J Neurooncol
DOI 10.1007/s11060-009-0084-1

CLINICAL STUDY - PATIENT STUDY

Patterns of failure after stereotactic radiotherapy of intracranial meningioma

Vasileios Askoxylakis · Angelika Zabel-du Bois · Wolfgang Schlegel · Jürgen Debus · Peter Huber · Stefanie Milker-Zabel

Received: 6 August 2009 / Accepted: 30 November 2009

Abstract The aim of this work is to evaluate patterns of failure in patients with recurrent meningioma after stereotactic radiotherapy. Of 411 patients with intracranial meningioma treated with radiotherapy at our institution, 22 patients with local tumor progression diagnosed by magnetic resonance imaging (MRI) after radiotherapy (RT) were identified and further investigated. The histologic grade of the meningiomas was World Health Organization (WHO) grade I in 54.5%, WHO grade II in 27.3%, and WHO grade III in 9.1% of cases. Fourteen patients had received fractionated stereotactic RT; five patients underwent intensity-modulated RT. The median total dose was 57.6 Gy at 1.8 Gy/fraction, five times weekly. Local recurrences were divided into the dosimetric categories "central" ("in-field") and "marginal" ("out-field"). Median follow-up was 59.5 months. Eleven local failures were found to be central, and 11 were marginal. Recurrence-free survival ($P < 0.05$) and site of local recurrence ($P < 0.05$) depended statistically significantly on histology. Median recurrence-free survival was 46 months for patients with benign meningioma (WHO grade I) and 31.5 months for patients with higher-grade meningioma (WHO grade II/III). In the WHO grade I group, three recurrences were central and nine were marginal, whereas in the WHO grade II/III group seven recurrences were central and one was marginal. Median time to local tumor progression and site of local recurrence significantly depended on histological grade of meningioma. Regarding site of failure, improvement of dose coverage for benign meningiomas and dose escalation for high-grade tumors might further improve therapy outcome.

Keywords Intracranial meningioma · Recurrence · Stereotactic radiotherapy

V. Askoxylakis · A. Zabel-du Bois · J. Debus · S. Milker-Zabel (✉)
Department of Radiation Oncology and Radiotherapy, University Hospital of Heidelberg, Im Neuenheimer Feld 400, 69120 Heidelberg, Germany
e-mail: stefanie_milker-zabel@med.uni-heidelberg.de

A. Zabel-du Bois · P. Huber · S. Milker-Zabel
Department of Radiotherapy, German Cancer Research Center, Heidelberg, Germany

W. Schlegel
Department of Medical Physics, German Cancer Research Center, Heidelberg, Germany

Introduction

Meningiomas are the most common benign nonglial brain tumors in adults, arising from cap cells of the arachnoid membrane and representing about 13–26% of all primary brain tumors [1]. Peak incidence is in the fifth, sixth, and seventh decades, with a predominance in women. The annual occurrence of the disease is estimated to 1–5/100,000/year for men and 2–7/100,000/year for women [2]. Histologically they are classified into three grades according to the World Health Organization (WHO) classification of tumors of the nervous system [3]. Up to 85% of meningiomas are benign lesions of WHO grade I, characterized by slow growth and good prognosis after complete resection. About 10% are atypical lesions of WHO grade II, and 3–5% are anaplastic lesions of WHO grade III. Meningiomas of WHO grade II/III represent a more aggressive subgroup, characterized by rapid growth, higher risk of recurrence after surgical resection, and shorter survival times.

Published online: 13 December 2009

The primary therapy of meningiomas is neurosurgical resection. Complete resection of the tumor, including resection of the dura mater margins and involved bone, is associated with high rates of cure. The 5-year recurrence-free rate after complete resection is 95% for WHO grade I meningiomas, 30–50% for WHO grade II meningiomas, and 38–78% for WHO grade III meningiomas [4]. However, complete resection of the tumor is not always possible, due to proximity to surrounding critical structures, such as the optic nerves, the brainstem, as well as neurovascular structures such as the venous plexus. Total resectability rates vary between 20% and 90%, depending on the localization and size of the tumor [5, 6].

