MEASURING OUTCOMES FOLLOWING BRAIN TUMOR SURGERY: A REGISTRY BASED APPROACH

Erik Thurin

Main supervisor: Asgeir S. Jakola

Co-supervisors: Anja Smits and Sasha Gulati

Department of Clinical Neuroscience

Institute of Neuroscience and Physiology

Sahlgrenska Academy, University of Gothenburg

Gothenburg 2021

UNIVERSITY OF GOTHENBURG

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erik.thurin@neuro.gu.se

ISBN 978-91-8009-380-4 (PRINT)
ISBN 978-91-8009-381-1 (PDF)
http://hdl.handle.net/2077/68061

Cover illustration: En Utblick från ett Avtryck by Emma Husmark 2021

Printed in Borås, Sweden, May 2021
Printed by Stema Specialtryck AB, Borås

"All right," said Deep Thought. "The Answer to the Great Question..."

"Of Life, the Universe and Everything..."

"Is..."

"Forty-two," said Deep Thought, with infinite majesty and calm.

“Forty-two!" yelled Loonquawl. "Is that all you've got

to show for seven and a half million years' work?"

"I checked it very thoroughly," said the computer, "and that

quite definitely is the answer. I think the problem, to be quite honest with you,

is that you've never actually known what the question is.”

— Douglas Adams, The Hitchhikers Guide to the Galaxy

ABSTRACT

Meningiomas and vestibular schwannomas (VS) are generally slow-growing and benign brain tumors, with low rates of tumor-related mortality. Surgery is rarely the only viable treatment option. In cases where there is no clear difference between treatments concerning survival, it is essential for patients and caregivers to have realistic expectations of how surgery will impact "softer" outcome measures. Surgical complications, reduced ability to return to work, depression, and anxiety can all have a large impact on the quality of life for these patients. Yet the exact rates of these outcomes after surgery for meningioma and VS have received little attention and have not been established. The aim of this thesis was therefore to analyze the postoperative rate of complications, the rate of sick leave, and the use of antiepileptic, antidepressant, and sedative drugs. We have done this using a nationwide registry-based approach, comparing patients to gender and sex-matched healthy controls. No controls were used in Study I.

In **Study I,** we found that the most common short-term complications after meningioma surgery were new or worsened neurological deficits after surgery (14.8%), symptomatic hematoma (9.4%), any postoperative infection (6.4%) new-onset seizure (4.5%), and venous thromboembolism (3%). The 30-day mortality rate was 1.5%.

In **Study II,** we demonstrated that long-term sick leave is common after meningioma surgery. The rates of postoperative sick leave among the included 956 meningioma patients (aged <60) were 51% at one year after surgery and 43% at two years after surgery, while the rate for controls was stable at 14-16%.

In **Study III,** we investigated the impact of meningioma surgery on the use of antiepileptic drugs (AEDs), antidepressants, and sedatives. We found that the use of all three drug groups was elevated at the time of surgery and remained elevated two years after surgery, compared to controls, with a unique pattern for each drug group.

In **Study IV,** we investigated the rate of sick leave and the rate of antidepressant and sedative drug use for VS patients. The rates of patients on sick leave were 34% at one year after surgery and 25% at two years after surgery. The rate for controls was stable at 9-11%. VS patients did not differ significantly in use of antidepressant or sedative drugs compared to controls at two years before surgery, at index date or at two years after surgery.

In summary, we have demonstrated that meningioma surgery has a considerable impact on the rate of sick leave, use of antidepressants and sedative drugs, while this was not seen to an equal extent after VS surgery. Our results will aid caregivers and patients to better predict the clinical outcome after surgery.

SAMMANFATTNING

Varje år diagnosticeras ca 1400 nya hjärntumörer i Sverige (exklusive metastaser), vilket utgör runt 2% av alla nya cancerfall. Den största gruppen, en tredjedel av alla hjärntumörer, utgörs av meningeom. Detta är en godartad tumörform i de flesta fall, och de växer långsamt. De utgår från hjärnhinnan och brukar inte invadera själva hjärnan. Genom att trycka på hjärnans yta kan de dock ge allvarliga symptom. En annan godartad tumör, som utgör 6–8% av alla hjärntumörer och som på vissa sätt liknar meningeom, är vestibularisschwannom (VS). VS är en tumör som växer från det fettrika höljet runt hörsel- och balansnerven i skallbasen. I tidigt skede ger den hörselnedsättning och yrsel. Den kan också, om den blir tillräckligt stor, trycka på hjärnstammen.

Vid kirurgi för intrakraniella tumörer jämförs behandlingar ofta utifrån mått på dödlighet, eller risk för att tumören återvänder. För mer godartade tumörer som meningeom och VS kan dock dödligheten vara låg oavsett behandling. För dessa patienter är det viktigt med kompletterande mått på kirurgiskt resultat, såsom risk för komplikationer, långtidssjukskrivning och psykisk hälsa, vilket vi därför undersökt i denna avhandling.

I Svenskt Kvalitetsregister för Hjärntumörer har vi identifierat de vuxna patienter som opererats i Sverige 2009–2015 för meningeom och VS. Vi har länkat samman information från kvalitetsregistret med bland annat information från Försäkringskassan, Läkemedelsregistret och Statistiska Centralbyrån. Varje patient har jämförts med fem personer ur befolkningen som har samma kön, ålder, utbildningsnivå och boendekommun, så kallade matchade kontroller.

De vanligaste tidiga komplikationerna efter meningeomkirurgi är nytillkomna neurologiska bortfall (15%) och nytillkomna epileptiska anfall (5%). Andelen sjukskrivna två år efter meningeomkirurgi är 43%, jämfört med 16% för kontroller. Betydligt färre är sjukskrivna två år efter VS-kirurgi, där andelen är 25% jämfört med 13% för kontroller. Användningen av antidepressiva och sedativa läkemedel är högre för patienter med meningeom än för deras kontroller, både före och efter kirurgi, medan detta inte sågs för patienter med VS. Både för patienter med meningeom och VS steg användningen av antidepressiva och sedativa kring operationsdatumet mer än för kontroller.

Sammanfattningsvis har vi visat att en betydande andel patienter är sjukskrivna lång tid efter meningeomkirurgi, att användningen av antidepressiva och sedativa jämfört med kontroller är förhöjd både före och efter meningeomkirurgi samt att detta skiljer sig från VS-kirurgi, där andelen sjukskrivna är lägre. Efter VS-kirurgi sågs inte heller förhöjd användning av antidepressiva och sedativa. Våra fynd bidrar till att ge vårdgivare och patienter bättre möjligheter att förutsäga vilket postoperativt resultat som är sannolikt, och vägleda både kliniskt och inför framtida studier.

LIST OF PAPERS

This thesis is based on the following studies, referred to in the text by their Roman numerals.

I. Alba Corell, Erik Thurin, Thomas Skoglund, Dan Farahmand, Roger Henriksson, Bertil Rydenhag, Sasha Gulati, Jiri Bartek Jr, Asgeir Store Jakola. Neurosurgical treatment and outcome patterns of meningioma in Sweden: a nationwide registry-based study. *Acta neurochirurgica, 2019*.

II. Erik Thurin, Alba Corell, Sasha Gulati, Anja Smits, Roger Henriksson, J Bartek, Jr, Øyvind Salvesen, Asgeir Store Jakola. Return to work following meningioma surgery: a Swedish nationwide registry-based matched cohort study. *Neuro-Oncology Practice, 2020.*

III. Erik Thurin, Isabelle Rydén, Thomas Skoglund, Anja Smits, Sasha Gulati, Göran Hesselager, Jiri Bartek Jr., Roger Henriksson, Øyvind Salvesen, Asgeir Store Jakola. Impact of meningioma surgery on use of antiepileptic, antidepressant and sedative drugs: A Swedish nationwide matched cohort study. *Cancer Medicine, 2021*.

IV. Erik Thurin, Petter Förander, Jiri Bartek Jr., Sasha Gulati, Isabelle Rydén, Anja Smits, Göran Hesselager, Øyvind Salvesen, Asgeir Store Jakola. Mood and ability to work after vestibular schwannoma surgery: a nationwide registry-based matched cohort study on antidepressants, sedatives and sick leave. *Acta Neurochirurgica, 2021.*

CONTENTS

ABBREVIATIONS

ATC	Anatomic therapeutic classification
CBTRUS	Central Brain Tumor Registry of United States
CNS	Central nervous system
CN8	Cranial nerve VIII (the vestibulocochlear nerve)
CPA	Cerebellopontine angle
CSF	Cerebrospinal fluid
CT	Computed tomography
DNA	Deoxyribonucleic acid
DWI	Diffusion-weighted imaging
EBRT	External beam radiotherapy
FLAIR	Fluid-attenuated inversion recovery
FK	*Försäkringskassan* – the Swedish Social Insurance Agency
GDPR	General Data Protection Regulation
GTR	Gross total resection
IAC	Internal acoustic canal
LA	Labyrinthine artery
LGG	Low-grade glioma
HDR	Health data registry
IMY	Integritetsskyddsmyndigheten
MCF	Middle cranial fossa
MRI	Magnetic resonance imaging
NBHW	National Board of Health and Welfare
NTR	Near-total resection
NF2	The gene Neurofibromin 2 on 22q
NF2 disorder	The disorder Neurofibromatosis type 2
PET	Positron emission tomography
RTB	*Registret över totalbefolkningen* - the total population registry
RTW	Return to work
SCB	*Statistiska centralbyrån* – Statistics Sweden
SCR	Swedish Cancer Registry
SRS	Stereotactic radiosurgery
SSTR2	Somatostatin receptor 2
STR	Sub-total resection
VS	Vestibular schwannoma
WHO	World Health Organization

INTRODUCTION

WHAT IS A BRAIN TUMOR?

In short, the term brain tumor refers to all intracranial tumors. A distinction is made between primary brain tumors, which have an intracranial origin, and secondary brain tumors, which are intracranial metastases from extracranial cancer (most commonly from the lung, breast, skin or kidneys). [4, 5] When the term brain tumor is used in this thesis, it will refer to primary brain tumors, excluding metastases. Brain tumors can be further separated into intra-axial tumors, growing in the brain parenchyma, and extra-axial brain tumors, growing outside of the brain parenchyma but inside the cranium. A schematic illustration of the difference between intra- and extra-axial brain tumors is available in Figure 1. It can be argued that extra-axial brain tumors, since they do not grow in the brain parenchyma, should instead be called intracranial tumors and be differentiated from brain tumors. However, the term brain tumor is the established term also for extra-axial tumors, used by authorities such as the Central Brain Tumor Registry of the United States (CBTRUS) and by Swedish authorities such as the National Board of Health and Welfare (NBHW). Lastly, the term sporadic brain tumor refers to a brain tumor occurring in a patient with no known predisposition for that tumor type. In contrast, syndromatic tumors are related to a genetic syndrome.

BRAIN TUMORS – AN OVERVIEW

In Sweden, 1400 new primary brain tumors are diagnosed each year, corresponding to an annual incidence of 14 per 100 000. They constitute 2-2.5% of all new annual cancer diagnoses. [6] Brain tumors are a diverse group of tumors. They include some of the deadliest tumors known, but also tumors that can remain asymptomatic throughout an entire human lifespan. According to CBTRUS data, the most common primary brain and other central nervous system (CNS) tumors in adult patients are non-malignant meningiomas (38%), non-malignant pituitary tumors (17%), glioblastomas (15%), other malignant gliomas (10%) and nerve sheath tumors (9%). [1] Vestibular Schwannomas (VS) make up two thirds of the nerve sheath tumors, or 6% of all primary brain tumors. It should be noted that primary brain tumors can be measured, defined and grouped in different ways, and that the tumor incidence rates varies between studies.

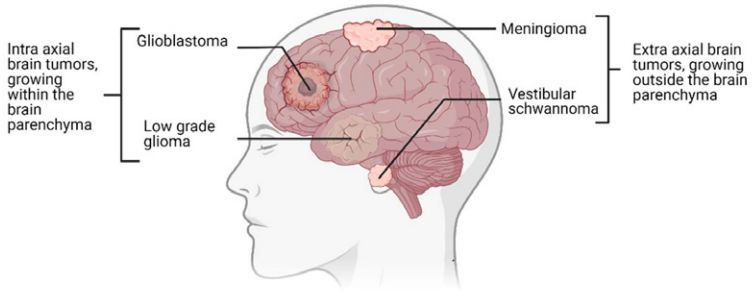

Figure 1, illustrating the difference between intra- and extra-axial brain tumors with examples. Image created using Biorender.com

The spectrum of diagnosed tumors depends on the age of the patient, with a distinct disparity between pediatric and adult patients. Medulloblastoma and pilocytic astrocytoma are the two most common brain tumors in children but are rare in adults. Conversely, the two most common brain tumor types in adults, meningioma and glioblastoma, are rare in children. [7] In this thesis we have focused on two of the most common extra-axial brain tumor types: meningiomas and VS. Compared to other brain tumors, these are relatively "good news". Brain tumors can be categorized as malignant or benign. The overall average 5-year survival in all malignant brain tumors is 36%, with the large group glioblastomas having the abysmal 5-year survival rate of 7%. On the other hand, meningiomas and vestibular schwannomas belong to the benign group, with an overall 5-year survival of 88% for non-malignant meningiomas, and 99% for nerve sheath tumors. A small subset of meningiomas (around 2% as we will discuss below) are malignant and have a 5-year survival of 68%. These estimates are all from the central brain tumor registry of the United States (CBTRUS). [8]

THE GRADING OF BRAIN TUMORS

Brain tumors are classified according to the World Health Organization (WHO) grading system, [9] based on histological appearance. The tumor grades are associated with outcome in the following way:

- Grade I: slow-growing, benign tumors, associated with long-term survival.
- Grade II: relatively slow-growing, relatively benign, but with potential to recur as a higher-grade tumor.
- Grade III: malignant, often recur as higher-grade tumors.
- Grade IV: fast-growing, aggressive and malignant tumors.

When distinguishing histologically between grades the general basis is the St. Anne-Mayo system, in which the number of morphologic criteria (nuclear atypia, mitosis, endothelial appearance, and necrosis) determines the grade. [10, 11] More specific grading criteria are also available for each tumor type, as will be outlined below. As the grading is based on histology performed on a tissue sample, it requires that the tumor is surgically resected or biopsied. [9]

HISTORICAL CONTEXT

In the 19th century, the only available method to localize a tumor was through a meticulous clinical neurological examination. In 1879, the removal of what was likely a meningioma was performed by William Macewen, localized through clinical examination alone. [12] This is sometimes credited as the first example of successful neurosurgical tumor removal. However, previous attempts had been made, including a resection by Laurence Heister in 1743. [13] Nevertheless, Macewen made great contributions to the field by introducing the antiseptic methods developed by Joseph Lister, increasing survival after brain tumor surgery. [12] An early attempt to venture past the meninges and resect a glial tumor was performed in 1884 by surgeon Rickman Godlee, guided by neurologist Hughes Bennet. While this was hailed as a great success at the time, the patient died four weeks later from meningitis and brain swelling. [14, 15] An impressive body of contributions were made by American surgeon Harvey Cushing in the first decade of the 20th century. While mortality rates of 30-50% after brain tumor surgery were common at the time, Cushing was able to achieve a mortality rate of 13%, in part by understanding the importance and physiology of intracranial pressure, and through improvements in surgical technique. He discovered and redefined many pathologic conditions, including the description and naming of meningiomas. Through Cushing, neurosurgery became more accepted, and Cushing is often quoted as the father of modern neurosurgery. [13, 15, 16]

Parallel to the surgical advances, important steps were taken towards more accurately verifying and locating brain tumors. After the discovery of x-rays by Wilhelm Röntgen in 1895, [17] early attempts were made to diagnose tumors on plain skull radiographs. Abnormal calcifications, aberrations in calvarial bone or a lateralized calcified pineal gland could sometimes be detected, as described by neuroradiological pioneer Schüller in 1912, [18] but for most brain tumor patients radiology was of little use. [19] A breakthrough was made when, inspired by a case report of air in the ventricular system following an accident in 1913, [20] Walter Dandy discovered that the ventricles could be visualized by deliberately injecting air, known as ventriculography. After his first description of this in 1918, [21] he went on to develop pneumoencephalography in 1919, where air is injected through a lumbar puncture into the subarachnoid space surrounding the brain.[22] The techniques were initially regarded with skepticism because they were painful, and had a low but relevant mortality rate. [19] A 1924 paper concludes that "the better the neurologist the less the need for ventriculography".[23] Spurred by this, the ambitious Egaz Moniz set out to find a better way to diagnose intracranial lesions and discovered the angiography in 1927. [24] Variations of these techniques became an important part of brain tumor diagnostics. However pneumoencephalography was made obsolete by the introduction of the Computed Tomography (CT), developed by Alan Cormack and Godfrey Hounsfield in the 60s and 70s.[25] While initially crude, the quality of CT images improved progressively and revolutionized medicine, awarding Cormack and Hounsfield the Nobel prize for their work in 1979. [26] The introduction of magnetic resonance imaging (MRI) was the next leap forward for brain tumor diagnostics. After a seminal article published by Paul Lauterbur in 1973, [27] the first MRI with a superconducting magnet was put in use in 1981. [26]

As the CT and MRI techniques have revolutionized healthcare, they have also changed the spectrum of brain tumors encountered in the clinic. Many of the small tumors detected today would not have been possible to find in the early 20th century. Because of improved imaging techniques, tumors are also found en passant in patients with no symptoms, termed incidentally discovered tumors. [28]

Since the early 20th-century neurosurgical tumor removal has become less dangerous. Techniques and knowledge concerning the avoidance and treatment of major complications, such as hemorrhage, infection and cerebral infarction, have caused the immediate surgical mortality to drop considerably. [15] Despite this, neurosurgical tumor removal is still a relatively dangerous endeavor, and it is important for caregivers to have accurate up-to-date information about what complications to expect.

As mortality rates have improved, the need to consider other effects of surgery has become increasingly relevant. Subtle side effects of surgery such as fatigue, personality changes and cognitive disturbances can severely impact the patient's life. If a subset of patients are left depressed or unable to continue their professional life after surgery, it is important that their surgeries were motivated. The point is particularly important for the relatively new phenomena in recent decades of small incidentally discovered tumors, for whom there is need to establish good guidelines, and to find the balance between achieving tumor control and avoiding overtreatment. [29-31]

EPIDEMIOLOGY

MENINGIOMAS

Meningiomas are tumors originating from the arachnoid cap (meningothelial) cells of the arachnoid membrane enveloping the brain. [32] The anatomic context of the arachnoid membrane is available in Figure 2. Meningiomas are extra-axial tumors, generally displacing and compressing the brain parenchyma rather than growing infiltratively. [4] They are reported to constitute 30-38% of all primary intracranial tumors.[8, 33-35] In Sweden 2009-2015 they constituted 32-34%. [36]

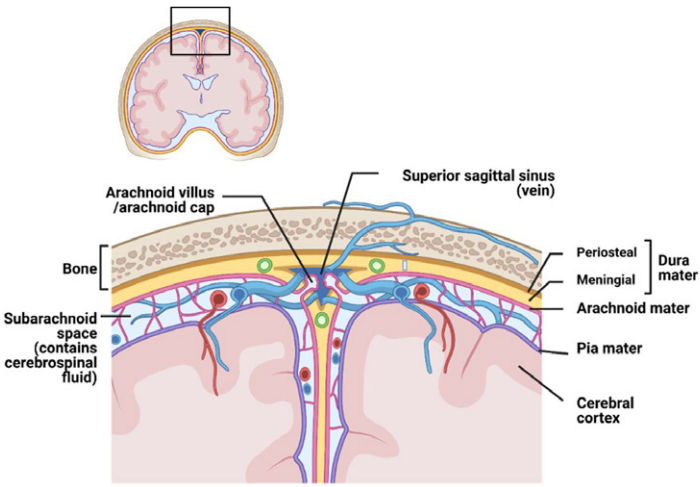

Figure 2, The anatomy of the arachnoid membrane and its relationship to adjacent structures. Image created using biorender.com

Meningioma incidence increases with age, particularly after the age of 65. Research on the epidemiology of meningiomas indicates that there is a reservoir of undiagnosed asymptomatic meningiomas among the elderly, as illustrated in Figure 3. While incidence rates of 42 per 100 000 in the age group 75+ are reported by the CBTRUS, [8] the rate of clinically healthy 75 year-old women harboring an undiagnosed asymptomatic meningioma has been estimated to be over 50 times higher, 2.8%, [37] and rates of undiagnosed asymptomatic meningiomas of 2-3% have been reported in autopsy studies.[38] In a population of younger patients (mean age 63 years) the rate was 0.9%. [39] Consequently, the rate of asymptomatic meningiomas that are found would be expected to increase almost linearly with the proportion of elderly patients undergoing an MRI examination of the cranium. Findings in the Norwegian population support this point, demonstrating a correlation between the number of brain tumors diagnosed and the number of head MRIs performed, at a rate of 0.004 new incidental brain tumors for each additional MRI per 100 000 persons, annually. The correlation was valid for extra-axial but not intra-axial tumors, [40] which may indicate that that most brain invading tumors will eventually cause symptoms, while many extra-axial will not. In line with this, the incidence of meningiomas has increased in the past decade, with an increasing proportion of meningiomas found incidentally. [40]

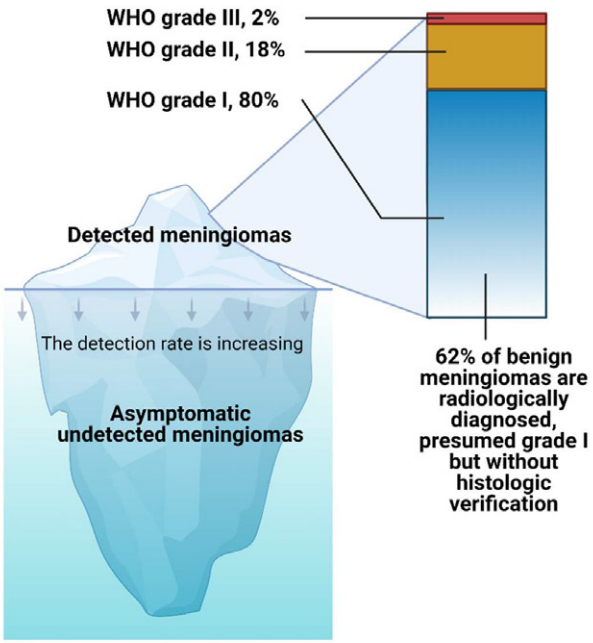

Figure 3, detected meningiomas in the elderly as the "top of the iceberg", separated into WHO grades. Based on data from CBTRUS 2020. [1] Note that some higher grade meningiomas are also diagnosed radiologically, and that the iceberg analogy is not valid for younger patients. Image created using Biorender.com

