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Clinical study

Intraoperative radiotherapy for glioblastoma: A systematic review of techniques and outcomes

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ABSTRACT

Background: Despite multimodality treatment, the prognosis of glioblastoma (GBM) has remained poor. Intraoperative radiation therapy (IORT) offers additional local control by directly applying a radiation source to the resection margin, where most recurrences occur.
Methods: We performed a systematic review on the oncologic outcomes and toxicities of IORT for GBM in the era of modern external beam radiation therapy (EBRT) and chemotherapy with temozolamide.
Results: Four studies representing 123 patients were included. Majority (81%) were newly diagnosed, and gross total resection was reported in 13–80% of cases. IORT modalities included electrons from a linear accelerator (LINAC) and photons from a 50-kV x-ray device. Median doses were from 12.5 to 20 Gy for electron-based studies and 10–25 Gy for photon-based studies. Adjuvant treatment consisted of 46–60 Gy post-operative EBRT in electron-based studies and the Stupp protocol in photon-based studies. Complications included radiation necrosis (2.8–33%), infection, hematoma, perilesional edema, and wound dehiscence. Median time to local recurrence was 9.9–16 months and the reported overall progression-free survival was 11.2–12.2 months. Median overall survival was 13–14.2 months for the electron-based studies and 13.8–18 months for the photon-based studies.
Conclusion: IORT resulted in improved local control and comparable overall survival rates with the Stupp protocol. Although photon-based IORT had better results than electron IORT, this may be due to improvements in other forms of adjuvant treatment rather than the IORT modality itself. The overall effect of IORT on GBM treatment is still inconclusive due to the small number of patients and heterogeneous reporting of data.

1. Introduction

Glioblastoma (GBM) is one of the most common and most aggressive brain tumors, comprising 48% of primary malignant brain tumors and 57% of gliomas [1,2]. Since the initiation of the Stupp protocol in 2005, treatment strategies to combat this disease involve maximal safe surgical resection followed by 60 Gy radiotherapy (RT) with concurrent daily temozolamide (TMZ), followed by TMZ maintenance for a minimum of 6 cycles [3]. Despite this aggressive treatment, prognosis remains poor with a median progression-free survival (PFS) of 6.2–7.5 months and median overall survival (OS) of 14.6–20.5 months [4]. The tumor recurs even after surgical resection and adjuvant treatment, and approximately 85% of recurrences occur near the resection margin [5].

Escalating treatment by increasing chemotherapy with a dose-dense TMZ regimen or adding targeted therapy with bevacizumab, nimotuzumab, or cilengitide did not significantly improve outcomes [4,6–8]. Similarly, escalating radiotherapy to an equivalent dose in 2 Gy fractions ranging from 66 to 126 Gy still resulted in similar PFS and OS rates, often at the cost of increased toxicities [9–14]. In prospective single arm studies, Tsien et al. and Iuchi et al. reported median overall survival of 20.1 months and 20.0 months, respectively. Both studies showed significant neurologic toxicities with higher radiation doses [11,13]. Particu-

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larly challenging to treat are recurrent lesions, for which reirradiation is limited due to increased risk of damaging nearby normal tissues [15].

Intraoperative radiotherapy (IORT), defined as the delivery of precise doses of radiation to the tumor bed during surgery (i.e., immediately following resection), allows the delivery of a higher dose of radiation to the contiguous regions at highest risk of recurrence, while minimizing the dose to the normal brain tissue. IORT may be delivered via low-kV x-rays, electrons, or high-dose rate brachytherapy [16]. The rationale for the use of IORT includes the anatomic advantage of applying the radiation source directly to the resection margin where most recurrences occur, as well as the temporal benefit of decreasing delay between surgery and adjuvant treatment, during which cancer cells may proliferate [17].

To our knowledge, there is no paper that has consolidated the current evidence on the outcomes of IORT using different modalities for GBM, especially in the era of modern external beam radiation therapy (EBRT) and chemotherapy with TMZ. This paper aims to review the oncologic outcomes and toxicities of IORT for GBM in the current era.

