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Efficacy and Tolerance of Intensity Modulated Radiation Therapy for Skull Base Meningioma

Youssef Brahimi MD [a], Delphine Antoni MD, MSc [a,b], Robin Srour MD [c], François Proust MD, PhD [d], Alicia Thiery MD [e], Pierre Wagner MD [f], Georges Noel MD, PhD [a,b,*]

[a]University Radiation Oncology Department, Comprehensive Cancer Center Paul Strauss, Strasbourg, France; [b]Laboratory of Radiobiology, Federation of Translational Medicine, Strasbourg University, Strasbourg, France; [c]Neurosurgery Department, Hôpital Pasteur, Colmar, France; [d]Neurosurgery Department, University Hospital of Strasbourg, Strasbourg, France; [e]Epidemiology and Biostatistics Department, Comprehensive Cancer Center Paul Strauss, Strasbourg, France; and [f]Radiology Department, Comprehensive Cancer Center Paul Strauss, Strasbourg, France

Abstract

Purpose: The purpose of this study was to evaluate the efficacy and tolerance of normofractionated stereotactic radiation therapy (RT) and intensity modulated RT with helical tomotherapy for skull base meningioma.

Methods and Materials: Between January 2009 and 2014, 46 patients with skull base meningioma were treated with normofractionated intensity modulated RT in stereotactic conditions (50%) or with helical tomotherapy (50%). Most of the lesions were localized in the cavernous sinus (59%). The mean planning target volume was 47.2 mL (range, 1.1-223 mL).

Results: After treatment, 5 lesions exhibited a partial response radiologically and 39 lesions were stable. At the time of treatment, 35 patients were symptomatic with a mean of 2 symptoms per patient. The most frequent symptoms were visual impairment (41%), cranial nerve dysfunction (20%), and headache (16%). The median follow-up time was 42 months (range, 10-76 months). After RT, 71% of patients exhibited an improvement of at least 1 symptom with a median interval of 15.6 months (range, 5.3-30.5 months). The most frequent improved symptoms were cranial nerve deficits (47%), visual impairment (45%), and headache (42%).The clinical response was correlated with the clinical target volume (CTV) margin ($P = .06$), extended clinical follow-up time ($P = .004$), and larger planning target volume ($P = .05$) by univariate analysis. Taking in account correlation factors, in the multivariate analysis, only CTV was a favorable significant factor of clinical improvement ($P = .049$; hazard ratio: 5 95%; confidence interval, 1.1-28). We observed 3 cases of trigeminal nerve dysfunction at 4.2, 5.7, and 24.6 months; 2 cases of visual disturbance at 10.1 and 24 months; 2 cases of neurocognitive disorders at 12.9 and 35.2 months; and 1 case of stroke at 20.3 months.

Conclusions: RT for skull base meningiomas is an effective and safe treatment, leading in most cases to clinical improvement. The addition of a CTV margin to meningioma volume improved the symptoms of patients.

Introduction

Meningiomas represent approximately 15% to 20% of all intracranial tumors.[1-5] These tumors are benign in 90% of cases, and mainly affect women with a sex ratio of 2:1.[6] The standard treatment of meningioma involves surgery with gross tumor resection. Progression-free survival after surgery is correlated with the extension of the resection.[7] For skull base meningiomas, especially those with cavernous sinus localization, tumor extensions, invasion of bony structures, and close vicinity to critical organs, resection opportunities are limited. Extended surgery leads to high rates of morbidity and mortality, even if surgery is performed by an expert surgical team.[2,8-14]

To reduce complications, exclusive or adjuvant radiation therapy (RT) after subtotal resection has been used with satisfactory results.[5,15-22] For lesions smaller than 3 cm and 3 to 5 mm away from the optic pathways, radiosurgery (SRS) is considered the best option.[23-25] For other lesions, normofractionated stereotactic RT (NFSRT) is generally proposed. NFSRT combines the precision of stereotactic repositioning and fractionation, yielding a low long-term toxicity rate.[16,20,21] Intensity modulated RT (IMRT) has demonstrated its applicability and efficacy in the case of large or complex shaped lesions.[1,3,5,26-28]