Meningiomas are 2-3 times more common in women, peaking at the time of menopause.[33, 41] There is no consensus on the reason for this. [42] A correlation to sex hormones would explain why the difference in meningioma incidence between men and women peak around the age of menopause (where the ratio is around 1:3) and subsides after that age, as demonstrated in Figure 4. Estrogen receptors and progesterone receptors are commonly expressed in meningiomas, but the similar rate of receptor expression in male and female meningioma patients has been interpreted as evidence that differences in receptor expression do not cause the difference incidence between sexes. [43] No increased meningioma frequency has been demonstrated as an effect of hormone replacement therapy, which would be expected if meningioma incidence was directly correlated to sex hormones. [44, 45] While benign meningiomas are more common in women, malignant meningiomas are slightly more common in men.[46]

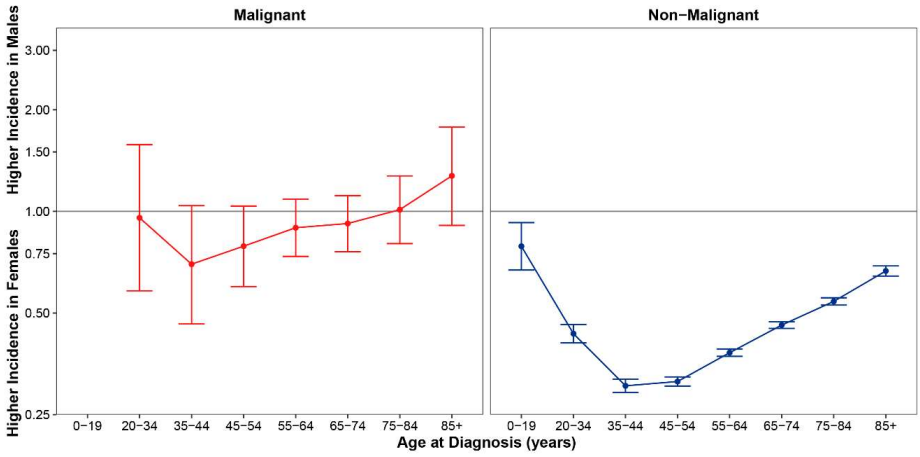

Figure 4, Incidence Rate Ratios for Meningioma with 95% Confidence Intervals by Behavior, Sex (Males:Females), and Age Group. Reproduced with kind permission from Carol Kruchko, president of CBTRUS. From CBTRUS Statistical Report supplementary material Figure 14. [1]

The histologic differences between meningioma WHO tumor grades will be discussed under *Histology* below. The majority of meningiomas are benign and are classified as WHO grade I. According to CBTRUS data on meningiomas with a histological diagnosis (i.e. surgically treated meningiomas) the rate of benign meningiomas (WHO grade I) is 80.4%, while the rate of atypical meningiomas (WHO grade II) is 17.9% and the rate of anaplastic (WHO grade III) is 1.7%. [1] As will be discussed, the rate of WHO grade II meningiomas has recently increased, to a large extent because of changes in classification. In data from the Swedish cancer registry, the rate of malignant meningiomas (WHO grade III) was around 1% during the studied years 2009-2015. [36]

Most meningiomas are sporadic, occurring without a known cause. One of the few risk factors that have been identified is ionizing radiation. Low-dose radiation therapy in childhood increases the risk for a meningioma to develop in adulthood [47] as first reported in the 60s in a cohort of Israeli patients having received low-dose irradiation for tinea capitis as children.[48] The average time from irradiation to tumor occurrence has been reported to be longer, 35 years, in cases of low dose (<10Gy) irradiation compared to 19-24 years in patients receiving high dose (>20Gy) irradiation. [49] Meningioma incidence is consequently also higher in atomic bomb survivors.[50] Radiation-induced meningiomas seem to have different pathogenesis than sporadic and display many separating features: they occur in younger patients, have higher recurrence rates and rates of multifocal tumor growth, and are related to a different set of genetic alterations. [47] Radiation sufficient for inducing meningiomas is also associated with local alopecia and with calcifications in vessels in the tumor vicinity. Because of the rising incidence of meningiomas in the 00s, concurrent with a rise in cell phone use, it has been debated if cell phone use could induce meningiomas. After several large-scale investigations, current evidence does not support the notion that cell phone use increases the risk for meningiomas.[51] The current consensus is that the increased incidence was related to an increased rate of detection. [52] Genetic predisposition may also give rise to meningiomas in a small subset of patients, mainly due to Neurofibromatosis type 2 (NF2 disorder), as will be discussed below. [53]

VESTIBULAR SCHWANNOMAS

Vestibular Schwannomas (VS) are benign tumors originating from the myelin-producing Schwann-cells insulating the vestibulocochlear nerve, the eighth cranial nerve (CN8). [54, 55] Historically, the tumor has also been referred to as acoustic neuroma. VS is now the preferred term, as the tumor lacks neural origin, and since more than 90% of VS arise in the vestibular (inferior) portion and not the acoustic (superior) portion of the nerve. [56] While it has previously often been claimed that VS originate in the Redlich-Obersteiner zone in the internal acoustic canal (IAC), where glial myelinization is replaced with Schwann-cells, [56] this has been refuted - VS can originate anywhere along CN8. [57]

CT and MRI neuroimaging has changed the spectrum of newly discovered VS into a smaller and more common tumor entity in the past decades. During a 30-year period the Danish annual incidence increased from 0.3 to 2 per 100 000 while the mean size decreased from 30mm to 10mm (1976-2008 and 1979-2008, respectively). [58] Similar to the situation for meningiomas, the presumed reason for the increased incidence is more incidental findings of asymptomatic tumors, as demonstrated by the previously mentioned Norwegian study finding correlation between the use of MRI and the rate of intracranial tumor diagnoses.[40] The rate of VS varies between countries, likely depending both on genetic factors and differences in health care systems. [59] The CBTRUS estimates the annual incidence of VS to 1.09 per 100 000. [60] In the US, Caucasian populations have a higher incidence compared to Black, Asian or Hispanic populations, but it is unclear to what extent this reflects genetic differences and to what extent it represents racial inequalities in MRI-availability.[61] Similar to meningioma, most VS are sporadic and occur without a known cause.

VS are more common in elderly patients, with the CBTRUS reporting a VS rate of almost 3 per 100 000 per year in the 65-74 year age group.[60] While the overall incidence of VS is around 1-2 per 100 000, there is data supporting the notion that the prevalence of undiagnosed asymptomatic VS may be considerably higher, such as a German autopsy-series reporting 60 VS in a series of 54946 patients (109 per 100 000),[62] and a recent study estimating prevalence to 69 per 100 000 adults (212 per 100 000 among those older than 70).[63] This indicates that the prevalence of asymptomatic or oligosymptomatic VS may depend on the rate of neuroimaging.

CLINICAL PRESENTATION

The symptoms of meningiomas depend on their location and size. Around 15-20% of meningiomas are found along the superior sagittal sinus, around 20-35% along the cranial convexity, and around 10% at the falx cerebri. Rarely meningiomas also develop from intraventricular meningothelial stroma cells in the choroid plexus. [3, 64] The distribution is outlined in Figure 5.

Symptoms of increased intracranial pressure (such as headache and nausea) are common in meningioma patients, and headache is the presenting symptom in 48% of meningioma patients. [65] Meningiomas can also compress adjacent brain or nervous tissue, causing focal neurological symptoms depending on the part of the brain being compressed. Focal neurological symptoms are the presenting symptom in 49% of convexity meningiomas, including motor symptoms or sensory symptoms if the tumor is adjacent to primary motor or sensory areas. Cranial nerve symptoms are instead common in skull base meningiomas, constituting the presenting symptom in 39% of these patients. Anosmia is common for olfactory groove meningiomas, while meningiomas adjacent to the chiasma opticum can cause bipolar hemianopia. [65] In about 30% of cases an epileptic seizure is the presenting symptom leading to a meningioma diagnosis. Seizures in meningioma patients is associated with edema adjacent to the tumor and are less common in tumors of the skull base. Seizures are also less common in male than female patients. [66]

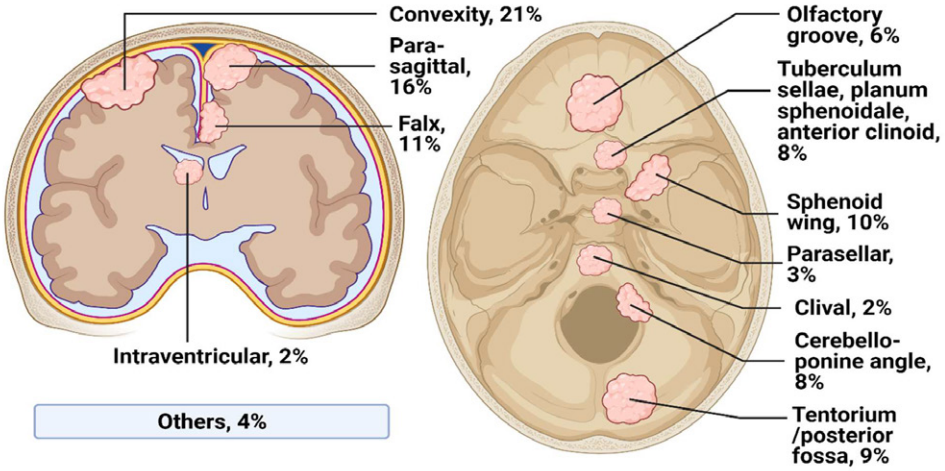

Figure 5, The most common locations of intracranial meningiomas, and the percentage of all meningiomas found at each location, with coronal view illustrating supratentorial meningiomas (left) and superior view of the bony skull base illustrating skull base meningiomas (right). Percentages are based on data from Sun *et al.*, 2020. [3] Image created using Biorender.com

Other symptoms are less noticeable. Change in personality, fatigue, loss of motivation or depressive symptoms can be the result of local compression in some meningioma patients, especially for olfactory groove meningiomas or those of the frontal falx. [33] The medial prefrontal cortex has a crucial role in regulating behavior, both its orbitofrontal, dorsolateral and limbic (anterior cingulate) parts, and is believed to be a pivotal structure for regulating depressive behavior. [67] Similarly, the mesolimbic dopamine pathway and its associated cortical regions (mainly orbitofrontal and anterior cingulate cortex) are important for action selection, addiction and motivation. [68] An overview of some of the main neural loops of the frontal lobe is available in Figure 6. Although further research is needed to fully understand the circuitry behind complex feelings like depression or motivation, it is not unreasonable that compression of these areas can have psychologic effects. However, while olfactory groove meningiomas constitute 6% of all meningioma cases, [3] fatigue and depression are reported to be a relatively common symptom, with 58% of patients having a very high result on one of the subscales of an instrument to measure fatigue in a recent report. [29] Thus, it is likely that not all cases of fatigue or depressive symptoms in meningioma patients are caused by local compression. The relationship between depression, fatigue and meningioma has only been directly investigated in a few studies. A recent review of the subject concluded that further research is needed. [29]

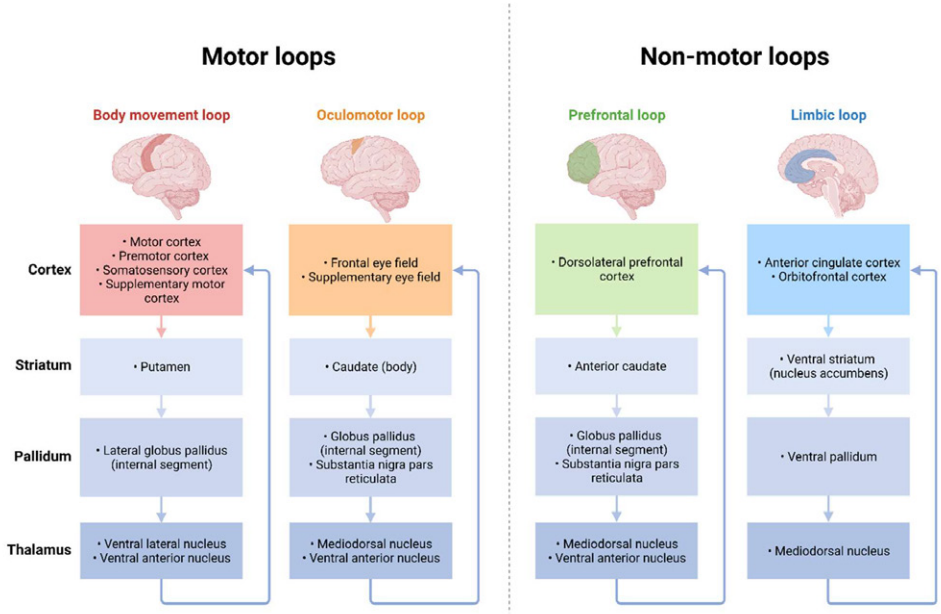

Figure 6, illustrating that different frontal lobe regions are involved in separate networks of neurons with diverging functions. While tumors compressing motor or oculomotor regions can cause motor symptoms, compression of limbic or prefrontal regions can cause more complex symptoms. Based on a review of frontal lobe functional neuroanatomy. [2] Image created using Biorender.com

RADIOLOGICAL FINDINGS

There are several useful radiological signs for diagnosing meningiomas. Supratentorial meningiomas can often be detected on a contrast-enhanced CT, but the CT-diagnosis is not always certain. Contrast-enhanced MRI has a better tissue resolution and is considered the gold standard for diagnosing meningiomas radiologically. The typical meningioma is rounded and has a wide contact with the dura. As meningiomas are extra-axial tumors outside the blood-brain barrier, they are homogenously contrast enhancing tumors. [52] The dura mater around the tumor is typically thickened (known as the dural tail sign). The radiating pattern of vessel distribution within a meningioma is known as the spoke wheel sign. MRI-images of a falx meningioma is provided in Figure 7. It has been proposed that when a meningioma is suspected, the following five signs indicate that it is some other form of tumor: lack of dural tail, osseous destruction, hypo- or hyperintensity of the tumor on T2, and leptomeningeal spread.[69] Some meningioma subtypes, including microcystic meningiomas, have particularly distinguishing features on MRI. [70]

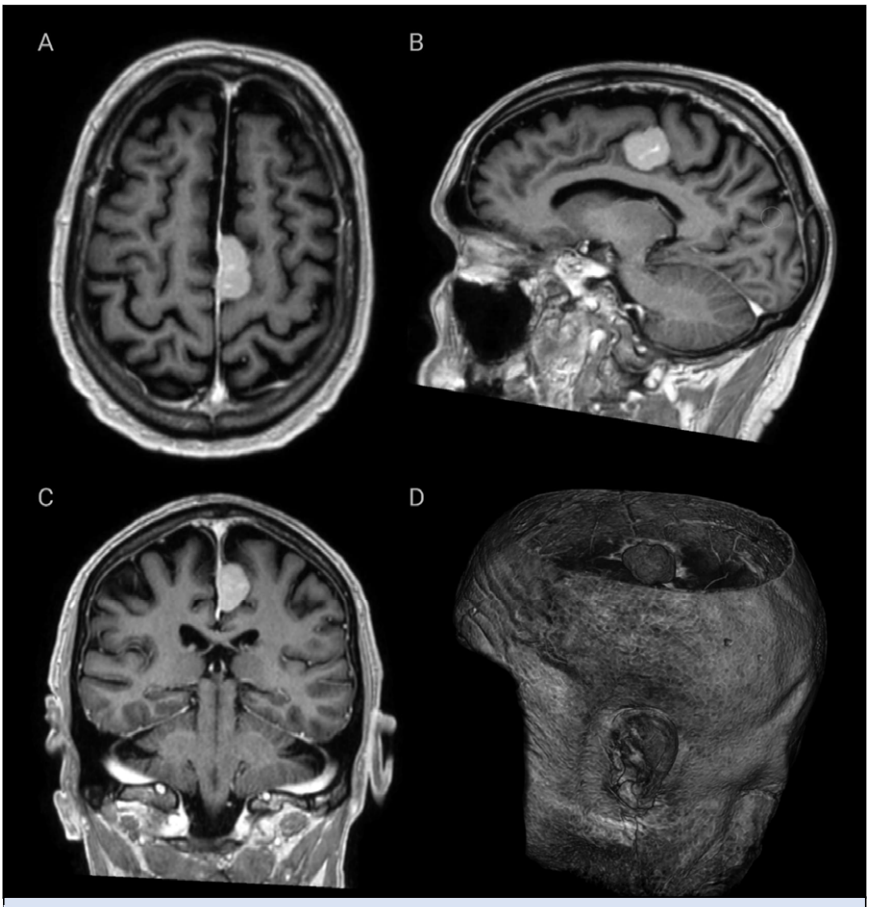

Figure 7, MRI with gadolinium-enhanced T1 images of an incidentally discovered asymptomatic falcine meningioma: A) transverse image, B) sagittal image, C) coronal image, D) 3D reconstruction. Note the dural tail sign on transverse and coronal images.

Peritumoral brain edema on MRI is present in 38%-67% of meningiomas. The relationship between edema and meningioma grade or subtype is complex. Peritumoral brain edema has been shown to be mainly associated with "uncommon type" grade I meningiomas (angiomatous, secretory, microcystic and lymphoplasmacyte-rich, psammomatous). It is rare in "common type" grade I meningiomas (meningothelial, transitional, fibrous), and intermediately frequent in higher-grade meningiomas. [71] Note that the mentioned meningioma subtypes, and features of these subtypes, will be categorized and described under the *histology* and *genetics* sections below.

Besides peritumoral edema, diffusion-weighted imaging (DWI) has been shown to be of value for classifying meningiomas radiologically, although with low sensitivity and specificity. [72] There is also ongoing work using radiomics (extracting image features, such as patterns in the tumor, using computer algorithms, and often also analyzing these patterns using machine learning) to distinguish between meningioma grades [73] but as of today no useful tool or test based on radiomics is available clinically. In a meta-analysis investigating radiological signs of growth in meningiomas, calcification was negatively and T2 intensity was positively associated with a high tumor growth rate. [74]

The use of radiolabeled somatostatin receptor 2 (SSTR2) ligands, such as positron emission tomography (PET) with radioligands DOTATATE or DOTATOC, are useful for verifying a meningioma diagnosis in unclear cases, [75, 76] and has a higher sensitivity than the current gold standard, contrast enhanced-MRI.[77] They can also aid in visualizing the border between a meningioma and healthy skull base structures, both before surgery and when planning a radiation-based intervention (discussed below). [52]

In an interesting longitudinal study, 17 patients diagnosed with NF2 disorder were followed over a mean time of 33 years. The patients had a total of 182 extra-axial brain tumors, and the study demonstrated that the growth patterns of meningiomas are rarely fixed. In 60% of meningiomas a saltatory growth pattern was seen, with periods of growth interrupted by periods of quiescence, without growth. The mean quiescence period was 2 years long. [78]

HISTOLOGY

While it is possible to diagnose meningiomas radiologically, current classification and grading are based on histological examination. Thus, classification requires surgical treatment or biopsy. This is relevant, as only 38% of benign meningiomas and 79% of malignant meningiomas have a confirmed histological diagnosis according to the CBTRUS, and the rate of radiologically diagnosed meningiomas is rising. [1]

Meningiomas are classified according to the WHO grading system, into WHO grade I, II or III. [9] In the 2007 edition, WHO lists nine subtypes under meningioma (grade I): meningothelial, fibrous, mixed, psammomatous, angiomatous, microcystic, secretory, lymphoplasmacyte-rich and metaplastic. Three subtypes are listed under atypical (grade II): choroid, clear cell and atypical. Lastly, three subtypes are listed as anaplastic/malignant melanoma (grade III): papillary, rhabdoid and anaplastic (malignant). [32, 79]

The WHO grading of meningiomas is based on four criteria: cytological atypia, mitotic activity, microvascular proliferation (endothelial cell proliferation) and necrosis. [9, 52] A meningioma is considered atypical (grade II) if it meets three of the following five criteria:

- spontaneous necrosis
- sheeting (a change in cytological architecture, with loss of the whorling or fascicular structure
- prominent nucleoli
- high cellularity
- small cells (high nuclear:cytoplasmic ratio in tumor clusters)

A mitotic count of 4-19 per 10 high-powered fields (HPF) is a criterion that alone is sufficient to diagnose a meningioma as atypical (grade II). A grade II meningioma is not considered malignant but has a higher mortality and recurrence rate than a grade I meningioma. If a meningioma with benign histology (grade I) demonstrates invasion into the adjacent brain, it has been shown to have a recurrence rate and mortality similar instead to that of atypical (grade II) meningiomas.[80] Therefore, since the publication of the 2016 WHO classification, tumors demonstrating invasion are classified as grade II tumors. [9] The change has sparked controversy, however, as the methods to determine invasiveness both macroscopically and microscopically are somewhat subjective, potentially resulting in a problematic selection of grade II tumors. [81, 82] Reliable histological analysis of invasiveness is difficult, especially if the brain-tumor interface is not included in the sample, and thus it has been proposed that the new classification requires techniques for intraoperative sampling to be adapted, such as taking several samples and including the brain-tumor interface. [83, 84]

A diagnosis of anaplastic meningioma, grade III, requires either ≥20 mitoses per 10 HPF or a loss of meningothelial differentiation that give the tumor a structure resembling sarcoma, carcinoma, or melanoma. [85] Meningiomas with a rhabdoid or papillary appearance are also, due to poor prognosis, considered anaplastic, grade III. These meningiomas are all considered malignant.[86, 87] The association between increased WHO grade and decreased overall mortality and recurrence-free survival has been repeatedly validated. The overall 5-year survival in meningioma patients has been estimated to be 78% in grade II tumors and 44% in grade III tumors. [88]

Although meningiomas can often be histologically diagnosed using ordinary hematoxylin and eosin staining they can, in some cases, be hard to distinguish from other brain tumors. The marker with the best known sensitivity is the Somatostatin 2 receptor (SSTR2), expressed in almost 100% of meningiomas, which can be very useful when the diagnosis is unclear. [89] Other useful markers are STAT6 and CD34. [90] Estrogen receptors and progesterone receptors are common in meningiomas but uncommon in meningioma-mimics and can also be useful markers in some cases. [43]

The histologic appearances of a grade I and a grade II meningioma are provided in Figure 8. As histologic grading of meningiomas has a degree of interrater variability, with discordance rates of around 20% for critical aspects like mitotic count, and since the histologic appearance may not predict future tumor behavior optimally, [82, 91] there is interest in establishing a classification system based on genetic or molecular characteristics. A landmark 2017 study reported the results of performing whole genome methylation analysis for 497 meningiomas. Unsupervised clustering based on their data generated six distinct groups, of which three contained mostly grade I meningiomas and had a low rate of tumor recurrence, two groups contained mostly grade II meningiomas and had worse survival and recurrence free survival. Lastly, one group contained mostly grade III meningiomas and had the worst survival. [92] The findings have generated interest in molecular classification of meningiomas. Recent genetic advances have presented several methods for classifying a tumor genetically, but such genetic information is currently not a part of the WHO classification system for meningiomas. Molecular classification may align better with the underlying biological properties of tumors than the current WHO classification, and it has been proposed that this will improve our ability to predict the best treatment course. [93] However, analyzing methylation patterns is still a resource-intense undertaking. Technical developments to make it easier and less expensive might be necessary for methylation-based classification to see widespread clinical use for meningioma patients. [94]

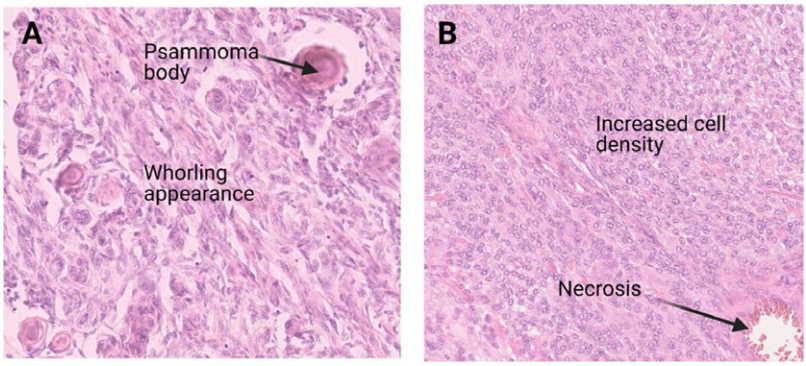

Figure 8, histologic slides of meningioma tumors stained with hematoxylin and eosin. A) WHO grade I meningioma with psammoma bodies and cell-whorls and syncytial patterns, B) atypical (WHO grade II) meningioma with increased cell density and necrosis.

