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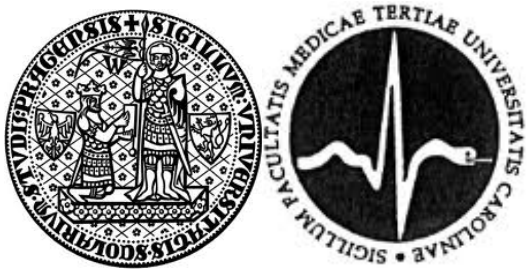

MUDr. Aurélia Kollová, MBA

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

ANALÝZA RIZIKOVÝCH FAKTORŮ V LÉČBĚ BENIGNÍCH MENINGIOMŮ GAMA NOŽEM

DOCTORAL THESIS

Consultant: Assoc. Prof. MUDr. Roman Liščák, Ph.D.

Prague, 2012

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Prague, May 28th, 2012 MUDr. Aurélia Kollová, MBA

Summary

Doctoral thesis represents results of the analysis of Gamma Knife radiosurgical treatment of meningiomas, benign intracranial tumors, and the risk factors related to the treatment in 368 patients with 400 meningiomas treated at the Department of Stereotactic and Radiation Neurosurgery, Na Homolce Hospital in Prague between 1992 and 1999.

Detailed analysis of the results of skull base meningiomas was performed, as well as analysis of long-term results. Edema prediction model was created in order to identify patients with higher risk for post treatment complications with its practical clinical implication.

The actuarial tumor 5- and 10- years control was 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, which was rarely disabling.

Radiosurgery as a minimally invasive technique is a treatment of choice of meningiomas in skull base fulfilling size criteria; as a part of multimodal approach in large meningiomas, in patients, who would not tolerate operative procedure and in elderly.

Dissertation thesis consists of six chapters and 5 appendices. The first chapter offers introduction and literature overview. Hypotheses and goals of the study are defined in the second chapter. The third chapter contains information on material and methods. Results of study, both mid-term and long-term, are featured in the fourth chapter. Theoretical and practical contribution of study results to neurosurgery is discussed in the sixth chapter. The seventh chapter deals with conclusions of the study.

Key words: meningioma - Gamma Knife - Stereotactic radiosurgery

Souhrn

Dizertační práce analyzuje výsledky stereotaktické rádiochirurgické léčby meningiomů gama nožem., se zaměřením na rizikové faktory spojené s léčbou, u 368 pacientu s 400 meningiomy léčených na Oddělení stereotaktické a radiační neurochirurgie, Nemocnice na Homolce v Praze v letech 1992-1999. 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% resp., která u většiny pacientů neomezuje jejich denní aktivity.

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.

Dizertační práce pozůstává ze 6 kapitol a 5 příloh. První kapitola poskytuje přehled relevantních literárních poznatků souvisejících se studovanou problematikou. Ve druhé kapitole jsou uvedeny hypotézy a cíle práce. Třetí kapitola pojednává o materiálu a metodice. Výsledky studie jsou uvedeny ve čtvrté kapitole, v páté kapitole jsou pak rozdiskutovány, se zaměřením na jejich klinický význam. Šestá kapitola obsahuje závěry práce.

Klíčová slova: meningiom - gama nůž - stereotaktická radiochirurgie

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Abbreviations

BUdR 5-Bromodeoxyuridine

CT **C**omputed **T**omography

MR **M**agnetic **R**esonance

GKS **G**amma **K**nife Radio**s**urgery

Gy **G**ray- SI unit of absorbed dose of energy

Ki-67 protein, cellular marker of proliferation

MIB-1 mooclonal antibody against Ki-67

VEGF **V**ascular **E**ndothelial **G**rowth **F**actor

"The tools used by the surgeon must be adapted to a task and where the human brain is concerned, they cannot be too refined." Lars Leksell

1. Introduction and literature overview

Meningioma is a nosology entity in a neurosurgeon` s daily practice. Because it is benign in most cases, there is a chance to cure the patient with its complete removal. On the other hand, there are other major challenges - difficult location and often large size, as meningiomas are slow growing neoplasms and the surrounding brain has time to adapt to its growth. Planning the treatment, one must consider the following - location and blood supply, proximity or encasement of vital structures like major blood vessels and cranial nerves, size, peritumoral edema, age and neurological symptoms of the patient. The goal is to deal with the meningioma to relieve reversible symptoms, prevent further expansion and at the same time to maintain quality of life, as longevity is usually not limited by meningioma itself. Wise decision-making leads almost always to a rewarding outcome.

1.1. Meningioma in historical perspective

The oldest reported finding of a skull with several features of the inner cranial table consistent with a diagnosis of meningioma is the fossil of Homo Steinheimensis from Steinheim/Murr (Baden-Wurttemberg, Germany), approx. 365 000 years old. It consists of plagiocephalic cranium, with most of the facial skeleton intact. The estimated tumor volume was 29 cm^3. In view of the demanding Pleistocene living conditions, a tumor of this size in conjunction with the small Steinheim cerebrum of only 1100-1200 cm^3 (modern brain 1300-1800 cm^3) might have caused continual headache, severe hemiparesis and finally death (Czarnetzki A. et al., 2003). (Fig. 1.)

Signs of hyperostosis were found in the skulls of pre-Columbian Incas in the Peruvian Andes. A finding of a highly destructive meningioma of the skull base was found in Alaska, from the Late Aleutian Phase and the skull with a frontal hyperostosis from medieval Rochester (cca 1000-1800 AD) (Anderson T., 1992; DeMonte F. et al, 2000; Jonsdottir B. et al., 2003).

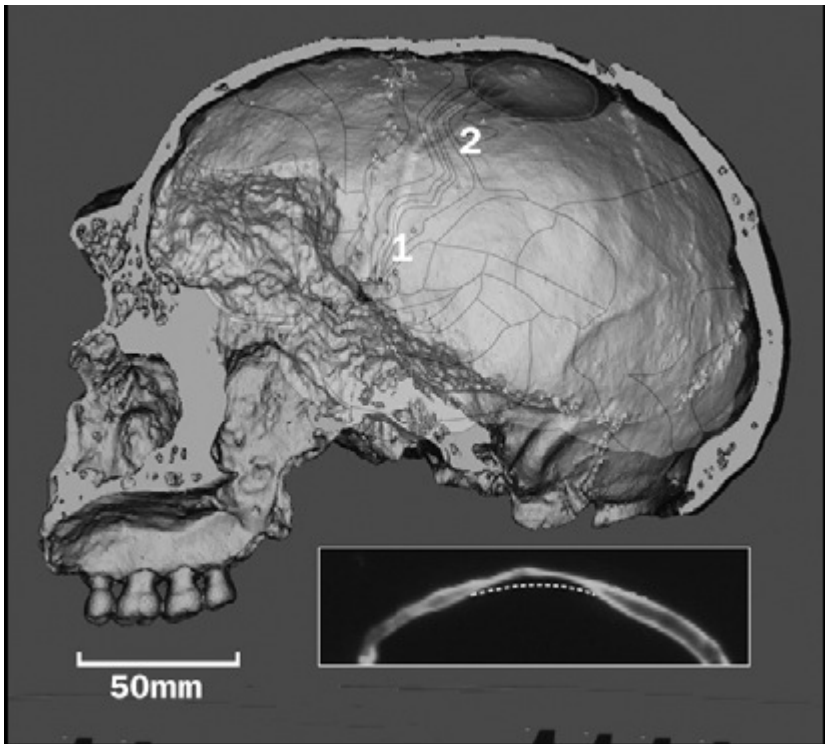

Fig. 1. Lateral view of the median section of the reconstruction of the intravital situation. Sphenoparietal sinus (1), two widen branches of middle meningeal artery (2). At the bottom is a CT scan through meningioma region indicating the thinning of parietal bone. (Czarnetzki A. et al., 2003)

Swiss Felix Platter (1536-1614) was the first person who described meningioma in the autopsy of his patient, whose case he followed for 3 years, with the symptoms of gradual mental deterioration.

Surgical treatment of meningiomas was pioneered by Heister in 1743, in Helmstead, Germany. The first successful operation on a meningioma was performed by Zanobi Pechhioli [1801-1866), who published his series of 1524 operations, in 1847; 16 of these were neurosurgical operations. In one of these, a large meningioma was removed from the right occiput; the operative site was covered with cambric soaked in sweet almond oil. The patient survived and was observed for more than 2 years. Sir William McEwen performed another successful operation, the removal of left olfactory groove meningioma in 1879. Reports of successful operations came from Francesco Durante, William W Keen, G.I.Pribytkov, A. Taubert and Vittorio Marchi (Al-Rodhan N.R., Laws E.R., 1990).

One of the most important names related to meningioma is Harvey Cushing, whose contribution to neurosurgery made him one of the most outstanding men in medical history. He

was the one who in 1922 introduced the term meningioma for the tumor which has the most frequently changed nomenclature in the history of medicine. (Fig. 2.) Harvey Cushing along with engineer William Bovie also introduced electro cautery and wire loops into neurosurgery in 1927. Prior to 1927, Cushing's practice had a case mortality for craniotomy of 52,9% and operative mortality of 27,2%. After the introduction of electro-cautery, case mortality dropped to 11,8% and operative mortality to 8,9% (Al-Rodhan N.R., Laws E.R., 1990, Cohen-Gadol A.A., Spencer D.D., 2007).

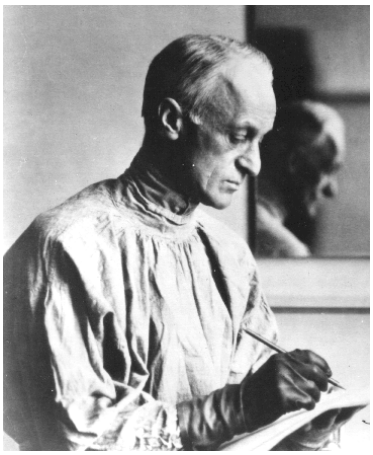

Fig. 2. Harvey Cushing (1869-1939) (Cohen-Gadol A.A., Spencer D.D., 2007)

A further milestone in meningioma surgery was the introduction of the operative microscope by M.G. Yasargil in the 1970ties. Names connected to meningioma surgery and especially skull base approaches are D. Simpson, H. Olivecrona, V. Dolenc, O. Al Mefty, M. Samii, L. Sekhar, and T. Kobayashi.

1.2. Histopathology of meningiomas

Meningiomas are defined as tumors arising from arachnoid cap cells of leptomeninges, that are commonly associated with arachnoid villi at the dural venous sinuses at the cranial nerve foramina, at the cribriform plate and medial middle fossa. Meningothelial cells of choroid plexus, tela choroidea and arachnoid villi at the spinal nerve exit zones are the origin of intraventricular and pineal region meningiomas. They are derived from neural crest (telencephalon meninges) and

from mesoderm (Black P.M., 1993; DeMonte F. et al, 2000; Látr I. et al., 2006; Sanson M.,Cornu P, 2000; Whittle I.R. et al, 2004).

Meningiomas comprise 10-26% of brain tumors, the occurrence of which varies between 1-6/100 000 population. The male to female ratio is 2-3:1, in Africans and Africans Americans the gender distribution is almost equal. Incidence for African Americans was found to be higher (3,1/100 000 population) than for Caucasian Americans (2,3/l100 000). The incidence of intracranial meningioma increases with age, with the peak in the seventh decade. Of all intracranial meningiomas, 85-90% are supratentorial, one third to one half of which are located along the base of the anterior and middle fossae. About 8% of meningiomas are multiple. In about 2-3% they are found in autopsy, previously asymptomatic (Black P.M., 1993; DeMonte F. et al, 2000; Kozler P., 2007; Nakamura M et al., 2003; Kunc Z, 1968; Sanson M.,Cornu P, 2000; Whittle I.R. et al, 2004).

Macroscopically meningiomas appear smooth and lobulated, with a fine vascular pattern on the surface. Most meningiomas are globular but according to specific location, they might be of different shapes, e.g. dumbbell (falcine, Meckels cave), tubular (optic sheath), flat or en plaque. Based on histological features correlated with aggressiveness, like nuclear atypia, mitotic figures, increased cellularity, sheeting, necrosis and brain invasion, World Health Organization (WHO) classifies and divides meningiomas into 3 grades (DeMonte F. et al, 2000; Kozler P., 2007; Kunc Z, 1968).

Meningiomas WHO Gr. I

Meningiomas WHO Gr. I show benign course and comprise about 90% of all meningiomas. Mitotic figures are seen only occasionally, although pleomorphic nuclei do occur. The group is subdivided into several different variants: meningothelial, transitional, fibroblastic, psammomatous, angiomatous, microcystic, secretory, chordoid, metaplastic, lymphoplasmacyte rich and clear cell. There are various architectural patterns and the tumour cells express epithelial membrane antigen. The commonest architectural patterns are meningothelial, fibroblastic and transitional. The most characteristic features are seen in transitional variant: cellular whorls and psammoma bodies. Fibroblastic meningiomas resemble schwannomas. Psammomatous meningiomas contain large amounts of psammoma bodies. Angiomatous meningiomas are highly vascular. Secretory meningiomas form intracellular lumina lined by cytokeratin – imunoreactive cells. The material inside lumina is immunoreactive for carcinoembryonic antigen. WHO Gr. I meningiomas may also present clinically-aggressive behaviours such as penetration of the arachnoid border, destruction of the bone, rapid regrowth of a residual tumor, or recurrence of a

totally resected tumor. Distinct molecular genetic and biochemical alterations differentiate clinically aggressive WHO Gr. I meningiomas from clinically benign WHO Gr. I meningiomas. This fact is clearly demonstrated by the 7 to 20% recurrence rate of histologically benign meningiomas. MIB-l labelling index is 1.0-1.35% (DeMonte F. et al, 2000; Hancq S., 2004; Kozler P., 2007; Kunc Z, 1968; Pfisterer W.K., 2007).

Meningiomas WHO Gr. II

Atypical meningiomas make up to 5-7%. Two subtypes of WHO Gr. II meningiomas are recognised on the basis of their architectural pattern: clear cell and chordoid meningiomas. Chordoid meningioma resembles chordomas, with trabeculae of epithelial cells in a mucinous stroma. The term atypical can be used for any architectural pattern, but has to fulfil certain criteria; the most important is the presence of at least four mitotic figures per ten high power fields. Others are increased cellularity, small cells with a high ratio of nucleus to cytoplasm; prominent nucleoli, sheet-like growth pattern and geographic necrosis. In the absence of the mitotic rate, at least three of the other five features must be present. WHO Gr. II tumors have a higher rate of recurrence (29 - 40%), particularly after partial resection. MIB-l labeling index is 1.9-9.3% (DeMonte F. et al, 2000; Kozler P., 2007; Kunc Z, 1968; Pfisterer W.K., 2007).

Meningiomas WHO Gr. III

Anaplastic or malignant meningiomas are found in about 1-2%. They are sub-classified on the basis of their architectural pattern into papillary and rhabdoid subtypes. Papillary meningiomas are rare variants and are mostly seen in children. There is evidence of brain invasion, cellular sheeting, nuclear pleomorphism, increased cellularity, mitoses and necrosis. Metastases from intracranial meningiomas occur rarely; if they occur, the common sites of implantation are the lungs, liver, lymph nodes and bones. Anaplastic meningiomas have obvious malignant cytology, high mitotic rates, or both. These tumors show local and brain invasion, recurrence and metastases. Brain invasion is histologically defined as islands of neoplastic cells that have invaded through the pia to involve underlying cortical tissue, commonly producing a gliotic reaction. Brain invasion is not a criterion for grading tumors in the WHO classification, but it should always be commented on in a pathological report, because brain invasion is associated with subtotal resection and a higher rate of recurrence. MIB-l labelling index is 5.6-19.5% (DeMonte F. et al, 2000; Kozler P., 2007; Kunc Z, 1968; Perry A. et al., 1999; Pfisterer W.K., 2007; Ware M.L. et al., 2004; Whittle I.R. et al, 2004).

1.3. Etiology

Among exogenic factors, the only one confirmed is cranial irradiation. Radiation induced neoplasm must fulfil the following criteria: 1. It must occur in an irradiated field, 2. It appears following appropriate, usually a long period of latency following irradiation and 3. It differs from any pre-existing neoplasms. There were meningiomas published after scalp irradiation with low doses for tinea capitis and after radiotherapy. Because radiation causes damage to DNA, it might be hypothesized, that radiation leads to injury of genetic material, found within the long arm of chromosome 22, in the locus subtending the tumor suppressor gene (Black P.M., 1993; DeMonte F. et al, 2000; Kozler P., 2007; Kunc Z, 1968; Whittle I.R. et al, 2004).

NF2 gene. Mutations of the NF2 gene, which is located at chromosome 22q12 are found in meningiomas of all grades and are thought to be an early event in tumorigenesis. Up to 60% of sporadic meningiomas show a somatic mutation of the NF2 gene resulting in a non-functional merlin or schwannomin protein. There is an connection between the histological variant and the frequency of NF2 mutations, with 70-80% of transitional and fibroblastic meningioma carrying NF2 mutations, compared with only 25% of meningothelial meningiomas (Kozler P., 2007; Lee J.H. et al., 1997; Leraud P. et al, 2004).

The majority of multiple meningiomas with an NF2 gene mutation are of somatic and clonal origin. The spread of tumor cells via cerebrospinal fluid is the most likely mechanism to account for the development of these multiple meningiomas that confirms that multiple meningiomas are not a fruste form of NF2 (Kozler P., 2007; Stangl A.P. et al., 1997).

Other genes. The product of the *DAL -1 gene* (18p11.3), a member of the protein 4.1 family, which has homology with merlin, has also been implicated in familial meningiomas, and meningioma evolution; loss of expression of this protein is an early event in tumorigenesis (DeMonte F. et al, 2000; Ware M.L. et al., 2004). The next most common generic mutation seen in meningiomas is deletions of 1p, 9p, 3p, 6q, 10q, and 14q. A putative suppressor gene is located at 1p36.21. Deletions of 1p, 9p, 10q, and 14q are associated with increasing histological grade and 14q deletions in benign meningiomas WHO Gr. I reflect a propensity for recurrence. Allelic gain and amplification of 17q occurs in up to 60% of anaplastic meningiomas. Molecular screening for telomerase activity and LOH / loss of heterozygocity on chromosomes 1p, 9p, 10q could be useful in a clinical setting to complete WHO grading of meningiomas and to determine the most

appropriate treatment of these locations (Claus E.B et al., 2008; DeMonte F. et al, 2000; Lee J.H. et al., 1997; Leraud P. et al, 2004, Pfisterer W.K., 2007).

Cathepsin D is associated with a lower tumor grade, low mitotic count and low recurrence. Cathepsin K expression is associated with aggressive phenotype meningioma; Cathepsins B and L are significantly higher in invasive types of benign meningioma. Cathepsin B may therefore be used as a diagnostic marker to distinguish histomorphologicaly benign but invasive meningiomas from histomorphologicaly clear benign tumors (Strojnik T. et al., 2001).

1.4. Hormone receptors in meningiomas

Progesterone receptors (PR) are expressed in about 50-88%, they are functional and play a role in meningioma growth. Several studies have shown a connection between high PR expression and good histological grade, lower frequency of recurrence and overall favourable prognosis. There is evidence that PR status seemed to be associated with changes near the NF2 gene on 22q (mutations which are identified as being an important initial event in meningioma development) continues to suggest that hormones are likely to play an important role in either the development or progression of some meningiomas and/or that PR status may be an important clinically measurable indicator variable of that role (Claus E.B et al., 2008; DeMonte F. et al, 2000; Fewings P.E. et al., 2000; Kozler P., 2007; Whittle I.R. et al, 2004).

Somatostatin receptos are expressed in 70-100% meningiomas. Their presence can be used to image tumors with radiolabelled substances, which is especially useful for postoperative detection of residual or early recurrent tumors (DeMonte F. et al, 2000; Kozler P., 2007; Whittle I.R. et al, 2004).

There is evidence of *growth hormone receptors* and *estrogen receptors;* their role is still unclear (DeMonte F. et al, 2000; Whittle I.R. et al, 2004).

1.5. Prediction of meningioma recurrence

Meningioma recurrence may have the most significant impact on patient survival and quality of life and, thus, may be the most important component in prognosis, yet the likelihood of recurrence of these tumors is difficult to predict in vivo. The best predicting factor is a Simpson grading system of resection (S I-IV). According to its definition, Simpson Grade I (S I) is

macroscopically complete removal, excision of the dural attachment and abnormal bone; S II is macroscopically complete removal, with coagulation of the dural attachment; SIII is macroscopically complete removal, without resection or coagulation of the dural attachment; S IV is a partial excision. Five-year recurrence rate for S I is 9% (4-15%), 16% for S II and 29% for S III. These numbers might however be imprecise, in a long-term perspective as well as with increasing diagnostic possibilities recurrent meningioma might be discovered in more cases. Clinical and pathological findings are the current standard for diagnosis and prognostication of meningiomas, but the behaviour of an individual meningioma may still be difficult to predict. Immunohistological methods such as MIB-1, progesterone receptor, and vascular endothelial growth factor (VEGF) staining as well as S100A5 protein have shown promise for evaluating aggressive potential in meningiomas (Hancq S. et al., 2004; Kozler P., 2007; Simpson D.; 1957).

