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Meningioma

Skull base meningiomas: Long-term results and patient self-reported outcome in 507 patients treated with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT)

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ABSTRACT

Purpose: To evaluate long-term outcome of high-precision photon radiotherapy in 507 patients with skull base meningiomas.

Methods and materials: At the time of radiation therapy, most patients presented with clinical symptoms including double vision, headache, nausea, trigeminal or facial nerve dysfunction or exophthalmus. In general tumors extended into several regions of the skull base. In 54%, prior neurosurgical intervention was performed, which was a partial resection or biopsy in 266 patients.

Treatment was delivered using a 6 MV linear accelerator or the tomotherapy system. Fractionated stereotactic radiotherapy (FSRT) was applied in 376 patients (74%) and intensity modulated radiotherapy (IMRT) in 131 patients (26%). A median total dose of 57.6 Gy (range 25–68 Gy) was prescribed in median single doses of 1.8 Gy (range 1.6–5 Gy).

To evaluate long-term toxicity as well as quality of life (QOL), we sent out a detailed questionnaire put together with special questions regarding the skull base location of the tumors. Special focus was long-term sequelae including visual deficits, cranial nerve deficits, headaches, fatigue or any other symptoms impairing overall QOL.

The median follow-up time was 107 months (range 1–270 months).

Results: Overall treatment was well tolerated.

Local control for the whole cohort was 95% at 5 years and 88% at 10 years. Patients with benign histology had significant higher local control than high-grade meningiomas. For benign meningiomas, local control was 91% at 10 years. For high-risk meningiomas, local control was 81% at 5 years and 53% at 10 years. QOL was unchanged in 47.7% of the patients, and 37.5% showed improvement. Most patients reported an improvement of symptoms or steady state; in only few patients disorders worsened over time or side effects developed.

Conclusion: Precision photon radiotherapy leads to long-term tumor control with minimal side effects, but also with preservation of QOL in patients with skull base meningiomas.

Highly conformal radiotherapy has become a clear treatment alternative to neurosurgical resection in patients with meningiomas of the skull base. Often tumor extension or invasion into bony structures and close vicinity to sensitive organs at risk (OAR) limit the resectability of skull base meningiomas, with the predominant areas being the cavernous sinus [1]. Additionally, due to the intricate anatomy at the skull base, surgical intervention may be associated with a significant risk for treatment-associated side effects [2–4].

In general, direct interventions are not immediately required in all patients with skull base meningiomas: Most meningiomas are benign, slow growing tumors. However, in spite of the benign histology, they tend to expand over time, or recur locally especially after partial surgical resections [5–11]. Besides benign histology, meningiomas can also be atypical or anaplastic tumors, with aggressive growth patterns and a very high tendency to recur even after aggressive treatment including surgery and postoperative radiotherapy; however, this group only represents a smaller subgroup of all skull base meningiomas [12,13].

Commonly, when typical low-grade meningiomas are diagnosed in the skull base region and no obvious clinical symptoms are present, a wait-and-see strategy may be followed with regular clinical examinations and MR-imaging; treatment may be held

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back until tumor progression becomes visible, or when clinical signs and symptoms worsen or develop. When treatment is indicated, neurosurgical resection was the treatment of choice over the last decades, however, depending on the series reported, high rates of surgery-associated side effects were observed; additionally, complete resections are not possible in a substantial number of patients [14,15].

Radiation therapy has been applied increasingly over the last decades due to the improvements in treatment planning and application. With high precision techniques such as fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT), it is now possible to apply required doses to the tumor while adhering to normal tissue tolerance of surrounding organs at risk (OARs) [16,17]. Several different groups have reported local control rates of 75–100%, with low rates of side effects [18–23]. However, most reports on fractionated treatments are focussed on smaller patient groups, and no data on long-term patient reported outcome and quality of life (QOL) have been reported to date.

This was therefore addressed in the present study: We evaluated long-term outcome in one of the largest study populations of patients with skull base meningiomas treated with high-precision photon radiotherapy with special focus on patient reported outcome and QOL, treatment-associated long-term side effects as well as local control.

Table 1
Patient characteristics of 507 patients treated with FSRT or IMRT for skull base meningiomas.

