Population-based studies of brain tumor surgery: surgical outcome and prognostic factors

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Till min älskade mamma Carina, pappa Bill, William, familj, vänner

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ABSTRACT

Neurosurgery is the cornerstone in the treatment of a majority of brain tumors. Surgery can sometimes cure or delay tumor progression. However, surgery is associated with risks, and adequate information about the anticipated peri- and postoperative course is important for informed consent. The identification of tumor markers in a preoperative setting is beneficial in lower-grade gliomas, a heterogeneous group in terms of biological behavior where molecular markers play an important role in diagnosis and treatment. We investigated the role of the non-invasive radiological marker T2-FLAIR mismatch by means of a population-based study. The mismatch sign is highly specific for *IDH*-mutated 1p/19q non-codeleted gliomas and thus useful in the preoperative setting. We examined how age affects lower-grade glioma treatment, in addition to short-term postoperative complications. Older patients (≥60 years) seem to tolerate neurosurgery compared with younger patients (<60 years), although a higher rate of neurological deficit occurred postoperatively. Meningioma is the most common intracranial tumor and surgery is the main treatment modality. The short-term postoperative risk for complications after meningioma surgery, both in symptomatic and asymptomatic, was studied. The complication rate in the short-term (30-day) postoperative period in Sweden lies in line with the relevant literature. Through a registry-based approach we studied the return to work long-term (up to two years) after meningioma surgery. The sick leave pattern after meningioma surgery revealed that surgery is associated with considerable risk of long-term sick leave two years after the operation as 57% in meningioma patients returned to work compared with 84% of matched controls. Risk factors for long-term sick leave were history of depression, surgical neurological deficit and higher tumor grade. The present work contributes with elucidating on a promising non-invasive radiological marker and the role of age in lower-grade gliomas, and in patients with meningioma data on the current postoperative risk after meningioma surgery and novel data with regard to return to work.

Keywords: Lower-grade gliomas; biomarkers; neurosurgery; segmentation; population-based; registry-based

Sammanfattning på svenska

Neurokirurgi är en hörnsten i behandlingen av majoriteten av hjärntumörer. Som med all kirurgi är neurokirurgi förenad med risker, relaterade dels till själva kirurgin såsom neurologiska bortfall och blödning, dels till medicinska komplikationer såsom tromboser och infektioner. Syftet med denna avhandling är att kartlägga neurokirurgisk behandling hos patienter med meningiom och låggradiga gliom (LGG) i en pre-, peri- och postoperativ fas.

LGG är en grupp intraaxiala tumörer som uppstår från hjärnans stödjeceller. Under det senaste decenniet har molekylära markörer, främst mutation i genen isocitrat dehydrogenas (*IDH*) och kodeletion av kromosom 1p och 19q, hos LGG gjort sitt genombrott i prognostiseringen och klassificeringen av dessa gliom. I artikel I utförde vi en kartläggning av den icke-invasiva radiologiska markören T2-FLAIR mismatch hos patienter med LGG och dess association med de molekylära markörerna *IDH*-mutation och 1p/19q kodeletion, samt biologiska och kliniska faktorer i relation till kliniskt utfall i en populationsbaserad studie med både retrospektiv och prospektiv inklusion. Den icke-invasiva markören T2-FLAIR mismatch har hög specificitet för IDH-muterade 1p/19q icke-kodeleterade gliom (astrocytom) och kan vara av värde preoperativt. För att studera hur ålder påverkar kirurgiskt utfall hos patienter med låggradigt gliom (WHO grad II), samt behandling och kliniska faktorer i olika ålderskategorier genomförde vi i artikel II en registerstudie med data från Svenska Hjärntumörregistret. Neurokirurgisk behandling av LGG hos äldre patienter (≥60 år) bedöms jämförbart med yngre patienter (<60 år), dock med högre grad av neurologiska bortfall postoperativt hos äldre patienter.

Meningiom är, å andra sidan, en extraaxial tumör som uppstår från hjärnhinnorna och kirurgi är den främsta behandlingsmetoden. I artikel III hade vi som mål att kartlägga de kortsiktiga riskerna postoperativt efter meningiomkirurgi på en nationell nivå, samt jämföra utfall för asymptomatiska och symptomatiska meningiompatienter genom en registerstudie med data från Svenska Hjärntumörregistret. Kartläggning av de kortsiktiga riskerna efter meningiomkirurgi på nationell nivå påvisade att resultaten i Sverige ligger i linje med relevant litteratur. För att undersöka hur återgång till arbete på längre sikt ser ut efter meningiomkirurgi jämförde vi i artikel IV patienter med meningiom med fem matchade unika kontroller genom data från multipla register. Patienter efter meningiomkirurgi har betydande risk för långsiktig sjukskrivning; två år efter kirurgi var 57% patienterna åter i arbete jämfört med 84% hos unika matchade kontroller. Negativa prediktorer för återgång till

arbete var anamnes på depression, högre tumörgrad, sjukfrånvaro under året innan kirurgi och postoperativa neurologiska bortfall.

Sammanfattningsvis bidrar studierna i denna avhandling till forskningen om gliom och meningiom genom att undersöka icke-invasiv markör hos LGG, kartlägga de aktuella postoperativa riskerna på kort sikt efter meningiomkirurgi och i olika åldersgrupper med låggradigt gliom (WHO grad II), utfall och behandlingsmönster hos äldre patienter med låggradigt gliom och utfall på sikt efter meningiomkirurgi avseende återgång till arbete.

List of papers

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

I. Corell A, Ferreyra Vega S, Hoefling N, Carstam L, Smits A, Olsson Bontell T, Björkman-Burtscher IM, Carén H, Jakola AS. The clinical significance of the T2-FLAIR mismatch sign in grade II and III gliomas: a population-based study. BMC Cancer. 2020;20(1):450.

II. Corell A, Carstam L, Smits A, Henriksson R, Jakola AS. Age and surgical outcome of low-grade glioma in Sweden. Acta Neurologica Scandinavica 2018;138:359-368.

III. Corell A, Thurin E, Skoglund T, Farahmand D, Henriksson R, Rydenhag B, Gulati S, Bartek J Jr, Jakola AS. Neurosurgical treatment and outcome patterns of meningioma in Sweden: a nationwide registry-based study. Acta Neurochir (Wien). 2019;161(2):333–341.

IV. Thurin E, Corell A, Gulati S, Smits A, Henriksson R, Bartek J Jr, Salvesen Ø, Jakola AS. Return to work following meningioma surgery: a Swedish nationwide registry-based matched cohort study. Neurooncol Pract. 2020;7(3):320-328.

Content

Abbreviations

1D	One dimensional
1p/19q	Short arm chromosome 1/Long arm chromosome 19
2D	Two dimensional
AI	Artificial intelligence
CBF	Cerebral blood-flow
CBV	Cerebral blood volume
cfDNA	Cell-free DNA
CNS	Central nervous system
CSF	Cerebrospinal fluid
CT	Computer tomography
ctDNA	Circulating tumor DNA
DIPG	Diffuse intrinsic pontine glioma
DNA	Deoxyribonucleic acid
DVT	Deep venous thromboembolism
EANO	European Association of Neuro-Oncology
EGFR	Epidermal growth factor receptor
EOR	Extent of resection
FLAIR	Fluid-attenuated inversion recovery
fMRI	Functional magnetic resonance imaging
GBM	Glioblastoma (astrocytoma WHO grade IV)
GIC	Glioma initiating cell
GTR	Gross total resection
HGG	High grade glioma
HPF	High-power field
HRQoL	Health-related quality of life
IDH1	Isocitrate dehydrogenase 1 gene
IDH2	Isocitrate dehydrogenase 2 gene
LGG	Lower-grade glioma WHO grade II and III
MDT	Multidisciplinary team
MGMT	O6-methylguanine-DNA-methyltransferase
MRI	Magnetic resonance imaging
MRS	Magnetic resonance spectrometry
NCR	National cancer registry
NF2	Neurofibromatosis type 2
PCV	Combination of procarbazine, lomustine and vincristine

PET	Positron emission tomography
RANO	Response Assessment in Neuro-Oncology
RTW	Return to work
SBTR	Swedish Brain Tumor Registry
SEER	The Surveillance, Epidemiology and End Results program
SNOMED	Systematized Nomenclature of Medicine
SNP	Single nucleotide polymorphism
STR	Subtotal resection
T1W	T1-weighted
T2W	T2-weighted
TERT	Telomerase reverse transcriptase
VTE	Venous tromboembolism
WHO	World Health Organization

x

1 Introduction

Tumors of the central nervous system make up approximately 2.5% of all cancers diagnosed annually and are categorized in accordance with the World Health Organization (WHO) classification based on origin [1, 2]. The most common brain tumors include glioma and meningioma, with the most common primary malignant tumor being glioblastoma (i.e. astrocytoma WHO grade IV, GBM) [3]. Pediatric brain tumors, in contrast to adult ones, are in 50-70% of cases located in the posterior fossa, the most common being astrocytomas, ependymoma, medulloblastoma and craniopharyngioma [4, 5]. The annual incidence of pediatric brain tumor is 4.2 per 100,000 children, making it the second most common form of childhood cancer [6]. Treatment protocols exist for some primary adult brain tumors, such as GBM, where maximal safe resection followed by adjuvant chemo- and radiotherapy in according with the Stupp regimen is widely accepted today [7]. However, in biological slower diseases, such as lower-grade gliomas (i.e. WHO grade II and III astrocytoma and oligodendroglioma, hereafter LGG) and meningioma the timing of management can be more difficult, hence understanding risk of treatment in addition to identify risk groups is motivated. Therefore, this thesis will focus on the clinical course of these tumor types, from diagnostics in a preoperative and perioperative setting to both short-term and long-term follow-up.

1.1 Epidemiology

In Sweden, around 1,300 patients are diagnosed with a primary brain tumor every year [1]. Meningioma is the most common primary intracranial lesion termed and reported to have an incidence rate from 1.3-8.33 per 100,000 individuals with a slight increase during recent decades [8-11]. The incidence of grade II glioma is traditionally reported at 1.05 per 100,000 persons per year [12, 13]. The exact incidence of LGG is difficult to estimate for various reasons. One is the removal of the mixed oligoastrocytic subclass of gliomas and another the recent transition from the term low-grade gliomas which included WHO grade II astrocytoma, oligoastrocytoma and oligodendroglioma to lower-grade gliomas which include both WHO grade II and III astrocytoma and oligodendroglioma (see Figure 1 as an example of an LGG on magnetic resonance imaging (MRI) scan). LGG account for approximately 15% of all glial brain tumors in the adult population [1, 9, 14]. LGG typically have an infiltrating growth pattern into the surrounding brain tissue, limiting more extensive and possibly curative surgery due to the risk of neurological deficit [15, 16]. The growth rate of LGG is typically slow at approximately 4-6 mm per year and higher growth rates are related to malignant transformation [17-19]. However, at some point the glioma will undergo malignant transformation, although the timing varies. This leads to questions regarding the optimal choice and timing of treatment for the individual patient with LGG.

Although the majority of LGG are thought to be caused by random, sporadic mutations, a family history has been identified in around 5% of cases, suggesting a possible genetic predisposition in some of the patients [20]. Studies have shown increased risk among first-degree relatives of patients with glioma [20, 21]. Established risk factors for glioma include high-dose radiation (not diagnostic radiation), hereditary syndromes and increasing age, while mutagen sensitivity, allergies and asthma are probable risks [22]. Hereditary germline gene mutations and syndromes leading to a predisposition for gliomas include Li-Fraumeni syndrome, neurofibromatosis 1 and 2 and Turcot's syndrome types 1 and 2 [23, 24]. However, there is no convincing evidence of an association between smoking and the risk of glioma [25]. Difference in genetic susceptibility have been studied through genome-wide association study, and the authors identified 13 new loci of glioma risk, strengthening the theory of polygenic base of genetic susceptibility of glioma

[26]. There is a genetic risk of glioma, although not established through the monogenic Mendelian way of heredity, genome-wide single nucleotide polymorphism (SNP) support idea of a Mendelian predisposition [27, 28].

Risk factors for meningiomas include high doses of ionizing radiation and genetic predisposition, such as patients with neurofibromatosis gene mutations (NF2) [29]. Exogenous and endogenous hormones have been suggested as a risk factor for meningioma due to the higher incidence in women compared to men [30]. There is some evidence of an association between exogenous hormones and meningiomas, although further investigation is required [31-33]. Other risk factors associated with meningiomas are breast cancer and occupational factors [10, 22, 29]. There is no clear evidence for increased risk of either glioma or meningioma with mobile phone use and further investigations are required [34, 35]. As with gliomas there is little to no evidence of an association between smoking and meningiomas [36].
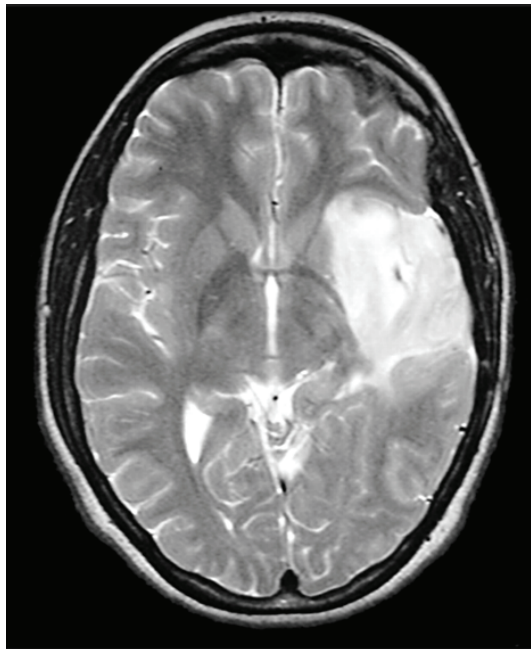
Figure 1. Magnetic resonance imaging (MRI) scan, T2-weighted (T2W) sequence of a lower-grade glioma involving insula and temporal lobe on the patients left side.

