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RESEARCH ARTICLE

Intra-operative electron beam radiotherapy for newly diagnosed and recurrent malignant gliomas: feasibility and long-term outcomes

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Abstract
Introduction Intra-operative electron beam radiotherapy (IOERT) is an alternative to dose escalation for the treatment of central nervous system tumors. The objective of this study was to describe the feasibility and long-term outcomes of IOERT in the treatment of primary and recurrent gliomas.
Materials and methods From January 1992 through December 2002, all patients treated with IOERT at the Hospital San Francisco de Asis, Madrid/Spain were retrospectively reviewed. The selection criteria included patients with superficial tumors, KPS >70 % and lesions <6 cm. Irradiation was administered in one section. The prescribed dose considered the amount of post-resection residual tumor, previous radiotherapy and the tolerance level of brain structures exposed to IOERT.
Results There were 17 patients (53 %) with newly diagnosed malignant brain gliomas and 15 patients with recurrent tumors. The delivered dose varied from 8 to 20 Gy (median 12.5 Gy) for primary and from 8 to 16 Gy (median 10 Gy) for recurrent tumors. The median overall survival for the entire cohort was 13 months (14 and 10.4 months for the primary and recurrent, respectively). Three patients presented with radionecrosis, one patient with osteomyelitis at the craniotomy bone flap, one with intracerebral hemorrhage, and another patient experienced a pulmonary embolism.
Conclusions IOERT is a feasible technique and can be viewed as a tool in the treatment of newly diagnosed or recurrent brain gliomas.

Keywords Gliomas · Intra-operative · Radiotherapy

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Introduction

Brain tumors represent the 15th most frequent type of cancer in Europe. Due to their high level of aggressiveness and the poor results obtained with standard therapy, there were approximately 43,000 deaths from this disease in this continent in 2008, which represent the 9th highest mortality rate for both sexes among every other type of cancer. In Spain, 19,800 men and 15,800 women were diagnosed in 2008, and 15,500 men and 12,200 women died from this disease, during that year [1].

Gliomas are the most frequent type of malignant brain tumor in adults, representing approximately 70 % of the total number of cases. Optimal treatment results in a median survival of approximately 12–15 months for glioblastomas (GBMs) and approximately 2–5 years for anaplastic gliomas [2]. It is known that multicentric or metastatic disease is not common [3], and approximately 90 % of all recurrences arise within 2 cm of the enhancing edge of the original tumor [4]. This finding may justify efforts to intensify dose delivery to the tumor bed. However, despite efforts to alternate fractionation [5] or escalate doses beyond 60 Gy with either radiosurgery [6], fractionated stereotactic radiotherapy [7], brachytherapy [8] or intra-operative electron beam radiotherapy (IOERT) [9–16], patient prognosis remains frustratingly dismal.

However, a small but interesting amount of evidence indicates that there might still be a use for dose escalation in the treatment of gliomas. Cardinale et al. [7], in a subset analysis of 76 patients treated with radiation therapy boosted with fractionated stereotactic radiation therapy (FSRT), showed a trend toward improved outcome in patients that had complete gross tumor resection, suggesting that patients with minimal residual disease could benefit from an escalated dose. Prior to that report, Fitzek et al. had shown that a dose equivalent to 90 Gy (applied under a strategy that mixed protons and photons) prevented central recurrence in most of their patients, resulting in a median overall survival of 20 months [17]. Finally, we still do not know what the results would be of escalating radiation doses in the promising era of temozolomide [18], with or without molecular targeted therapy.

An important limitation for dose escalation in glioma therapy is the toxic effects resulting from the delivery of high doses of radiation to the normal surrounding tissues. IOERT, however, allows the physician to directly visualize the tumor volume and areas at risk and exclude normal structures. IOERT presents the theoretical advantage of allowing the precise application of a high radiation dose with a minimal exposure of surrounding tissues, which maximizes the radiobiological effect of a single high dose of irradiation and achieves total dosage levels beyond those obtained with standard conformal therapy [19]. All of this information together may justify the use of this technique for the management of newly diagnosed gliomas.

IOERT can also be a useful tool in the treatment of recurrent brain tumors. The patients with recurrent lesions have often been exposed to high doses of radiation when first diagnosed, which may limit the delivery of a curative dose with standard techniques. Despite its invasiveness, in the era of modern technology, along with intensity-modulated radiation therapy (IMRT) or stereotactic fractionated radiotherapy (SFRT), IOERT remains a safe and feasible alternative without a significant augmentation of surgery times [20] and with interesting results. However, these results are almost always based on small series with a high level of patient heterogeneity [10, 13, 16].