2. Methods

We performed a systematic review in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (Supplemental Material A). The included studies assessed the outcomes of GBM patients who underwent resection surgery and IORT. Relevant study types considered were case series, retrospective cohort, case-control, and prospective studies. Relevant outcomes were complications attributed to IORT, PFS, and OS. Only studies written in English were included.

Of note, we included only studies that were published from 2005 onwards as this was when the Stupp protocol was established, giving uniform adjuvant treatment of GBM [3]. Since one of the advantages of IORT is to bypass the residual tumor cell doubling-time that may occur during the delay between surgery and RT, we excluded studies that administered IORT during a second surgery [18,19]. We also excluded studies which left implanted radiation sources or devices as these required a second surgery for removal, which is not the design of the single-surgery set-up of conventional IORT [20].

2.1. Search methods for identification of included studies

We performed a search of the major scientific databases such as Pubmed, Scopus, EBSCOhost, CENTRAL by Cochrane, and clinicaltrials.gov from March 2005 to March 2021. The search strategy employed the use of the search terms [“Intraoperative radiotherapy” or “intraoperative radiation therapy” or “intraoperative radiation” or “intraoperative photon” or “intraoperative electron” “electron IORT” or “photon IORT” or “IORT” or “IOERT”] AND [“glioblastoma” or “GBM” or “glioblastoma multiforme” or “malignant glioma” or “WHO grade IV glioma”]. Handsearching for additional articles was done by reviewing the references of relevant and included studies.

Independent searches of the above databases and identification of relevant articles using the above search strategy were done by two study authors (ADY and JSGP). After duplicates were removed, the titles and abstracts of the remaining articles were assessed using predetermined eligibility criteria. Once the titles and abstracts were screened, the full-text articles meeting the criteria were evaluated. Disagreements were resolved by consensus with two other authors (EMDC and KHDI). Eligible studies that remained after this screening and scrutinization were included in the analyses.

2.2. Data collection and analysis

The data extracted from the included studies included the setting, design, duration, total number and demographics of the population, and the type of IORT done. Outcome data included IORT-related complications, local recurrence rate, time to progression, and survival rates. Descriptive statistics were used to summarize the data (Table 1).

3. Results

3.1. Literature search

We identified a total of 344 studies from the electronic database search. A total of 303 articles remained upon excluding duplicates. We excluded 288 studies after assessing titles and abstracts. The full-texts of 15 articles were subjected to eligibility criteria. Finally, 4 studies were included in the qualitative analysis. (Fig. 1) [21–24].

3.2. Study characteristics, descriptions, and outcomes

There were 3 retrospective studies [21,22,24] and 1 prospective study [23], representing 123 GBM patients. There was a male predilection (60%), and the patients’ age ranged from 43 to 62 years old. A large majority (81%) of the GBM cases were newly diagnosed, and gross total resection was reported in 13–80% of cases. Two studies reported the O [6]-methylguanine–DNA methyltransferase (MGMT) status, with absence of MGMT hypermethylation found in 39% and 87% of cases [23,24].

Two main modalities of IORT were used: 9–18 MeV electrons from a linear accelerator (LINAC) [21,22] and photons from a 50-kV x-ray device (INTRABEAM, Carl Zeiss, Meditec, Oberkochen, Germany) [23,24]. Median doses were from 12.5 (range 8–20) to 20 (range 15–25) Gy for the studies that used electrons and 10 to 25 Gy for those that used photons. All patients received IORT during the time of resection surgery. The patients who underwent IORT with electrons were transported to the LINAC suite after the tumor was excised, then returned to the operating room (OR) after the IORT procedure. Meanwhile, the ones who underwent photon-based IORT were treated within the OR, with the IORT applied to the surgical field once resection was completed.