1.2 Symptoms and clinical presentation

There is a wide spectrum of brain tumor symptoms that vary in accordance with the tumor location, type, growth rate and age of the patient [37]. General symptoms due to an increased intracranial pressure caused by the tumor or the surrounding edema include headache, nausea and/or vomiting and altered consciousness, while focal symptoms depend on location of the tumor [38, 39]. The lesion can also cause displacement of structures leading to obstruction of cerebrospinal fluid (CSF) and vascular compromise [40]. Parietally located lesions cause disturbances in coordinating sensory information, perception and spatial awareness [41]. Symptoms such as cognitive changes, personality change, impulse control and lack of concentration may arise from lesions affecting the frontal lobes [42]. In a similar way occipital lesions may cause disturbances of visual fields [43], while lesions in the dominant temporoparietal and frontal region can cause dysphasia. CSF obstruction usually leads to obstructive hydrocephalus, which in turn may be symptomatic. Seizures may also be a symptom in patients suffering from brain tumors, which is the most common symptom in patients with LGG, but may also be a present in those with meningioma [44, 45]. Tumors with a slower growth rate allow the brain to adapt to the lesion, which more often causes seizures than focal symptomatology or symptoms related to increased intracranial pressure [46, 47].

1.3 Classification of brain tumors

Brain tumors in the central nervous system have been categorized according to the WHO classification system since 1979 [48]. The most recent revised version was published in 2016 and, compared to its predecessor from 2007, contains additional molecular markers as a complement to the previous histological definitions [2]. There have been major changes in the field of diagnosing and classifying LGG. From a traditional point of view, histology has been the basis of diagnosing LGG, but this method is associated with interrater variability that has caused major concerns both in clinical management and research settings [49, 50]. The nomenclature "lower-grade glioma" include astrocytoma and oligodendroglioma with histological classification of grade II and III [2, 51] and has recently been implemented following molecular diagnosis.

Histological techniques include staining the sample with hematoxylin and eosin. Astrocytomas consist of well-differentiated fibrillary or gemistocytic neoplastic astrocytes on a loose matrix. Oligodendrogliomas contain cells with uniform-appearing nuclei and perinuclear clearing in a honeycomb pattern, sometimes referred to as having the appearance of "fried egg" [2, 52, 53].

According to the WHO 2016 classification, LGG form a group that includes astrocytoma and oligodendroglioma grades II and III [2, 51]. The term oligoastrocytoma was included in the previous WHO classification from 2007 and described as a mixed LGG, but that term was removed from the revised classification, and LGG are now divided into astrocytoma and oligodendroglioma according to their molecular status [2, 53].

During the last decade advances have been made in the molecular genetic field. In the area of LGG, two markers have been of particular interest; the presence or absence of mutation in gene isocitrate dehydrogenase (*IDH*) I and II, and codeletion or lack of codeletion in the short arm of chromosome 1 and in the long arm of chromosome 19 (1p/19q) [51, 54, 55]. These markers have been associated with prognosis, where patients with *IDH*-mutation with 1p/19q codeletion (referred to as oligodendroglioma in WHO 2016 classification) have the best prognosis, while patients without *IDH*-mutation (referred to as *IDH wild-type*) have the worst [55-57]. Additional methylation analysis of

IDH-mutant astrocytomas has revealed another possible grading system for this subgroup [58]. Patients with *IDH* wild-type have a more aggressive disease course with impaired survival, similar to patients with GBM [51, 57]. *IDH* wild-type is, however, not pathognomonic for gliomas with a more aggressive biology. Other tumor of glial origin such as pediatric low-grade gliomas and pleomorphic xanthoastrocytoma also lack the *IDH*-mutation and are classify as *IDH* wild-type [59, 60]. Consequently, absence of *IDH*-mutation is not sufficient to classify a glioma as WHO grade IV, as molecular glioblastomas are identified by other molecular features including amplification of the epidermal growth factor receptor (*EGFR)*, combined chromosome 7 gains and chromosome 10 losses (whole chromosome, or loss of long or short arm), or telomerase reverse transcriptase (*TERT)* promotor mutation [61, 62]. The cIMPACT-NOW group concluded that the minimal molecular criterion for identifying the aggressive *IDH* wild-type glioma histologically classified as WHO grades II or III was at least one of the previously mentioned molecular genetic findings [63]. This further stratification will support decision-making about adjuvant treatment in the clinical setting and inclusion of this subgroup in clinical trials.

In the recently revised WHO classification, the grading of meningiomas has not undergone any revision and are still classified as grades I – III [2]. Traditional histological features of benign meningioma include lack of infiltration, absence of cell atypia and a mitotic index of less than 4 mitoses per 10 high-power field (HPF). Atypical and malignant meningiomas show increased mitotic activity and cell atypia [64]. In the latest revision of the WHO classification of tumors in the central nervous system brain invasion of meningioma is classified as a criterion of WHO grade II, in contrast to the 2007 version where brain invasion was a hallmark of WHO grade I meningiomas [2, 53]. The new classification will lead to more meningiomas being classified as WHO grade II and possibly receiving adjuvant postoperative radiotherapy, despite the fact that on a group level they are likely to have a more benign course [65, 66]. Recent advances have taken place in the molecular genetic landscape of meningiomas, where clinically relevant subgroups have been identified using methylation analysis [67]. This will probably further stratify clinically relevant meningioma patient subgroups to optimize treatment for individual patients.

1.4 Diagnostics

The definite diagnosis of intracranial lesions is histopathological in nature, although advances in the radiological field have improved the non-invasive recognition and possible diagnosis of brain tumors [68]. Furthermore, the introduction of molecular parameters into the glioma field in the 2016 WHO classification has made further categorization possible [2]. When the patients present to either their primary health center or the emergency ward, a computerized tomography (CT) scan is usually the primary investigation of choice due to its availability, which is later supplemented by an MRI scan with and without contrast enhancement to confirm the suspected lesion, see Figure 2a-b as example of LGG on MRI scan.
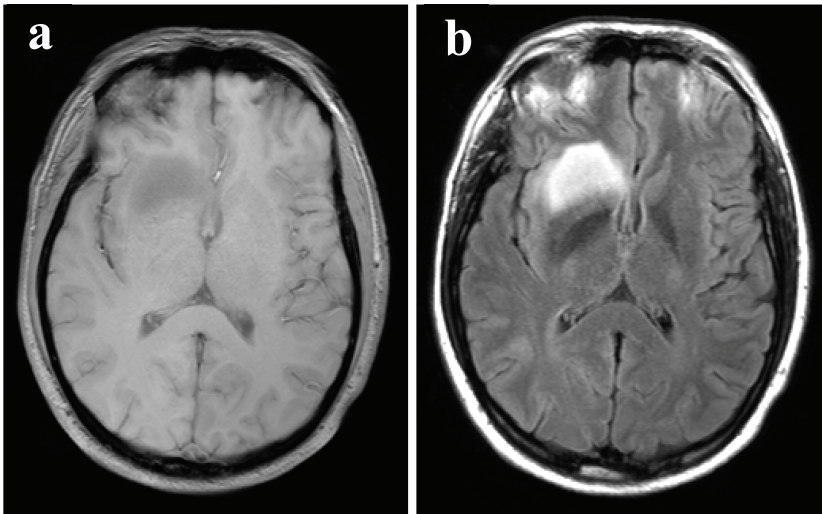
Figure 2a-b. MRI of lower-grade glioma located in the right frontal lobe. 2a: T1 weighted sequence. 2b: FLAIR sequence.

After the initial diagnostic procedures with CT and MRI, further investigations can be performed. MRI provides further non-invasive techniques such as cerebral blood volume (CBV) and measurement of the choline/N-acetyl aspartate ratio on MR spectroscopy (MRS) which can be useful in the diagnosis of LGG [69]. Typically, LGG exhibit reduced CBV compared to high-grade gliomas and on MRS increased choline and a lower level of N-

acetyl aspartate compared to the normal brain [70]. However, not all LGG show this pattern, but MRS can help to detect areas with more aggressive behavior which can be suitable for biopsy or valuable during resection [71, 72]. The detection of high levels of 2-HG by MRS has been shown to correlate with *IDH*-mutation in glioma, which can be used in a non-invasive setting to differentiate *IDH*-mutated gliomas from *IDH* wild-type gliomas [73, 74].

Non-invasive diagnostic methods have been of interests since the dawn of molecular markers in the field of LGG, especially the status of *IDH* and the presence of absence of 1p19 codeletion. After surgical resection, the prognosis and recurrence are highly correlated with these markers [51, 75]. Positron emission tomography (PET) with tracers such as ^{18}F-FET has been found valuable in a preoperative setting with machine-learning for non-invasive information regarding molecular subtypes and the malignant transformation of the tumor as well as for revelation of possible "hot-spots", which could be of interest in e.g. biopsy and in a postoperative setting to detect recurrence or progression [76-78].

The radiological marker T2-FLAIR mismatch sign, which is characterized by a hyperintense signal on a T2-weighted sequence (T2W) on MRI scans and hypointense signal on a fluid attenuation inversion recovery (FLAIR) sequence with the exception of a hyperintense ring (see Figure 3a-b), has gained interest in recent years after demonstrating high specificity for *IDH*-mutated astrocytomas [79]. Since the initial study by Patel et al. (2017), this finding has been validated and a high specificity has been presented in multiple studies [80-83]. The unique characteristic of the mismatch sign raises questions about the underlying biology, although investigation of methylation analysis showed no specific clustering of the *IDH*-mutated astrocytomas harboring the mismatch sign [82].
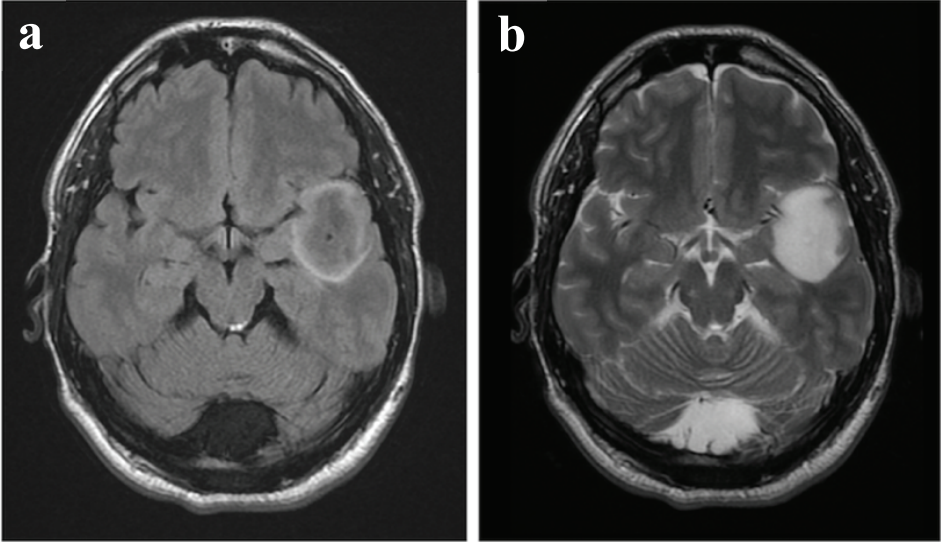
Figure 3a-b. MRI scan of IDH-mutated astrocytoma with the T2-FLAIR mismatch sign. 3a: FLAIR sequence with hyperintense peripheral ring and hypointense center. 3b: T2W sequence showing a homogeneous hyperintense signal. From Corell and colleagues, The clinical significance of the T2-FLAIR mismatch sign in grade II and III gliomas: a population-based study, Supplementary material, BMC Cancer 2020.

On the other hand, invasive diagnostics include methods for obtaining tissue samples for the pathologist to analyze and classify according to the cell characteristics, such as cell nuclei atypia, mitosis, necrosis and vascular proliferation [84]. The methylation analysis does as well require tumor tissue for DNA extraction [85]. As surgical intervention is associated with the risk of complications, less invasive methods for obtaining diagnostic material are desirable. Methods to obtain so-called circulating tumor DNA (ctDNA) in blood samples have been examined, although evidence of clinical validity is lacking [86]. However, CSF, which only requires a minor procedure in contrast to invasive neurosurgery, has been of interest due to the possibility of detecting ctDNA of glioma both for disease classification and for monitoring the progression of glioma over time [87, 88].

1.5 Treatment guidelines

The European Association of Neuro-Oncology (EANO) has established guidelines to serve as a recommendation for diagnosis and treatment of lower- and high-grade gliomas [89, 90]. The treatment strategy of early, safe surgery in patients with suspected LGG followed by adjuvant treatment based on molecular markers is in line with the literature.

EANO has also formulated guidelines for treatment of patients with meningioma, where the recommendations support the combination of surgical and radiosurgical treatment with adjuvant radiotherapy in malignant meningiomas or incompletely resected atypical meningiomas [91]. The role of adjuvant radiotherapy in completely resected atypical meningiomas is still not clear, and shared decision-making with the patient is recommended. The recommendation for asymptomatic meningiomas is an initial wait-and-see approach with follow up by MRI and clinical evaluation.

Guidelines for the treatment of tumors in brain and spinal cord have also been established on a national level in Sweden and were last revised on 14/01/2020. The following is a link to the program: https://www.cancercentrum.se/globalassets/cancerdiagnoser/hjarna-cns/vardprogram/nationellt-vardprogram-tumorer-hjarna-ryggmarg.pdf.

