**CHARLES UNIVERSITY IN PRAGUE**
**THIRD FACULTY OF MEDICINE**

Doctoral Thesis Summary

# THE ANALYSIS OF THE RISK FACTORS IN GAMMA KNIFE RADIOSURGERY FOR BENIGN MENINGIOMAS

## ANALÝZA RIZIKOVÝCH FAKTORŮ V LÉČBĚ BENIGNÍCH MENINGIOMŮ GAMA NOŽEM

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## Souhrn

Doktorandská práce analyzuje výsledky stereotaktické rádiochirurgické léčby meningiomů, benigních mozkových nádorů a rizikové faktory spojené s léčbou, u 368 pacientu s 400 meningiomy. Detailně jsou pak analyzovány výsledky léčby meningiomů báze lební a dlouhodobé výsledky. Součástí práce bylo vytvoření modelu predikce edému, na základe kterého lze určit riziko komplikací po stereotaktickém rádiochirurgickém výkonu.

Kontrola růstu meningiomu po 5 a 10 letech byla 97,9% a 94,7%, co potvrzuje efektivitu rádiochirurgické léčby, s nízkou dočasnou a permanentní morbiditou 9,6% and 1,3% .

Radiochirurgie jako minimálně invazivní technika je metodou volby léčby meningiomů ve vybraných lokalizacích, např. meningiomy báze lební, jako součást multimodálního přístupu u rozsáhlých meningiomů, kde úplné operační odstranění není možné, u pacientů s komorbiditou neumožňující operační výkon a u seniorů.

**Klíčová slova:** meningiom- gama nůž-stereotaktická radiochirurgie

**Summary**

Doctoral thesis is based on the results of the analysis of stereotactic radiosurgical treatment of meningiomas, benign intracranial tumors, and the risk factors related to the treatment of 368 patients with 400 meningiomas. Detailed analysis of mid-term and long-term results was performed, as well as the analysis of the skull base meningiomas in particular.

An edema prediction model was created in order to identify patients with a higher risk for post treatment complications with its practical clinical implication.

The actuarial tumor control at 5 and 10 years 97,9% and 94,7% respectively, what confirms efficiency of radiosurgical treatment, with low temporary and permanent morbidity of 9,6% and 1,3% respectively.

Radiosurgery is a minimally invasive technique. It is used as a treatment of choice for meningiomas in selected locations, e.g. skull base; as a part of multimodal approach in large meningiomas, which cannot be completely excised, in elderly patients and those that would not tolerate the operative procedure.

**Key words:** meningioma - Gamma Knife - Stereotactic radiosurgery

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## 1. Introduction

Meningioma is about in 80 % a benign tumor and it usually does not limit the longevity of the patient. Successful treatment must control the disease itself, but also should have the lowest possible rate of complications. Meningiomas occur often in areas where complete surgical removal is impossible due to its location and the proximity of vital structures. The most important issue is to maintain the patient`s quality of life (DeMonte F. et al, 2000; Kozler P., 2007).

Stereotactic radiosurgery is an established treatment option for benign tumors with well-defined margins, which fulfills the size criteria of 3 cm in diameter or 10 $cm^3$ of the tumor volume. Tumor control of meningiomas after radiosurgical treatment has been published between 87% and 100%, with low morbidity of 3%-43%, an average of 8% (Di Biase et al., 2004; Kondziolka et al., 1999; Maruyama et al., 2004; Pollock et al., 2003)

## 2. Hypotheses and the goals of the study

Meningiomas are slow growing tumors with an unclear natural history. They require a long term follow up, of at least 10 years, to assess the efficacy of the treatment (DeMonte F. et al, 2000; Kuratsu J. et al., 2000)

The goal of the study was to identify the risk factors related to Gamma Knife radiosurgery. The questions were as follows:

1. What are the results of Gamma Knife treatment on skull base meningiomas and which are the most difficult meningiomas to treat with acceptable results?
2. What are the temporary and permanent complications of meningioma radiosurgery?
3. What is the risk of edema after Gamma Knife surgery, which contributes to post-treatment morbidity and how can it be influenced by treatment strategy?
4. What are the results of Gamma Knife treatment of meningioma from a long-term perspective?

## 3. Material and Methods

The entire cohort of analyzed meningiomas consisted of 368 patients with 400 meningiomas treated between 1992 and 1999. Out of this group, 226 patients with 249 meningiomas with a long-term follow up, with a follow up period ranging from 1 to 168 months with a median of 96 months. Male to female ratio was 1:4. The age of the patients ranged from 18 to 84 years, the median being 61 years.  There were 133 (53,4%) meningiomas located at cerebral convexities and 116 (46,6%) in the skull base. The Karnofsky score of treated patients was between 30% and 100%, the median 80%.

Patients, who underwent operative surgery before radiosurgery, had cranial nerve palsy in 28 cases (12,4%), hemiparesis in 19 cases (8.4%) and cerebellar symptoms in 8 cases (3,5%). Fifty-three patients (23,4%) had neurodeficits after previous surgery; in two of them two different symptoms were recorded. Neurological deficits before Gamma Knife treatment were found in 134 patients (59,3%), epilepsy in 32 patients (14,2%), 60 patients were asymptomatic (26,5%). Fifteen patients had multiple meningiomas.

