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Radiation-associated grade 2 meningiomas: A nine patient-series and review of the literature

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ABSTRACT

Introduction: Radiation-associated meningiomas (RAM) remain rare but recognized to harbor a high potential of aggressiveness. Only few studies focused on grade 2 histological variants.
Objective: Our study aims to report the natural history of patients with radiation-associated grade 2 meningiomas followed in a single institution.
Materials and methods: This retrospective study included all patients with grade 2 RAM operated in our institution between 1994 and 2011. We used the WHO 2007 classification for histological grading. The degree of resection was evaluated using Simpson Classification. The tumor was considered radiation-associated, if the patient had a medical history of cranial irradiation for another medical condition (1 year before at least). Patients benefited from a post-operative close clinical and radiological (cranial MRI) follow-up every 4 months during 2 years and annually thereafter, to detect any tumor progression. Adjuvant therapy and/or monitoring were systematically decided during a multidisciplinary team meeting.
Results: Nine patients (6 men and 3 women) were included in the study. The mean age at diagnosis was 34 years old (range 20–55 years). The mean follow-up was 77 months (range 31–180 months). The mean delay between initial cranial radiation therapy and the diagnosis of grade 2 RAM was 23 years (range 16–33 years). Among all patients, 4 harbored a meningiomatosis, while 5 patients harbored a single tumor. Post-operative local tumor progression was noted in 4 patients. Progression free survival (PFS) after the first surgery in these 4 patients was 15, 23, 35, and 47 months. In these 4 progressive patients, 7 surgical resections, 3 GKS and 1 fractionated radiation therapy have been performed. Post-operative tumor progression was noted at distance from the operated meningioma in 1 patient with meningiomatosis. At final control, 2 patients had severe oculomotor palsy and 1 patient needed palliative cares related to progressive meningiomatosis with anorexia and swallowing disturbance.
Conclusion: Grade 2 RAM is a severe radiation-associated disease occurring preferentially in younger male patients. Although, surgery remains the mainstay treatment, the high potential of tumor progression often requires adjuvant therapeutic tools. Thus, new radiation therapy should be discussed in some cases and the role of radio surgery is still to be better defined.

1. Introduction

The side effects of cerebral radiation therapy are well studied in the literature. Neurocognitive disorders and radionecrosis are the most frequently described complications [10,29]. Even if less commonly reported, radio-associated tumors are important concerns as they can be life-threatening. Radiation-associated meningiomas (RAM) and gliomas are the most frequent histological types [7]. Fortunately, the recent improvement of radiation therapy techniques is likely to reduce the occurrence of these adverse events [6,19]. Radiation-associated tumors often occur after an interval of several years [28], and some predisposing factors have been identified (neurofibromatosis) [14]. Some authors suggest that RAM are more aggressive and require looking for any history of whole brain radiation therapy (WBRT) [21,37], as this is

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Table 1
Summary of main demographical data.

Patient	Age at diagnosis (years)	Initial irradiated disease	Delay between radiotherapy and diagnosis of grade 2 meningioma (years)	Meningiomatosis	Location	Simpson	Local progression	Distant progression
1	20	Medulloblastoma	16	1	Convexity	4	0	+
2	29	Leukemia	20	0	Convexity	1	0	0
3	54	Lymphoma	17	0	Convexity	1	0	0
4	24	Leukemia	21	1	Falx cerebri	1	0	0
5	38	Astroscytoma	29	1	Cranial base	2	0	0
6	34	Leukemia	33	0	Convexity	2	+	0
7	27	Leukemia	25	1	Convexity	1	+	0
8	55	Cutaneous angioma	25	0	Convexity	1	+	0
9	28	Leukemia	22	0	Cranial basis	1	+	0

rarely spontaneously reported by patients. As grade 2 RAM is of rare occurrence, there is a lack of studies, which focused on this particular histological subtype. Moreover, the studies concerning RAM, were performed before the WHO 2007 classifications [23] and they mixed between all grades of meningiomas [27,31,37]. Our study aims to report the natural history of patients with radiation-associated grade 2 meningiomas operated in our institution.