Radiotherapy (RT) represents one of the main therapeutic modalities of meningioma. Although the role of this modality in treatment of meningioma was controversial for a long time, it is now considered standard for atypical and malignant meningioma after surgical intervention independent of the resection grade as well as in recurrent meningioma. In case of benign meningioma, radiation therapy is used after incomplete resection or in case of tumor progression. Evaluation of the long-term results of fractionated stereotactic radiotherapy of subtotally resected or unresectable WHO grade I base-of-skull meningiomas revealed 5-year survival rates of up to 97% and 10-year survival rates of up to 96%, with very low incidence of subacute or late side-effects, demonstrating the effectiveness of this treatment modality [7]. Within recent years, the development of advanced radiation therapy strategies, such as intensity-modulated radiotherapy (IMRT), has allowed the application of higher doses to the target volume, while sparing the surrounding radiosensitive healthy structures and minimizing side-effects [8].

Meningiomas that have recurred once tend to recur again at shorter intervals [9]. After first recurrence the probability of 2- to 5-year progression-free survival is about 50% after neurosurgical retreatment, enhanced to about 80% when followed by additional radiation therapy. However, although the development of therapy techniques has led to more effective treatment of the disease, and the progression-free survival rates of meningioma patients has been evaluated extensively, published data about characteristics of patient collectives that recurred after radiotherapy are scarce. Therefore, patients with recurrent meningioma after surgery and radiotherapy still represent a therapeutic challenge.

The present article is an analysis of patterns of failure after stereotactic radiotherapy of intracranial meningioma of a large patient cohort treated at a single institution with modern radiotherapy techniques. Aim of the study was to investigate factors that may influence radiation outcome, and eventually optimize the treatment strategies to further improve the efficacy of the therapeutic modalities.

Patients and methods

Between October 1985 and December 2004, 411 patients with intracranial meningioma were treated with radiotherapy at our institution. The WHO grade distribution of the initial 411 patients is summarized in Table 1. Of these, 28 patients (6.8%) who experienced local recurrence after radiation therapy [10, 11] were identified and further investigated. Six cases were excluded from this analysis. In two cases the meningioma recurred after primary radiotherapy as well as after re-irradiation, which was considered as one case, respectively. In one patient the meningioma was initially described as progressive on MR imaging; however, in the mid-term follow-up after 3 months the meningioma proved to be stable in the long-term follow-up and was excluded from this study. In another patient the irradiated meningioma remained stable, while a second synchronous untreated meningioma showed local progression. Two patients were lost to follow-up, leaving 22 cases for evaluation. The male/female ratio was 1:2.1 (7:15); median Karnofsky performance score was 80% (70–90%). Median age at initiation of radiation therapy was 53.8 years (range 12.3–75.1 years).

Twenty patients had histologically proven diagnosis of meningioma. In two cases the clinical and radiological characteristics of the tumor were consistent with the clinical diagnosis of meningioma. The most frequent histology was WHO grade I (12 patients), followed by WHO grade II (6 patients) and III (2 patients). Twenty patients received postoperative radiotherapy, while in two patients primary radiotherapy after diagnosis was performed, due to inoperability of the meningioma. The number of resections before RT was variable. Thirteen patients had been operated once, six underwent two surgical interventions, and one patient underwent three interventions. The mean delay between last surgery and irradiation was 11.3 months with a median of 7.5 months (range 1–58 months).

Of 19 patients treated after the year 1990, 14 received fractionated, stereotactic radiation therapy (FSRT) and 5 were treated with intensity-modulated radiation therapy (IMRT). Three patients were treated before the year 1990 using other radiation techniques but also three-dimensional treatment planning. Two of them had electron radiation

Table 1 WHO grade distribution of the initial 411 patients treated at our institution

Histologic grading	Frequency
WHO grade I	204
WHO grade II	35
WHO grade III	4
Unknown	168

therapy and one patient was treated with a cobalt unit. The median dose for the entire population was 57.6 Gy (range 44–68 Gy) with a median daily fraction of 1.8 Gy.

Patient characteristics and localization of all 22 intracranial meningiomas are summarized in Tables 2 and 3.

