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ORIGINAL PAPER

Role of external beam radiotherapy in the treatment of relapsing meningioma

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Abstract The role of radiotherapy in the treatment of relapsing meningiomas is not well established. Data of patients treated with radiotherapy for a relapsing meningioma were retrospectively analyzed. Overall survival (OS) was the primary endpoint of the analysis. Local control and acute and late toxicity rates have been also reported. From April 1986 to February 2011, 37 patients with a diagnosis of recurrent meningioma were treated. Median age was 64 years (range 36–79). A total of 18, 10, 5 and 4 patients were affected by relapsing benign, atypical, malignant meningiomas and meningiosarcomas, respectively (WHO classification). Median dose was 60 Gy (range 46–66 Gy). The median follow-up was 42 months (range 3–300 months). OS at 1, 3, 5 and 8 years was 81, 55.6, 43.9 and 25.8 %, respectively (median OS 45 months). A strong statistical trend was observed toward better OS rates in patients treated with radiotherapy at first recurrence compared to those treated at the second (or more) recurrence (OS 50.5 vs. 30.8 %, $p = 0.055$). A statistical impact of the histology (WHO I vs. II, III and IV) on 5-year OS was also observed (OS 60 vs. 30 %, 0 and 0 %, $p = 0.010$). Radiotherapy has been well tolerated, with no G2-4 neurological toxicity (RTOG toxicity score). Conventional radiation therapy has an important role in multidisciplinary approach in the treatment of recurrence of meningiomas. The histological type and the timing of the radiotherapy are prognostic factors in terms of survival.

Keywords Relapsing meningioma · Surgery · Radiotherapy · Overall survival · Local control

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Introduction

Meningiomas are the second most common neoplasm of the central nervous system in adults and account for 15–34 % of all primary brain and central nervous system tumors [1–3]. Although most meningiomas are benign, approximately 10 % of them show more aggressive clinical and histological features (atypical and malignant meningiomas), suggesting malignant behavior, with a higher tendency to metastatic spread [3, 4]. Globally, local recurrence rates of 7 % (1 year), 41 % (5 years) and 48 % (10 years) are reported in the literature [5, 6]. The treatment of local relapse is controversial, even if surgery is generally considered the primary therapeutic option, when the site of relapse and/or clinical condition of the patient allows it [7].

The role of adjuvant radiotherapy (RT) in relapsing meningiomas is not well defined, as only few retrospective studies are available in the literature [8–10], but a recent review by Marta et al. [11] concluded that "…radiotherapy can be used as an alternative treatment to surgery either as a first-line treatment or at its recurrence." The use of adjuvant RT in recurrent meningiomas is often based on the evidence of its potential efficacy in the treatment of residual lesions [3, 5, 6, 12, 13].

In this paper, we retrospectively investigated the long-term efficacy and toxicity of radiotherapy in patients with recurrent meningiomas. The role of some potential prognostic factors of recurrence and survival was also studied and reported.

Materials and methods

Clinical charts of patients treated with radiotherapy for a relapsing meningioma were retrospectively reviewed. After

the radiotherapy, the first follow-up visit was planned at 3 months. Then, the patients have been generally followed every 6 months for 2 years and then yearly. Before each control, patients underwent a contrast-enhanced brain CT or an MRI (since 2000). In order to update the data for this study, we contacted by phone the patients visited at least 6 months before the data collection. The patients have been followed alternatively (and separately) by the radiation oncologist and the neurosurgeon following the schedule described above until 2005. After this date, the patients were visited in the context of a multidisciplinary visit of a neuro-oncological group (formed at least by a neurosurgeon, a radiation oncologist and a medical oncologist).The histological classification was based on the WHO classification [14], and all of the specimens were retrospectively re-classified following this new classification. The overall survival (OS) was the primary endpoint of this analysis. The disease-specific survival (DSS) and the local control (LC) are also reported, as well as the acute and late neurological toxicity rates (scored with the RTOG toxicity score, [15]).

