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Phase II trial

Adjuvant postoperative high-dose radiotherapy for atypical and malignant meningioma: A phase-II parallel non-randomized and observation study (EORTC 22042-26042)

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ABSTRACT

Purpose: The therapeutic strategy for non-benign meningiomas is controversial. The objective of this study was to prospectively investigate the impact of high dose radiation therapy (RT) on the progression-free survival (PFS) rate at 3 years in WHO grade II and III meningioma patients.

Materials and methods: In this multi-cohorts non-randomized phase II and observational study, non-benign meningioma patients were treated according to their WHO grade and Simpson's grade. Patients with atypical meningioma (WHO grade II) and Simpson's grade 1–3 [Arm 1] entered the non-randomized phase II study designed to show a 3-year PFS > 70% (primary endpoint). All other patients entered the 3 observational cohorts: WHO grade II Simpson grade 4–5 [Arm 2] and Grade III Simpson grade 1–3 or 4–5 [Arm 3&4] in which few patients were expected.

Results: Between 02/2008 and 06/2013, 78 patients were enrolled into the study. This report focuses on the 56 (median age, 54 years) eligible patients with WHO grade II Simpson's grade 1–3 meningioma who received RT (60 Gy). At a median follow up of 5.1 years, the estimated 3-year PFS is 88.7%, hence significantly greater than 70%. Eight (14.3%) treatment failures were observed. The 3-year overall survival was 98.2%. The rate of late signs and symptoms grade 3 or more was 14.3%.

Conclusions: These data show that 3-year PFS for WHO grade II meningioma patients undergoing a complete resection (Simpson I–III) is superior to 70% when treated with high-dose (60 Gy) RT.

The majority of meningiomas are benign [1,2] but atypical (WHO grade II) or malignant meningioma (WHO grade III) can be observed in approximately 5–34% [3] and 1–3% of meningioma cases [4], respectively. These non-benign meningiomas are associated with less favorable clinical outcome when compared to their benign counterpart [5,6] and usually display a more aggressive behavior locally with early recurrence or tumor progression.

The management of these tumors is controversial. Some small retrospective studies have shown that administrating higher doses of radiation could optimize meningioma patient's outcome for grade WHO II and III tumors alike [7–10]. Conversely, some other series have shown no advantage of radiotherapy (RT) for Simpson 4–5 atypical meningioma in the adjuvant setting [11]. Moreover, it is unclear if patients with grade II meningiomas undergoing complete resection (i.e. Simpson 1–3) will benefit at all from postoperative RT [12]. As such, prospective data are urgently needed [13] so as to define how these patients should be treated and if RT would optimize patients' outcome with a favorable therapeutic ratio.

In view of lack of therapeutic consensus and of the available data in the literature containing merely small retrospective series stemming from single center only, the EORTC decided to perform a prospective study assessing the efficacy and toxicity of high dose

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radiotherapy, for atypical and malignant meningiomas. The objective of this study was to prospectively investigate the impact of high dose RT on the progression-free survival rate.

Methods and materials

Study design

This was a multicenter non-randomized phase II and observational study conducted in four independent cohorts assessing the efficacy of high-dose radiotherapy for non-benign meningioma patients WHO grade II Simpson stage 1–3 [arm 1], Simpson stage 4–5 [arm 2], WHO grade III Simpson grade 1–3 [arm 3] and Simpson grade 4–5 [arm 4]. The resection level was assessed by the surgeon after verification with a postoperative MRI and was classified according to Simpson staging [14]. For patients with atypical meningioma (WHO grade II) and any Simpson's grade [arm 1&2] the trial was initially designed as a non-randomized phase-II with 3-year PFS as primary endpoint. However, in October 2010, patient recruitment in arm 1 appeared unexpectedly fast, whereas that in arm 2 was much slower than expected. On that basis, the protocol was amended to enlarge the sample size in arm 1 lowering type I and type II design error rates, and to remove the statistical objectives for arm 2 who would now enter an observational cohort (Fig. 1). For the WHO grade III meningiomas and any Simpson's grade [arm 3&4], given the small numbers expected to enter the study, the patients were registered and were followed-up similarly to arm 1.