Long-term outcomes of glioma patients who received IOERT have been sparsely reported in the literature. The purpose of the present study is to describe the feasibility and long-term outcomes of patients with primary or recurrent gliomas treated more than 10 years ago with IOERT, with a long-term follow-up.

Methods

From January 1992 through December 2002, all patients with newly diagnosed brain tumors or with recurrent gliomas that were treated with IOERT at the Hospital San Francisco de Asis, Madrid/Spain, were retrospectively reviewed. The patients had undergone maximal surgical resection prior to the procedure. The decision to use IOERT was made by the operating neurosurgeon together with the radiation oncologist in charge, and the decision depended on the tumor site (deep tumors were avoided), the Karnofsky performance status (70 % or better), and the size of the lesion (up to 6 cm on a preoperative CT scan). The decision to apply IOERT also depended on the availability of the linear accelerator; during one period of time, only one operating unit was functioning, and access was severely restricted. All patients with newly diagnosed tumors had a previous biopsy, and no further histological analysis were done in patients with recurrent tumors, before the procedure.

The procedure

A craniotomy was performed to surround the tumor by a margin of 2 cm. When the team decided that IOERT would be feasible and that the patient and tumor characteristics fit the criteria, following the maximal possible tumor resection, the surgical cavity was packed with saline-saturated gauze as a tissue-compensating material to maintain dose homogeneity. Then, the size and the shape of the electron beam cone were selected as well as the depth to be treated based on the thickness of the tumor or of the tumor bed. The patients were transported from the surgical suite to the LINAC room, which was approximately 15 m away (wall to wall). Sterilized applicators were placed on the surgical cavity. The radiation field was selected to penetrate an area 1–2 cm from the surface. Irradiation was delivered in one section perpendicularly to the tumor bed. The dose prescription required that the 90 % isodose covered at least 1 cm in excess of the deepest aspect of the resection cavity and potential residual tumor extension. The total operative time was prolonged approximately 30 min including transportation time and IOERT cone-positioning time. The total radiation beam-on-time ranged from 2 to 5 min.

Dose planning was performed to conform to the target as precisely as possible. The applicator size was chosen according to the estimated size of the target volume, taking into account the extension of craniotomy limits. The dose of IOERT followed conventional recommendations from the available expert literature and took into account the amount of residual tumor, previous radiotherapy and the tolerance level of the brain structures to be exposed to IOERT [21].

Follow-up and statistical analyses

All patients were followed at 3-month intervals for the first 2 years, every 6 months for the next 3 years, and annually

thereafter, unless supplementary consultations were clinically indicated. Imaging studies included CT and MRI scans and, after 1999, PET/CT imaging. Late toxicity in each long-term survivor was assessed by a team of neurosurgeons and radiation oncologists. The Kaplan–Meier method was used to estimate patient overall survival (OS).

Results

Thirty-two patients were treated with IOERT at the Hospital San Francisco de Asis during this 10-year period. The median follow-up time was 30.4 months. Every patient was followed until death except for three long-term survivors who are still under surveillance. The patient and tumor characteristics are listed in Table 1.

Table 1 Patient characteristics

	Newly diagnosed gliomas	Recurrent gliomas	All patients
Total number of patients	17	15	32
Age (years) [median (range)]	59 (8–76)	47.5 (34–50)	48 (8–76)
Sex			
Men	9 (53 %)	9 (60 %)	18 (56.3 %)
Women	8 (47 %)	6 (40 %)	14 (43.7 %)
Histology			
Glioblastomas	6 (35.3 %)	6 (40 %)	12 (37.5 %)
Anaplastic astrocytomas	6 (35.3 %)	3 (20 %)	9 (28.1 %)
Anaplastic oligodendrogliomas	1 (6 %)	4 (40 %)	5 (15.6 %)
Grade II astrocytomas	4 (23.5 %)	1 (7 %)	5 (15.6 %)
Oligodendrogliomas	0	1 (7 %)	1 (3 %)
Diameter app[a] (cm) [median (range)]	5 (5–7)	5 (5–7)	10 (5–7)
Energy (MeV) [median (range)]	15 (8–18)	12 (6–18)	15 (6–18)
Total dose (Gy) [median (range)]	12.5 (8–20)	10 (8–16)	10 (8–20)
EBRT			
Previously	0	12	12
After IOERT	15	3	18
Median OS (months)	14	10.4	12.2