Adjuvant treatments consisted of 46 to 60 Gy post-operative EBRT in the earlier studies that used electrons, and the Stupp protocol in the studies that used photons.

The reported complications included infection, hematoma, perilesional edema, wound dehiscence, CSF leak, and intracranial cyst formation. Radiation necrosis ranged from 2.8 to 33%. Three of the studies reported tumor progression or recurrence [21,23,24]. Local recurrence occurred in 13–96% of patients throughout the median follow-up that ranged from 13.8 to 30.4 months. The median times to local recurrence were 9.9–16 months and the reported overall PFS ranged from 11.2 to 12.2 months. The median overall survival rates were 13–14.2 months for the electron-based studies and 13.8–18 months for the photon-based studies. A summary of the included studies can be found in Table 1.

4. Discussion

Despite maximal therapy using surgery with adjuvant RT and TMZ, the prognosis of GBM has remained dismal. Part of this may be due to the fact that most GBM recurrences occur locally, and escalating radiation doses to increase tumor cell kill often led to increased toxicities. IORT offers additional local control by providing direct application of a radiation source to the tumor bed, thus obviating the need to traverse normal tissues. Given

Table 1
Summary of included studies in the review.

	Schueller [21] 2005	Usychin [22] 2013	Giordano [23] 2019	Sarria [24] 2020
Country	Germany	Spain	Germany, USA, Canada	Germany, Peru, China
Study design	Retrospective cohort	Retrospective cohort	Prospective	Retrospective cohort
Sample size	45 GBM (Total 71, including WHO Gr III)	12 GBM (Total 32, including WHO Gr III)	15 GBM	51 GBM
Newly diagnosed GBM	73%	50%	100%	100%
Median age	56	48	62	55
% Female	32%	44%	47%	45%
GTR	80%	NR*	13%	NR
IORT Details				
Type	Electrons: standard electron tube; 9-18 MeV	Electrons: generated by linear accelerator; 12-15 MeV	Photons: 50-kV x-rays	Photons: 50-kV x-rays
Median dose (Gy)	20 (15–25)	12.5 (8–20)	25 (20–40)	10 (10–40)
Median delivery time (minutes)	NR	NR	NR	17 (5–58)
Outcomes				
Median KPS				
Pre-treatment	70 (NR)	NR	80 (50–90)	80 (20–100)
Post-treatment	80 (NR)	NR	NR	NR
Adjuvant treatment	60 Gy postop EBRT, no chemo	46-60 Gy postop EBRT, chemo - NR	60 Gy postop EBRT + concurrent & maintenance TMZ	60 Gy postop EBRT + concurrent & maintenance TMZ
Radiation necrosis	2.8%	9.4%	33%	25.5%
Post-op site Infection	1.4%	3.1%	–	–
Hemorrhage	5.6%	3.1%	–	–
Lesion edema	1.4%	–	–	–
Wound dehiscence	–	–	6.7%	–
CSF leak	–	–	6.7%	–
Intracranial cyst formation	–	–	6.7%	–
Recurrence	96% (24 mos)	NR	13% (time frame NR)	39% (12 mos), 62% (24 mos), 87% (36 mos)
Median time to local recurrence	9.9 mos (NR)	NR	14.3 mos (8.4-20.2)	16 mos (10.2-21.8)
Median progression-free survival	12.2 mos (NR)	NR	11.2 mos (5.4-17)	11.4 mos (7.6-15.2)
Median overall survival	14.2 mos (NR)	13 mos (NR)	16.2 mos (11.1-21.4)	18 mos (14.7-21.3)
Median follow-up	15.2 mos (NR)	30.4 mos (NR)	13.8 mos (4.5-30.7)	18 mos (2-42.4)

*All were reported to have undergone "maximal safe resection".
Abbreviations: EBRT external beam radiotherapy, GBM glioblastoma, Gy gray, KV kilovolt, mos months, MeV megaelectronvolts, NR not reported, TMZ temozolamide, WHO World Health Organization.

these advantages, IORT appears to be a promising addition to the current treatment arsenal against GBM.

