective cohort" or "retrospective cohort"	869.042
4. #1 and #2 and #6	126
5. Limit Document Type to Article	37

Table 3. Search terms and items found in Cochrane

Search Terms	Items Found
1. "Intraoperative radiotherapy" or "intraoperative radiation therapy" or "intraoperative radiation" or "intraoperative photon" or "intraoperative electron" or "intraoperative brachytherapy" or "stereotactic interstitial radiosurgery" or "interstitial radiotherapy" or "IORT"	1.468
2. (brain or CNS or "central nervous system" or cerebral) and (mets or metasta*) or "metasta* brain tumor" or "metasta* brain neoplas*" or "neoplas* brain metasta*" or "secondary brain neoplas*"	4.793
3. #1 and #2	32

Table 4. Search terms and items found in EBSCOHOST

Search Terms	Items Found
1. "Intraoperative radiotherapy" or "intraoperative radiation therapy" or "intraoperative radiation" or "intraoperative photon" or "intraoperative electron" or "intraoperative brachytherapy" or "stereotactic interstitial radiosurgery" or "interstitial radiotherapy" or "IORT"	7.580
2. (brain or CNS or "central nervous system" or cerebral) and (mets or metasta*) or "metasta* brain tumor" or "metasta* brain neoplas*" or "neoplas* brain metasta*" or "secondary brain neoplas*"	110.269
3. #1 and #2	66

Table 5. Search terms and items found in ClinicalTrials.gov

Search Terms	Items Found
1. ["Intraoperative radiotherapy" or "intraoperative radiation therapy" or "intraoperative radiation" or IORT] and ["brain metastases" or "metastatic brain tumor" or "secondary brain neoplasm"]	0