Additionally, fluorescent in situ hybridization (FISH) and 1H magnetic resonance spectroscopy (MRS) may show promise for the development of diagnostic and prognostic tools to enhance clinical and pathological diagnostic criteria. FISH may be especially sensitive in predicting clinical behaviour because it allows direct observation of chromosomal abnormalities that can be correlated with a specific phenotype or clinical parameter such as recurrence. Tumors that present with complex genetic alterations, even those with a benign histological grade, are potentially aggressive and require a closer follow-up. (Pfisterer W.K. et al., 2007; Sayagues J.M. et al., 2004).

Meningiomas that recur within a 5-year follow-up period may share a significant amount of genetic and biochemical characteristics sufficient to classify them more adequately than is currently done within the WHO grading system. In Magnetic Resonance Spectroscopy (MRS), the ratio of glutamine to glutamate tends to be higher in rapidly recurring meningiomas (Al-Rodhan N.R., Laws E.R. et al., 1990; Claus E.B. et al., 2008, Perry A. et al., 1999).

Proliferative potential of tumors can be quantified, using BUdR (5-bromdeoxyuridine), Ki-67 (antigen), MIB-l (monoclonal antibody) or PCNA (proliferating cell nuclear antigen), which are helpful in the prediction of clinical behaviour of the tumor. BUdR, 5-bromdeoxyuridine is incorporated into cells during the S phase and the monoclonal antibody, Ki-67 (Ki LI) reacts with a human nuclear antigen which is expressed only in cycling cells but not in quiescent cells. The monoclonal antibody MIB-1 can detect the Ki-67 antigen. Labelling indices of BUdR LI and Ki LI represent the proliferation activity of brain tumors. Invasive phenotype, positively correlated with histological grading, may be observed in WHO Gr. I meningioma. BUdR LI is in benign less than l%, in recurrent meningiomas 1%, in malignant meningiomas 5%. Ki LI of recurrent meningiomas increased from 5% to 20%. They correlate with tumor doubling time. Identification is effective in

predicting the clinical course and planning the best individual treatment. Other biological factors, such as apoptosis related proteins (p53, p21WAF1, and p27Kip1) or growth factors (transforming growth factors alpha and beta and PDGF) are important in meningioma progression or recurrence; this link is also suggested by findings in childhood meningiomas in which MIB-1 labelling indices are similar to those in adults, although meningiomas in children behave more aggressively (DeMonte F. et al, 2000; Kakinuma K et al., 1998; Sanson M, Cornu P et al., 2000; Whittle I.R. et al., 2004).

Cathepsin B may be used as a diagnostic marker to distinguish histomorphologically benign but invasive meningiomas from histomorphologicaly clear benign tumors (Strojnik T. et al., 2001). Benign meningiomas that are PR (progesteron receptors) positive are less likely to recur (Fewings P.E. et al., 2000; Nakasu S., et al., 1999). According to Yamasaki et al. (2000) the best predicting factor for recurrence is VEGF, followed by MIB-1.

1.6. Peritumoral edema

Meningiomas are surrounded by edema in 40-60%. The causative factors of peritumoral edema are the type of arterial blood supply; pial blood supply in particular; and vascular endothelial growth factor (VEGF). VEGF is an endothelial cell specific cytokine, produced by meningothelial cells, which induces proliferation and migration of endothelial cells and dramatically increases capillary permeability. VEGF is both an angiogenic and vascular permeability factor; it plays a central role in neovascularisation and tumor stroma generation. It is also related to stromal degradation through activation of proteolytic enzymes that are involved in tumor invasiveness and angiogenesis. Meningeomas are variable in its expression, whereas all gliomas secrete significant amounts of VEGF (Harrigan M.R., 2003; Yoshioka H. et al., 1995).

Peritumoral edema requires both an expression of VEGF as well as a mechanical factor such as obliteration of the subarachnoidal space that allows VEGF to penetrate and act on the peritumoral brain vasculature. Secreted VEGF from the tumor enters the brain tissue through the disrupted arachnoid, promotes the proliferation of microvessels, increases the number of pial feeding arteries and promotes edemagenesis which induces adhesion to the surrounding brain tissue. Such adhesion make separation of the tumor capsule from pia mater difficult and causes tumor cells to remain in the surrounding brain after surgery. Remnant tumor cells secrete VEGF, which would induce neovascularisation and support the growth of meningioma cells. VEGF is a

strong predictor of recurrence (Bitzer M, 1997, Kozler P., 2007; Pistolesi S. et al., 2004; Provias R. et al., 2007; Yamasaki F et al., 2000; Yoshioka H et al., 1995, Nagashima G et al., 2006).

1.7. Dural invasion

There are several patterns of meningioma invasion into the dura mater: a papillary-shaped invasion with destruction of the dural structure, infiltration along the fibers of the dura mater, and invasion of several tumor cell units with a fibroblast infiltration. Strong immunostaining was obtained with MMP-1 (matrix metalloproteinase -1), followed by AQP-1 (aquapourin-1) and uPA (urokinase-type plasminogen activator), within the invading tumor cells. Neovasculature and extravasated erythrocytes, which stained with AQP-1, were also occasionally observed around the invading tumor cells. The fact that AQP-1 was highly expressed at the dural attachment and the invading front of meningioma may indicate that dural invasion of the meningioma may be facilitated by an AQP-1-induced water flow and neovascularization and have important roles in meningioma invasion into the dura mater (Nagashima G et al., 2006). There is also evidence of meningioma infiltration into soft tissues, cranial nerves and blood vessels (Kotapka M et al., 1994, Larson J.J. et al., 1995; Látr I. et al., 2006).

1.8. Natural history of meningiomas

Natural history of meningioma is not fully understood, even though it is possible to predict its growth to a certain extent based on typical radiological features. Benign meningiomas are slow growing tumors and it takes often years, sometimes decades, until they become symptomatic. The growth of benign incidental meningioma is often well tolerated by surrounding brain, which can adapt to slow increase of tumor volume, as the opposite to rapid growth of malignant tumor. Natural history of meningiomas can be studied in patients, in whom incidental meningiomas were found and who are not candidates for operative surgery due to various reasons, such as asymptomatic meningiomas in elderly, serious health conditions, refusal of treatment etc. Incidental meningiomas are diagnosed more frequently with increased availability of computed tomography (CT) and magnetic resonance (MR) scanners. The majority of scans are performed due to non-specific complaints, such as headache and dizziness.

Few published studies on natural history of meningiomas came to the same conclusion, that meningiomas containing calcifications in elderly, without perilesional edema, have low growth

potential and can be observed. Large meningiomas in younger patients, especially the ones with collateral edema are symptomatic, or become symptomatic during short period of time. There is an evidence of meningiomas behaving more aggressively in male patients. Growth rate of meningioma might vary between 0,2 cm to 1 cm annually (Kuratsu J et al., 2000; Mádlová V.,Fusek I., 1980; Nakamura M et al., 2003; Niiro M. et al., 2000; Olivero W.C. et al.,1995; Van Havenberg T. et al., 2003; Yoneoka Y. et al., 2000).

The growth pattern of meningiomas is not linear and during its life, meningioma might show different growth patterns. In patients who underwent surgery for their meningiomas, it is possible to predict behaviour of eventual remnant of the tumor by investigating their growth potential by Ki-67 and MIB-1. Remnants of resected meningiomas have, however, higher growth potential (Van Havenberg T. et al., 2003; Yoneoka Y. et al., 2000).

Natural history of each incidental meningioma should be followed by follow up scans. After the diagnosis of meningioma is set, first follow up scans are recommended in 2-3 months, to rule out malignant meningioma with higher growth potential, or other lesions that might mimic benign meningioma. Further follow up scans should be performed annually, or when the patient becomes symptomatic (Niiro M. et al., 2000; Yoneoka Y. et al., 2000).

1.9. Presenting symptoms

There is no single symptom or sign that alone identifies the patient with intracranial meningioma. Meningiomas arise from dura at any site, most commonly the skull vault, skull base, sites of dural reflexions (falx, tentorium). Less common is the optic nerve sheath and choroid plexus. Approximately 10% of meningiomas arise in the spine. Very rarely, meningiomas have arisen wholly outside the craniospinal axis, in the ear and temporal bone, mandible, foot, mediastinum and lung.

The most common symptoms are headaches, paresis, seizures, personality changes and visual impairment. Meningiomas in a specific location may have a typical clinical presentation. Olfactory groove meningiomas present themselves with anosmia and the Foster-Kennedy syndrome (optic atrophy and scotoma in the ipsilateral eye and papilledema on the contralateral side). Tuberculum sellae meningiomas cause ipsilateral optic atrophy and incongruous bitemporal hemianopsia. Cavernous sinus meningiomas often present with proptosis and diplopia. Optic nerve sheath meningiomas often lead to progressive visual acuity decline, color blindness, and finally complete loss of vision because of the lesions' intimate circumferential relationship with the optic

nerve and its vascular supply. Foramen magnum meningiomas present themselves with nuchal and suboccipital pain (DeMonte F. et al., 2000; Eddlemann C.S., Liu J.K.,2007; Kozler P., 2007, Sameš M. et al., 2005).

Some meningiomas are diagnosed incidentally in asymptomatic patients as a result of the patients having CT or MR scans carried out on them for a different reason. For an asymptomatic patient, an individual approach according to location, size and the age of patient should be utilized.

1.10. Diagnostic modalities

Computed Tomography (CT) and enhanced Computed Tomography

CT identifies most meningiomas and has the advantage of bone window, which shows bone involvement, e.g. hyperostosis or bone lysis. Also, calcifications are clearly seen. Non- enhanced CT scans of typical meningioma shows an isodense or slightly hyperdense mass; calcification range from punctate calcifications to dense areas. Intravenous contrast shows intense, homogenous enhancement. About 15% of meningiomas have atypical appearance, with the presence of cysts, a haemorrhage or necrosis (DeMonte F. et al., 2000).

Magnetic Resonance (MR)

MR is necessary to perform on every patient with meningioma, as it shows details important for surgery as well as for radiosurgery, i.e. the proximity of cranial nerves, major vessels and their distortion. On T1 images 60-90% of meningiomas are isointense, whereas 10-30% are mildly hypointense. T2 images show hyperintense meningiomas in 30-45% and isointense in about 50%. Specifically, meningothelial and angioblastic variants have a higher signal on T2 than fibroblastic and transitional meningiomas. It is also important in the assessment of peritumoral edema, hyperintense on T2 images. In contrast MR provides the highest level of meningioma detection. It shows often „dural tail“ enhancement beyond the margins of mass lesion of meningioma, showing infiltration of dura, which needs to be resected to prevent recurrence, whenever possible. Postoperative MR shows residual or recurrent meningioma (DeMonte F. et al., 2000; Kozler P., 2007).

Angiography

Angiography to assess the blood supply has been recently replaced by CT or MR angiography. Selective angiography is often combined with embolization to decrease blood loss

during operations. It offers valuable information about the vascular blood supply, which can predict the resectability of meningioma, obtaining the plane of cleavage (DeMonte F. et al., 2000; Kozler P., 2007).

Magnetic resonance spectroscopy

Magnetic resonance spectroscopy (MRS) helps to distinguish different pathologies preoperatively. *Alanine* has generally been found to be elevated in meningiomas relative to other tumors and the normal brain. Its occurrence is lower in those meningiomas that rapidly recur. Its concentration correlated to the presence of chromosomal aberrations and was found to be lower in meningiomas with aberrations. Alanine is thought to be a so-called "normal" part of the metabolism of meningioma cells or the progenitor cells of a meningioma (i.e., arachnoid cap cells or the dura).

Choline is generally elevated in tumors compared with the normal brain; it is a generic marker for brain cancers and tumors of other tissue types. Elevated choline peaks are also seen in regions of high tumor cell density where tissue has not necessarily been anaplastic. Meningiomas have been shown to have choline concentrations comparable to Grade III astrocytomas, and meningioma cells may have phosphocholine/glycerophosphocholine ratios as high as those seen in glioblastoma cells.

Creatine is typically very low in meningiomas, especially in comparison with levels seen in more malignant tumors such as medulloblastomas and glioblastomas. A creatine level thus could be an indicator of aggressive behaviour (Perry A. et al., 1999).

A typical proton MR spectrum shows a marked increase in the choline signal, which reflects an increased pool of membrane components necessary for cell proliferation. This feature is typical for most intracranial neoplasms and therefore it is not specific for meningioma. A marked reduction of NAA (N-acetyl aspartate) and PCr/Cr peaks is typical for meningioma (Perry A. et al., 1999).

1.11. Surgery

Surgery is the most common primary management of meningioma. Simpson described the recurrence rates according to the extent of surgical resection (Simpson D., 1957). Although his series was retrospective and was done before CT and MR and microsurgery, the importance of the extent of tumor and dural resection has been confirmed in several subsequent studies. On the other hand, CT and MR available today would probably cause the re-grading of the meningioma excision. However, in all these studies the rate of meningioma recurrence increased when the follow up period was extended. Even after a Simpson grade I resection, a recurrence rate of 20% 10 years later has been reported. The recent published study by Petterson-Segerlind et al., (2011) analysing 25 years –follow up of surgically treated patients with parasagittal meningiomas found, that total recurrence rate was 47%; for radically operated meningiomas (Simpson grade I-II) there was a 10-and 25 years recurrence rate of 13% and 38% respectively.

With recent advances in the design of interventional neuroradiology, the importance of endovascular therapy has increased. Selective embolization of feeding arteries reduces blood loss during subsequent surgery. The question remains the precise timing between embolization and resection. Embolization can induce histological atypical changes associated with benign WHO Gr. I meningioma, since tumor necrosis will follow embolization. Although atypical features might be seen in embolized meningiomas, they may reflect a primary tumor grade (DeMonte et al., 2000).

Even though total excision is the ideal goal, many tumors cannot be totally excised because they are enveloping vital neural or vascular structures or are en plaque. With the introduction of MR, many of these cases were diagnosed when the tumor was small, which led to a trend of attempted total excision of these lesions by various novel skull base and microsurgical approaches. Most of these case series have methodological problems and are subject to bias. Subsequent long term follow-ups suggested that successful complete excision is rare and that the morbidity associated with attempted removal is significant, particularly for meningiomas involving cavernous sinus, the petroclival region, the posterior part of the superior sagittal sinus, the optic nerve sheath and for spheno-orbital en-plaque tumors. For skull base meningiomas, the chance of complete excision is 20-97,8%, with a risk of up to 46% of cranial nerve deficit and 0-11% mortality. Attempts at excision of these lesions can cause catastrophic vascular injury or disabling cranial neuropathies. By contrast, most convexity and spinal meningiomas and many falcine can be excised without significant morbidity. Parasagittal meningiomas infiltrate superior sagittal sinus, which is difficult to manage especially in its posterior part. One can either resect meningioma

completely with the reconstruction of the superior sagittal sinus or leave the residual for stereotactic radiosurgery (Aichholzer M. et al., 2000; Akagami R. et al., 2002; Asari S. et al., 1995; Couldwell W.T. et al., 1996; Cudlip S.A. et al., 1998; DeMonte F. et al., 1994; Fahlbusch R. et al., 2002; Hirsch W.L. et al., 1993; Jung H.W. et al., 2000; Linskey M.E. et al., 2005; Maruyama K. et al., 2004; Mathiesen T. et al., 1996; Obeid F. et al., 2003; O'Sullivan M.G. et al., 1997; Sameš M. et al.; Samii M. et al., 1996; Schaller C. et al., 1999; Sekhar L.N. et al., 1994; Sindou M.M. et al., 1998; Stippler M., Kondziolka D., 2006; Voss N.F. et al., 2000).

1.12. Radiotherapy

Radiotherapy as a treatment modality in selected meningiomas is well established. Published series report on 50-92% tumor control rates, depending on follow up period, histology and treatment techniques The clinical benefit is clear in atypical WHO Gr. II and anaplastic WHO Gr. III, after incomplete resection, in recurrent tumors too large for stereotactic radiosurgery or in a patient in whom serious health conditions preclude surgical resection. Published series report on 50-92% tumor control rates, depending on follow up period, histology and treatment techniques. However, there is a risk of significant complications related to treatment, such as loss of vision, cataract or retinopathy, delayed radiation injury to brain parenchyma, vasculature and pituitary, as well as the risk of secondary neoplasms and therefore radiotherapy should be recommended for young patients cautiously. (Eddlemann, Liu, 2007; Lunsford, 1994; Maire et al., 1995; Minniti et al., 2011; Nutting et al., 1999; Pechlivanis et al., 2011).

At the borderline between stereotactic radiosurgery and radiotherapy stands stereotactic radiotherapy benefiting from both precise targeting based on stereotactic principles combined with radiotherapy, i.e. small doses of radiation delivered in multiple sessions. As a result, treatment options for meningiomas in contact with sensitive structures can be treated. In cases where a tumor is close to optic pathways or encases it, high precision fractionated stereotactic radiotherapy is recommended as the treatment of choice. Published studies show tumor control rate of 97,4%. Among adverse effects are listed headaches, fatigue, retroorbital pain in patients with meningiomas located in parasellar region (Bria et al., 2011; Eddleman, Liu, 2007; Selch et al., 2004; Shrieve et al., 2004). Radiotherapy, both conventional and stereotactic, has recently been shown to have good efficacy for growing optic nerve sheath meningiomas, with local tumor control and stabilization or improvement of the visual function in about 80% (Eddleman, Liu, 2007; Pechlivanis et al., 2011).

For meningiomas that recur even after radiotherapy, hydroxyurea, interferon alpha and progesterone agonist have been used experimentally (Whittle I.R. et al., 2004).

1.13. Stereotactic radiosurgery

1.13.1. Historical background of radiosurgery

Stereotactic radiosurgery is a technique for the non-invasive affecting of intracranial tissues or lesions that may be inaccessible or unsuitable for open surgery; the term was introduced by Lars Leksell back in 1951. (Fig. 3., 4.)

Fig. 3. Professor Lars Gustaf Leksell 1907-1986 (Liščák R et al., 2009)

During era, when morbidity and mortality of intracranial procedures was very high, Leksell thought about avoiding the drawbacks of surgery. The result of his cooperation with physicist and radiobiologist prof. Borje Larsson in Uppsala, Sweden was the first clinical use of stereotactic-guided proton beams produced by cyclotron, which was however too cumbersome for hospital use. The first prototype of the Gamma Knife was installed at the Sophiahemmet Hospital in Stockholm in 1967. The first patient treated in 1968 was a patient with craniopharyngioma. The first meningioma was treated by Backlund in 1971 (Gildenberg P.L., Tasker R.R., 1998; Karlsson B., 1996).

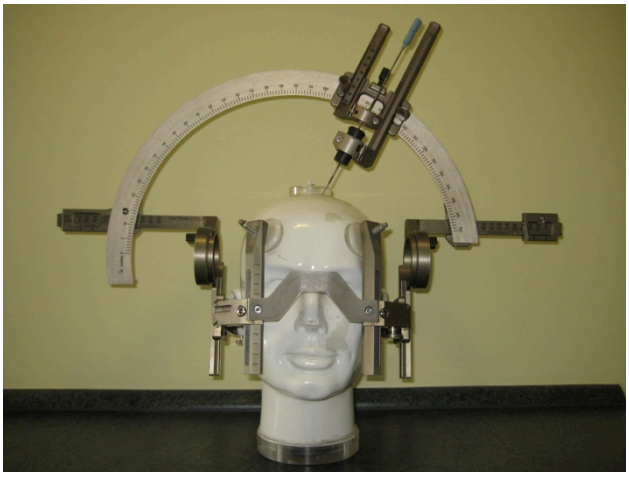

Fig. 4. Leksell stereotactic frame

A golden standard for planning today is MR. Planning has been developing as well, from manually calculated and plotted isocenters through to the first computerized planning system KULA to GammaPlan software (Elekta Instruments Inc. Stocholm, Sweden).

In spite of the fact, that radiation has been used Leksell introduced the term radiosurgery, because the procedure is performed by a combination of mechanically directed instruments and modern radiation physics, albeit using another physical agent in place of the knife or radiofrequency heat lesion (Karlsson B., 1996; Leksell L., 1983).

The greatest advantage of radiosurgery is its precision as well as the fact, that it delivers a high focused radiation dose to the tumor with a steep fall-off of the dose and thus sparing normal brain tissue (Leksell L., 1983). At present, stereotactic radiosurgery is most commonly used for the treatment of arteriovenous malformations, vestibular schwannomas, meningiomas, pituitary adenomas, metastases and trigeminal neuralgia (Leksell L.,1983; Liščák R. et al., 2009; Steiner L. et al., 1991).

1.13.2. Radiobiology of radiosurgery

The impact of irradiation can be detected at various levels of organisms at different times after the tissue was irradiated. In general, three phases can be distinguished:

The physical phase covers the interaction of ionizing radiation with atoms and molecules. The secondary electron with high energy passes through DNA in about 10^{-18} to 10^{-14} s. During this phase interaction between secondary electrons and orbital electrons occur, resulting in ionization or excitation of atoms and molecules. In the case of the energy of released electrons being high enough to affect other molecules, a cascade process of ionization can occur. For the dose of 1 Gy, there are 10^5 of ionizations in the volume of every irradiated cell of approx. 10 μm (Bernstein M., Berger M.S., 2008; Novotný J. Jr, 2009).