The main objective of skull base meningioma treatment is to obtain local tumor control combined with the preservation of neurologic functions.[2,8,12,29] However, most skull base meningiomas are associated with clinical symptoms at the time of radiation referral. The most commonly related symptoms are visual impairment, cranial nerve deficits (CND), and headache.[2,16,30]

Clinical analyses are not standardized, which results in some heterogeneity among the available clinical data. However, visual impairment is noted in 26.4% to 81% of patients,[2,18-22,30-32] and CND is stated in 22.3% to 82% of cases.[2,4,18,31-33] The purpose of this study was to evaluate the efficacy and tolerance of NFSRT and IMRT with helical tomotherapy (HT) for skull base meningioma.

Methods and Materials

Patient characteristics

Clinical data from 46 consecutives patients treated for skull base meningioma from January 2009 to December 2014 were retrospectively analyzed. Table 1 presents the patients' characteristics. Twenty-three patients were treated with NFSRT, and 23 patients with HT. Most of the patients were women (87%), and the average age was 59 years (range, 27-81 years). The lesions were mainly located at the cavernous sinus (27 cases), cerebellopontine angle (10 cases), and retroclival area (4 cases). Eighteen patients were already followed for a meningioma before being referred to the radiation department. Fourteen patients underwent operation (1 operation for 13 patients, and 2 operations for 1 patient), and the 4 remaining patients were supported with a watch-and-wait strategy.

At the time of this study, 26 patients (57%) were treated exclusively with RT, 8 patients (17%) with adjuvant RT, and 12 patients (26%) with salvage RT. For patients treated with adjuvant irradiation, resection was always considered incomplete according to the conclusion of the postoperative magnetic resonance imaging (MRI) scans.

Thirty-five patient files were suitable for post-RT clinical efficacy analysis. These symptomatic patients had an average of 2 symptoms (range, 0-4 symptoms) for a total of 76 symptoms (Fig 1). The main symptoms were visual impairment (41%), CND (20%), and headache (16%). The presence of a CND at the time of RT was not significantly correlated with a surgical antecedent (47% vs 40%; $P = .9$). Eight patients had asymptomatic hyperprolactinemia. No other initial endocrinologic disorder was diagnosed.

Planification treatment

For each patient, a 2.5 mm slice thickness computed tomography scan without intravenous contrast was performed. Patients were placed supine and immobilized in a custom-made contention mask. A T1 3-dimensional multiplanar reconstruction (MPR) gadolinium-enhanced and T2-weighted 2 mm slice thickness MRI scan was obtained. Computed tomography-MRI fusion was assessed using the iPlan RT Image 4.1.2 workstation (BrainLAB, Feldkirchen, Germany) for NFSRT or FocalSim workstation (CMS Focus, St Louis, MO) for HT to delineate target volumes and organs at risk. The gross tumor volume (GTV) included the enhancing volume observed on the T1 3D MPR sequence. The GTV was expanded in 3 dimensions by 5 mm to create the clinical target volume (CTV) for 27 patients. For the remaining patients, the CTV corresponded to the GTV. The variation of margin was related to a department policy with a change of protocol after literature analysis.

Table 1	Patients and treatment characteristics
	Number of patients (n = 46)
Sex	
Female	40 (87%)
Men	6 (13%)
Median follow-up time, months (min-max)	37 (5-76)
Median age, years (min-max)	59 (27-81)
Karnofsky performance status, median (min-max)	90 (70-100)
Antecedent of meningioma	
One previous surgery for meningioma	13 (28%)
>1 previous surgery for meningioma	1
Wait-and-watch approach for previous meningioma	4
Median time before relapse/ progression, months (min-max)	29.6 (10.6-294.7)
Histology	
Grade 1	20 (44%)
Unknown	26 (56%)
Skull base localization	
Cavernous sinus	27 (59%)
Cerebellopontine angle	10 (21%)
Clival	4 (9%)
Others	5 (11%)
Laterality	
Left	24 (52%)
Right	18 (39%)
Bilateral	4 (9%)
Median planning target volume (min-max)	47.2 (1.1-223)
Indication of radiation therapy	
Exclusive	26 (57%)
Salvage	12 (26%)
Adjuvant	8 (17%)
Median interval with surgery, months (min-max)	4.9 (1.3-10.9)

Abbreviations: max = maximum; min = minimum.