1.6 Surgical treatment

The clinical presentation of patients with brain tumor comprises a wide spectrum of possible symptoms. Both conservative and surgical treatment should be tailored to benefit patients. Conservative treatment includes symptom relief, where steroids and antiepileptic drugs play an important role. The aim of surgery is to establish a diagnosis, reduce tumor burden, to alleviate symptoms or, if possible, total removal of the tumor [92]. The decision regarding the extent of resection during surgery should benefit the patient and be weighed against the risks of postoperative deficit, i.e. do no harm [93]. Surgery plays an important role in the treatment of brain tumors and a maximal safe resection provides a superior point of departure for adjuvant treatment and, ultimately, improved survival in the long-term [94, 95].

1.6.1 Neurosurgery for brain tumors

Neurosurgery is a cornerstone in the treatment of most intracranial tumors. It can provide a cure in patients with meningioma and prolong survival in those with gliomas [96, 97]. Nevertheless, neurosurgery is associated with risks and complications that could lead to devastating consequences including permanent neurological deficits and even death [98].

Before the introduction of CT scan and MRI scan it was difficult to diagnose an intracranial neoplasm [99]. At the beginning of 20th century, ventriculography and pneumoencephalography were used to detect intracranial lesions with a mass effect causing midline shift. The introduction of the CT scan in the 1970s and MRI in the 1980s not only led to improved diagnostic possibilities of intracranial lesions but also laid the foundation for other methods, such as stereotactic neurosurgery [100]. Since then, CT and MRI scans have become more and more available, in even more remote locations. However, this wide access has led to more incidental findings, which can pose surgical dilemmas in asymptomatic patients [101-103].

Extent of resection in the molecular era
The extent of resection (EOR) in the field of malignant gliomas (i.e. GBM) has been well studied, and patients who underwent gross total resection (GTR)

instead of subtotal resection (STR) or biopsy showed improved in overall survival [97, 104]. Similarly, EOR has been associated with increased overall survival in previous studies in patients with LGG and maximal safe surgical resection is now considered a basis in the treatment strategy [95, 105-108].

After the introduction of molecular markers in the field of LGG, the question pertaining to the impact of surgery was raised. Historically, the diagnosis of LGG was based purely on histological features of the tumor sample, although with low interrater agreement in both type as well as grade [49]. With the introduction of the molecular markers, i.e. *IDH*-mutational status and 1p/19q codeletion, a more robust classification system was implemented, which is superior to the assessment of histological features in terms of performance [109]. Wijnenga et al. (2018) studied the influence of maximal safe surgery in patients with molecularly defined LGG in a retrospective setting and their findings revealed that postoperative volume is a prognostic factor for overall survival [110]. Additionally, it seems that the impact of smaller tumor residue is not as extensive in oligodendrogliomas, although in *IDH*-mutated astrocytomas an even smaller residue was shown to impact overall survival. Similar findings regarding GTR in *IDH*-mutated astrocytomas were demonstrated in the study by Delev and colleagues, where only GTR was associated with improved survival [14]. In addition, patients with *IDH*-wildtype astrocytomas seem to benefit from more aggressive treatment such as GTR, repeated resections and postoperative oncological therapy. The role of surgical intervention in *IDH*-mutated 1p/19q codeleted LGG (i.e. oligodendrogliomas) is still not fully clear, although surgery is still assumed to be of importance but with less of an impact than is the case in *IDH*-mutated astrocytomas or *IDH*-wildtype LGG [14, 110-112].

Asymptomatic – when to treat?
As the incidence of meningioma is rising due to the generally aging population and increasing availability of imaging scans, neurosurgeons are more frequently faced with the ethical medical dilemma of choosing a treatment plan. The recommended treatment plan for asymptomatic meningiomas according to the EANO guidelines for meningiomas is observation with repeated MRI scan after 6 months [91]. The recommendation for suggesting surgical treatment of asymptomatic meningiomas include radiologically

confirmed growth, new-onset neurological symptoms or in those where exclusion of other diagnoses is needed, such as metastases.

Role of the Simpson grade – is it still relevant?
In 1957 Simpson published a paper presenting factors associated with the risk of recurrence in patients with intracranial meningiomas and summarized the findings into the Simpson grading system [113]. The grades extend from Simpson grade I through V with increasingly more incomplete resection of the meningioma; Simpson grade I include complete removal including affected dura and Simpson grade V is classified as simple decompression with or without biopsy. The extent of removal is classified by the neurosurgeon perioperatively. Many decades have now passed since his initial finding and, in the era of modern neurosurgery, the relevance of the Simpson grade has been questioned. In a paper published in 2010, Sughrue and colleagues investigated the relevance of Simpson grade I and II resection in WHO grade I meningiomas [114]. They found no statistically significant evidence of an association between Simpson grade and recurrence suggesting, suggesting that aggressive excision is of limited benefit in patients with WHO grade I meningioma, a surprising finding that contradicts the previously accepted neurosurgical belief of aiming for complete excision of meningiomas. However, many subsequent studies validated the initial findings by Simpson and demonstrated a significant association between Simpson grade and the rate of recurrence. For example, Nanda and colleagues presented data validating the Simpson grade as a significant predictor of recurrence of both skull base and convexity meningiomas [115-119].

1.6.2 Neurosurgical improvements

Anesthetic medications and the field of anesthesia revolutionized surgical medicine with the possibility to treat patients without sensation or awareness (anesthesia, from Greek, meaning "without sensation") [120]. In the mid-19th century, a dentist called Morton applied chloric ether to the affected area, whereby the idea of using ether to influence the whole system was born [121]. During the 19th century, the microbiologist Pasteur proposed the germ theory of disease, which at the time was refuted by many, although nowadays his theory is widely accepted [122]. With Pasteur's microbiological explanation

of infection, the British surgeon Joseph Lister developed the principles of antiseptic surgery [123]. Through his relentless work and interest in postoperative infections he discovered carbolic acid, which he used in both the treatment of surgical wounds and the sterilization of instrumentation, leading to a decrease in mortality [122]. Thanks to the collective contributions of Morton, Pasteur and Lister, the surgical field could advance further to where we are today.

In 2004, it was estimated that 234.2 million major surgical procedures were performed worldwide [124], which in turn demand safe and antiseptic techniques. In 2009 the WHO released the *Guidelines for safe surgery* to improve the safety for patients undergoing surgical treatment, and since its introduction there has been a reduction of both mortality and morbidity worldwide [125, 126]. Prevention of surgical site infection includes preoperative scrub with antiseptic soap, preparation of the surgical site with antiseptic wash, appropriate hair removal and preoperative antibiotics, although which guidelines are the most effective guidelines is still being debated [127-130]. Regarding antiseptic preparation, the Cochrane Collaboration performed a review of preoperative bathing with skin antiseptic to prevent surgical site infection and found no clear evidence of chlorhexidine being superior to other wash products [131].

After the introduction of CT scan and MRI, more precise diagnoses could be made, in addition to improved preoperative planning. Today, the preoperative radiological diagnosis provides important information regarding the suspected diagnosis. Physiologic imaging methods such as brain perfusion, metabolic information of lesions (e.g. MR spectroscopy and/or PET), the relationship between important fiber tracts with diffusion tensor imaging and functional areas (e.g. language laterality and motor cortex using functional MRI (fMRI) aid in the preoperative setting [132-136]. However, with the discovery and development of more non-invasive radiological markers an even more precise diagnosis could be made [137]. Improved diagnostics has had significant impact on neurosurgical practice panorama as patients present with smaller lesions thus leaving room for few intraoperative surprises.

Tools in neurosurgery

Neurosurgical techniques have increased with the introduction of more refined diagnostic possibilities in combination with improved radiological methods. Modern neurosurgeons have a well-equipped toolbox to perform challenging surgeries efficiently and safely, with the aim of minimal blood loss. Hemostasis is crucial in neurosurgery and minimal blood is best achieved by preventing bleeding in the first place by respecting vascular anatomy. Nevertheless, techniques such as the use of bipolar or hemostatic materials including oxidized cellulose are necessary to control bleeding [138]. The introduction of the microscope into the neurosurgical field in the late 1950s greatly improved microsurgical techniques, leading to the birth of modern neurosurgery [139]. Neurosurgeons adopted the ideas of the pioneers behind the operating microscope and integrated microneurosurgery into the field, which meant safer surgery for patients.

Since the introduction of the operating microscope, a vast range of different tools has emerged, enabling individual neurosurgeons to optimize the treatment for their patients. In addition to the previously mentioned bipolar instrument, tools include the ultrasonic surgical system for resection of brain tumors [140], the neuronavigation system for visualization and targeted surgery [141], ultrasound for intraoperative assessment before and after resection [142], intraoperative angiography during neurovascular procedures [143] and fluorescence-guided surgery with the use of 5-aminolevulinic acid in resection of malignant gliomas [144], among many others. Recent advances in the field include operating theatres with intraoperative MRI scans and digital subtraction angiography equipment, making radiological examinations prior to wound closure possible and thus allowing the surgeons to continue the procedure if necessary [145, 146].

1.6.3 Complications related to neurosurgery

Surgery in all fields is associated with risks and neurosurgical interventions are no exception. Comparing the rate of complications between different centers or time periods is difficult, if not impossible due to the lack of a standard reporting system. Nevertheless, there are factors associated with increased mortality and morbidity, such as multiple concomitant diseases [147]. Age,

comorbidities and laboratory hyponatremia, -albuminemia and anemia increase the risk of readmission [148]. Ibanez et al. (2010) published a classification system suitable neurosurgical and spinal procedures, based on previously proposed classification systems by Clavien and Dindo [98, 149, 150]. Postoperative data pertaining to complications are highly important in the preoperative setting for evaluating both the short-term risk and the long-term benefit of surgery and, not least, for patient information about the postoperative period.

1.7 Non-surgical treatment

Patients with brain tumors present with a wide range of symptoms, and edema surrounding a brain lesion may be a contributory factor [151]. Dexamethasone, a corticosteroid discovered in 1958, is today considered the gold standard for treatment of tumor edema [152, 153]. Such treatment alleviates the symptoms related to increased intracranial pressure and brain tissue compression by the edema.

Epileptic seizure is the most common presentation among patients with LGG, who are initially treated with more recently developed antiepileptic medications, such as levetiracetam or topiramate, although more than 50% of cases are resistant to pharmacological treatment [154]. The location of the tumor influence risk of developing epilepsy, with frontal, temporal and parietal lobes being associated with seizures and infratentorial lesions more rarely so [155]. Seizures are also common in meningiomas, observed in roughly a third of patients [45]. Two thirds of patients with meningioma and seizures prior to surgery experience relief, although some patients without any preoperative seizures may have new-onset seizures in the postoperative phase, both early and late [156]. The use of preoperative prophylactic antiepileptic medication has evoked interest due to the risk of onset of seizures after surgical treatment for meningioma. However, there is no clear evidence that preoperative administration if beneficial for preventing either early or late postoperative seizures [157-159].

Treatment of patients with LGG does not only include the surgical perspective but also the adjuvant treatment. Historically, the management of LGG has been controversial. The decision regarding surgical treatment in otherwise healthy and younger individuals constitutes an ethical dilemma. Some have advocated a conservative approach with watchful waiting until progression was established [160]. Others have advocated early surgical intervention to delay malignant transformation [105, 161, 162]. In 2012, Jakola and colleagues published a study on the difference between watchful waiting and early surgical resection by comparing two different neurosurgical centers in Norway, where one had the preference of watchful waiting and the other favored early resection [95]. The authors concluded that patients treated in the center that favored early surgical resection had better overall survival in

comparison to those at the center where biopsy and watchful waiting were advocated.

Even though the molecular biology of the tumor indicates its biological behavior, some aspects of the clinical assessment cannot be overlooked. The Karnofsky performance score is a widely used assessment of the patient's functional ability and applied to select patients for oncological treatment [163, 164]. Even in the molecular era, studies examining the impact of surgery still find that good clinical status is a factor that influences overall survival [14].

1.7.1 Radiotherapy in patients with LGG – dose and timing

The role of postoperative radio- and chemotherapy in the heterogeneous group of patients with LGG has been widely debated. Earlier studies in the field have shown that LGG are moderately sensitive to radiotherapy, although the appropriate dose and timing of radiation are still not fully known [165-167]. The dose-response of adjuvant postoperative radiotherapy in patients with LGG has been investigated in two large randomized trials; the EORTC 22844, which studied the outcome of lower and higher dose radiotherapy [168], and a prospective randomized study by Shaw et al. (2002) on low- versus high-dose radiation in patients with low-grade glioma [169]. The former found no difference in progression free or overall survival (lower dose of 45 Gy and higher dose of 59.4 Gy), while the latter found lower survival and a higher incidence of radiation necrosis in the cohort with higher radiotherapy dose (lower dose being 50.4 Gy in 28 fractions, and higher dose 64.8 Gy in 36 fractions). In the EORTC study 22845, the timing of postoperative radiation was investigated and patients undergoing radiation were randomized into two groups; one group received 54 Gy over 6 weeks and in the other group radiation was postponed until signs of tumor progression (clinical deterioration or radiological progression) were observed [167]. The group undergoing early postoperative radiotherapy were found to have a longer time to progression compared to the cohort undergoing watchful waiting, although there was no difference in overall survival.

Both the EORTC 22844 and 22845 were performed prior to the introduction of molecular markers. More recent research in the field suggests that subgroups

divided by the molecular markers they harbor will be better stratified for further investigation [170].

Brachytherapy, which employs iodine-125 seeds to treat inoperable brain tumors, has been used since the 1970s and recently gained more attention, particularly in relation to eloquent gliomas [171]. Studies of brachytherapy with iodine-125 seeds WHO grade II and III gliomas have shown to be a minimally invasive, local treatment for both adult and pediatric patients [171-173]. When studying long-term survival in recurrent or progressive LGG after resection in eloquent areas, it was found that brachytherapy seems to prolong progression-free survival and can possibly postpone further radio- and/or chemotherapy [174].