The chemical phase; during this phase damaged atoms and molecules interact with other cell components in chemical reactions. Ionization and excitation lead to the disruption of chemical binding between atoms and molecules and give rise to free radicals. Free radicals are very active and they interact further with other chemical substances to achieve a new equilibrium. The reactions run for 1 ms from the beginning of irradiation.

The biological phase covers all subsequent processes. It begins with an enzymatic reaction of damaged DNA. Many single strand breaks are repaired by the second part of DNA helix and represent thus sublethal damage. Double strand breaks are usually not repaired, or repaired imperfectly, what leads to structural chromosomal aberrations: dicentric chromosomes, ring chromosomes, fragments, and translocations.

Ionizing radiation causes changes to the genetic information of cells as well as to the cells in general. The effect of radiation depends on its type, absorbed dose, volume of irradiated organs and tissues. It can be direct or indirect.

Direct effect is a result of interactions between electrons, neutrons and photons with important structures. It requires a sufficient dose and a target, which might be the cell with large or doubled nuclei; they are radiosensitive, e.g. stem cells and proliferating cells. Their proliferation depends on enzymatic systems, which can also be affected by radiation via direct or indirect mechanisms (electrons, free radicals). Proliferating, quickly dividing cells have short cell cycles that leave the cell with less time to repair radiation damage.

Indirect effect caused by X ray and gamma rays, is mediated by free radicals, which interact with the DNA, leading to damage of DNA bases, saccharides, bindings within DNA helix, single and double breaks (Bernstein M., Berger M.S., 2008; Novotný J. Jr, 2009).

The goal of radiosurgery in benign tumors is not the eradication or removals of tumorous population in terms of complete regression; it is its impact on proliferating cells. After the treatment, changed stroma and differentiated cells in the G0 phase persist. The treatment response is late, 2-5 years. However, there is a histological evidence of radiation necrosis within the tumor, as well as in cases, where collateral edema as an result of irradiation occurred; signs of demyelination, coagulation necrosis, vascular sclerosis and active vasculitis with transmural T cell infiltration was found (Bernstein M., Berger M.S., 2008; Rauch P.J. et al., 2011).

1.13.3. Principles of radiosurgery

Stereotactic radiosurgery is a treatment method of brain lesions utilizing a focused external beam ionizing radiation. The goal is to apply a sufficient dose precisely to the target volume of a particular size, shape and location to achieve the desired radiobiological effect within the lesion and at the same time to spare the surrounding brain tissue. Three different sources of ionizing radiation are used for radiosurgery:

1. Focused ionizing gamma irradiation from nuclear sources Co (Gamma Knife)
2. Focused ionizing X irradiation in a linear accelerator (LINAC)
3. Charged heavy particles in cyclotron

The specific biological effect of radiation is determined by the absorbed dose in tissue. Absorbed dose is quantified as energy deposition per unit mass and has SI units gray (Gy), where 1 Gy = 1 J/kg. Radiosurgery requires a large dose deposition within the target volume and a steep dose gradient resulting in very little dose delivered to a normal tissue. The basic photon radiosurgery paradigm relies on the use of multiple tightly focused beams, each of which uses unique entry paths and all converging on a point of interest, i.e. the isocenter. The region, in which beam intensity is rapidly decreasing, is called the penumbra and its width is quantified as the distance between 80% and 20 % regions. Since radiosurgery relies on steep dose gradients outside the irradiated volume, sharp penumbra is important. Factors affecting the slope of the penumbra are the physical size of the radiation source, the distance from the radiation source to the final beam collimation, and the distance from the final beam collimation to the point of interest (Gildenberg P.L., Tasker R.R., 1998).

1.13.4. Gamma Knife

The Gamma Knife is a highly sophisticated device, utilizing 201 60Co pellets. Co decays to an excited state of 60Ni through the process of beta decay, in which the 60Co nucleus emits an electron and neutrino. Excited 60Ni nuclei stabilize by emitting photons with energy levels of 1,17 MeV and 1,33 MeV, which are emitted per radioactive disintegration. Average photon emission is thus 1,25 MeV. Photons emitted from 201 sources are directed through the 201 channels drilled in a high-density metal helmet attached to the stereotactic frame during the process of treatment. High density metal absorbs photons that are not directed along the axis of the channel. To design variable field sizes to treat lesions of different sizes and shapes, each channel entails removable 4, 8, 14 and 18 mm diameter tungsten collimators that project particular circular fields at the focal point of the radiation beams. Any of the channels might be plugged if it is determined that a beam passes through radiosensitive critical structures and thus avoids their damage.

The Gamma Knife consists of the following parts:

a) The radiation unit, enclosing 201 60 Co sources.
b) The treatment couch with the collimator helmets attached.
c) The control panel and couch driving mechanisms.
d) The stereotactic frame for target localization and for supporting the patient's head during the treatment.
e) The computerized dose planning system. (Fig. 5.)

Leksell Gamma Knife, model C (Elekta Instruments Inc., Stockholm, Sweden) was used until November 2009; in December 2009, a new model-Perfexion was installed, which differs from previous models in terms of technology and shielding of the radiation unit.

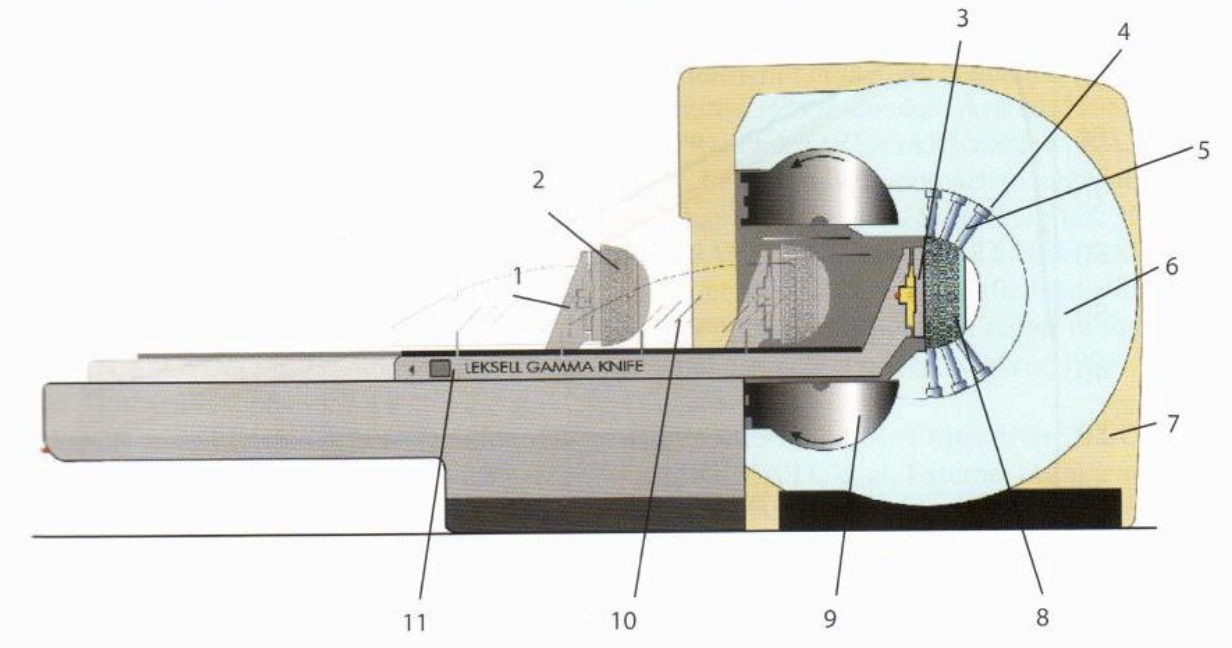

Fig. 5. Structure of Leksell`s Gamma Knife. 1-collimator helmet holder, 2-collimator helmet with collimators, 3-system for fixation of patient, 4-radioactive sources of 60Co, 5-internal collimators, 6-shielding, 7-cover, 8-collimator helmet in treatment position, 9-shielding doors, 10-lateral panels for patient protection, 11-treatment couch (Liščák R. et al., 2009).

1.13.5. Process of treatment

Stereotactic frame

The stereotactic frame is attached to the skull of the patient by four titanium pins under local anesthetic, after premedication has been administered. Special caution is required in patients with bone defects after craniotomy and hydrocephalus shunt systems. The frame is placed by the neurosurgeon. (Fig.6.)

Defining the size of the skull and its position inside the helmet is used for planning; data are collected after attaching the plastic sphere to the stereotactic frame and measuring the distance of the skull from the plastic sphere, which corresponds with the treatment helmet. It is performed by a physicist and the result is the correct position of the patient`s head within the helmet as well as avoidance of any spatial collisions during the treatment.

Fig. 6. A. Patient JK, 52 years old, treated for right intra- and parasellar meningioma, with fitted Leksell`s stereotactic frame, with a localizing box, anterior view. B. Lateral view. Planning scans and histogram for the same patient featured in Fig. 8., 9.,10.

Imaging

Treatment of meningioma requires MR imaging with a stereotactic frame attached to the skull. Therapeutic imaging differs from diagnostic imaging in terms of position, slice thickness, contrast media (Gadolinium) administration as well as requirements for accuracy of imaging. The MR scanner has specific conditions, which have to be considered to create accurate images to prepare a precise treatment plan. It is the magnetic field inhomogeneity, gradient field nonlinearity, and artifacts coming from the interface of air/tissue, image distortion and eddy currents (Gildenberg P.L., Tasker R.R. et al., 1998; Vymazal J., 2009).

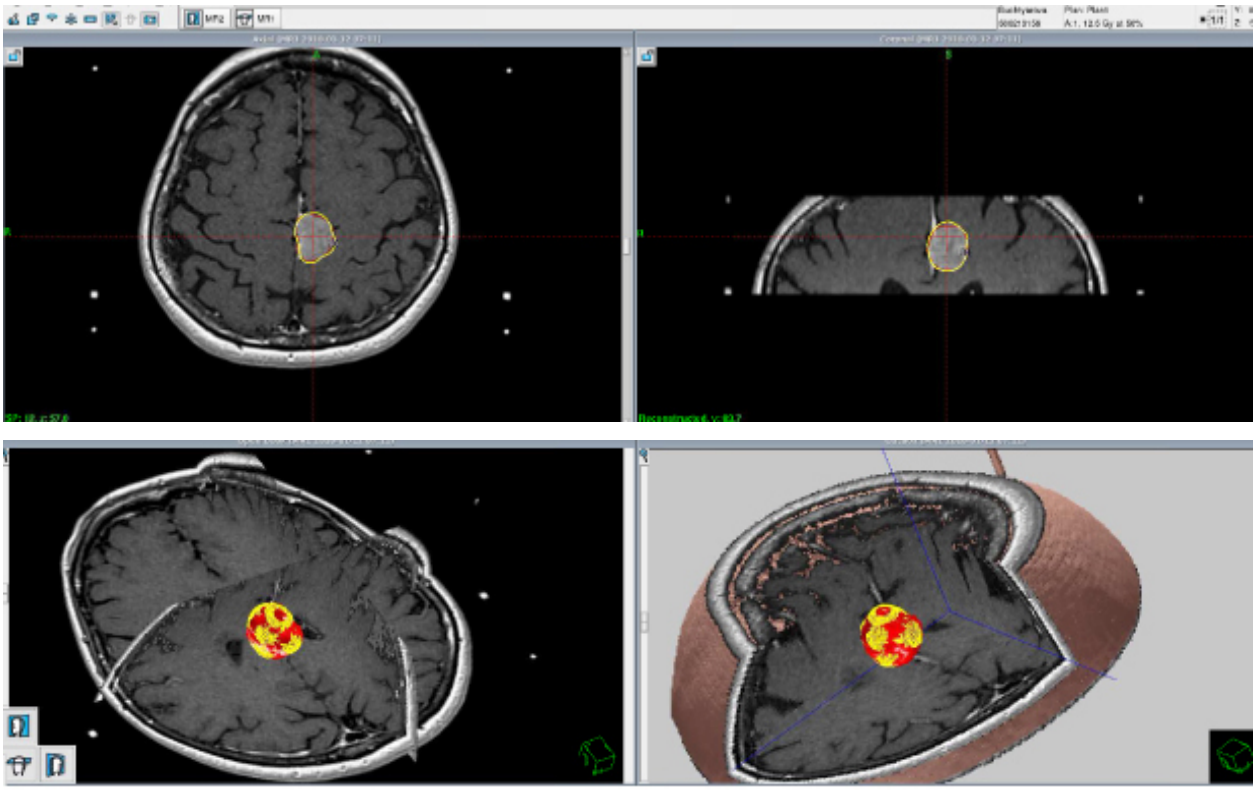

Fig. 7. Patient VB, woman, 60 years old, treated for left falcine parietal meningioma. Planning scans and 3D reconstruction in the Gamma Plan (Elekta Instruments, Inc. Stockholm, Sweden)

Preparation of the treatment plan

Planning is programmed in the Gamma Plan (Elekta Instruments Inc., Stocholm, Sweden) planning system. It contains the personal data of the patient, actual physical data of the Gamma Knife, DICOM images and final treatment plan data that is exported to the operating console. The first radiosurgical treatment plans, however, were created entirely by a graphic display of isodose distributions superimposed on the patient`s imaging scans.

Defining the target volume is based on reliable imaging. It is important not only to draw the target itself, but also critical structures in its vicinity before deciding on the dose. Preparation of the treatment plan requires covering the target by “shots” which are single isocenters delivered through one of four collimators. The result of the process might be a simple one-shot plan, or a complex plan, in which the neurosurgeon covers the lesion of irregular shapes with multiple shots of different sizes. (Fig. 7., 8., 9., 10.)

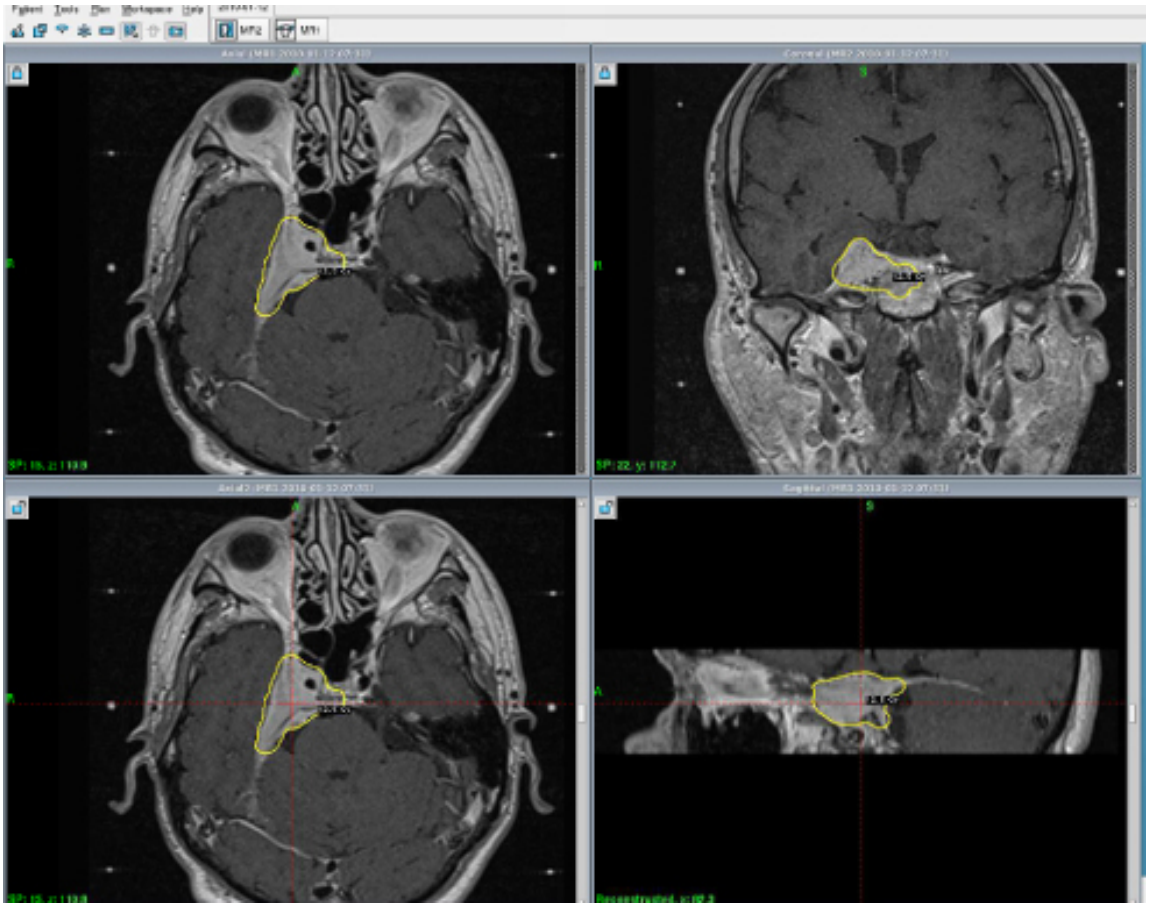

Fig. 8. Patient JK, man, 52 years old, treated for right intra and parasellar meningioma. Planning scans with marked up lesion in the Gamma-Plan (Elekta Instruments, Inc. Stockholm, Sweden)

The dose distribution is influenced by adding shots, by weighing of the shot (for a particular shot less than 100% of its power will be utilized), plugging of certain shots and the change of angle of the patient`s head within the helmet.

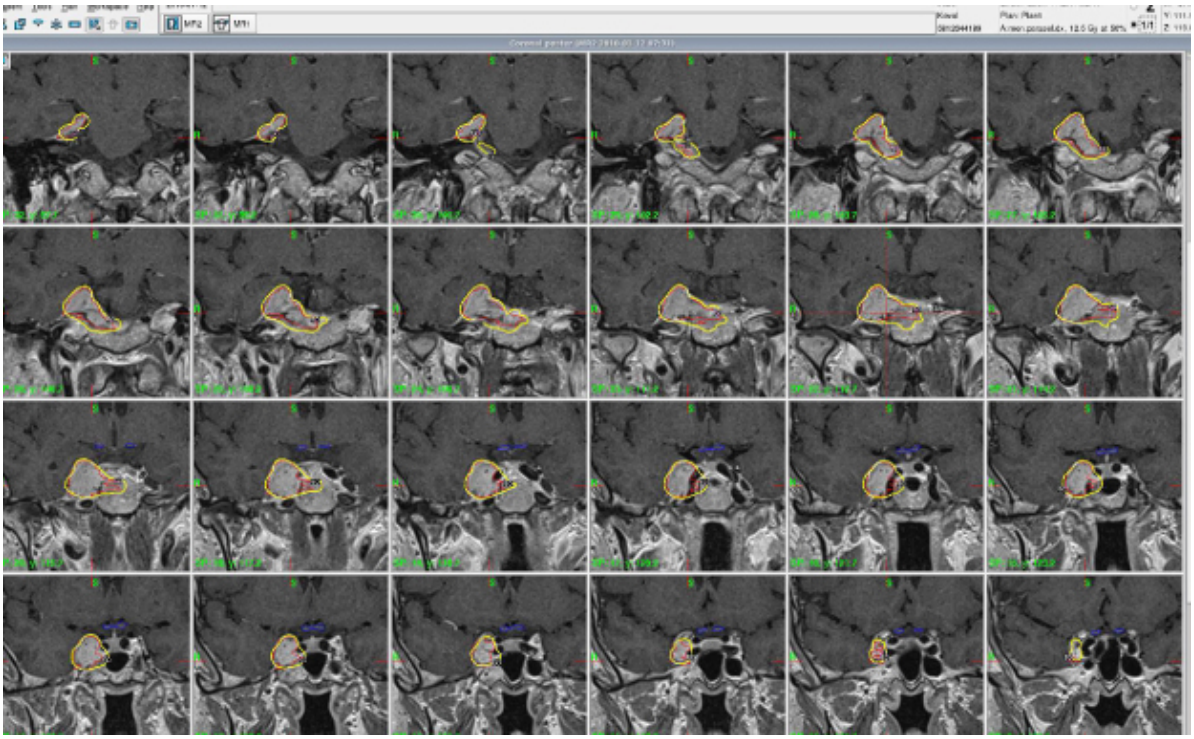

Fig. 9. Patient JK, man, 52 years old, treated for right intra and parasellar meningioma. Planning scans with marked up lesion and chiasm, sequentional 1 mm slices, in the Gamma-Plan (Elekta Instruments, Inc. Stockholm, Sweden)

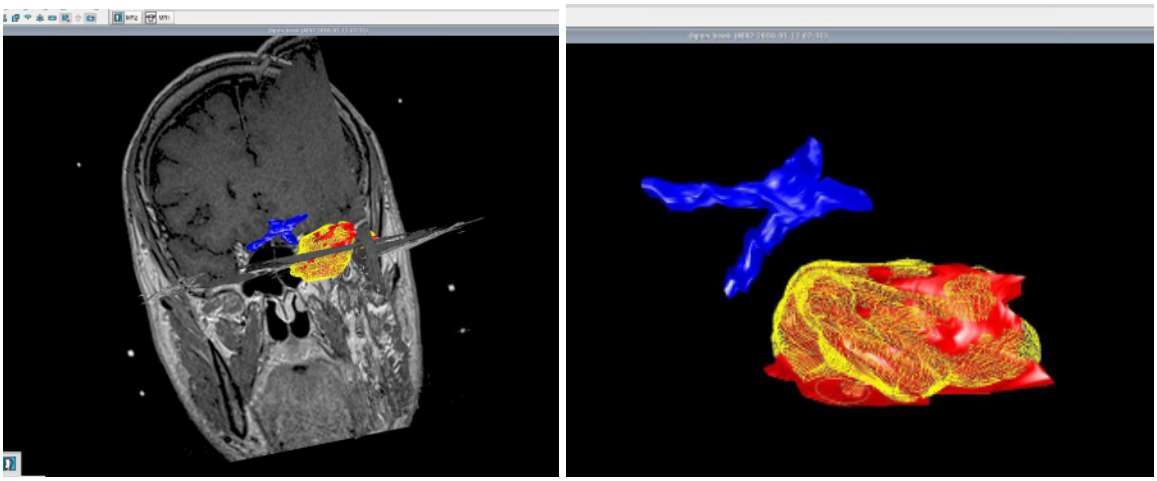

Fig. 10. Patient JK, man, 52 years old, treated for right intra and parasellar meningioma. 2D and 3D visualisation of meningioma and its relationship to the chiasm, in the Gamma-Plan (Elekta Instruments, Inc., Stockholm, Sweden)

The nature of the lesion determines the minimal effective dose, referred to as the margin or prescription dose. This dose should be delivered to the surface of the target volume. The goal of the treatment is to prescribe this dose to all parts of the surface of the target volume with a surface dose gradient steep enough to minimize the dose and thus the risk to adjacent normal structures. In some situations, e.g. in planning the treatment of tumors displacing the optic chiasm it might be necessary to compromise and so the dose to the surface of the target volume would receive less than the optimal dose. The dose delivered to the treated lesion is determined by the exposure time to radiation.