2. Patient and methods

2.1. Population

This study is the retrospective analysis of prospectively collected data. The patient population is the same than from the previous paper [1]. This is a subgroup for further analyzing RAM and its natural history and outcome. Using the local database we studied the medical records of all patients who underwent the resection of a grade 2 meningioma at the Lille University Hospital between 1994 and 2011. Surgical resection has been measured using the Simpson Classification. Histological grading has been confirmed using the WHO 2007 classification [23]. Grade 2 meningiomas are defined by one or more of following criteria: (1) chordoid or clear cell histologic subtype, (2) 4–19 mitoses per 10 high-power field (HPFs), (3) brain infiltration, and (4) three or more of the following five histologic features: small cell change, increased cellularity, prominent nucleoli, sheet-like growth, or necrosis. The diagnosis of grade 2 RAM has been retained for patients with a medical history of cranial irradiation at least 1 year before, while other patients have been defined as sporadic grade 2 meningiomas. We noted if patients underwent early postoperative radiotherapy or not.

2.2. Clinical and radiological follow-up

Patients benefited from a close postoperative clinical and radiological (cranial MRI) follow-up every 4 months during 2 years and annually thereafter, to detect any tumor recurrence or progression. The size and the location of the tumor were evaluated by the neuro-radiologists of our institution. Adjuvant therapy and/or monitoring were systematically decided during a multidisciplinary team meeting.

2.3. Progression criteria

Local recurrence has been defined as the occurrence of a newly visible tumor (cranial MRI) in the surgical site or directly in contact with the surgical border. For patients with incomplete resection (Simpson 3–5), local progression was considered when the residual tumor increased in size. Distant recurrence was defined by the occurrence of a newly visible tumor on MRI at distance from the surgical site. Distant progression was defined by the increase in size of a known distant tumor in case of meningiomatosis. All tumor recurrences or progressions were confirmed by the neuro-radiologist of our institution.

2.4. Statistical analysis

Survival estimates have been computed using the Kaplan–Meier method. Comparisons of survival curves have been performed using the Log-rank test. Statistical analysis was performed using the SAS Software (Cary, NC, USA), V9.3.

3. Results

3.1. Population

Among all patients ($n = 167$) operated in our institution between 1994 and 2011 for a grade 2 meningioma, 9 harbored a RAM (5.3%). Among all patients, 4 harbored a meningiomatosis (2 or more tumors), while 5 patients harbored a single tumor. There were 6 men and 3 women with a mean age at diagnosis of 34 years old (range 20–55 years). No patient harbored a neurofibromatosis. The mean follow-up was 77 months (range 31–180 months). The indications for prior WBRT (Table 1) were leukemia ($n = 5$), lymphoma ($n = 1$), medulloblastoma ($n = 1$), astrocytoma ($n = 1$), cutaneous angioma ($n = 1$). The mean delay between initial cranial radiation therapy and the diagnosis of grade 2 RAM was 23 years (range 16–33 years).

3.2. Initial presentation

All patients were symptomatic as they were referred to our institution for the onset of progressive neurological symptoms: intracranial hypertension was noted in 5 patients, neurocognitive disorder in 3 patients, hemiparesis and aphasia in 1 patient, seizure in 5 patients and visual disturbance in 2 patients. Cranial MRI revealed a unique tumor in 5 patients and 2 or more tumors in 4 patients (meningiomatosis). Concerning the operated meningiomas, 6 were located on the convexity, 2 on the cranial basis and 1 on the falx cerebri.

3.3. Postoperative course

No excessive bleeding and no particular complication were noted during the procedures. The extent of resection was considered as Simpson 1 in 6 patients, Simpson 2 in 2 patients and Simpson 4 in 1 patient. Two patients experienced transient oculomotor nerve palsy after the resection of a meningioma located on cranial basis. No other complication has been reported. Histological findings revealed atypical meningioma in 7 patients, chordoïd meningioma in 1 patient and clear-cell meningioma in 1 patient. No patient benefited from early postoperative radiotherapy.