OS was calculated from the end of radiotherapy to the date of death, using the Kaplan–Meier method. Relapse after total resection was defined as the evidence of a new mass in the surgical bed at a contrast-enhanced CT scan and/or MRI. Relapse after subtotal resection or in patients that were not operated was defined as an increase in the diameter of the residual mass demonstrated by CT scan and/or MRI.

Data in the clinical charts, or the information obtained by calling the parents of the dead patients, allowed us to know the cause of the death and the date (month and year) of the death for all the patients. With these data, it has been always possible to calculate the OS and the DSS.

On the contrary, because of the retrospective nature of the study, even if it has been possible to identify the event "relapse," the date and the reason of the death, it has not been possible to know the exact date of relapse for some patients (21 patients), especially those followed partly elsewhere after treatment. For this reason, the LC has been calculated as crude rate, and it has not been possible to have an actuarial evaluation for this outcome. Acute and late toxicity have been reported with a descriptive statistics.

We also analyzed and compared these endpoints in some subgroups of patients in order to identify which ones would mostly benefit of adjuvant treatment. Univariate analysis was performed with the log-rank test or, for the LC, with the chi-square test. Clinical and therapeutic variables evaluated in the univariate analysis are the following: KPS (80–100 vs. <80 %); timing of radiotherapy (after first vs. subsequent relapses); extent of resection (gross total resection vs. no resection + subtotal resection); histology (WHO classification I vs. II vs. III vs. meningiosarcomas); radiotherapy technique [2D vs. 3-dimensional conformal radiotherapy (3D-CRT)]; surgery for relapse before radiotherapy (yes vs. not).

A p value <0.05 was considered as statistically significant. Statistics were performed with the SPSS software (SPSS Statistics 17.0© 1993–2007).

Table 1 Characteristics of the population

Whole population	37
Median age (range)	64 (36–79)
Female/male	21/16
Female/male ratio	1.3
Histological grade (WHO)	
Grade I	18 (49 %)
Grade II	10 (27 %)
Grade III	5 (13 %)
Meningiosarcomas	4 (1 %)
Number of lesions	
Single lesion	29
Multiple lesions	8

Results

Patients and tumor characteristics

From April 1986 to February 2011, 37 patients with recurrent meningiomas were treated with external beam radiation therapy in our Institution. Median age at the time of irradiation was 64 years (range 36–79), with 21 females and 16 males (sex ratio 1.3). The Karnofsky performance status (KPS) was 100–90 in 11 patients, 80–60 in 22 patients and <60 in four patients. All the patients underwent radiotherapy, 26/37 in an adjuvant setting after surgery for relapse and 11/37 as exclusive treatment. Of these 11 patients, five were treated for the first recurrence and 6 for second or subsequent recurrence.

The evaluation of resection extent was based of postoperative imaging with brain contrast-enhanced CT scan or, more recently, with brain MRI: 11/26 patients received a radical resection and 15/26 a subtotal resection of the relapsing tumor.

Data about patients and tumor characteristics and about the symptoms at the presentation of the relapse are resumed in Tables 1, 2 and 3. Eighteen tumors were classified as benign lesions (49 %), ten as atypical lesions (27 %), five as malignant lesions (13 %) and four as meningiosarcomas (1 %), based on WHO classification [14]. Twenty-nine patients presented a single lesion, and eight patients had multiple lesions.

Table 2 Sites and histological features of the tumors (number by site)

Localization	WHO I	WHO II	WHO III	Meningiosarcomas
Convexity	4	5	4	2
Falx and parasagittal	0	3	1	2
Cavernous sinus and sphenoid ridge	10	0	0	0
Posterior fossa	4	1	0	0
Parasellar area	0	1	0	0
Total	18	10	5	4

