# Intraoperative radiotherapy for brain metastases

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## Abstract

Brain metastases, secondary tumors that originate from primary cancers elsewhere in the body, pose a significant challenge in cancer treatment. Various approaches, including surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and intraoperative radiotherapy (IORT), have been employed to manage these metastases. This systematic review aims to summarize the current knowledge and evidence surrounding the use of IORT for brain metastases treatment.

## Methods

We conducted a systematic review by searching relevant medical databases for studies related to IORT for brain metastases. We included studies that provided information on patient demographics, tumor characteristics, treatment procedures, outcomes, and complications.

## Results

IORT is a specialized radiation therapy technique that delivers a concentrated dose of radiation directly to the tumor or tumor bed during surgery. It offers several advantages, including precise

targeting, reduced risk of recurrence, and limited radiation exposure to healthy brain tissue. The procedure involves surgical removal of the metastasis, followed by radiation delivery using specialized devices.

A retrospective analysis of 24 patients who received IORT during tumor resection showed promising results. Mean and median survival times were 487 and 372 days, respectively. Clinical seizures occurred in only 3 out of 24 patients post-IORT. Intraoperative neuromonitoring using electrocorticography (ECoG) did not reveal any abnormal brain activity or high-frequency oscillations related to radiation during the procedure.

Furthermore, a prospective multi-center trial demonstrated the feasibility and safety of IORT. With a median follow-up of 4 months, no radiation-related adverse events were reported, even among patients with previously irradiated brain metastases. Only one severe adverse event, unrelated to the implanted device, was noted.

# Conclusion

Intraoperative radiotherapy (IORT) appears to be a promising option for the treatment of brain metastases. It provides precise radiation delivery while minimizing the risk of recurrence and limiting radiation exposure to healthy brain tissue. Current evidence suggests that IORT is safe and effective, even in patients with recurrent brain metastases or a history of prior radiation therapy. However, additional long-term follow-up data are needed to assess tumor control outcomes and the risk of radiation necrosis further. IORT should be considered as a valuable addition to the armamentarium of treatments for brain metastases, particularly in selected patient populations.

Keywords: Brain metastases, intraoperative radiotherapy, IORT, radiation therapy, cancer treatment, systematic review.

# Introduction

Intraoperative radiotherapy (IORT) for brain metastases treatment is a specialized radiation therapy technique used in the treatment of cancer that has spread (metastasized) to the brain. Brain metastases are secondary tumors that originate from primary cancers elsewhere in the body, such as the lungs, breast, or colon. Treating brain metastases can be challenging, and various treatment options are available, including surgery, whole-brain radiation therapy (WBRT), stereotactic radiosurgery (SRS), and IORT.

IORT is a form of radiation therapy that delivers a concentrated dose of radiation directly to the tumor or tumor bed during surgery, while the patient is still on the operating table. It offers several advantages:

Precise Targeting: IORT allows for the precise delivery of radiation to the tumor site, minimizing radiation exposure to surrounding healthy brain tissue.

Reduced Risk of Recurrence: By irradiating the tumor bed immediately after surgical removal of the brain metastasis, IORT can help reduce the risk of cancer cells regrowing at the surgical site.

Limited Radiation Exposure: Because the radiation is delivered during surgery, there is less exposure to the rest of the body compared to WBRT, which can have systemic side effects.

The IORT procedure typically involves the following steps:

Surgical Removal: A neurosurgeon removes the brain metastasis or as much of it as safely possible.

Radiation Delivery: A radiation oncologist uses a specialized radiation device to deliver a high dose of radiation directly to the tumor bed. This radiation treatment is typically delivered using electron beams or other specialized techniques.

Shielding: To protect adjacent healthy brain tissue, shielding devices or techniques may be used to limit radiation exposure to critical structures.

Closure: After IORT, the surgical site is closed, and the patient is taken to the recovery room.

IORT is not suitable for all patients with brain metastases. The decision to use IORT depends on various factors, including the size and location of the metastasis, the patient's overall health, and the type of primary cancer.