FSRT was performed as described elsewhere [12]: The patients were immobilized in an individual head-mask fixation system made of scotch-Cast^{TM}, assuring a setup accuracy of 2 mm [13]. Treatment planning was based on computed tomography (CT) and MRI of the head under stereotactic guidance. In particular, treatment planning was performed on a three-dimensional CT data cube generated from continuous 3-mm CT scans after stereotactic fusion of MRI scans, obtained in treatment position. The treatment planning system Virtous/in-house developed by DKFZ (available as Virtuoso; Leibinger Co., Freiburg, Germany) has been used. The planning target volume (PTV) and organs at risk such as eyes, optic nerves, chiasm, and brain stem were delineated on each slice of the data cube. Irregular beam shaping was achieved by customized field shapes generated by beam eye-view (BEV) technique, using a multileaf collimator (leaf width: 5 mm at isocenter). A noncoplanar field arrangement with a median of four isocentric fields was used. FSRT was delivered with a 6/15-MV linear accelerator (Siemens AG, Erlangen, Germany). PTV was covered by the 90% isodose and included the macroscopic tumor visible on CT/MRI with a safety margin of 1–2 mm to healthy brain tissue, 3 mm to adjacent osseous structures, and 5 mm along the dura. Intensity-modulated radiotherapy (IMRT) was performed with a 6/15-MV linear accelerator (Siemens AG, Erlangen, Germany). Treatment plan was based on CT/MRI scans of the head in an individual scotch-Cast^{TM} mask fixation. Treatment plan was created using the Konrad inverse treatment planning program (MRC Systems GmbH, Heidelberg, Germany), developed at the German Cancer Research Center, Heidelberg [14]. For IMRT a median of seven beams were used. Radiation treatment was performed using a commercial integrated motorized multileaf collimator in a “step and shoot” technique [15].

Table 2 Patient characteristics ($n = 22$)

Sex (female/male)	15/7
Median age (years)	53.8 (range 12.3–75.1)
Median Karnofsky performance scale (%)	80 (range, 70–90)
Median tumor volume (cc)	95 (range, 11.8–457)
Histologic grading	
WHO grade I	12 (54.5%)
WHO grade II	6 (27.3%)
WHO grade III	2 (9.1%)
Unknown	2 (9.1%)
Primary therapy	
Total resection	4 (18.2%)
Subtotal resection	16 (72.7%)
Primary radiotherapy	2 (9.1%)
Radiation technique	
FSRT	14 (63.6%)
IMRT	5 (22.7%)
e^-	2 (9.1%)
Co-60	1 (4.6%)
Median total dose (Gy)	57.6 (range 44–68)

Table 3 Localization of the meningiomas, recurred after radiation therapy

Localization	Frequency	%
Sphenoidal	5	22.7
Petroclival	3	13.7
Cavernous sinus	4	18.2
Sellar	1	4.5
Convexity	3	13.7
Falx	1	4.5
Cerebellar	1	4.5
Frontobasal	2	9.1
Multilocular	2	9.1

Follow-up was performed at 6 weeks, 3 months, 6 months, and 12 months for the first year and then once a year. Follow-up included radiologic imaging (MRI) and clinical and neurological examinations. Inclusion criterion for this study was radiologically proven local recurrence, defined as local tumor progression on MRI.

In order to evaluate the site of local failure, recurrent events were divided into two dosimetric categories: those within the region that received at least 90% of the prescribed dose (high-dose region) were considered “central” or “in-field,” and those in regions that received less than 90% of the prescribed dose (low-dose regions) were considered “marginal” or “out-field.”

For evaluation of the influence of histological grading on recurrence localization and recurrence-free survival, subanalysis was carried out for patients with benign meningioma (WHO grade I) versus patients with higher-grade disease (WHO grade II/III). Statistical analysis was performed with the Fisher exact test for localization of local recurrence and Shapiro-Wilk normality test for recurrence-free survival. Results were considered significant for P value <0.05.

Results

Median follow-up was 59.5 months (range 16–161 months). All patients were followed for more than 12 months, 17/22

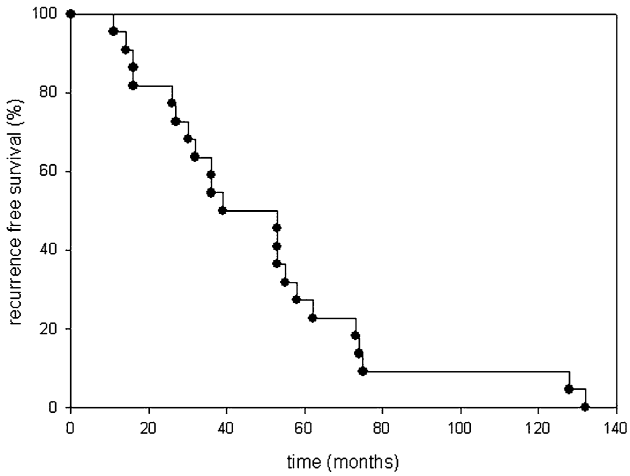

Fig. 1 Recurrence-free survival calculated from time of radiotherapy according to Kaplan–Meier method

(77.3%) patients for more than 36 months, 15/22 (68.2%) patients for more than 48 months, and 11/22 (50%) patients for more than 60 months. The median PTV was 95 cm^3 (range 11.8–457 cm^3).