Ethical approval was obtained by competent committee(s) and according to national legislation.

Treatment

All patients received radiotherapy of 60 Gy and 70 Gy given in 30 and 35 daily fractions for patients with Simpson grade 1–3 and 4–5, respectively independent of the meningioma WHO grade. Treatment with RT started within 6 weeks after surgery. The target delineation definitions and dose constraints for organs at risk are detailed in Supplemental Tables 1 and 2. The quality assurance (RTQA) results of this study have been published previously [15]. Treatment after disease progression was left to the discretion of the treating physicians.

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.radonc.2018.06.018.

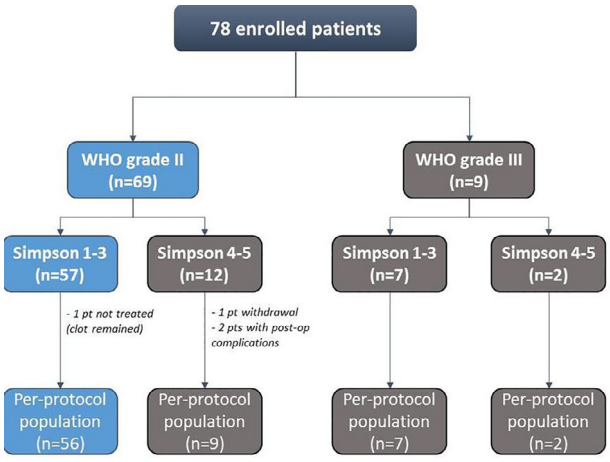

Fig. 1. EORTC 22042-26042 study chart and CONSORT diagram for the EORTC 22042-26042 study.

Follow-up assessments

Patients were followed up weekly during RT and 6 weeks after the last day of irradiation for performance status, cognition and acute adverse events. Then, patients were followed up at 6 and 12 months after registration and yearly thereafter for performance status, cognition, signs and symptoms, contrast enhanced MRI scan and survival. Tumor progression was determined by the radiologists from the recruiting centers. Signs and symptoms were scored with the National Cancer Institute Common Toxicity Criteria for Adverse Events version 3.0 and cognition with the Mini-Mental State Examination (MMSE) questionnaire.

Outcomes

The primary endpoint was progression-free survival at 3 years, defined as the time from study inclusion to the date of first progression (demonstrated by an MRI showing either appearance of new lesions or increase in tumor size by 25% using three-dimensional measurement) or death from any cause, whichever was earlier. Overall survival (OS) was a secondary endpoint and calculated from the date of study inclusion to the date of death from any cause. Other endpoints were cognitive effects, signs and symptoms. For the latter, the relationship with radiotherapy was not recorded in the database, we report, in line with RTOG 0539 [16] all emergent (new or worsening) dermatologic/skin (excluding hair loss/alopecia), neurological and ocular/visual signs and symptoms between start of treatment and disease evolution or new treatment, categorized as either acute (during RT and up to 90 days after RT) or late (>90 days after RT). For PFS and OS endpoints, patients still alive and had not met the endpoint at the last follow-up visit were censored.

Statistical analysis

PFS at 3 years was estimated by the Kaplan–Meier technique. The two-sided 95% confidence interval was calculated using Log–Log transform and the Greenwood formula to assess the primary protocol conditions for success. The sample size was estimated by simulation ($N = 5000$) of exponentially distributed time to event showing that 54 patients accrued uniformly over 5 years and followed a median of 3 years, would give 95% power to reject the null hypothesis of 70% 3-year PFS rate, under the alternative of a 3-year PFS rate of 90%, using a 1-sided type I error rate of 2.5% (i.e. 2-sided type I error rate of 5%). The analysis in the 3 other cohorts is purely descriptive.