Table 2 presents the treatment planning. An isometric margin of 2 to 3 mm was applied to the CTV to generate the planning target volume (PTV). The mean PTV was 47.2 mL (range, 1.1-223 mL). Patients were either treated with NFSRT (23 patients) or HT (23 patients). The choice of the appropriate irradiation technique was decided during a technical meeting board with a physicist and radiation oncologist. The largest complex-shaped meningiomas or those close to the organs at risk were preferentially treated with HT.

For NFSRT, patients were treated on a dedicated 6 MV stereotactic linear accelerator, Novalis TX (Varian Medical Systems, Palo Alto, CA and BrainLAB, Feldkirchen, Germany). Treatment planning was achieved with 4 to 7 noncoplanar beams shaped using a micromultileaf collimator. The beams were modulated in intensity by the dynamic movement of leaves during irradiation (ie, sliding window).

The remaining patients were treated with the Tomotherapy Hi-ART system. The prescribed dose was 54 Gy in 30 fractions of 1.8 Gy, except for 1 patient with histologic-confirmed bone invasion who benefitted from 60 Gy in 30 fractions of 2 Gy.

Follow up and clinical evaluation

Patients were examined once a week during RT, and acute toxicity was assessed using the Common Terminology Criteria for Adverse Events, version 4. Data with regard to efficacy and late toxicity of RT were collected from follow-up consultation reports. Patients were reviewed 6 months on average after completion of treatment and every year thereafter. The evolution of symptoms described at the time of the initial consultation and the appearance of new symptoms were assessed. RT was considered effective in cases of at least partial improvement of minimum 1 symptom without concomitant progression of another symptom. The improvement could be objective and observed on clinical examination and on complementary examinations, or subjective and reported by the patient. The onset of a new symptom 3 months after the end of irradiation or aggravation of a symptom without associated tumor progression was considered late toxicity of RT. Local control data were recorded on clinical and radiologic follow-up reports. There was no consensual definition of radiologic answer. Information on deaths was collected regardless of cause. Survival data are not further detailed in this study owing to the small number of patients included and the low number of events observed.

Statistical analysis

The influence of prognostic factors on outcome was assessed. The statistical analyses were performed by the department statistician using R software.

Results

The median follow-up time was 42 months (range, 10-76 months). No cases of radiologic progression were reported. Available radiologic data reported tumor stability in 39 cases and 5 cases of partial response.

Among the 35 patients with initial symptoms, 25 patients (71%) experienced either complete or partial improvement of at least 1 initial symptom within a median time frame of 15.6 months (range, 5.3-30.5 months). Eight patients (23%) remained stable and 2 patients (6%) worsened. Of the 76 symptoms, 26% were completely resolved, 20% partially resolved, 39% stable, and 3%
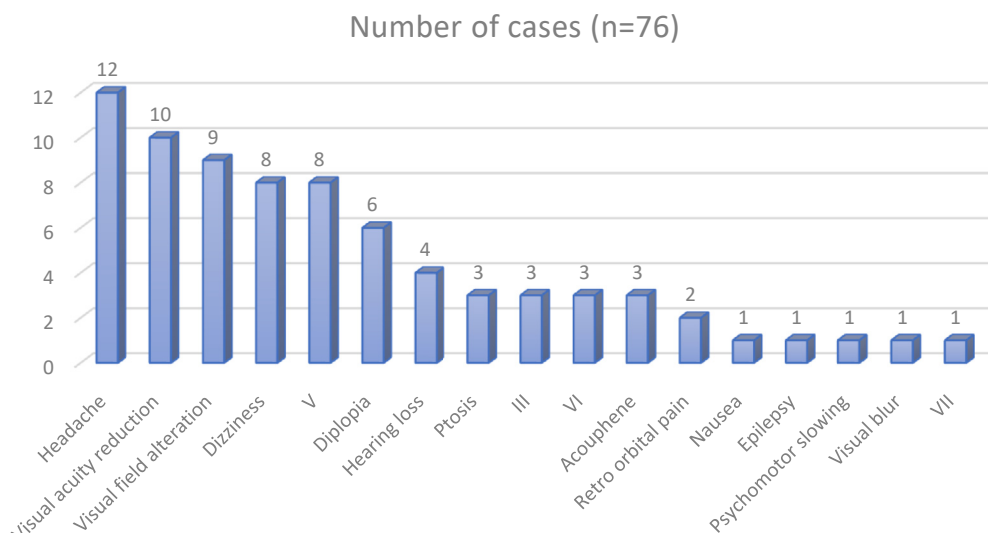
Figure 1   Distribution of symptoms.