4.1. Type, timing, and dose of radiation

There are several methods of delivering IORT: photons, electrons, and brachytherapy [16]. Only the first two were used intraoperatively after tumor excision; hence, they were the ones included in this review.

An advantage of IORT would be the ability to deliver the dose directly to the tumor bed immediately after surgery. Theoretically, IORT would attenuate tumor regrowth after surgery, while awaiting healing and post-operative radiotherapy [25]. However, this is largely a theoretical advantage since there is no scientific proof that IORT can prevent tumor cell regrowth.

Blumenthal et al. did not see a statistically significant difference in OS between >4 and $\leq$4 weeks delay in radiation therapy from the time of operation [26]. Giving radiation immediately after surgery may also trigger accelerated tumor repopulation of glioma stem cells. In Gao et al.'s study, tumors that were irradiated with 3 fractions of 2 Gy had a shorter doubling time of 10 days, compared to 14 days for unirradiated gliomas [27].

The ideal dose for IORT still has to be determined. Pragmatically, the higher the dose, the higher the chance of eliminating residual disease, but this also translates to higher neurologic morbidity. It is difficult to directly compare doses because the target prescription point and mode of delivery were not standardized, with studies prescribing to different doses at different depths from the surface. When comparing different radiation methods, the relative biologic effectiveness (RBE) has to be considered. IORT delivered via low-kV x-rays offers a higher RBE of 1.26 to 1.42, but this decreases significantly beyond a depth of 1.3 cm. This may be a concern with GBM since it has been reported to recur within 2–3 cm of the initial tumor site [28–30].

4.2. Outcomes of GBM IORT studies

The key advantage of photon-based IORT over traditional LINAC is that the former utilizes a portable RT machine inside the OR, making RT possible without leaving the OR suite. This obviates the need for patient transport while the operative site is exposed, as in the case of traditional LINAC machines. The risks of infection and the logistical difficulties of intraoperative patient transport are thus mitigated. In our review, post-operative infection was reported in 1.4–3.1% of cases which used a traditional LINAC [21,22], and zero in the studies that used photon-based IORT [23–25], although wound dehiscence and cerebrospinal fluid leak were encountered in one series [23]. Since IORT is local therapy, it is difficult to distinguish whether the complications were from IORT or the surgical procedure [23,24]. By far, the most commonly reported complications in GBM treatment in recent series were wound breakdown and infection, with rates as high as 59% in some