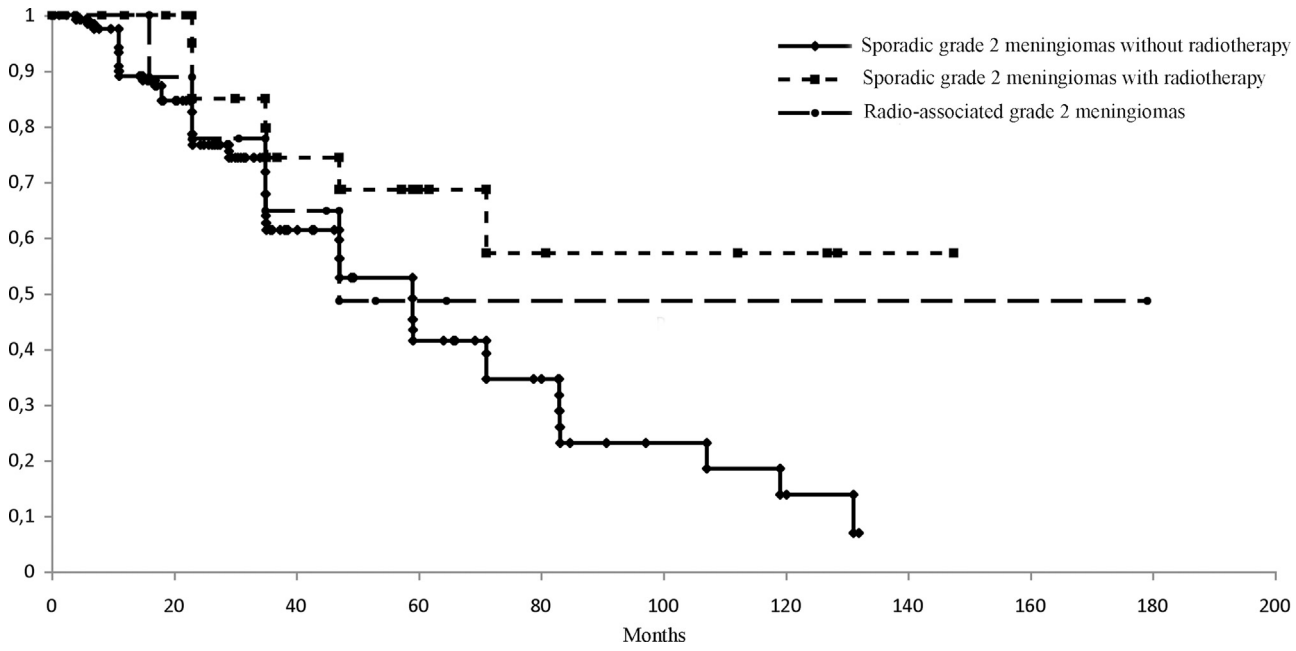

Fig. 1. Progression free survival after surgery in patients with sporadic and radiationassociated grade 2 meningiomas.

3.4. Recurrences and progressions

Among the 9 patients, 4 harbored a local recurrence, which required further therapies (Table 1). One patient (patient #6) developed a recurrence in contact with the surgical field 23 months after the Simpson 2 resection. He underwent a Gamma knife Radiosurgery (GKS) (14 Gy on marginal isodose 50%). The tumor remained stable at the last 24 months follow-up. The second patient (patient #7), who harbored a meningiomatosis developed a local recurrence 35 months after the Simpson 1 surgical resection of a meningioma located on the convexity, while other tumors remained stable. She underwent a new surgical resection (Simpson 2). At 24 months she harbored a new local recurrence treated by GKS (15 Gy on marginal isodose 50%). Unfortunately, the tumor grew rapidly 24 months after the GKS. Her general condition worsened and she refused any new therapy. She died few months later. The third patient (patient #8) developed a local recurrence 47 months after the Simpson 1 resection of a convexity meningioma. He underwent a new Simpson 1 surgical resection followed by a fractionated radiation therapy (54 Gy), and the follow-up remained uneventful at 72 months. The fourth patient (patient #9) underwent the Simpson 1 resection of a cranial basis meningioma. A local recurrence occurred at 24 months requiring a new Simpson 4 surgical resection. The remnant tumor was early treated by GKS (15 Gy), as it was located on the Galen vein and as the size allowed such procedure (lower than 3 cm in diameter). The tumor remained stable at a follow up of 36 months. For these 4 patients, no complication related to the adjuvant therapies has been reported during the follow-up. Using the Kaplan Meier method (Fig. 1), we compared the local progression free survival of patients with grade 2 RAM ($n = 9$) to patients with sporadic grade 2 meningioma followed in our institution during the period of inclusion. We separated patients who underwent surgical resection alone ($n = 132$) to those who underwent surgical resection followed by early radiotherapy ($n = 26$). Concerning, sporadic grade 2 meningiomas, patients who benefited from early postoperative radiation therapy had a significantly longer median PFS (not reached vs 59 months, $p = 0.021$). Despite the lack of statistical significance due to the small number of patients with grade 2 RAM, the prognosis of grade 2 RAM appears to be similar to the prognosis of patients with sporadic grade 2 meningioma who have not benefited from early postoperative radiation therapy.