The median time to recurrence after radiation therapy was 46 months for the entire population (range 11–132 months). One-, 2-, 3-, 4-, and 5-year local control rates for the entire group of patients were 95.5%, 81.8%, 63.6%, 50%, and 27.3%, respectively (Fig. 1).

Evaluation of the local recurrence events revealed 11 events as central or in-field, while 11 events were found to be marginal or out-field.

The median PTV for patients with WHO grade I meningioma was 86.3 cm^3 and for patients with WHO grade II or III meningiomas was 152.4 cm^3. The recurrence-free survival rate after radiation therapy for benign WHO grade I intracranial meningiomas was 66.7% at 3 years and 25% at 5 years. Patients with WHO grade II or III meningioma had a recurrence-free survival rate after radiotherapy of 50% at 3 years and 25% at 5 years. The median time to recurrence after radiotherapy was 46 months (range 11–128 months) for patients with WHO grade I meningioma and 31.5 months (range 14–75 months) for patients with WHO grade II or III meningioma ($P > 0.05$).

Differences were revealed in regard to the site of local recurrence between the two subgroups. In particular, among 12 patients with WHO grade I meningioma, 9 recurrences were found to be marginal or out-field (75%) and 3 recurrences were found to be central or in-field (25%). Among eight patients with WHO grade II or III intracranial meningioma who recurred after radiation therapy, seven recurrences were identified as central or in-field (87.5%) and one recurrence was identified as marginal or out-field (12.5%) (Table 4). The correlation between

Table 4 Recurrence site in patients with intracranial meningioma after radiotherapy ($n = 22$)

Histological grading	In-field	Out-field
WHO grade I	3 (25%)	9 (75%)
WHO grade II or III	7 (87.5%)	1 (12.5%)
Unknown	1 (50%)	1 (50%)

WHO grade and localization of the local recurrence was statistically significant ($P < 0.05$).

Two patients with intracranial meningioma WHO grade I received re-irradiation after local failure. One of them showed a re-recurrence event 32 months after retreatment. Within the collective of patients with WHO grade II or III meningiomas, three received re-irradiation treatment after diagnosis of local recurrence. In two cases a re-recurrence event occurred, with mean re-recurrence-free survival calculated to be 23.5 months.

In regard to overall survival, four patients died, a median of 6.9 years (range 3.4–10.4 years) after radiation therapy. In two cases cause of death was progressive heart disease. Only one patient died of progressive primary disease, while the fourth patient died of other causes.

Discussion

Radiation therapy is one of the main therapeutic modalities for treatment of intracranial meningiomas. Since it is possible to treat meningiomas effectively with highly conformal radiotherapeutic techniques, only a few local failures were reported. Evaluation of the results of radiotherapy in large collectives of patients with intracranial meningiomas revealed very good long-term tumor control and low local recurrence rates. Vendrely et al. [16] evaluated the results of fractionated radiation therapy on a collective of 156 patients with intracranial meningiomas and described a recurrence rate of 13.5% and a local control rate of 79.4% after median follow-up of 40 months. In another retrospective study of 82 patients with benign skull-base meningioma treated by fractionated external-beam radiation after surgery, Nutting et al. [17] described 5- and 10-year progression-free survival rates of 92% and 83%, respectively. Evaluation by Hamm et al. [18] of the results of stereotactically guided radiation techniques in a collective of 224 patients with skull-base meningiomas revealed overall survival and progression-free survival rates at 5 years of 92.9% and 96.9%, respectively.

In order to analyze the long-term results of fractionated stereotactic radiation therapy in patients with benign or atypical intracranial meningioma, a retrospective investigation of 317 patients was performed in our department in the past [10]. This study revealed a local tumor control rate of 93.1% after median follow-up of 5.7 years, with radiological local tumor progression rate of 6.9%. Within this study the influence of potential prognostic factors on local control was investigated, revealing that histologic grade of the meningioma and volume of the tumor had a statistically significant influence on therapy outcome. Local tumor failure was significant higher in patients with WHO grade II meningioma ($P < 0.002$) than in patients with unknown histology or patients with WHO grade I meningioma. Patients with tumor volume greater than 60 cc showed a recurrence rate of 15.5% versus 4.3% in patients with tumor volume less than 60 cc ($P < 0.001$).

However, although various studies have investigated the survival and local control rates of radiotherapy for intracranial meningioma, there are no published data regarding the site of local recurrence with respect to the exact dose distribution of the applied treatment plan.