The final dose prescription is made to maximize the chances for success and minimize the risks of the treatment. The basic elements used in dose prescription are the nature of the lesion, anatomic location, volume of lesion, the clinical status of patients, dose volume histograms, dose to adjacent structures and previous radiation treatment (Gildenberg P.L., Tasker R.R. , 1998)

Once all these considerations were taken into account, the dose was defined and the plan evaluated, the treatment plan is signed by the neurosurgeon, radiation oncologist and radiation physicist.

Treatment

Treatment is carried out according the treatment plan inside the Gamma Knife unit. Between the treatments, the door of the radiation unit is closed and the couch is outside the unit. The patient, lying on the couch, with the stereotactic frame is connected to the collimation helmet. Calculated coordinates define the treated isocenters. The couch with the patient is shifted to the radiation unit and the collimation helmet aligns with the primary stationary collimators. Prescribed isocenters are irradiated sequentially; the position is changed by APS (Automatic Positioning System) or manually. Collimator helmets are changed according to the treatment plan. Once the treatment is finished, the couch with the patient comes out of the radiation unit; the stereotactic frame is removed from the patient`s head and pin sites are covered by sterile band-aids. During the treatment process, the computer of the operation panel controls all the parameters, e.g. size of collimators, number of isocenters, time of irradiation, stereotactic coordinates etc.

Fig. 11. Checking the position of the patient, collimation helmet and gama knife setting before the beginning of treatment (Source: Courtesy of Ass. Prof. R. Liščák, PhD.)

Radiosurgical treatment is multidisciplinary teamwork of the neurosurgeon, the radiation oncologist and the physicist with the assistance of the radiological assistant. (Fig. 11.)

2. Hypotheses and the goals of the study

The results of the treatment of meningiomas as slow growing tumors would not show fully the benefit of the treatment within 5 years; to assess its efficiency together with its adverse effects, at least 10 years of follow up is necessary. Therefore, we designed our study to cover the aspects mentioned above.

The goal of the study was to identify the risk factors related to Gamma Knife radiosurgery. The work was sequential and particular results yielded the answers to the following questions:

1. What are the results of Gamma Knife treatment of 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

According to the goals of the study, we have designed the set of statistical methods, to show the results from the perspective of descriptive statistics, as well as univariate analysis 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, to demonstrate the relationship between variables (treatment parameters) and events occurring after radiosurgical treatment. Defined independent variables were as follows: patient`s gender, patient`s age, previous operative surgery, edema before radiosurgical treatment, lobulated tumor margin, heterogeneity in tumor appearance, tumor volume, tumor location (convexity/skull base), maximum and marginal dose applied to treated meningioma. Studied events and their dependence on variables were as follows: tumor sizes increase and decrease, edema occurrence, neurodeficits improvement, temporary and permanent deficits impairment and seizure improvement (Swinscow T.D.V., Campbell M.J.,2002). Analyses were undertaken using SPSS statistical software version 10.0. ,13.0 a 16.0 (SPSS Inc., USA).

The entire cohort of analysed meningiomas consisted of 368 patients with 400 meningiomas treated between 1992 and 1999. The median follow up of the patients in the group studied was 60 months - 90% of the patients had a follow up 24 months after their treatment. In the next stage we analysed a cohort of 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.

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 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. (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

4.1. Skull base meningiomas

As a first step we have analysed in great detail data on treated meningiomas in the skull base. During the time period from 1992 till 1999, 192 patients with 197 meningiomas were treated. The ratio of women to men was 4:1. The age of the patients ranged from 23 to 82 years and the median age was 60 years. Gamma Knife radiosurgery was used as a primary treatment modality in 66% of patients; 34% underwent operative surgery before radiosurgery. In 3 (2%) of the patients, subsequent radiotherapy was necessary to obtain tumor control. The majority of treated meningiomas were located in the cavernous sinus (51%) followed by the pontocerebellar angle (25%) and in the clivus (21%), 15% of meningiomas were intrasellar and in the sphenoid wing, 6% in the anterior skull base and 4% in the orbit. The volume of skull base meningiomas ranged from 0,12 cm^3 to 36,5 cm^3 and the median was 5,3 cm^3. The minimum margin dose was 6,5 Gy, the maximum 20,4 Gy, the median 12 Gy, and the dose was delivered in a 40-80%, median 50% isodose. The maximum dose ranged from 13 Gy to 36 Gy, with a median of 24 Gy. Nine patients have undergone staged radiosurgery in two sessions 6 months apart because of the size of the tumor; in the first step the part in the more eloquent area was treated. One of the most important issues in radiosurgery of skull base meningiomas is the contact or compression of the optic chiasm and the brain stem. In cases where the vision was intact, the margin dose to the optic tract did not exceed 8 Gy (higher margin doses were applied only in the case of there being pre-existent postoperative damage). In cases where the patient underwent previous fractionated radiotherapy, the dose to the optic tract did not exceed 3 Gy. The dose to the brain stem was in our study below 14 Gy.

The group of patients with skull base meningiomas were followed up for an average of 36 months, ranging from 6 to 110 months. Tumor volume decrease was recorded in 73% of the patients (129 patients), the growth of the tumor after radiosurgery was found in 3 (2%) patients; in 44 patients (25%) the tumor remained unchanged. One patient underwent a second session of radiosurgery, one patient with fractionated therapy and one with operative surgery followed by radiotherapy. Clinical symptoms present before radiosurgery improved in 111 patients (63%). The most frequent improved symptom was with headaches, which improved in 71 patients, oculomotor palsy in 31 patients, imbalance and ataxia in 21, hemiparesis in 11, visual loss in 24, facial nerve palsy in 10, hearing improved in 6 patients, mental changes in 3 patients. We presume, that in

patients with radiosurgery as a primary treatment modality clinical improvement is attributable to the shrinkage of the tumor, whereas in patients who underwent operative surgery, clinical improvement might be due to the time period of rehabilitation. There was a clinical deterioration observed after Gamma Knife treatment. Overall, clinical symptoms worsened or a new neurological deficit was found in 19 patients (11%), from 15 days to 48 months, with the median being 5 months. Impairment included worsened trigeminal symptoms in 9 patients, oculomotor deficit in 9, vertigo in and mental changes in 2 patients and impaired epilepsy in 1 patient. Persistent morbidity remained in 8 patients (4,5%). Edema after radiosurgery was detected in 19 patients (11%), 1-3 months, a median of 12 months after radiosurgery. In 7 patients, edema was asymptomatic. Radiological and clinical resolution of edema was found in 8 patients, 2-44 months, the median was 18 months after radiosurgery. Twelve patients who developed edema after radiosurgery required steroid medication.

Statistical analyses of the group of patients with skull base meningiomas have shown, that statistically significant tumor size decrease occured in patients in whom radiosurgery was a first treatment modality (p=0,028 log rank). Also, significantly lower edema occurrence was found in meningiomas after a previous surgical resection (p=0,030 log rank), in patients with meningiomas in the posterior skull base (p=0,029 log rank, p=0,041 Cox) and in patients treated with a margin dose lower or equal to 14 Gy (p=0,035 log rank, p=0,041 Cox). Patients with perilesional edema before Gamma Knife treatment were at higher risk of edema occurrence after treatment (p<0,001 log rank, p=0,006 Cox).

Skull base meningiomas and their treatment display specific features as shown in the results. However, the size of the whole group of patients treated for the diagnosis of meningioma represents the background for statistical analysis, which has yielded significant and reliable results.

4.2. Mid-term results (skull base and convexity)

The entire cohort of analysed meningiomas consisted of 368 patients with 400 meningiomas treated between 1992 and 1999. Radiosurgery was used as a primary treatment modality in 259 patients (70,3%).

Location of treated meningiomas is in Table 1.

LOCATION		
Site (sites overlapping - multiple fossae)	Number	%
Cavernous sinus	103	25.8
CP angle	51	12.8
Clivus	42	10.5
Intrasellar	34	8.5
Sphenoid Ridge	30	7.5
Anterior Fossa	13	3.3
Orbit	9	2.3
Tentorial	46	11.5
Parafalcine	45	11.3
Parasagittal	33	8.3
Frontal	22	5.5
Parietal	21	5.3
Temporal	14	3.5
Cerebellar	7	1.8
Pineal	5	1.3
Intraventricular	4	1.0
Torcular	3	0.8
Occipital	3	0.8

Table 1. Location of treated meningiomas

The median follow up of the patients in the studied group was 60 months, 90% of patients had a follow up of longer than 24 months. Out of this group of patients, 12 (3,3%) were lost to follow-up and 10 were suspended from the follow up, because the treated meningioma was deemed controlled. Thirty-one patients underwent a follow up shorter than 24 months afterwards; however we included six of these patients in our descriptive analysis to investigate post-treatment

complications, which occur within the first two years following treatment. Although 25 out of 31 patients had a shorter follow-up, 11 of them died of unrelated causes and the rest refused the follow-up because of their advanced age, and so they were not included in our descriptive statistics. Their data could however be used for actuarial analysis without limitations. Follow-up data was analysed in 331 patients (90%) with 355 meningiomas (88,7%) for descriptive statistics and in 368 patients for actuarial analysis Kaplan-Meier statistics and Cox regression. Follow-up protocol included follow up scans and follow up in clinics 6 months, 1 year and annually thereafter, up to 5 years and then every 3 years. In patients with intra- and parasellar meningiomas, visual fields were tested before treatment and during the follow up.

The average age of patients was 57 (ranged between 18 and 84 years old) and the median tumor volume was 4,4 cm^3, (range: 0,11-44,9 cm^3). The number of treated meningiomas ranged from one to six in each patient. The median margin dose to the 50% isodose line was 12,55 Gy (range 6,5 Gy-24 Gy). The volume of treated meningiomas showed a regression in 69,8% of cases (248 meningiomas), remained stable in 27,8% (99 meningiomas) and progression was found in 2,5% (9 tumors).

The actuarial tumor control rate was 97,9% at 5 years after Gamma Knife treatment. Ten patients underwent further treatment: 5 patients (1,5%) excision, 4 patients with a second session of stereotactic radiosurgery and 1 with fractionated radiotherapy. Among these 10 patients, the tumor showed growth in 6, surgery was performed in two patients due to post-irradiation edema and in another two for unknown reasons, even though the tumor growth had not been detected.

Perilesional edema was found in 51 patients (15,4%), symptomatic in 32 (9,6%). It was temporary in 23 (6,9%) and persistent in nine (2,7%). The onset of edema was observed at a median of 9 months (range: 1-36 months). From radiological point of view, edema resolved 7-55 months after radiosurgery; clinical symptoms related to edema resolved 0,5-48 months (a median of 12 months) after treatment. Eighteen patients (4,9%) were on steroids at the time of the treatment and in another 16 patients (4,3%), steroids were administered after the treatment for an average of 4 months (mean 5,8 +-5,3 months).

Neurological deficits without evidence of edema were temporary in 11 patients (3,3%) and permanent in 10 patients (3,0%). Overall, temporary morbidity was 10,2% and permanent morbidity was 5,7%. In seven patients of the studied group the tumor initially increased in size due to intra-tumoral edema, and shrank subsequently. Onset of intra-tumoral edema was detected from 5 to 16 months after the treatment and resolved in 6 to 36 months after the treatment. Six out of these 7 patients experienced intra-tumoral edema along with collateral postirradiation edema. (Table 2.)

	Temporary deficit	Permanent deficit
Symptoms impaired after GKS (n=331)	**Number (%)**	**Number (%)**
Seizures	9 (2,7)	6 (1,8)
Trigeminal symptoms	10 (3,0)	4 (1,2)
Hemiparesis	7 (2,1)	3 (0,9)
Oculomotor palsy	5 (1,5)	2 (0,6)
Vertigo	3 (0,9)	2 (0,6)
Headache	13 (3,9)	0
Mental change	3 (0,9)	2 (0,6)
Imbalance	1 (0,3)	0
Dysphasia	1 (0,3)	0
Hearing loss	1 (0,3)	1 (0,3)
Total – symptoms	*53 (16)*	*20 (6,0)*
Total – patients	***34 (10,2)***	***19 (5,7)***

Table 2. Complications after radiosurgery (in some patients more than 1 symptom could be observed)

Two patients died as a result of edema, which developed after radiosurgery around the treated meningioma. The first patient, a 77-year-old man unfit for operative surgery underwent staged radiosurgery for a large parasagittal meningioma (the largest treated volume in our study was 44.5cm³). Pre-existing perilesional edema worsened progressively 9 months after radiosurgery and despite the administration of steroids; the patient died 18 months after treatment. The second, a 52-year-old woman with parasagittal meningioma causing a mass effect refused operative surgery for religious reasons. Staged radiosurgery was planned; however, after the first irradiation of a part of the tumor, the pre-existing edema had increased and despite the administration of steroids, the patient died 4 months after treatment.

Other patients died of following causes: 6 patients due to cancer, 5 patients due to ischemic heart disease, 5 due to strokes and in 10 patients the cause of death remained unknown. As the onset of postiradiation edema is delayed (about 6-9 months) and neurological deterioration is gradual, it was presumed, that in case of 10 patients, in whom the cause of death was unknown, general practitioner or referring specialist would consult Department of stereotactic and radiation neurosurgery regarding further management of posttreatment complications. This was the case of two above-mentioned patients with worsening of perilesional edema.

Overall improvement of neurological symptoms in patients treated for meningioma was observed in 61,9%. (Table 3.)

Symptoms improved after GKS (n=331)	**Total**	**%**
Imbalance	38	11,4
Trigeminal symptoms	29	8,7
Oculomotor palsy	31	9,3
Seizures	29	8,7
Hemiparesis	25	7,5
Vertigo	21	6,3
Facial nerve palsy	14	4,2
Mental change	9	2,7
Dysphasia	6	1,8
Hearing	6	1,8
Hydrocephalus	1	0,3
Total – symptoms	*209*	*63,1*
Total - patients	***205***	***61,9***

Table 3. Symptoms improved after radiosurgery (in some patients more than 1 symptom could be observed)

The results of univariate and multivariate analysis of studied factors on events related to meningioma radiosurgery are shown in Table 6.

Tumor volume decrease after GKS

There was a significantly higher incidence of tumor volume decrease observed in patients where the tumor maximal dose was higher than 22 Gy (p=0.005 log rank, p=0.045 Cox) and the tumor marginal dose was higher or equal to 12 Gy (p=0.012 log rank).

Tumor volume increase after GKS

There was a significantly higher incidence of tumor volume increase observed in men compared to women (p=0.005 log rank, p=0.013 Cox) and for patients where the tumor marginal dose was lower than 12 Gy (p=0.047 log rank).

Edema occurrence after GKS

There was a significantly higher incidence of edema occurrence observed in patients older than 60 years (p=0.019 log rank), with no surgical procedure before GKS (p=0.013 log rank, p=0.035 Cox), with edema present before GKS (p<0.001 log rank, p<0.001 Cox), with tumor volume larger than 10 cm^3 (p=0.002 log rank, p<0.001 Cox), with tumor location in the anterior fossa (p=0.025 log rank, p=0.001 Cox), where the tumor maximal dose was higher than 30 Gy

(p=0.013 log rank, p=0.018 Cox) and the tumor marginal dose was higher than 16 Gy (p<0.001 log rank). (Fig. 24., 25., 26., 27, 28,29).

Neurodeficit improvement after GKS

There was a significantly higher incidence of neurodeficit improvement observed in patients who underwent surgical procedures before GKS (p=0.003 log rank), with a lobulated tumor margin (p=0.032 log rank), with a tumor volume larger than 5 cm^3 (p<0.001 log rank), with a skull base tumor location (p<0.001 log rank, p<0.001 Cox), with tumor location in the middle and posterior fossa (p<0.001 log rank), when the tumor maximal dose was lower or equal to 30 Gy (p=0.047 log rank) and the tumor marginal dose was lower or equal to 16 Gy (p=0.018 log rank, p=0.002 Cox).

Temporary neurodeficit impairment after GKS

There was a significantly higher incidence of temporary neurodeficit impairment observed in patients with a tumor volume larger than 10 cm^3 (p=0.014 log rank, p=0.002 Cox).

Permanent neurodeficit impairment after GKS

There was a significantly higher incidence of permanent neurodeficit impairment observed in patients with edema present before GKS (p=0.008 log rank) and with a tumor volume larger than 10 cm^3 (p=0.050 log rank, p=0.002 Cox).

Seizure improvement or disappearance after GKS

There was a significantly higher incidence of seizure frequency improvement or disappearance observed in patients without perilesional edema before GKS (p=0.017 Cox), with a skull base tumor location (p=0.008 log rank, p=0.027 Cox) and with a tumor located in the anterior fossa, middle fossa and posterior fossa (p=0.009 log rank, p=0.009 Cox).

	Tumor decrease	***Tumor Increase***	***Edema Occurrence***	***Neurodeficit improvement***	***Temporary neurodeficit impairmnet***	***Permanent neurodeficit impairment***	***Seizure improvement***
Gender	X	p=0.005 (log rank) p=0.013 (Cox)	X	X	X	X	X
Age	X	X	p=0.019 (log rank)	X	X	X	X
Previous surgery	X	X	p=0.013 (log rank) p=0.035 (Cox)	p=0.003 (log rank)	X	X	X
Edema before GKS	X	X	p<0.001 (log rank) p<0.001 (Cox)	X	X	p=0.008 (log rank)	p=0.017 (Cox)
Lobulated margin	X	X	X	p=0.032 (log rank)	X	X	X
Heterogeneity	X	X	X	X	X	X	X
Tumor volume	X	X	p=0.002 (log rank) p<0.001 (Cox)	p<0.001 (log rank)	p=0.014 (log rank) p=0.002 (Cox)	p=0.050 (log rank) p=0.002 (Cox)	X
Tumor location	X	X	p=0.025 (log rank) p=0.001 (Cox)	p<0.001 (log rank)	X	X	p=0.009 (log rank) p=0.009 (Cox)
Dose to maximum	p=0.005 (log rank) p=0.045 (Cox)	X	p=0.013 (log rank) p=0.018 (Cox)	p=0.047 (log rank)	X	X	X
Dose to margin	p=0.012 (log rank)	p=0.047 (log rank)	p<0.001 (log rank)	p=0.018 (log rank) p=0.002 (Cox)	X	X	X

Table 4. Overview of studied events and factors in meningioma radiosurgery. Significant p values are also presented for factors having a significant influence on the subject studied.

4.3. Edema prediction model

The most frequent side effect of meningioma radiosurgery is edema, which might cause deterioration in the clinical state of the treated patient. One of the aims of our study was to create a model to predict the occurrence of the edema. We presumed, that it would be possible to create an empirical multifactorial prediction model based on the results of treatment on a large group of patients. The model is based on the data of 381 patients with meningiomas treated between the years 1992 and 1999. Ten predictive factors were proposed as possible predictors for occurrence of perilesional edema after Gamma Knife treatment: patient`s age, gender, previous surgery, edema before GKS treatment, tumor volume, tumor location and tumor margin dose, lobulated margin of meningioma and 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 Cox Proportional hazards model by using the backward stepwise conditional likelihood ratio method and binary logistic regression analysis with the backward stepwise method. Analyses were performed with SPSS statistical software version 10.0. (SPSS Inc., USA).