Diameter app diameter of the applicator, *EBRT* external beam radiotherapy, *OS* overall survival

Newly diagnosed gliomas

There were 17 patients (53 %) with newly diagnosed malignant gliomas. Their ages ranged from 8 to 76 years (median 59), and there were 9 men and 8 women. Considering the histological diagnosis, this group was composed of 6 GBMs, 6 anaplastic astrocytomas (AA), 1 anaplastic oligodendroglioma and 4 grade II astrocytomas. The cone size was chosen according to the tumor size with an added margin of at least 1 cm; the cone size ranged from 5 to 7 cm (median 5 cm), and the energy oscillated from 8 to 18 MeV (median 15 MeV). The particles utilized were electrons, with a median total dose of 12.5 Gy (range 8–20 Gy). Fifteen patients received post-operative adjuvant external beam radiotherapy (EBRT) with doses ranging from 46 to 60 Gy (median 50 Gy). In 2 patients with a grade II astrocytoma, no additional radiation was applied, and they were kept under surveillance.

Recurrent gliomas

With respect to recurrent gliomas, there were a total of 15 patients that were treated with IOERT at our institution: 9 men and 6 women. Their ages ranged from 34 to 49 years (median 47.5). With respect to histological diagnosis, there were 6 patients with GBMs, 3 with anaplastic astrocytomas, 4 with anaplastic oligodendrogliomas, 1 with an oligodendroglioma and 1 with a grade II astrocytoma. Similar to the first group of patients, the diameter of the applicator was chosen according to the size of the tumor with an added margin of at least 1 cm, depending on the surrounding structures (median 5 cm, range 5–7 cm). The energy ranged from 8 to 18 MeV (median 12 MeV). All but three patients had undergone EBRT at the time of the diagnosis; therefore, only those three patients received a post-operative adjuvant radiation treatment in addition to IOERT. The intra-operative dose, in those 3 cases, was 10 Gy. In previously irradiated patients, the median dose delivered was also 10 Gy (range 8–16 Gy).

Survival

The median OS for the entire cohort was 13 months. The median OS was 14 months for patients with newly diagnosed gliomas and 10.4 months for patients with recurrent gliomas (Fig. 1). At the time of the present analysis (8 years after the last patient was treated), there are three long-term survivors, all without any evidence of disease after 9, 13, or 18 years of follow-up.

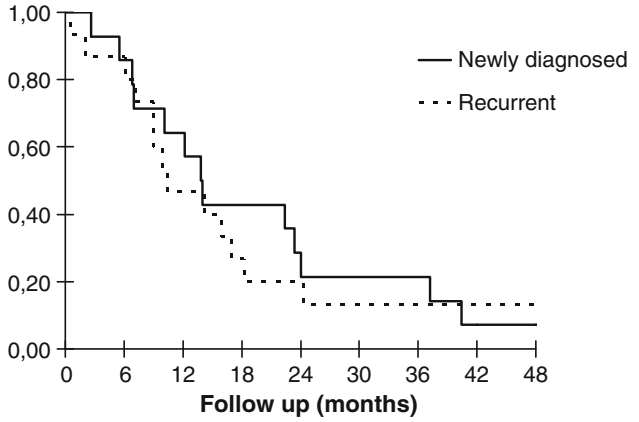

Fig. 1 Overall survival of patients presenting with newly diagnosed or recurrent gliomas

Toxicity

In three patients, radionecrosis was suspected based on MRI imaging. All had received high-dose IOERT (20 Gy) and post-operative EBRT. Moreover, three other patients presented with other toxicities: one osteomyelitis at the craniotomy bone flap, one intracerebral hemorrhage and one pulmonary embolism. The latter two patients had a fatal outcome 1 and 3 months after tumor resection, respectively.

Long-term outcomes

As mentioned, there were three long-term survivors: a women with a previously irradiated recurrent anaplastic grade 3 oligodendroglioma, who had surgical tumor resection and a 10-Gy IOERT boost; a man with a previously irradiated recurrent grade 2 astrocytoma, who underwent IOERT alone as a salvage treatment; and a male patient with primary grade 3 anaplastic oligodendroglioma, who underwent surgical resection with a 12.5-Gy IOERT boost followed by 60 Gy EBRT concomitant with three cycles of chemotherapy (procarbazine, lomustine and vincristine). The last patient presented with a tumor recurrence 2 years after the first treatment and underwent stereotactic radiosurgery (dose 10 Gy).