Distant recurrence has been recorded for only one patient (patient #1). This patient underwent the Simpson 4 resection of a meningioma located on the right convexity. The remnant tumor remained stable without any adjuvant therapy at 180 months of follow-up. At 110 months of follow-up, the patient developed a new tumor, located on the left convexity, which benefited from a complete surgical resection (Simpson 1). The follow-up is still uneventful at 180 months.

4. Discussion

4.1. Demographical characteristics

Grade 2 RAM is a rare but life-threatening disease, which generally occurs many years after the initial cranial irradiation, whatever its indication. No series focused only on grade 2 RAM and their risk of occurrence is still to be defined after radiation therapy. Grade 2 RAM are characterized by younger age at presentation. The mean age at diagnosis of patient with sporadic grade 2 meningiomas is almost 50 years [1,2,11]. In patients with RAM, the age at diagnosis is related to the age of cranial irradiation. In our series, the mean age at diagnosis was 34 years. This is related to the fact that lot of patients underwent cranial prophylaxis irradiation in childhood in order to treat leukemia [13]. The usual irradiation doses were around between 12 and 18 Gy according to those reported in the literature [32,36]. RAM are also characterized by a higher male-to-female ratio and by biologically more aggressive histological variants compared to primary spontaneous meningiomas [35]. On the other side, sporadic meningiomas are known to occur preferentially in women with a reported sex ratio of 2:1 [23]. This is especially true for grade 1 meningiomas. Indeed, the role of hormonal factors is likely to be less important in sporadic grade 2 meningiomas, probably due to the presence of less mature cells with lower quantity of hormonal receptors [40]. Many series of sporadic grade 2 meningiomas confirmed a balanced sex ratio between men and women [1,2]. Despite the lack of clear evidence, grade 2

RAM appears in the same manner to occur preferentially in men [37]. Our series included 6 men for only 3 women. This data, which remains to be confirmed, is important to be considered, since some authors argued that the prognosis of intracranial meningiomas is more pejorative in men, whatever the histological grade [9].

Multiple locations were also more common in the RAM [27,33]. In our series, among the 9 patients, 4 patients harbored radiation-associated meningiomatosis (Table 1), 1 of them being operated in 2 different progressive tumor locations. RAM should then not be considered as a focal disease since all irradiated meninges are concerned.

There is also a difference in genetic mutations between RAM and sporadic meningiomas [34]. Nevertheless, the NF2 gene mutations may not play an important role in RAM compared to sporadic meningiomas [17].

4.2. Latency period of grade 2 RAM

The diagnosis should be considered in patients with a medical history of cranial irradiation. In Europe, cranial irradiation has been usually performed for the treatment of acute leukemia, retinoblastoma, tinea capitis or previous brain tumor. Many authors reported a long delay between radiation therapy and the occurrence of RAM [5], and some authors recorded a delay of 63 years [21]. In our series the mean delay was 23 years (range 16–33 years). The latency period can indeed be rarely less than 5 years, especially when cranial irradiation has been performed during childhood [28]. Nevertheless, Choudhary [8] reported a case of 11-year-old boy, who developed a grade 2 RAM 14 months after a cranial irradiation performed for the treatment of a medulloblastoma. Some authors emphasized that the latency period is shorter when the age at cranial irradiation was lower than 5 years, especially for high grade RAM [37]. Paulino presented a recent meta-analysis of RAM whatever the grade, including 143 patients from 66 studies. He suggested that a short latency period was associated to male patient, initial diagnosis of leukemia and high dose of irradiation [28]. In our series, dedicated only to grade 2 meningiomas, the latency period was longer (23 years). Even if many patients underwent radiation therapy during childhood (1–9 years old) for the treatment of leukemia, no short latency period has been recorded. This result is in disagreement with Paulino's study (Table 1). Hence these patients require long-term clinical and radiological monitoring to detect tumor occurrence as early as possible in order to optimize treatment option.