exhibited clinical aggravation. The symptoms that most often improved included CND (47%), visual impairment (45%), and headache (42%). One-third of cases of CND improvement were related to the trigeminal nerve. The results were not available in 1 case. Table 3 summarizes the clinical responses. Two patients developed symptom aggravation, including a left scotoma and a case of right trigeminal neuralgia that worsened 18.7 and 31.6 months, respectively, after irradiation. No related tumor progression was noted on follow-up MRI scans for these 2 patients. Neuralgia evolved favorably under medical treatment with carbamazepine.

No correlation was noted between clinical efficacy and sex (men [67%] vs women [72%]; $P = 1$), lesion topography (cavernous sinus [76%] vs other skull base localizations [64%]; $P = .7$), surgery (operated patients [63%] vs non-operated [79%] patients; $P = .5$), and techniques of RT (NFSRT [75%] vs HT [68%]; $P = .9$).

The clinical efficacy rate was 85% for patients with a CTV margin of 5 mm versus 53% for patients treated without a CTV margin ($P = .06$). An analysis of types of IMRT subgroups (ie, upfront, adjuvant, or salvage) did not show any statistical implication of CTV. The median PTV of patients with a clinical improvement was significantly increased (65 mL; range, 7.8-184.5 mL) compared with those without improvement (18.2 mL; range, 1.1-216 mL; $P = .05$). The median PTV for HT was 72.7 cc (range, 12.7-223 cc) and the median PTV for NFSRT was 27.9 cc (range, 1.1-149.2 cc; $P = .0006$). A larger PTV was not correlated with the number of symptoms per patient ($P = .8$). If PTV can be a significant factor of symptom improvement, this is independent of the type of device used to treat the patient. However, there was a strong correlation between PTV and the use of CTV.

Patients with a clinical improvement exhibited a longer follow up compared with patients who were stable or worsened (median: 39 months [range, 25-76 months] vs median: 20 months [range, 5-54 months), respectively; $P = .0037$). However, no improvement of clinical symptoms was observed after 30.5 months of follow up in the groups of patients treated with or without CTV.

Table 2   Treatment protocol

Technical details	
NFSRT	23 (50%)
HT	23 (50%)
Median dose (min-max)	54 Gy (54-60)
Number of fractions, median (min-max)	30 (27-30)
Dose per fraction, median (min-max)	1.8 (1.8-2)
Isodose of prescription	95%
NFSRT median PTV (min-max)	27.9 (1.1-149.1)
HT median PTV (min-max)	72.8 (12.7-223)
NFSRT margins	
CTV = GTV + 5 mm	13 (57%)
No CTV	10 (43%)
PTV = CTV + 2 mm	4 (17%)
PTV = CTV + 3 mm	9 (39%)
PTV = GTV + 2 mm	8 (35%)
PTV = GTV + 3 mm	2 (9%)
HT margins	
CTV = GTV + 5 mm	14 (61%)
No CTV	9 (39%)
PTV = CTV + 2 mm	0
PTV = CTV + 3 mm	13 (56%)
PTV = GTV + 2 mm	8 (35%)
PTV = GTV + 3 mm	2 (9%)

Abbreviations: CTV = clinical target volume; GTV = gross tumor volume; HT = helical tomotherapy; max = maximum; min = minimum; NFSRT = normofractionated stereotactic radiation therapy; PTV = planning target volume.

