Tampereen yliopisto

Lassi Jaatinen

LONG-TERM OUTCOME OF OPERATED INTRACRANIAL MENINGIOMA PATIENTS IN TAMPERE UNIVERSITY HOSPITAL

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Intracranial meningiomas usually have a good prognosis in the long-term, but large studies about the subject are lacking. In our study, we retrospectively looked at the survival data from the years 1983 to 2017 in one Finnish (Tampere University Hospital) university hospital for 1272 intracranially operated meningiomas. We compared this survival data for the life-expectancy of the accompanying catchment area of the hospital. Our data shows that the life-expectancy for meningioma patients for age groups 60 to 69, 70 to 79 and 80 and older is as good and better than that of the life-expectancy of the catchment population. The for the under 60 year age group is slightly worse than that of the catchment population. We also studied the general characteristics of meningioma patients and the median age for an intracranial meningioma patient is 59,8 years. Grade I accounted for 94,5% (N=1202), grade II for 5,0% (N=64) and grade III for 0,5% (N=6). Grade II and III prevalence were lower than in previous studies. We also compared the grading to certain characteristics where our study suggests that grade II and III meningiomas are more common for the over 80 year age group than for younger patients. Lastly, we compared the prognosis of supra- and infratentorial meningioma patients to each other where our data rather surprisingly suggests that infratentorial patients fared better in the short- and long-term than their supratentorial counterparts. Previous studies about this comparison contradict our results. Overall our study found out that the prognosis in a single Finnish university hospital was good for meningioma patients. Similar patient selection process should be recommended in other neurosurgical departments.

Avainsanat: prognosis, brain tumour, infratentorial

Tämän julkaisun alkuperäisyys on tarkastettu Turnitin OriginalityCheck –ohjelmalla.

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1 Introduction

1.1 Definition

Meningiomas are the second most common intracranial tumours after metastases and the most common primary intracranial neoplasms for adults accounting for 13-26% of all primary intracranial tumours. (Whittle et al. 2004, Bi et al. 2016, Claus et al. 2005). Meningiomas are primarily benign tumours of the meninges' that arise from the dural arachnoid cells (Splavski et al. 2017, Apra et al. 2018). Most common sites for meningiomas appear to be in the supratentorial compartment along with the dural venous sinuses in the cerebral convexity, parasagittally in the falx cerebri and in the sphenoid wing regions(Buetow et al. 1991, Saraf et al. 2011). They appear to be far more common for women than men with a 2-4:1 ratio (Klaeboe et al. 2005, Apra et al. 2018, Claus et al. 2005).

1.2 Grading

Meningiomas are graded into three grades by the WHO 2016 classification (Louis et al. 2016). Grade I are benign in nature and account roughly 80-90% of meningiomas, grade II are borderline/atypical and account about 5-14% of meningiomas and grade III or anaplastic/malignant tumours account 2-5% of meningiomas (Bi et al. 2016, Larjavaara et al. 2008, Apra et al. 2018).Even though meningiomas are mainly benign in nature their intracranial or spinal location can cause serious health problems or even death (Wiemels et al. 2010, Sankila et al. 1992).

1.3 Prevalence

The prevalence of asymptomatic meningiomas varies from around 0.050-0,098% from reported Cancer registry cases (Cea-Soriano et al. 2012,Claus et al. 2005) to 0,52-0,90% found in randomized MRI studies in general population (Yue et al. 1997, Vernooij et al. 2007). In autopsy studies the prevalence of asymptomatic meningiomas for a population of over 60 years was found to be as high as 3% and 8% of these asymptomatic meningiomas were found to be multiple in nature. (Nakasu et al. 1987, Nakamura et al. 2003, Whittle et al. 2004).

1.4 Incidence

The incidence rate has been estimated to be 4.2-6/100 000/year (Zouaoui et al. 2018, Whittle et al. 2004). The corrected age-standardised incidence rates were 1.9-3.05/100 000/year for men and 4.5-13.0/100 000/year for women and 5.3/100 000/year for the whole population in different studies. (Klaeboe et al. 2005, Larjavaara et al. 2008, Cea-Soriano et al. 2012). The incidence rate in Finland by the Finnish Cancer Registry was estimated to be 1.6/100 000/year for men and 5.5/100 000/year for women (Larjavaara et al. 2008).