Characteristics	Number (%)
Gender	
Male	139 (27)
Female	368 (73)
Age	
Mean (range)	53 (16–83)
Histologic classification	
No histology	238 (47)
WHO Grade I	234 (46)
WHO Grade II	20 (4)
WHO Grade III	15 (3)
Predominant clinical symptoms	
Headache	106 (21)
Double vision	131 (26)
Vision impairment	134 (26)
Exophthalmia	64 (13)
Seizures	24 (5)
Trigeminal impairment	178 (35)
Facial impairment	171 (34)
Time of radiation	
Definitive	145 (28.6)
Postoperatively	231 (45.6)
For tumor progression	131 (25.8)

Patients and methods

Between 1985 and 2010, we treated 632 consecutive patients with meningiomas with fractionated stereotactic radiotherapy (FSRT) or intensity modulated radiotherapy (IMRT). Of these, 507 (80%) tumors were located in the skull base region and were included into the present evaluation. All patients were treated at the Department of Radiation Oncology in Heidelberg, Germany or at the German Cancer Research Center (dkfz) in Heidelberg, Germany; they were prospectively enrolled in a continuous and regular follow-up program including thorough clinical-neurological assessment as well as contrast-enhanced imaging.

At the time of radiation therapy, most patients presented with clinical symptoms including double vision, headache, nausea, trigeminal or facial nerve dysfunction or exophthalmus. Table 1 summarizes patients' characteristics and clinical symptoms.

Tumor location

Tumor location was defined by reviewing all images acquired for treatment planning. Most tumors extended into several regions of the skull base. A common classification for all tumors was based on the tumor origin and/or main tumor extension grouping the tumors; 127 tumors were located in the sphenoid wing, 105 in the cavernous sinus, petroclival location was seen in 85 meningiomas, and 66 were located in the sphenoorbital region; other locations included the sella ($n = 34$), the tentorial fold ($n = 27$) or olfactory meningiomas ($n = 17$).

Prior treatment

In 269 out of 507 patients (53%), prior neurosurgical intervention was performed, which was partial or biopsy in 266 patients. Of all patients undergoing surgery, in 79% only one surgical resection was performed, in 17% two neurosurgical interventions had been performed in the past, and only 4% of the patients received 3 or more interventions. In 238 patients (47%) no neuropathological confirmation of meningioma was available, and the diagnosis was based on clinical presentation as well as on the typical aspect of meningiomas on CT- and MR-imaging. In 234 patients, histology revealed WHO Grade I meningioma (46%), and in 20 patients (4%) and 15 patients (3%) histology was WHO Grade II and III meningioma (referred to as high-grade meningiomas). Patients with previous malignancies in the medical history were required to undergo biopsy.

Additionally, in most cases without neuropathological diagnosis additional Ga^{68}-DOTATOC-PET examinations were performed. The PET-examination was taken and used to support the diagnosis of meningioma; also, it was taken into account for target volume definition as stated below and as published previously [24–26].

Radiation therapy was performed directly after initial diagnosis in 145 patients (28.6%), and the median time from diagnosis to radiation therapy was 6 months (range 1–252 months). In 231 patients (45.6%), radiation therapy was performed postoperatively; the median time from diagnosis to radiation therapy was 12 months (range 1–276 months), either directly for remaining tumor after partial resection, or for progressive disease during a wait-and-see strategy. In this group, 86/231 were treated directly after surgical resection (within a time period of up to 6 months) without tumor progression. Indication for radiation therapy was based on individual decisions in an interdisciplinary consensus and after thorough assessment of all clinical criteria, as well as in accordance with the patients' preference.

In the third group of patients, radiotherapy was applied after a wait-and-see strategy and initiated for tumor progression or progression of clinical symptoms ($n = 131$; 25.8%); radiation therapy was performed for recurrent or progressive tumor after a median time interval of 60 months (range 1–324 months).

Radiation therapy was performed either in stereotactic set-up, or as image-guided radiotherapy (IGRT). For stereotactic treatment planning and subsequent irradiation, patients were fixed in an individually manufactured head mask made of Scotch Cast™; for treatment planning, contrast enhanced CT and MRI were performed in stereotactic set-up as described in detail previously [27]. For image-guided treatments, thermoplastic head masks were used for treatment planning and radiation, and position verification was performed. In the treatment planning system, image fusion was performed and target volume definition as well as definition of organs at risk (OARs) was performed on each 3 mm slice of the three-dimensional data cube.