GENETICS

The neurofibromin 2 (NF2) gene on the long arm of chromosome 22 (usually at band q12 but sometimes q11 or q13) and the protein produced by this gene, Merlin, have consistently demonstrated a crucial role in the development of meningiomas. Patients with the syndrome Neurofibromatosis type 2 (NF2 disorder) have monoallelic dysfunction (through, for instance, deletion or mutation) in one of their NF2 genes. Around 50% of patients with NF2 disorder are diagnosed with a meningioma during their lifetime, with as much as 80% in the oldest age groups.[53] But the NF2 gene is involved in the tumorigenesis also in patients without NF2 syndrome, in around half of sporadic meningiomas a local dysfunction in the NF2 gene can be demonstrated. [95, 96] The rate of NF2 mutations varies between meningioma subgroups. In grade I meningiomas, an NF2 mutation is seen in most fibrous, psammomatous and transitional meningiomas, while it is generally not seen in meningothelial, microcystic and secretory meningiomas. [32] AKT1 mutations are seen in several subtypes, most commonly in the subtype metaplastic meningiomas (grade I).[52] One subtype with a particularly clear genetic profile is secretory meningiomas (grade I), which appear never to have NF2 mutations, but to always have mutations in the two genes KLF4 and TRAF7. [97] The ELAV4 gene may be related to male, but not female, meningioma development [98] TERT mutations are present in approximately 8% of meningiomas. While TERT mutations do not currently impact the grading of meningiomas, they are associated with considerably worse survival in meningioma patients. [99, 100]

An initially benign meningioma will, as it progresses towards malignancy, accumulate genetic changes. Loss of function of the NF2 gene, through mutation or deletion, is considered the usual first step, generally causing a grade I meningioma. A subsequent deletion on the short arm of chromosome 1 may be a common second step towards atypia, followed by several other chromosomal deletions or alterations. Loss of genetic material in the following regions is common for atypical (but not benign) meningiomas: 14q, 10q, 8q, 7p, 21q, 19, 9q34, and 4p16. [101]

A wide range of further genetic alterations separates anaplastic or malignant meningiomas (grade III) from atypical (grade II). [32] Transcriptional profiling of anaplastic meningiomas revealed two genetic subtypes with diverging survival rates, illustrating the benefits of a genetic basis for outcome prediction. Among the mutations in the genetic group with worse a prognosis were mutations in the gene complex SWI/SNF. [102]

The genetic variations of meningiomas are also related to location. Convexity meningiomas are derived embryonically from neural crest cells, while skull base meningiomas are derived from mesodermal progenitor cells, with potential relevance for the distribution of mutations and prognosis. [103] Medial skull base meningiomas have a distinct lack of NF2 mutations, and are slow-growing, benign, and chromosomally stable compared to other meningiomas. [104, 105] Meningiomas of the medial anterior skull base are associated with SMO mutations. [32] In addition, post-zygotic mutations can result in mosaicism of NF2 dysfunction, with a population of cells showing NF2 abnormalities while other tissues are unaffected. Mosaicism of the NF2 gene is believed to be present in a subset of sporadic meningiomas. [106]

CLINICAL PRESENTATION

The initial symptoms in VS patients are presumably related to compression of the vestibulocochlear nerve. The anatomic context of the vestibulocochlear nerve is illustrated in Figure 9. Cochlear symptoms, like hearing loss (90-94%) and tinnitus (55-83%), as well as vestibular symptoms, like vertigo attacks or imbalance (49-61%), are common. The combination of hearing loss and tinnitus (34%), headache (18%) and light headedness (18%) are also reported. [107, 108] The tinnitus in VS can persist even if the nerve is severed, and has been suggested to be caused by deafferentation. [109] Large VS can compress brain stem structures, which can result in hydrocephalic symptoms, [110] or cranial nerve symptoms, typically from the trigeminus nucleus.[108] While symptoms of brain stem compression from large VS can be relieved by surgical resection, tinnitus and hearing loss are generally not, but progress can be slowed. [111] An increasing proportion of newly discovered VS patients are asymptomatic. Some VS never grow to cause symptoms,[112] and around 4% of VS shrink on follow-up.[113, 114]

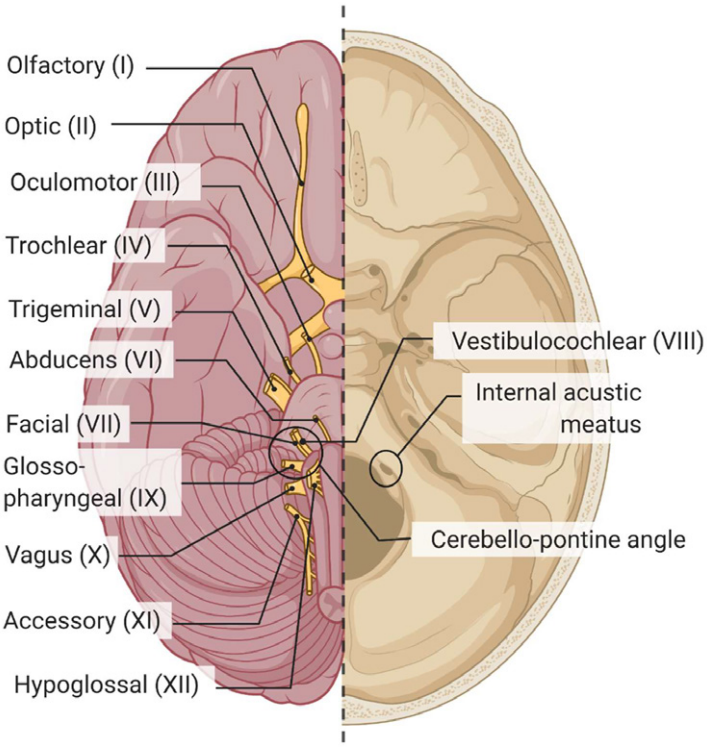

Figure 9, schematic illustration of cranial nerve anatomy. Inferior view of the brain and brainstem with numbered cranial nerves (left) and superior view of the base of skull (right). Image created using Biorender.com

Hearing loss, tinnitus, and balance disturbances are symptoms that are common in the elderly population. Therefore, establishing proper and efficient guidelines for patient selection in this group is an important issue. In Sweden, no clear national guidelines exist for when to suspect VS in primary care, or how to investigate symptoms related to VS. Regional recommendations from southwestern Sweden recommend referral to an otorhinolaryngologist in cases of unilateral hearing loss, and request that Weber and Rinne tests, ear examination and an audiogram have been performed before the referral. [115] Non-imaging screening methods in suspected VS, such as pure-tone audiometry, auditory brainstem response, electronystagmography, caloric irrigation have been explored, but have low accuracy compared to radiology. [116] Since 2010, local guidelines in Sweden recommend, based on a 2009 systematic review, [117] that skull base MRI without contrast should be the first line of investigation when a VS is suspected in secondary care. This approach has been criticized, based on calculations that in practice only around 2% of exams discover a VS. [118] According to a systematic review providing evidence-based guidelines, MRI screening is recommended in patients with unilateral hearing loss verified by audiometry, unilateral tinnitus and sudden deafness, with a discovery rate of <1% for tinnitus but >3% for sudden deafness. [119]

RADIOLOGICAL FINDINGS

Contrast-enhanced MRI is today the gold standard for diagnosing VS radiologically. The essential protocol for detecting VS and for post-operative follow-up imaging is the T1 weighted contrast-enhanced images. In addition to this, T2-weighted images, DWI and fluid-attenuated inversion recovery (FLAIR) sequences are useful to distinguish VS from differential diagnoses or tumor mimics. [120] An annotated T2-image of the relevant anatomy is provided in Figure 10.

The typical small VS grows inside the IAC. Inwards growth along the nerve through the IAC cause larger tumors to protrude into the subarachnoid space of the cerebellopontine angle (CPA). As this region is occupied by several important structures, including the pons, a sufficiently large VS can displace the pons and upper part of the medulla oblongata. Distortion of these anatomical structures by a VS can cause obstructive hydrocephalus. More rarely, communicating hydrocephalus can also be caused by VS, presumably through elevated protein levels in CSF. [121] The labyrinthine artery (LA), supplying arterial vascularization to the inner ear, runs along the vestibulocochlear nerve in the internal auditory canal. The branching of the LA into the cochlear, vestibulocochlear and vestibular arteries occurs, with considerable anatomic variation, in the area of the vestibular ganglion. Thus, through compression of the LA, VS can interfere with the vascular supply of the inner ear. [122]

According to the 2019 guidelines from the VS task force of the European Association of Neuro-Oncology (EANO), the radiological diagnosis of vestibular schwannoma is made with MRI, and histological verification is not always necessary as many VS present with a location and radiological appearance that are pathognomonic for VS. [120] Indeed today around 50% of VS are diagnosed radiologically, and this rate is likely to increase further. [8]

Although the majority of VS demonstrate a slow and continuous growth, this is not always the case. In 132 patients with vestibular schwannoma identified on radiology and observed for a mean time of 5 years, 60% had the same size, 5% shrank and 35% grew. [123] It has also been shown that VS can alternate between slow growth and long periods of quiescence. [78] When diagnosed radiologically, a sign proposed to predict tumor shrinkage on follow-up for VS is if multiple curves in the outline of the tumor are detected, giving it a corrugated or festooned appearance. [114]

A widely used system for radiological stratification of VS is the Koos grading system, ranging from small intracanalicular tumors (grade I), small tumors protruding into the cerebellopontine angle but with no brainstem contact (grade II), tumors occupying the cerebellopontine cistern with brainstem contact but which do not displace the brain stem (grade III) and large tumors displacing the brain stem (grade IV). [124] The system has a good intra- and inter-rater agreement. [125]

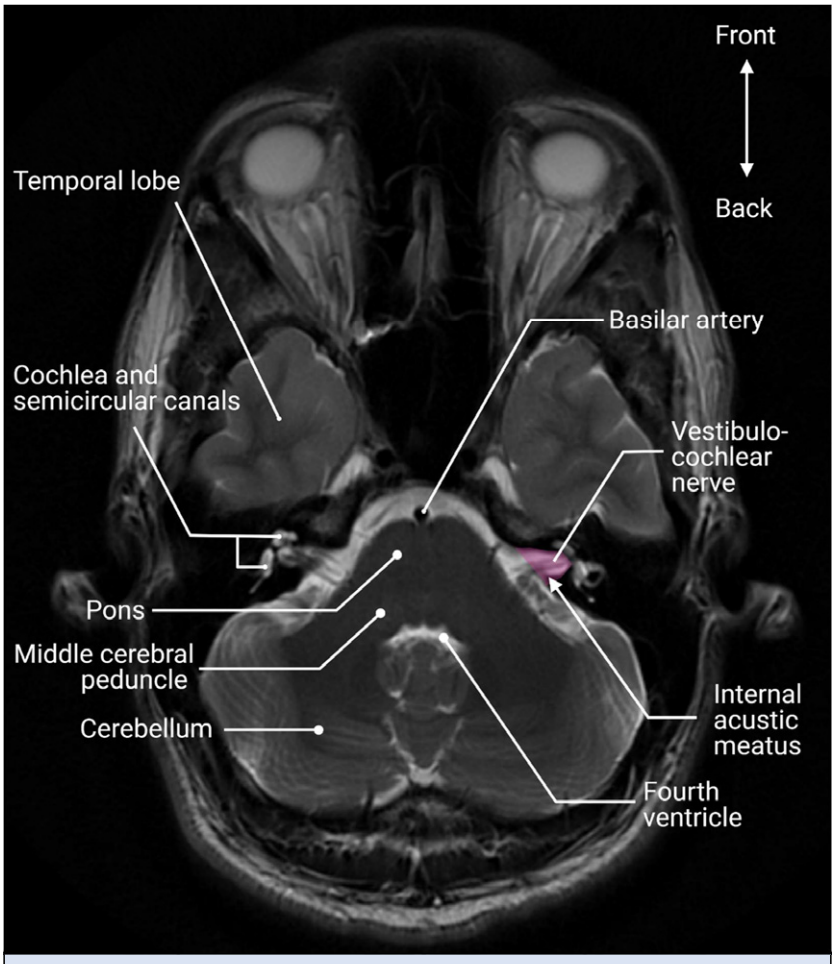

Figure 10, demonstrating normal anatomy of a patient without VS, T2 MRI sequence without contrast. On a T2 image like this, water is white and bone is black. White structures close to pons consist of cerebrospinal fluid (CSF) in basal cisterns. A VS growing in the IAC will eventually bulge into the cleft of CSF separating the pons from the IAC, and eventually compress the pons. This can in turn compress the fourth ventricle, causing obstructive hydrocephalus. Note that the facial nerve (VII) runs close to the vestibulocochlear nerve in the IAC.

HISTOLOGY

VS are benign (WHO grade I). They have an appearance characteristic for Schwannomas on hematoxylin and eosin staining, with a whirling palisaded appearance and Verocay bodies. [4] Malignant transformation has been described in case reports but is extremely rare.[126] As CPA tumors are rather uncommon, and VS have many distinguishing features, the differential diagnoses are often quite limited. VS, like other Schwannomas, are positive to S-100 antibodies, which can be useful when distinguishing VS from other tumors of the CPA using immunohistochemistry. [127]

GENETICS

The majority, around 90-95%, of VS are sporadic, while 5-10% are secondary to NF2 disorder. As with meningiomas, the single most important genetic event in the development of sporadic VS is the inactivation or loss of the NF2 gene on chromosome 22q12, occurring in 77% of all sporadic VS. [128] As the NF2 product Merlin is absent in VS tumor cells on histological examination, it has been proposed that the development of VS precludes inactivation of NF2 in some way, either through uni- or biallelic loss of 22q, point mutations or epigenetic changes. [4, 129, 130] Bilateral vestibular schwannomas are diagnostic of NF2 disorder, [4] and it has been shown that 90% of patients with the NF2 disorder develop bilateral VS. [131] While VS are very common in patients with NF2 disorder, they also have a higher risk for other CPA tumors, and in some NF2 disorder patients a neurofibroma is mistaken for a VS. [132]

NON-SURGICAL TREATMENT

The main non-surgical treatment alternative for meningiomas is irradiation. Conventional fractioned external beam radiotherapy (EBRT) has long been both an alternative in meningiomas not possible to resect surgically and as an adjuvant treatment after surgery. EBRT can also be used for meningiomas that recur after previous surgical treatment, or as an adjunct in meningiomas with a higher tumor grade. The delivered dose is often around 50 Gy for grade I meningiomas and 60 Gy for grade II-III meningiomas. The irradiation is usually delivered in 1.8- 2Gy per session over 25-30 sessions. An alternative to EBRT is stereotactic radiosurgery (SRS). While EBRT delivers the planned dose throughout many sessions, SRS instead delivers the dose during a single session or up to five sessions. EBRT traditionally utilized radiation from one angle, but in a modern setting both EBRT and SRS techniques use confocal beams from many angles all directed at the tumor center, to allow the dose delivered to the tumor center to be high while keeping the dose to adjacent tissues relatively low. [133] For superficial tumors proton beam radiation has advantageous physical properties, [134] and has shown promising results in treating selected meningioma cases. [135]

When treating WHO grade I meningiomas with SRT, a delivered marginal dose of less than 10 Gy has been associated with worse outcome,[136] while a marginal dose >16 Gy was not associated with better outcome compared to doses <16. [137] Thus, a delivered marginal dose around 12-16 Gy is often recommended. The main limitation of SRS is limited in the size of the tumor that can be treated. SRS treatment alone has proven effective for small tumors (<3cm) in radiologically presumed WHO grade I meningiomas. [138] After SRS, the 10-year local control rate has been reported as high as 99% in small skull base meningiomas treated with 16 Gy SRS, with a 9% rate of permanent complications, including cranial nerve deficits, headaches, or hemiparesis (2%). [138] The complication rate varies in different studies depending on the treated patient cohort, on how complications were defined and on properties of the treatment. A comparison between surgical treatment and SRS was performed for presumed WHO grade I meningiomas <3.5 cm. SRS and Simpson grade I resection had similar rates of local control, while the rate of local control was superior for SRS compared to Simpson grade II-IV resections. The complication rate was 10% for SRS and 22% for the surgical arm of the study. [139] Irradiation can cause side effects in tissues adjacent to the tumor, inducing peritumoral edema in cerebral tissue. Irradiating cerebral tissue may induce fatigue in some patients. [140] Alopecia and skin disorders in the irradiated scalp are also relatively common and depends on the delivered dose.[141, 142]

Most of the studies that have been done comparing EBRT or SRS to surgery are observational retrospective studies, in which the choice to treat with radiation has been associated with tumors in inaccessible locations, close to sensitive structures, or situations in which the patient is medically frail or unfit for surgery, potentially biasing results towards better outcome after surgery. Irradiation treatment for presumed WHO grade I tumors may, in some cases, be a treatment of a WHO grade II tumor, as no histologic verification is made, also biasing results towards better outcome for surgical treatment. However, as most studies on SRS are single institution series there is potential for publication bias in favor of better SRS results. Also, surgery can alleviate neurological symptoms caused by compression, while irradiation generally cannot. Small asymptomatic incidentally discovered meningiomas may have a considerably more benign natural history, compared to larger or symptomatic meningiomas. If the rate of small asymptomatic meningiomas is higher among irradiated patients this may bias results towards seemingly better outcome after radiation.

Chemotherapy currently does not have any established role in the treatment of meningiomas. However, promising results have been reported for treating recurring or higher-grade meningiomas with bevacizumab, a monoclonal antibody against the angiogenic protein VEGF. Only limited data is currently available and larger trials are needed to determine the role of bevacizumab in meningioma treatment. [143] Peptide receptor radionuclide therapy in conjunction with EBRT has also shown promising results and could become a future treatment for refractory higher grade meningiomas. [144] For tumors with mass effect or edema, corticosteroids can reduce symptom burden and the risk of seizures. For patients with seizures, AEDs can reduce the frequency of seizures, although prophylactic use of AEDs is not recommended. [52]

Embolization of tumor vessels prior to meningioma surgery can induce necrosis in the tumor tissue, reducing the tumor size and facilitating removal. It has, however, not been proven to improve recurrence-free survival or overall survival. Embolization is costly, exposes the patient to radiation and is also associated with a small but significant risk of cerebral ischemia. [145, 146] EANO does not have a general recommendation for embolization before meningioma surgery, but it may be beneficial in certain special cases.[52]

SURGERY

The first description of a resection of a presumed meningioma in a living patient was by Prussian doctor Laurence Heister in 1743. Despite attempts to use caustic lime to disinfect the wound, the patient, a 34-year old soldier, died shortly after the procedure from an infection. [13] The episode is representative of the era. Most early attempts of brain tumor surgery resulted in mortality from complications like infections or hemorrhage. Work by notable pioneers like Arthur Walker and Harvey Cushing helped establish meningioma surgery as a viable treatment with acceptable survival rates. The introduction of antibiotics and modern anesthesia, as well as techniques for treating complications, and surgical advances, have continuously improved outcome. [13, 147] Technical improvements also include the introduction of microsurgery, [148] neuronavigation, [149] and the 3D printing of bone replacements. [150]

Surgery remains the main treatment modality for meningiomas today. But the decision to treat a meningioma surgically, and how this should be done, is highly dependent on the characteristics of the tumor and the patient. The main goals that surgical resection of meningiomas can achieve are tumor control (prohibiting further growth), reducing symptoms caused by tumor compression, and providing tissue for histological diagnosis. In cases where none of these goals are achievable or desirable, the risks may outweigh the benefits. Therefore, as will be discussed below, in many cases observation or radiation may be more appropriate than surgical treatment. [52]

An impactful work by Simpson *et al.* 1957 demonstrated that the recurrence rate after meningioma surgery depends on the rate of resection and provided a useful grading system for stratifying the extent of resection in the following way: [151]

- Grade I: Gross total resection (GTR) of the tumor, resection of dural attachment and abnormal bone
- Grade II: GTR of the tumor, coagulation of dural attachment
- Grade III: GTR of tumor
- Grade IV: Subtotal resection (STR)
- Grade V: biopsy/decompression

A lower Simpson grade with a more extensive resection was demonstrated to have a lower rate of recurrence. Because of this, it has traditionally been considered appropriate to aim for grade I resections when possible. The relevance of the Simpson grading was questioned in 2010, as no correlation between recurrence rate and Simpson grade was found in a single-institution cohort of 373 meningioma patients with WHO grade I meningiomas. [152] Several other studies have since contradicted this finding, validating the Simpson grade as a predictor of recurrence rate, [153, 154] including a Norwegian single-institution cohort of 391 WHO grade I-II meningioma patients. [155] However, the debate may require a randomized controlled trial to be settled, since the current evidence relies on retrospective data. As the decision to aim for a higher or lower Simpson grade is biased by properties of the tumor, the grading could be associated with confounders, such as if tumors are inaccessible, large or malignant looking, or if complications arise during surgery, making retrospective data hard to interpret. A weakness of the Simpson grading is also that it is performed by the surgeon at the time of surgery, who may be biased regarding his work. It is therefore recommended by EANO that intraoperative grading should be confirmed by a postoperative MRI within 48 hours after surgery. [52] The EANO consortium considers the distinction between GTR (Simpson grade I-III) from STR (Simpson grade IV) equally useful as the Simpson-grading. [52]

As meningiomas are a heterogenous group of tumors, side effects of surgery will depend to a great extent on the location and size of the tumor, the proximity to sensitive structures such as blood vessels, and on tumor grade. [156] Meningiomas of the skull base and posterior fossa can be problematic to reach, potentially increasing the risk for complications. [157] Taking this into consideration, an attempt to predict complications has been proposed, the Milan complexity score, awarding one point for each of the following variables: major brain vessel manipulation, posterior fossa surgery, cranial nerve manipulation, eloquent area and tumor size >4cm. [156] The benefit of such a scoring system is that it can put crude complication rates into perspective. An issue, however, is that the Milan Complexity score leaves room for divergent interpretation of these variables.