1.5 Etiology

The etiology of meningiomas remains largely unknown. Ionizing radiation during childhood remains well-known risk factor (Sadetzki et al. 2002, Bondy et al. 1996, Godlewski et al. 2012), hereditary causes include abnormalities in chromosome 1 and 22 and neurofibromatosis type 2 (Hansson et al. 2007, Sulman et al. 1998). Other causes have been studied such as hormones, viruses, head injuries and electromagnetic fields, but substantial evidence is lacking (Klaeboe et al. 2005, Korhonen et al. 2006, Ahlbom et al. 2004).

1.6 Treatment

The preferable treatment option for meningioma is a total surgical resection if the tumour is in an anatomically suitable location. Other treatment options include subtotal resection, endovascular embolisation, stereotactic surgery, and external-beam radiotherapy. Post-operative adjuvant radiotherapy is also suitable for subtotal resections. (Whittle et al. 2004, Saraf et al. 2011)

1.7 Survival

Several studies have been made about the survival of meningioma patients after surgery and the indications for surgery in the first place (Dziuk et al. 1998, Durand et al. 2009, Apra et al. 2018). In previous Finnish study surgically treated patients fared better than patients that didn’t receive surgery (Sankila et al. 1992). Also, some studies have been made to compare the location of the tumour to the survival and the neurological outcome of the patient (Splavski et al. 2017, Adachi et al. 2009).

1.8 Aims

In this study, our aim was to see the general demographics of operated meningioma patients. This study also aims to see retrospectively how surgically treated meningioma patients survived after their initial surgery in the short and long-term. Some studies have been made about the disease-specific survival of meningioma patients (Aghi et. al 2009, Champeaux et al. 2017, Dziuk et al. 1998, Durand et al. 2009). We also compared the life expectancy of the patients age-specified to the catchment population. The age-specified life expectancy of the Finnish population was gathered from the Statistics Finland - a national statistical institution and National Institute for Health and Welfare (THL). This study also aims to see if the life expectancy of the operated intracranial meningioma patients had any difference compared to the catchment population. Fourthly, we compared the prognosis of patients with supra- and infratentorial tumours.

This study was conducted as a retrospective, single-center long-term follow-up cohort study in Tampere University Hospital.

2 Patients and Methods

The department of neurosurgery at Tampere University Hospital is the only neurosurgical unit in the defined geographical area in South-West Finland which encompasses the regions of Pirkanmaa, Southern Ostrobothnia, Tavastia Proper and Päijänne Tavastia. The area has a catchment area of over 1 million inhabitants and accounts for a fifth of the whole country of Finland. All patients with meningiomas in the catchment area are transferred to Tampere, establishing a bias-free study population.

2.1 Patients

We studied retrospectively all meningioma patients who received surgical resection for their primary tumour in the Tampere University Hospital during years 1983-2015. The patient data was gathered from meningioma database which covers all meningioma patients treated at the Tampere University Hospital. All the patients were registered into the Finnish Cancer Registry (Leinonen et al. 2017) in which all the cancer cases are registered in Finland. Patients' follow-up information was also received from the Cancer Registry. The follow-up information of the patients was up to the date of 01/01/2017.

From the Cancer Registry we received information about the overall survival of patients and whether surgically treated patients' had any tumour recidivation or if patients' stayed in remission. The cause of death was also gathered from this national database (Lahti et al. 2001).

The information about the grade of the meningiomas was received from the Pathology department of Tampere University Hospital where neuropathologists have graded the tumours according to the classification provided by the WHO of the time (Louis et al. 2016).

2.2 Anatomical grouping of tumours

Meningiomas were categorized into nine different anatomical locations in the study. Spinal meningiomas were excluded from the study and eight anatomical regions remained. Of these anatomical locations the seven first mentioned are supratentorial in nature. The lastly mentioned 'infratentorial' location was the only infratentorial location

<u>Anatomical locations of the meningiomas</u>

-Convexital

-Frontobasal

-Parasagittal (falx cerebri)

-Parasellar

-Sphenoidal

-Intraventricular

-Orbital

-Infratentorial

2.3 Life-expectancy

The age-specified life expectancy was calculated from two different databases. From Statistics Finland (Tilastokeskus) data was gathered about the life expectancy for different age groups. The age groups were grouped as follows: under 60, 60 to 69, 70 to 79 and 80 to 80 to 90 years. 90 years was selected because that's the oldest patient selected in this study. The life-expectancy numbers were from the years 1996 to 1998 and were available for the specific region the Tampere University Hospital encompasses (Regions of Pirkanmaa, Southern Ostrobothnia, Tavastia Proper and Päijänne Tavastia).