Gamma Knife radiosurgery was a primary treatment in 159 patients (70,3%) of the studied group.

The tumor volume of treated meningiomas ranged from 0,1 to 44,9 $cm^3$, the median was 4,37 $cm^3$ and the mean 5,9 $cm^3$. The margin dose in the studied group ranged from 6,5 to 24 Gy, the median 12,9 Gy (the isodose margin was between 40 - 90 %, with a median of 50%).

One of the aims of our study was to create a model to predict edema occurrence. The model is based on the data of 381 patients with meningiomas treated between 1992 and 1999. Ten predictive factors were proposed as possible predictors for the occurrence of perilesional edema after Gamma Knife treatment: the patient`s age, gender, previous surgery, edema before Gamma Knife radiosurgery treatment, tumor volume, tumor location and the tumor margin dose, lobulated margin of the meningioma and the heterogeneous appearance of the tumor. To find out the factors influencing edema occurrence univariate analyses were performed using Kaplan-Meier statistics with a log rank test and a multivariate using a Cox Proportional hazards model by using the backward stepwise conditional likelihood ratio and binary logistic regression analysis with the backward stepwise method. Analyses were undertaken using SPSS statistical software version 10.0.,13.0 a 16.0 (SPSS Inc., USA). Variables with statistically significant values ($p<0,05$) in at least two tests were considered as risk factors for the studied cases.

**4. Results**

Tumor control or stabilization of the disease was achieved in 94,7% after 10 years. Tumor volume regression was found in 163 meningiomas (68,2%), remained stabilized in 70 (29,3%) and a progression of the disease was recorded in 6 (2,5%) of the patients. Improvement of clinical symptoms was detected in 89 (41%) patients.

Postirradiation edema occurred in 40 (18,4%) of the patients, 1-21, a median of 7 months after the treatment. Edema was symptomatic in 24 (11,1%) patients. In another 6 patients (2,8%), impairment of clinical symptoms was recorded, without radiological evidence of edema. In 16 (7,4%) patients the symptoms improved, in 14 (6,4%) patients they remained permanent.

Based on the statistical analysis of the patient data, the binary logistic regression equation for the probability (Prob) of intracranial edema occurrence was created:

***Prob (edema occurrence) = 1/(1+ $e^{-z}$), where z = - 5,080 – 0,786 (previous surgery) + 3,896 (edema before GKS) +0,104 (tumor volume) + 0,855 (tumor location) + 0,170 (margin dose)***

Input variables in the model are presented as the following values: “1” or “0” for “yes” or “no”, respectively for the case of previous surgery, edema before radiosurgery and tumor location, volume in $cm^3$, and dose to the tumor margin in Gray for tumor volume and margin dose, respectively. Tumor location was divided into two categories: risk location (defined as “1”- the anterior cranial fossa, convexity and falx) and non-risk location (defined as “0” - the middle cranial fossa, the posterior cranial fossa, the tentorium and the cerebellum). In general, if the probability is greater than 0.5, it is predicted that the event will occur (in this case edema will occur). If the estimated probability of the event is less than 0.5, it is predicted that the event will not occur.

## 5. Discussion

The actuarial 5- and 10- year tumor control rate in the studied group of patients was 97,9% and 94,7% respectively, which is within the range between 84,3% and 100% in the published studies of mid- and long- term results (Di Biase et al., 2004; Kondziolka et al., 1999; Maruyama et al., 2004; Pollock et al., 2003). Our results in the upper part of the range reflect the successful strategy of the treatment in terms of dose selection as well as the patient selection (size of tumor).

***Tumor Margin and Maximum Dose***

In the present study there is a significantly larger decrease in the volume of meningioma treated with a marginal prescription dose of greater than 12 Gy. The dose of the optic tract was kept below 8 Gy. No visual field loss was detected in our study (Morita et al., 1999)

In patients treated with margin doses of higher than 16 Gy, there was a significantly greater occurrence of postirradiation edema. Neurological impairment was statistically significant in patients treated with a margin dose of higher than 16 Gy and a maximum dose of higher than 30 Gy. The current practice at our center is to apply a margin dose of 12-16 Gy for benign meningiomas (Kondziolka et al., 1999; Pollock et al., 2011).

***Patient sex and age***

The majority of tumors that increased in size after radiosurgery were in men, which was statistically significant. On the other hand, men have a higher chance of meningioma regression after treatment, as confirmed by the analysis of our long- term results (Di Biase et al., 2004).

Patients younger than 40 years old were found to have an increased chance of tumor regression. Meningiomas in younger patients behave also more aggressively and therefore these patients are often candidates for surgery in the first instance.

Our research showed that patients younger than 40 and older than 60 years old had a significantly increased frequency of adverse effects. It has also been reported, that meningioma in the elderly shows a lower progression rate. These facts suggest that a prescribed dose should be kept at the lower end of the therapeutic window, e.g. 12-16 Gy to prevent posttreatment complications, as life expectancy becomes shorter.