TREATMENT GUIDELINES

In Sweden, the main guidelines utilized for treatment guidance are those outlined by EANO in 2016. [52] According to these, it is recommended that meningiomas are diagnosed with MRI. A histologic diagnosis is not required for all patients. Thus, treating patients for the sole purpose of obtaining histologic material is not supported if there is good reason to believe the tumor is an asymptomatic grade I meningioma. For all brain tumors, discussing the treatment and follow-up decisions on a multidisciplinary tumor board is recommended.

In asymptomatic meningiomas, with typical appearance of WHO grade I, initial observation with a second MRI after six months is recommended. If no growth is detected and the patient remains asymptomatic continued observation with annual MRI examinations is recommended, with bi-yearly intervals after five years. If the tumor demonstrates growth on follow-up, produces symptoms, or has a radiological appearance where a higher-grade tumor cannot be ruled out, treatment is recommended. It is also recommended to discontinue the observation if the patient is no longer considered appropriate for treatment, for instance due to a short life expectancy or severe comorbidities.

When treating meningiomas of WHO grade I, II, or III, surgery is the preferred treatment. However, surgery requires that the patient and tumor are appropriate candidates. In patients older than 65 years, or with inaccessible tumors, SRS may be preferrable. When surgery is performed, it is recommended to aim for a Simpson grade I resection, removing all tumor tissue, all attached dura, and any abnormal bone. The recommendations from the European Organisation for Research and Treatment of Cancer, EORTC, instead considers GTR, defined as Simpson grade I-III, the most appropriate aim.

EBRT after STR has similar tumor control rates and mortality rates as GTR. [158] Thus if STR has been achieved and continued surgery is considered risky, it may be better to abandon the goal for GTR and instead arrange postoperative EBRT. According to EANO guidelines, adjuvant EBRT is generally recommended after grade II meningioma resection. However, in several centers in Sweden EBRT is not performed immediately if the surgery was considered a GTR but the patient is instead followed, and EBRT added in case of radiological growth. The EANO recommendations are identical for grade III meningiomas, except that the follow-up of grade II meningiomas are recommended every six months (and then annually for five years) while grade III meningiomas are recommended to be followed up every three to six months indefinitely. Histologic examination is recommended after surgery. It is also recommended to save tissue to allow molecular classification of the tumor in the future.

NON-SURGICAL TREATMENT

For VS, the inaccessible location and the proximity to vital structures makes surgery a difficult and risky endeavor. Investigations of the wait-and-scan approach have demonstrated that only 22-48% of tumors grow during a 3-7 year period. Tumors with a smaller size than 1,5 cm have a particularly low rate of growth, [108] and for most VS the risks of sudden complications is low. [123] Therefore, as outlined under treatment guidelines below, the most suitable course of action is often a wait-and-scan approach.

If treatment is required, radiation in the form of SRS has a prominent role. SRS for VS is generally performed in a single session delivering 12-14 Gy marginal dose through high energy photons, such as GammaKnife treatment. SRS for tumors larger than 2.5-3cm is associated with increased risk for brain stem edema or facial nerve palsy. [108]

SRS results are excellent for VS up to 3cm. A series of SRS-treated patients had a 10-year progression-free survival of 94%. [38] In VS sized <3 cm SRS has been shown in several prospective studies, compared to surgery, to have similar rates of progression free survival but better outcomes concerning hearing preservation and facial nerve function. [159, 160] However it has been proposed that the hearing benefit from SRS declines over time and is, after ten years, at the level of patients having undergone surgery, also in patients with previously normal hearing. [119] Inadvertently high doses delivered to sensitive inner-ear structures in a subset of patients may be involved in long-term hearing disturbances. [161] A trial of fractioned SRS for VS has been shown to have a local control rate of >90% and a risk for hearing loss of less than 5%. [162]

Chemotherapy currently is not recommended in the treatment of VS. However, the antiangiogenic agent bevacizumab has been shown to improve hearing and to reduce the tumor volume when used in patients with NF2 disorder not eligible for other treatments. [163]

SURGERY

Surgery for VS is preferred mainly when the tumor is large and causes brain stem compression, as will be discussed below. Because VS surgery is relatively rare, and a consistently low complication rate in performing VS surgery is associated with having a high case-load, there is need for some degree of centralization. [164] The three main surgical approaches for treating vestibular schwannomas are the translabyrithine approach, suboccipital / retrosigmoidal approach and middle cranial fossa (MCF) approach. [108]

The **translabyrinthine approach** reaches the tumor through the bony labyrinth of the inner ear, eliminating the function of the cochlea, vestibule, and semi-circular canals, causing irreversible hearing loss. It allows visualizing CN8 from a lateral angle. In cases where hearing loss on the affected side is already manifest and irreversible, the benefits from accessing all parts of the IAC and being able to visualize the facial nerve at an early stage of the surgery make this an attractive option. At the conclusion of surgery, fat tissue transplantation into the resected area is usually performed.

In the **suboccipital / retrosigmoidal approach** the skull is entered through the lower posterior occipital bone below and behind the sigmoid sinus, and the CN8 is visualized from a posterior angle. This way the tumor can be accessed lateral to the cerebellum, gently pushing the cerebellum to the side may be required. This exposes the CN8 as it enters the cerebellopontine angle and allows for hearing preserving surgery. The method is particularly well suited for large VS in patients with preserved preoperative hearing, but because the lateral part of the IAC is hard to access in the suboccipital approach, mainly due to the angle at which the brainstem is visualized, it can be hard to remove all tumor remnants there.

The **medial cranial fossa approach** enters the skull laterally, anterior to the ear, and the CN8 is visualized from a lateral and superior angle. The technique allows for hearing preservation but has a slightly increased risk for facial nerve palsy. As it involves gently pushing the temporal lobe to the side to reach the cerebellopontine angle, it may also cause temporal lobe gliosis. The approach has the best outcome in tumors <1cm in size (although these tumors are often treatable with SRS, as discussed below), with the risk for complications increasing with size. [165] It is less suitable for large tumors because the deeper parts of the cerebellopontine fossa may be hard to reach.

In general, GTR or NTR is recommended as the goal of surgery when possible. The risk for recurrence after VS surgery is linked to the extent of resection, with recurrence rates of 3.8% after gross total resection (GTR), 9.4% after near-total resection (NTR) and 27.6% after subtotal resection (STR). While GTR was also associated with an increased risk for facial nerve palsy at short-term follow-up, no significant difference was seen at long-term follow-up. [166] However, in these cases a viable option can be to leave a remnant of the tumor and arrange for postoperative radiation, as this can reduce the risk of facial nerve palsy while still offering adequate tumor control.[108]

TREATMENT GUIDELINES

The guidelines outlined by the 2019 EANO recommendations for the treatment of VS are divided into the following specific groups, based on the Koos classification (see above): small asymptomatic tumors (Koos grade I-II), small tumors with impaired hearing (Koos grades I-II), small tumors with complete hearing loss (Koos grades I-II), medium-sized tumors (Koos grade III-IV, <3cm) and large tumors with brainstem compression (Koos grade IV and >3cm).

- In small (Koos grade I-II), asymptomatic, incidentally discovered VS initial observation is recommended. As an alternative SRS may be utilized to prevent further growth. Surgery is not recommended.
- In small tumors (Koos grade I-II) with partial hearing loss, treatment with SRS is recommended. SRS is associated with a higher degree of hearing preservation and a lower risk for facial nerve palsy compared to surgery.
- In small tumors (Koos grade I-II) with complete hearing loss, observation is recommended. If the patient desires treatment, SRS has a smaller risk for facial nerve palsy, and an equal rate of tumor control. If the patient desires surgery, that is also acceptable.
- In medium-sized tumors (Koos grade III-IV, <3 cm), treatment should be provided. This can be done surgically or with SRS, with similar results. Surgery has a slightly higher degree of long-term tumor control, while also associated with slightly more risks. An alternative may be to perform subtotal resection in conjunction with SRS.
- In large tumors (Koos grade IV, >3cm) debulking is needed and should be done surgically. This procedure is associated with risks. If GTR is difficult to achieve safely, SRS can be utilized as an addition to surgery.

For all VS, it is recommended that a multidisciplinary tumor board discuss the patient, to obtain a nuanced perspective before deciding on a clinical recommendation to the patient. [120]

REGISTRIES IN SWEDEN

OVERVIEW

INTRODUCTION

A *registry* is, in essence, a list containing ordered information. The word stems from the Latin *re-gerere* "to record, to carry back" and was adopted into English through the Old French word "registre" in medieval times, meaning "list, note down" or a book in which this is done. The similar term *index* refers to a list containing less extensive information (but often with more emphasis on the order of the indexed items, e.g., alphabetical). [167] In this thesis, the term registry will be used implicating a registry of personal information, mainly *medical registries*. A medical registry contains information about patients and is usually organized as rows of patients, starting with a patient identifier such as a number or a name, and columns of variables with information about the patients (e.g., age, sex, blood pressure). A proposed definition for a medical registry is "a database of identifiable persons containing a clearly defined set of health and demographic data collected for a specific public health purpose". [168]

Today, most registries have been digitalized, and information is stored in files rather than books. As early paper- or book-based medical registries were limited in size, it was not feasible to include an unlimited number of variables. Most digital registries, however, do not have such limitations. Therefore, registries with a hundred or a thousand variables have become feasible. The advent of digital tools for processing information in registries has also changed the utility of large registries. Even if it had been possible to create a paper-based registry of thousands of data points for millions of patients, it would not have been useful without the means to analyze the information efficiently. Today, a multivariable regression of 15 variables for 10 000 patients can, in optimal conditions, be set up in minutes and performed in seconds, while it would take years to perform manually (if even possible).

A medical record generally contains information in text, while a registry instead contains variables. Although a registry can contain text-based variables, these are generally organized to allow statistical analysis. Of relevance, electronic health records (EHR) have become the main instrument of recording health care work. Data from registries can be extracted from EHR, in some cases semi-automatically but in some cases through more cumbersome processes. Some modern EHRs are designed to allow the integration of registries. When compared to clinical trials, medical registries have several issues making results from them harder to interpret. Registries allow for retrospective studies, but patients cannot be randomized to treatment arms, frequently causing selection bias. Inclusion and follow-up of patients may be less standardized or coherent compared to clinical trials. [169] Attempts to resolve these issues have been made through registry-based randomized clinical trials. [170]

A 2002 review proposed that the quality of medical registries can be described with two parameters: accuracy (is the data correct?) and completeness (how much of the total data is included?). The same literature review found that the intended use of the registry is important. High completeness is required for calculating incidence rates of diseases, while accuracy is more important if one intends to use the registry for case-control studies. [171] It is crucial when setting up a registry to choose appropriate variables to include, as this determines what analyses that can be performed when the data is accessed, but also how time-consuming the registration will be. It is equally important to develop an organization around the registry, so that data is entered correctly for each patient. An elaborate registry may provide unreliable data if systematic errors of registration are built into the system. Thus, when setting up a registry, it is important to establish methods for checking the data systematically, both regarding accuracy and completeness.

For Swedish registries, it has also become increasingly important to harmonize with similar data collection efforts in other countries. Combining national registries from several similar countries, such as the Nordic countries, can provide powerful cohorts and reliable results if implemented carefully. It requires, however, agreement both regarding what variables should be registered and details of how the information should be organized. Thus, if a variable is registered similarly in all countries, the information gains additional value. [172] Combined data from several countries also allow for large scale retrospective studies of the implementation of guidelines or healthcare systems, that can be informative in areas that are otherwise hard to study.

HISTORICAL ASPECTS OF SWEDISH REGISTRIES

Sweden has a strong tradition of maintaining national registries. As far back as the 16th century the Swedish king Gustav Vasa formed the allotment system (*Indelningsverket).* This early conscription system required knowledge regarding the number of citizens in Sweden, as well as their age and geographical location (to find able-bodied men for the army). During the same era, Sweden converted to Protestantism, and the reorganized clergy was tasked with recording basic information about citizens, including birth, death, marriage status and profession. As Sweden was increasingly militarized and centralized in the following two centuries, the interest in maintaining good registries was high. In 1749 a central Swedish agency for gathering information from the church books was formed, the *Tabellverket.* All regional priests were required to send information to the Tabellverket every three years. A central agency to process the information into comprehensible tables, the Tables commission or *Tabellkomissionen,* was formed in 1756*.* A first official report about the population of Sweden (including Finland which was a part of Sweden at the time) was published in 1764. The total population in Sweden and Finland was 2 383 113 citizens.

Tabellkommissionen evolved into the *Central Bureau* in 1858, tasked with both registries of the population and registers of farming, financial registries and registries of the care of the poor. Thus, the king and his council could obtain comprehensible information not only about the population but also about the economy of Sweden, to guide decisions. The *Central Bureau* was reorganized and renamed again in 1886 to *Statistiska Tabellkommissionen*. During the early 20th century many large reforms were made, including the introduction of democracy in 1919. In the 1940s the *Statistiska Tabellkomissionen* was dissolved and reorganized into several government agencies and institutions. [173, 174]

Swedish registries today are based around the unique personal identification number given to all Swedish citizens since 1947. It contains ten digits. The first six digits constitute the date of birth. The next three are based on where the person was born, with the ninth digit even for girls and odd for boys. The birthplace digits have become problematic because of the progressive urbanization, with a disproportionate number of people born in some regions, mainly the Stockholm-region. Therefore, since 1990, digits 7-9 are no longer based on place of birth, but are randomized for the entire country. The last digit is a control-digit, added in 1967, calculated based on the other digits to allow detection of a falsified number. As the personal identification number is used in all contacts with the government, and many other situations, it allows for the identification of the same individual in different registers. This system, in turn, allows the linking of registries for the same individual. [173, 175]

Sweden and 70 other countries (including Great Britain but not including the US) have a principle of public access to official records, *offentlighetsprincipen,* granting citizens the right to access all public records that are non-classified. In Sweden, this principle has a particularly strong formulation and is part of the fundamental laws of Sweden through the Freedom of Press Act (*Tryckfrihetsförordningen*). Thus, Swedish citizens, including researchers and journalists, have relatively good access to information about the workings of government agencies. The law stipulates among other things, that a journalist or citizen has the right to read information from government agencies, including emails sent by employees in government agencies.

On the other hand, the privacy of citizens is protected by the Personal Data Act, which was replaced in 2018 by the EU-wide General Data Protection Regulation (GDPR). The Swedish Authority for Privacy protection or Integritetsskyddsmyndigheten (IMY) is responsible for protecting the integrity of Swedish citizens and enforcing the GDPR. This agency was renamed (previously Dataskyddsinspektionen) in January 2021.

The GDPR laws are formulated to include all personal data handling, including collection, storage, alteration and destruction. According to the IMY the main principles of GDPR are that data handling should be:

- **Lawful, correct, transparent:** There should be a legal reason for handling the data. Current regulations should be obliged. The data handling should be transparent, not secret, and correct, in logical agreement with the law that allows it.
- **Collected for specified purposes:** The data should be correct, not disproportional or skewed. Handling of data should not be excessive compared to the expected benefits. There should be a defined reason for handling the data, and the reason should be reasonably specified. “For future research” would not be sufficiently specific, but “to investigate outcome after surgery” would be.
- **Adequate and limited to what is necessary:** Data should be handled in agreement with the defined reason.
- **Accurate and up to date:** Data should not be systematically falsified, and data should be kept correct.
- **Retained only for as long as necessary:** There must be a reason for storing data long-term. It is allowed to store data long-term for research purposes, but then care should be taken to maintain secrecy.
- **Handled with responsibility, protecting integrity and confidentiality:** It is the responsibility of an organization handling data to maintain strict integrity protection, including protection and backups against disasters or accidents, such as hacking or a fire in a server. [176]

Specific rules for registries of treatments are in place, requiring such registries to be available in electronic form, be updated, and that they should, if requested, be made available to the IMY for inspection. The registry should have a defined person responsible for the personal data handling, generally the registry holder, and an ombudsman responsible for protecting the integrity of the handled personal data. The rules to these registries generally only apply if the company or organization is larger than 250 employees. A commission investigated if there should be additional regulations and clarifications defining the use of personal data for research, resulting in the legislation-proposal named “The right to perform research” in 2018, but it was criticized by the Dataskyddsinspektionen 2019 and has not been ratified as of today.

The registers most relevant for medical research can broadly be divided into *Quality registers* and *Health data registries (HDR)*. The HDR are regulated by the Swedish law *Hälsodatalagen*, making it illegal not to report to these registers. Therefore, today, most organizations obliged to report information to the NHR have automated or semi-automated this process, to guarantee continuous high-quality reporting. Quality registers on the other hand, are not subject to law-regulated mandatory reporting. They can, however, still have routines, regulations or systems for automatic reporting in place that allow for reliable and complete information.

NATIONAL BOARD OF HEALTH AND WELFARE (SOCIALSTYRELSEN)

The National Board of Health and Welfare (NBHW), *Socialstyrelsen*, is a government agency with a wide range of activities and duties within social and health services. According to the official webpage NBHW works "*to ensure good health, social welfare and high-quality health and social care on equal terms for the whole Swedish population. The activities concern social services, health and medical care, and communicable disease prevention*."

Responsibilities of the NBHW include issuing medical licenses, handling complaints about mistakes in the healthcare system, distributing research grants and producing knowledge support and guidelines for care. It is also involved in organ donation, developing screening programs for cancer, dentistry, tracking sexually transmitted diseases and handling questions of equality (particularly for gender and sexual orientation).

One of the responsibilities of the NBHW is to govern several registries. These include the Swedish Cancer Registry (SCR) the Drug Registry and the Patient Registry. All these registers are HDR, regulated by the law *Hälsodatalagen.* They, therefore, receive mandatory reporting.

SWEDISH CANCER REGISTRY (CANCERREGISTRET)

The Swedish Cancer Registry (SCR) is a HDR under the NBHW, established in 1958. Reporting to SCR has been mandatory since it was established. It gathers information about malignant cancer cases in Sweden. Around 60 000 new cases are reported each year. Cases are reported per tumor, not per patient. Since the 1980s the register organizes six regional oncological centers to facilitate regional control of the quality of the registry data, including a system for checking and correcting data. The regionalization is aimed at enabling more direct communication with reporting physicians.

Patients are organized based on personal identification numbers. Registered variables include sex, age, place of residence, tumor site and tumor type, histological diagnosis based on ICD-classification, date of diagnosis. In the case of mortality, the registry also includes the date and cause of death. In the case of migration (making the patient unavailable for follow-up), the migration date is included.

The cancer registry has also been compared to the cause of death registry. It was shown that the rate of underreporting differs between tumor types. Pancreas cancer and lung cancer have a high degree of underreporting, while breast cancer has a very low degree of underreporting. [36]

One of the main ways that cancer cases are detected and reported to the SCR is through histopathological examination of a tumor sample. Pathological clinics in Sweden systematically report to SCR for each cancer that is found. However, radiologically diagnosed tumors are not systematically reported in the same way. The rate of radiological to histopathological diagnoses varies between tumor type and between regions. Some tumors, like breast cancer, are more often available for biopsy. In contrast, lung- and pancreas tumor biopsies are harder to arrange, and it may therefore be more common to accept the radiological diagnosis as definitive. The rate of radiological diagnoses reported to SCR is higher in some regions. The underreporting of the SCR has been estimated to be 3.7% in an investigation performed in 1998. [177]

PRESCRIPTION REGISTRY (LÄKEMEDELSREGISTRET)

The national prescription registry is an HDR organized under the NBHW. It has received mandatory reporting from distributers of prescription drugs since 2005. When the registry was established the government-owned store *Apoteket* was the only store allowed to sell prescription drugs. All private prescription drug retailers in Sweden were purchased and centralized into the government-owned company *Apoteket* 1970, and all other retail of prescription drugs was prohibited 1970-2009. In 2009 a reorganization and privatization resulted in private companies being allowed to sell prescription drugs, while mandatory reporting to the national prescription registry was maintained. Reporting is performed automatically and digitally on each purchase. The registry uses the Anatomical Therapeutic Chemical (ATC) classification system to classify drugs into different drug types. To purchase a prescription drug, a patient must first legitimize themselves in the store with their personal ID number, and their ID is connected to a prescription made by a physician. Usually the whole process is digital, but if the physician has made a physical paper-based prescription, this is registered digitally by the distributing drug store. The patient's personal ID number is used as an identifier in the registry, and for each purchase a date and ATC code are registered. The registry does not contain information on the size of the prescription, so a purchase of 10, 30, or 90 tablets of a drug is registered in the same way.

PATIENT REGISTRY (PATIENTREGISTRET)

The national patient registry of Sweden is an HDR under the NBHW. It was established in 1964 but became a national registry in 1987. It receives data from all private and public hospitals concerning the main diagnosis that the patient was receiving care for and, if applicable, when they were admitted to and discharged from the hospital. Since 2001 the patient registry also receives information from all private and public specialized care outside of hospitals, concerning the main diagnosis causing the visit to the clinic. The patient registry does not receive data from primary care. Official statistics from the NBHW website estimates the overall rate of main diagnosis reporting 2019 to be 99% in hospital care and 97.2% in specialized non-hospital care. The data on the main diagnosis is reported in the form of ICD-10 codes, and dates.

SWEDISH SOCIAL INSURANCE AGENCY (FÖRSÄKRINGSKASSAN)

The Social Insurance agency or *Försäkringskassan* (FK) is an independent Swedish government agency that administers social insurance. It is not a part of NBHW. Its main responsibilities are to economically support citizens in need during temporary or long-term illness or disability and provide economic support for families and childcare. It is also responsible for investigating the need for long-term support, with the help of administrators and physicians with special competence in insurance medicine.