Population mean-numbers for the years of 1996-1998 were gathered from National Institute for Health and Welfare (THL) open-access, web-accessible *Sotkanetti*-database. This database also offered specific regional data for the before-mentioned regions. Combining the mean population and life expectancy data we were able to calculate a weighted average life expectancy for specific age groups. The data we gathered only offered a single average life expectancy-value for the whole age group. Therefore only a linear approximation is shown in the results.

2.4 Statistical analysis

All the statistical analyses were done with SPSS for Windows 25.0. In survival analysis Kaplan-Meier curves were used. For the significance of associations $\chi 2$, Mann-Whitney and Kruskal-Wallis tests were used. A P-value of $<0{,}05$ was used for statistically significant findings.

The study was approved by the ethics committee of the hospital (Register number R07042).

3 Results

3.1 Overall Characteristics

Characteristics of the patient population are listed in *table 1*. Our study included 1272 patients that met the criteria. 952 (74,8%) of these patients were women and 320 (25,2%) men. Average combined age was 59,8 years (SD 13,1 years, min 4, max 90). For women the average age was 59,8 years (SD 12,6 years) and for men 59,7 (SD 14,4 years).

Overall 1202 (94,5%) of the tumours were pathologically grade I. Only 64 (5,0%) and 6 (0,5%) were grade II and III respectively. When grade of the tumours was compared to sex, age, anatomical position and removal of the tumour only slight differences were seen in the age category.

	Grade I, N (%)	Grade II, N (%)	Grade III, N (%)	Pearson Chi-Square asymp. Sig. (2-sided)=P-value
Sex				0,357
-Female, N=952	902 (94,7%)	47 (4,9%)	3 (0,3%)	
-Male, N=320	300(93,8%)	17 (5,3%)	3 (0,9%)	
Age				0,002
4-60, N=614	579 (94,3%)	32 (5,2%)	3 (0,5%)	
-60-69, N=342	330 (96,5%)	12 (3,5%)	0 (0,0%)	
-70-79, N=273	255 (93,4%)	17 (6,2%)	1 (0,4%)	
-80-90, N=43	38 (88,4%)	3 (7,0%)	2 (4,7%)	
Anatomical position of the tumour				0,652
-Supratentorial, N=1063	1000 (94,1%)	57 (5,4%)	6 (0,6%)	
-Infratentoreal, N=200	194 (97%)	6 (3,0%	0 (0,0%)	
-Both, N=1	1 (100%)	0 (0,0%)	0 (0,0%)	
-NOS, N=8	7 (87,5%)	1 (12,5%)	0 (0,0%)	
Removal of the tumour				<0,001
-Extirpation, N=928	882 (95,0%)	44 (4,7%)	2 (0,2%)	
-Resection, N=337	315 (93,5%)	19 (5,6%)	3 (0,9%)	
-Both (multiple), N=5	3 (60,0%)	1 (20,0%)	1 (20,0%)	
-NOS, N=2	2 (100,0%)	0 (0,0%)	0 (0,0%)	

Table 1; sex, age, anatomical position of the tumour and the extent of the removal of the tumour compared to the grades of their respective tumours. Chi-square test is shown in the right column. NOS=not specified.

3.2 Anatomical location

The anatomical position of the tumour can be seen in *chart figure 1.* Convexital, parasagittal and frontobasal tumours accounted for over two-thirds of the tumours.