Table 3 Number of clinical responses of the patients with interval of improvement

Clinical efficacy	Complete response	Interval in months, mean (min-max)	Partial response	Interval in months, mean (min-max)	Stability	Aggravation	Interval in months, mean (min-max)	Not reported	Total
Headache	1	12	4	16 (9.2-45.7)	4	0		3	12
Dizziness	2	5.3	2	16 (12-19.3)	3	0		1	8
Nausea	1	5.3	0		0	0		0	1
Epilepsy	1	30.5	0		0	0		0	1
Psychomotor slowing	0		0		1	0		0	1
Visual impairment	9	15.6 (4.9-42.4)	5	18.1 (12-48.3)	12	1	18.7	4	31
Cranial nerve deficit	6	13.5 (5.3-25.4)	1	13.4	6	1	31.6	1	15
Hearing impairment	0		3	17.1 (19.3-48.3)	4	0		0	7
Total	20		15		30	2		9	76

Abbreviations: max = maximum; min = minimum.

Furthermore, there was a clear correlation between longer follow up and the use of CTV. When taking correlation factors into account, in the multivariate analysis, only CTV was a favorable significant factor of clinical improvement (P = .049; hazard ratio: 5; 95%, confidence interval, 1.1-28).

The main late toxicities are described in Table 4. There were 3 cases of neuralgia of the trigeminal nerve at 4.2, 5.7, and 24.6 months. These impairments did not require medical treatment and spontaneously resolved at 10.6, 32, and 36 months of follow up. Two cases of visual disturbance were reported. A right lower scotoma was observed 24 months after NFSRT. Doses in the chiasma (D_{max} = 54.2 Gy), right optic nerve (D_{max} = 12.4 Gy), and right eyeball (D_{mean} = 9.7 Gy) were below the prescription constraints.

A case of bilateral cataract was reported 10.1 months after completion of RT in an 89-year-old patient treated with HT for a bilateral cavernous sinus meningioma. D_{max} in the lenses were each <3 Gy. One case of transient aphasia at 12.9 months spontaneously resolved 18 months after NFSRT. A 72-year-old patient complained of slight memory loss 35.2 months after HT completion. Finally, a stroke occurred in a 34-year-old patient 20.3 months after the end of RT. With regard to late endocrine toxicity, 6 new cases of hyperprolactinemia were observed and 1 patient was treated with thyroid replacement therapy 19.4 months after the end of RT. No new late complications occurred beyond 3 years after the end of RT (Fig 2). The rate of late complications at 36 months was 17%. No predictive factor of late complications was identified.

Discussion

RT is commonly recommended in the management of skull base meningiomas, both for exclusive treatment and after subtotal resection.[2,5,18,19,28,30,32,33] Although the results from our institutional experience with NFSRT and HT are consistent with those of previously published series, comparisons should be made cautiously because all these studies are retrospective in nature with non-standardized clinical analyses.[2,20,30,32,34]

Table 4 Details of 8 late toxicities with interval of appearance

Complications	No. of patients	Details	Interval from end of radiation therapy (months), median (min-max)
Cranial nerve deficit	3	3 cases of trigeminal nerve deficiency	11.5 (4.2-24.6)
Neurocognitive disorders	2	1 case of transient aphasia 1 case of slight loss memory	24 (12.9-35.2)
Visual impairment	2	1 case of visual field alteration contralateral to the lesion 1 case of bilateral cataract	17 (10.1-24)
Stroke	1	Stroke sylvian left	20.3