In this study we further analyzed the results of 22 of 411 patients treated with stereotactic radiation therapy for intracranial meningiomas who showed local tumor progression on MRI. Aim of the study was to investigate the parameters that negatively influence the outcome of the therapy. We focused especially on identification of the site of local recurrence with respect to the dose distribution.

The target volume was found in previous studies to be important for therapy outcome. A statistically significant correlation between tumor volume and relapse after FSRT has been observed. The recurrence rate for patients with tumor volume >60 cm^3 was 15.5% versus 4.3% for patients with tumor volume <60 cm^3 ($P < 0.001$) [10]. The hypothesis of the significance of target volume for therapy outcome is strengthened by the results of our analysis. The median PTV of the patients who showed a recurrence after radiotherapy was 95 cm^3. Compared with results of previous studies in the literature, the median target volume of the recurrent patients in our study is larger. This correlation can find several explanations: high tumor volume is associated with higher cell density and therefore enhanced probability of hypoxic tumor regions, which is found to be one of the most important reasons for therapy resistance [19]. Furthermore, tumors with high volume have greater possibility to have closer proximity to critical anatomical structures, such as the optic nerve or brain stem, which is a limiting factor for optimal dose distribution.

The influence of the dose distribution on therapy outcome was shown by studies on radiation therapy techniques with advanced dose distribution, such as IMRT. A previous investigation of IMRT for complex-shaped meningioma of the skull base revealed a recurrence rate of 6.1% after median follow-up of 4.4 years; the median target volume was 81.4 cm^3 and the median total dose was 57.6 Gy [11]. Subanalysis of the results for patients treated with FSRT with the same median total dose after median follow-up of 5.7 years revealed a recurrence rate of 15.5% for tumors with volume >60 cm^3 [10]. The higher recurrence rate in the group of patients treated by FSRT could be explained by the longer median follow-up, but it could also be explained by optimized dose homogeneity achieved by IMRT.

One of the most important prognostic factors for intracranial meningioma was found to be the histological grading of the disease. In order to better understand the correlation between histological grade and local control we performed subanalysis of our results separately for patients with benign meningioma (WHO grade I) and higher-grade meningioma (WHO grade II or III). This analysis revealed a statistically significant influence of the histological features of the tumor on recurrence site (in-field versus out-field) and therefore on the mechanism of recurrence. WHO grade I tumors recurred more often at the margin, while WHO grade II or III tumors recurred more often centrally. A possible explanation for this result is that, for WHO grade I tumors, it was dose homogeneity coverage that influenced the outcome of the therapy more, while for atypical or anaplastic meningiomas the prescribed dose level seemed to be insufficient. The median recurrence-free survival for patients with WHO grade I meningioma that recurred after RT only exhibited a trend to be higher than that for WHO grade II or III patients (46 versus 31.5 months).

Conclusions

High-precision radiation therapy offers the possibility of an effective local treatment modality in meningiomas. Due to the effectiveness of stereotactic radiotherapy in patients with intracranial meningiomas, only a few patients with recurrent disease (22/411 patients) could be analyzed in this evaluation regarding the question of topography of local recurrences after radiotherapy. However, these data based on a large cohort from a single institution show that median time to local recurrence and site of local recurrence significantly depend on histological grading of meningioma. Recurrences in WHO grade I meningioma are rare; only 14 of all 365 patients (3.8%) with grade I meningioma or unknown histology treated at our institution were recurrences. Recurrences in high-grade meningioma are more common after radiotherapy, occurring in 8 out of 46 treated patients having high-grade meningioma (17.4%). In WHO grade I meningioma most local recurrences were found to be marginal, while high-grade (grade II and III) meningioma more often recurred centrally. Although the number of recurrences after radiotherapy is relatively small, the aim of all therapeutic interventions is to reduce recurrences after therapy during follow-up. Therefore, dose escalation in patients with high-grade tumors may be useful. Further improvements may be achieved with the use of particle therapy and optimized target volume definition by the use of molecular imaging such as positron emission tomography (PET).

Conflict of interest statement All authors disclose any financial and personal relationships with other people or organisations that could inappropriately influence (bias) their work.