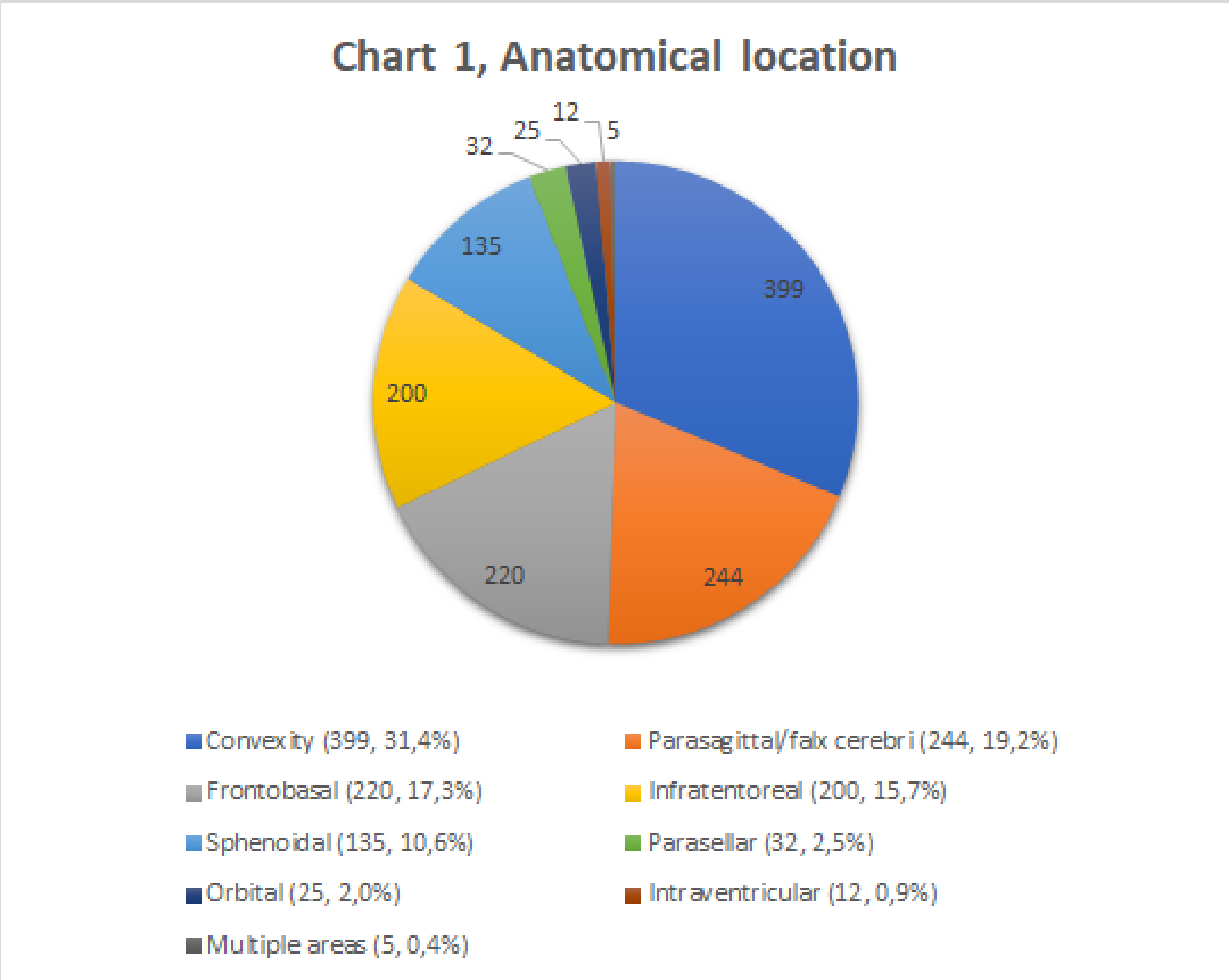

Chart figure 1; overall anatomical distribution of the intracranial meningiomas.

3.3 Overall survival

The overall survival life expectancy can be seen in *chart figure 2*. Weighted regional life expectancy can be seen as straight dotted lines with corresponding colours for their operated counterparts. In the youngest age group of 0 to 59 the life expectancy of the operated patients was a few years shorter than in the catchment population. In the age groups 60 to 69 and 70 to 79 years the operated patients actually had slightly better average life expectancy when compared to the average life expectancy of the catchment area population. 80 to 90 the average life expectancy was the same for both groups.