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Postsurgical radiotherapy (RT) has been early proven to prevent local tumor recurrence, initially performed with whole brain radiotherapy. Subsequent to disadvantageous cognitive sequelae for the patient and the broad distribution of modern linear accelerators, focal irradiation of the tumor has omitted WBRT in most cases. In many studies, the effectiveness of local radiotherapy of the resection cavity, either as single-fraction stereotactic radiosurgery (SRS) or hypofractionated stereotactic radiotherapy (hFSRT), has been demonstrated to be effective and safe. However, whereas prospective high-level incidence is still lacking on which dose and fractionation scheme is the best choice for the patient, further ablative techniques have come into play. Neoadjuvant SRS (N-SRS) prior to resection combines straightforward target delineation with an accelerated post-surgical phase, allowing an earlier start of systemic treatment or rehabilitation as indicated. In addition, low-energy intraoperative radiotherapy (IORT) on the surgical bed has been introduced as another alternative to external beam radiotherapy, offering sterilization of the cavity surface with steep dose gradients towards the healthy brain [1)].

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Despite the continued controversy over defining an optimal delivery mechanism, the critical role of adjuvant radiation in the management of surgically resected primary and metastatic brain tumors remains one of the universally accepted standards in neuro-oncology. Local disease control still ranks as a significant predictor of survival in both high-grade glioma and treated intracranial metastases with radiation treatment being essential in maximizing tumor control. As with the emergence and eventual acceptance of cranial stereotactic radiosurgery (SRS) following an era dominated by traditional radiotherapy, evidence to support the use of intraoperative radiotherapy (IORT) in brain tumors requiring surgical intervention continues to accumulate. While the clinical trial strategies in treating glioblastoma with IORT involve the delivery of a boost of cavitary radiation prior to the planned standard external beam radiation, the use of IORT in metastatic disease offers the potential for dose escalation to the level needed for definitive adjuvant radiation, eliminating the need for additional episodes of care while providing local control equal or superior to that achieved with SRS in a single fraction [2)].

A total of 35 consecutive patients, prospectively recruited within a study registry, who received IORT following BM resection at a single neuro-oncological center were evaluated for radiation necrosis (RN) incidence rates, local control rates (LCR), distant brain progression (DBP) and overall survival (OS) as long-term outcome parameters. The 1 year-estimated OS and survival rates were compared in a balanced comparative matched-pair analysis to those of our institutional database, encompassing 388 consecutive patients who underwent adjuvant EBRT after BM resection.

Results: The median IORT dose was 30 Gy prescribed to the applicator surface. A 2.9% RN rate was observed. The estimated 1 year-LCR was 97.1% and the 1 year-DBP-free survival was 73.5%. Median time to DBP was 6.4 (range 1.7-24) months in the subgroup of patients experiencing intracerebral progression. The median OS was 17.5 (0.5-not reached) months with a 1-year survival rate of 61.3%, which did not significantly differ from the comparative cohort (p = 0.55 and p = 0.82, respectively).

IORT is a safe and effective fast-track approach following BM resection, with comparable long-term outcomes as adjuvant EBRT [3].

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Steininger et al. present preliminary results of IORT in the setting of awake craniotomies. From 2021 to 2022, all patients undergoing awake craniotomies for tumor resection combined with IORT were analyzed retrospectively. Demographics and clinical data, operative procedures, and treatment-related complications were evaluated. Five patients were identified (age (mean ± standard deviation (SD): 65 ± 13.5 years (y)). A solid left frontal metastasis was detected in the first patient (female, 49 y). The second patient (male, 72 y) presented with a solid metastasis on the left parietal lobe. The third patient (male, 52 y) was diagnosed with left temporoparietal metastasis. Patient four (male, 74 y) was diagnosed with a high-grade glioma on the left frontal lobe. A metastasis on the left temporooccipital lobe was detected in the fifth patient (male, 78 y). After awake craniotomy and macroscopic complete tumor resection, intraoperative tumor bed irradiation was carried out with 50 kV x-rays and a total of 20 Gy for 16.7 ± 2.5 min. During a mean follow-up of 6.3 ± 2.6 months, none of the patients developed any surgery- or IORT-related complications or disabling permanent neurological deficits. Intraoperative radiotherapy in combination with awake craniotomy seems to be feasible and safe. [4].