1.7.2 Lower-grade gliomas and chemotherapy

There is an ongoing debate about the efficacy of adjuvant postoperative radio- and chemotherapy. In the molecular era, further stratifications in patient cohorts will be useful for establishing the optimal treatment strategy for patients with LGG, such as in the 1608-EORTC-BTG study (NCT03763422), Trial in Low Grade Glioma Patients: Wait or Treat (IWOT). The study is investigating whether outcomes of *IDH*-mutated astrocytomas improve with early adjuvant radio- and chemotherapy (in form of temozolomide) and if the benefits of early treatment overcome the possible side effects, e.g. deterioration in seizure activity, neurocognitive function or quality of life.

During 1970 two articles were published regarding the treatment of glioma with the chemotherapeutic agent 1,2-bis(2-chloroethyl)-1-nitrosourea (BCNU) [175, 176]. BCNU was mainly used in patients with high-grade glioma and studies regarding the use of BCNU compared to the combination of procarbazine, lomustine (CCNU) and vincristine (combined called PCV) suggested longer survival in patients treated with PCV in both patients with anaplastic and high-grade glioma [177]. The alkylating agent temozolomide was introduced as a part in the postoperative treatment strategy in GBM in the study by Stupp et al. (2005), which showed a significant prolonged survival in patients undergoing radiotherapy with addition of temozolomide compared with radiotherapy alone [7]. Numerous studies have been made regarding role

of chemotherapy in LGG. In the Baumert trial from 2016 patients with high-risk low-grade glioma WHO grade II received either radiotherapy or temozolomide chemotherapy alone [164]. Findings suggest no significant difference in progression-free survival in patients with low-grade glioma undergoing treatment with either radiotherapy alone or chemotherapy (temozolomide) alone. The patients with *IDH*-mutated 1p/19q non-codeleted tumors treated with radiotherapy had a longer progression-free survival compared with those treated with chemotherapy alone, and patients with *IDH* wild-type gliomas had the worst prognosis independent of treatment modality.

In the subgroup of *IDH*-mutated 1p/19q codeleted gliomas, i.e. oligodendrogliomas, the role of chemotherapy is more defined. The mainstay of chemotherapy treatment in oligodendrogliomas have traditionally been PCV [178-180], although challenged by temozolomide as a better tolerated treatment alternative and very good response rate [181]. Emerging data in the field suggests that primary single chemotherapy with temozolomide may be a valid alternative in patients with oligodendrogliomas [182], and further stratification in the EORTC 22033-26033 trial revealed a subgroup of oligodendrogliomas with the retention of chromosome 1p showing inferior overall survival compared with the group with 1p deletion which showed more favorable overall survival, suggesting selecting patient with retention of 1p for radiotherapy postoperatively [164].

Cancer therapeutics to target *IDH* to inhibit the IDH1/2 enzyme have been evaluated in clinical and preclinical trials, and have shown promising results [183, 184]. The pharmacokinetics behind the inhibitors include inhibition of IDH enzyme and as a result normalize the 2-hydroxyglutarate (2-HG) levels, which in turn reduces histone modification and the resulting DNA hypermethylation [185]. In addition to IDH inhibitors, vaccines targeting the R132H mutation in the *IDH1* gene shows potential as an immunotherapeutic in patients with *IDH1* mutated gliomas [186, 187].

The anti-vascular endothelial growth factor-A antibody called bevacizumab have been shown to prolong progress-free survival in patients with progressive GBM, but not overall survival [188]. It is associated with potential side-effects, although showing success in the treatment of pediatric low-grade glioma [189-191]. The role of bevacizumab in LGG is not completely clear, and there are

currently scarce evidence supporting the choice of bevacizumab in early treatment of LGG [192, 193]. There are, however, a possibility that bevacizumab has a role in the LGG which has undergone transformation to histologically GBM, and may in those cases be used as a last-line treatment [194].

The EANO guidelines for treatment recommendations in patients with LGG is depending on the *IDH* mutational status and presence of 1p/19q codeletion [89]. The general primary recommendation for newly diagnosed glioma is maximal safe resection followed by either active surveillance or radiotherapy followed by either PCV or temozolomide. There are still controversies regarding adjuvant treatment of diffuse astrocytoma WHO grade II with *IDH* wild-type, where treatment options range from watch-and-wait to radiotherapy as single treatment or followed by PCV or temozolomide. In anaplastic astrocytomas, both *IDH*-mutated and *IDH* wild-type, is the main treatment recommendation radiotherapy followed by concomitant or adjuvant temozolomide. For oligodendrogliomas a watch-and-wait approach or radiotherapy with adjuvant PCV is the general recommendation, while in anaplastic oligodendroglioma radiotherapy followed by PCV is the recommended treatment strategy.

1.7.3 WHO grade II meningiomas – early radiotherapy?

In the latest revised version of histological diagnostic criteria for atypical meningiomas, i.e. WHO grade II meningiomas, brain invasion is considered a characteristic of atypia [2]. Atypical and malignant meningiomas are usually treated with both surgical excision or resection followed by adjuvant radiotherapy with photon beam therapy, proton beam therapy or a combination of both [195, 196]. While early radiotherapy is essential for obtaining long-term control in the management of malignant meningioma [197], the role and timing of postoperative radiotherapy for atypical meningiomas after Simpson grade I or II remains controversial [198-202]. Some studies indicate lower recurrence rate in patients with atypical meningioma undergoing early postoperative radiotherapy [203]. After the recent revision of the WHO classification where brain invasion is considered a criterion for atypical

meningioma, more will classify as such with the risk of overtreatment in this subgroup.

1.7.4 Chemotherapy and meningiomas

The role of chemotherapeutic agents has been investigated in the treatment protocol for meningiomas. A review by the Response Assessment in Neuro-Oncology (RANO) working group in 2014 investigated 47 publications that included numerous agents such as hydroxyurea, temozolomide, irinotecan, interferon-alfa, mifepristone, bevacizumab, imatinib, and the study confirmed poor outcome of medical therapy in further inoperable or radiation-refractory meningioma [204]. One in vitro study investigated the effects of trabectedin, a tetrahydroisoquinoline, and observed a strong antimeningioma activity, and an EORTC phase 2 trial is currently investigating the efficacy of this drug (NCT02234050) [205]. In the EANO recommendations for meningioma, pharmacotherapy should be considered for further progression of atypical meningioma [91].

1.8 Tumor types

1.8.1 Lower-grade gliomas

In a heterogeneous group such as patients with LGG who experience different time periods to malignant transformation and survival, prognostic factors can provide support in the decision-making process [206]. Factors traditionally related to lower survival are older age (40 years or older), functional status, eloquency of tumor, presence of neurological deficit, tumor crossing the midline and large tumor size [206-209]. However, how these clinical prognostic factors have performed since the introduction of the molecular classification and the not frequent clustering of WHO grade II and III astrocytomas and oligodendrogliomas is less studied. It is known that age is related to unfavorable variables in LGG, such as higher frequency of *IDH* wild-type gliomas and eloquent lesion location [210-213]. The impact of age on outcome in patients with LGG have been scarcely systemically studied, and the impact of surgery is largely unknown in the age group of patients 60 years and older.

During the last decade important findings regarding molecular markers in LGG have emerged, highlighting the fact that LGG with different molecular profiles represent tumors with dissimilar disease courses and outcomes [56]. The mutational status of epigenetic modulator gene isocitrate dehydrogenase genes 1 or 2 (*IDH1/2*) and the status of 1p/19q codeletion are now common markers in clinical practice and have revolutionized the diagnosis [2, 55]. Better survival is associated with *IDH*-mutation and 1p19 codeletion, today considered to be oligodendrogliomas, while *IDH* wild-type is related to the poorest survival [2, 51]. At present, surgical resection is an important part of LGG treatment and the extent of resection is associated with survival [57, 89, 95, 214-216].

1.8.2 Molecular markers in lower-grade gliomas

According to the 2016 WHO classification, LGG are divided into astrocytoma and oligodendroglioma depending on the mutational status *IDH1/2* and presence or absence of 1p/19q codeletion. However, further categorizations

can be made based on methylation data, as demonstrated by Shirahata and colleagues [58]. This raises thoughts of further possible subgroups in the field of LGG. Today, there is a wide range of different molecular markers, although for many of them the individual importance is not yet fully documented in patients with LGG [217].

IDH have been identified as an important molecular marker in the diagnosis and prognostication of LGG, which constitute heterogeneous group in terms of biological activity [51, 54, 55]. IDH enzymes are involved in the catalysis of the decarboxylation of isocitrate to generate α-ketoglutarate. *IDH*-mutations results in a reduction of α-ketoglutarate into D-2-hydroxyglutate which is an oncometabolite. This process is believed to create a malignant transformation due to alteration of the cellular epigenetics and blocking of the normal differentiation process [212, 218]. The status of *IDH*-mutation in either *IDH1* or *IDH2* is clinically analyzed by either immunohistochemistry or DNA sequencing and further understanding of glioma biology has been made through DNA methylation [219]. Epigenetic changes do not involve the DNA sequence, instead, epigenetics is involved in alteration of activity in genes and gene expressions [220]. Examples of epigenetic mechanisms include DNA methylation and histone modification [221]. LGG with mutations in either *IDH1* or *IDH2* are associated with better overall survival [55, 57]. *IDH*-mutation together with 1p/19q codeletion status constitute the main molecular subgroups of LGG where *IDH*-mutation with 1p/19q codeletion is considered oligodendrogliomas, *IDH*-mutation without 1p/19q codeletion is called *IDH*-mutated astrocytomas, and lack of *IDH*-mutation is called *IDH* wild-type [2]. These subgroups have in multiple studies shown strong correlation to clinical outcome where the group of *IDH*-mutated oligodendrogliomas showed a mean survival of 8 years, *IDH*-mutated astrocytomas 6.3 years and the *IDH* wild-type LGG having lowest survival at 1.7 years [51].

Patients with LGG with *IDH* wild-type shows impaired survival similar to GBM patients [57]. There are also studies suggesting a heterogeneity among the patients with *IDH* wild-type LGG, and they often contain similar molecular alterations which are observed in GBM, including the combination of chromosome 7 gains and chromosome 10 deletion, EGFR amplification, *TERT* promotor mutation and cyclin-dependent kinase inhibitor (CDKN2A) deletion [61, 222]. These markers are of important for the individual prognosticating

within this subgroup, as *IDH* wild-type LGG with EGFR amplification or *TERT* promotor mutation have impaired survival compared to those without [223].

Since before the turn of the millennium, prior to the discovery of mutation in the isocitrate dehydrogenase gene, loss of the short arm of chromosome 1 and long arm of chromosome 19 (i.e. 1p/19q) has been associated with the oligodendroglial phenotype [224-226]. This important finding was later confirmed by multiple studies [227-230]. It is believed that this chromosomal aberration occur after the *IDH*-mutation since many of the LGG with 1p/19q codeletion shows *IDH*-mutation [51]. The loss of 1p/19q will promote cell migration, inhibit apoptosis and interfere with the citric acid regulation due to the association of mutation in CIC and FUBP1, which are located on the affected chromosomes [231].

In GBM the methylation status of the DNA repair enzyme O(6)-methylguanine-DNA methyltransferase (MGMT) promotor is a strong prognostic and predictive biomarker in response to alkylating chemotherapeutic agent such as temozolomide in patients with GBM [232]. A methylated MGMT promotor provides a survival benefit in patients treated with temozolomide by epigenetic silencing of this DNA repair enzyme; 23 months overall survival in patients with methylated MGMT promotor compared to 16 months in patients with an unmethylated promotor [233]. DNA methylation in glioma research has led to important advances in diagnosis and classification [234, 235]. The role of MGMT in anaplastic gliomas with regards to *IDH*-mutation have been studied, and findings suggest MGMT promotor methylation status as a prognostic marker for patients with *IDH*-mutated WHO grade III glioma and that *IDH* wild-type tumors with MGMT promotor methylation benefit from alkylating chemotherapeutics [236]. Methylation of MGMT promotor is found in the majority of both *IDH*-mutated 1p/19q codeleted and non-codeleted and unmethylated in half of the *IDH* wild-type gliomas [237]. Although, the role of MGMT in the clinical management WHO grade II gliomas is still controversial [89].

Other molecular markers include glioma CpG island methylator phenotype (G-CIMP), CDKN2A, *TERT* promotor mutation, mutation of the *p53* gene and loss of alpha-thalassemia/mental retardation X-linked (ATRX) function.

G-CIMP is defined as hypermethylation of CpG islands (CGIs) through the whole genome [238, 239]. The identification of the relevant G-CIMP high and G-CIMP low subgroups constitutes a classification of glioma that is not based on the histopathology or grade of the tumor. Despite the fact that G-CIMP was first identified in GBM, it is mostly associated with *IDH*-mutated gliomas and G-CIMP has been further analyzed in LGG [240, 241]. In *IDH*-mutant LGG G-CIMP low show poor survival similar to *IDH* wild-type gliomas [237].

Losses involving chromosome 9p21 has been detected in higher frequencies in infiltrating gliomas, with one consequence of this deletion being loss of CDKN2A which codes for the gene *p16* [242-244]. The loss of CDKN2A results in cellular proliferation and dysregulation of pathways involved in pro-apoptosis [245]. The loss of 9p21 and subsequent loss of CDKN2A/p16 have been associated with impaired survival in multiple studies [245-247]. The subgroup of *IDH*-mutated gliomas with loss of CDKN2A shows a strong association with poor overall survival, which may in provide further subgroups in the clinical practice.