Table 3 Symptoms at the moment of the diagnosis of relapsing disease

Symptom	No. of symptomatic patients before treatment (%)	No. of symptomatic patients 6 months after the treatment[a] (%)
No symptoms	5 (11.4)	4 (11.1)
Headache	8 (18.2)	9 (25)
Weakness	6 (13.6)	2 (5.6)
Seizure	5 (11.4)	0 (0)[b]
Paresthesia (arms)	1 (2.3)	5 (13.9)
Paresthesias (facial)	4 (9)	1 (2.8)
Trigeminal neuralgia	2 (4.5)	2 (5.6)
Focal aphasia	1 (2.3)	0 (0)
Exophthalmos	2 (4.5)	1 (2.8)
Decreased visual acuity	3 (6.8)	3 (8.3)
Dysmetria	1 (2.3)	3 (8.3)
Diplopia	4 (9)	2 (5.6)
Irritability	1 (2.3)	0 (0)
Postural instability	2 (4.5)	2 (5.6)

The number of patients in the table seems superior to the number of patients of the whole population as each patient could present one or more of the described symptoms

[a] Presented data concern only the patients with at least 6 months of follow-up

[b] Patients presenting seizures as a symptom of relapse of the disease received also anticonvulsant drugs

Treatment characteristics

All patients underwent radiotherapy, 26/37 in an adjuvant setting after a surgery for relapse and 11/37 as exclusive treatment. Nineteen patients received RT after the first recurrence and 18 after the second (or more) one. RT was delivered with a 2D technique in 25 patients and with a 3D-CRT technique in 12 patients. Median dose was 60 Gy (range 46–66 Gy), delivered with a daily fractionation of 1.5–2 Gy.

The median dose delivered to the WHO I tumors was 56.7 Gy (range 46–66 Gy), while the median dose delivered to the WHO II–III tumors and to meningiosarcomas was 60 Gy (50–66 Gy). Clinical target volume (CTV) was the tumor bed with an adequate margin. A margin of 5/10 mm was added to obtain the planning target volume (PTV) following the institutional protocol, respectively, with 3D/2D technique.

Clinical outcomes

Study closing date was December 31, 2012. The median follow-up period was 42 months (range 3–300 months), and 29/37 patients were followed for more than 24 months. In particular, a total of 28, 19, 13 and 4 patients have been followed for at least 1, 3, 5 and 8 years, respectively.

Concerning the primary endpoints of this study, median OS and DSS were equal to 45 and 61 months, respectively.

1-, 3-, 5- and 8-year OS rates were 81, 55.6, 43.9 and 25.8 %, respectively.

1-, 3-, 5- and 8-year DSS rates were 86, 66.7, 52.6 and 40 %, respectively.

Table 4 summarizes the results of the univariate analysis on the OS and DSS.

A local recurrence was evident in 21/37 patients. Three out of 37 patients are still alive and disease-free at the moment of this analysis, 3/37 patients are alive with disease, 18/37 died because of the meningioma and 13/37 deceased for other reasons.

Chi-square test was also used to analyze the impact of some therapeutic and clinical variables on the risk of developing a local relapse (Table 5).

Radiotherapy has been well tolerated, with only 8/37 patients (21.6 %) having experienced a G1 acute toxicity. No acute grade 2–4 toxicity was reported. A total of 18 patients (48.6 %) reported G1-2 late toxicity. Fourteen (43.2 %) presented a late neurological G1 toxicity, usually mild headache.

Four patients (10.8 %) reported a G2 late neurological toxicity: two patients treated on the posterior cranial fossa presented persistent moderate dysmetria and two patient reported moderate headache due to edema. The two late G2 headaches were successfully treated with steroids.

Table 3 shows the evolution of the symptoms of the patients 6 months after the end of the treatment.

Discussion

To our knowledge, we report the largest experience on the role of radiotherapy in the treatment of patients with a recurrent meningioma.