Results

Between February 2nd, 2008 and June 28th, 2013, 78 eligible patients from 15 centers (7 countries) were enrolled into the study: 69 patients with WHO grade II meningioma (88.5%) and 9 patients with WHO grade III (11.5%). The majority ($n = 64$; 82.1%) of these accrued patients underwent complete resection (i.e. Simpson 1–3). Four patients did not start RT due to postoperative complications ($n = 2$), informed consent withdrawal ($n = 1$) and vascular event prior to RT ($n = 1$). In total, 74 eligible patients were treated with RT. The present report will focus on the 56 WHO grade II meningioma Simpson 1–3 patients [arm 1]. The descriptive results of the three other cohorts of patients are given in Supplemental Table 3. The characteristics of the 56 patients are detailed in Table 1.

Fifty-one out of the 56 treated patients (91.1%) received 60 Gy in 30 fractions as per protocol, with treatment duration from 16 to 73 days (Table 2). Five patients did not receive the planned RT dose: one patient prematurely stopped RT after 20 Gy (10 frac-

Table 1
Patient baseline characteristics (all treated patients).

	WHO grade II Simpson 1–3 [Arm 1] *N* = 56
Age (years)	
Median	54
Range	28–72
Gender	
Male	29 (51.8%)
Female	27 (48.2%)
Performance status	
0	42 (75.0%)
1	8 (14.3%)
2	6 (10.7%)
Simpson stage	
1	13 (23.2%)
2	27 (48.2%)
3	16 (28.6%)
MMSE	
≤26	10 (17.9%)
≥27	43 (76.8%)
Missing	3 (5.4%)
Localization	
Convexity	39 (69.6%)
Falx/parasagittal	10 (17.9%)
Medial Sphenoid Wing/parasellar	4 (7.1%)
Olfactive groove	1 (1.8%)
Posterior fossa	2 (3.6%)
Time from surgery to registration (days)	
Median	34
Range	13–61
Corticosteroids	11 (19.6%)
Anti-epileptic treatment	28 (50.0%)

Abbreviations: MMSE: mini-mental state evaluation.

Table 2
Treatment exposure.

	WHO grade II Simpson 1–3 [Arm 1] *N* = 56	
Duration of RT (days)		
Median	44	
Range	16–73	
Median RT dose (Gy)	60	
RT dose, *n*(%)		
20 Gy (10 fractions)	1 (1.8%)	
56 Gy (28 fractions)	1 (1.8%)	
58 Gy (29 fractions)	1 (1.8%)	
60 Gy (30 fractions)	51 (91.1%)	
70 Gy (35 fractions)	2 (3.6%)	
Dose per fraction (Gy)		
Median	2	
Range	2–2	
Type of RT, *n*(%)		
IMRT*	28 (50.0%)	
3DCRT	26 (46.4%)	
SFRT	2 (3.6%)	
	Before RT	During RT
Corticosteroids during RT	11 (19.6%)	8 (14.3%)
Anti-epileptic treatment during RT	28 (50.0%)	29 (51.8%)
Anti-emetic treatment during RT	1 (1.8%)	4 (7.1%)

Abbreviations: 3DCRT: 3D conformal RT; IMRT: intensity-modulated RT; SFRT: stereotactic fractionated RT.
* Including VMAT and Tomotherapy.

tions) due to grade 3 cerebrospinal fluid (CSF) leakage (unrelated to RT), two patients interrupted RT due to symptoms (vertigo associated with vomiting and epidermitis on scar) and two patients received 70 Gy instead of the planned 60 Gy. In addition, three patients temporarily interrupted RT for RT-technical issues, holidays or other reason but received the planned RT dose (60 Gy).

The rate of late emergent signs and symptoms grade 3 or more was 14.3% (Table 3). Serious adverse events related to RT were observed in 5 patients who had grade 3 ($n = 2$) or 4 ($n = 1$) seizure, grade 4 optic neuritis and retinopathy ($n = 1$) and grade 3 ischemia brain within the irradiated area ($n = 1$). No toxic death was observed.