Mutations in the promotor region of *TERT* leads to an upregulation of the enzyme activity which causes increase in telomere length and bypasses a step in cell apoptosis and the mutation has been found to be associated with glioma [248]. Studies indicate that this mutation is associated with self-renewal in GBM cells as the *TERT* promotor mutation in patients with GBM has been shown to be associated with shorter survival [249, 250]. In LGG, *TERT* has mainly been identified in oligodendrogliomas and less frequent in astrocytomas, showing an inverse relationship with *IDH*-mutation [251]. Additionally, *TERT* mutations are strongly associated with 1p/19q codeletion and are also seen in *IDH* wild-type LGG [51, 237, 252-254]. The impact of *TERT* promotor mutation on survival in patients with LGG has been studied and *TERT* promotor mutation was found to be associated with the worst prognosis when comparing the molecular groups of *IDH*-mutation, 1p/19q codeletion and *TERT* promotor mutation [57]. Subanalysis of *IDH* wild-type LGG showed that *TERT* promotor mutation without the combination of gain of chromosome 7 and loss of chromosome 10 may represent a molecular subgroup with close resemblance to GBM [255].

The transcription factor p53 regulates the cell cycle to suppress oncogenic cell proliferation and is encoded by the *TP53* gene [256, 257]. The status of *TP53* and p53 have been investigated in LGG, where increased cell differentiation have been shown to be associated with p53 immunopositivity [257]. A large, comprehensive genomic analysis of LGG found that the great majority of *IDH*-mutated astrocytomas showed mutation in *p53* and ATRX [217]. In several investigations, the gene *TP53* and the transcription factor p53 have not been found to be related to prognosis [256, 258]

The specific function of ATRX proteins, which coded by the ATRX enzyme, is unknown but these proteins play a crucial role due to their development and function as a regulator of chromatin remodeling and transcription [259]. Loss of the ATRX function has gained interest in the field of glioma, and studies point towards an improved prognosis in patients with gliomas characterized by such loss [260, 261]. ATRX mutations has rarely been shown in gliomas with 1p/19q codeletion and occurring in majority of *IDH*-mutated 1p19 non-codeleted gliomas [254].

1.8.3 Meningiomas

Meningiomas are believed to arise from the arachnoid cap cells in the arachnoidea [262]. The majority are histologically benign and slow-growing in nature but cause difficulties due to their intracranial or intraspinal location [263, 264]. The main diagnostic procedure for meningiomas is MRI, mainly a T1-weighted sequence with and without intravenous contrast (see Figure 4a-b), although advances in other modalities such as positron emission tomography (PET) are valuable in the cases of recurrence [265].

Despite the emergence of molecular markers in meningiomas, diagnosis is based on histological features [266]. The categorization criteria for meningioma were revised in the WHO classification of tumors in central nervous system from 2016 and brain invasion is now considered a criterion for meningioma grade II, also called atypical meningioma [2]. Further investigation by means of DNA methylation analysis of meningiomas has revealed six distinct methylation classes associated with expression patterns [67]. The study by Sahm et al. (2017) revealed that meningiomas could be

classified with higher precision using DNA methylation profiling rather than the WHO classification, where the former was strongly correlated with outcome. Other studies in the field of meningioma have revealed genomic subgroups and molecular mechanisms associated with tumor location, grade and histopathology [267, 268]. *TERT* promotor mutation have been assessed in meningiomas as well and is similarly associated with shorter time to progression [269]. *TERT* promotor mutation and CDKN2A gene alternations are possible molecular markers for diagnosing malignant meningiomas [270]. Surgery with excision is the main treatment modality, and the extent of resection is estimated perioperatively by the surgeon and classified in accordance with the previously mentioned Simpson grading system [113].
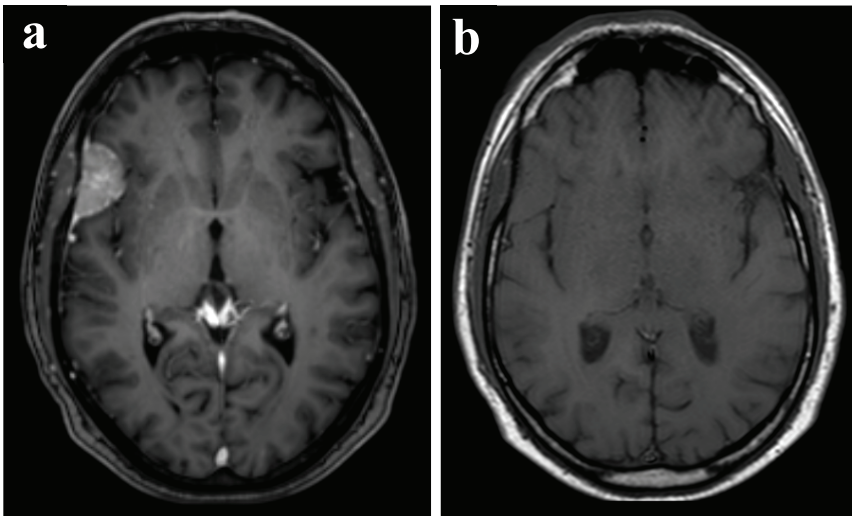

Figure 4a-b. Meningioma in the right frontal region. 4a: T1-weighted sequence with contrast enhancement. 4b: T1-weighted sequence without contrast enhancement.

1.9 Outcome

1.9.1 Outcome in patients with lower-grade glioma

Complications in the neurosurgical field suffer from lack of a unanimous reporting system, making comparisons difficult. The rate of postoperative complications in patients with intracranial neoplasms when studying the literature range from 9% to 40%, with deep venous thromboembolism (DVT) being the most common adverse event followed by new or worsened neurological deficit [271]. The risk of postoperative hematoma is highest the first 6 hours after surgery and the majority diagnosed without 24 hours of surgery [272-274].

For patients with low-grade glioma (i.e. WHO grade II) in Sweden new short-term (30-day) postoperative neurological deficit occur in approximately 18-21% of cases, and new onset seizure in 2.4-3.1% [275, 276]. Furthermore, postoperative infection was reported at 2.5%, DVT in 2.5%, hematoma in 5.0%, and reoperation due to any complication in 5.0%.

Even though neurological deficits occur in the short-term a smaller part of the patients seem to suffer from permanent neurological deficit in the long-term [215, 277]. In contrary to their more malignant counterparts, low-grade gliomas are believed to involve perilesional functional reshaping where the glioma invades eloquent areas that are involved but not essential to the function [278]. Seizure is the most common presentation in patients with LGG [154] and the vast majority of patients with LGG experience partial or total alleviation of their epilepsy after surgical resection of the lesion [279].

Return to work in patients with low-grade glioma have been studied and one year after surgery 52% of patients were working and 63% after two years [280]. Factors associated with not returning to work included older age, lower functional status and previous sick leave. The rate of return to work seems higher in studies with incidental low-grade gliomas; 91.2% returned to their employment within one year after surgery [281].

1.9.2 Outcome in patients with meningiomas

The main treatment modality for meningioma is surgery, and risks associated with surgery is hard to estimate due to multiple reasons; the lack of a standardized reporting system for complications makes comparison difficult and meningiomas have different risk profiles depending on location (such as skull base or convexity). Nevertheless, the rate of complications in Sweden after meningioma surgery is reported at an incidence of 14.8% new deficit, new-onset seizure in 4.5%, a symptomatic hematoma in 9.4%, reoperation due to any complication in 5.2%, infection in 6.4% and finally venous thromboembolism (VTE) in 3.0% [264]. When analyzing complication in the subgroup of patients with asymptomatic meningioma 8.3% suffered from new deficit postoperatively and 3.7% new-onset seizure.

Deficit in patients with meningioma WHO grade I in the long-term was studied by Alkemade and colleagues and found that only a third reported not showing any long-term deficits [282]. Within one year after surgery two thirds of patients reported that symptom or sign had completely or partially been resolved.

Seizure as presenting symptom is relatively common among patients with meningioma. A large part of the patients with preoperative seizures experience improvement postoperatively [45, 283, 284]. The use of antiepileptics in a prophylactic setting has been discussed, but there is no evidence supporting use of these in patients without seizures [157, 159]. Perilesional edema seems to be a risk factor for continued seizures in those with preoperative epilepsy [156]. New-onset epilepsy postoperatively is reported in the range 1.9-19.4% making this an important cause of postoperative morbidity [264, 285]. Risk factors for developing new-onset seizures postoperative include major surgical complications including infection in central nervous system, symptomatic intracranial hematoma, younger age and tumor progression [283, 286].

Return to work (RTW) after surgery for meningioma is a scarcely studied area, although emerging data shows a considerable risk for sick leave postoperatively with 57% of meningioma patients at work two years after surgery compared with 84% of matched controls [287]. Patients unable to return to preoperative activity range from 17-33% and factors associated with

increased risk are higher tumor grade, longer sick leave in the year prior to surgery and history of depression [287-290].

2 Aims

The principal aims of this research are to:

I.   Explore the non-invasive radiological marker T2-FLAIR mismatch in LGG and associated biological as well as clinical factors in relation to clinical outcome, evaluate the extent of resection connected to the mismatch sign and finally, to examine the interrater variability between neurosurgeons and neuroradiologist. In other words, what is the underlying biological and clinical implication of the mismatch sign – or is it simply an imaging marker?

II.   Study the impact of age on treatment, outcome and clinical characteristics of patients with low-grade glioma WHO grade II through a nationwide, register-based study.

III.   Benchmark the 30-day postoperative risks posed by meningioma surgery at national level, in addition to investigate the outcome in the relevant subgroups of asymptomatic and symptomatic patients.

IV.   Study the sick leave patterns in patients with meningioma preoperatively as well as return to work at one and two years after surgery compared to matched controls, in addition to investigate possible predictors for postoperative sick leave in patients undergoing surgery for meningioma.

3 Patients and Methods

3.1 Imaging acquisition and segmentation lower-grade gliomas (Paper I)

LGG are best depicted by means of T2-weighted (T2W) sequences. In Paper I both T2 and FLAIR sequences were used for tumor segmentation, depending on the sequence in which the tumor was most visible. The MRI examinations reviewed for this project were performed at different hospitals in the region as part of the clinical work-up prior to surgery. MRI systems included both 1.5 and 3.0 Tesla scanners from different vendors, such as GE Healthcare (US), Phillips (The Netherlands) and Siemens Healthcare (Germany). Slices 5 mm or less were accepted.

FLAIR is a T2W sequence that suppresses fluid, this highlighting white matter lesions. Hyperintense lesion can be better visualized by adding enhanced contrast to the image [291]. As a result, FLAIR is often used in preoperative MRI examinations. Due to surgically-induced artefacts that are sometimes are more pronounced in FLAIR images compared to T2 images, T2 is occasionally preferred for postoperative MRI and evaluation. However, this was done on a case-by-case basis and the selection was done in advance, thus we did not segment both T2 and FLAIR sequences in order to later select the more "beneficial" one.

The tumor volume was evaluated by semi-automatic segmentation performed with the open-source software "3DSlicer", version 4.6.2 [292]. For the segmentation of tumor volume, we used the "LevelTracingEffect", "WandEffect", "DrawEffect" and "PaintEffect" in the "Editor" module where appropriate. Tumor volumes were computed by the segmentation of hyperintense areas on the T2 or FLAIR sequence in MRI examinations. Areas mainly attributed to edema without convincing signs of tumor invasion were excluded, see Figure 5 as an example of the segmentation process.
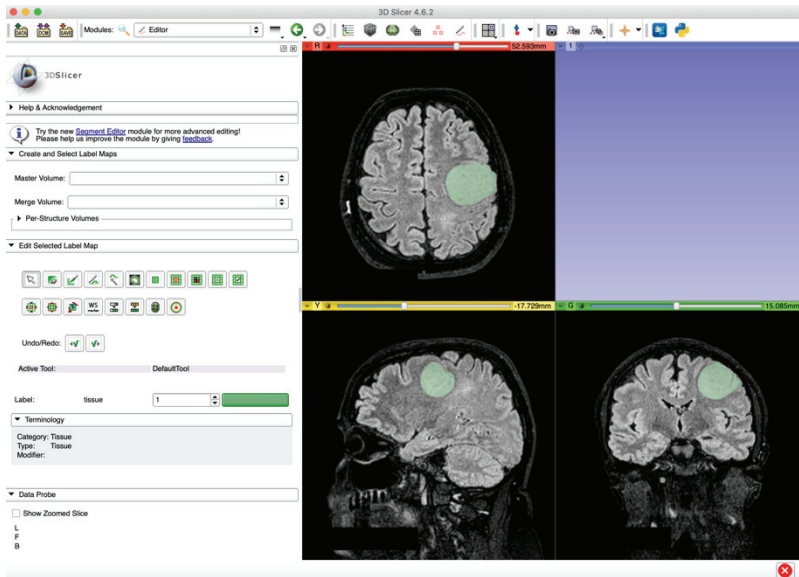
Figure 5. Example of the segmentation process of an LGG in the "3D slicer" software, version 4.6.2.

The extent of resection (EOR) was calculated as a percentage of the tumor resected with the formula: preoperative tumor volume minus remaining segmented tumor volume then divided by preoperative tumor volume and multiplied by 100 [105]. The area segmented was assessed as the remaining tumor compared with the preoperative MRI scan. The areas attributed to edema were excluded in the segmentation. All segmentations were discussed and validated with experienced neurosurgeon and an experienced neuroradiologist assisted in the more difficult segmentation cases.