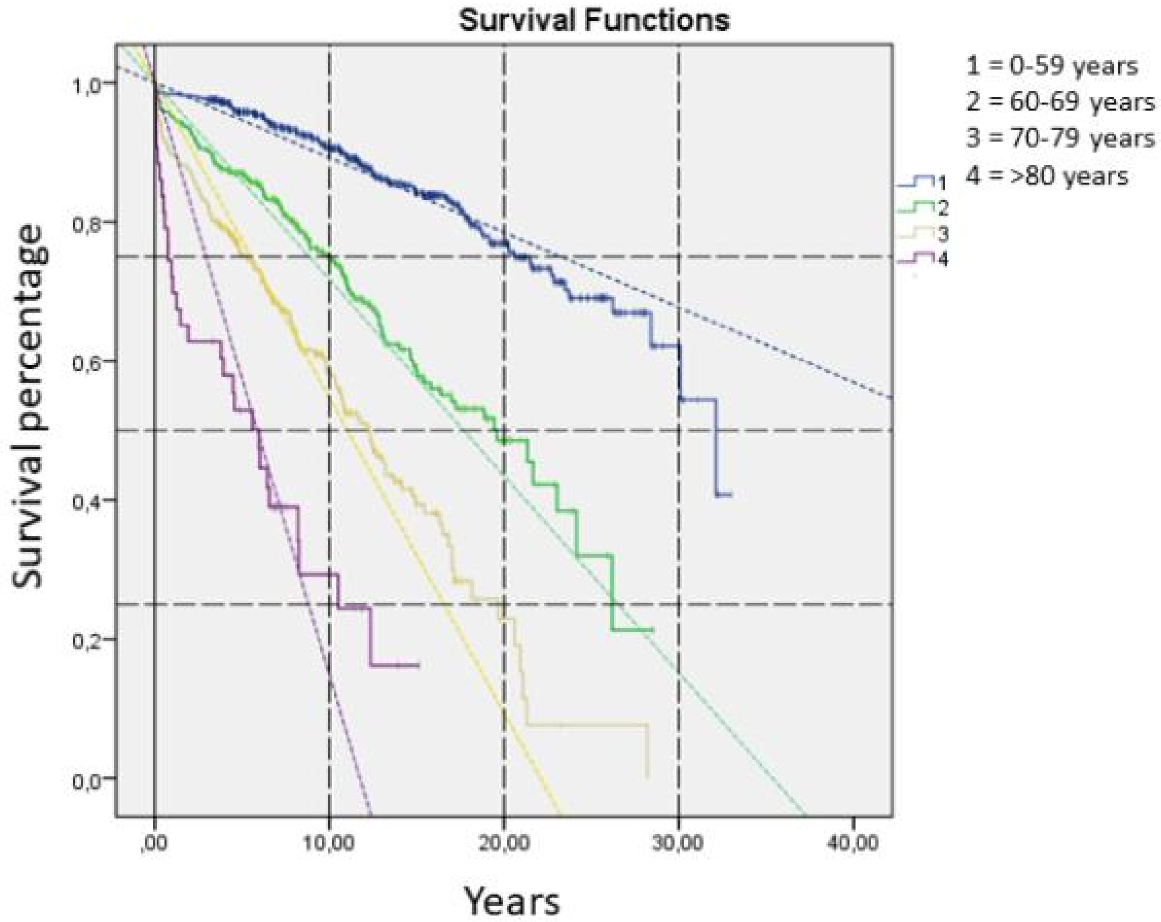

Chart 2 (dotted lines are weighted life expectancy averages for specific age groups). X-axis in years. P-value <0,00.

3.4 Survival of patients with supra- and infratentorial tumours.

We also compared the overall survival of patients with supra- and infratentorial tumours that can be seen in *chart 3*. The Kaplan-Meier estimator shows that patients who were operated for infratentorial tumours fared better in the short- and long-term outcom*es tha*n patients with supratentorial tumours.