References

1. Marosi C, Hassler M, Roessler K, Reni M, Sant M, Mazza E, Vecht C (2008) Meningioma. Crit Rev Oncol Hematol 67:153–171
2. Longstreth WT, Dennis LK, McGuire VM, Drangsholt MT, Koepsell TT (1993) Epidemiology of intracranial meningioma. Cancer 72:639–648
3. Louis DN, Scheithauer BW, Budka H, von Deimling A, Kepes JJ (2000) Meningiomas. In: Kleihues P, Cavenee WK (eds) Pathology and genetics. Tumors of the nervous system, WHO classification of tumors. IARC, Lyon, pp 176–184
4. Bartolomei M, Bodei L, De Cicco C, Grana CM, Cremonesi M, Botteri E, Baio SM, Aricò D, Sansovini M, Paganelli G (2009) Peptide receptor radionuclide therapy with (90)Y-DOTATOC in recurrent meningioma. Eur J Nucl Med Mol Imaging 36(9):1407–1416
5. O'Sullivan MG, Van Loveren HR, Tew JM (1997) The surgical resectability of meningiomas of the cavernous sinus. Neurosurgery 40:238–245
6. Colli BO, Assirati JA Jr, Deriggi DJ, Neder L, dos Santos AC, Carlotti CG Jr (2008) Tentorial meningiomas: follow-up review. Neurosurg Rev 31(4):421–430
7. Debus J, Wuendrich M, Pirzkall A, Hoess A, Schlegel W, Zuna I, Engenhart-Cabillic R, Wannenmacher M (2001) High efficacy of fractionated stereotactic radiotherapy of large base-of-skull meningiomas: long-term results. J Clin Oncol 19(15):3547–3553
8. Pirzkall A, Debus J, Haering P, Rhein B, Grosser KH, Höss A, Wannenmacher M (2003) Intensity modulated radiotherapy (IMRT) for recurrent, residual, or untreated skull-base meningiomas: preliminary clinical experience. Int J Radiat Oncol Biol Phys 55(2):362–372
9. Mirimanoff RO, Dosoretz DE, Linggood RM, Ojemann RG, Martuza RL (1985) Meningioma: analysis of recurrence and progression following neurosurgical resection. J Neurosurg 62:18–24
10. Milker-Zabel S, Zabel A, Schulz-Ertner D, Schlegel W, Wannenmacher M, Debus J (2005) Fractionated stereotactic radiotherapy in patients with benign or atypical intracranial meningioma: long-term experience and prognostic factors. Int J Radiat Oncol Biol Phys 61(3):809–816
11. Milker-Zabel S, Zabel-du Bois A, Huber P, Schlegel W, Debus J (2007) Intensity-modulated radiotherapy for complex-shaped meningioma of the skull base: long-term experience of a single institution. Int J Radiat Oncol Biol Phys 68(3):858–863
12. Milker-Zabel S, Zabel-du Bois A, Huber P, Schlegel W, Debus J (2006) Fractionated stereotactic radiation therapy in the management of benign cavernous sinus meningiomas. Strahlenther Onkol 182:635–640
13. Menke M, Hirschfeld F, Mack T, Pastyr O, Sturm V, Schlegel W (1994) Photogrammetic accuracy measurements of head holder systems used for fractionated radiotherapy. Int J Radiat Oncol Biol Phys 29(5):1147–1155
14. Preiser K, Bortfeld T, Hartwig K, Schlegel W, Stein J (1998) Inverse radiotherapy planning for intensity modulated photon fields. Radiologe 38(3):228–234
15. Keller-Reichenbecher MA, Bortfeld T, Levegrün S, Stein J, Preiser K, Schlegel W (1999) Intensity modulation with the "step and shoot" technique using a commercial MLC: a planning study. Multileaf collimator. Int J Radiat Oncol Biol Phys 45(5):1315–1324
16. Vendrely V, Maire JP, Darrouzet V, Bonichon N, San Galli F, Celerier D, Causse N, Demeaux H, Trouette R, Dahan O, Recaldini L, Guerin J, Caudry M (1999) Fractionated radiotherapy of intracranial meningiomas: 15 years' experience at the Bordeaux University Hospital Center. Cancer Radiother 3(4):311–317
17. Nutting C, Brada M, Brazil L, Sibtain F, Westbury C, Moore A, Thomas DG, Traish D, Ashley S (1999) Radiotherapy in the treatment of benign meningioma of the skull base. J Neurosurg 90(5):823–827
18. Hamm K, Henzel M, Gross MW, Surber G, Kleinert G, Engenhart-Cabillic R (2008) Radiosurgery/stereotactic radiotherapy in the therapeutical concept for skull base meningiomas. Zantralbl Neurochir 69(1):14–21
19. Brown JM (2007) Tumor hypoxia in cancer therapy. Methods Enzymol 435:297–321