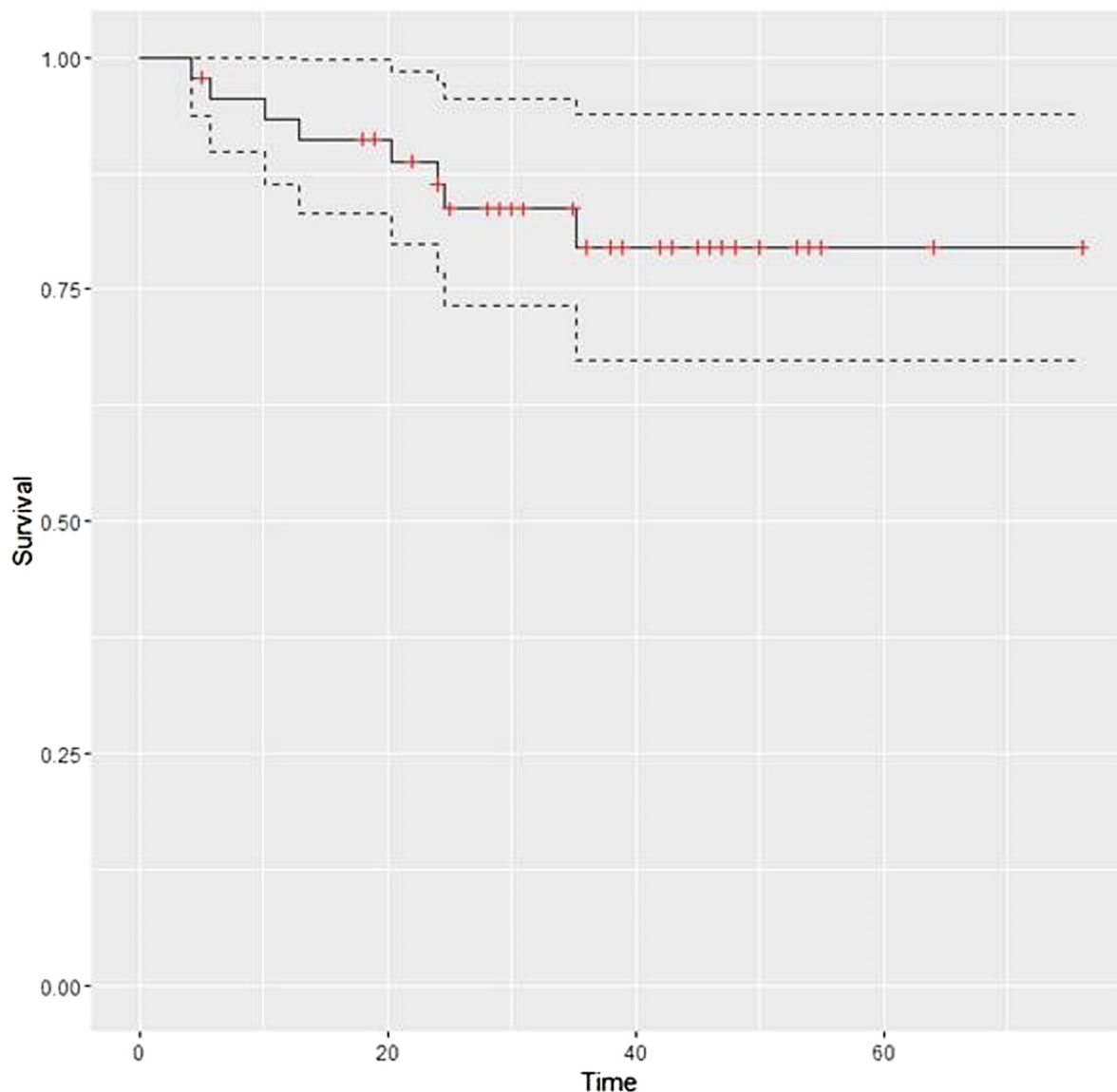*Abbreviations:* max = maximum; min = minimum.

Figure 2   Survival without complications.