All 10 potential predictors were included in the binary logistic regression. The backward stepwise elimination with the likelihood ratio test for automated model building was used. The parameters of the model were estimated by using the maximum–likelihood method (the coefficient that made our observed results more likely were selected). An iterative algorithm implemented in the SPSS software was used for parameter estimation. As a result of this process, the binary logistic regression equation including selected predictors and coefficients was built to best fit our data. The following parameters were selected based on the elimination process for the edema occurrence model (the significance level for the Wald statistic probability and the 95% CI of the odds ratio are given as well for each parameter): previous surgery (p=0,059, 95% CI 0,202-1,030), edema before GKS treatment (p<0,001, 95% CI 5,774-419,128), tumor volume (p<0,001, 95% CI 1,051-1,171), tumor location (p=0,012, 95% CI 1,204-4,591) and margin dose (p=0,012, 95% CI 0,991-1,417).

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

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 GKS and tumor location, volume

in cm^3, and dose to the tumor margin in Gray for tumor volume and margin dose. Based on Kaplan-Meier statistics with a log rank test and a Cox proportional hazards model, tumor location was divided into two categories: risk location (defined as "1" in the model) and non-risk location (defined as "0" in the model) As risk locations the following were considered: anterior cranial fossa, convexity and falx). As non-risk locations middle cranial fossa, posterior cranial fossa, tentorium and cerebellum were considered. 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 and consequently the second complementary event will occur (in this case no edema will occur). If the probability is 0,5, it is not possible to make any decision.

The model was tested on 381 meningiomas in 368 patients. The model made an overall correct decision in 87,7% of cases. In those patients with no edema the model decided correctly in 99,4%, in those with edema it predicted correctly in 21,1% of cases. These results point out the fact, that the number of meningiomas with edema after radiosurgery was relatively small. The model is stronger in predicting that edema will not occur. These results are used to counsel the particular risk of patients in risk of edema development to arrange for more detailed posttreatment care. As the model was created using a studied group of patients, it entails bias caused by the group itself. In the future, it will be necessary to test the model on a number of new patients, whose data are fully unrelated to the derivation of our model.

4.2. Long-term results (skull base and convexity)

In the next step we intended to confirm the efficacy of the treatment, as well as to learn about factors important for radiosurgical treatment of meningioma from a long-term perspective.

We analysed a group of 226 patients with 249 meningiomas where at least 10 years had elapsed since treatment. The studied group consisted of 179 women (79,2 %). The age of the patients ranged from 18 to 84 years with 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 the treated patients was between 30 and 100%, with a median of 80%.

In patients, who underwent operative surgery before radiosurgery, cranial nerve palsy was found in 28 (12,4%), hemiparesis in 19 (8,4%) and cerebellar symptoms in 8 (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%) and 60 patients were asymptomatic (26,5%). (Table 5.) Fifteen patients had multiple meningiomas.

Symptoms	**Symptoms before GKS**	**Number of improved symptoms**
n. I	8	4
n. II	29	16
n. III, n. VI	30	17
n. V	37	23
Impaired hearing	14	7
Hemiparesis	36	18
Ataxia	40	23
Vertigo	42	30
Nausea	14	10
Mental change	10	8

Table 5. Overview of clinical symptoms before Gamma Knife treatment (note that more than 1 symptom was found in some patients)

Sixty-seven patients (29,6%) underwent operative surgery, 1-3 operations, 2-132 months prior to Gamma Knife treatment. In patients in whom Gamma Knife radiosurgery was a first treatment modality, and who therefore did not have a formal confirmation of the histopathology of the tumor, diagnosis of meningioma was set upon typical radiological features. In three patients, the diagnosis of benign meningioma was changed based on clinical features and/or tissue diagnosis. In one patient after previous surgery of meningioma spreading into the orbit, malignant features were confirmed. The second patient had his tumor reclassified as pituitary adenoma and in third, tissue diagnosis confirmed hemangiopericytoma. Six patients underwent radiotherapy.

Gamma Knife radiosurgery was a primary treatment in 159 patients (70,3%) of the group examined. Compression of optic pathways by meningioma was found in 30 cases (12%) and brain stem compression in 45 (18%). Perilesional edema was recorded in 11 (4,9%) of the patients. In 10 patients (4,4%) the meningioma was spread through both the middle and posterior cranial fossae; radiosurgical treatment was therefore performed in two stages. The first part treated was the part in the most eloquent area followed by irradiation of the second part of the tumor in six months.

Target localisation was performed according to CT scans in 64 (25,7%) and according to MR scans in 185 (74,3%) of meningiomas.

Tumor volume of treated meningiomas ranged from 0,1 to 44,9cm³, median 4,37 cm³, and mean 5,9 cm³. The margin dose in the studied group ranged from 6,5 to 24 Gy, median being 12,9 Gy (the margin isodose was between 40 - 90 % and the median 50%).

For the analysis, the data were available on 217 patients with 239 meningiomas. 81 patients had a follow up longer than 120 months. In 10 patients the follow up was terminated because of controlled meningioma and advanced age. The follow up period ranged from 1 to 168, median - 96 months. 25 (11,5%) patients died during the follow up course, two of them because of progression of perilesional swelling related to parasagittal meningioma; in the rest of them the cause of death was not related to meningioma.

Tumor control, or stabilisation of the disease was achieved in 94,7% after 10 years. (Fig.12.). Tumor volume regression was found in 163 meningiomas (68,2%), remained stabilised in 70 (29,3%) and progression of the disease was recorded in 6 (2,5%) of patients. Improvement of clinical symptoms was detected in 89 (41%) of patients.

Postirradiation edema occured in 40 (18,4%) of 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 it remained permanent.

Clinical symptoms after Gamma Knife treatment are featured in Table 6.

Symptom after GKS	**Number**	**%**
Hemiparesis	6	2,8
Epilepsy	6	2,8
Trigeminal symptoms	5	2,3
Headache	3	1,4
Anosmia	3	1,4
Vertigo	3	1,4
Mental change	2	0,9
Hearing impairment	1	0,5
Speech disorder	1	0,5
All symptoms	**30**	**14**

Table 6. Adverse symptoms of Gamma Knife treatment

Intra-tumoral edema developed in two patients, the volume of meningioma increased during the first 12 months after treatment and subsequently settled within 30 months after treatment. In 4 patients, a second session of radiosurgery was performed because of disease progression, 3 patients underwent operative surgery, one of them despite a volume decrease after Gamma Knife radiosurgery.

Detailed display of univariate and multivariate statistical analysis results is featured in Table 7.

	Event				
Factor	**Decrease**	**Increase**	**Edema**	**Impairment**	**Improvement**
Gender	Men greater prop. of decrease than women p = 0.008 (log rank), p = 0.006 (Cox)	Men greater prop. of increase than women p = 0.029 (log rank), not significant using Cox regression p = 0.653	Not significant (log rank, Cox)	Not significant (log rank)	Not significant (log rank, Cox)
Age	Significant, p = 0,034 (log rank), using Cox regression not significant (p = 0,117)	Not significant (log rank, Cox)	Significant p = 0,025 (log rank), not significant using Cox regression (p = 0,068)	Not significant p = 0,214 (log rank), significant using Cox regression p = 0.040 (Cox)	Not significant (log rank, Cox)
Previous operation	Not significant (log rank, Cox)	Operated greater prop. of increase than not operated p = 0.047 (log rank), p = 0.016 (Cox)	Not operated greater prop. of edema incidence than operated p = 0.015 (log rank), not significant using Cox regression (p = 0.334)	Not significant (log rank, Cox)	Not significant (log rank, Cox)
Edema before treatment	Not significant (log rank, Cox)	Not significant (log rank, Cox)	With edema before GKS greater prop. of edemas incidence after GKS p < 0.001 (log rank), p < 0.001 (Cox)	Not significant (log rank, Cox)	Not significant (log rank, Cox)
Lobulated margin	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Not significant (log rank, Cox)
Heterogenity	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Not significant (log rank, Cox)
Tumor volume	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Significant p = 0,001 (log rank), p = 0,002 (Cox)	Significant p = 0,021 (log rank), p = 0,004 (Cox)	Not significant (log rank, Cox)
Location – skull base	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Not significant (log rank, Cox)	Skull base lower rate of impairment than other location p = 0.028 (log rank), p = 0.029 (Cox)	Skull base higher rate of improvement than other location p < 0.001 (log rank), p < 0.001(Cox)
Maximum dose	Dmax > 22 Gy p = 0.028 (log rank), p = 0.023 (Cox)	Not significant (log rank, Cox)	Dmax > 30 Gy p = 0.016 (log rank), not significant using Cox regression p = 0.114	Dmax > = 30 Gy higher rate of impairment p = 0.023 (log rank), Cox regression not significant p = 0.062	Dmax 30 Gy not significant (log rank, Cox)
Margin dose	Not significant (12 Gy, log rank, Cox)	Dmarg < = 12 Gy p = 0.048 (log rank), not significant using Cox regression p = 0.053	Dmarg > 16 Gy p < 0.001 (log rank), p < 0.001 (Cox)	Dmarg 16 Gy not significant (log rank, Cox)	Dmarg 16 Gy not significant (log rank, Cox)

Table 7. Studied factors of Gamma Knife meningioma treatment in the long-term group of patients

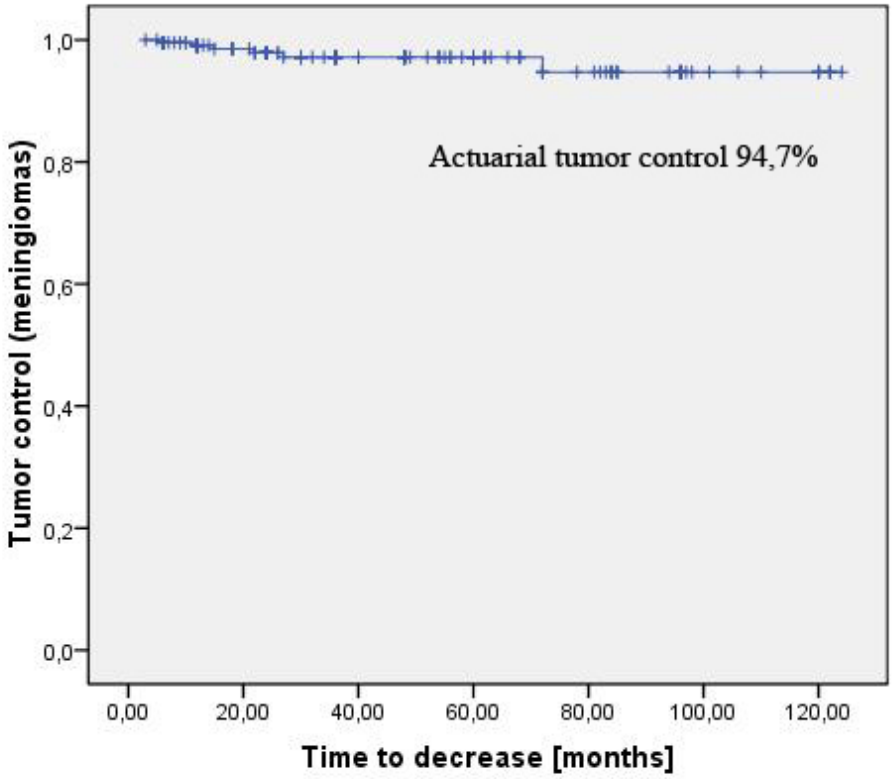

Fig. 12. Kaplan-Meier cumulative curve for 10 years of meningioma growth control

The Kaplan-Meier univariate analysis has shown, that actuarial control of tumor growth was achieved in 94,7%. This result is in continuity with our mid-term results of actuarial tumor control of 97,9%. (Fig. 12.) Such a long-term analysis is possible only in circumstances of careful follow-up data storage and a high measure of cooperation between the treating department and patients, as well as their relevant physicians. Gamma Knife units globally serve in the majority of locations vast geographical areas in different health care systems, which is reflected in the different percentages of patients with a completed long term follow-up. The database of the department and the organisation of the follow-up of treated patients ensure further study of meningioma control after Gamma Knife treatment. In the time period beyond 10 years after treatment, we would perhaps not expect treatment-related complications related to edema; we would be interested in further actuarial tumor control rate as well as the risk of newly occurred malignancy related to the treatment.

Margin and maximum dose

As shown in the Table 4., and in the Table 7., both margin and maximum doses were statistically significant for tumor volume increase and decrease, edema occurrence and clinical impairment, both in the mid-term and long-term follow up studies. (Fig. 13., 14.)

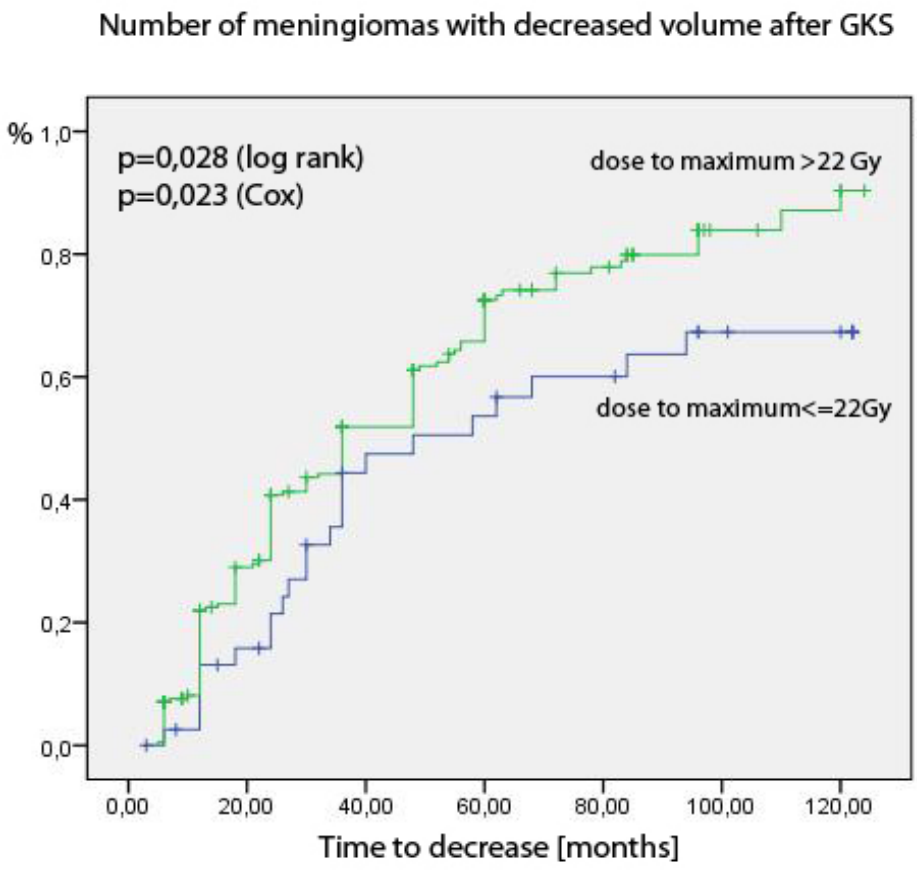

Fig. 13. Kaplan-Meier cumulative curve of meningioma volume decrease according to maximum dose

Statistically significant in both log rank (p=0,028) and Cox (p=0,023) tests of multivariate analysis was the maximum dose; tumors treated with maximum doses of 22 Gy have shown in higher percentages a decrease of their volumes; these meningiomas are controlled in radiosurgical terms. A maximum dose of 22 Gy is advocated in meningiomas where the size, location and proximity of the optic tract do not lead to the necessity of dose reduction. As will be shown further, the maximum dose of 30 Gy was a significant risk factor for edema occurrence and for clinical impairment. Therefore, a maximum dose of 22 Gy from a long-term perspective is high enough to

achieve tumor control and at the same time does not pose an increased risk of post-treatment complications.

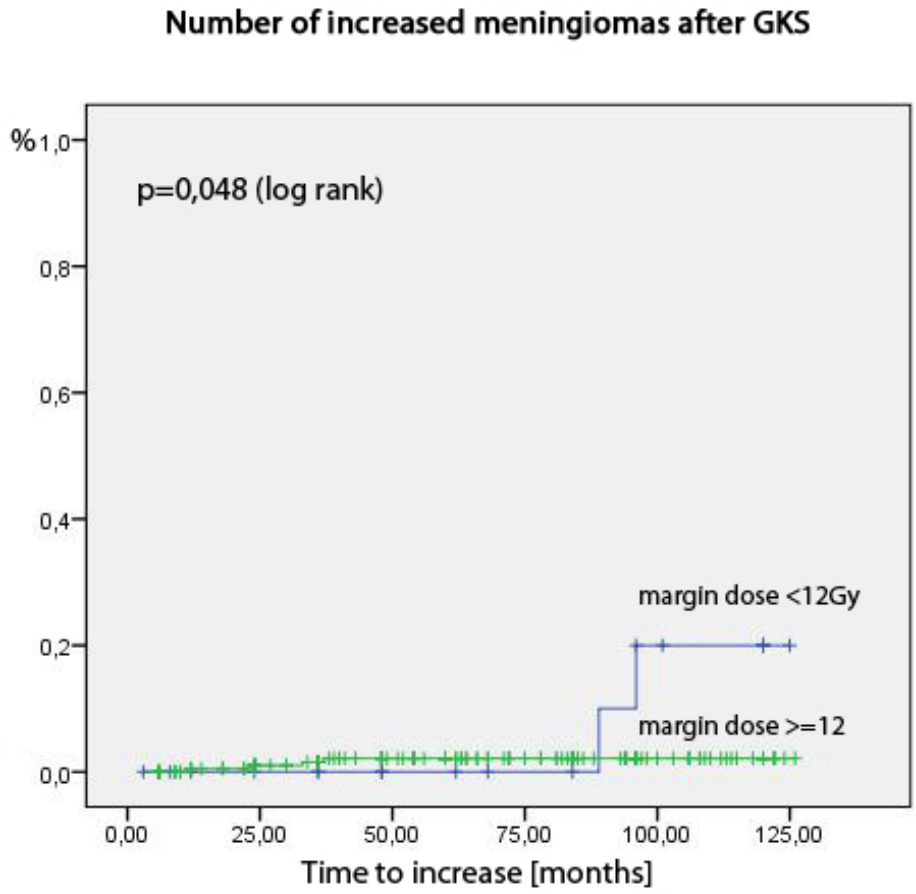

Fig. 14. Kaplan-Meier cumulative curve of meningioma volume increase according to the margin dose

A margin dose of lower than 12 Gy has shown statistical significance for meningioma volume increase both in mid-term and long-term results in the log rank test (p=0,048). According to the results of the study, dose applied to the margin of the tumor is always above 12 Gy, the only exception are the cases, where the chiasm or the brain stem is in contact or compressed by the meningioma. Similarly as with the maximum dose, margin dose is also important when considering the risk of post-treatment complications. A margin dose of 16 Gy was found to be critical in this respect and therefore a recommended margin dose for meningioma treatment lies in the space between above 12 Gy and below 16 Gy, to achieve tumor control with the lowest possible risk of posttreatment complications. (Fig.14.)

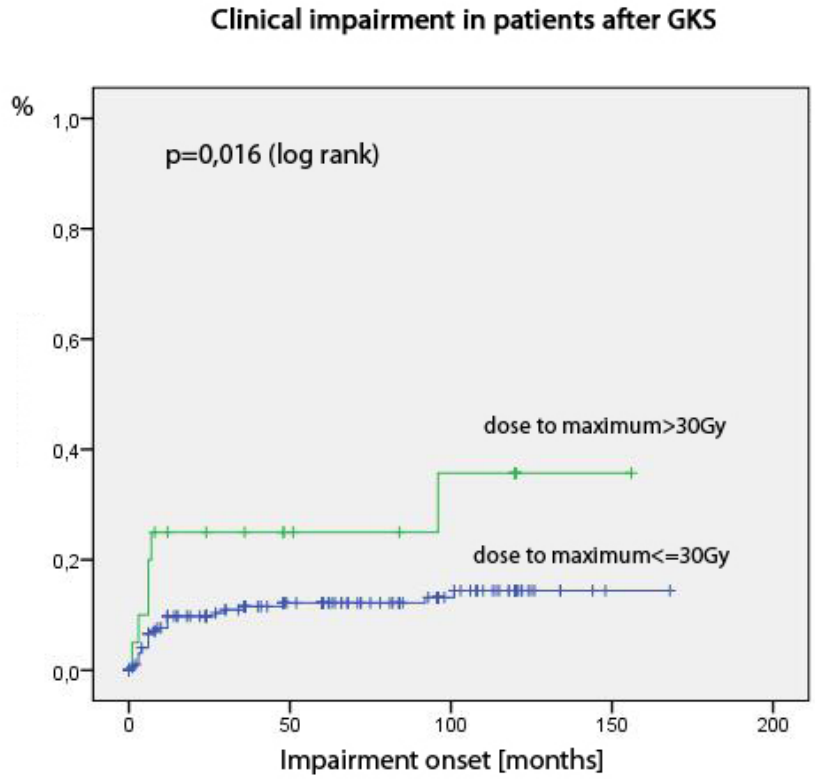

Fig. 15. Kaplan-Meier cumulative curve of clinical impairment according to a maximum treatment dose

A maximum dose of 30 Gy was a significant risk factor for clinical posttreatment impairment in the log rank test (p=0,016) in the long-term study; this factor was not statistically significant in a mid-term results. (Fig.15.) The results can be influenced by a small number of studied cases, as a vast majority of posttreatment complications occurred during the time period covered by our mid-term study. As will be discussed further in the discussion in this thesis, the increase of maximum and margin dose at a certain level does not improve tumor control, but almost certainly will increase the risk of posttreatment complications.