According to official statistics from the FK, out of the 234 billion SEK administered 2018 by the FK (6% of the Swedish GNP), 87 billion was paid in support of the family and childcare, allowing parents to be free from work during the first years after birth, supporting families in placing children in kindergarten-care and providing small subsidies to families for each child in their care. Sick leave compensations in different forms constituted 123 billion SEK, with the highest costs being 36 billion for temporary sick leave compensation, 40 billion for long-term sick leave compensation, and 25 billion for assisting disabled persons. In 2018, out of the 10.18 million citizens of Sweden 5.68 million (56%) were between 19-65 years, and 89% of them had earned a salary of at least 10 000 SEK during the year. Around 10% of the citizens between 19-65 years, 602 000 citizens, had received some degree of temporary sick leave compensation during the year, of which 64% were women and 36% men. In total, the rate of sick leave compensation provided for psychiatric disorders was 53% for women and 40% for men, but the rates were above 60% in the 30–39-year age group. There are also regional differences in sick leave patterns, with the most rural northern parts of Sweden (Norrbotten) and the most urban region (Stockholm) having relatively low rates of any temporary sick leave at a specified time (December) with around 1.6-1.8% for men and 3.2-3.9% for women, while some "semi-urban" regions, including the Gothenburg region (Västra Götaland and Södermanland), have 2.3-2.5% for men and 4.6-4.9% for women. There may be inequalities in the distribution of work and health conditions explaining these differences.

If a person is temporarily unable to work because of disease in Sweden, the first sick day is paid for by the citizen as a deduction from the salary, day 2-14 is paid for by the employer. From day 8 a doctor's certificate declaring that the sick leave is medically reasonable (and to what extent) is required to be sent to the FK through an electronic form. Day 15 and subsequent days are paid by the social insurance agency, provided that the electronic form has been sent in by a physician and approved by an administrator at the FK. The bulk of these medical sick leave decisions are made in primary care after a brief examination and are generally approved without inquiry by the administrator at FK. Most common ICD-10 diagnoses are associated with a guideline for the appropriate time to be on sick leave, so if a form is sent to the FK requesting three months sick leave for a common cold, it would likely be questioned. For more uncommon diagnoses however, there is no standardized time-frame available to the administrator. In these cases, if the administrator questions the length of sick leave but is insecure about what to consider reasonable for the diagnosis, they can consult an insurance physician employed by the FK or request a telephone-meeting with the physician who sent the electronic form. If a medical doctor has certified that it is medically reasonable for a patient to be on sick leave for a longer time and the patient returns to work before that time has passed, the compensation from FK will end at the time that the patient returns, and this will be reflected in the register.

In patients with a chronic disease and an established contact with a specialized clinic, the sick leave is to a greater extent administered by the specialized care. For instance, a patient with a brain tumor could have an established contact with a neurologist or neurosurgeon. After brain tumor surgery, it is common to request sick leave from FK for the treated patient until a follow-up visit. As knowledge of the expected outcome after surgery for an unusual brain tumor may be limited, and since neurosurgery is a very specialized part of healthcare, administrators at FK may be less likely to challenge a request for sick leave in such a scenario compared to a request regarding a more common disease for which there are guidelines.

The FK is one of the 28 government agencies (including the NBHW) with a responsibility to provide statistical information to the public and for research. As part of this responsibility, the FK maintains a registry over all sick leave days registered in Sweden, based on the electronic forms submitted by doctors for sick leave longer than 14 days, including more permanent forms of sick leave. The registry is not an HDR, but the data is registered automatically, and it is not possible to receive compensation from the FK if the sick leave is not registered. Self-employed citizens receive sick leave compensation after seven days. Unemployed citizens receive sick leave compensation (replacing unemployment compensation) after one day if an electronic form is sent in but may be less inclined to do so as the difference may be small. The sick leave is registered as 0, 25%, 50%, 75%, or 100% and for each sick leave period there is a start date and an end date. [178]

STATISTICS SWEDEN (STATISTISKA CENTRALBYRÅN, SCB)

Statistics Sweden or *Statistiska Centralbyrån* (SCB) is a government agency, officially under the supervision of the financial department of the Swedish government but with an independent organization. The responsibilities of SCB are regulated by Swedish law, and include the development, production, and distribution of statistics for the government. The agency is also responsible for coordinating statistics and distributing Swedish data to international organizations. It receives assignments from the Swedish government, including the calculation of the Consumer Price Index, *Konsumentprisindex*, used as a measure of inflation. SCB is also allowed to perform assignments for other government agencies, organizations, researchers or private companies.

One of the registries that are, by law, the responsibilities of SCB is the Registry of the Total Population, *Registret Över Totalbefolkningen* (RTB). The RTB contains basic demographic data of all citizens, including age, sex, relationship status, citizenship, municipality of residence. The RTB data is often useful to include in other registry-based investigations and surveys and is frequently requested by researchers.

The data from Statistics Sweden is protected by secrecy. Anonymized data can be accessed on demand by scientists and other organizations, provided that SCB considers the applicant to have sufficient grounds for processing the data. SCB performs a confidentiality check to ensure that the access is in line with current laws and regulations and is reasonable. Statistics Sweden performs these services for a fee depending on the complexity of the service, on a non-profit basis. The fee is usually more dependent on the complexity of the data than the actual number of citizens included. Statistics Sweden can also perform telephone-based surveys.

SWEDISH BRAIN TUMOR REGISTRY

The Swedish Brain tumor registry is a National Quality Registry for health care. It is not an HDR and is not a part of any government agency. It is based regionally in six regions, with each region corresponding to a part of Sweden, a University Hospital, and a neurosurgical clinic. The SBTR data is based on forms filled out by surgeons performing tumor surgery at these clinics. These forms are then often transcribed into digital forms by a research nurse. The reporting to the registry has been good, with an 80% or higher registration rate compared to the national cancer registry in all regions except one. For three regions, the reporting has been close to 100%.[179] For the period studied in this thesis, 2009-2015, the region with the lowest rate of reporting had a reporting rate above 80% only during 2012-2013, and was, therefore, when efforts were made to provide population-based data, excluded 2009-2011 and 2014-2015. As no other clinics performing neurosurgical tumor removal in Sweden, the SBTR data constitutes close to all brain tumor surgery performed in Sweden.

The SBTR contains basic information regarding the patient, including age and sex. It also includes basic information about the tumor, both concerning the date and imaging modality of the radiological diagnosis, tumor size, some information on tumor location (including skull base location or not in applicable cases). It has many surgical variables, both concerning the status of the patient when admitted to the neurosurgical clinic, such as preoperative symptoms, and concerning the surgery itself. Radicality, histological diagnosis, short-term complications, and the rate of postoperative radiation are all registered variables. The included variables are also adjusted for each tumor (e.g., the Simpson grade variable is used for VS but not for meningioma).

The registry includes adult patients (≥18 years) and only patients with a first-time histological diagnosis of a primary brain tumor. Recurring tumors or metastatic tumors are not included. Radiologically diagnosed tumors without histologic diagnosis are not a part of the SBTR. This is important for this thesis because a large and growing portion of meningiomas and VS is not treated surgically, as discussed above.

The description of the SBTR in this section is accurate for the registry providing data for the studies included in this thesis. However, although this does not affect the data in the thesis, it is important to note that the SBTR was reorganized in many ways in 2018. It was renamed to *the Swedish registry for CNS-tumors* and now includes all CNS tumors, including spinal tumors, cytologically diagnosed CNS tumors (e.g., lymphomas) and, importantly, also radiologically diagnosed tumors. Not only neurosurgical clinics will be involved in the reporting. The molecular data included in the registry has been broadened, and the quality-of-life data has been reorganized to also include the data form EORTC QLQ-C30. The registry will also include data on if the patient has been diagnosed with NF2 disorder. The pre-and postoperative complications have been updated to be more specific. Postoperative complications are scored according to the Clavien-Dindo classification. The registry is event-based, reporting on reoperations as well as primary surgery. An interactive tool is under development that will allow researchers to access the data directly. Thus, future use of the Swedish CNS tumor registry will allow many interesting venues for retrospective studies of brain tumor patients.

AIM

Meningiomas and VS are generally slow-growing and benign tumors with a low mortality-rate. Surgery is rarely the only viable treatment option. When a clear difference in mortality between treatments is lacking, it is essential for patients and caregivers to have realistic expectations of how surgery will impact "softer" outcome measures. Surgical complications and postoperative sick leave, depression and anxiety can all have a large impact on the quality of life for patients. Yet the exact rates of these outcomes after surgery for meningioma and VS have received little attention and have not been established. Therefore, the general aim of this thesis project was to quantify the "softer" outcome after surgery for meningioma and VS with a nationwide registry-based cohort methodology. The specific aims were to describe:

I) short-term complications after meningioma surgery (Study I)

II) patterns of sick leave before and after meningioma surgery, including predictors for long-term sick leave (Study II)

III) rate of antiepileptic, antidepressant and sedative use before and after meningioma surgery, including predictors for long-term use. (Study III)

IV) patterns of sick leave and use of antidepressants and sedatives after vestibular schwannoma surgery, including predictors for long-term sick leave and drug use. (Study IV)

PATIENTS AND METHODS

STUDY DESIGNS

The patients included in this thesis have all been identified in the SBTR. Many of the defining features of the cohort, such as patient age and date of surgery, are based on data from the SBTR. Study I was designed as an uncontrolled cohort study of all surgically treated meningioma patients in Sweden, with a date of surgery during 2009-2015. Studies II-IV were instead matched cohort studies based on a cohort with a date of surgery 2009-2015. However, for studies II-IV each patient was also individually matched to five controls from the general population, based on age, sex, municipality of residence and level of education. SCB performed the matching of patients and generated the control-population. In a few cases it was not possible to identify five controls for a patient. This could occur if the patient had an unusual set of matching variables, such as a highly educated older woman in a small rural municipality (the smallest municipalities in Sweden only have 3000 inhabitants). For studies II-IV, the index date is a central concept. The index date is equal to the date of surgery for patients. The index date for controls was equal to the index date for the patient to whom they were individually matched. Most variables, including age, education level and municipality of residence, are defined at the index date.

The Elixhauser comorbidity index has been used in studies II-IV. It consists of a system for counting the number of certain predefined conditions that a patient has been diagnosed with, based on ICD-10 codes. [180, 181] To perform the calculation of Elixhauser comorbidity index we used ICD-10 data from the Patient Registry. We excluded conditions that were too closely related to the tumor diagnosis, and these have been defined for each study. When discussing our findings, the term *long-term sick leave* refers to sick leave two years after surgery, and the term *short-term complications* refers to complications within 30 days of surgery.

The number of net days absent was calculated for patients and controls in studies II and IV. Net days absent was a construct of days and grade of compensation. It was calculated by multiplying the degree of compensation (0, 0.25, 0.50, 0.75, or 1) with the number of days on that degree of compensation. Through this process, we obtained a value between 0 and 365 for each year. For studies II and IV, when studying sick leave and return to work, we excluded patients 60 years or older, as has been done in other research on sick leave, [182] because differences in retirement age and the decision to retire earlier was considered to interfere too much with the analysis.

All studies were approved by the Swedish regional ethical board of the Västra Götaland Region, and the need for individual informed consent was waived (DNR 363-17).

STUDY I

The study aimed to describe the short-term complications after meningioma surgery. We identified all patients surgically treated for a meningioma in Sweden between 2009-01-01 until 2015-12-31 through the SBTR. Data from other national registries was not used and linking of registries was not performed for this study, because SBTR contains both basic patient data, surgical variables and short-term complication rates. Study I was designed as an uncontrolled cohort study, no controls were used. Asymptomatic patients were compared to symptomatic patients in a subgroup analysis.

The included baseline characteristics were age, sex, symptom at diagnosis, WHO performance status (ranging from grade 0: fully active to grade IV: completely disabled). Surgical variables were date of radiological diagnosis, laterality, multifocality, largest diameter of the tumor (stratified as <4, 4-6 or >6cm), date of surgery, type of surgery (biopsy or resection), Simpson grade (ranging from grade I: total removal to grade V: biopsy/decompression only). Post-operative variables were the presence of the following complications within 30 days: new or worsened focal deficit, new-onset seizures, infection, VTE, symptomatic hematoma, complication leading to reoperation within 30 days. The histopathological diagnosis, registered as a SNOMED code, was also included.

Kaplan-Meier curves were created to visualize differences in longer-term outcome for patients with WHO grade I, II or III tumors, and to visualize the longer-term outcome for asymptomatic vs. symptomatic patients.

STUDY II

This study aimed to determine the sick leave rate after meningioma surgery and to provide predictors for long-term sick leave. Patients surgically treated in Sweden for a meningioma 2009-2015 were identified. The end of the studied time-frame was set to 2015-07-31, to enable analysis of sick leave data two years after surgery for all patients.

Return to work (RTW) was assumed to have occurred if the patient or control was no longer receiving compensation. It could be partial (25%, 50% or 75%) or complete (100%). Patients were considered to have a history of depression if they, at any point before surgery, had either any diagnosed depressive disorder, as defined by the Elixhauser comorbidity index (ICD10: F20.4, F31.3-F31.5, F32, F33, F34.1, F41.2, F43.2) or a previous prescription of any antidepressant (ATC: N06A). Patients were considered to have a history of seizure if they, at any point before surgery, had either an epilepsy diagnosis (ICD-10: G40) a prescription of an AED (ATC: N03A), or if they had “seizure” as a registered symptom in SBTR. The following diagnoses were removed from the Elixhauser comorbidity index as they were considered too strongly associated with the diagnosis of meningioma, or because they are reported separately as history of depression or history of seizure: G40, G41, R56, R47, C70-72, and depression (F20.4, F31.3-F31.5, F32, F33, F34.1, F41.2, F43.2).

Uni- and multivariable regression models were created to analyze predictors for sick leave (partial or complete) two years after surgery. We included the following variables in the models: age, sex, yearly income (per 100 000 Swedish krona), education (basic to high school vs higher education), net days absent in the year preceding surgery (per 10 days), WHO functional status, tumor size (< 4 cm, 4-6 cm, > 6 cm), history of seizures, history of depression, number of comorbidities according to Elixhauser comorbidity index, WHO tumor grade, new neurological deficit after surgery, reoperation because of any complication. Variables were chosen based on assumed relevance.

STUDY III

This study aimed to determine the rate of AED, antidepressant, and sedative drug use before and after meningioma surgery compared to matched controls. We also aimed to define predictors for the long-term use of these drugs. The study was designed as a matched cohort study, as described above.

Active use is a central concept in this study. An active user was defined as a patient or control who has purchased a drug in the past 90 days. This timeframe was chosen based on that, according to guidelines in Sweden and the clinical experience of the authors, these drugs are generally prescribed in packages of 90 days use or less. We analyzed the status of active use for each patient, and for all studied drug groups, for each day from 730 days before index date until 730 days after index date. A patient would, for instance, be considered as an active antidepressant drug user from the day that they purchase an antidepressant until 90 days after the purchase. A second purchase, for instance after 60 days, would not mean that the patient was counted twice, but would prolong the active use time by 90 days from the second purchase. A patient could simultaneously be an active user of two different drug groups (e.g., both an AED user and an antidepressant user). Drug-prescriptions were not analyzed per se, but it is not legally possible to purchase the studied drugs in Sweden without a prescription. For sedatives, as they are more often prescribed for short durations in smaller packages, we used 30 days instead of 90 days as the time we considered a patient an active user. This was based on Swedish guidelines and the clinical experience of the authors.

The drug use data were analyzed based on drugs purchased by the patient, requiring first a medical prescription and that the patient actually purchased the drug. Although it is theoretically possible that patients continued to purchase drugs regularly while not taking them, it would be hard to explain the motivation for continuing to do so two years after surgery. Drug use data were available from the start of 2007, while we included patients with surgery dates starting from January 2009. For patients with a date of surgery during the first three months, active drug use two years before surgery could not be calculated accurately, as they could have purchased a prescription at the end of 2006. We, therefore, excluded patients that had a date of surgery in the first three months of 2009.

Three multivariable regression models were created to analyze predictors for active drug use at two years after surgery, one for AEDs, one for antidepressants and one for sedatives. We included the following variables in all three models: index year, sex, age, education level (basic to high school vs higher education), yearly income (per 100 000 Swedish krona), being asymptomatic before surgery, number of comorbidities according to Elixhauser comorbidity index, WHO tumor grade (grade I or grade II-III), reoperation because of any complication within 30 days, new neurological deficit after surgery, tumor size (< 4 cm, 4-6 cm, > 6 cm), skull base location, WHO functional status, if postoperative radiation was planned and wait time between radiological diagnosis to surgery (per increasing quartile). For each model, the use of the analyzed drug group at the time of surgery was included as a variable. For the AED model, we added AED use at index date. For the antidepressant model we instead added antidepressant use at index date. Lastly, for the sedative model, we instead added sedative use at index date as a variable. Variables were chosen based on assumed relevance.

STUDY IV

This study aimed to determine the rate of sick leave in patients undergoing VS surgery, and the rate of antidepressant and sedative use, compared to controls. The aim was also to provide predictors for long-term sick leave. A similar approach as in studies II and III was employed. The study was designed as a matched cohort study comparing VS patients to matched controls.

The index date was defined as the day of surgery. Like in study II, return to work (RTW) was assumed to have occurred if the patient or control was no longer receiving compensation. For each day from 730 days before the index date to 730 days after, we calculated the rate of patients and controls in full, partial or no sick leave, as well as mortality. Concerning the Elixhauser comorbidity index, the following diagnoses were removed from the index because of a too strong association with the diagnosis of VS: C70-72. Like in study III, the active use of antidepressants was defined as a patient or control who has purchased an antidepressant (N06A) in the past 90 days. The same reasoning as in study III motivated using 30 days instead of 90 days as the time we considered a patient an active user of sedatives. The active use of sedatives was thus defined as having purchased a sedative drug (N05B or N05C) in the past 30 days. For each patient and each day from 730 days before index date until 730 days after index date, we analyzed the status of active use. Results were compared between patients and controls.

LINKING OF REGISTRIES AND STATISTICS

For studies II-IV, where linking of registries was performed, the data was accessed by SCB. Based on the data from the SBTR, the personal ID numbers of patients were matched to the other registries for each patient, and data was acquired. Each patient obtained a temporary ID-number. Data from each register was made available to the researchers, where the temporary ID could link the patients between datasets. However, the personal ID number or name of individual patients was never known to the authors.

The datasets could now be linked. Using an SQL database, with the program mySQL, data from the registries were imported into corresponding tables. The degree and dates of sick leave compensation were collected from two datasets and combined into a single library using Python programming, while the other calculations required for the data preparation were performed in the mySQL program. Statistical analysis was performed using the program R.

The index date was defined based on the date of surgery variable from SBTR. The index dates of controls were set to be identical to the patients to which they were matched. Drug use for a given day was defined as having a prescription of a drug of the studied type purchased in the 90 days previous to the given day, or 30 days for the sedatives group. Calculations on sick leave and drug use were made for each patient and control for each day, in conjunction with mortality calculations. The calculations of the rates of patients on full, partial, or no sick leave were presented graphically for studies II and IV. The rate of use among alive patients and controls for each drug group was displayed graphically. From these calculations we also derived the net days absent.

Continuous variables were summarized using the median, first, and third quartiles and compared between cases and controls using the Mann-Whitney U test. Categorical variables were summarized using counts and proportions and compared between cases and controls using the Fisher exact test. The level of statistical significance was set at <0.05. In Study I, we utilized Kaplan-Meier curves for the longer-term survival data, tested for the statistical difference using the log-rank test, and adjusted using the Cox proportional hazards model. In studies II-IV, logistic regression models were used to examine independent predictors of RTW and drug use. In studies II and IV, RTW at two years was defined as any work-related activity (partial or complete) at two years postoperatively. For drug use, active use was defined as explained above. Covariates were chosen based on presumed relevance. In all works of this thesis, SPSS version 24, 25 or 26 has been used, sometimes in conjunction with Microsoft Excel, to organize data, check for anomalies, and perform uni- and multivariable regression analyses.

RESULTS

MENINGIOMAS

STUDY I

From the SBTR, 2324 adult patients surgically treated for a meningioma in Sweden between January 1st 2009 and December 31st 2015 were identified. 1638 patients (70,5%) were female. The mean age was 58 years. The presenting symptom for patients in the study was a neurologic deficit in 62.4% and seizures in 24.3%, while 327 patients (14.1%) were asymptomatic. In the asymptomatic group, tumors were smaller, with 70.2% of tumors measuring <4cm compared to 49.3% in patients that were symptomatic (n=1996). The rate of skull base tumors was also lower in the asymptomatic group (11.6% vs 15.5%, p=0.07). The mean age was lower in the asymptomatic group (56.1 years vs 59.1 years) and the rate of female patients was lower (69.8% vs 74.3%).

The outcome was measured as the rate of complications within 30 days after surgery. The most common complications were new or worsened neurological deficits after surgery (14.8%), symptomatic hematoma (9.4%), postoperative infection (6.4%), new-onset seizure (4.5%) and venous thromboembolism (3%). The 30-day mortality was 1.5%. Reoperation, for any reason, was performed within 30 days in 5.2% of patients. The rates are presented graphically in Figure 11. Among the 327 asymptomatic patients there was a lower 30-day rate of new or worsened neurological deficit (8.3%), symptomatic hematoma (4.6%), and venous thromboembolism (0.6%) compared to symptomatic patients. Asymptomatic patients also had a lower 30-day reoperation rate (2.1%) and 30-day mortality (0.3%). All these rates were significantly lower than for symptomatic patients.

An increasing degree of resection according to the Simpson grading system was linearly associated with a lowered risk for new or worsened neurologic deficits (the risk was 12% for Simpson grade I and 28% for Simpson grade 5), but Simpson grade was not correlated to the risks for other complications. We also evaluated the long-term risk for mortality among patients, comparing different WHO grades and comparing symptomatic to non-symptomatic patients. Mortality was lowest in the WHO grade I group and highest in the WHO grade III group (p<0.01). Asymptomatic patients had a better outcome than symptomatic patients (p<0.01).

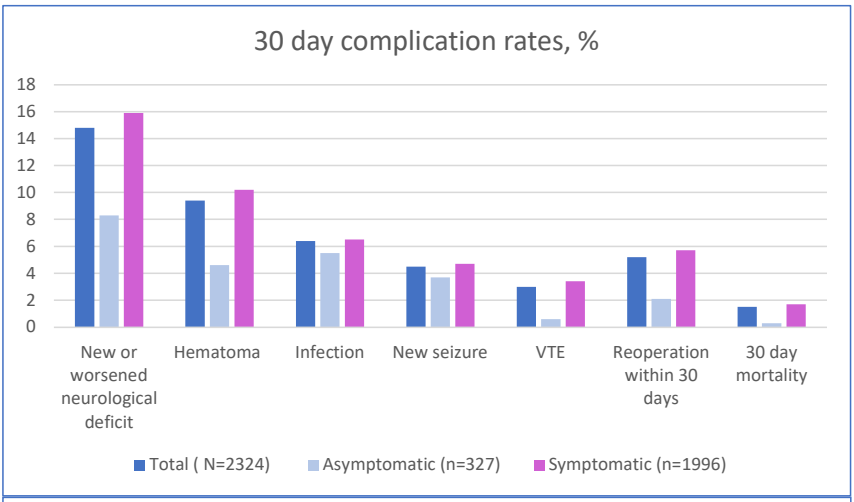

Figure 11, rate (%) of 30-day complications, as well as reoperations within 30 days and 30 day mortality, in Study I.