Clinical efficacy

After NFSRT, clinical improvement rates of 20% to 67% have been reported.[2,19-22,30,32,33] Clinical response was obtained between 2 and 16.8 months after radiation completion.[32,33] There are few series evaluating clinical efficacy after HT.[4,28,35,43] Most studies about HT were in silico dosimetric comparisons.[36-41]

Only 1 study evaluated clinical efficacy, with a very short follow-up period of 7.5 months. Among 28 patients, the clinical improvement rate was 18%, and headache and CND were mainly reported.[4] Our results are comparable given that 11% of patients exhibited clinical improvement at 7.5 months of follow up. Finally, with a clinical improvement of 71% of symptoms within an average time frame of 15.6 months, our results compare favorably with those of other studies.

Complications

Eight patients developed late complications (17%). This rate may be increased compared with other studies. However, questionable symptoms were assumed as late toxicity. We considered complications as all new symptomatic complaints. However, none of these complaints appeared related with a nonprotocol dose or a dose superior to those classically published and recommended as a dose constraint. Most complications were slight or transient. Notably, cognitive troubles and stroke are always more unmanageable.

Uy et al reported on the case of an 87-year-old patient who underwent irradiation for a cavernous sinus meningioma and developed memory and personality disorders that led to a loss of autonomy 6 weeks after completion of irradiation. The patient died 19 months after RT, although

meningioma remained controlled on the last follow-up MRI scan.

Brell et al presented 2 cases of moderate cognitive disorders. Mini-Mental State Examination scores were <25 for both patients. The MRI scans obtained at the time of the neurocognitive deficit did not show any progression or other complications. These cases are comparable with the 2 cases of late cognitive disorders reported herein. The first case involved transient aphasia 12.9 month after RT in a 56-year-old woman treated for a left cavernous sinus meningioma. The transient aphasia was nevertheless assumed as a late toxicity of RT, even if the doses to the cortex areas controlling language were not known. The second case of cognitive impairment developed in a 76-year-old woman treated for a right cavernous sinus meningioma. Neurocognitive assessment confirmed slight memory disorders. The follow-up MRI scans for these 2 patients did not detect any tumor progression or other abnormality that may explain these impairments.

Solda et al reported on 2 cases of stroke (59 and 73 months after treatment) and 1 case of transient ischemic attack (27 months after treatment) after NFSRT for skull base meningioma.[22] Selch et al reported on 1 case of stroke 6 months after irradiation of skull base meningioma.[31] We reported on the case of a 33-year-old patient treated for right cavernous sinus meningioma who presented a left sylvian ischemic stroke 24 months after completion of NFSRT. This patient previously underwent total body irradiation in childhood for Fanconi disease. Five months after the onset of the stroke, the patient experienced inhalation pneumopathy and died.

Predictive factors of clinical response

Surgery before RT has been described as a negative predictive factor of clinical response in several series. These results are reported both after NFSRT and SRS.[17,21,29,30,32,42,43] Kano et al reported clinical improvement rates of 37% compared with 14% after exclusive SRS versus postoperative SRS, respectively (P = .001).[17] Spiegelmann et al published the same observation with 43% in the case of exclusive SRS compared with 19% clinical improvement in the postoperative SRS group.[43] Shen et al identified a surgical antecedent as a negative predictor of clinical response (odds ratio: 0.47; 95% confidence interval, 0.25-0.86).[32] Surgery could cause irreversible neurologic lesions unrecoverable even after RT.