At a median follow up of 5.1 years, 8 patients progressed: 2 patients presented with distant metastasis (cranial, $n = 1$; extracranial, $n = 1$), both of them with concomitant local failure and 6 patients presented with local failures only. The majority (75.0%) of those patients were salvaged by additional RT ($n = 3$), RT and surgery ($n = 2$) and surgery alone ($n = 1$). One patient died due to cardiovascular disease and two as a result of meningioma progression. The estimated 3-year PFS rate was 88.7% (95% CI: 76.5, 94.8), in line with the alternative hypothesis and the 3-year OS rate was 98.2% (95% CI = 87.6, 99.7; Fig. 1 & Table 4).

Secondary cancers were observed in 4 (7.1%) patients, none of them radiation-induced. One patient presented with uveal melanoma, 26.6 months after RT treated conservatively with proton therapy, another patient presented with a basal cell carcinoma inside the irradiation field, 9.4 months after RT treated with surgery, one patient presented with a tonsillar epidermoid carcinoma treated with chemo-radiotherapy, 38.4 months after RT and finally three other non-radiation-induced WHO grade II meningiomas in one patient treated by a second course of RT, 26.9 months after RT.

The mean MMSE score remained stable during the study: 28.5 ± 2.1 at baseline ($n = 53$), 28.7 ± 1.5 at 3 months ($n = 39$), 28.8 ± 1.9 at 1 year ($n = 46$ out of 52 alive at 1 year), 28.6 ± 1.9 at 2 years ($n = 33$ out of 51 patients alive at 2 years) and 28.7 ± 2.1 at 3 years ($n = 29$ out of 45 patients alive at 3 years).

Discussion

Our results indicate excellent patient's outcome, with approximately 90% (Fig. 2) progression-free survival rate at 3 years for WHO grade II patients undergoing complete resection and adjuvant high-dose RT to 60 Gy and with only two (3.6%) patients dying of meningioma during the follow-up period. This clinical result is superior to clinical outcomes reported in former RT series that administered a 'standard' radiation dose. Milosevic et al. reported on 59 WHO grade II–III meningioma patients treated with RT (median dose: 50 Gy) at presentation or recurrence and observed a 3-year disease-free survival of only 45% [8]. Several retrospective analyses have suggested higher historical tumor control with dose escalation [5,7,9,10,17] for non-benign meningiomas. Possible explanations for this dose-escalation finding may include small patient numbers, imbalances between the dose groups with respect to known and unknown baseline prognostic factors, imbalances in the use of second and third-line surgical procedures, disparities between radiation techniques and/or imaging modalities, statistical chance or a true dose–effect difference. The EORTC decided thus to embark in a prospective study in non-benign meningiomas and our results are in line with the recently published results of the phase II RTOG-0539 study assessing the outcome of intermediate risk meningioma (i.e. recurring grade I and newly diagnosed grade II meningiomas) patients receiving 54 Gy [16]. Of note, high risk (i.e. recurring or Simpson 3–4 WHO grade II or WHO grade III meningioma) patients in this study received 60 Gy delivered with IMRT or 3D-CRT. Although the results of this prospective study are not directly comparable to ours, as WHO grade I meningiomas were not included in our study, the primary endpoint was identical to our study and was compared to historical controls. Forty-eight eligible patients of intermediate risk were analyzed and a 93.8% 3-year PFS rate was observed. The EORTC and RTOG phase II studies, the first prospective clinical studies in

Table 3
Emergent signs and symptoms[#] (using CTCAE version 3.0).