STUDY II

From the SBTR, 2324 patients were identified treated for an intracranial meningioma between January 1st 2009 and December 31st 2015. The final cohort consisted of 956 patients and 4767 controls, selected through the inclusion and exclusion process outlined in the methods section. Most patients were female (75%), with a mean age of 48 years. At the time of surgery, 60.6% were fully active (WHO functional status = 0) and 15% were asymptomatic. The tumor size at surgery was <4cm in 57%, 4-6 in 30% and >6 in 14%. For 87% of patients a complete resection (Simpson grade I-III) was accomplished. After surgery, in 13% of patients, a new neurologic deficit was observed.

One year before surgery, 79% of patients and 86% of controls did not have any registered sick leave compensation (p<0.001). The rates of patients and controls without sick leave compensation was 49% vs 85% (p<0.001) at one year after surgery and 57% vs 84% (p0.001) at two years after surgery (Figure 12).

A predictor for long-term sick leave in the meningioma cohort was prior sick leave (p<0.01), with the net days absent (number of days of sick leave in the year before surgery) increasing the risk for being on sick leave at two years after surgery. Patients with 365 net days of sick leave in the year before surgery (n=116) had a >90% risk of being on sick leave two years after surgery, while patients with 0 days of sick leave in the year before surgery (n=32) had a 13% risk of being on sick leave two years after surgery (Figure 13). Other predictors were tumors of WHO grade II-III (p=0.02), a history of depression (p=0.03), and new neurological deficits postoperatively (p<0.01).

The median wait time from radiological diagnosis to surgery was 76 days. Patients with a history of depression had smaller tumors on average.

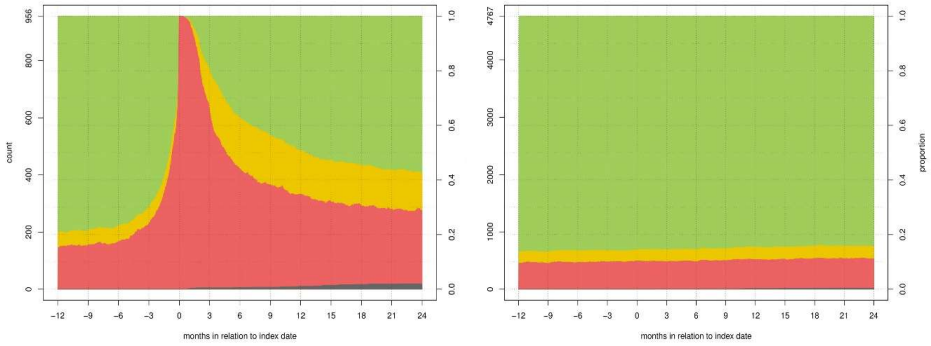

Figure 12: Stacked graphs of the rate of sick leave for patients (n=956, left) and controls (n=4767, right), from 12 months before the index date to 24 months after the index date, calculated for each day, with no sick leave compensation (green), partial sick leave compensation (yellow) and full sick leave compensation (red). Dark grey represents mortality. From Thurin *et al.*, Return to work following meningioma surgery, Neuro-Oncology Practice 2019, pages 320-328.

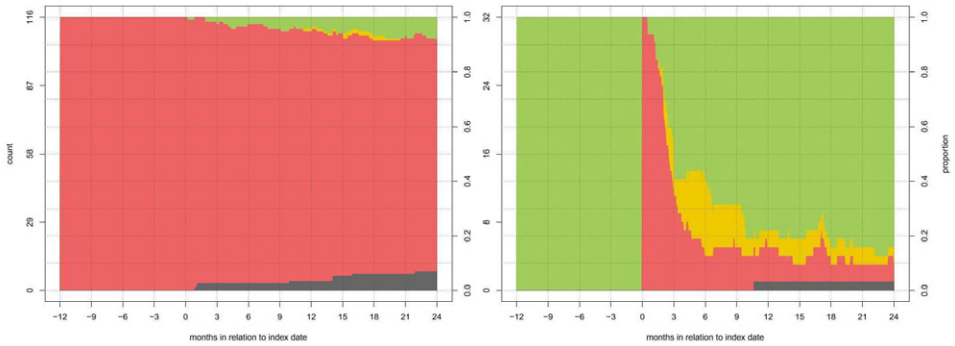

Figure 13: Stacked graphs of the rate of sick leave for patients with 365 sick leave days in the year preceding surgery (n=116, left) and patients with 0 sick leave days in the year preceding surgery (n=32, right), from 12 months before the index date to 24 months after the index date, calculated for each day, with no sick leave compensation (green), partial sick leave compensation (yellow) and full sick leave compensation (red). Dark grey represents mortality. From Thurin *et al*, Return to work following meningioma surgery, Neuro-Oncology Practice 2019, pages 320-328.

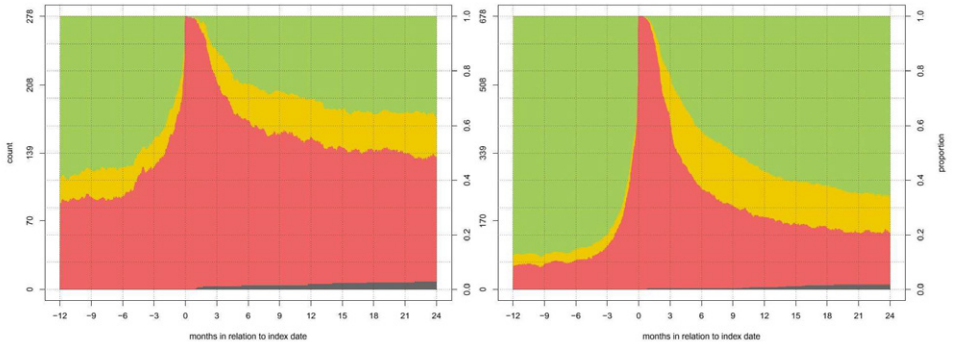

Figure 14: Stacked graphs of the rate of sick leave for patients with a history of depression in the year preceding surgery (n=276, left) and patients with no history of depression (n=678, right), from 12 months before the index date to 24 months after the index date, calculated for each day, with no sick leave compensation (green), partial sick leave compensation (yellow) and full sick leave compensation (red). Dark grey represents mortality. From Thurin *et al.*, Return to work following meningioma surgery, Neuro-Oncology Practice 2019, pages 320-328.

STUDY III

From the SBTR, through the inclusion and exclusion process outlined in methods, we identified 2080 patients treated for an intracranial meningioma between April 1st 2009 and December 31st 2015. The final cohort consisted of 2070 patients and 10312 controls. The rate of asymptomatic patients was 14%. Most patients (72.4%) could perform at least light work according to the WHO functional status (grade I-II) before surgery. The median wait time from radiological diagnosis to surgery was ten weeks, with the 25th percentile at four weeks and the 75th percentile at 24weeks.

The rate of patients with active use of AEDs, compared to controls, was higher both at index date (22.0% vs. 1.9%, p<0.001) and at two years after the index date (19.7% vs. 2.3%, p<0.001). This was also true for antidepressant use, although the difference was smaller, with an elevated use-rate for patients compared to controls both at index date (12.9% vs. 9.4%, p<0.001) and at two years after (14.8% vs. 10.6%, p<0.001). Use of sedatives peaked at the time of surgery and directly after surgery. Also for sedatives use was higher for patients than controls both at index date (14.4% vs. 6.1%, p<0.001) and at two years after (9.9% vs. 6.9%, p<0.001). Graphs of drug use for patients and controls are provided in Figure 15a-c.

We performed an analysis of the patterns of change in drug use. Half of the 455 patients with active AED use at index date (48.1%) did not need AEDs at two years after surgery. On the other hand, out of the 1615 patients with no AED use at surgery, 167 patients (10.3%) had an active AED use after two years. Thus, since the number of patients that stopped using AEDs was slightly larger than the number of patients that started using AEDs (219 vs. 167), the total number of patients using AEDs declined slightly.

A similar pattern of change was seen for antidepressants. Almost half of the 264 patients using antidepressants at index date (42.8%) did not use them at two years after surgery, while 8.6% of the 1806 patients without antidepressant use at index started during the follow-up years, yielding a slight increase in the total number of users (156 vs. 133). For sedatives, more than half (62.6%) of the 298 patients with active use at index date were no longer using sedatives at two years after surgery. As it was rare (6%) for patients on sedatives at index date to have become active users at the two-year follow-up, there was a marked decline in the total number of sedative users (188 vs. 106).

We identified the following predictors for using AEDs at two years after surgery: AED use at index date, a higher education, more comorbidities, having a new neurological deficit postoperatively, a larger tumor size, worse preoperative functional level, having a shorter wait time from radiological diagnosis to surgery and requiring postoperative radiation treatment. For antidepressant use, only two predictors were identified for active use two years after surgery: antidepressant use at index date and worse functional level preoperatively. Predictors for using sedatives at two years after surgery were: sedative use at index date, a higher age, having more comorbidities, having a new or worsened neurological deficit postoperatively, or having a worse functional level.

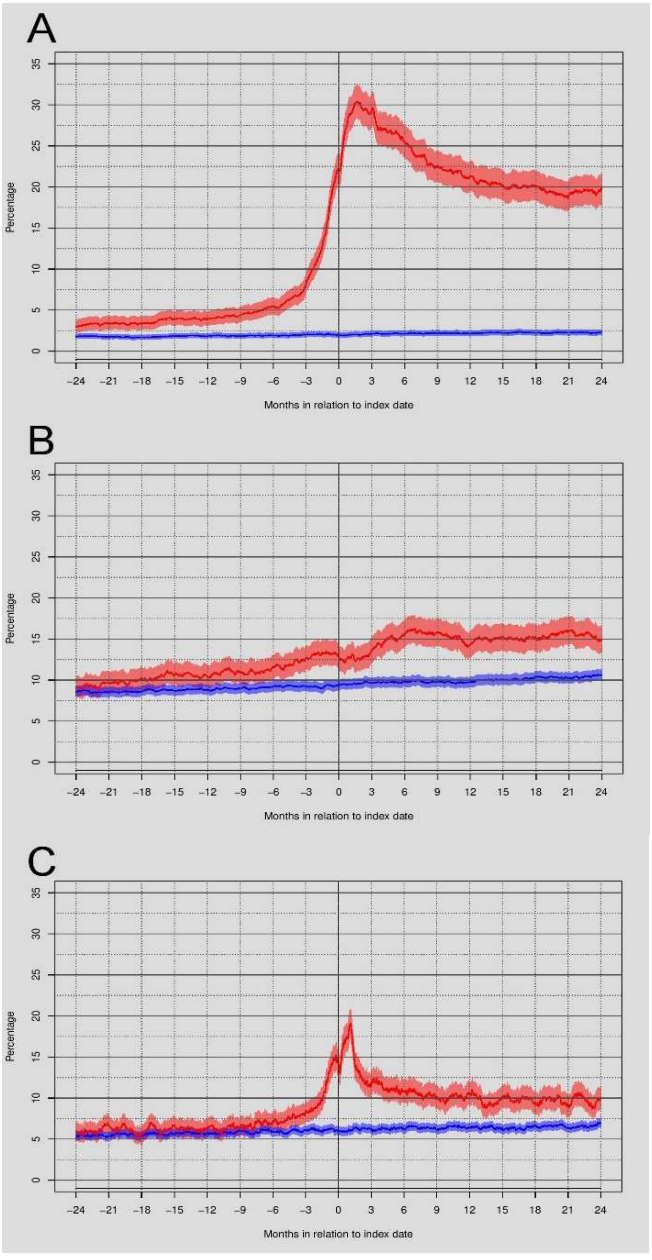

Figure 15a-c: Graphs depicting, in patients (red) and controls (blue), from two years before index date until two years after, the rate (95% CI) of active use of the following drug types: A) AED, B) antidepressants, C) sedatives. From Thurin *et al.*, Impact of meningioma surgery on use of antiepileptic, antidepressant and sedative drugs: A Swedish nationwide matched cohort study, Cancer Medicine 2021.

STUDY IV

In SBTR we identified vestibular schwannoma (VS) patients treated surgically between April 1st 2009 and December 31st 2015. Details of patient selection are outlined in the methods section. The final cohort consisted of 333 patients with 1662 controls. The return to work cohort (RTW cohort) consisted of 206 patients with 1025 controls. The median age was 52 years, 48% were females. Before surgery, the most common symptom was neurologic deficits (including hearing disturbances) present in 87% of patients, while 7% were asymptomatic before surgery. Most patients (64%) were fully active (WHO functional status 0). Tumors were <4cm in 86%, between 4-6 cm in 13% and >6cm in 4 patients (1,4%). GTR was achieved in 67%, a near-total resection (NTR) in 5% and partial resection in 28%.

After surgery, 28% of patients had a new or worsened neurologic deficit (including worsened hearing). The most common complications after surgery were infections (10%) symptomatic hemorrhage (3%), and venous thromboembolism (3%). The rate of patients undergoing reoperation because of a complication was 6%. The rates of antidepressant use for patients and controls were 6.0% vs. 6.3% (p=1.0) at two years before surgery 7.5% vs. 6.4% (p=0.64) at the date of surgery and 10.1% vs. 7.5% (p=0.15) at two years after surgery, respectively. The rates of sedative use for patients and controls were 3.9% vs. 4.3% (p=0.88) at two years before surgery 6.9% vs. 3.8% (p=0.08) at the date of surgery and 4.8% vs. 5.3% (p=0.85) at two years after surgery, respectively.

The rates of patients and controls on full-time or partial sick leave were 8.8% vs. 9.9% (p=0.62) at two years before index date, 12.1% vs. 9.7% (p=0.46) at one year before index date, 33.5% vs. 9.6% (p<0.01) at one year after index date and 24.8% vs. 11.5% (p<0.01) at two years after index date. Predictors negatively associated with not having returned to work two years after surgery were: an increased number of net days absent in the year before surgery (95% CI 0.89-0.93), the active use of sedatives at index date (95% CI 0.38-0.94) and having a new or worsened neurological deficit, including hearing

DISCUSSION

This thesis aimed to explore "softer" outcome measures after surgical treatment for meningioma and VS. We have focused on the rate of short-term complications, the rate of sick leave, and the use of AEDs, antidepressants, and sedative drugs before and after surgery.

We found that 43% of patients are still on sick leave two years after meningioma surgery. Meningioma patients also had an elevated rate of sick leave one year prior to surgery. For VS patients, there was no such difference at baseline, and the rate of patients on sick leave at two years after surgery was 25%. For meningioma patients compared to controls the use of AEDs, antidepressants and sedatives was higher both at index date and two years after surgery. The use of AEDs, antidepressants and sedatives two years after surgery were 19.7%, 12.9% and 14.8%, respectively. In contrast to this, no significant difference was seen for VS patients in the use of antidepressant or sedative drugs two years before surgery, at the index date or two years after surgery. The main short-term complications after meningioma surgery were new neurological deficits, infections and hemorrhage. The 30-day reoperation rate and mortality rates were 5% and 1.5%, respectively.

COMPLICATIONS

Ever since the meticulous and impressively self-critical surgical records of Harvey Cushing, who in detail described the undesired consequences of his work, [16] neurosurgical complications have been a subject of study, and attempts have been made to reduce their frequency. The most commonly used modern definition of a surgical complication is "any deviation from the normal postoperative course". [183] While this definition does not stipulate that a complication must be preventable, many complications that were initially common in neurosurgery have, through recognizing them as problems and finding ways to prevent them, been reduced efficiently. For this process to be possible, openly sharing and comparing outcome results (sometimes referred to as benchmarking) is important for identifying areas in need of improvement. [184, 185]

The data on complications in Study I of this thesis is based on the manually registered complications in SBTR, defined as having occurred within 30 days of the procedure. The most common short-term complication after meningioma surgery in our material was new or worsened neurological deficits after surgery (14.8%), symptomatic hematoma (9.4%), any postoperative infection (6.4%) new-onset seizure (4.5%) and venous thromboembolism (3%).

The rate of new or worsened neurological deficits after meningioma surgery reported by us of 14.8% is in line with reports of 10-14% in previous studies. [186, 187] However, the rate of neurological deterioration after surgery varies between studies. Reports as low as 3.9% have also been published. [188] As will be discussed below, future SBTR data will include more detailed information regarding the nature of neurological deficits, with the potential to clarify in greater detail how short- and long-term neurological function is affected by meningioma surgery. Our results indicate that a considerable fraction of meningioma patients suffer from new or worsened neurologic deficits after surgery, highlighting the importance of avoiding unnecessary surgery. It is noteworthy that among patients registered as asymptomatic, over 8% had new neurological deficits. Because the reason for surgery cannot be discerned in our data, it is unclear how many of these deficits could have been avoided if the patient selection would have been different.

The second most common complication in our material was a symptomatic hematoma, occurring in 9.4% of patients. As blood loss and hematomas were traditionally among the greatest causes of mortality in neurosurgery, [15] techniques for effective neurosurgical hemostasis have been an important development. Wounds have been cauterized using heat long before the era of modern medicine, pioneered by the Andalusian doctor Al-Zahrawi (who also recorded the first neurosurgical treatment of hydrocephalus) in the 10th century. [189] Noting that high-frequency electric currents could induce heat in tissue, Nikola Tesla proposed that this could be used therapeutically in 1891. [190] The concept was developed into techniques for electro-cauterization in the 20th century by William Bovie and Harvey Cushing, initially as monopolar and later as bipolar cauterization. [191, 192] Several other methods for surgical hemostasis have been developed, including oxidized cellulose, gel foam and fibrin glue, [193] and more recently gelatin thrombin matrix sealant. [194] Methods for optimizing coagulation have also improved, both by being able to detect deficient blood clotting, [195] and through coagulation enhancing drugs. [196] Microsurgical techniques to avoid bleeding have also been developed. Although the rate of mortality from neurosurgical bleeding complications has been reduced, [197] and while residual blood or a minute bleeding is common and often expected after brain tumor removal, [197] hematomas have been shown to still cause one-third of all mortality after brain tumor surgery today. [198] Because of the lack of consensus regarding how postoperative bleedings should be measured, the rates vary widely between studies. Rates of symptomatic bleeding leading to clinical deterioration are estimated between 1-7%, while rates of radiologically discovered bleedings are markedly higher, sometimes reported as high as 50%. [197] Similar rates of intracranial hematoma to the rate in our material can be found, with reports of 7-10%, [199, 200] although the definition of hemorrhage in these studies is non-identical to the one in SBTR. As hematoma was defined as symptomatic in SBTR, and thus have all caused some level of distress, the numbers remind us of the importance of preventing neurosurgical hematoma.

The rate of postoperative infection after meningioma surgery in our material was 6.4%, although this rate also includes pneumonia and other infections. The rate in SBTR is comparable to a study using a similar definition and finding an overall rate of postoperative infections of 5.7%. [201] In comparison, the incidence of CNS infections after neurosurgery has been estimated to be lower than 1%. [202] As not only CNS infections but also pneumonia can cause mortality and hospitalization in the postoperative setting, [203] benchmarking the rate of postoperative infections as defined in SBTR is important. However, when comparing the rates of infections, the CNS infections and general postoperative infection rates should not be confused. In the early days of neurosurgery, infections were major causes of mortality, and many attempts to prevent infections have been made. [14, 15] After initial trials in the field hospitals of World War II, [204] Pennybacker *et al.* demonstrated in a 1947 study that topical prophylactic penicillin reduced the rate of infections from 4.4% to 0.9% in a series of 670 neurosurgical patients, also concluding that the formulation could be used without causing seizures. The study set the stage for future developments and prophylactic antibiotics have been widely accepted as standard of neurosurgical care today, although rarely administered topically. The evidence for prophylactic antibiotics in neurosurgery is strong, with a clear reduction in postoperative infections demonstrated in meta-analyses, [205, 206] but may be dependent on choosing the correct antibiotic. [207] Prophylactic antibiotic treatment has also been challenged, based on that discontinuing routine use of antibiotic prophylaxis in selected neurosurgical patients in a Chinese study did not result in a significant increase in rate or severity of postoperative infections. [208] As there is strong evidence that prophylactic antibiotics are useful, further studies would be needed to verify this finding. It is also noteworthy that the rate of serious CNS infections has repeatedly and consistently been correlated to CSF leakage, [202, 208, 209] indicating that it is important to create a robust dural zeal when closing the surgical wound to prevent bacterial CNS invasion.

A more extensive resection, as measured by the Simpson grading system, was associated with a lower risk for complications in our material. Although this may seem counter-intuitive, radical surgery is less likely to be attempted in difficult tumors with a high risk for complications, and complications during surgery, such as a difficult bleeding, are associated with surgeons lowering the ambition for radicality. Illustrating this point, a lower Simpson grade (more extensive resection) has previously been shown to correlate with a lower likelihood of

serious intracranial hemorrhage. [200] The Simpson grade is problematic in this sense. Evidence for Simpson grading is generally based on retrospective studies. It can be argued that such studies constitute insufficient evidence to determine if Simpson grade I, II or III yield better results, because the decision to aim for a higher or lower Simpson grade is biased by confounding properties of the tumor, such as if tumors are inaccessible, large or malignant looking, or if complications arise during surgery. Similar to this situation, it has been shown that adjunctive radiotherapy is associated with a worse outcome for atypical meningioma patients, a result that is likely best explained as a result of bias. [210] A small, randomized trial would be more helpful and convincing in determining the true value of using Simpson grades I-III than additional large retrospective studies.

For VS surgery, the short-term complications have not been included as a study in this thesis. However, short-term complications after VS surgery have been described by us previously using a similar methodological approach as in study I. [211] The cohort is nearly identical to the cohort in study IV except that in study IV patients treated during the first three months, as described in methods, were excluded to enable the full analysis of drug use for all patients. We also excluded patients from study IV based on missing data and low registration rate of the reporting region in a different way than was done for the 2019 study. [211] In the 348 patients treated surgically for VS, the most common short-term complications were new or worsened neurological deficits (including new or worsened hearing loss), occurring in 28.7% of patients, infection in 10.1%, symptomatic hematoma in 3.2%, and VTE in 2.9%. The rate of patients undergoing reoperation within 30 days because of a complication was 6.6%. No 30-day mortality occurred. A subgroup analysis comparing large tumors (≥4cm) to smaller tumors (<4cm) determined that patients with larger tumors were more likely to be male, have ICP related symptoms, and have a shorter time from radiological diagnosis to surgery. [211] The notably higher rate of neurological deficits compared to the rate after meningioma surgery is likely related to that new or worsened hearing loss would be regarded as a neurological deficit.

