

Research article

Intraoperative radiation therapy (IORT) for previously untreated malignant gliomas

Kenji Nemoto*¹, Yoshihiro Ogawa¹, Haruo Matsushita¹, Ken Takeda¹, Yoshihiro Takai¹, Shogo Yamada¹ and Toshihiro Kumabe²

Address: ¹Department of Radiation Oncology, Tohoku University School of Medicine, Sendai, Japan and ²Department of Neurosurgery, Tohoku University School of Medicine, Sendai, Japan

E-mail: Kenji Nemoto* - knemoto@rad.med.tohoku.ac.jp; Yoshihiro Ogawa - ogaway@rad.med.tohoku.ac.jp; Haruo Matsushita - peropero@hosp.tohoku.ac.jp; Ken Takeda - takedara@rad.med.tohoku.ac.jp; Yoshihiro Takai - y-takai@rad.med.tohoku.ac.jp; Shogo Yamada - yamada@rad.med.tohoku.ac.jp; Toshihiro Kumabe - kuma@nsg.med.tohoku.ac.jp

*Corresponding author

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Abstract

Background: Intraoperative radiation therapy (IORT) is one of the methods used to deliver a large single dose to the tumor tissue while reducing the exposure of normal surrounding tissue. However, the usefulness of intraoperative electron therapy for malignant gliomas has not been established.

Methods: During the period from 1987 to 1997, 32 patients with malignant gliomas were treated with IORT. The histological diagnoses were anaplastic astrocytoma in 11 patients and glioblastoma in 21 patients. Therapy consisted of surgical resection and intraoperative electron therapy using a dose of 12–15 Gy (median, 15 Gy). The patients later underwent postoperative external radiation therapy (EXRT) with a median total dose of 60 Gy. Each of the 32 patients treated with IORT was randomly matched with patients who had been treated with postoperative EXRT alone (control). Patients were matched according to histological grade, age, extent of tumor removal, and tumor location.

Results: In the anaplastic astrocytoma group, the one-, two- and five-year survival rates were 81%, 51% and 15%, respectively in the IORT patients and 54%, 43% and 21%, respectively in the control patients. In the glioblastoma group, one-, two- and five-year survival rates were 63%, 26% and 0%, respectively in the IORT patients and 70%, 18% and 6%, respectively in the control patients. There was no significant difference between survival rates in the IORT patients and control patients in either the anaplastic astrocytoma group or glioblastoma group.

Conclusions: IORT dose not improve survival of patients with malignant gliomas compared to that of patients who have received EXRT alone.

Background

Surgery and radiotherapy have been used to treat malignant gliomas for many years, but the prognosis of malig-

nant glioma patients has been remained unsatisfactory. Since local recurrence rather than distant metastasis is the main pattern of recurrence [1–3], improvement in the lo-

cal control rate may greatly improve the survival of patients with malignant gliomas. Increasing the total radiation dose is one possible way of improving local control. However, damage to the normal brain tissue increases with increase in total radiation dose [4].

Intraoperative radiation therapy (IORT) is one of the methods used for delivering a large single dose to the tumor tissue while reducing the exposure of normal surrounding tissue. However, the usefulness of IORT for malignant gliomas has not been established. In this retrospective case-control study, the results of treatment with IORT and external radiation therapy (EXRT) for previously untreated malignant glioma patients were compared with those EXRT alone.

Methods

From 1987 through 1997, 32 patients with previously untreated malignant gliomas were treated with IORT. Histological diagnoses were anaplastic astrocytoma (AA) in 11 patients and glioblastoma (GBM) in 21 patients. The decision to use IORT was made by neurosurgeons and radiation oncologists. IORT was not used for patients with deep-seated tumors or infra-tentorial tumors. Moreover, since there were only two linear accelerators in our hospital during the period 1982 to 1998, the use of a linear accelerator for IORT was severely restricted and only a limited number of patients could be treated with IORT. Following as much tumor removal as possible, patients were transferred from the operating room to the linac room. Then cones of 4–8 cm in diameter attached to the linac gantry were placed directly onto the tumor bed. The energy of the electron beams ranged from 4 to 15 MeV depending on the estimated tumor depth. The IORT dose ranged from 12 to 15 Gy (median, 15 Gy; mean, 14.9 Gy). The IORT dose was evaluated at the peak point.

Following IORT, all patients EXRT at a median total dose of 60 Gy (mean dose, 57 Gy; range, 17–72 Gy). A 10 MV X-ray generated by a linear accelerator was used for EXRT. The clinical target volume was gross tumor (determined by CT or MRI images postoperatively) with a 2-cm margin. The median time interval from IORT and start of EXRT was 15 days (range, 9–41 days). Written informed consent was obtained from all of the eligible patients. Each of the 32 patients treated with IORT was randomly matched with a malignant glioma patient treated with EXRT alone from 1982 to 1997 (number of patients, 236). Patients were matched according to histological grade (AA or GBM), age (≤ 59 years old or > 59 years old), extent of tumor removal (total removal, subtotal removal or partial removal, biopsy only), and tumor location. However, performance status could not be used as a matching criterion in many of the patients due to lack of clinical information.