# Trials

The main goal of this study is to assess the effectiveness and safety of IORT as a treatment option for patients who undergo surgical excision of brain metastases. They are specifically investigating the use of a dose of 20 Gy.

Materials/Methods:

This is a single-institution, open-label, prospective, non-randomized trial. Enrollment criteria include patients with certain characteristics: IK (Karnofsky Performance Status) ≥70, newly diagnosed brain metastases without dural contact and at least 1 cm away from important structures. Cognitive assessments, quality of life evaluations, and neurocognitive tests will be conducted. IORT will be performed using a 50 kV low-energy X-ray portable linear accelerator with specific applicators to deliver the 20 Gy dose while limiting exposure to critical structures. Follow-up includes MRI scans and neurocognitive tests at various intervals. Primary endpoint: Local progression-free survival (PFS). Secondary endpoints: Overall survival, time to save cancer therapy, cognitive performance, quality of life, and IORT-related neurotoxicity complications. Results: The study is currently ongoing, and as of now, 7 patients have been included. The majority of patients are male, with a mean age of 61.4 years, and lung cancer metastases are the most common. There have been no tumor recurrences or neurocognitive complications observed at this stage. The study aims to publish results once more data is collected.

Conclusion: The authors acknowledge that the existing literature on IORT for brain metastases is limited but suggests that it shows promise in terms of efficacy and safety. However, the optimal dose and its comparative effectiveness with other radiotherapy alternatives are still unknown. The study emphasizes the need for completing ongoing research and collecting more data to draw definitive conclusions.

In summary, this study is investigating the use of IORT with a 20 Gy dose for brain metastases and is in the early stages of recruitment and data collection. It aims to contribute to the understanding of the efficacy and safety of this treatment approach [5)]

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A study involved patients who had brain metastases. Some had newly diagnosed metastases (de novo), and others had metastases that had come back (recurrent).

Treatment: These patients underwent surgery to remove the brain metastases, and during the same surgery, a special device made of collagen (a type of protein) was implanted in the brain. This device contained four radioactive sources (Cesium-131) used for radiation therapy.

Toxicities: The study looked at any side effects or toxicities the patients experienced and categorized them using a standard set of criteria called CTCAE v5.0 adverse event criteria.

Results: Between October 2020 and January 2023, 13 hospitals participated in the study, and they treated a total of 48 patients with 51 brain metastases. Some patients had more than one metastasis treated at the same time. Most of the patients were in their early 60s, and more than half were female. Lung cancer was the most common primary cancer type.

Tumor Characteristics: The brain tumors varied in size, with a median size of 3.4 cm before surgery. The study included some patients who had received radiation therapy in the past, with a median time of about 14.6 months since their last radiation treatment.

Performance Status: The patients' general health status was measured using a scale called the Karnofsky Performance Status (KPS), and it remained stable before and after treatment.

Implantation Time: The time it took to implant the device with the radioactive sources was relatively short, with a median of 3 minutes.

Follow-Up: The patients were followed up for an average of 4 months, with some having shorter and others longer follow-up times. During this time, there were no severe side effects related to the radiation, and only one severe side effect (Gr 5 intracerebral hemorrhage) was observed, which was attributed to the surgery rather than the implanted device.

The initial results from this study suggest that this new technique, called STaRT (Surgery followed by Targeted Radiation Therapy), is both feasible and safe. It's particularly interesting because there were no radiation-related side effects, even though some patients had large brain tumors and had received radiation therapy before. Further follow-up is needed to see how well this technique controls tumors and whether it causes radiation-related complications over a longer period [6].