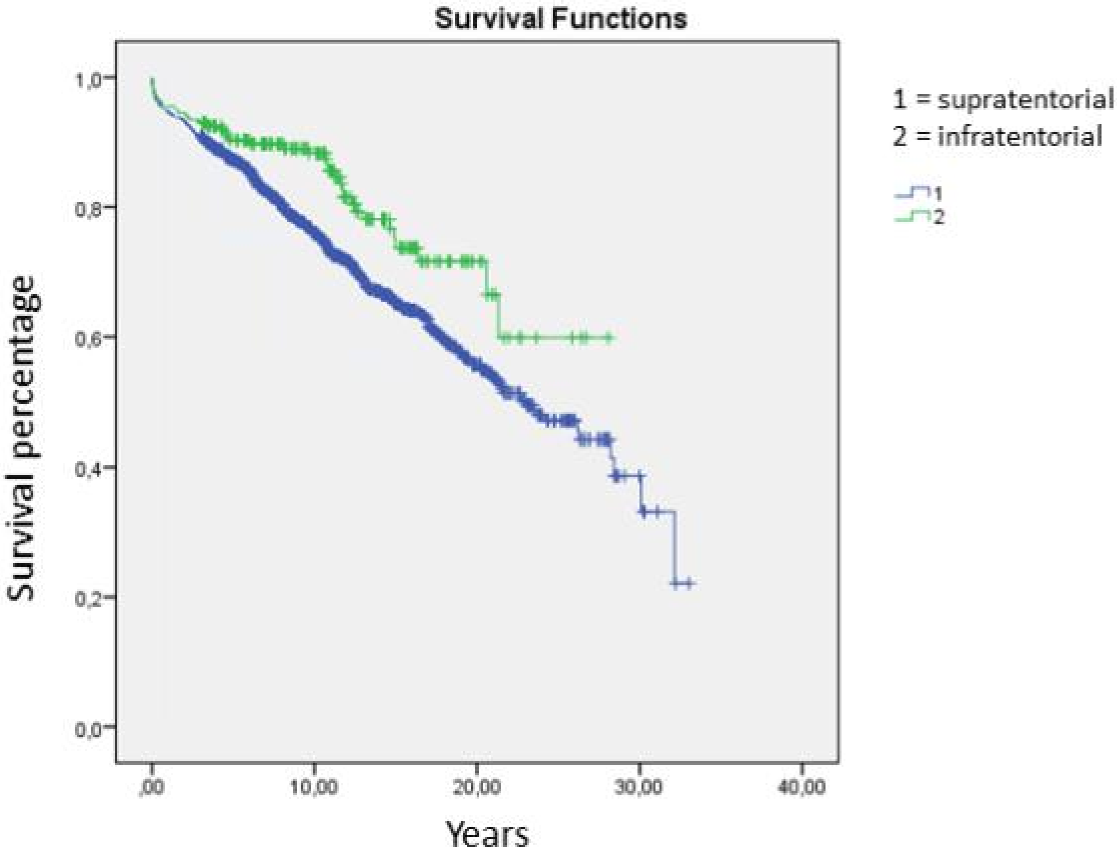

Chart 3, prognosis of supra- and infratentorial patients. X-axis in years. P-value <0,00

4 Discussion

4.1 Characteristics

The distribution regarding the grades follows mostly the same characteristics as reported in previous studies (Bi et al. 2016, Larjavaara et al. 2008, Apra et al. 2018). The prevalence of grade I tumours of all the tumours was slightly higher (94,7% for women and 93,8% for men) than in most previous studies (Claus et al. 2005,Perry et al. 1997). The prevalence of malignant grade III meningiomas was also lower (0,6%) than in these studies (Claus et al. 2005, Perry et al 1997). Some studies also note that atypical grade II meningiomas are diagnosed more frequently in the newer WHO 2000 and 2007 grading systems than before (Willis et al. 2005, Backer-Grøndahl et al. 2012). This might also be the case in our study since the first operated patients in this study were operated in 1983. A higher proportion of grade III tumours (4,7%, N=2) is seen in the over 80 year-age group which corresponds to a review made by Japanese study that defines grade characteristics for over 80 year-age group (Ikawa et al. 2017).

In our series there were more supratentorial tumors than previously reported (84,3% to 15,7%). Studies about the anatomical location of the tumours have been referenced in other studies concerning Simpson grading (Voss et al. 2017), but thorough comparing is not possible due to different anatomical terms. However, our study suggests that the most prevalent location for an operable meningeal tumour is in the convexital area followed by parasagittal and frontobasal locations. Infratentorial or posterior fossa tumours accounted for almost 1 out of 6 (15,7%) of every operated tumour which is a larger proportion than in previously reported studies which suggest a smaller 9-14,5% of all meningiomas (Roberti et al. 2001, Natarajan et al. 2004, Velho et al. 2012). This might be because infrantentorial patients were operated more keenly in this neurosurgical department than in previous studies and not because infrantentorial tumours are more common in this area. This study cannot give an unambigous answer to this question.