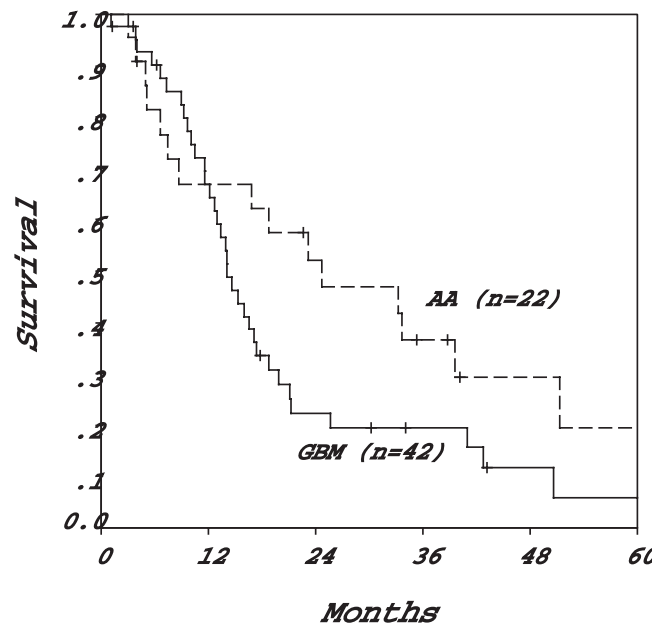


Figure 1
Survival curves by histological diagnosis.

The patients' characteristics are listed in Table 1: The treatment characteristics are listed in Table 2.

The length of survival was measured from the time of surgery until the patients died or until the time of final analysis. The last follow up examination was performed in October 2000. The Kaplan-Meier method was used to calculate the survival rate. The differences between survival curves were evaluated by the logrank test.

Results

The median survival times for AA patients and GBM patients were 24.7 months and 14.1 months, respectively. The one-, two- and five-year survival rates in AA patients were 67%, 52% and 19%, respectively, and those in GBM patients were 67%, 22% and 6%, respectively (Fig. 1). The difference between survival rates of AA patients and GBM patients was statistically significant ($p = 0.046$).

In the AA group, the median survival times in IORT patients and control patients were 24.7 months and 33.6 months, respectively. The one, two, and five-year survival rates in IORT patients were 81%, 51% and 15%, respectively, and those in control patients were 54%, 43% and 21%, respectively. There was no significant difference between survival rates in the treatment groups (Fig. 2).

In the GBM group, the median survival time in IORT patients was 13.3 months and that in control patients was 14.6 months. The one-, two- and five-year survival rates in

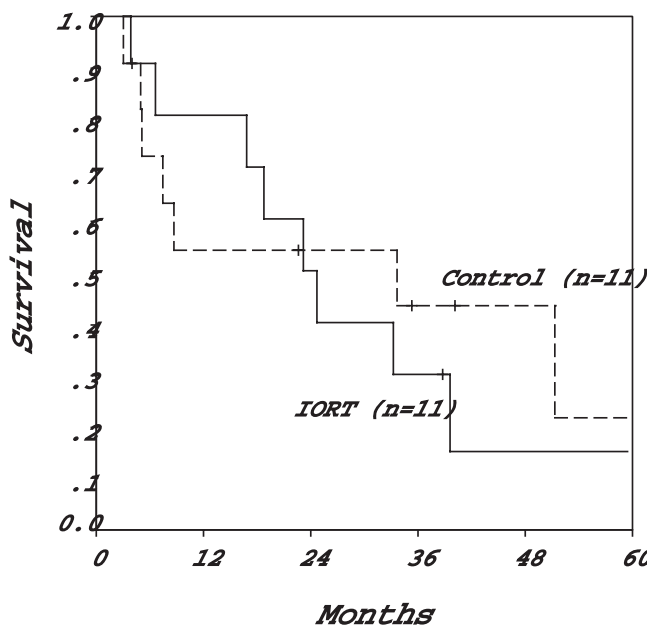


Figure 2
Survival of patients with anaplastic astrocytoma by use of IORT.

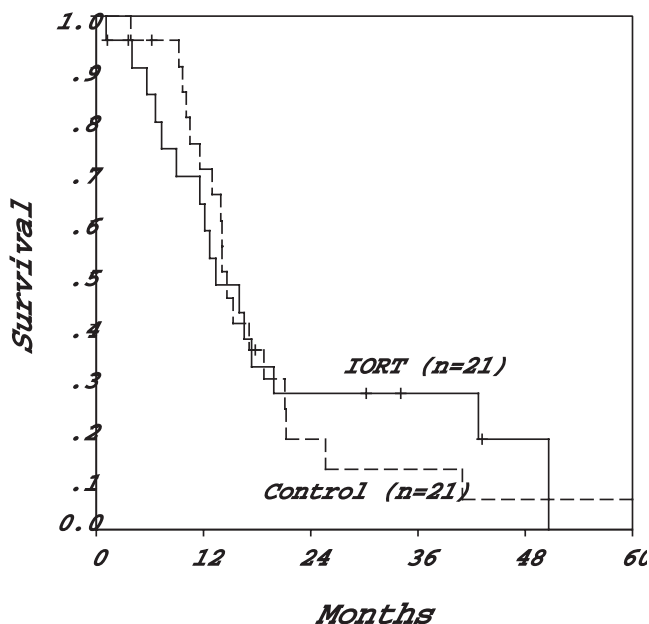


Figure 3
Survival of patients with glioblastoma by use of IORT.