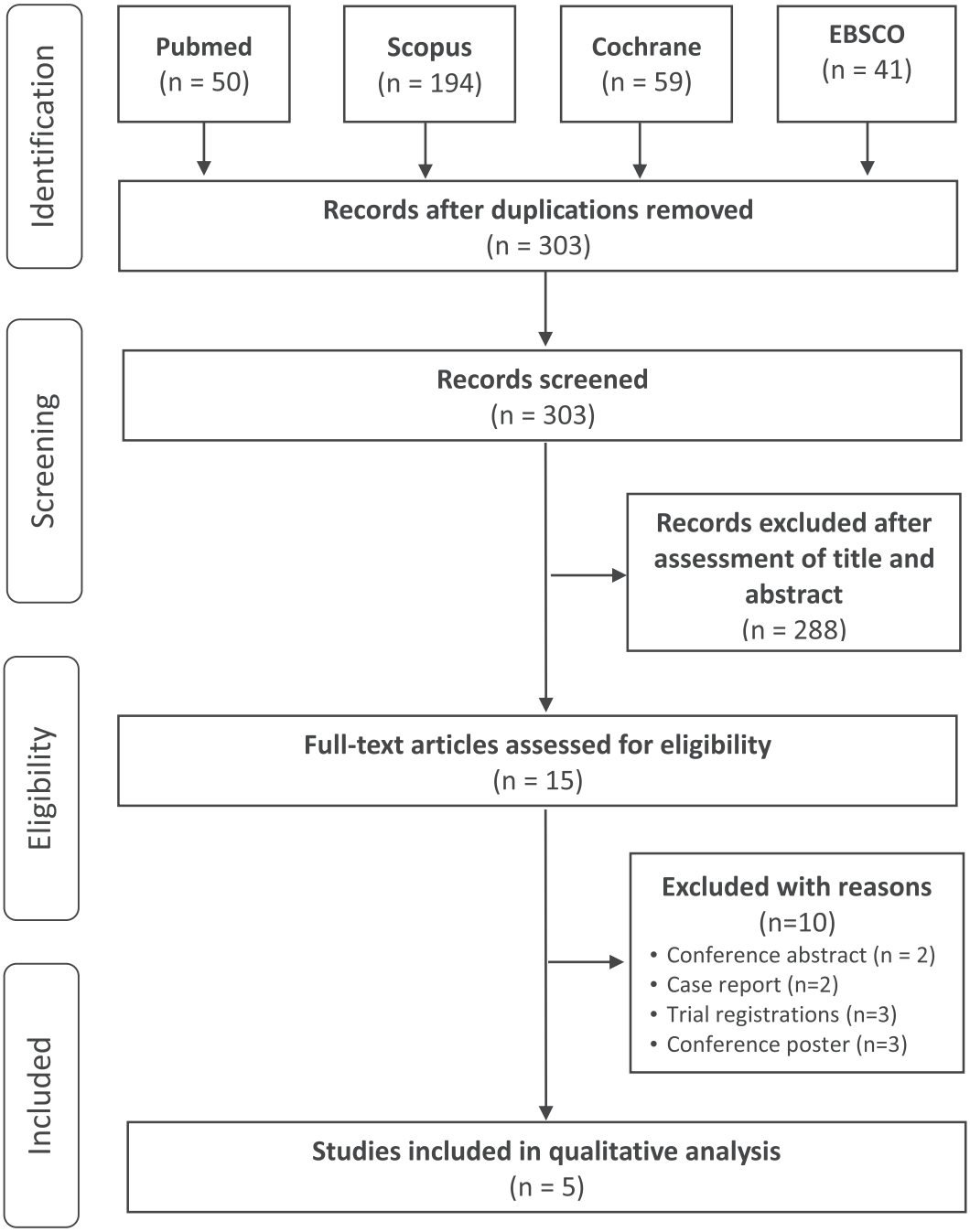

Fig. 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram.

reports [31]. Other complications of GBM treatment included neurologic sequelae such as seizures (41%) and motor deficits (23%) [31,32].

Radiation necrosis (RN) is a unique complication of RT. In our review it occurred in 2.8–33% of IORT cases. The occurrence of RN is directly related to increasing RT doses with observed dose limits of 24–33.3 Gy in studies involving stereotactic radiosurgery [33,34]. The paper of Giordano et al. was a Phase I/II dose-finding study for IORT in GBM using photons, where IORT was given in 20, 30, and 40 Gy fractions [23,24,35]. It was the first dose-escalation study performed that aimed to evaluate the safety and tolerability of IORT when added to standard therapy for GBM [23]. This trial, entitled INTRAGO, was the basis of the 20 to 30-Gy limiting doses employed in subsequent studies and ongoing trials, such as NCT0268560 [33,36]. Hence, compared to the other studies which employed these limits, INTRAGO reported the highest RN rate (33%) in this review [33,36].

Generally, all GBMs will recur locally, given enough time [21,23,24], so the effect of IORT on local recurrence is extremely important. The original article for the Stupp protocol reported a median PFS of 6.9 months (range 5.8–8.2 months), with 73.1% and 89.3% exhibiting progression at 12 and 24 months, respectively [3]. In this review, one study that used conventional LINAC reported a median PFS of 12.2 months [21], while two studies using photon-based IORT reported median PFS of 11.2–11.4 months [23,24]. Reported time to local recurrences ranged from 9.9 to 16 months. In comparison, estimates of PFS in recent studies on GBM ranged from 8.9 to 10.7 months [37,38].