PREVENTING COMPLICATIONS

It is often preferrable to prevent complications rather than to handle them after they have occurred. Airlines have long been aware of the power of checklists in formalizing routines to prevent undesired events. [212] Inspired by success in aviation safety, and by previous successful attempts of lowering infection rates through procedural checklists, [213] WHO has developed a checklist for safe surgery. [214] The checklist includes instructions for maintaining normothermia during the procedure, removing hair from the operating site in a hygienic way, checking that sterility of the procedure is adequate, that prophylactic antibiotic and antithrombotic drugs have been considered, as well as ensuring that the planned procedure, patient and side of the body are all correct. The WHO surgical checklist has been correlated to a small but statistically significant reduction in the overall rate of complications, depending on how well the hospital implements these routines. [215] A small reduction in the overall 30-day mortality after surgery has also been correlated to compliance with the checklist. [216] Although the proven effect size is small, it is an easy way to reduce the rate of preventable complications. Variants of the WHO checklist are therefore part of the neurosurgical standard of care in Sweden.

Although far from all neurosurgical complications are caused by medical mistakes, it is inevitable that some complications will be. Neurological deficits are sometimes predicted and accepted before surgery but may also be unexpected consequences of an error of judgement or surgical technique. Attitudes towards mistakes is a delicate matter in neurosurgery, as mistakes can have dire consequences for the patient. Although it is widely accepted that the reporting of mistakes is an important part of practicing medicine, not all medical errors made by a physician are acknowledged. Interview studies have revealed that reasons for not transparently disclosing an error can include shame and fear of consequences. [217-219] After a medical error had occurred, it was common for patients to feel the need for an acknowledgement of the error and preferably an apology. It was also common to desire a plan for avoiding similar errors in the future. Among physicians who had made an error, on the other hand, it was common to present the occurrence without assuming personal responsibility, and uncommon to apologize. [217]

The 2000 Institute of Medicine report *To err is human* has sparked intense discussion regarding medical mistakes. [220] It concluded that medical mistakes are an important issue, perhaps one of the ten most common causes of death in the US, but that it is desirable to move away from regarding mistakes as personal and instead take a wider perspective of how organizational changes can be made to avoid mistakes. In summary, it states that we will likely have more success in striving towards a perfect system than demanding doctors to be perfect. It also concludes that it is important to gather information on when mistakes almost happened, as this too can be used to prevent future mistakes. [221]

STANDARDIZED REPORTING

It is problematic to compare overall neurosurgical complication-rates as there is no consensus on how they should be defined and measured. In a review of neurosurgical complications after meningioma surgery, the overall rate of complications varied, frustratingly, from 2.7%-29.8%, [157] illustrating the lack of standardization. Another example is a 2019 Norwegian study reporting significantly lower rates of 30-day complications than those reported from SBTR and others, with worsening of neurologic status in 3.9%, postoperative infection in 2.7%, and hematoma in 2.6%. While SBTR data is based on reports made at the time of treatment, the method for evaluation by the authors of the Norwegian study was to review the description of neurological status before and after surgery to assess if the status was worse. A seemingly small difference in methodology or definition like this can significantly impact the reported rate of complications. It is unlikely that the results represent superior short-term outcomes, as the 30-day mortality was 5.4%, three times higher than the rate in SBTR. [188]

In response to this, several attempts have been made to establish a classification system for neurosurgical complications, including the three-tiered system published by Bosanto 2001. [222] The currently most accepted classification system was proposed by Landriel Ibanez 2011, [223] based on the more general surgical complication classification system by Clavien and Dindo. [183] The Landriel Ibanez system defines a complication as any deviation from the normal postoperative course. Complications are categorized as medical or surgical. Complications are further graded as mild (grade I): not life-threatening and requiring only non-invasive treatment, moderate (grade II): requiring invasive procedures, severe (grade III): life-threatening events requiring ICU, and grade IV: mortality as a result of a complication. [223] Although the system is easy to understand and use, it has been critiqued for leading to unreasonable situations, where severe brain infarctions should be classified as grade I while extra sutures bedside due to a CSF leakage should be classified as grade II. [224] Thus, misleading conclusions could be drawn if comparisons rely on Ibanez-graded data. Instead, a grading system for neurosurgical complications based on the impact they have on Quality of Life (QOL), even if that makes the system more complex and increases the threshold to start using it, has been suggested to be more appropriate. [225, 226] This is in line with a general shift towards a more patient-centered view on neurosurgical outcome, with a welcome increase in the interest of QOL, including the role that cognition and fatigue as well as professional status has for the patient. [30, 227, 228] If an intervention is surgical or medical may not matter much to the patient, but if an intervention leads to, for instance, losing the ability to work likely does matter. Other classification systems have been proposed, but no clear consensus has been reached.

Looking ahead, a novel five-grade system for classifying adverse events, Therapy-Disability-Neurology, has been proposed by Terrapon *et al*. [229] This system may prove useful for future efforts to standardize reporting of neurosurgical complications. Also, while the SBTR did not utilize a formal system for classifying complications when collecting the data on which this thesis is based, since the major structural update of SBTR in 2018, the Clavien-Dindo classification is used as an integrated part of the registry, facilitating future comparisons.

SICK LEAVE

The rates of meningioma patients on sick leave compensation (full or part-time) were 21% at one year before surgery, 51% at one year after surgery and 43% two years after surgery, while their controls were stable at 14-16%. Sick leave was more common two years after surgery for meningioma patients than VS patients, for whom the corresponding rate was 25%. For VS, the literature on sick leave after surgery is scarce. For meningioma, comparisons to the few relevant published studies are thwarted by the lack of standardized methods for measuring sick leave, similar to the situation for neurosurgical complications. One of the major issues that are not adequately addressed in many studies of sick leave is the definition of time. While we have analyzed the rate of sick leave on an individual day-to-day basis, most of the existing literature on sick leave for meningioma patients have a cross-sectional approach, counting patients at vastly different timepoints after surgery into the same category and calculating a proportion of sick leave based on this. [228, 230] One of the clear conclusions that can be drawn from our data is that the time from surgery is crucial to the sick leave rate for these patients. Therefore, data on sick leave without defining time from surgery may yield confusing results.

A 2020 study by Wirschung *et al.* found a high rate of patients not working after surgery. They evaluated the rate of sick leave and other socioeconomic variables for meningioma patients, concluding that among patients working full time before surgery, the rate of patients that had transitioned into partial work or stopped working completely one year after surgery was 21% and 24%, respectively. [231] While the study did evaluate the status at a defined time, the retrospective design with questionnaires sent out 3-16 years after surgery and excluding a large part of patients due to loss in follow-up has potential for bias, including recall bias and response bias. In addition, they did not exclude patients close to retirement age. [231] Two previous studies have reported the rate of meningioma patients not able to return to their pre-surgical professional level, with rates of 14%,[230] and 19%,[228]. Our results indicate that 43% of patients were on sick leave compensation at two years after surgery, compared to 21% at baseline. Thus, the rate of postoperative sick leave that we have found is likely higher also when compared to the pre-surgical level, perhaps related to that we studied the two-year timepoint, and it is possible that the rate would decline somewhat if the patients were followed for an even longer time. Since the pre-surgical professional level can be problematic to define, we would argue that absolute numbers are more comparable and should be used as the preferred measurement when possible.

Prior sick leave predicted long-term sick leave in the meningioma cohort, with the net days absent (number of sick-days in the year before surgery) increasing the risk for being on sick leave at two years after surgery. Illustrating this, patients with 365 net days absent in the year before surgery had a >90% risk of being on sick leave two years after surgery (Figure 14). Consequently, if meningioma surgery is attempted in a patient with long-term sick leave, it is unlikely to succeed in making the patient able to return to work. The finding in our study makes sense when considering that prior sick leave consistently has been shown to predict future sick leave [232, 233] and that the rate of patients returning to work is decreased among patients with prior sick leave. [234, 235] Thus, the large portion of patients in our study that were still on sick leave two years after surgery may have a hard time returning to work, underpinning the importance of preventing long-term sick leave.

In the general population, long-term sick leave can have far-reaching negative effects on individuals' health and social context. It has been shown that many forms of interventions to reduce sick leave are effective. [236] This statement is likely true also for meningioma patients. For patients with disabilities, returning to work can provide meaning and be an important part of life. [237] A systematic review concluded that work-directed interventions increase the rate of patients returning to work after an acquired brain injury (mainly trauma or stroke). The interventions that were found to be most effective were a combination of adaptation of working tasks and coaching / emotional support. The chance of returning to work was increased by the willingness of the employer to adjust working conditions and decreased if unemployment had occurred. [238] It has also been shown that work-directed interventions increase the return to work rate for patients with depression, [239] and that vocational services can have a positive effect for unemployed cancer survivors (18-25 years old). [240] For meningioma patients, no formal studies have tested the effectiveness of a work-directed intervention program. However, it could be an interesting avenue for further studies on surgically treated meningioma patients of working age. Inpatient rehabilitation for meningioma patients has shown promising results, in line with those for stroke rehabilitation, and should perhaps be considered for a wider selection of surgically treated meningioma patients. [241]

After VS surgery, long-term sick leave was less common than after meningioma surgery. The rates of VS patients on sick leave at two years before VS surgery were 12% at two years before surgery, 9% one year before surgery, 34% at one year after surgery, and 25% at two years after surgery. The VS controls were stable around 9-10%. The lower rate of sick leave among VS controls compared to the meningioma controls (14-16%) could be that the meningioma controls had a higher rate of female patients (75% vs. 48%). In our data, females had higher rates of sick leave compared to men, both before and after surgery. This finding is in line with that 60% of the Swedish citizens receiving sick leave compensation at least once in a year are female, as outlined in the section above regarding FK. The rate of female patients was identical also in the patient cohorts. Thus, some of the differences between meningioma patients and VS patients regarding the sick leave rate may be related to gender differences. However, as gender was not a significant predictor in our multivariable regression models for meningioma and VS, other factors may be more relevant. Predictors for sick leave after VS surgery were prior sick leave, sedative use, and new-onset neurological deficits. As discussed regarding meningiomas, it is expected that prior sick leave predicts future sick leave. For meningioma patients, the risk was higher among those with WHO grade II-III tumors. Thus, the benign nature of VS may also be important. Having a higher grade tumor is also related to more adjuvant therapy (radiation) and while this treatment is ongoing, patients are unlikely to return to work. Another factor worth considering is that the risk for complications is higher in meningioma surgery than in VS surgery.[211] While VS surgery is usually predictable in terms of outcome, with standardized surgical procedures and well described risk-benefit considerations, meningioma surgery is a more heterogenous endeavor.

FATIGUE

There may also be factors involved in the high rate of sick leave among meningioma patients that we have not measured, including fatigue. Fatigue, the subjective feeling of tiredness or loss of motivation, has been described as the most frequently reported complaint in cancer patients, and as one of the most severe symptoms.[242] While physiological fatigue is common in normal life, pathological fatigue is characterized by not being alleviated by rest and being disproportional to current tasks. [243] Due to the subjective nature of fatigue, it has been hard to quantify objectively. No clear consensus is established concerning how “energy” or motivation should be measured. Consequently, the reported incidence rates of fatigue among cancer patients vary ridiculously, from 4% to 99%, depending on definition and the method used for measuring. [242] A proposed definition for cancer-related fatigue by the National Comprehensive Cancer Network is “a persistent, subjective sense of tiredness related to cancer or cancer treatment that interferes with usual functioning”. [244] Although this definition is comprehensible, it does not specify how fatigue should be measured. This ambiguity is evident in the study of

fatigue in brain tumor patients. A systematic review of the literature on fatigue in low-grade glioma patients demonstrated that across the 19 studies included, seven different scales or measurement tools for self-reporting fatigue were used. The reported rate of mild or moderate fatigue was 20-76%, and the rate of severe fatigue was 4%. [29]

One of the obstacles in the scientific study of fatigue is that it consists of several interrelated but different phenomena: such as lack of motivation, sleepiness, boredom and physical exhaustion. Studying these facets separately may be more a more productive approach than to study them together. [245] For instance, inflammation-induced sickness-behavior is a well-known adaptive response in animals and humans, which most of us have experienced, where elevated levels of interleukins I and 6 cause lethargy, depression, anorexia and reduced grooming behavior. [246, 247] Sickness behavior may be an important part of fatigue for some cancer patients (those with elevated levels of interleukins), and irrelevant for others. Anemia is another example of a biological factor that can independently cause fatigue in some, but not all, patients. [248] The component of fatigue that is caused by physical exhaustion is sometimes separated from central or mental fatigue in studies. [243] As brain tumors, especially intra-axial ones, can impact the functions of the brain in a more direct way than other tumors, evaluating fatigue in brain-tumor patients has an extra layer of complexity. Illustrating this, left-sided tumors may have a higher likelihood of causing fatigue,[249] although no correlation has been found between QOL and brain tumor laterality.[250]

While fatigue is difficult to study, it is a very real and important issue that deserves considerably more scientific attention. It is a symptom that affects the patient in many areas of life, both professionally and privately, and is tightly correlated to the quality of life. [251] Fatigue is relevant for meningioma patients, as impairments in both quality of life and cognitive functions have been demonstrated for them. [227, 252] While the SBTR data that we utilized did not include any tool for measuring fatigue directly, it is possible that the elevated rate of sick leave that we have demonstrated for meningioma patients is, to some extent, related to fatigue.

Sick leave at two years after meningioma surgery was associated with a history of depression, with >40% in partial or complete sick leave at one year before surgery and >60% sick leave two years after surgery in this group. Sick leave at two years was also associated with tumors of WHO grade II-III and with having new neurological deficits postoperatively. It would be highly interesting to have data on fatigue in these groups. However, as evident by the discussion above, fatigue should be separated into well-defined parts for this estimation to be helpful. Including validated and nuanced methods for measuring fatigue into SBTR or other registries of brain tumor patients, preferably using methods validated specifically for brain tumors, [253] could help explain fatigue's role for these patients.

DRUG USE

For meningioma patients, compared to controls, we found that the use of AEDs, antidepressants and sedatives were higher both at the index date and two years after surgery. The extent of this difference varied across drug groups. For AEDs, use was increased already two years before surgery, while for antidepressants and sedatives, the baseline use two years before surgery was similar between patients and controls. For VS patients, a rather different pattern emerged. VS patients did not significantly differ in the use of antidepressant or sedative drugs two years before surgery, at index date, or two years after surgery.

As the data is based on purchases rather than prescriptions, and since we were able to include patients without bias from non-responders or patients lost in follow-up, the data is an excellent source of information on drug use among surgically treated meningioma and VS patients. However, we are somewhat limited in our ability to determine the reasons for the drug prescriptions and use. According to the clinical experience of the authors in Study III-IV, AEDs are almost exclusively prescribed to prevent or treat seizures in the Swedish healthcare system, except for certain drugs prescribed for pain (which were excluded from our analysis). Thus, it was presumed that AEDs were used in attempts to prevent seizures.

The main indication for antidepressants is major depressive disorder (MDD), but they are also prescribed for other conditions. A recent study investigating reasons for antidepressant prescriptions in the general population found that a majority were prescribed as treatment of depression. However, other major reasons for prescribing antidepressants were anxiety, stress, sleep disorders, and pain. [254] These disorders are not equivalent to depression, but there is interrelation and overlap between them. For instance, anxiety and sleep disorders are part of the diagnostic criteria for depression. [255] Further, the rate of antidepressant use is tightly correlated to the severity of depressive symptoms,[256] and the use of antidepressants has been previously been utilized to indicate the prevalence of depression.[257] The rate of antidepressant use is likely indicative of the rate of depressive symptoms, but we cannot discern the actual rate of MDD among the patients we have studied.

Regarding the sedatives group, as our overarching aim was not to study sleep disorders *per se* but to study the well-being of patients after brain tumor surgery, we did not present separate data for hypnotics/sedatives. Similar to antidepressants, sedatives are prescribed for several different but related conditions. It has been suggested that sleep disorders span over many diagnoses, and that there are multiple and complex associations between anxiety and sleep disorders. [258] Sleep disorders are also tightly correlated to anxiety and depression [259] and may exacerbate anxiety. [258] Thus, while the use of sedative drugs indicates mental distress, we cannot determine based on our data how much of the sedative use was caused by anxiety, sleep disorders or depressive symptoms.

ANTIEPILEPTIC DRUGS

The use of AEDs was considerably higher for meningioma patients than controls, particularly at index date when the rate of AED use was over ten times higher for patients than controls, with 22% vs. 1.9%. This result is expected because AED use is relatively uncommon in the general population, while seizures constitute the presenting symptom of meningioma in almost one-third of patients. [66] The steep rise in AED use in the months preceding surgery likely represent patients diagnosed with a meningioma because of a seizure and receiving surgical treatment within a few months. The rate of use remained elevated throughout follow-up, with 19.7% for patients two years after surgery vs. 2.3% for controls. However, this does not mean that most patients on AEDs remained on AEDs throughout follow-up, as there was a substantial cross-over of patients. Half of the 455 patients with active AED use at index date (48.1%) did not need AEDs at two years after surgery. On the other hand, out of the 1615 patients with no AED use at surgery, 167 patients (10.3%) had an active AED use after two years.

The rate of patients able to quit AED use after surgery in our material (48%) was low compared to a 2016 meta-analysis reporting that the overall rate of patients with seizures preoperatively that were seizure-free after surgery was 69%. [66] However, as we have studied drug use and not actual seizures, some patients with preoperative seizures may be seizure-free but remain on AED treatment as a precaution. Conversely, freedom from AEDs is not equivalent to freedom from seizures. A seizure occurring within seven days of a neurosurgical procedure can be regarded as provoked, and long-term AED treatment may not be initialized if the risk for future seizures is considered too low. [260] The rate of previously AED-free patients that became AED users during follow-up (10%) was in line with the 12% new-onset seizures after surgery in previously seizure free patients reported in the 2016 meta-analysis. [66] The agreement between our data and the seizure data could reflect that it was uncommon to initiate long-term AED treatment if the patient had not experienced a seizure.

One of the contributing factors to the elevated rate of AEDs at the time of surgery in our material could be prophylactic preoperative AEDs. Although it is generally not recommended, and despite the lack of proven benefit to patients from using prophylactic AEDs, [66, 261-263] it is not uncommon for AEDs to be prescribed for that reason in the neurosurgical community, as demonstrated in a survey of tumor-treating North American neurosurgical centers, where 63% of respondents reported always or almost always prescribing postoperative AED prophylaxis in patients with no seizure history. [264] In Sweden however, prophylactic AED prescription is not common practice. The issue is currently being investigated in a randomized trial, STOP'EM, aiming to provide Class I evidence for if a short-term AED-prescription after supratentorial meningioma surgery decreases the risk for long-term seizure in patients with no previous seizures. [265]

While seizures are an important cause of reduced QOL in meningioma patients, [266] side effects from AEDs also have the potential to impact QOL negatively [266, 267]. Therefore, it is important to identify patients with a high risk of postoperative seizure, to treat a selected group of patients. Based on a thorough analysis of pre and postoperative variables and relative risk for postoperative seizures, a system guiding AED treatment after meningioma surgery has been proposed: the STAMPE2-score. [268] This system proposes that sensorimotor deficit, tumor progression, age <55 years, and peritumoral edema all yield 1 point each. Major surgical complications, preoperative epilepsy, or epileptiform potential on postoperative EEG, yield 2 points each. A total score of 2 or more indicates that AEDs should be initialized. [268] Although promising, this scoring system has not been validated on an independent cohort, perhaps in part due to that routine use of EEG is uncommon. A modified STAMPE2 scoring, ignoring the EEG points, was not reliable in predicting postoperative seizures in a validating study, concluding instead that large tumor size and sphenoid wing location were important predictors. [269] STAMPE2 is not established in clinical practice in Sweden, and the SBTR does not collect the variables necessary to provide STAMPE2 scores. Several other attempts have been made to define what patients should receive AEDs after surgery, including a Swedish study reporting that postoperative seizures were predicted by preoperative seizures and by large tumor size. [270] In summary, a validated system for predicting postoperative seizures would be useful but has not been established.

ANTIDEPRESSANTS AND SEDATIVES

The use of antidepressants was elevated for meningioma patients compared to controls with a rate of 12.9% at the time of surgery and 14.8% at two years after surgery. During this time, the use for controls was 9.4-10-6%. Antidepressant use for meningioma patients compared to controls was also increased at one year before surgery, but not at two years prior to surgery. For VS patients we did not find a difference in antidepressant or sedative use between patients and controls.

As the median time from radiological diagnosis to surgery was ten weeks, with over 25% of patients waiting more than six months, the rapidly increasing rate of antidepressant use in the preoperative year could be related to a subset of patients reacting with depressive symptoms to being diagnosed with a tumor, or to anxiety before the surgical procedure. An interesting epidemiological study demonstrated that the likelihood of being diagnosed with a meningioma was associated with recently being started on AEDs, antidepressants, corticosteroids or drugs treating migraines. They also showed that the likelihood was related to a recent diagnosis of cerebrovascular disease, headache, epilepsy or other cancers, but not if these diagnoses were more than five years old. The authors concluded that bias due to increased MRI use associated with these conditions is a likely explanation, [271] relevant to the interpretation of our data. As discussed above, there is a reservoir of undiagnosed asymptomatic meningiomas in the population. If depressive symptoms are related to increased use of head MRI, this will create an association between incidentally found meningiomas and antidepressants. Similarly, if concurrent depression increases the likelihood that an asymptomatic meningioma is interpreted as symptomatic, this will create an association between antidepressant use and meningioma. This could be part of the explanation for the increased use of antidepressants in the meningioma cohort, compared to controls, that we have found.

Contrary to this reasoning, it has been proposed that depression should be considered an early symptom of meningioma. The prefrontal cortex, especially the medial and inferior surfaces (including the orbitofrontal cortex, medial prefrontal cortex, the anterior gyrus cinguli, and deeper circuits relevant to these areas), are involved in action selection and regulating desires and behavior, although our current understanding of these phenomena is in its infancy.[67, 272, 273] Meningiomas that compress such areas of the brain have a biological basis for producing depressive symptoms, and depressive symptoms caused by meningiomas have been demonstrated in a large number of case reports, especially for frontal meningiomas. [274] However, the notion that depression would be an early symptom in meningiomas with a location and size that do not have a biological basis for producing depressive symptoms is highly questionable.