IORT patients were 63%, 26% and 0%, respectively, and those in control patients were 70%, 18% and 6%, respectively. The survival rate from 24 to 48 months was better in IORT patients than in control patients, but the

difference was not statistically significant. The only patient who survived more than five years was in the control group (Fig. 3).

There were no treatment-related deaths in the patients who received IORT and in those who did not. In four IORT patients and in one control patient, CT and MRI findings suggested brain necrosis. However, differential diagnosis of brain necrosis from tumor regrowth was difficult in these patients.

Discussion

Increasing the total radiation dose is the possible way to improve the local control of malignant gliomas. A study by Walker et al showed beneficial effect of dose escalation up to 60 Gy [5]. On the other hand, Chang et al. reported that there was no advantage of a radiation dose of 70 Gy for 8–9 weeks over a dose of 60 Gy for 6–7 weeks [6]. Therefore, the standard radiation dose used for malignant gliomas has been 60 Gy/6–7 weeks, and the usefulness of dose escalation over 60 Gy for malignant glioma has been controversial. On the other hand, since recurrences occur from the initial tumor regions in most malignant gliomas patients, attempts have been made to deliver a large dose to the tumors while avoiding surrounding normal tissue using IORT [7–9], brachytherapy [10,11], conformal radiation therapy [12], particle radiation therapy [13], and radiosurgery [14].

Several authors reported that IORT improved survival of malignant glioma patients. Matsutani et al. treated 30 glioblastoma patients with IORT (mean dose, 18.3 Gy) combined with EXRT (mean dose, 58.5 Gy), and the median survival period and 2-year survival rate were 119 weeks and 61%, respectively, in their series [9]. Ortiz et al. used IORT for malignant glioma patients and reported that the overall 1-year survival rates were 67% for AA patients and 56% for GBM patients [8]. Fujiwara et al. used IORT with EXRT for 20 previously untreated malignant glioma patients. They reported that the survival of patients who had undergone IORT was better than that of patients who had been treated with EXRT alone. The median survival periods were 14 months for the patients who had been treated with IORT and 10 months for the patients who had been treated with EXRT alone [7].

However, we must be careful when comparing the results of treatment with IORT with the results in controls, because IORT can not be used for patients with deep-seated tumors, multifocal tumors, diffuse infiltrating tumors, very large tumors, or infra-tentorial tumors. Therefore, it is possible that the selection criteria of patients for IORT greatly influence the treatment outcomes. In this study, a matched-pair group of patients who had been treated with EXRT alone was used for the control group to minimize

confounding. As a result, there was no significant difference between survival rates of either AA or GBM patients who had received IORT and those who had not.

In our series, the settings of cones in the linac room were made by neurosurgeons and radiation oncologists, depending on the findings at tumor removal. However, it was difficult to determine the optimal position and direction of the cones in the linac room, because radiotherapy planning based on CT and MRI images was impossible in such situations. Therefore, the method of cone and patient setting in the linac room might have resulted in geographic errors and might have influenced the treatment outcomes. In order to correct such possible setting errors, intraoperative CT-based planning with a mobile CT and a fixation device that is used for radiosurgery may be useful. The usefulness of IORT should be tested again in a randomized clinical trial after the establishment of radiotherapy planning methods for IORT and a method to reproduce the planned setting in the linac room.

Conclusions

IORT did not improve survival of malignant glioma patients compared to that of following conventional radiation therapy alone.

Table 1: Patients characteristics.

	IORT	Control
Age (years old)		
median	59	59
range	24-72	27-73
Sex		
male	22	22
female	10	10
Histology		
AA	11	11
GBM	21	21
Tumor site		
frontal	12	12
temporal	13	13
parietal	4	4
occipital	3	3
Performance status (WHO)		
0	1	3
1	2	0
2	6	5
3	8	11
4	3	2
unknown	12	11

IORT = Intraoperative radiation therapy AA = Anaplastic astrocytoma
GBM = Glioblastoma

Table 2: Treatment characteristics.

	IORT	Control
EXRT dose (Gy)		
median	60	60
range	18-72	30-84
IORT dose (Gy)		
median	15	-
range	12-15	-
IORT energy (MeV)		
4	1	-
6	9	-
8	13	-
10	5	-
12	2	-
15	2	-
Cone diameter (cm)		
3	1	-
4	10	-
5	1	-
6	17	-
8	3	-

EXRT = External beam radiation therapy IORT = Intraoperative radiation therapy

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