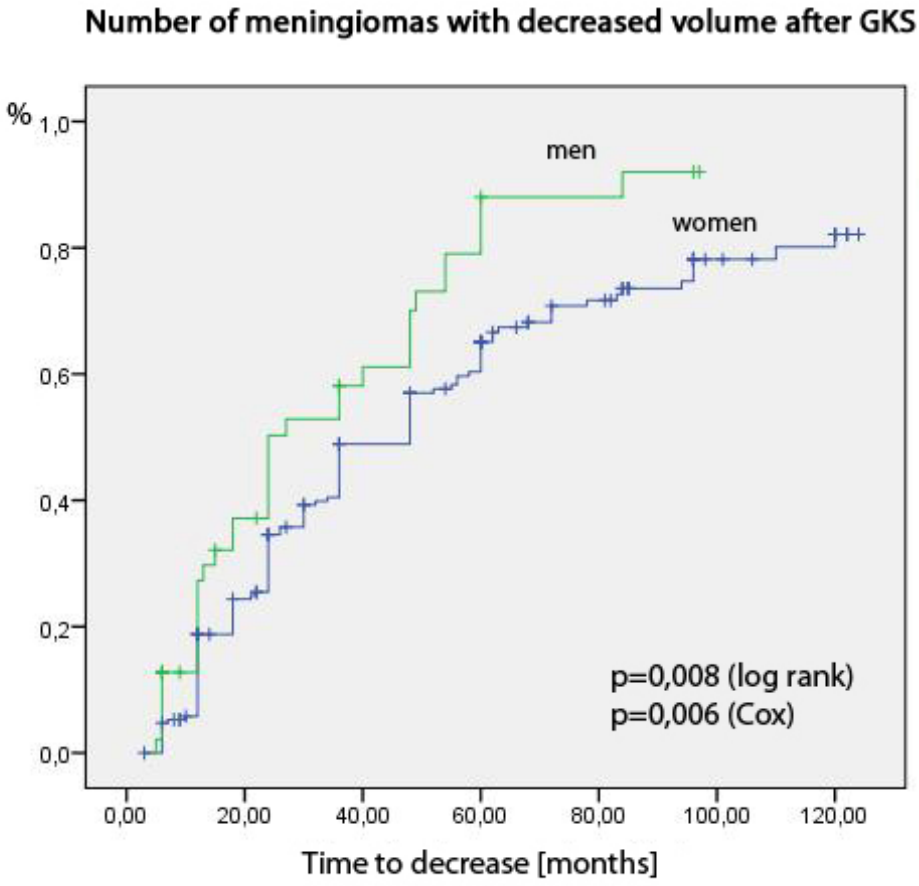

Fig. 16. Kaplan-Meier cumulative curve of meningioma volume decrease according to the patient`s gender

Long-term results have shown an interesting finding of a significant decrease of volume of treated meningioma in men, in both Cox (p=0,006) and log rank tests (p=0,008). (Fig.16.) This finding is part of a new understanding of the biological behavior of meningioma in men. As will be examined further in the discussion, meningiomas in men behave differently than those in women due their chromosomal and hormonal conditions and differences; still more aspects of these differences have yet to be discovered. Men with meningioma are at higher risk of radiosurgical treatment failure (Fig. 18.), but at the same time, once the meningioma is responding to the treatment, it is more likely that its volume will gradually decrease in the long-term.

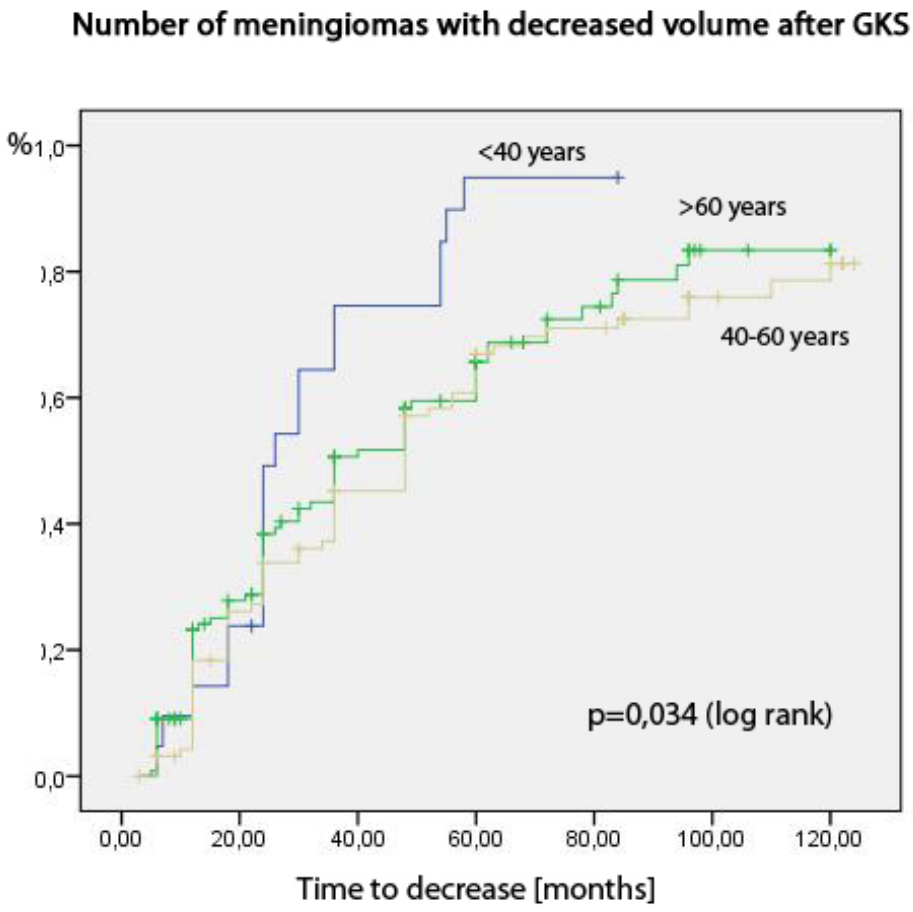

Fig. 17. Kaplan-Meier cumulative curve of meningioma volume decrease according to the patient`s age

Meningioma volume decrease after Gamma Knife treatment has shown a statistical significance in the log rank test for patients younger than 40 years with regard to long-term results (p=0,034 log rank). (Fig. 17.) There was no statistical significance found in mid–term results. This finding suggests, that meningiomas in older patients are often calcified to a higher extent than in younger patients; calcified tumors do not decrease their volume after irradiation. In younger patients we can therefore expect tumor shrinkage and thus reduction of mass effect, which is often beneficial, besides control of the growth of meningioma as a result of Gamma Knife treatment.

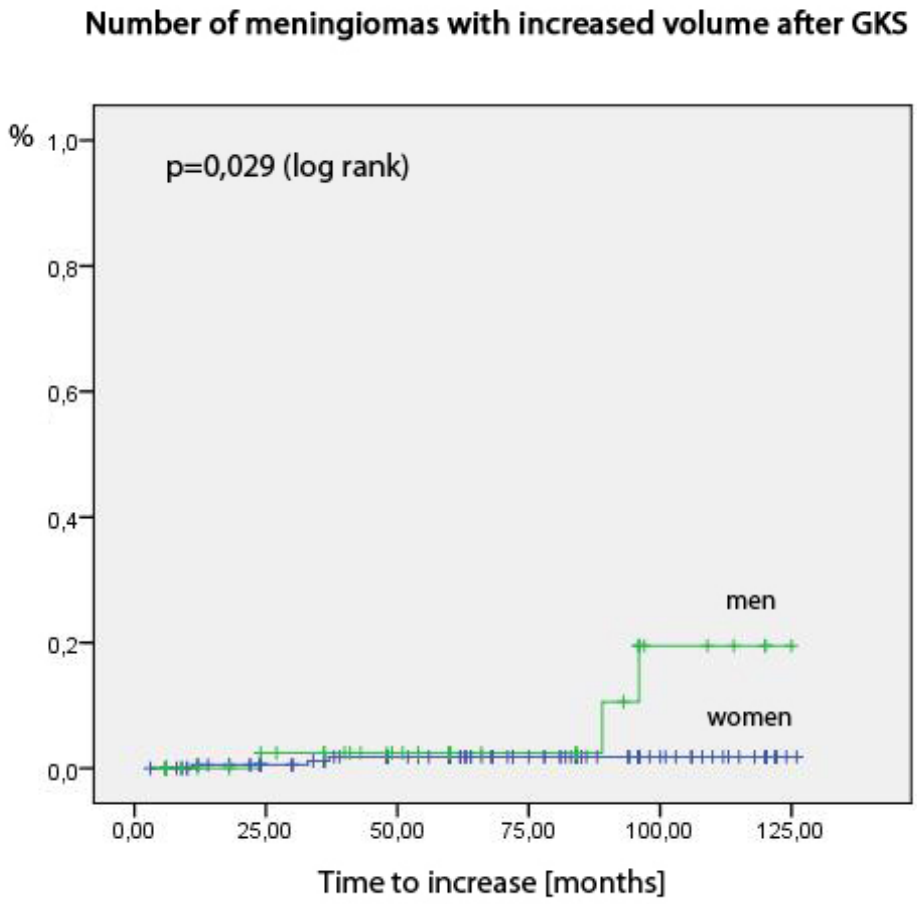

Fig. 18. Kaplan-Meier cumulative curve of meningioma volume increase according to the patient`s gender

Both mid-term (p=0,005 log rank, p=0,005 Cox) and long-term (p=0,029) results have shown a statistically significant increase of tumor volume after radiosurgery in men. Increase of irradiated volume of meningioma occurred during the time period investigated in the mid-term study, as the failure of the treatment is detected usually between 2 and 6 years after the treatment. Long-term results only confirmed more aggressive biological behavior in men. (Fig. 18.)

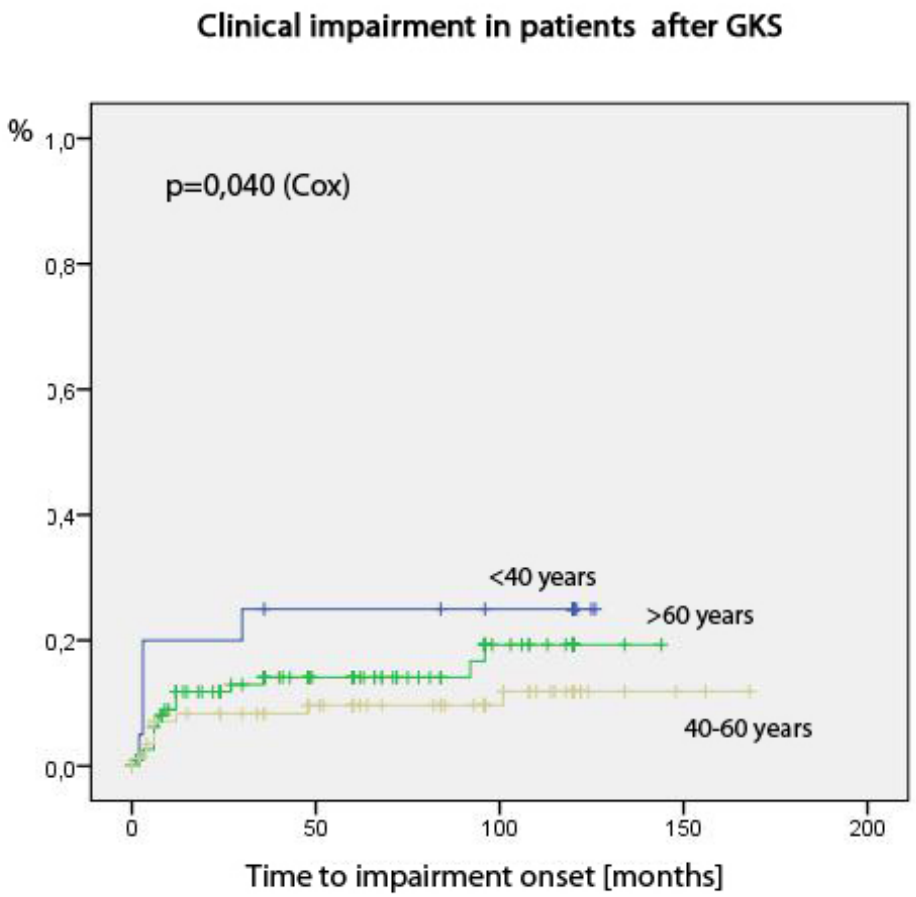

Fig. 19. Kaplan-Meier cumulative curve of clinical impairment according to the patient`s age

A surprising finding was a statistically significant impairment of clinical symptoms in patients younger than 40 years in the Cox test (p=0,040). (Fig. 19.) It was unexpected becase there was no evidence of statistical significance in mid-term results; clinical impairment is usually an issue of posttreatment period of two years after the treatment, which was the time period covered by the mid-term study. The finding can be explained by the low number of patients with posttreatment complications and censored cases in the statistical analysis. A logical explanation of this finding can be a higher number of calcifed meningiomas without a tumor-pial interface causing perilesional edema; these patients are at lower risk of posttreatment complications and edema occurrence than patients with meningiomas with a pial blood supply.

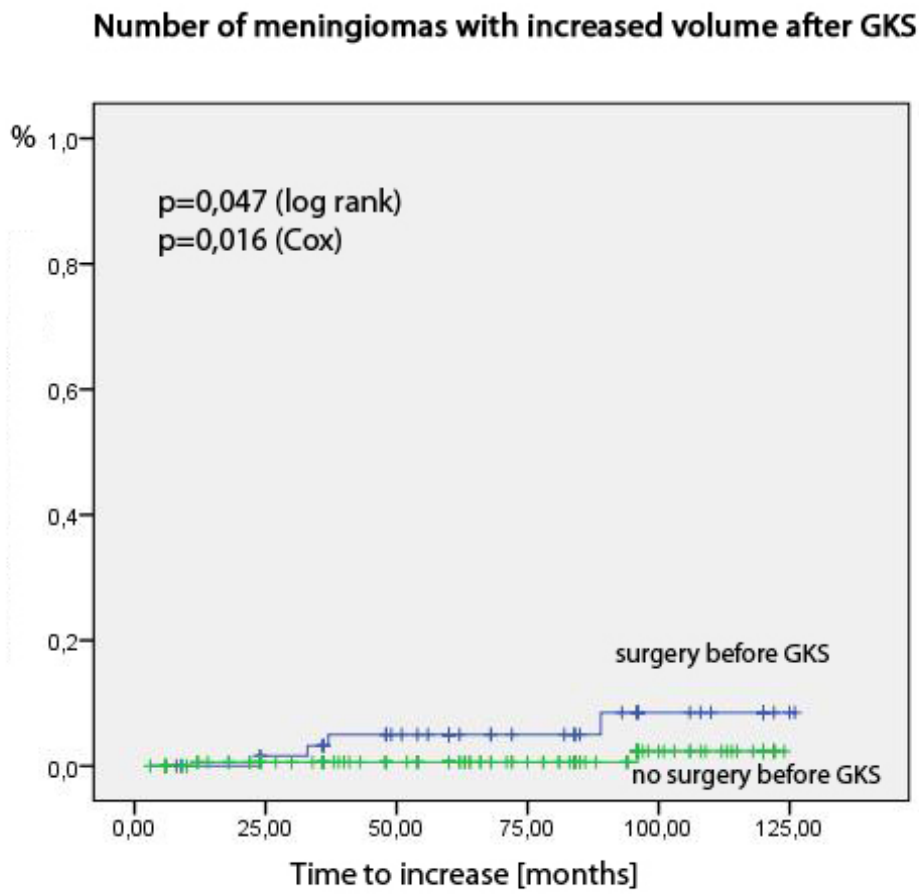

Fig. 20. Kaplan-Meier cumulative curve of meningioma volume decrease according to previous surgery

From a long-time perspective we have found that patients who underwent operative surgery for meningioma, were at higher risk of radiosurgical treatment failure, both in the Cox (p=0,016) and the log rank (p=0,047) tests. (Fig. 20.) Our statistical analysis did not show significance in mid-term results. Meningiomas which required operative surgery as a first modality usually have a higher growth potential leading to mass effect and clinical symptoms. From a long-term perspective, the growth potential of resected meningiomas could lead to failure of radiosurgical treatment.

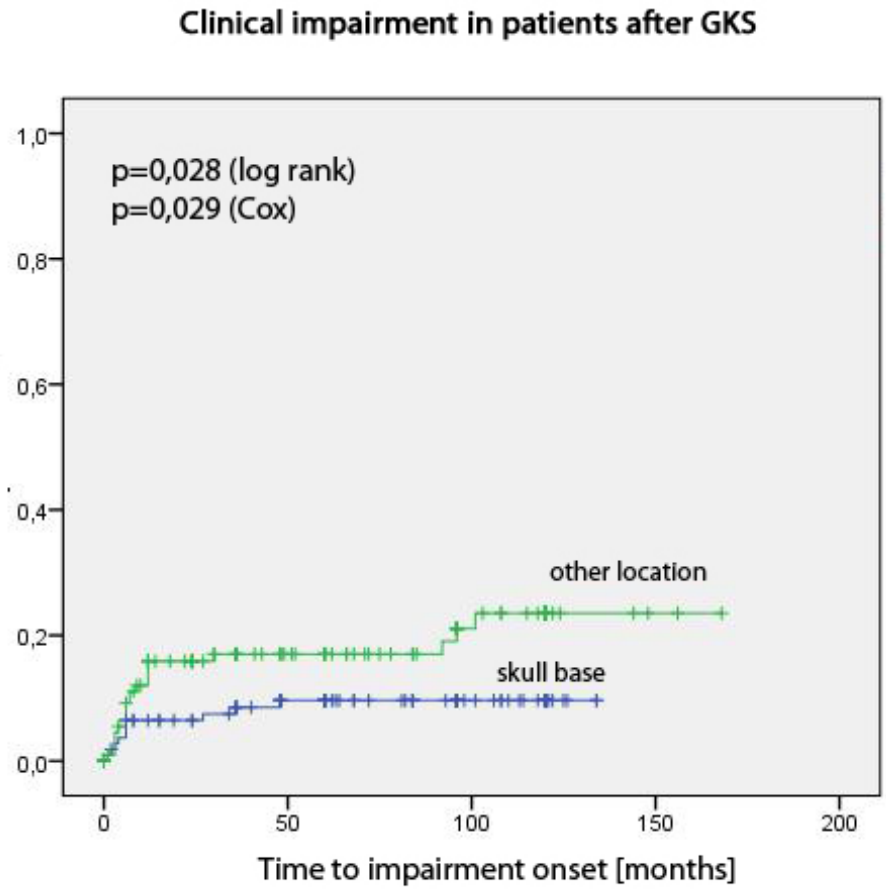

Fig. 21. Kaplan-Meier cumulative curve of clinical impairment according to the location of meningioma

From a long-term analysis (p=0,028 log rank, p=0,029 Cox) we have found, that patients with meningiomas in the skull base are at a lower risk of clinical impairment after radiosurgical treatment. In other words, patients with meningiomas located in convexity, parafalcine and parasagittal, with perilesional edema and a pial blood supply experience posttreatment impairment more frequently. (Fig. 21.) This finding is important as an indication of radiosurgical treatment and suggests, in which patients clinical impairment can be expected. Even though impairment after Gamma Knife treatment is in the majority of cases temporary and rarely disabling, for selected meningiomas with collateral edema surgery it should be considered, at least as a first step.