Discussion

Intra-operative radiation therapy was a safe strategy for the treatment of patients with newly diagnosed gliomas or recurrent tumors. Although forming conclusions about the efficacy of a treatment is more complicated in the temozolomide era [18], our results were comparable to those previously reported in the literature [9, 12–14, 16], as were the complications and the maintenance after a long-term follow-up.

Abe et al. were the first to describe their experiences with the treatment of gliomas with IOERT [22]. After that report, other small series have been described. In most of these reports, IOERT was used as a boost technique; however, it has also been used as an alternative method to irradiate previously treated recurrent brain tumors [9–16, 23]. These series of patients were almost always heterogeneous. The patients presented with a wide range of tumor differentiation levels resulting in a wide range of patient prognoses, making comparisons among them very difficult. Matched-pair analyses report conflicting results, as well [9, 11, 12].

To evaluate the comparability of published results, we used the number of glioblastoma patients treated in each series as a marker. Although imprecise, this marker almost certainly represents the level of aggressiveness of the treated tumors. Glioblastomas, in addition to being the most frequent central nervous system tumors, also present with the worst prognosis. The higher the number of GBM patients in the series of cases, the shorter should be the median overall survival.

In our series, glioblastomas represented 37.5 % of the patients. Our median overall survival of 14 months is comparable with Fujiwara (also 14 months) that had almost half of their cases represented by glioblastomas but used a remarkably higher dose of radiation. This group initially administered 20 Gy and, after a low level of complications, 25 Gy. An increase in adverse effects, such as brain edema, forced the authors to return to 20 Gy or decrease the electron energy when at the higher dose level. But still, the authors believe that this dose is the best explanation for the better results experienced by their patients when compared with their historical data for similar patients not receiving IOERT (10 months) [14]. However, no control group with a lower dose was used for comparison. Our similar results with notably lower doses (although with a slightly lower number of GBMs) point to the opposite direction. In our opinion, there is no clear evidence of the minimal necessary dose for the treatment of gliomas. This remains a question that needs to be answered in future trials (Table 2).

It must be noted that both series present outcomes that are clearly inferior to those presented by patients with GBM undergoing the current standard treatment (post-operative radiotherapy with temozolomide, given concomitantly and sequentially). Those patients, as reported by Stupp et al. [18], had a median survival time of 14.6 months. Whether IOERT is effective as a boost in patients receiving temozolomide is still an open question.

The results presented by Sakai et al. [11] in a series comprised almost entirely by GBM patients (approximately

Table 2 Series of patients with newly diagnosed or recurrent gliomas that underwent IOERT

Reference	Newly diag	GBM	Rec	rGBM	RT	Dose IOERT	mOS	Complic (%)	FU
Goldson [23]	12	1	0	0	11	15	–	27.3	–
Sakai [11]	32	26	0	0	32	26.7	26.2	3	12
Yamada [12]	10	2	0	0	10	15	15[a]	30	–
Shibamoto [13]	2	1	17	5	2	25	12[b]	16	15.5
Chung [10]	2	1	8	4	8	15	–	30	3
Fujiwara [14]	20	11	0	0	17	20–25	14	30	–
Hara [15]	0	0	6	0	6	25	29[c]	16.7	–
Nemoto [9]	32	21	0	0	32	15	24.7/14.1[d]	12.5	–
Schueller [16]	52	–[e]	19	–[e]	52	20	14.9/12.5[f]	14.1	12
This study (2011)	17	6	15	6	18	10	14/10.4	18	13.5

Newly Diag newly diagnosed gliomas, *GBM* absolute number of glioblastoma multiformes, *Rec* recurrent gliomas (all histologies), *rGBM* absolute number of recurrent glioblastoma multiformes, *RT* adjuvant external beam radiotherapy, *Dose* mean dose (Gray), *mOS* median overall survival (months), *Complic* complications rate, *FU* median follow-up (months)

[a] Only grade III tumors

[b] Only grade III and IV tumors

[c] Only grade II tumors

[d] Results for GIII/GIV lesions

[e] Total cases of GBM (among newly diagnosed and recurrent: 45)

[f] Results for primary/recurrent tumors

80 %) are noteworthy—a median survival of 26.2 months with only a 3 % complication rate. The median survival of the GBM patients was 22.4 months, which is impressive even if compared with results from the temozolomide era (Stupp). We believe that those promising results can be explained, in part, by a very restrictive selection of patients (only patients with small and superficial lesions and with high KPS scores). Again, radiation doses higher then 20 Gy were frequent. Marginal recurrences found during autopsies may indicate that the central dose was satisfactory, while the dose to the field borders was probably insufficient. These very good results though, as the authors themselves state, should be confirmed by others in a prospective manner, due to the difference in comparison to other series (Table 2).