Even if surgery represents the standard initial therapeutic approach to operable meningiomas [16, 17], adjuvant

Table 4 Overall survival and univariate analysis

	Median OS (months)	5-year OS	8-year OS	Median DFS (months)	5-year DSS	8-year DSS
Whole population (37 pts)	45	43.9 %	25.8 %	61	52.6 %	40 %
KPS						
80–100 (11 pts)	119	71.6 %	54 %	157	74.4 %	59 %
<80 (26 pts)	35	28.7 %	12.1 %	33	23.1 %	9.1 %
p		0.028			0.001	
Timing of RT						
After first recurrence (19 pts)	66	50.5 %	38.5 %	Not reached	54.2 %	54.2 %
After ≥2 recurrences (18 pts)	24	30.8 %	12.2 %	54	41.4 %	27.6 %
p		0.055			0.172	
Extent of the resection						
Gross total resection (11 pts)	71	51.9 %	26.2 %	71	57.7 %	38 %
Subtotal resection or no resection (26 pts)	36	36.8 %	21 %	54	39.5 %	28.3 %
p		0.589			0.822	
WHO						
I (18 pts)	153	60 %	54.5 %	Not reached	88.2 %	88.2 %
II (10 pts)	35	30 %	0 %	54	33.3 %	20 %
III (5 pts)	33	0 %	0 %	33	0 %	0 %
Meningiosarcomas (4 pts)	27	0 %	0 %	27	0 %	0 %
p		0.010			0.0001	
RT technique						
2D (25 pts)	45	44 %	27.8 %	67	52.8 %	39.3 %
3D-CRT (12 pts)	54	32.4 %	15 %	54	37.5 %	11.0 %
p		0.768			0.887	
RT after operated recurrence or not						
Operated recurrence (26 pts)	60	46.9 %	34.1 %	61	51.5 %	40 %
Not-operated recurrence (11 pts)	27	27.7 %	0 %	Not reached	41.3 %	Not reached
p		0.066			0.9	

KPS Karnofsky performance status, *OS* overall survival, *DFS* disease-free survival, *pts* patients, *RT* radiotherapy; *2D* 2 dimension, *3D-CRT* 3-dimensional conformal radiotherapy

radiotherapy has a quite established role in the therapeutic approach to primary meningioma [18–20], in particular for subtotally resected grade I–II and for malignant meningiomas [21, 22], while the role of adjuvant radiotherapy in totally resected atypical meningioma still remains to be defined. Moreover, some recent reports about the efficacy and the tolerance of stereotactic radiotherapy in the therapeutic approach to primary or relapsing meningiomas have been also published [22, 23]. Recurrent meningioma after the first surgical intervention shows a more unfavorable prognosis when compared with not-relapsing meningiomas with the same WHO grade and for this reason, these recurrences should deserve, theoretically, a more aggressive approach.

The National Comprehensive Cancer Network (NCCN) clearly stated that a recurrent meningioma should be resected (if clinically and technically possible) and an adjuvant radiotherapy should be delivered. Non-surgical patients should receive radiation, and the chemotherapy is reserved to the patients presenting a progression of the disease after RT [7]. However, the level of evidence remains low, and to define as standard any of the available therapies (except for the surgery) still remains a difficult issue.

The role of chemotherapy in the treatment of relapsing meningioma is limited only to the subset of patients who are refractory to surgery and/or to radiation. However, at present, there is only a limited number of available, standard systemic therapies. NCCN consensus expert opinion suggests as treatment options hydroxyurea, interferon-[alpha] or Sandostatin LAR (Novartis, Basel, Switzerland), a somatostatin agonist.

Concerning the interferon-[alpha], in vitro studies showed its activity in inhibiting the growth of cultured human meningioma cell lines [24]. The largest study about the efficacy of the interferon-[alpha] in this clinical setting enrolled 35 patients with a recurrent unresectable and previously irradiated WHO grade 1 meningiomas [24]. No radiographic

Table 5 Chi-square test for LC

	Relapsed after RT	Not relapsed after RT
Timing of adjuvant RT		
After first operated recurrence	11	8
After ≥2 operated recurrences	10	8
p	0.57	
Extent of the resection		
Gross total resection	6	5
Subtotal resection or no resection	15	11
p	0.57	
WHO		
I	6	12
II–III meningiosarcomas	15	4
p	0.006	
RT after surgery for recurrence (yes/not)		
Operated recurrence	12	14
Not-operated recurrence	9	2
p	0.048	

RT radiotherapy

responses were seen, with a median PFS of 7 months (6- and 12-month PFS were 54 and 31 %, respectively). Median OS was 8 months (range 3–28 months).