	WHO gr II, Simpson 1–3 [Arm 1] *N* = 56				
	Grade1 *N* (%)	Grade2 *N* (%)	Grade3 *N* (%)	Grade4 *N* (%)	Grade ≥ 3 *N* (%)
Emergent signs and symptoms on-study	**17 (30.4)**	**18 (32.1)**	**8 (14.3)**	**3 (5.4)**	**11 (19.6)**
Late emergent (>90 days after end of RT) signs and symptoms	**16 (28.6)**	**18 (32.1)**	**6 (10.7)**	**2 (3.6)**	**8 (14.3)**
Dermatology/skin					
Dermatitis Radiation	9 (16.1)	2 (3.6)	1 (1.8)		1 (1.8)
Hyperpigmentation	10 (17.9)	2 (3.6)			
Hypopigmentation		1 (1.8)			
Pruritus	2 (3.6)				
Rash: Erythema Multiforme (e.g., Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis)	1 (1.8)				
Ulceration			1 (1.8)		1 (1.8)
Neurology					
Agitation	2 (3.6)	1 (1.8)			
Anxiety	1 (1.8)	3 (5.4)			
Ataxia					
Cns Necrosis		1 (1.8)			
Cognitive Disturbance	7 (12.5)	5 (8.9)	1 (1.8)		1 (1.8)
Confusion	5 (8.9)		1 (1.8)		1 (1.8)
Depression	2 (3.6)	5 (8.9)			
Dizziness	8 (14.3)	2 (3.6)			
Encephalopathy			1 (1.8)		1 (1.8)
Leak, Cerebrospinal Fluid (Csf)			1 (1.8)		1 (1.8)
Leukoencephalopathy	1 (1.8)				
Memory Impairment	11 (19.6)	4 (7.1)			
Mental Status		4 (7.1)	1 (1.8)		1 (1.8)
Neuropathy Cranial Cn Ii Vision	1 (1.8)				
Neuropathy Cranial Cn V Motor-Jaw Muscles; Sensory-Facial		1 (1.8)			
Neuropathy Cranial Cn Vii Motor-Face; Sensory-Taste		1 (1.8)			
Neuropathy Motor	3 (5.4)	3 (5.4)			
Neuropathy Sensory	4 (7.1)	1 (1.8)			
Seizure		9 (16.1)	3 (5.4)		3 (5.4)
Somnolence/Depressed Level Of Consciousness		1 (1.8)			
Speech Impairment				1 (1.8)	1 (1.8)
Tremor		1 (1.8)			
Other AE	2 (3.6)	1 (1.8)	1 (1.8)	1 (1.8)	2 (3.6)
Ocular/visual					
Blurred Vision	3 (5.4)				
Cataract	1 (1.8)		3 (5.4)		3 (5.4)
Dry Eye Syndrome	2 (3.6)	1 (1.8)			
Glaucoma	1 (1.8)			1 (1.8)	1 (1.8)
Keratitis	1 (1.8)	1 (1.8)			
Photophobia	1 (1.8)				
Retinopathy				1 (1.8)	1 (1.8)
Watery Eye					
Other AE	4 (7.1)			1 (1.8)	1 (1.8)

[#] RTOG 0539 items: any neurology, ocular/visual, dermatologic/skin (excluding hair loss/alopecia). As relationship to study treatment was not collected, all numbers in the table overestimate the rate of adverse events linked to radiotherapy since we cannot exclude events "not related" to radiation.

Table 4
Long-term outcome.

	WHO grade II Simpson 1–3 [Arm 1] *N* = 56
Progression-free survival	
Alive without progression	47 (83.9%)
Progression or death	9 (16.1%)
3-Year PFS (95% CI)	88.7% (95%CI: 76.5, 94.7)
Overall Survival at 3 years	
Alive	53 (94.6%)
Dead	3 (5.4%)
3-Year OS (95% CI)	98.1%(95% CI: 87.6, 99.7)

the meningioma literature, support the use of postoperative RT for newly diagnosed WHO grade II meningiomas undergoing complete resection. However, the different radiation dose levels administered in the two trials complicate the identification of the optimal dose strategy for these challenging patients. Additionally, the indication of RT for this type of meningioma undergoing complete resection is controversial, as reflected by several surveys [18,19]. This is currently being investigated in an ongoing phase III (ROAM-EORTC 1308) trial recruiting patients in the UK and elsewhere in Europe [20]. Some but not all [21,22] recent published data suggest excellent tumor control only for WHO grade II meningioma patients undergoing complete resection only with no adjuvant RT [11,23–25]. We are thus presently left with the conundrum of how to best treat these patients in terms of RT timing and radiation dose. The results of the ROAM-EORTC 1308 study are critically needed for Simpson 1–3 WHO grade II meningioma patients and will definitively answer the former question.