4.3. Treatment of grade 2 RAM

Although, many authors demonstrated a higher recurrence rate in patients with grade 2 meningiomas, surgery remains the mainstay treatment. However, the extend of resection appears to have low influence in progression free survival, as reported by many series [1]. The dural infiltration is more diffuse in grade 2 meningiomas compared to grade 1 meningiomas, which may explain that resection could often be incomplete despite the surgeon's opinion. Indeed, in our series local progression occurred in 3 patients for whom surgical resection has been considered Simpson 1. Other adjuvant therapeutic tools, such as radiation therapy or radiosurgery, should be considered early after surgery. Committees of neuro-oncology now propose to carry out external radiation therapy at an early stage in patients carrying sporadic grade 2 meningiomas which underwent complete resection or not [12,26]. However, prospective randomized studies are required [30]. Nevertheless, two major controversies exist concerning irradiation of grade 2 RAM. First, radiation therapy is considered to be the cause of the disease [25]. However, it is well-known that radiation-associated tumors occur preferentially for low doses (<20 Gy), generally applied for the treatment of leukemia [38]. Postoperative irradiation of grade 2 meningiomas requires "therapeutic doses" (50–60 Gy) [1,12], that are less likely to induce such tumorigenic side effects. Secondly, cranial re-irradiation is still disputed [18] as it can induce various brain damages. In recent years, cranial re-irradiation has been considered as a valuable option for the treatment of various brain lesions such metastasis, gliomas, and medulloblastoma [4,24,39]. In these indications, irradiation must be as conformal as possible, to preserve normal brain tissue. Moreover, dose and fractionation should be evaluated according to the data of the first procedure, which must be searched rigorously. In our prior study, patients with sporadic grade 2 meningiomas harbored a better local control when early postoperative radiotherapy was performed (Fig. 1) [1]. In the present study, it was likely that grade 2 RAM and sporadic grade 2 meningioma without postoperative radiation therapy had the same postoperative prognosis. As for grade 2 sporadic meningiomas, it is likely that the local control could be improved with early postoperative radiotherapy. In our series, a fractionated radiation therapy has been performed early after the second surgery in patient #8. Tumor control was still obtained 5 years after the second treatment without radiation induced side effects. When technically feasible, postoperative radiation therapy should be discussed as an additional tool in the management of this severe disease. Radiosurgery is another therapeutic tool for tumors of limited size that can be performed at different time of their management [16]. It can be proposed immediately after incomplete surgical resection, to enhance the local tumor control [15,20]. This combined treatment can be proposed deliberately to limit the functional risk of surgery, especially for tumors located in critical areas [22]. During follow-up, radiosurgery can be performed for local tumor progression or for distant progression in patients with meningiomatosis. The efficiency of radiosurgery in patients with grade 2 meningiomas has been well reported by many authors [3,6,19]. They advocated applying higher doses, similar to those applied for malignant tumors. Radiosurgery can be recommended, even if the patient harbors a history of brain irradiation but its role in the management of RAM is under evaluation [22].

However, the effectiveness of target therapies or chemotherapies should be better defined in the future and these treatments might play an important role in the management of patients with grade 2 meningiomas [22].

A larger study, including any grade of RAM would be useful to better analyze the clinical characteristics of these patients and define clear therapeutic options.

5. Conclusion

Grade 2 RAM is a severe radiation-associated disease occurring preferentially in younger male patients, with a mean delay of 23 years after initial radiation exposure, for which surgery remains the mainstay treatment. The postoperative local control appears to be similar to sporadic grade 2 meningiomas. The high potential of tumor progression often requires postoperative adjuvant therapeutic tools. Thus, new conformal radiation therapy should be discussed in some cases and the role of radiosurgery is still to be better defined.

Conflict of interest

None.

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