After the in vitro demonstration of the efficacy of the hydroxyurea on cultured meningioma cells, several subsequent clinical trials suggested its in vivo efficacy. Looking at the available studies, the response rate (defined as stable disease) ranged between 8 and 88 %, with a time to progression (TTP) ranging between 2 and 20 months [25]. Despite these data seem to be interesting, and to be comparable to those obtained in our analysis, some important biases exist and should be underlined. Indeed, in these studies, the proportion of patients presenting a benign (relapsing) lesion ranged between 0 and 100 %, with a rough mean of 60 %. Moreover, a mean of 77 % of the patients enrolled in these studies have received a previous RT. In one of these studies, RT was delivered concurrently to the salvage CT [26]. Last but not least, the incidence of severe toxicity was not negligible, ranging between 8.5 and 25 %. Only the study of concurrent chemo-radiation by Hahn et al. [26] showed a quite surprising rate of severe toxicity of 0 %. These results in these retrospective case series demonstrate that hydroxyurea, although generally quite well tolerated and convenient, appeared to have very limited activity.

Data about the role of RT in this clinical scenario are lacking

Historical data about the role of RT in context of the multidisciplinary approach to recurrent diseases are quite consistent [27–29]. In the report of Stafford et al. [27], authors concluded that "…patients treated at the time of recurrence seem to benefit of radiation therapy with or without surgical resection…." These data are confirmed by Dziuk et al. [28]: in a population of 48 patients treated for malignant meningioma, of which 23/48 for a relapsing disease, authors showed that adjuvant radiotherapy improved the 2-year DSS of recurrent patients from 50 to 89 % ($p = 0.015$). Their multivariate analysis indicates that the extent of the resection, the delivery of the adjuvant radiotherapy and the recurrence status are independent prognostic factors. Results of Condra et al. [29] confirm the important role of adjuvant RT in the primary treatment of patients with a benign meningioma undergoing a subtotal resection: At 15 years, the LC was 76 % after total excision (TE) and 87 % after subtotal excision plus RT (SE + RT), both significantly better ($p = 0.0001$) than after SE alone (30 %). The 15-year DSS was inferior in patients treated with SE alone (51 %), compared with those receiving with TE (88 %) or SE + RT (86 %) ($p = 0.0003$). Authors also concluded that "…Atypical pathologic features predict a poorer outcome, suggesting possible benefit from more aggressive treatment."

In all the situations in which a radical intervention is not allowed, sub-total resection followed by postoperative irradiation is able to offer a reasonable therapeutic option, reducing the risk of functional deficits, as demonstrated in many retrospective studies [30–33].

In the case of patients with atypical or malignant meningiomas, characterized by high rates of local recurrence, more aggressive approaches (surgery + adjuvant radiotherapy) are probably necessary [29]. Indeed, these meningiomas present a more aggressive biological behavior, they are more refractory to conventional treatments and they show higher recurrence rates. A complete radical resection is, in the therapeutic approach to these meningiomas, the most important prognostic factor [32].

Despite these "theoretical assumptions," the optimal therapeutic strategy for relapsing meningiomas, in particular for those presenting a more aggressive behavior, is still not well defined. Several authors reported a long-term LC rates similar to that achieved for benign lesions [27, 29, 34]. The same authors recommended radiation therapy in the immediate postoperative setting for operated atypical meningiomas, presenting a macroscopic or a microscopic residual disease [27, 29, 34].