3.2 DNA methylation analysis (Paper I)

In Paper I we investigated gliomas with the T2-FLAIR mismatch sign and this sign raised questions regarding possible underlying biology. DNA methylation analysis is in the front line when it comes to diagnostic technology in the field of gliomas. The methylation analysis was performed in a laboratory setting with *IDH*-mutated astrocytomas from the retrospective cohort. Tissue samples were collected from the Department of Pathology at Sahlgrenska University Hospital.

The DNA was extracted from the formalin-fixed paraffin embedded (FFPE) tumor specimens where the neuropathologist concluded that sufficient tissue was available and samples with a high tumor content of at least 70% were collected. DNA was then extracted from the FFPE tumors with a QIAamp® DNA FFPE kit (Qiagen, Hilden, Germany) in accordance with manufacturer's instructions. The DNA concentration was measured with the Qubit Fluorometer (Life technologies™, Carlsbad, CA, USA) and from 500-1000 ng DNA used for bisulfite-conversion with an EZ DNA methylation kit (D5001, Zymo Research, Irvine, CA, USA). The methylation levels of converted DNA were analyzed with Infinium MethylationEPIC BeadChip (Illumina®, San Diego, CA, USA) in line with instructions.

Employing the statistical software R (version 3.6.1), the methylation data were processed by means of the Minfi and ChAMP packages [293-295]. The status of *IDH*-mutational status was assessed by the use of a published DNA methylation-based classifier (MNP, version 11bb4) [85] and the status of 1p/19q codeletion status was assessed through copy number variations profiles acquired from the methylation data.

In order to analyze whether tumors with the T2-FLAIR mismatch sign differ in terms of underlying biology from those without the sign, the DNA-methylation profiles were evaluated by unsupervised hierarchical clustering of the 5,000 most variable CpG sites, in which only included tumor tissue from gliomas with *IDH*-mutation but without 1p/19q codeletion (n=29).

3.3 Baseline population characteristics (Paper I)

The neurosurgical department of Sahlgrenska University Hospital in Gothenburg, Västra Götaland region, with a population of roughly 1.7 million, is one of six clinics in Sweden that provide neurosurgical care. Hence, all patients in the region with newly diagnosed suspected primary intracranial lesions are referred to this hospital.

Data were collected retrospectively in the period 2010 – 2016 and prospectively between 2017 and 2018 where patients with a suspected LGG in a diagnostic MRI were included. The rationale was to test the T2-FLAIR mismatch sign in a prospective cohort where other diagnoses such as different types of tumor, or even non-neoplastic conditions, could occur.

A total of 215 patients with available MRI examinations were identified in both the retrospective and the prospective cohort. Of these, 135 had a known status *IDH* mutational status and 1p/19q codeletion status; 82 in the retrospective cohort and 53 in the prospective one. DNA methylation analysis was performed in patients from the retrospective cohort with available tissue from *IDH*-mutated 1p/19q non-codeleted gliomas (n=29).

Clinical parameters comprised gender, age, symptoms at diagnosis and functional status [163]. Radiological variables included tumor border, eloquence and main lobe involvement, among others [209]. The patients in the clinical analyses included those with *IDH*-mutated, 1p/19q non-codeleted gliomas. They were divided into two groups, with and without the T2-FLAIR mismatch sign.

3.4 Register-based research (Paper II, III, IV)

The Swedish Brain Tumor Registry (SBTR) is a nation-wide registry-based register of adult patients (18 years and over) with a histological diagnosis of primary brain tumor. It was established in 1999 and covers the six regions in Sweden that provide neurosurgical care with one department per region. All regions report to the SBTR, although the coverage has varied over time. To ensure a population-based setting and reduce risk of selective reporting to be included regions needed a minimum of 80% in coverage rate for any given year to be included in our papers. Due to this minimum coverage level data from some regions was excluded during years with lower coverage. The overall coverage rate was compared to the compulsory National Cancer Registry (NCR).

Multiple parameters are reported to the registry, including age, sex, presence and type of symptoms prior to surgery, WHO performance status (on a five-graded scale), largest tumor diameter (<4 cm, 4-6 cm or >6cm), tumor location (central, bilateral, skull-base, posterior fossa, multifocal, convexity, right or left), type of surgery, extent of surgery (assessment by neurosurgeon or early postoperative radiology), diagnosis according to Systemized Nomenclature of Medicine (SNOMED) and WHO classification, and postoperative complications (infection, symptomatic hematoma, thromboembolism, neurological deficit, new-onset seizure and reoperation due to any complication) [1].

With the use of the SBTR we could in paper II identify patients 18 years or older with a histologically confirmed low-grade glioma WHO grade II astrocytoma, oligoastrocytoma or oligodendroglioma between 2005–2015, totaling 548 patients [276]. We used the registry in a similar fashion in paper III where we identified 2,324 patients in the period from 2009 to 2015 with histological verified meningioma WHO grade I–III [264]. Finally, for Paper IV data on 965 patients aged 18-60 years with histologically verified meningioma WHO grade I – III between 2009–2015 were retrieved from the registry, in addition to the 4,765 unique controls matched through Statistics Sweden [287].

In paper IV we used data from Statistics Sweden, the Swedish Social Insurance Agency and the National Board of Health and Welfare. The government agency Statistics Sweden is responsible for coordination of Sweden's official statistics. Swedish Social Insurance Agency is the government agency responsible for administration of financial compensation for long-lasting illness and responsible for statistics on sick leave in Sweden. The official statistics of sick-leave, including temporary, longer-lasting and permanent illness, is registered by the agency. The National Board of Health and Welfare covers a range of responsibilities including social and health services and registries. One of these registries are the National Patient Registry which receives data from in- and outpatient visits from private and public hospitals, not including primary health care. In 2005 the National Prescription Registry was established to register drug prescriptions and registration is mandatory.

3.5 Study design

Paper I
Histologically verified LGG, WHO grade II and III astrocytoma, oligoastrocytoma and oligodendroglioma were retrospectively collected from adult patients 18 years or older between 2010 and 2016 in the Västra Götaland region of Sweden. In the period 2017-2018 patients with suspected radiological LGG were prospectively included. Clinical, radiological and molecular data were collected, in addition to DNA methylation profiles of *IDH*-mutated astrocytomas in the retrospective cohort in where sufficient tissue samples were available. The whole cohort were divided into those with and without the T2-FLAIR mismatch sign in relation to clinical factors, outcome and methylation profiles.

Paper II
Adults 18 years or older with a histological diagnosis of a supratentorial WHO grade II low-grade glioma, comprising astrocytoma, oligoastrocytoma and oligodendroglioma (SNOMED codes per entity), were included during the period 2005–2015. A total of 548 patients were identified from the SBTR. The cohort was divided into three different age groups; 18-39 years, 40-59 years and ≥60 years.

Paper III
To analyzed the short-term (30-day) postoperative complications we used data from the SBTR. 2,324 patients with histological diagnosis of intracranial meningioma WHO grade I – III (SNOMED codes) between 2009 and 2015 were identified. The cohort was further divided into the subgroups of symptomatic and asymptomatic meningioma patients.

Paper IV
In this study we included 956 adult patients between 18 and 60 years from the SBTR with a histological diagnosis of meningioma between 2009 and 2015. To these patients we matched 4,765 unique controls through the Statistics Sweden, a state agency that compiles statistical data. In this way we matched the year of birth, place of residency, gender and level of education of each patient who underwent surgery for meningioma with those of five unique matched controls per meningioma patient. Further, patients undergoing

surgery for meningioma who were not on sick-leave on the index date (date of surgery) were excluded due to the indication that these patients were no in work related activity during the studied period.

The National Board of Health and Welfare hold different registries including the National Prescription Registry and the National Patient registry. We used these registries to classify comorbidity according to the Elixhauser comorbidity index and information regarding drugs prescribed (for this study antiepileptics and antidepressants). We analyzed through the Swedish Social Insurance Agency absence from work in both patients and matched controls one year prior to the index date and both one and two years after.

3.6 Statistics

Papers I-III - Statistical analysis was performed with the software SPSS, version 24.0 (Chicago, IL, USA). The level of statistical significance was set at <0.05, and the tests performed were two-sided. For central tendencies, means were used for presentation of plus/minus standard deviation (SD). Median and first quartile (Q1) to third quartile (Q3) (interquartile range) were applied for skewed data. Pearson's Chi-Square test, independent sample t-test or the Mann-Whitney U-test was utilized for categorical data where appropriate, and Fishers exact test was applied in 2x2 tables with small samples. In the survival analysis we employed Kaplan-Meier curves and compared them with the log-rank test. The Cox multivariable model was applied for adjusted survival analysis. Uni- and multivariable logistic regression analyses were employed to identify possible predictors.

Additionally, in Paper I we performed the analysis using Cohen's kappa test (k) to assess interrater agreement. A value of >0.6 is considered to be substantial agreement, 0.41-0.6 moderate agreement, 0.21-0.4 fair agreement and ≤0.2 slight agreement [296].

Paper IV – The statistical program R was employed for the statistical analysis. Index date and date of diagnosis were defined as date of surgery. The Mann-Whitney U-test was used for continuous variables summarized and data summarized as median, first and third quartiles. The Fischer Exact test was applied for dichotomous categorical variables between cases and controls.

The rates of sick leave and rates of mortality for both cases and controls were investigated for each day from the year before to two years after index date. Data extracted from the different registries were transferred into a mySQL database and sick leave compensation (level and duration) for each individual was combined from two sources with the use of Python. Return to work (RTW) was defined as any degree of work-related activity two years postoperatively. Predictors of RTW were examined by means of univariable logistic regression, while multivariable logistic regression was applied to investigate independent predictors of RTW. The covariates were chosen based on presumed relevance. Age and sex were included as demographic variables, in addition to other socio-economic and clinical variables.

3.7 Ethical considerations

The Ethics committee for Medical Research in the Västra Götaland Region of Sweden approved the projects included in Paper I to IV. Papers II-IV were retrospective in design without any individual patient participation and the medical risk was considered low. Although a part of Paper I was prospective in design, where patients were included when presenting to the neurosurgical clinic or to the multidisciplinary conference, it did not include participation by individual patients. Nor does the paper contain studies in which an intervention was performed on human participants by any of the authors. Individual patient consent was waived by the ethical committee.

Study I - (DNR 1067-16), Study II - (DNR 702-16), Study III - (DNR 363-17), Study IV - (DNR 363-17).

4 Results

4.1 Paper I

The clinical significance of the T2-FLAIR mismatch sign in grade II and III gliomas: a population-based study
Corell A, Ferreyra Vega S, Hoefling N, Carstam L, Smits A, Olsson Bontell T, Björkman-Burtscher IM, Carén H, Jakola AS
BMC Cancer 2020

In this paper, the aim was to investigate the T2-FLAIR mismatch sign (see Figure 6a-b as an example) in a population-based setting, both in a retrospective cohort with histologically confirmed LGG and in a prospective cohort in which other diagnoses than glioma could occur. Additionally, we wanted to examine possible underlying biological differences through methylation analysis in those with and without the mismatch sign. 215 patients were identified in two cohorts; one retrospective cohort with 157 histologically confirmed LGG and one prospective cohort with 58 radiologically suspected LGG, where other diagnoses could also occur. The mismatch sign was assessed by two independent neurosurgeons and one neuroradiologist. Another experienced neuroradiologist reviewed the discordant cases. The interrater agreement between neuroradiologists and clinical neurosurgeons for the T2-FLAIR mismatch was tested by means of examining 215 MRI scans and a significant Cohen's kappa value was found, $\kappa = 0.77$ (p<0.001).

Out of the 215 patients, 135 had known *IDH* mutational status and status of 1p/19q codeletion, while 50 patients of these had a molecular status of *IDH*-mutated astrocytoma (*IDH*-mutation 1p/19q non-codeletion). In the latter group, 12 patients (24.0 %) had a glioma with the T2-FLAIR mismatch sign. The sensitivity of the mismatch sign in detecting *IDH*-mutated 1p/19q non-codeleted gliomas was 26.4% and the specificity 97.6%. Further examinations were performed pertaining to baseline characteristics, clinical outcomes and methylation profiles. There were no differences between astrocytomas (*IDH*-mutated 1p/19q non-codeleted) with or without the T2-FLAIR mismatch sign.

In conclusion, we found no association of the mismatch sign with either the presentation or outcome. The methylation analysis indicated no clustering of

the mismatch group together, suggesting that gliomas showing the mismatch sign do not constitute a subentity. Further investigations into the underlying difference between gliomas with and without the mismatch sign are warranted.
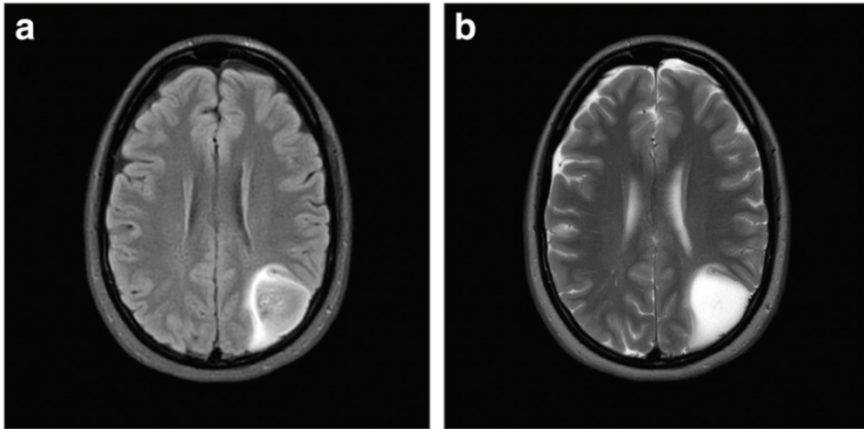

Figure 6a-b. A glioma in the left parietal region showing the T2-FLAIR mismatch sign. It was histologically diagnosed as a glioblastoma (i.e. astrocytoma WHO grade IV) IDH-mutated). 6a: FLAIR sequence demonstrating a relative hypointense signal with the exception of a hyperintense peripheral rim. 6b: T2W sequence demonstrating homogeneous hyperintensive signal with a conspicuous border.