The emergent signs and symptoms rate was 19.6% on study and 14.3% restricted to events more than 90 days after RT. These rates however include an unknown proportion of events not related to radiation. We observed in total 12 serious events reported in 9 patients. Six 6 events (50%) were likely related to RT. Caution must be heeded when administrating radiotherapy to brain tumors, as adverse events secondary to radiotherapy, not limited to but including cognitive impairment [26], pituitary dysfunction [27] and secondary brain tumors [28] are well known. The majority of

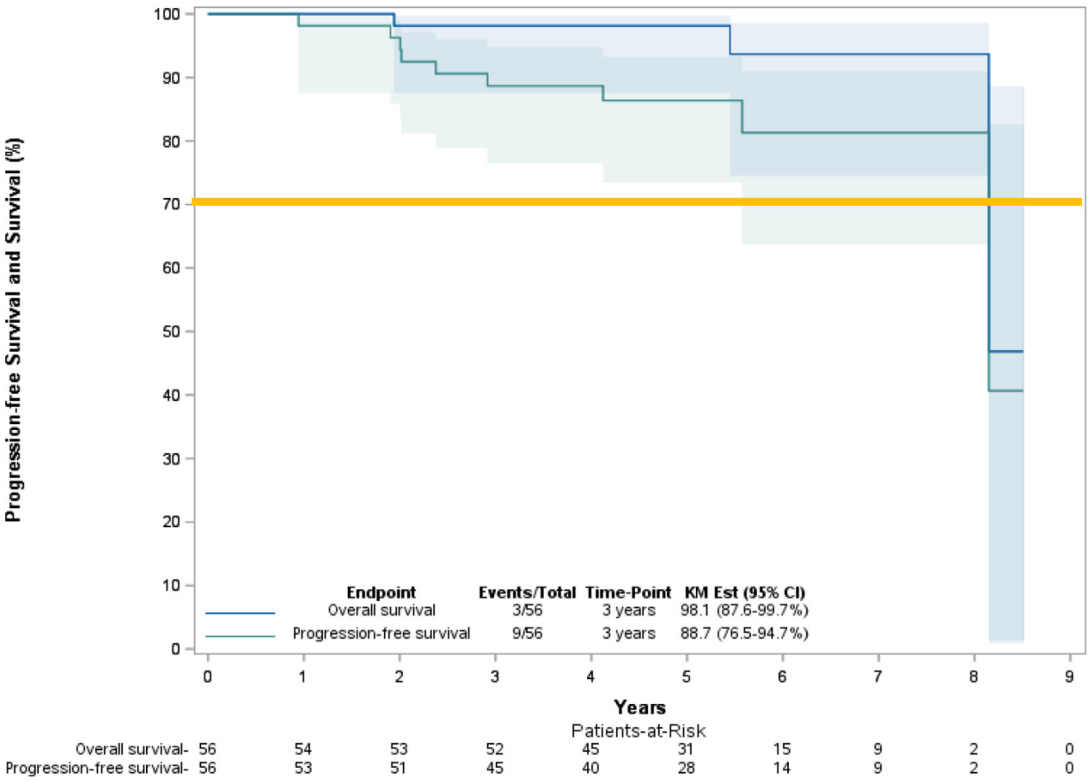

Fig. 2. PFS and OS Kaplan–Meier's curves for 56 Grade WHO 2 meningioma patients (Simpson 1–3) included in the EORTC 22042-26042 study. Hypothesis of this study was that high dose radiation therapy would increase the 3-year PFS in patients with meningioma WHO grade II.