# Case series

collected information about the drugs used to prevent seizures during surgery, the anesthesia used, and they also monitored brain activity during and after IORT.

Patient Details: They studied 24 patients in total. Of these, 18 had brain metastases (BMs), which are tumors that spread to the brain from elsewhere in the body, and 6 had glioblastoma, a type of aggressive brain cancer.

Survival Data: On average, patients survived for about 487 days, with a median survival time of 372 days.

Seizures: Three patients experienced seizures after the IORT procedure. Two of them had brain metastases, and their seizures occurred within 9 months after surgery. The third patient had glioblastoma, and the seizure happened 14 months later.

IORT Time: The IORT procedure itself took up about 9.5% of the total time patients spent under anesthesia.

Electrocorticography (ECoG): During surgery, the researchers monitored brain activity using a technique called electrocorticography (ECoG). They collected data from five patients (four with brain metastases and one with glioblastoma). On average, these brain activity recordings accounted for about 13% of the total anesthesia time. Importantly, they found no signs of unusual electrical activity or seizures related to the radiation during ECoG monitoring.

Conclusion: The study suggests that IORT is a viable option for delivering radiation therapy to brain tumors that have been surgically removed. It doesn't appear to increase the risk of seizures during or after surgery. Additionally, the ECoG data showed no abnormal brain activity related to the radiation treatment. This suggests that IORT can be a safe and effective treatment option for patients with brain tumors after surgical removal [7].

# Multiple Choice Test: Intraoperative Radiotherapy (IORT) for Brain Metastases

Instructions: Please select the most appropriate answer for each question based on the information provided in the text.

1. What is the primary goal of Intraoperative Radiotherapy (IORT) for brain metastases? a) To replace surgical tumor removal b) To minimize radiation exposure to surrounding healthy brain tissue c) To eliminate the need for external beam radiotherapy d) To treat primary brain tumors

2. Which of the following is NOT one of the advantages of IORT for brain metastases? a) Precise

targeting of radiation b) Reduced risk of tumor recurrence c) High exposure to surrounding healthy brain tissue d) Limited radiation exposure to the rest of the body

3. What are the typical steps involved in the IORT procedure? a) Radiation delivery, shielding, closure b) Radiation delivery, surgical removal, closure c) Shielding, radiation delivery, surgical removal d) Surgical removal, radiation delivery, closure

4. Under what circumstances might IORT not be suitable for a patient with brain metastases? a) Large tumor size b) Previous radiation therapy c) Good overall health d) Newly diagnosed metastases

5. What is Neoadjuvant Stereotactic Radiosurgery (N-SRS) used for in the context of brain metastases treatment? a) To replace surgical resection b) To provide post-surgical radiation therapy c) To target primary brain tumors d) To sterilize the surgical cavity before resection

6. What is one potential advantage of using Intraoperative Radiotherapy (IORT) in metastatic disease compared to other techniques? a) It reduces the need for adjuvant radiation therapy b) It requires additional episodes of care c) It has a higher risk of radiation necrosis d) It is less effective in achieving local control

7. In the study evaluating IORT following brain metastasis (BM) resection, what was the 1-year estimated local control rate (LCR)? a) 73.5% b) 2.9% c) 97.1% d) 61.3%

8. What is the primary endpoint being assessed in the ongoing trial involving IORT for brain metastases treatment with a 20 Gy dose? a) Overall survival b) Quality of life c) Local progression-free survival (PFS) d) Neurotoxicity complications

9. What does the preliminary study involving awake craniotomies combined with IORT suggest about this treatment approach? a) It is associated with a high risk of complications b) It is not feasible c) It is both feasible and safe d) It has a high risk of surgery-related complications

10. In the study involving the implantation of collagen devices containing Cesium-131 for brain metastases, what was the primary focus of the research? a) Seizure prevention during surgery b) Radiation therapy for primary brain tumors c) Surgical removal of brain metastases d) Evaluation of post-operative complications