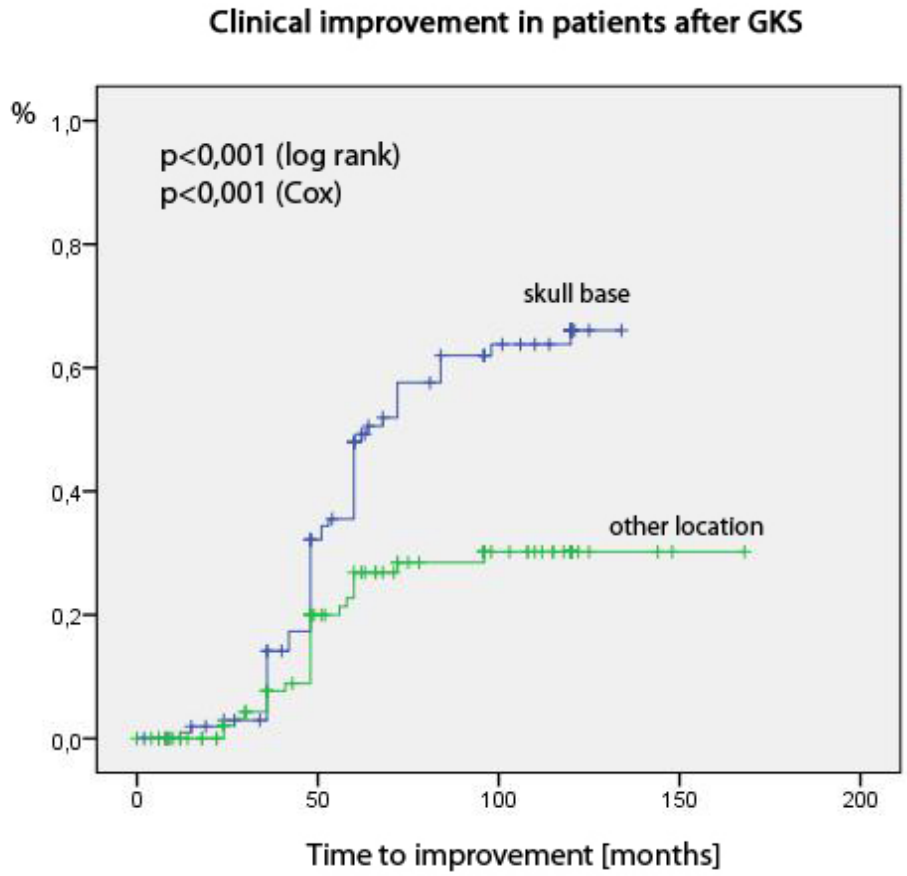

Fig. 22. Kaplan-Meier cumulative curve of clinical improvement according to meningioma location

Both mid-term (p<0,001 log rank) and long-term (p<0,001 log rank, p<0,001 Cox) studies have confirmed the statistical significance of clinical improvement after Gamma Knife treatment in patients harbouring skull base meningiomas. (Fig. 22.) Improvement as such can be attributed to the decreased volume of the treated meningioma as well as recovery after surgery, in cases when Gamma Knife treatment is performed within one year after operative surgery. The results presented advocate radiosurgical treatment as the treatment of choice for selected meningiomas in the skull base, where complete operative removal is impossible.

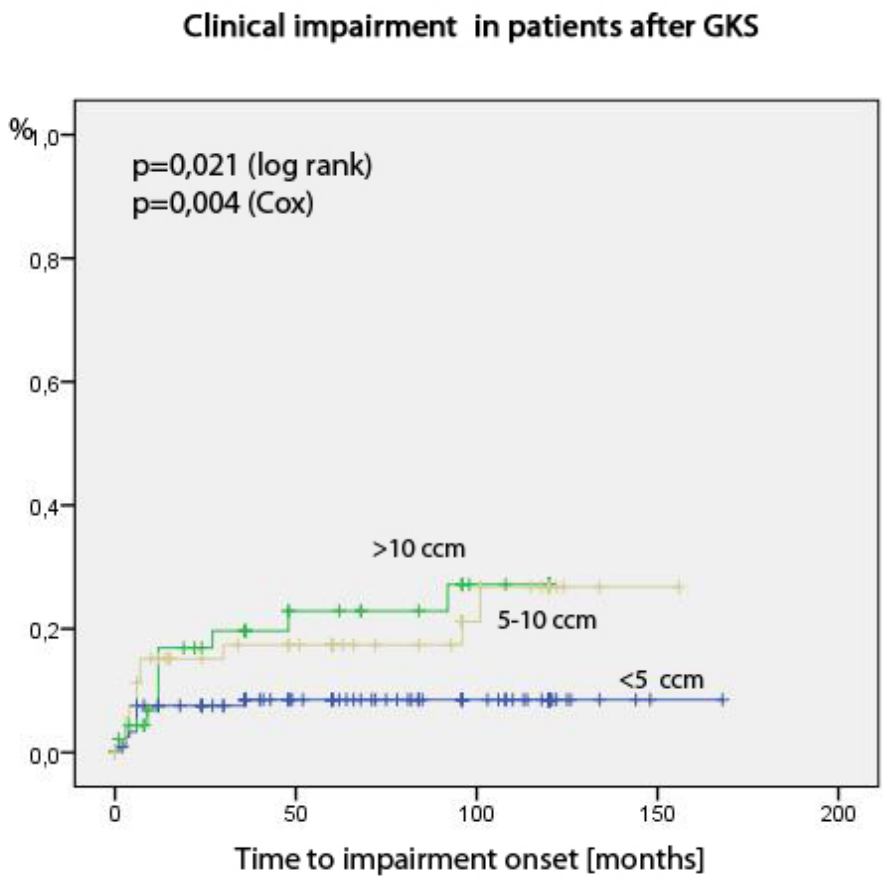

Fig. 23. Kaplan-Meier cumulative curve of clinical impairment according to the size of the treated meningioma

The statistical significance of tumor volume as a risk factor for clinical improvement after Gamma Knife treatment was found in both mid-term (p=0,014 log rank, p=0,002 Cox) and long-term (p=0,021 log rank, p=0,004 Cox) results; in both Cox and log rank tests, which suggests its clinical importance. (Fig. 23.) The bigger the treated volume, the higher the cumulative dose necessary to cover the whole meningioma with an adequate dose. The bigger the irradiated volume, the higher the risk of complications. Therefore, volume is a very important issue when considering Gamma Knife treatment.

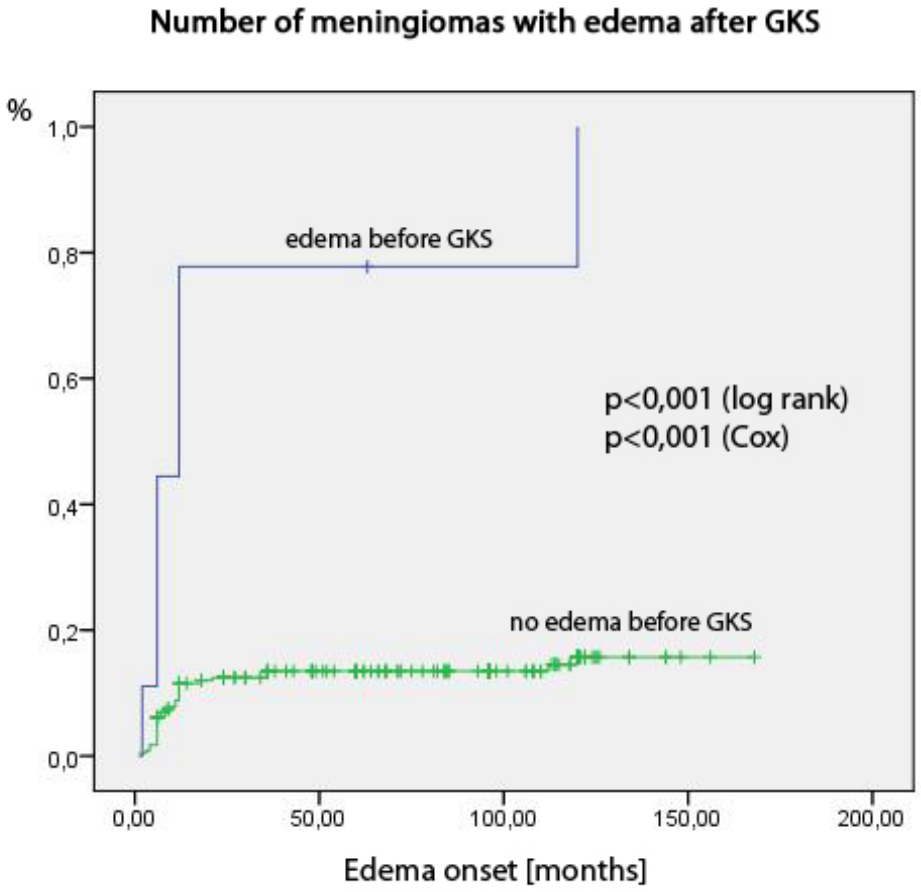

Fig. 24. A Kaplan-Meier cumulative curve of patients weth postiradiation edema according to evidence of edema prior to treatment

Both Cox and log rank tests showed statistical significance in both mid-term (p<0,001 log rank, p<0,001 Cox) and long-term (p<0,001 log rank, p<0,001 Cox) results for the analysis of perilesional edema after treatment and its relation to edema occurrence before the treatment. (Fig. 24.) The finding is not surprising, as edema present before treatment would be aggravated by Gamma Knife treatment; Gamma Knife treatment itself can induce edema also in tissues without edema before treatment. This finding is taken into account when deciding about the indication of radiosurgery in meningiomas with perilesional edema.

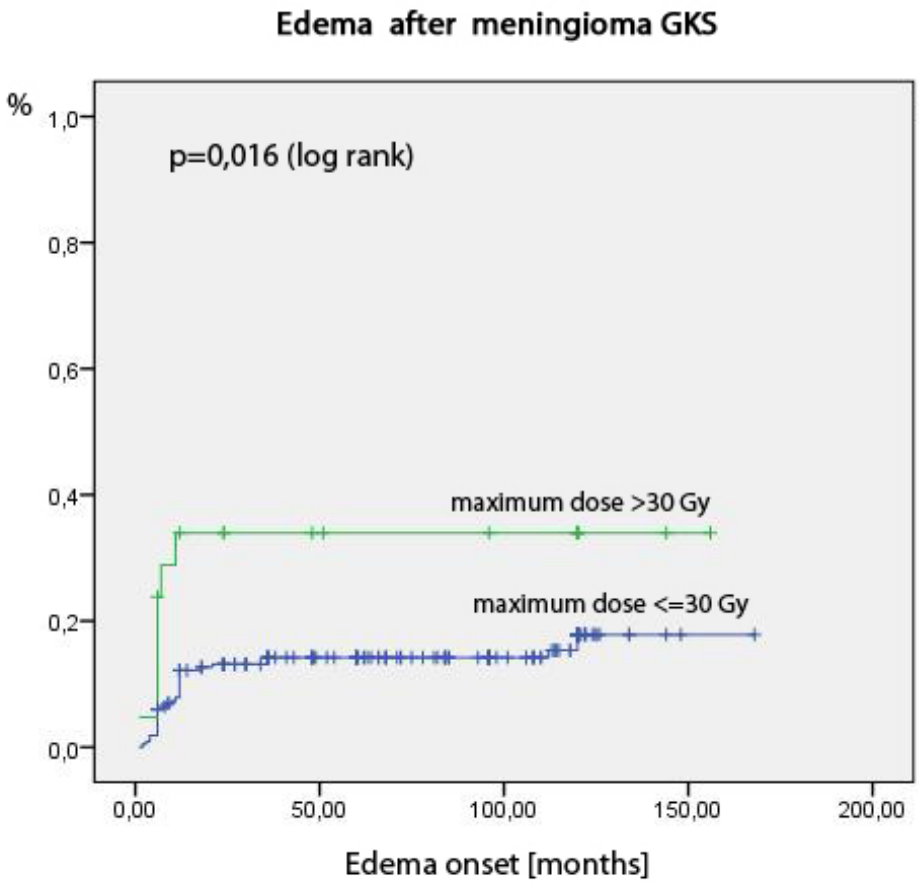

Fig. 25. Kaplan-Meier cumulative curve of posttreatment edema according to treatment with the maximum dose

Both mid-term (p=0,013 log rank, p=0,018 Cox) and long-term (p=0,016 log rank) studies have confrmed the significance of a maximum dose higher than 30 Gy as a risk factor for edema occurrence after Gamma Knife treatment. (Fig. 25.) Edema is a consequence of irradiation induced changes, mostly within the treated lesion and thus inducing edema directly, as well as perifocal edema caused by vascular factors increasing the permeability of the blood vessels (VEGF).

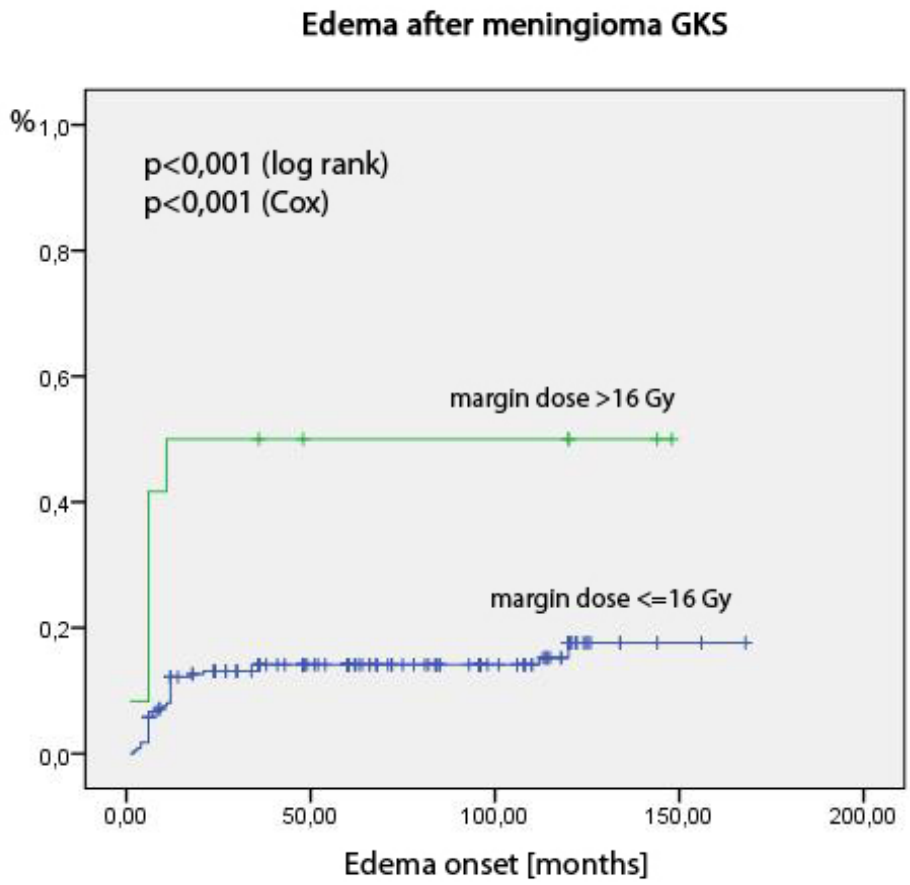

Fig. 26. Kaplan-Meier cumulative curve of posttreatment edema according to treatment margin dose

Dose to margin is equally important for edema induction, which was confirmed by mid-term results (p<0.001 log rank) and long-term results (p<0,001 log rank, p<0,001 Cox), which further confirms the effect of irradiation that induces edema in treated areas as well as in its vicinity. (Fig. 26.) Both findings of edema occurrence after treatment with a maximum dose of higher than 30 Gy and a margin dose of higher than 16 Gy have practical clinical implications during the planning of Gamma Knife treatment.

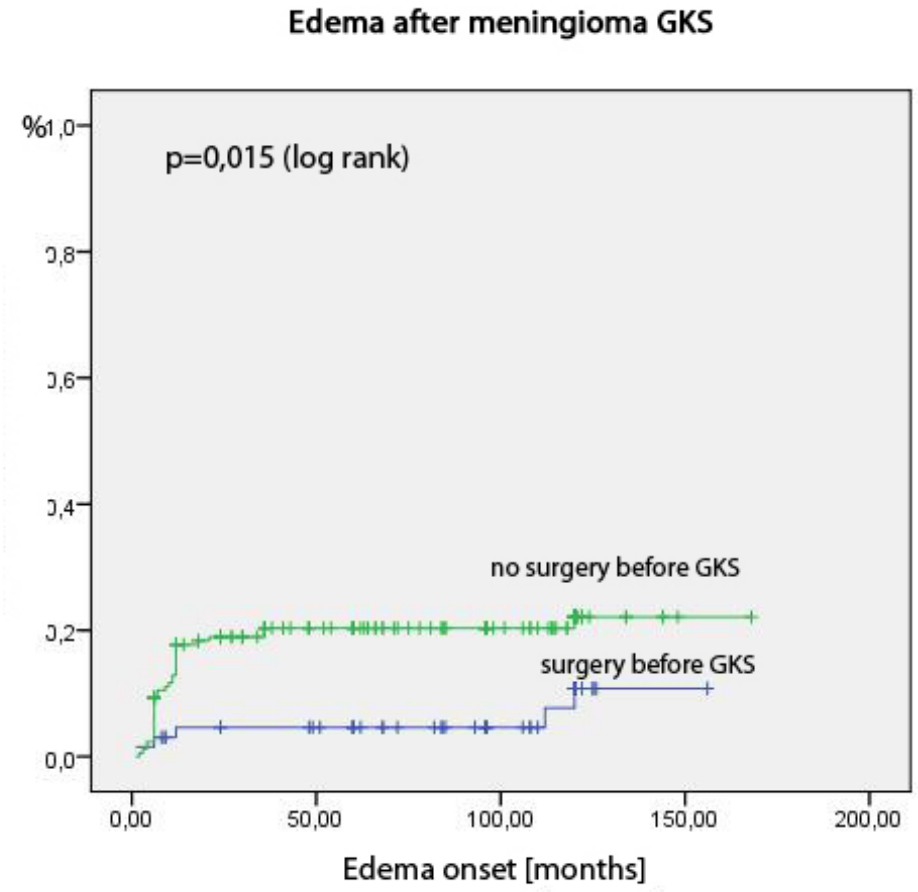

Fig. 27. Kaplan-Meier cumulative curve of posttreatment edema according to previous surgery

Patients who have undergone surgery for their meningiomas were at lower risk of edema occurrence after Gamma Knife treatment both in the mid-term (p=0.013 log rank, p=0.035 Cox) and in long-term studies (p=0,015 log rank). (Fig. 27.) This finding is discussed in more detail in the Discussion chapter; it is attributed to the disruption of the tumor-pial interface and thus the limited effect of VEGF on brain tissue.

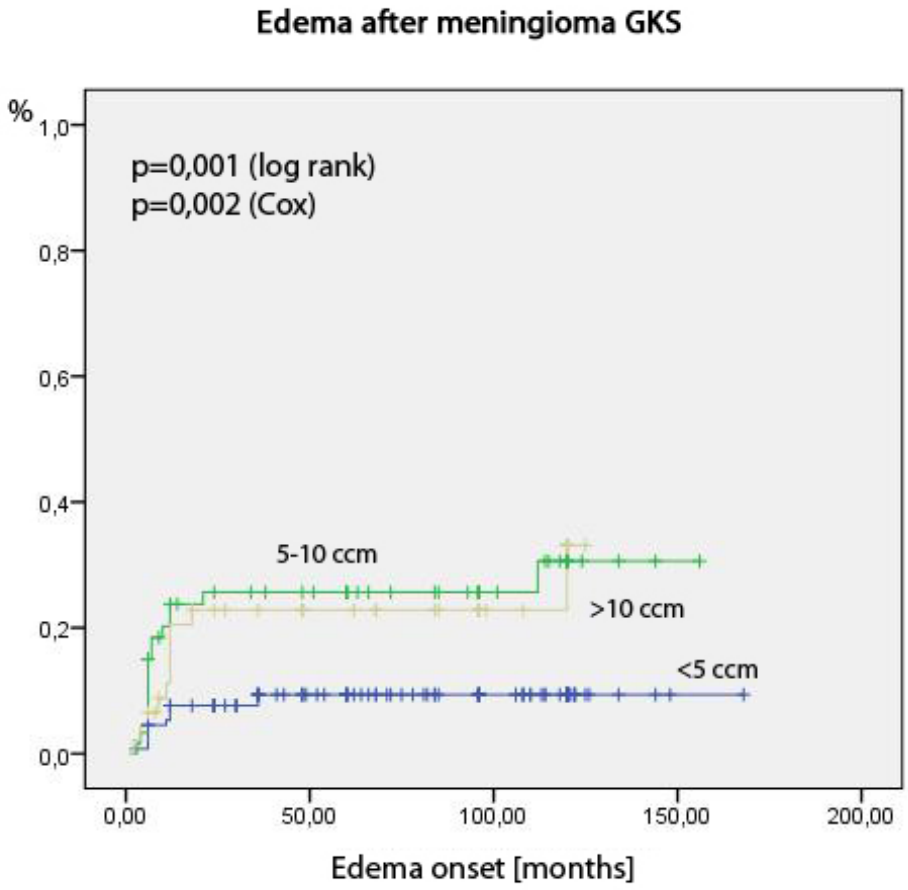

Fig. 28. Kaplan-Meier cumulative curve of posttreatment edema according to tumor volume

Tumor volume was found to be a statistically significant factor both in mid-term (p=0,002 log rank, p<0,001 Cox) and in long-term (p=0,001 log rank, p=0,002 Cox) studies. (Fig. 28.) The finding is a logical consequence of the size of the irradiated volume; the bigger the volume irradiated, the higher cumulative dose and the higher the impact to the tissue of meningioma resulting in perilesional swelling. Again, this finding has a practical implication and patients are consulted about increased treatment risk if it is found to be necessary to treat the meningioma at an upper volume limit.