For two of the studies, the median time to recurrence within 1 cm from the cavity was at 14.3 months and 16 months [23,24]. This suggested improved local control within 1 cm from the cavity with IORT since both studies showed more distant progression (>1cm) as the predominant failure pattern [23,24].

Overall survival rates reported in this review were 13–14.2 months for the conventional LINAC studies [21,22] and 16.2–18 months for the photon-based studies [23,24]. More recent survival estimates for treated GBM patients have improved over the years, with a median OS of 15 months (range 11–28 months) [39,40]. The reported OS in the studies included in this review fell within the range, with the photon-based cohorts reporting slightly higher OS than the median [23,24].

Though it may seem that photon-based IORT may have improved time to recurrence and survival rates compared to electron-based IORT, it must be noted that the adjuvant therapies performed during the timeframes of the two modalities differed [21,24]. Since the studies on electron IORT were done much earlier, the adjuvant therapies only consisted of 46–60 Gy EBRT without chemotherapy [21,22]. The more recent studies using photons adopted the standard Stupp protocol (EBRT plus TMZ) [23–24]; thus, the effect of the Stupp protocol cannot be discounted when comparing the two modalities of IORT used in this review.

4.3. IORT and other radiation modalities

Since they are both conformal radiotherapy techniques that are able to deliver steep dose gradients, IORT has been compared to stereotactic radiosurgery (SRS). Matsuo et al. reported that SRS resulted in better tumor control for GBM, and in cases wherein there was residual tumor, SRS techniques also allowed for more meticulous target planning of the irradiation boost [19]. However, in contrast to the retrospective studies it preceded, the Radiation Therapy Oncology Group (RTOG) 93–05 study demonstrated no improvement in outcomes when SRS was given prior to EBRT [41].

The proposed advantage of using IORT to deliver precise doses to the tumor bed is also achievable with less invasive EBRT techniques using flattening filter-free energies and image guidance, such as intensity modulated radiation therapy (IMRT) and image-guided conventional fractionated radiotherapy.

It should also be kept in mind that the use of IORT does not negate the need for the standard 6–7-week regimen of EBRT. The additional dose from IORT may be easier to deliver as a simultaneous integrated boost, especially as this has been shown to result in minimal toxicity [9,11].

4.4. Future directions

Because of the heterogeneity of the current available studies on IORT for GBM, especially with regard to adjuvant therapy, more prospective research studies are needed. There are currently 3 trials listed on clinicaltrials.gov, and some of them use IORT modalities other than conventional LINAC and photon-based IORT. It may also be worthwhile to compare the results of IORT versus modern conformal radiotherapy techniques such as SRS and IMRT.

4.5. Limitations of the study

Our study has numerous limitations. First, it has the inherent limitations of a systematic review, such as reviewer and selection bias. Second, the sample sizes of the included studies were relatively small. Third, some of the studies included recurrent GBM in addition to newly diagnosed cases, thereby introducing a confounding factor. Fourth, the extent of resection was not reported in some of the studies, and this is an important factor determining survival in GBM. Fifth, the type and dose of IORT, as well as the adjuvant treatment, were not uniform. Lastly, the reporting of outcomes such as complication and survival rates were heterogeneous, and were not even reported in one of the studies. This makes outcome comparisons between groups more difficult.

5. Conclusion

The addition of IORT to standard surgery and adjuvant therapy seemed to have improved local control and comparable overall survival rates with the Stupp protocol. Photon-based IORT seemed to have better results than electron IORT, but this may be due to improvements in other forms of adjuvant treatment rather than the IORT modality itself. The overall effect of IORT on GBM treatment is still inconclusive due to the small number of patients and heterogeneous reporting of data.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jocn.2021.08.022.

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