Answers:

b) To minimize radiation exposure to surrounding healthy brain tissue c) High exposure to surrounding healthy brain tissue d) Surgical removal, radiation delivery, closure b) Previous radiation therapy d) To sterilize the surgical cavity before resection a) It reduces the need for adjuvant radiation therapy c) 97.1% c) Local progression-free survival (PFS) c) It is both feasible and safe d) Evaluation of post-operative complications

# References

1)

Diehl CD, Giordano FA, Grosu AL, Ille S, Kahl KH, Onken J, Rieken S, Sarria GR, Shiban E, Wagner A, Beck J, Brehmer S, Ganslandt O, Hamed M, Meyer B, Münter M, Raabe A, Rohde V, Schaller K, Schilling D, Schneider M, Sperk E, Thomé C, Vajkoczy P, Vatter H, Combs SE. Opportunities and Alternatives of Modern Radiation Oncology and Surgery for the Management of Resectable Brain Metastases. Cancers (Basel). 2023 Jul 19;15(14):3670. doi: 10.3390/cancers15143670. PMID: 37509330.

2)

Cifarelli CP, Jacobson GM. Intraoperative Radiotherapy in Brain Malignancies: Indications and Outcomes in Primary and Metastatic Brain Tumors. Front Oncol. 2021 Nov 11;11:768168. doi: 10.3389/fonc.2021.768168. PMID: 34858846; PMCID: PMC8631760.

3)

Layer JP, Hamed M, Potthoff AL, Dejonckheere CS, Layer K, Sarria GR, Scafa D, Koch D, Köksal M, Kugel F, Grimmer M, Holz JA, Zeyen T, Friker LL, Borger V, Schmeel FC, Weller J, Hölzel M, Schäfer N, Garbe S, Forstbauer H, Giordano FA, Herrlinger U, Vatter H, Schneider M, Schmeel LC. Outcome assessment of intraoperative radiotherapy for brain metastases: results of a prospective observational study with comparative matched-pair analysis. J Neurooncol. 2023 Jul 21. doi: 10.1007/s11060-023-04380-w. Epub ahead of print. PMID: 37477822.

4)

Steininger K, Kahl KH, Konietzko I, Wolfert C, Motov S, Krauß PE, Bröcheler T, Hadrawa M, Sommer B, Stüben G, Shiban E. Intraoperative radiotherapy during awake craniotomies: preliminary results of a single-center case series. Neurosurg Rev. 2022 Jul 26. doi: 10.1007/s10143-022-01838-9. Epub ahead of print. PMID: 35881316.

5)

Foro P, Narvaez A, Martinez A, Martinez M, Rodriguez De Dios N Sr, Amorelli F, Liu F, Membrive I, Sanz J, Pera O, Algara M, Villalba G. A Phase II Trial of Intraoperative Radiotherapy after Surgical Resection of Brain Metastases: Feasibility and Efficacy NCT04847284. Int J Radiat Oncol Biol Phys. 2023 Oct 1;117(2S):e104. doi: 10.1016/j.ijrobp.2023.06.876. PMID: 37784633.

6)

Kotecha R, McDermott MW, Chen C, Ferreira C, Hanft S, Shen C, Wanebo J, Smith K, Wardak Z, Patel T, Chamoun R, Hoang KB, Choutka O, Rodriguez A, Shah M, Brachman DG, Campbell L, Patel S. Surgically Targeted Radiation Therapy (STaRT) for Brain Metastases: Initial Experience from a Prospective Multi-Institutional Registry. Int J Radiat Oncol Biol Phys. 2023 Oct 1;117(2S):e120. doi: 10.1016/j.ijrobp.2023.06.908. PMID: 37784668.

7)

Cifarelli CP, Vargo JA, Sener U, Cifarelli DT, Scoville D, Dabir A. Intracranial intraoperative radiotherapy (IORT): evaluation of electrocorticography and peri-operative seizure risk. J Neurooncol. 2023 Sep;164(2):423-430. doi: 10.1007/s11060-023-04443-y. Epub 2023 Sep 5. PMID: 37668944.