There is only one Japanese retrospective study that specifically studied the role of radiotherapy in patients with a diagnosis of recurrence of meningioma [10]. Kokubo et al. evaluated 20 patients treated with radiation therapy with Co-60 machine or linear accelerator for recurrence of benign meningioma (ten patients), atypical (four patients) and malignant (six patients) meningiomas after one (13/20 patients), two (4/20 patients) or three surgical procedures

(3/20 patients). The median age of patients was 55 years (range 14–79). After a postoperative irradiation with median dose of 59.4 Gy (range 50–61.2 Gy), and a minimum follow-up of 2-year for 18/20 patients, 12/20 (60 %) patients presented a relapse after radiotherapy.

The 5- and 8-year LC rates were 36 and 27 %, respectively. Looking at the histological features of the tumors, the 5- and 8-year LC rates were 41 % for the ten patients with a benign meningioma, and 30 and 0 % at 5- and 8-year, respectively, for the ten patients with anaplastic or malignant meningioma.

The 5- and 8-year OS rates were 47 and 33 %, respectively. Looking at the histological features of the tumors, the 5- and 8-year OS rates were 45 and 33 % for the ten patients with a benign meningioma, and 50 and 0 % at 5- and 8-year, respectively, for the ten patients with anaplastic or malignant meningioma.

Our data are comparable with the Japanese study with an OS rates at 5 and 8 years of 43.9 and 25.8 %, respectively.

In our series, 18/37 patients (48.6 %) died because of the disease, against 12/20 (60 %) in the Japanese study. It should be noted that our study included 19 (51.3 %) meningiosarcomas, atypical and malignant meningiomas (vs. 50 % in the study of Kokubo et al.), 26/37 cases of patients with IK < 80 (information not provided in the study of Kokubo et al.) and a median age of the population of 64 years (vs. 55 years in the study of Kokubo et al.), and it is known that all of them are unfavorable prognostic factors.

The subgroup analysis in our study highlighted the statistically significant differences in terms, respectively, of 5-year OS and DSS between patients with recurrence of benign meningioma (60 and 100 %) and those patients with WHO II meningioma (30 and 66 %), WHO III meningioma (Both 0 %) and meningiosarcomas (Both 0 %), confirming the prognostic value on survival of the histological grade (Table 5).

Retrospective studies indicate that the best results occur if the radiotherapy is given after the first recurrence [32, 33, 35]. Our results seem to confirm this trend: patients treated after the first recurrence showed an OS reaching 50.5 %, which is strongly (but not statistically, $p = 0.055$) better than the OS of the patients treated for a second or subsequent relapse (30.8 %).

In the study by Miralbell et al. [32], 16 patients incompletely resected at the time of first recurrence were irradiated and 78 % were progression free at 8 years while 11 % of a similar group treated by surgery alone were progression free ($p = 0.001$).

Another study by Taylor et al. [33] showed that postoperative radiation therapy was also effective for relapsing patients, with a 10-year actuarial LC rate after salvage treatment for a first recurrence of 30 % for patients treated with surgery alone and 89 % for patients receiving postoperative radiation therapy at the time of salvage surgery. This analysis suggests that radiotherapy has a significant role in the treatment not only in sub-totally excised meningioma, but also in the recurrent disease.

On the issue of timing of radiotherapy in case of recurrence, Pourel et al. [3] reported a better 5-year RFS when radiotherapy is performed postoperatively rather than after first recurrence (90 vs. 73 %, respectively).

All these results support the use of an immediate radiotherapy approach after the first recurrence as opposed to a treatment given after the second relapse.

Conclusion

Our findings suggest that conventional radiation therapy has an important role in the multidisciplinary approach to relapsing meningiomas. The histological type and the timing of the radiotherapy are important prognostic factors influencing survival and LC. The impact of the new techniques and technologies in radiation oncology should be further evaluated in the future as it potentially allows a better sparing of the Organs at risk and, then a dose escalation at target level, in particular for patients with residual or inoperable disease.

Conflict of interest No conflict of interests exists. Authors did not received funds for this research.

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