Littre et al did not identify significantly increased clinical efficacy rates in non-operated patients, whereas surgery patients had more CND.[21] In the current study, there was neither a tendency for more CNDs in operated patients nor better RT efficacy in non-operated patients. Spiegelman et al reported that when SRS was delivered <1 year after the onset of a CND, the results in terms of

neurologic recovery were better. In 43 cases of CND where the duration of symptoms was short, the improvement or disappearance of symptoms in 49% of patients was observed. In contrast, in 58 cases of CND with a duration of >1 year, improvement was only observed in 19% of patients (P < .03).[43]

The addition of a CTV margin, prolonged follow-up period, and voluminous PTV has never been reported as a predictive factor of clinical efficacy. However, these factors in univariate analysis have a strong correlation. The addition of a CTV margin is rarely reported in published studies.[30] A CTV margin of 5 mm was described in 27 current patients, and led to enhancement in clinical efficacy without increasing the risk of complications. The explanation for this result is likely not unique. Only some assumptions can be proposed. The margin can improve the insufficiency of imaging to visually separate brain and meningioma, although we use an MPR MRI sequence. Another reason could be that some small vessels invaded the brain parenchyma but are not clearly visible, even with gadolinium MRI sequences. Our choice of doses and margins was based on our local delineation guidelines on the basis of data from the literature.[34,44-46]

Clinical efficacy was significantly increased in patients with prolonged clinical follow up. Subjectively, the longer tissue is subjected to injury, the longer the time required for recovery is important. However, we were unable to calculate the duration of impairment given that the lack of data concerning the precise time of symptom onset did not permit this analysis. In the current series, the median time to clinical improvement was 15.6 months (range, 5.3-30.5 months). No improvement was observed after 30.5 months in both groups of patients treated with or without CTV margin.

This is an additional argument for the major role of CTV margin to improve clinical symptoms for patients with meningioma. Some authors reported a shorter time of recovery, but the range of this timing was similar to ours. Shen et al reported a 57% clinical improvement, mainly within 6 months (range, 2.4-16.8).[32] Minniti et al reported a 20% improvement in CND within a period varying between 2 and 16 months from the end of RT.[33] The length of clinical improvement was longer in our study, but the rates were also significantly increased.

Interestingly, clinical efficacy was significantly improved in cases with a large PTV. The first hypothesis was that patients with large meningiomas had significantly more symptoms and therefore more likely to have clinical improvement. However, this hypothesis was not confirmed. Thus, the explanation could be mechanical. First, larger lesions might be more sensitive to the decompressive effect of RT, and potentially lead to symptom improvement. Second, the correlation between CTV and PTV can lead to the improvement of clinical symptoms owing to the addition of CTV margins.

Clinico-radiologic dissociation

In our study, 24 patients exhibited clinical improvement, whereas tumor reduction was reported in only 5 cases (11%). The dissociation between clinical and radiologic response was previously reported by other authors who observed clinical improvement combined with low rates of radiologic response.[16,30-32] After NFSRT, the rate of decrease in tumor volume varied between 9% and 32%.[20,22,30-33] After SRS, the highest rate of tumor reduction ranged from 19% to 74%, but higher rates obtained with SRS could be related to the lower volumes of the irradiated lesions, which rarely exceeded 10 mL.[2,17,23,24,42,43,47,48] Pirzkall et al assumed that the regression of possible peri-tumoral edema not visible on MRI scans could explain the early effectiveness of RT.[16] Shen et al proposed that a redistribution of vascular flow from the tumor to the affected cranial nerves could improve neurologic function.[32]

In this series, we attempted to provide the most accurate description of clinical efficacy and tolerance after RT. After a median follow-up time of 3 years, approximately 90% of the expected late complications attributable to RT had already occurred.[49] Our results are consistent with these findings. With a median of 42 months of follow up, no late complications were detected after a follow-up period of 36 months. Radiologic response was demonstrated based on radiologic and clinical follow-up reports, and there are no definite radiologic response criteria after irradiation of meningiomas.[2,17,30,31,43]

The limitations of this current study are similar to those reported in the other publications, namely, a retrospective study, a small number of patients, and a relatively short follow-up period that does not offer sufficient events to draw definitive conclusions.

Conclusions

The main objective of skull base meningioma treatment is to preserve neurologic function with minimal morbidity. In this perspective, RT provides an excellent compromise between these 2 constraints despite the lack of objective radiologic response in most cases. Furthermore, IMRT provides a high rate of clinical symptom improvement, and the current study demonstrated that adding a CTV margin is the only predictive factor of this improvement.

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