Recurrent tumors

When gliomas recur, they can be particularly difficult to manage. Scarring can make additional surgeries challenging, and complete tumor resection is extremely difficult to achieve once those tumors are infiltrative [20]. In addition, those patients were likely to have received radiation after their first diagnosis, which increases the difficulties in an eventual second irradiation. Our series, although with only 15 patients (6 of whom were GBMs), is among the most representative already published. Schueller et al. had treated 19 patients, while Shibamoto et al. treated 17. Both authors had similar inclusion criteria and presented median overall survival times (12.5 and 12 months, respectively) [13, 16] similar to our series (10.4 months) (Table 2). Other available techniques, such as stereotactic radiosurgery (SRS), SFRT, brachytherapy or IMRT, may also be useful depending on the characteristics of the recurrent tumor and/or patient. However, comparisons among series were not feasible, as only retrospective studies have been reported with different inclusion criteria and with a wide range of final results [20, 24].

Currently, there is also the possibility of a systemic treatment for patients with recurrent gliomas. Temozolomide can be used as first option, even in patients that have been treated with this drug before [25, 26]. Bevacizumab is an interesting possibility as well, once it has shown interesting results when used isolated [27], with SRS [28] or with SFRT [29]. Again, inclusion criteria, in those studies, were variable, and prospective data are warranted before more solid conclusions can be taken. Once IOERT has presented interesting results before the era of systemic treatment, it can hypothesized that maybe there is a group of patients in which it could be the option of choice, since it is delivered in a single dose, with a very high level of anatomic precision.

Toxicities

One important concern with IOERT is its feasibility, as it is an invasive procedure, and high doses of radiation are delivered. We had three patients that presented with

radionecrosis, and three other patients had other complications that may be directly linked to the procedure. The level of adverse events presented by other authors varies from 3 to 30 % (Table 2), and this high variability may be due to the retrospective nature of the series, with some level of underreporting. Among the higher toxicity rates, Fujiwara et al. [14] establish a direct cause–effect relationship to the higher doses: 25 Gy represented a limiting toxicity level, which was considerably greater that the toxicity of patients that received 20 Gy. Other authors have also reported increased complication rates. Chung et al. [10] treated a relatively small series of patients with recurrent tumors, normally more difficult to treat and thus, subject to a higher rate of complications. Yamada et al. [12] report worse survival results for patients receiving IOERT compared with other glioma patients. This result may be an indication of case selection, although the inclusion criteria are not clearly stated. Treating patients with a worse prognosis may, in fact, result in a higher level of complications.

This study has the limitations of a single institutional retrospective series of cases, with a relatively small number of patients that were treated a long time ago. In addition, although studies (including this one) have suggested the feasibility and clinical potential of IOERT, the long-term benefits need to be studied in prospective trials. This technique, IOERT, almost certainly does not suit all patients. It would be better applied to patients with small, superficial lesions [16] that are located in the periphery of the brain after the macroscopic complete removal of the tumor [7] with no at-risk structures in the surrounding area [16]. However, those patients would also theoretically benefit from other less invasive techniques, such as IMRT or SRS [20]. Therefore, the described advantages of IOERT, sparing normal tissue and delivering a higher dose of radiation to the tumor, have to be proven effective compared with all other available techniques and concomitantly with temozolomide. It would be probably interesting to investigate this alternative in the future.

In conclusion, IOERT is a safe treatment option for newly diagnosed and recurrent gliomas. Our results suggest that an IOERT post-resection boost does not increase the complication rate compared with surgical resection followed by post-operative EBRT, and these complication levels are maintained over a long-term follow-up. There are insufficient data supporting its use in the primary treatment of patients with newly diagnosed glioma, but it may be an interesting option for recurrent tumors, although prospective data are needed, in the current era of systemic therapy.

Conflict of interest The authors do not have any conflicts of interest to disclose.

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