the late serious adverse events, namely retinitis and optic nerve neuritis (Table 3) were observed in one patient treated in a low-accruing center and we cannot exclude that this patient received non-protocol compliant RT that could have been responsible of the observed adverse events. Although the dose levels of the retina and optic nerve of this patient were under the dose constraints detailed in Supplemental Table 2 (retina, D2% 49.4 Gy; optic nerve, D2% 57.7 Gy), it may well be that the observed toxicity was secondary to non-optimal RTQA of the plan delivered to this patient. In the US study, only grade 1–2 events were observed [16]. Interestingly, RTQA of this trial was excellent, with only 4.8% of the reviewed plans being non-protocol compliant. In the present study, RTQA was performed prospectively and each plan had to be uploaded in a secure server and reviewed prior to the initiation of the RT [15], using the same RTQA platform than the US trial [16]. Importantly, 18% of plans could not be prospectively analyzed as result of either corrupted or late data submission. Overall, one third of submitted plans presented minor (10%) or major (22%) protocol variations, superior to the RTQA violation rate observed by Rogers et al. [16]. Interestingly, the protocol variations were negatively associated ($p = 0.0013$) with the number of accrued patients per EORTC center. In 22042-26042 study, we observed major issues in RTQA, ranging from wrong dose prescription in arm 1 (70 Gy instead of 60 Gy) to the delivery of a wrong RT plan to a patient motivating the termination of the treatment. RTQA within the framework of prospective trials is an issue in brain tumor trials [29,30] and suboptimal RT may impact patient's outcome [31].

These data suggest that dose-escalation may be beneficial for non-benign meningiomas. If this treatment strategy is to be pursued, then modern radiation techniques should be administered to these patients, including but not limited to intensity-modulated RT, volumetric modulated arc therapy and particle therapy [5]. All these delivery techniques can achieve near optimal dose-conformation and further research is needed so as to define which meningioma patients may have a clinical benefit from non-photon RT. Particles should probably be reserved to volumetrically challenging meningiomas (regardless of the WHO grade) or WHO grade III tumors [32].

At baseline, only a minority of patients (17.9%) presented with cognitive impairment (MMSE score <27 before RT). The cognitive profile of the study population compares favorably to the reported cognitive status in meningioma patients in other series. Prior to surgery, mean MMSE score was 19.9 ± 11.4 in a series of 10 WHO grade I–II meningioma patients with a mean age of 68.1 ± 13.1 ye ars [33]. In this study, cognitive impairment was define as MMSE scores $\leq$23 which was observed in a substantial number of patients [33], unlike our study cohort in which only 1 patient presented cognitive impairment with this cutoff value at baseline. Other studies, analyzing the cognitive status of approximately 200 meningioma patients in total prior to treatment have shown undisputedly that cognitive function is indeed usually impaired in meningioma patients, except for individuals with incidentally defined meningiomas which may be cognitive-benign [34]. In our study, the mean MMSE score remained stable from 28.5 ± 2.1 to 28.7 ± 2.1 at 3 years. As such, these data suggest that high-dose RT does not impair the cognitive functioning of WHO grade II meningioma patients. These data are also in line with other series [26,35,36]. Although we acknowledge that using MMSE as a screening test is not sensitive enough to distinguish between mild cognitive impairment and normal cognitive functioning [37] we have been able to capture prospectively the cognitive status of these meningioma patients, as in another brain tumor EORTC trial [38], in all but 7 (13.2%) patients at follow-up due to the simplicity of the screening questionnaire in a framework of a prospective trial.

Finally, in the light of the observed radiation-induced adverse events in this study and others [39], it would be desirable to optimally tailor adjuvant radiation therapy for those patients at higher risk of progression/recurrence using other risk factors than WHO grading or histological subtypes prone to misinterpretations [40]. In addition to the investigation of the timing of RT for meningiomas, further research regarding the use of molecular information for clinical management of meningioma patients is justified in the framework of future prospective trials.

In summary, these data from a phase II study successfully showed that 3-year PFS for atypical meningioma undergoing complete resection is superior to 70% when treated postoperatively with high-dose RT.

Conflicts of interest

The author & co-authors have no potential Conflict of Interest.

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