Our data indicate that meningioma surgery does not decrease the average level of depressive symptoms on the group level, at least within two years, in line with several previous reports. [29] Contrary to this, it has been reported that the rate of depressive symptoms is high before meningioma surgery but recedes to the level of the normal population six months after surgery. [275] However, the study was performed in a small, single-institution case series of patients, with a preoperative evaluation immediately before surgery, when the level of anxiety is presumably high, and the failure to detect a difference between patients and controls at the later time points may be related to the small sample size.

While the impact of neurosurgical treatment on the patient's mental health may be underestimated, it should also be taken into consideration that not performing surgery, in patients wishing to do so, may also cause distress. Patients in a wait-and-scan situation were significantly more likely to be depressed. [276] Thus, it is not certain that avoiding surgery would lower the use of antidepressants and sedatives. However, the use of antidepressants and sedatives surged in the months around the date of surgery, indicating an effect of the surgical procedure.

It is also possible that the increased attention from the healthcare system after receiving surgery and being followed up at specialized clinics would increase the likelihood of being prescribed medications for conditions that would otherwise not have been treated, but this does not explain the difference between meningioma patients and VS patients.

The use of antidepressants and sedatives is more common in women than men. [277] The higher rate of female patients in the meningioma cohort compared to the VS cohort (75% vs. 48%) could be an important part of the higher rate of antidepressant and sedative use. Gender-related differences may explain why the meningioma controls had a higher rate of antidepressant use than the VS controls, but because controls were matched based on sex, gender-related differences cannot explain why there was a significant difference between controls and patients for meningioma but not VS. However, there was a trend towards a difference also for VS patients concerning antidepressant use, with 10.1% vs. 7.5% (p=0.15), and it is possible that the VS patients would have had an increased rate if the cohort had been larger. This is also supported by the fact a few months after surgery the rate for VS patients was significantly elevated for a brief period. It would be interesting to study the use of antidepressants and sedatives after VS surgery in an even larger cohort, perhaps after combining data from several Scandinavian registries.

The use of sedatives peaked around the time of surgery for meningioma patients with 14.4% vs. 6.1% used for patients and controls, respectively. We interpreted this as a sign of anxiety and sleeplessness among meningioma patients. The rate of sedative use among both meningioma controls (6.1%-6.9%) and VS controls (3.8-5.3%) was similar to the rate of patients having used sedatives within the past month (5.5%) reported from a Canadian cohort. [277] Sedative use is more common in females than males and is more common in elderly patients, [277] potentially contributing to the increased incidence among meningioma patients. Corticosteroids have the potential to disturb sleep and are prescribed to many meningioma patients. They are less commonly prescribed in VS patients, potentially contributing to the sharp increase for meningioma patients not seen in VS. Based on that VS surgery is an equally large surgical procedure with many risks involved, it would be expected that VS surgery causes an equal peak in sedative use. However, it is possible that the main risks associated with VS surgery, including hearing loss and facial nerve damage, are not perceived as equally threatening as the risks associated with meningioma surgery. The smaller cohort size could also have contributed to the lack of peak in sedative use for VS patients in our material.

It is concerning that the long-term use of sedatives was elevated for meningioma patients. Long-term use of benzodiazepines is generally discouraged as they are addictive drugs with the potential for detrimental health effects. [278, 279] While it is understandable that clinicians may want to provide short-term relief to patients, it is an important finding that this may come at the cost of causing long-term sedative use.

OVERTREATMENT

In the meningioma cohort, 14% of patients receiving surgery were registered as asymptomatic. It is not clear what indication the surgery had, but we know that these patients were younger, had smaller tumors, and a lower rate of WHO grade II-III tumors. In light of the recently discovered pool of undetected asymptomatic meningiomas and VS, it has become increasingly important to weigh the risks of surgery carefully against the expected benefits.

Overtreatment of tumors can escalate quickly, as shown by the "thyroid cancer epidemic" of South Korea. A surge of ultrasound-screening for thyroid cancer in the early 2000s increased the incidence of diagnosed papillary thyroid cancers 15-fold and increased the rate of thyroid tumor surgery by almost as much. But while an increasing number of progressively smaller tumors were being treated, mortality in thyroid cancer remained unchanged. For thyroid cancer there is a large reservoir of subclinical cases, one-third of all adults have small papillary thyroid cancers in autopsies. It is very uncommon for these to become symptomatic during life. Side effects among Koreans treated for thyroid cancer was hypoparathyroidism in 11% and vocal cord paralysis in 2%. [280]

What can we learn from this? The situation parallels in many ways the situation for extra-axial brain tumors and MRI. There is a reservoir of asymptomatic extra-axial brain tumors in around 3% of elderly patients. Most of these do not cause symptoms during the lifetime of the patient. [37, 38] If these are exposed to MRI-investigations in a system that tends to treat progressively smaller tumors surgically, there would be many unnecessary surgeries and many unnecessary side effects. The situation where a tumor is treated vastly more often with no effect on mortality rate for that tumor has been described as "pathognomonic" for overtreatment. [280] Although surgery can be performed for other reasons than to improve overall mortality, if the patient is asymptomatic, there is little to gain in terms of function.

Luckily, this has been widely recognized. Attempts have been made to counteract this, including guidelines regarding tumor size refraining surgeons from resecting progressively smaller tumors. For VS, treatment is mainly guided by actual size, measured on MRI, and a predefined symptom, hearing loss.[120] For meningiomas, treatment is more vaguely guided by size. The guidelines recommend initial observation as long as patients are considered asymptomatic and as long as there is no growth on subsequent radiologic examination. [52] But there is room for interpretation regarding what symptoms should be attributed to a meningioma, e.g., when the patient presents with common and unspecific symptoms like pain or fatigue. If such symptoms occur unrelated to the meningioma, and the patient performs an MRI as a part of the investigation, if no other reason is found explaining the symptoms, they may be wrongfully attributed to the tumor. Because of random fluctuations in symptom severity and the well-known strong placebo effect of surgical interventions, [281, 282] it may be hard to discover that the surgical indication is wrong in such cases without a randomized study. Another possible source of overtreatment concerns tumor that are asymptomatic but have demonstrated growth. As many tumors grow very slowly, alternating between growth and quiescence, growth between two MRI exams does not mean that the tumor will ever become symptomatic. Based on the number of incidentally discovered tumors among elderly patients compared to the number of patients experiencing symptoms from their tumors, it must be assumed that most incidentally discovered meningiomas have a low risk of causing symptoms.

When predicting the likelihood of a slowly growing tumor becoming symptomatic, it must also be considered that the total brain volume decreases with increasing age, especially over the age of 70, because of atrophy. [283] Thus, a large intracranial tumor that could cause distress in a young patient could go unnoticed in an elderly patient. An illustration of the difference between normal brain volume and severe atrophy is available in Figure 16.

As we cannot accurately determine if an asymptomatic tumor will cause symptoms during the patient's lifetime or not, we treat many who would never have become symptomatic. For this reason, the natural history of untreated asymptomatic incidentally discovered meningiomas deservers meticulous study.

It is also relevant to point out that if surgery is performed on wider indications, including healthier and less symptomatic patients, the average outcome after surgery may be artificially improved by the confounder that the average patient receiving surgery is less sick. This way, measures of mortality, complications or even quality of life could be improved in the group considered patients. At the same time, the average quality of life in the total population of the country where this happens might be reduced.

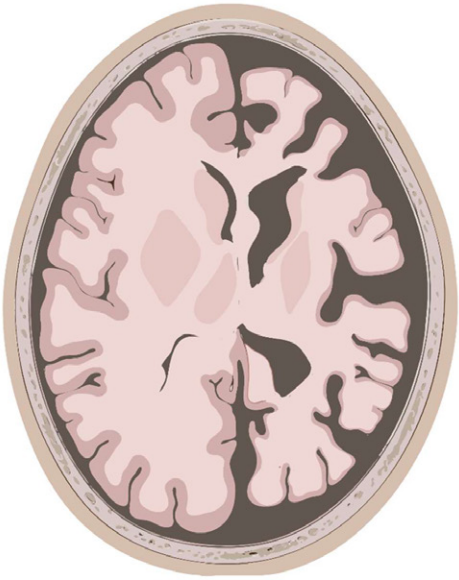

Figure 16. Transverse image of brain illustrating normal brain volume (left) and severe brain atrophy with reduced brain volume and increased amount of CSF (right). Image created using biorender.com

STRENGTH AND WEAKNESSES

The nationwide cohort approach we have used included all patients treated surgically for meningioma and VS during the specified time as the basis for the research, avoiding many forms of bias. In addition, the cohorts are relatively large, providing statistical power and making it possible to perform meaningful analyses even as we are studying the uncommon tumor VS in a small country. As we did not rely on questionnaires, we avoided losing patients in follow-up, and avoided bias from incomplete return-rate. It is a strength that we have taken the time from surgery into consideration, aligning all patients individually to an index date to provide data with a day-to-day resolution instead of cross-sectional data of patients at differing time-points after surgery. The drug use data was based on purchased prescriptions by patients, which is more reliable than data on prescriptions. It is also more reliable than self-reported drug use, which is frequently underreported. [284] We have compared our results to matched controls, allowing us to discern the effects of meningioma and VS surgery from general trends in the population.

However, our analysis was limited by the set number of predefined variables included in the registry. Because of the observational study design, we are also limited in our ability to draw causal conclusions about the associations we find. A controlled trial, randomizing patients to receive or not receive surgery, would have provided superior evidence and allowed us to discern better the effects of surgery from the effect of having a tumor diagnosis. However, it seems unlikely that a large, randomized trial will be performed to answer these questions in the near future. Retrospective studies may therefore currently be the most reasonable approach. A retrospective study comparing our results to the outcome for meningioma and VS patients not receiving treatment, or receiving radiation treatment, would have been informative, but we did not have a suitable cohort of such patients available. An important limitation of the studies we have performed is also that we have not used patient reported outcomes, as external evaluation of outcome risks focusing on things that do not matter to the patient. [285]

MAIN CONCLUSIONS

The studies included in this thesis have demonstrated that although surgical treatments for meningioma and VS are associated with low mortality rates, they have a considerable impact on “softer” outcome measures. We have also shown that it is useful to define the time in relation to surgery when studying the rate of sick leave and drug use for these patients.

The most common short-term complications after meningioma surgery were new or worsened neurological deficits after surgery (14.8%), symptomatic hematoma (9.4%), any postoperative infection (6.4%) new-onset seizure (4.5%), and venous thromboembolism (3%). The 30-day mortality rate was 1.5%.

The rate of meningioma patients on sick leave at one and two years after surgery was 51% and 43%, respectively, compared to 15-16% for controls. The baseline rate of preoperative sick leave was one year before surgery was also slightly elevated for meningioma patients compared to controls (21% vs. 14%). Predictors for being on sick leave two years after meningioma surgery were preoperative sick leave, preoperative depression, having a higher grade (WHO grade II-III) tumor, and having new or worsened neurological deficits. After VS surgery, long-term sick leave was less common than after meningioma surgery. At one and two years after surgery, the rates of patients and controls on sick leave were 34% vs. 10% at one year and 25% vs. 11% at two years after surgery. No elevated sick leave rate was observed before VS surgery: the rates of patients and controls on sick leave at two and one years before VS surgery were 12% vs. 10% and 9% vs. 10%, respectively. Predictors for being on sick leave two years after VS surgery were preoperative sick leave, sedative use and a new or worsened neurological deficit (including hearing loss) after surgery.

For meningioma patients, the use of both AEDs, antidepressants and sedatives was elevated for patients compared to controls both at baseline, at the time of surgery and the end of follow-up. Two years after meningioma surgery, the rate of AED use among patients compared to controls was 19.7% vs. 2.3%. The corresponding rates were 14.8% vs. 10.6% for antidepressant use and 9.9% vs. 6.9% for sedative use. For VS patients, the use of antidepressants and sedatives was less common. VS patients did not significantly differ in the use of antidepressant or sedative drugs two years before surgery, at index date or two years after surgery. Two years after VS surgery, the rate of antidepressant use of patients compared to controls was 10.1% vs. 7.5%. The corresponding rate of sedative use was 4.8% vs. 5.3%.

FUTURE PERSPECTIVES

The growing number of incidentally discovered tumors on radiological examinations necessitates improved methods for accurately determining which of these patients will benefit from treatment. A more comprehensive grading system for brain tumors based on radiology would be helpful in clinical practice. Regarding VS, the radiological diagnosis has become accepted as sufficient, and Koos grading of tumors based on MRI imaging and current symptom-level can provide clear recommendations regarding the course of action. [120] Thus, for VS, we are approaching a radiological classification system. VS is a relatively homogenous tumor with a similar location and WHO grade. Despite this, the treatment recommendations for VS must consist of a decision tree with many branches.

Meningiomas are a more complex tumor group. They are divided into 15 subgroups across three WHO grades [9, 79] all with different molecular profiles,[52] and the tumor location varies across the inner surface of the skull (and intraventricularly). [3] Despite this complexity, it is becoming increasingly important to find good radiologically based recommendations for meningiomas, as the incidence of incidentally discovered asymptomatic meningiomas in elderly patients is high and is likely going to increase.

For a useful recommendation tree, we need reliable radiological signs to rule out or verify that a finding is a meningioma, and predict if radiation, surgery, or observation is the best course of action. Liu *et al.* proposed a system based on multiple radiological features for stratifying convexity meningiomas into three groups. They demonstrated that this system could predict both WHO grade and, importantly, the three radiological groups were predictors of survival outcome. The features used by Liu were signal intensity on DWI, heterogeneity on contrast-enhanced T1, no subarachnoid cleft in brain-tumor interface, peritumoral edema on T2, and irregular shape of the tumor. [286] Suppose such a system also included information from meningioma specific radiolabeled ligands, such as DOTATOC or DOTATATE, and perhaps other markers. In that case, it could be safe and reliable enough to provide a clear recommendation regarding treatment. It could be an impactful and useful clinical tool if it was validated through a large, randomized study.

Moving forward, using molecular markers instead of histological appearance as the basis for which to divide the groups of meningiomas may improve diagnostics, especially if we can determine the molecular profile of the tumor through radiological imaging. Since the histological WHO grading is mainly a form of marker for predicting outcome, it may be more useful to create independent radiological markers to guide treatment decisions than to predict histological WHO grades through radiology. The WHO-grading of meningiomas was founded on a body of research outlining differences in survival and recurrence rate depending on histological appearance.[85] It is not unreasonable that a similar grading will be in place based on radiology within ten or twenty years.

Clinical parameters (such as age and sex) are crucial for making correct risk assessments on imaging data. A path forward could be to integrate radiological grading as a part of a greater decision algorithm, similar to work that has been done to combine radiological and histological data into the same model. [287] For instance, the radiologist could grade the finding. The clinician could then use the grading on a web-based form where s/he also uses age, sex, symptoms, if the tumor was incidentally discovered, if there is a known NF2 disorder, etc. The tool could be managed and continuously updated by a resourceful international scientific organization, to provide accurate recommendations. In this way, a complex set of considerations could be combined into an easy-to-use tool for clinical guidance. Clinical scores like CHADS2 [288] or STAMPE2 [268] combine clinical data into a single tool for clinical guidance but are limited in the amount and complexity of information that can be included. A digital tool could be almost infinitely complex, and be an integrated part of the EHR, minimizing the need for double documentation, as well as integrated with a clinical registry, facilitating research. Much like digital registries has opened new avenues for data analysis, compared to registries based on books and ink, the integration of registries with EHR and web-based decision guiding tools will change the environment of clinical research and medical care in the future.

The studies included in this thesis are small steps on the long road towards providing better care for patients with brain tumors. While they provide clinically useful information regarding the risk for postoperative sick leave and drug use, several questions remain unanswered. The relatively low rate of meningioma patients returning to work two years after surgery is an interesting finding, inviting future studies testing work-directed interventions to improve this rate. Comparing our results to surgical cohorts in other countries with similar systems, such as Denmark or Norway, could unveil important differences. Perhaps even more interesting would be to use the same methodology for a cohort treated with SRS or EBRT, to determine if other treatment options impact patients to an equal extent. Another avenue of future research would be to validate the findings with patient reported outcome measures, to provide a deeper understanding of what the sick-leave and antidepressant/sedative use means to these patients. In this way, the studies of this thesis will hopefully serve as a framework for future research to build upon.

ACKNOWLEDGEMENTS

I am grateful to the **Sahlgrenska Academy**, **Gothenburg University**, the **Institution for Neuroscience and Physiology** and the **Section for Clinical Neuroscience** for providing me with an excellent third cycle education.

Asgeir Jakola, my main supervisor. Thank you so much. Your energy, patience and competence never ceases to amaze me. You have not only guided and encouraged me through this work, but also been a general life-inspiration. The kind of person who makes you see the world differently. You have been a great supervisor, advisor and friend. I look forward to working with you on future projects.

Thank you **Anja Smiths,** my co-supervisor, for believing in me, providing support and council when I needed it, and for all the good suggestions and ideas. You have a gift for scientific writing, I hope I will one day be as skilled as you are. My co-supervisor **Sasha Gulati:** Thank you for helping me, sharing good times and giving wise council. You always seem to pinpoint what is important. It has been great to share this journey with you.

Thank you **Øyvind Salvesen,** for being a fantastic person, a squash-prodigy and for making the hard statistical parts of this project so much better. This thesis would not have been possible without you, and I have really enjoyed working with you. I hope I will be able to visit you in Trondheim again soon.

I am grateful to all co-authors who have contributed to this thesis. I am lucky to be a part of such a strong team of talented researchers! **Isabelle Rydén**, thank you for great collaborations and conversations on both research and life. We need to do more research-trips together. **Alba Corell,** thank you for aiding me in successful teamwork many times, and guiding me through the dissertation process. **Jiri Bartek Jr,** always radiating positive energy, thank you for many great collaborations, I hope there will be many more! **Tomás Gómez Vecchio**, thank you for all the help over the years, I am so happy you are a doctoral student and I think we will find interesting projects together. **Thomas Bontell,** thank you for helping me understand the microscopic world of meningiomas, and providing histologic images for the thesis. I look forward to working with you again. **Olivia Näslund,** it is always a pleasure interacting with you, I look forward to our future projects. I also want to celebrate the fantastic researchers **Thomas Skoglund, Bertil Rydenhag,** and **Petter Förander** for contributing valuable ideas to the studies of this thesis, as well as **Dan Farahmand** and **Göran Hesselager** for their contributions. Thank you **Johan Zelano** for teaching me Cox regression. Thank you also to **Isabella Björkman-Burtscher**, **Johan Ljungqvist** and **Lisbeth Claesson** for giving valuable advice on my half-time seminar. I would like to express my gratitude to fellow PhD-students **Ida Lindman** and **Elin Svedlund Eriksson** for reviewing the thesis frame thoroughly and making great suggestions. I owe you one (each)!

This thesis would not have been possible without the continuous work of the **SBTR**, and I would like to credit all the doctors, nurses and patients involved in this project. In particular, I admire **Roger Henriksson,** whose continuous enthusiastic work lifts the SBTR off the ground to enable studies like the ones I have written. Thank you also to **Carol Kruschko**, president of CBTRUS, for taking the time to personally answer some of my questions and allowing me to use Figure 4. The work presented in this thesis could also not have been done without the funding from **Vetenskapsrådet** and **Göteborgs läkaresällskap**, for which I am honored and grateful.

To my brilliant and empathic ST-chef **Caroline Sandahl Molinder,** thank you for believing in me and for encouraging me at every step. You hired me, arranged time-off from clinical work and have been 100% supportive to my research. I am also grateful to ST-studierektor **Dan Bibac**, sektionschef **Johanna Lundin** and verksamhetschef **John Brandberg** for enabling me to finish my PhD project. Without all of you the dissertation would not have been possible. Thank you **Darko Sarovic** for helping me to find radiological images, you are a gentleman and a bro. I am grateful also to all other colleagues in the radiology department. **Simon, Johanna,** and **Fredrik** have a special place in my thoughts for making me feel welcome when I first started, and **Göran** for being my clinical mentor.

Mia Ericson and **Bo Söderpalm**, my former supervisors, I am incredibly grateful to you for your mentorship and friendship, and for teaching me so much about neuroscience. I am happy that I worked with you and I am certain that my time in the lab with you has made me a better scientist. I am also grateful to all the other colleagues I met in the **Addiction Biology Unit,** including **Julia, Louise, Lisa, Anna, Yasmin, Clara, Rosita** and **Amir**, for putting up with me and showing me the ropes.

Magnus Rudenholm, thank you for your friendship. You have taught me everything I know about teaching, and most of what I know about neuroanatomy. I am also grateful to **Magnus Braide, Mikael Nilsson** and **Läkarprogrammets programkommitte** for believing in me and making https://brain.it.gu.se possible. Thank you **Luisella Sibilla** for helping me with latin nomenclature and **Alex Belko** at **Xlent** for tirelessly programming and fixing bugs. Of course, thank you also to the awesome neuroradiologist **Brett Young**, the man behind the original headneckbrainspine.

And then, to all my friends who fill my life with happiness, and without whom I would be utterly lost, thank you all so much! Especially **Jonathan, Therese, Anton, Malin, Erik, Erik, Erik, Viktoria, Fredrik, Sophie, Anders, Anton, Patrik, CJ, Mai, CB, Glenn, Amanda, Markus, Mikaela, Simon, Patricia, Daniel, Tomoko, Martin, Jonas, Amanda, Nima, Annabel, Marta, Elin, Camilla, Anna, Joanna.** A special thank you goes to **Richard,** who sheltered this struggling scientist, and to **Emma Husmark** who created the amazing artwork for the front-page(!).

Lastly, I want to thank my fantastic family for teaching me everything that really matters. I love you all. My mother, **Ann Thurin**, the dura and pia, you are awesome. My father, **Anders Thurin**, the kindest and most intelligent man I know. Thank you both for everything you have done for me. My sister **Sigrid Thurin**, you are a splash of sanity in this mad world. You rock. Keep being just the way you are (also, Skärp dig!). Thank you to **Marianne** and **Inga-Lena**, two very impressive ladies, and to **Svante, Sara, Per, Alexander, Linus, Jakob, Kristina and Jesper.** I would also like to express my appreciation to an Italian protagonist, with arms and legs.

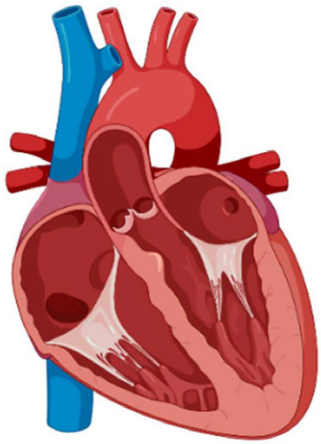

Figure 17, cross-section of a human heart, without the pulmonary trunk. This and many other images were made using Biorender.com, a service I can warmly recommend.

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