***Previous surgery***

In our study, previous surgery was significantly related to the improvement of neurological deficits detected before treatment. Our results can be explained by the fact that more than 40% of patients have undergone radiosurgery within one year after operative surgery, which is the recovery time period. A combination of surgery and radiosurgery keeps the risk of surgical damage to minimum (Fahlbusch R. et al, 2002; Náhlovský et al., 2006; Petterson-Segerlind J. et al., 2011)

***Location of the meningioma***

There is a lower risk of clinical impairment in patients with meningiomas located in the skull base (the only exception is the anterior cranial fossa). The reason for that finding might be the fact that skull base meningiomas have a smaller surface directly in contact with brain tissue, with the pial blood supply, that enables angiogenic factors produced by meningioma to enter brain tissue and induce perilesional edema. Especially patients with meningiomas located in the convexity and parasagittal/falcine meningioma are at a higher risk of posttreatment complications. Patients harboring skull base meningioma have a higher chance of clinical improvement (Liščák R. et al., 2009).

***Adverse effects***

In the majority of cases, morbidity associated with stereotactic radiosurgery is temporary. Results of the 10 year follow up analysis have shown 9,6% temporary and 1,3% permanent morbidity. These numbers reflect the fact that in the early stages of Gamma Knife meningioma treatment, patients were selected very carefully with regard to the size of their tumor.

The published permanent complication rate ranged from 2,5% to 9% (Di Biase et al., 2004; Kondziolka et al., 1999; Maruyama et al., 2004; Pollock et al., 2003). A post treatment deficit is rarely disabling.

The results of our study show that meningiomas bigger than 5 $cm^3$ have an increased risk of perilesional edema and patients are more likely to experience neurological impairment. Seven patients in the present study experienced intratumoral edema, which developed 5 to 16 months after radiosurgery. In all of them the tumors finally shrank and the symptoms settled.

To distinguish intratumoral edema from further growth of the tumor, one must consider the time since the treatment. In our experience, intratumoral edema occurs within 2 years following radiosurgery, whereas the growth of the tumor is detected at least 2 years after radiosurgery (Liščák R. et al., 2009).

***Peritumoral edema***

According to our results, patients with peritumoral edema before radiosurgery are at an increased risk of the development of postirradiation complications and the worsening of pre-existing edema.

The risk of radiation induced complications increases with the volume irradiated (Kondziolka et al., 1999; Pollock et al., 2003). A tumor volume of greater than 5 $cm^3$ was a risk factor for the development of perilesional edema, temporary and permanent neurological deficits after radiosurgery.

According to our data, it is possible to predict the occurrence of post-treatment edema with regard to the location of the meningioma. Patients with meningioma in the anterior skull base have a higher risk, followed by those of convexity and parafalcine meningiomas. Also, patients with skull base meningiomas have a higher chance of neurological improvement after treatment, when compared to convexity meningiomas. The edema prediction model, which was developed as a part of the study, improves the ability to predict edema occurrence after Gamma Knife treatment and it is used in the identification of patients, who will develop this adverse effect eventually. These patients are counseled about the increased risk of post-treatment complications, with practical recommendation for further care.

**6. Conclusions**

Radiosurgery as a treatment of choice is recommended in patients harboring skull base meningiomas fulfilling size criteria, in patients who cannot be treated by operative surgery due to their age or because of other medical reasons in the case where meningioma is not causing mass effect requiring excision. The actuarial 5 and 10-year tumor control rate is 97,9% and 94,7% respectively, which confirms the efficiency of the treatment from a long-term perspective. Permanent morbidity associated with Gamma Knife treatment was 5,7% and 1,3% respectively, although it was rarely disabling. The low percentage of side effects makes Gamma Knife treatment also attractive for patients, who are deciding on a treatment option in cases where both radiosurgery as well as operative surgery are feasible.

Radiosurgery is a part of a multimodal approach in large meningiomas in areas where complete removal is impossible, or where it could be risky due to damage to the cranial nerves and major vessels in the skull base. In such cases, operative surgery to remove the meningioma is planned in the first instance, followed by radiosurgery.

Observation is a treatment option for meningiomas in the elderly and especially in patients in whom meningiomas show signs of calcium deposits. These meningiomas grow rarely and usually do not cause mass effect towards an atrophic brain. On the other hand, observation in younger patients might lead to meningioma progression to the extent where radiosurgery is limited, or impossible, e.g. in skull base meningiomas approaching or compressing the optic pathways.

From a technical point of view, we suggest a prescription dose of 12-16 Gy to the tumor margin. Higher margin doses are associated with higher treatment risks, but they do not improve the tumor control rate.

Patients with tumors larger than 5 $cm^3$, peritumoral edema, meningiomas in the anterior skull base and parasagittal meningiomas should be informed about the higher risk of post-treatment complications.

The results of radiosurgery increase the standard of meningioma treatment with low adverse effects and thus maintaining the quality of life of the patient with benign tumors. Treatment options or combinations of them should be assessed for every patient individually.

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