4.2 Paper II

Age and surgical outcome of low-grade glioma in Sweden
Corell A, Carstam L, Smits A, Henriksson R, Jakola AS
Acta Neurologica Scandinavica 2018

LGG usually affects younger patients aged between 30 and 40 years, thus information regarding the treatment of LGG in the older population is lacking. To investigate this, we identified a total of 548 adult patients with low-grade (WHO grade II) glioma in the period 2005–2015 contained in the Swedish brain tumor registry (SBTR). Of these, 204 patients were aged 18–39 years (37.2%), 227 were 40–59 years (41.4%) and 117 were over 60 years of age or older (21.4%). We found that the older patients more often presented with neurological deficits when compared to the younger cohorts. The performance status was worse in the intermediate age group compared to the youngest cohort, while that of the older patients was more impaired than that of the intermediate cohort (p=0.002). Increased age was associated with unfavorable prognostic factors such as poorer functional status and neurological deficits (p<0.001). The overall survival differed between groups and was significantly lower in patients aged 60 years and older (p<0.001). When subanalyzing patients in the intermediate age group, we divided them into two groups; 40–49 and 50–59 years. There was a clear separation of survival curves at 50 years, see Figure 7a-b. When comparing surgical techniques between groups, we found that biopsy was more common in the group of patients aged 60 years and older (p<0.001). A subgroup analysis of those who underwent tumor resection revealed a higher level of postoperative neurological deficit found in older patients (p=0.029).

To conclude, older patients more often present with neurological deficit and worse performance status compared to their younger counterparts. A majority of the older cohort underwent biopsy rather than surgical resection and suffered from a new neurological deficit postoperatively to a larger extent than the younger cohorts. However, they appear to tolerate surgery in a similar fashion in relation to other postoperative complications such as infection, hematoma and new onset of seizures. Our findings showed reduced survival in patients aged 50–59 years and older compared to those between 40–49 years, suggesting 50 years as a cut-off to identify high-risk patients.
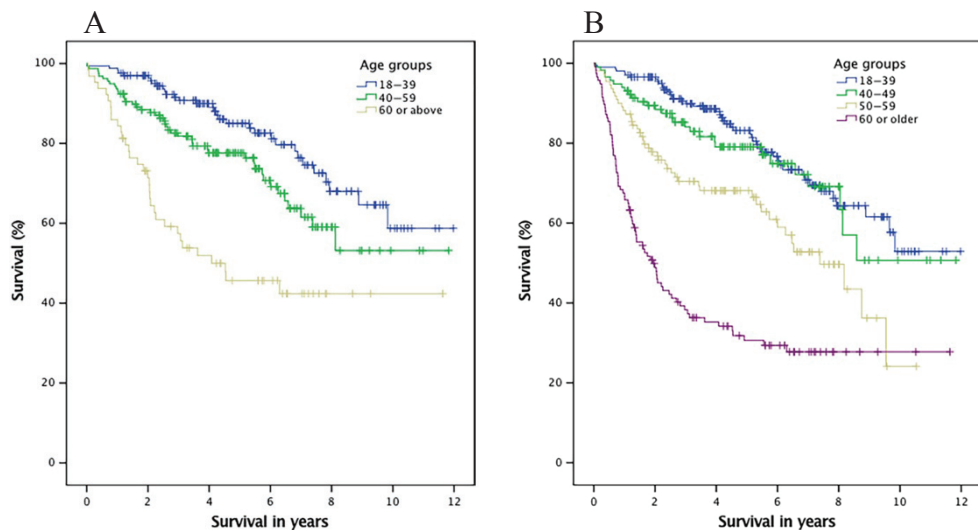
Figure 7a-b. 7a: Survival curves of patients undergoing resection according to age group, p<0.001. 7b: Survival curves of age groups with division of the 40–59 year group into 40–49 and 50–59 years, p<0.001. From Corell et al, Age and surgical outcome of low-grade glioma in Sweden, Acta Neurologica Scandinavica 2018, pp. 359-368.

4.3 Paper III

Neurosurgical treatment and outcome patterns of meningioma in Sweden: a nationwide registry-based study

Corell A, Thurin E, Skoglund T, Farahmand D, Henriksson R, Rydenhag B, Gulati S, Bartek J Jr, Jakola AS

Acta Neurochirurgica 2019

Meningiomas are the most common intracranial tumors and the overall incidence overall is rising, probably partly due to the increased availability of CT and MRI scans, which makes the identification of incidental meningiomas more frequent. The main form of treatment for meningiomas is surgery, which is inevitably associated with risks. We aimed to benchmark the current short-term 30-day complication rate for patients undergoing neurosurgical treatment for intracranial meningioma, in addition to examining the short-term postoperative course for the subgroups of symptomatic and asymptomatic meningiomas. We identified 2,324 patients through the SBTR. The mean age of the cohort was 58.7 years (SD 13.5) and 14.1% were asymptomatic prior to neurosurgical treatment. A focal deficit was the most common symptom, affecting 1,450 patients (62.4%). Unfortunately, the indication for surgery was unknown in the group of asymptomatic patients, but possible indications could be radiological growth of the meningioma, large size upon discovery or the patient's wish.

In the short-term postoperative period reoperation due to any complication was performed in 120 patients (5.2%). Postoperative symptomatic hematoma was more common in the symptomatic group (p=0.001), as well as venous thromboembolism and a new postoperative neurological deficit. 344 patients of the cohort as a whole (14.8%) developed such a deficit postoperatively compared to 8.3% of the asymptomatic patients. In the asymptomatic cohort, 3.7% developed new onset seizure in the short-term postoperative period (p=0.43). The overall 30-day mortality was 1.5%, but lower in the asymptomatic group (0.3%) compared to the symptomatic (1.7%) (p=0.06).

In this study we present data on the incidence of postoperative complications and benchmarked the short-term postoperative outcome in patients undergoing

surgery for both symptomatic and asymptomatic meningioma. It seems that asymptomatic patients suffer less from postoperative complications compared to symptomatic ones, although 8.3% of asymptomatic patients suffered from neurological deficit postoperatively. The information regarding short-term risks is important for patients and caregivers when deciding about the treatment plan and for enabling patients to prepare for the possible postoperative course.

4.4 Paper IV

Return to work following meningioma surgery: a Swedish nationwide registry-based matched cohort study
Thurin E, Corell A, Gulati S, Smits A, Henriksson R, Bartek J Jr, Salvesen Ø, Jakola AS
Neuro-Oncology Practice 2020

In the majority of cases meningiomas are characterized by benign biological activity and mainly considered an innocuous disease. However, surgical interventions are associated with risk of both physical and cognitive deficit. Studies have shown that employment is positive for patients with brain disorders, but in a more recent study, data revealed that a third of patients who underwent surgery for meningioma were unable to return to work after a mean follow up of 32 months. We aimed to investigate the rate of sick leave among patients with meningiomas compared to matched controls, both one year prior to and at one and two years after surgery (index date) in a population-based matched cohort study. A total of 956 patients were identified through the SBTR and 5 unique matched controls per meningioma patient were included from Statistics Sweden, totaling 4,765 controls. One year prior to surgery, 79% of meningioma patients and 86% of controls were working (p<0.001). The meningioma cohort had a higher rate of depression both one year prior to and on the index date compared to controls; one year prior to treatment 21.3% of meningioma patients compared to 16.5% of controls, and at the index date 29.1% respectively 19.0% (p<0.001).

When analyzing predictors for returning to work, high tumor grade (p=0.002), history of depression (p=0.03), days absent from work in the year prior to surgery (p<0.001) and postoperative neurological deficit (p=0.004) were negatively associated with RTW. Two years after index date, 57% of patients with meningioma had returned to work compared to 84% of the controls (p<0.001), see Figure 8a-b.

In this study we concluded that patients undergoing surgery for intracranial meningioma are at a considerably higher risk of not returning to work two years after surgery compared to matched controls. Negatively associated

factors regarding RTW were presented, and the predictive potential of depressive symptoms indicates a possible area of preoperative interventions for patients undergoing surgery for meningioma with a history of depression.

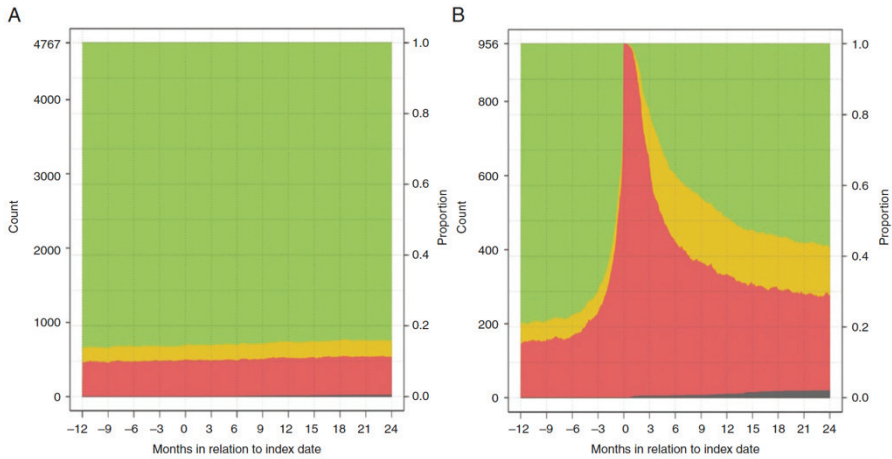*Figure 8a-b. Green represents rate without sick leave, yellow patients with partial sick leave and red those on full sick leave, from one year prior to index date (date of surgery) up to 730 days after. Deceased patients are represented as the grey stack at bottom. 8a: Controls, n=4767. 8b: Meningioma patients, n=965. From Thurin et al, Return to work following meningioma surgery, Neuro-Oncology Practice 2019, pp. 320-328.*

5 Discussion

5.1 Lower-grade gliomas (Paper I-II)

During the last decade the field of LGG ranging from diagnostic properties and non-invasive diagnosis to surgical and adjuvant treatment has been revolutionized by the introduction of the molecular markers of *IDH* mutational status and presence or absence of 1p/19q codeletion [2]. As a result, previously accepted findings will need to be re-evaluated by means of this new classification system and ensuing stratification. The most recent WHO classification from 2016 provides us with a new basis for diagnosis with a reduced degree of interrater disagreement, and leading to safer decision-making in terms of treatment plans for individual patients. Similarly, in the field of malignant melanoma, the discovery of genetic aberrations such as mutation in *BRAF* or *NRAS* has led to further stratification of patients with this condition and subsequently improving their treatment [297]. In this new era of molecular classification of LGG there is a need for re-evaluation of clinical prognostic factors, further investigation of the role of surgery in LGG subgroups and appropriate adjuvant treatment for these lesions.

5.1.1 Clinical prognostic factors in the molecular era

Traditionally, clinical prognostic factors in patients with LGG have been used to identify those at high risk of progression of their lesion [207]. However, at the dawn of the molecular marker era, risk assessment of LGG progression employing only clinical and radiological factors has been questioned. Pignatti and colleagues identified clinical prognostic factors to identify high-risk patients with LGG [207]. Their multivariate analysis demonstrated that age equal to or over 40 years, tumor diameter equal to or over 6 cm, bilateral tumor growth, astrocytoma subtype and preoperative neurological deficit were all associated with unfavorable prognosis. A few years later, Chang and colleagues revisited the area of prognostic factors in patients with LGG [209]. They presented a scoring system to preoperatively prognosticate the degree of resectability of the glioma, as well as progression-free and overall survival. Four factors were found to be associated with impaired overall survival; age older than 50 years, tumor diameter over 4 cm, tumor with eloquent location

and Karnofsky performance score of 80 points or lower [163, 209]. Presumed eloquency in the field of LGG has been associated with both lower progression-free survival and lower overall survival, although further preoperative mapping to specify the eloquency improved survival in those where the tumor spared eloquent areas [298, 299].

Patients with LGG constitute a heterogeneous and multifaceted group with individual risk of malignant transformation and time to progression [300]. Even though molecular markers such as *IDH* mutational status and 1p/19q codeletion are now widely used in clinical practice and have a strong association with survival [51, 57], clinical factors such as age, performance score and tumor location still influence the treatment strategy [299]. In the study by Etxaniz et al. (2017), the findings point to *IDH* mutational status being a more important factor than clinical parameters in differentiating between high- and low-risk patients with LGG [56]. Although, other genetic alterations are present that stratifies the new subgroups further.

It is largely accepted that LGG is today divided into three subgroups depending on the status of *IDH* mutational status and codeletion of 1p/19q; *IDH*-mutation with 1p/19q codeletion (oligodendroglioma), *IDH*-mutation without 1p/19q codeletion (*IDH*-mutated astrocytoma) and *IDH* wild-type LGG. The effect on survival of additional genetic mutations in these subgroups have been further evaluated, and in oligodendrogliomas incomplete resection and *NOTCH1* mutations were associated with impaired survival [301]. Further, in *IDH*-mutated astrocytomas alteration of *RB1*, *CDKN2A* and *CDK4* genes and *PIK3R1* mutations were associated with shorter survival, and in the *IDH* wild-type LGG WHO grade III histology, mutation in *TERT* promotor and the combination of gain of chromosome 7p and loss of chromosome 10q (+7p/-10q) were all associated with poor survival. Further subgrouping provides possibility for more precise research to identify suitable treatment options for individual patients, depending on the genetic profile of their glioma.