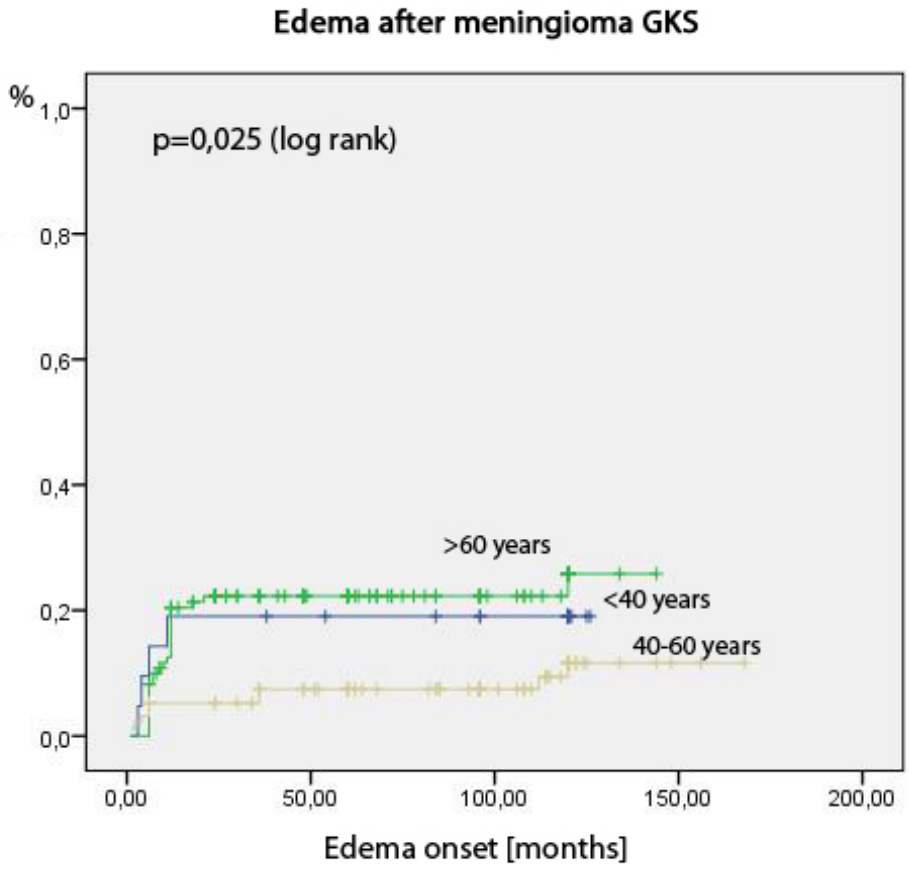

Fig. 29. Kaplan-Meier cumulative curve of posttreatment edema according to the patient`s age

Both mid-term (p=0.019 log rank) and long-term (p=0,025 log rank) results suggest that patients older than 60 years are at a higher risk of edema occurrence after Gamma Knife treatment. (Fig. 29.) Also, younger patients more often have meningiomas resected by operative neurosurgery and therefore the surface of the brain in contact with possibly edemagenic meningioma is reduced. The practical implication of this finding is reflected in the more conservative approach to meningioma radiosurgery in the elderly.

5. Discussion

The results of the treatment of meningiomas as slow growing tumors would not show fully the benefit of the treatment within 5 years; at least 10 years of follow up is necessary (Gildenberg, Tasker, 1998; Leksell 1983; Steiner et al., 1991).

The actuarial 5 and 10-year tumor control rate in our 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 middle and long term results (Chang, Adler 1997; Di Biase et al., 2004; Ganz et al., 2004; Hakim et al., 1998; Iwai et al., 1999; Kollová et al., 2011; Kondziolka et al., 1999; Lee JY et al., 2002; Linskey et al., 2005; Liščák et al., 2009; Malik et al., 2005; Maruyama et al., 2004; Muthukumar et al., 1998; Nicolato et al., 2005; Pan et al., 1998; Pendl et al., 1997; Pollock, 2003; Pollock et al., 2011; Roche et al., 2003; Santacroce et al., 2012, Shafron et al., 1999; Spiegelmann et al., 2002; Stafford et al., 2001, Williams et al., 2011). (Table 8.)

Author	Number pts.	Location	Years	Margin dose Gy	Volume (cm^3)	Follow up (months)	Tumor control	Morbidity
Gamma Knife								
Kollová et al, 2007	***368***	***all***	***1993-1999***	***12,55***	***4,4***	***60***	***97,9%***	***5,3%***
DiBiase et al., 2004	162	all	1992-2000	14	4,5	54	91,70%	8,3%
Kondziolka et al., 1998	99	all	1987-1992	16	4,7	NA	93%	5%
Linskey et al., 2005	38	all	1998-2003	16	7,85	21,5	97%	5%
Malik et al., 2005	309	all	1994-2000	20	7,3	39	87%	3%
Pollock, 2003	330	all	1990-2002	16	7,3	43	94%	8%
Stafford et al., 2001	190	all	1990-1998	16	8,2	40	93%	3%
Aichholzer et al., 2000	46	skull base	1992-1995	16,3	NA	48	96%	9%
Iwai et al., 1999	24	skull base	1994-1996	10,6	10,1	17,1	100%	4%
Pendl et al., 2007	97	skull base	1992-1996	13,8	13,7	18,5	96%	5%
Lee et al., 2002	176	cavernous sinus	1987-2000	13	6,5	39	93%	7%
Roche et al., 2003	32	petroclival	1992-1998	13	2,28	52,6	100%	6%
Kim et al., 2005	23	convexity	1998-2003	16	4,7	33	95%	43%
Kondziolka et al., 1998	203	parasagittal	10 years	15	7,5	42	93%	16%
Muthukumar et al., 1998	41	tentorial	9 years	15,3	NA	36	98%	3%
LINAC								
Shafron et al., 1999	70	all	1989-1997	12,7	10	23	100%	3%
Chang et al., 1997	55	skull base	1989-1996	18,3	7,33	48,4	98%	5%
Spiegelmann et al., 2002	42	cavernous sinus	1993-2001	14	8,4	36	98%	6%

Table 8. Overview of published data on meningioma radiosurgery

Our results in the upper part of the range reflect the successful strategy of the treatment in terms of dose selection as well as patient selection (size of tumor). The difference in percentage of tumor control between mid-term (97,9%) and long-term (94,7%) is the result of Kaplan- Meier analysis. Kaplan- Meier analysis, or survival analysis, is concerned with study the time between entry to study and occurrence of studied event. (Originally designed to study the treatment until death, hence name survival analysis"). The method is dealing with issues as patients, who become lost to follow up; thus the only information possible to obtain is the one gained at the time when they were still alive (censored observation). Therefore obtained percentages are the result of statistical formula and not the absolute numbers and percentages. (Swinscow T.D.V., Campbell M.J., 2002). (Fig. 12.)

An often-addressed issue is the natural biological behaviour of meningioma versus meningioma treated by radiosurgery. Meningiomas are slow growing tumors and especially in the elderly, do not increase in size during follow up years. From a long-term follow up view of surgically treated meningiomas it was found, that there was a 5 year recurrence rate of 4-20% in meningiomas which were radically removed; in sub-totally resected meningioma the percentage is higher, 18,4-37%. All these patients have to be followed up with MR scanning for years, as recurrence can occur even 30 years after surgery. Long-term studies show however, inaccuracy in terms of removal quantification, as accurate imaging techniques were not available in the past, as we know them today (Black P.M., 1993, Mathiesen T. et al., 1996, Petterson-Segerlind et al., 2011).

Radiosurgery as a treatment modality does not remove the tumor; tumorous cells lose the ability to divide, they remain in the G0 phase of the cell cycle. Also, as a result of postirradiation changes, fibrosis and necrosis will occur. All the above-mentioned features can be found when analysing specimen obtained during surgery of meningioma after stereotactic radiosurgery. The mere presence of viable meningioma cells is not proof of treatment failure (Liščák et al., 2009, Steiner et al., 1991)

Tumor Margin and Maximum Dose

An optimum treatment dose for meningioma is still a topic of controversy, as shown in Table 8. In the present study, both in 5-year follow-up and 10-year follow-up, there was a

significantly higher decrease in the volume of meningioma treated with a marginal prescription dose greater than 12 Gy. (Table 4.)

In our study, a margin dose of lower than 12 Gy was applied only to patients who had undergone previous fractionated radiotherapy. In the case of meningioma compressing optic pathways, this part of the tumor was covered with a reduced dose of 10-12 Gy. The experience of the department shows that the strategy of reduced marginal dose has controlled the growth of tumors (Kollová et al., 2010; Liščák et al., 2004; Novotný et al., 2006).

With regard to location, the most vulnerable structure is the anterior visual pathways, especially regarding the dose necessary for the treatment of intrasellar and parasellar menigiomas. No visual field loss was detected in our study. The dose to the optic tract exceeded the recommended 8 Gy only in cases where the patients had become blind since primary operative treatment, and for the dose to the patients who had previously undergone radiotherapy; the dose was always lower than 3 Gy. There are papers advocating a dose to the optic tract of higher than 10 Gy (Kenai H. et al., 2005; Morita et al., 1999). Nonetheless, we believe that delayed damage can occur up to 10 years after treatment (Shrieve D.C. et al., 2004, Tischler R.B. et al., 1993). The dose to pituitary gland in the treatment of intra- and parasellar meningiomas did not exceed 15 Gy, which we consider a safe limit to avoid damage to the pituitary. No clinical evidence of hypopituitarism was confirmed in our study (Vladyka et al., 2003).

In patients treated with margin doses of higher than 16 Gy, there was a significantly greater occurrence of postirradiation edema, confirmed both in 5 and 10- year cohorts. Additionally, in 10 year follow ups we have found, that 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.

According to our results, a higher margin dose was not related to tumor control, although the risk of complications was increased. As reported by Kondziolka et al., (1999), margin doses of over 16 Gy did not provide better tumor control. The current practice at our centre is to apply a margin dose of 12-16 Gy for benign meningiomas.

Patient sex and age

The relationship between meningioma and the hormonal status of patients has been confirmed (DeMonte et al., 2000, Kozler P., 2007). Analysing tumors that increased in size after radiosurgery we have found that the majority of them were in men, which was statistically significant. On the other hand, men have higher chance of meningioma regression after treatment,

as confirmed by analysis of long-term results. (Table 4., 7., Fig. 8.) Similar findings of meningioma behaving more aggressively in men, were also reported by other authors (DiBiase et al., 2004; Nakamura et al., 2003; Niiro M. et al., 2000).

Patients younger than 40 years were found to have an increased chance of tumor regression, which can be explained by the fact that these meningiomas contain less calcium than in older patients. (Fig. 19.) Meningiomas in younger patients also behave more aggressively and therefore these patients are often candidates for surgery in the first instance.

A significantly increased frequency of adverse effects was observed in patients younger than 40 years old and older than 60. It has also been reported, that those meningiomas in the elderly show a lower progression rate (Black P.M., 1993; Niiro M. et al., 2000). These facts suggest that prescribed dose should be kept at the lower end of the therapeutic window, i.e. 12-16 Gy to prevent post-treatment complications, as life expectancy is shorter (Kollová et al., 2007).

Previous surgery

In our study, previous surgery was significantly related to the improvement of neurological deficits detected before treatment. The other authors report higher improvement rates in patients with no history of surgery before radiosurgery (Aichholzer et al., 2000; Stafford S.L. et al., 2001). 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. Nevertheless, a combination of surgery and radiosurgery to keep the risk of surgical damage to a minimum is reported as beneficial by many authors (Asari S. et al., 1995; Couldwell W.T. et al., 1996; Cudlip S.A. et al, 1998; Fahlbusch R. et al, 2002; Jung H.W. et al., 2000, Linskey M.L. et al., 2005).

Analysing our 10-year cohort it was found that patients who had undergone surgery for their meningiomas were at a greater risk of tumor progression after radiosurgery; this fact can be explained by the aggressive behaviour of tumors that required surgery as a first treatment modality.

In our study, previous surgery was associated with a lower risk of postiradiation edema. This fact can be explained by follow up MR scans, where it is difficult to distinguish between postoperative changes and edema, unless there are clear signs of mass effect. Also, surgical removal decreases the portion of meningioma in contact with brain parenchyma, disrupts the pial blood supply, thus reducing the risk of edema (Bitzer et al., 1997; Kollová et al., 2007).

Interestingly, Cox regression does not indicate a previous operation as a significant factor for tumor increase after radiosurgery. (Table. 4.) This can be partially explained by the higher

amount of censored cases. Another explanation might be that the previous operation is somehow related to the age of the patients – for example Fisher's exact test indicates that there is a significant association between a previous operation and age – in the age categories <40 and >60 years there is a higher rate of previous operations (Fisher's two tailed p = 0.018) compared to the 40-60 year-old category. Using Kaplan-Meier statistics we can stratify the data according to the previous operation into "yes" and "no" groups and each group into three subgroups <40, 40-60, >60 years. Now we can observe that in the previous operation, in the "yes" group the age is no longer a significant factor, while in the "no" group the age is significant, p = 0.032 (log rank).

In addition vice versa we can make three age groups (<40, 40-60, >60 years) and divide each group into two subgroups - previous operation "yes" and "no". We can test the rate of edema incidence for the previous operation in the "yes" and "no" groups in each age category separately. In that case the previous operation was not found significant in any of the age categories (p = 0.094, p = 0.101, p = 0.812). However, note the low number of patients in some age categories.

Location of the meningioma

In both groups of patients we have found, that there is a lower risk of clinical impairment in patients with meningiomas located in the skull base (the only exception is anterior cranial fossa). The reason for that finding might be the fact that skull base meningiomas have a smaller surface directly in contact with the brain tissue, with a pial blood supply, that enables angiogenic factors produced by meningioma to enter the brain tissue and induce perilesional edema (Bitzer et al., 1997; Kollová et al., 2007). Especially patients with meningiomas located in the convexity and parasagittal/falcine meningioma are at higher risk of posttreatment complications. Higher chances for clinical improvement have patients who harbour skull base meningioma. (Fig. 22.)

Adverse effects

In the majority of cases, morbidity associated with stereotactic radiosurgery is temporary. In our 5-year cohort, temporary morbidity was 10,2% and permanent 5,7%. 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 early stages of Gamma Knife meningioma treatment, the patients were selected very carefully with regard to the size of tumor (median 4,4 cm^3 vs. median 3,78 cm^3 respectively).

Published permanent complication rate ranges from 2,5% to 9% (Chang S.D. et al., 1997; Kim D.G. et al., 2005; Kondziolka D. et al.; 1999; Morita A. et al., 1999; Roche P.H. et al., 2003; Rowe J.G et al., 2004; Shuto T. et al., 2005; Singh V.P. et al., 2000; Stafford S.L. et al., 2001). Posttreatment deficit is rarely disabling. Surgical treatment, especially for skull base meningiomas, would result in major changes in lifestyle for more than 50% of patients due to new neurological deficits. One also cannot underestimate the impact on the patients' family and carers (Lang D.A et al., 1999). As confirmed by our data, complications could be predicted by the characteristic features of meningioma, its location, size and peritumoral edema.

The results of our study show, that meningiomas larger than 5 cm^3 carry an increased risk of perilesional edema and patients are more likely to experience neurological impairment. (Table 4., 7.)

Seven patients in the present study experienced intra-tumoral edema, which developed 5 to 16 months after radiosurgery. In all of them the tumors finally shrank and the symptoms settled. This information is very important, because a referring neurosurgeon might mistake intra-tumoral edema for the growth of the tumor, and proceed with microsurgery at the least favourable time due to acute postirradiation changes. When intra-tumoral edema occurs, use of steroids is recommended (Kollová et al., 2007, Kondziolka D. et al., 1998).

To distinguish intra-tumoral edema from further growth of the tumor, one must consider the time period since treatment. In our experience, intra-tumoral edema occurs within 2 years after radiosurgery, whereas the growth of the tumor is detected at least 2 years after radiosurgery.

Peritumoral edema

Overall, peritumoral edema is reported in 40-60% of meningiomas. Patients with edema surrounding meningioma are not ideal candidates for stereotactic radiosurgery, as irradiation of meningioma can increase this perilesional swelling and subsequently leads to neurological deterioration. This fact is reflected in low percentage of meningiomas with surrounding edema in patients treated with radiosurgery- around 4% (Bitzer et al., 1997; De Monte et al., 2000; Yoshioka et al., 1995).

In our study it was found only in 3,8% of treated patients. This fact can be explained by the need for operative surgery, when edema is causing mass effect and clinical symptoms. According to our results, the patients with peritumoral edema before radiosurgery are at an increased risk for the development of postirradiation complications and the worsening of pre-existing edema.

This result was confirmed both in the 5- and 10-year cohort analysed. Moreover, patients with seizures and perilesional edema have less chance for seizure improvement. (Table 4., 7.)

Further risks for the induction of posttreatment edema are those with a tumor volume larger than 10 cm^3, a prescription dose of higher than 16 Gy and a tumor located in the anterior fossa. (Table 4., 7.)

Meningiomas located in the convexity and in the anterior skull base have a higher risk of perilesional edema occurrence compared to other skull base meningiomas. In addition, larger tumors can be associated with edema after being exposed to lower doses; higher doses can induce extensive edema in small tumors in the same location. A unifying factor for these findings could be the pial interface, which enables VEGF to enter surrounding brain tissue, after its release from damaged tumorous cells after irradiation.

The risk of radiation induced complications increases with the volume irradiated (Feigl G.C., 2005; Ganz J.C., 1993; Shrieve D.C. et al., 2004; Stafford S.L. et al., 2001). A tumor volume of greater than 10 cm^3 was a risk factor for the development of a temporary and permanent neurological deficits after radiosurgery, as shown by the 5-year follow up cohort. Therefore, patients with meningiomas larger than 10 cm^3 must be consulted concerning the increased risk of treatment. Progression of preexisting edema facilitated by stereotactic radiosurgery can have severe consequences. In the largest study published, there were 3 fatalities in a series of 4565 patients related to edema progression (Santacroce et al., 2012).

Note that the other authors have not found a relationship between tumor volume and margin dose, and the occurrence of complications. In contrast, patients in the present study with a larger tumor volume (more than 5 cm^3) had a greater chance of improvement in any neurological symptom if it was present before treatment. A greater likelihood of improvement under these circumstances could be attributable to tumor shrinkage as well as to somatostatin receptors on meningioma cells (Nicolato A. et al., 2005).

Ten patients in the present study received staged treatment for meningioma; the bigger portion or the portion in the posterior fossa was treated first; in another 6 months the smaller portion was treated. Postiradiation edema occurred in two patients, it was symptomatic in one. This approach was used to improve tolerance in treating two smaller parts instead of one large part, and therefore to decrease the risk of treatment. This option was used in patients with large skull base meningiomas, who would not tolerate surgery.

According to our data, it is possible to predict the occurrence of posttreatment edema with regard to the location of 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 chances to predict edema occurrence after Gamma Knife treatment and it is used in the identification of patients who can develop this adverse effect eventually. These patients are counselled about the increased risk of posttreatment complications, with practical recommendation for further care.

Other factors

The lobulated tumor margin and its heterogeneous appearance after contrast media administration as a sign of higher biological activity failed to show a significant relation to the studied events in both the 5- and 10-year follow up cohorts, which suggests no change in the treatment strategy with regard to morphological appearance.

6. Conclusions

The results of the study confirm efficacy and safety of stereotactic radiosurgery in meningiomas. 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. Therefore, stereotactic radiosurgery should be a treatment of choice in skull base meningiomas fulfilling size/volume criteria of diameter up to 3 cm or volume up to 10 cm^3, especially in young patients. In this group of patients it is expected, that untreated tumor will grow and affect important structures like cranial nerves or major vessels and with increasing size of tumor, complications are more likely to occur. Active approach to this group of patients is recommended therefore more often, because life expectancy is longer.

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 is planned in the first instance, followed by radiosurgery. Radiosurgery is also recommended in patients who cannot be treated by operative surgery due to their age or because of other medical reasons in cases where meningioma is not causing a mass effect requiring excision.

Observation is a treatment option for meningiomas in the elderly, especially in patients in whom meningiomas show signs of calcium deposits. These meningiomas grow rarely and usually do not cause a mass effect towards the atrophic brain. On the other hand, observation in younger patients might lead to meningioma progression to an 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, w a prescription dose of 12-16 Gy is suggested to the tumor margin. Higher margin doses are associated with higher treatment risks, not improving 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 posttreatment complications.

Long-term temporary and permanent morbidity associated with Gamma Knife treatment was 9,6% and 1,3% respectively, although it was rarely disabling. The low percentage of side effects make 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.

The importance of multifactorial model for the prediction of edema occurrence after radiosurgery as well as the significant predictive factors in this study is in identification of

subgroup of patients, which are at higher risk of post treatment complications. The model should be tested and validated in the future in patients of the department as well as by other centers treating meningiomas.

Initial hypothesis, that it is possible to identify the risk factors related to stereotactic radiosurgery of meningiomas from a long-term perspective was confirmed, with further implication in clinical practice.

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 a benign tumor. Treatment options or combinations of them should be assessed for every patient individually.

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Appendix 1

List of Figures and Tables

Appendix 2

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Appendix 4

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Appendix 5

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