The age distribution of the patients was roughly divided by the age year of 60. Nearly half the patients were younger than 60 years of age and the mean age for operation was 59,8 which is almost the same as in other reported studies where the median age for surgery was established (Champeaux et al. 2019, Zouaoui et al. 2018, Voß et al. 2017,).

4.2 Survival

The long-term outcome of the under 60 year age group was found to be slightly worse than that of the catchment population by a few years. This might be due to the fact that younger patients have generally longer life-expectancy and time to develop a recidive tumour that might affect the outcome, although this hypothesis was not found in a study where elderly (over 65 years) and younger (under 65) were compared for survival and recurrence rates (Brokinkel et al. 2017). This study also concludes that the long-term outcome for operated meningioma patients is comparable or even better to the overall catchment population in the age groups 60 to 69 years, 70 to 79 years and over 80 years and older. Therefore a surgical removal of meningioma does not seem to affect life-expectancy in the elderly population. Our finding was observed also in another study for the elderly population (Brokinkel et al. 2017). This may indicate two things. Operable meningioma patients are healthier than the catchment population because they have been evaluated to sustain an intracranial procedure by a surgeon and an anaesthesiologist. Patients who have been evaluated to *not* endure the procedure are excluded from this study. Secondly, the operated patients in Tampere University Hospital have a good possibility to not develop complications that result in premature death.

Our study also concludes that, rather surprisingly, patients with infratentorial posterior fossa tumours fared better after surgery than their supratentorial counterparts. Infratentorial tumours are usually in a more anatomically complex location closer to the vital brainstem and require more thorough consideration for surgery and therefore the operated infratentorial patients might have their tumours in a more preferable location than supratentorial patients. Although there is a discrepancy to another study that compared the survival of posterior fossa meningiomas to supratentorial meningiomas. (Corniola et al. 2019). Another study also notes that skull base meningiomas have a shorter time for retreatment for their condition, but did not find any difference in the overall survival. This study did not differentiate skull base meningiomas into posterior fossa infratentorial and supratentorial meningiomas (Meling et al. 2018). Non-skull base meningiomas were observed also to have a higher WHO grade than their skull base counterparts and seem to have a higher probability for recurrence than skull base meningiomas, although survival was not researched (Cornelius et al. 2013, Voß et al. 2017). Therefore Voß et al. even suggest that aggressive skull base meningioma operations in challenging locations are unnecessary. This study also found out that operated infratentorial tumours seem to be lower grade than supratentorial tumours. Substantial evidence for comparing infra- and supratentorial tumour patients survival seems to be lacking. Our study suggests that infratentorial patients have a better prognosis post-surgery in the short- and long-term than supratentorial patients.

The strengths of this study stem from the fact that the operated patients form a bias-free population Tampere University Hospital acts as the only neurosurgical department in the geographical vicinity. The life-expectancy numbers for the catchment area were gathered P only for the corresponding geographical area that the neurosurgical department serves and therefore are comparable.

The limitations of this study come from the fact that overall life expectancies for different age groups are rough a estimators gathered from the years 1996 to 1998 and don’t necessarily explain the whole picture. The portrayed lines only portray the average time for the 50% survival and is linear, therefore not giving an exact estimate for the rest of the life expectancy beyond that point. Simpson grading wasn't fully established in the data and in our study we only have two modes for the removal of the tumour. This study also has single-center study limitation and also forms a selection bias towards conservatively treated patients. The patients evaluated to be too morbid for craniotomies were not included to study matherial.

5 Conclusions

Older patients operated for meningioma in Tampere University Hospital have a good prognosis for life-expectancy in age groups over 60 years of age. Infratentorial tumours were also more frequent than in previous studies which might indicate that these tumours are more aggressively surgically treated than in most places. Therefore a well evaluated and the suitable elderly patient has a good prognosis from intracranial meningioma surgery. Patients with infratentorial tumours also have a better prognosis than their supratentorial counterparts. Authors recommend more studies about the these subjects.

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