The EORTC study from 2011 examined prognostic factors for patients with LGG, where 1p/19q codeletion was found to be a prognostic factor, and histology and tumor size were strongly associated with the prognosis [208]. This finding still proves today, where patients with gliomas with *IDH*-mutation

and 1p/19q codeletion have longer survival and are considered the chemosensitive glioma [302].

5.1.2 Age and lower-grade glioma

Glioma subtypes differ over the age spectrum, with low-grade gliomas being more common than high-grade ones in the pediatric population in contrast to older patients, where malignant gliomas are more common [303, 304]. In the pediatric population, gliomas are divided into three categories, which include high-grade glioma, low-grade glioma and diffuse intrinsic pontine gliomas (DIPG) [305]. Even though the morphology of adult and pediatric gliomas is similar, there are important underlying biological differences in tumor biology [306]. The molecular biology of pediatric low-grade gliomas shares similarities with adult gliomas, although they differ in some respects such as lack of *IDH*-mutation in a majority of cases, suggesting that *IDH*-mutation is not involved in the onset or progress of pediatric glioma [303, 307, 308]. Instead, pediatric gliomas are characterized by rearrangements in other genes such as *BRAF*, *FGRF1* and *MYB* [309].

Thus, it is unclear how age per se contributes to prognosis with the improved classification. Age is of particular interesting in view of the Buckner trial, which used the historical age cut-off of 40 years to identify high-risk patients with LGG, similar to the study by Pignatti [207], resulting in premature treatment in some patients. Some studies indicate towards an age cut-off of 50 years [276, 310], although in the molecular era there is a debate about whether *IDH*-mutation outweighs age as a clinical factor, which often influences clinical decision-making [56, 311]. In our study, we found that older patients (aged 60 years and over) seem to tolerate surgery in a similar fashion to their younger counterparts in terms of postoperative complications. However, they more often exhibit a neurological deficit postoperatively; 58.4% compared to 26.3% in the 18–39 year age group and 36.8% in the 40–59 year age group (p<0.001). The short-term mortality within 30 days postoperatively was not statistically significant, although the 1-year mortality was much higher in the older age groups compared to younger patients (p<0.001). Previous studies have shown higher frequency of eloquent location and association of *IDH* wild-type in older patients with LGG, suggesting a more aggressive underlying

biology combined with a more inaccessible lesion location that leads to limitations in surgical treatment [210, 312-314]. As a larger proportion of the general population grows older, the health status among older citizens will vary to a greater degree. Therefore, glioma in the older population should not only be determined on chronological age but rather on biological age in relation to performance status, presence of comorbidities and tumor characteristics.

5.1.3 Non-invasive or minimally invasive molecular diagnostics, radiomics and liquid biopsies

The area of non-invasive diagnostics has evoked interest in numerous medical disciplines. Extensive analysis of radiomic features in relation to underlying gene expression was initially performed in datasets of patients with lung and head-and-neck cancer [315]. It was found that radiomics could identify prognostic phenotypes in these types of tumors, which triggered further research in the field of radiomics [316]. Radiomics is of great importance for many aspects in the course of oncological diseases. During the initial diagnostic course, radiomics provides important information regarding possible histological diagnosis, molecular characterization and biological behavior, all of which are important for both surgeons and patients in relation to informed consent to treatment. Furthermore, radiomics provides caregivers with important information about the progression of the disease both in cases selected for careful monitoring and those undergoing treatment. All information regarding the possible clinical course is of great importance for shared decision-making with the patient, an approach that has become more common during the last decade [317, 318]. Shared decision-making is important in patients with LGG due to the wide variety of possible treatment strategies, including possible surgical treatment, which involves the risk of complications, postoperative adjuvant radio- or chemotherapy, and the timing of the interventions.

In the field of meningioma, simpler clinical imaging markers have been used to obtain non-invasive information regarding the possible course [319, 320]. The use of radiomics in the LGG group has been challenging. The LGG growth rate is related to the malignant potential of the glioma [17, 18], and recently information regarding molecular status has been called for [321]. In relation to

molecular status in LGG, Patel et al. (2017) described the T2-FLAIR mismatch sign, which is a radiological marker in LGG where the lesion shows a hyperintense signal on T2W sequences and a hyperintense ring around a hypointense lesion on FLAIR sequences [79]. The authors found a very high specificity of the mismatch sign for *IDH*-mutated astrocytomas, a finding that was validated by Broen [79, 80]. Radiological signs with some similarities have also been previously investigated in relation to the histology of brain tumors. In 2007 a hyperintense ring on FLAIR sequences was investigated in patients with dysembryoplastic neuroepithelial tumor (DNET) and found in 9 out of 11 cases [322]. This finding may correspond to peripheral loose neuroglial elements, although interestingly, the hyperintense ring was also found in two of the control cases; one astrocytoma and one ganglioglioma. Additionally, a more recent study investigated the T2-FLAIR mismatch sign in relation to DNET, there is was observed in more than half of included DNET cases [323].

Further investigations regarding histological characteristics in relation to the mismatch sign have been performed. In a recent study by Deguchi el al. (2020) tumor samples from *IDH*-mutant astrocytomas were evaluated and microcysts were found in the lesions with the mismatch sign [324]. Additionally, when analyzing multiple samples from different locations in the same lesion microcysts were present in the T2-FLAIR mismatch region, but less so in the region of the lesion not showing the mismatch sign. Furthermore, all of the protoplasmic astrocytomas with *IDH*-mutation showed the T2-FLAIR mismatch sign, suggesting that it may reflect the formation of microcysts in these gliomas. Protoplasmic astrocytomas are a rare subtype of astrocytomas with histological characteristics of astrocytes with a background of microcysts [325, 326]. However, the protoplasmic astrocytoma classification was removed from the updated WHO classification of 2016 with the explanation that the diagnosis was defined in vague terms and that tumors with histopathological appearance are usually characterized as other, more narrowly defined lesions [2]. The T2-FLAIR mismatch sign possibly reflects a higher water content, a theory that is strengthened by the fact that DNET cases often present with cysts [327]. The mismatch sign probably does not represent a unique subentity due to the lack of clustering in methylation analysis, which reflects the underlying biology, and probably lacks in clinical importance [82].

Blood serum markers of cancer have gained interest since the wide availability of blood samples and to in a minimally invasive was diagnose and follow patients with oncological diagnosis under the course of the disease [328]. The tumor markers are released into the blood stream and produced as a response by the body (tumor-associated) or by the tumor cells (tumor-derived) [329]. Numerous markers use in clinical practice including, but not limited to, carcinoembryonic antigen (CEA), prostate-specific antigen (PSA), human chronic gonadotropins, cancer antigen 125 and mitochondrial markers [330, 331]. However, there are factors that need to be taken into consideration when discussing blood serum markers, such as the lack of specificity and accuracy, consequences of false-positive samples and the discussion pertaining to screening and mass testing [332]. Circulating cell-free DNA (cfDNA) and circulating tumor DNA (ctDNA) have gained interest as possible markers of tumor activity and/or burden in patients with GBM, where concentrations of cfDNA varied during the course of the disease with highest concentrations during tumor progression [333]. The concentration of cfDNA has also been shown to be elevated in patients with traumatic brain injury, suggesting that cfDNA may be more related to brain injury than to the malignancy itself [334].

Minimally invasive diagnostic methods are always of importance due to the risk profile associated with invasive diagnostic procedures, especially in neurosurgery. Liquid biopsies, such as examination of CSF obtained through lumbar puncture, have gained interest due to the possibility of obtaining biological information about a lesion with a less invasive method. Liquid biopsies are not only useful in diagnosis of a newly discovered lesion, but also in assessing treatment response, detect possible tumor relapse and monitoring. In a study examining liquid biopsies from patients with glioma, ctDNA was found in half of the patients (42 out of a total 85) and the genomic characteristics resembled those in the tumor biopsies [335]. Furthermore, the study also suggests that the detection of ctDNA in CSF may be an early indicator of glioma progression. Perhaps the combination of minimally invasive diagnostics such as liquid biopsies and non-invasive methods will improve the care of patients both with newly discovered lesions and those patients with known lesion during or after adjuvant oncological treatment.

In addition to cfDNA and ctDNA, tumor-derived microRNA (miRNA) may be a potential biomarker in patients with malignant glioma [336]. MiRNA has

been further evaluated and specific RNA strands, namely miR-210, miR-185, miR-5194 and miR-449, have been identified and analyzed in relation to GBM, low-grade astrocytoma and traumatic brain injury. The results suggest that these strands are promising for diagnosis and prognosis in glioma patients [337]. Other studies indicate that additional miRNA strands are able to differentiate GBM from LGG, which could be useful in the follow-up of glioma and for early detection of possible transformation [338]. Further investigations into specific miRNA strands are warranted before adopting this promising minimally invasive method in clinical practice.

5.1.4 Classification beyond WHO 2016

After the introduction of molecular markers in the 2016 WHO classification of tumors in the central nervous system (CNS) more objective tools for classification such as DNA methylation profiling has gained interest [85, 339, 340]. Epigenetics includes numerous mechanisms of underlying embryonic development and cell identity [341]. These mechanisms of epigenetics include DNA methylation and histone modifications, and epigenetic alterations can lead to tumor initiation, uncontrolled cell division, growth, invasiveness and metastasis [342]. The epigenetic modifications are reversible alterations in gene expression without changing the primary DNA sequence [342]. A comprehensive study of DNA methylation patterns in 1,628 human samples including 424 normal tissue samples (including leucocytes and colon mucosa), 1,054 tumorigenic samples (premalignant lesions, primary tumors and metastases) and 150 non-cancerous lesions such as brain tissue from Alzheimer's disease, myopathies and autoimmune disorders, revealed progressive gain of CpG-island hypermethylation in promotor regions of tumor suppressor genes and loss of CpG methylation in non-CpG-island promoters during tumorigenesis [343].

As mentioned, DNA methylation profiling have been shown to be highly robust and widely used tool to re- and subclassify CNS tumors [340, 344-346]. A comprehensive CNS tumor reference cohort was generated with genome-wide DNA methylation profiles [85]. DNA methylation profiling have proven to be an important tool for tumor classification which not only can aid in the molecular refinement of tumors but also improve the diagnostic accuracy in

difficult cases [234, 347], resulting in an improved clinical management of patients who can receive appropriate treatment [348]. An example of DNA methylation profiling can be seen in Figure 9.
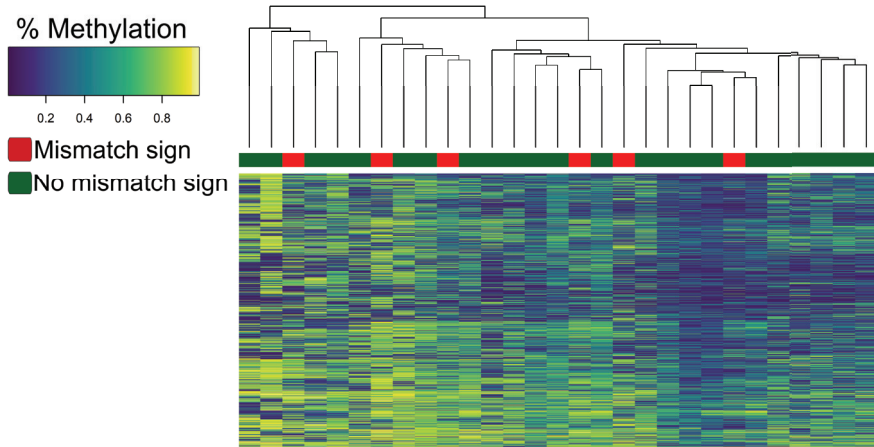
Figure 9. DNA methylation profiling for IDH-mutated astrocytomas, n=29. Unsupervised hierarchical clustering analysis does not cluster IDH-mutated astrocytomas with the T2-FLAIR mismatch sign (red) together. From Corell et al, The clinical significance of the T2-FLAIR mismatch sign in grade II and III gliomas: a population-based study, BMC Cancer 2020.

The Consortium to Inform Molecular and Practical Approaches to CNS Tumor Taxonomy (cIMPACT) was established in 2016 with a goal of a faster integration of the advances of brain tumor molecular pathogenesis [349, 350]. The third update included recommended diagnostic criteria for *IDH* wild-type astrocytoma WHO grade II and III with molecular features of GBM WHO grade IV [63]. They concluded the concluded that the minimal molecular criterion to be identified by one of the following molecular features; amplification of *EGFR*, combined chromosome 7 gains and chromosome 10 losses (whole chromosome, or loss of long or short arm), or *TERT* promotor mutation [61, 62].

5.2 Meningiomas (Paper III-IV)

5.2.1 Short and long-term follow up after meningioma surgery

The main treatment modality for meningioma is surgery, which is associated with risks and neurological deterioration, as previously discussed. Meningiomas are in the majority of cases benign in histology, and considered to be a benign lesion, although studies show that not all patient are able to return to work after surgical treatment, even in the long-term perspective [288, 289, 351]. When benchmarking the current short-term complication rate after meningioma surgery in Sweden, we found that 14.1% of the cohort was asymptomatic prior to their treatment, although reason for the surgical decision is unknown [264]. Interestingly, new deficit arose in 8.3% and new-onset seizure in 3.7% of the previously asymptomatic patients. Some of these patients may not have long-term deficit, since this data shows the 30-day postoperative course, although again confirms that no surgery goes without risk.

Postoperative complications are often measured in robust numbers and values; hematoma, reoperation due to complications, rate of DVT, and further [98]. However, it is known that intracranial surgery may lead to mental fatigue and cognitive disturbances [352, 353]. During the past decade, health-related quality of life (HRQoL) have gained much important recognition in the field of brain tumor surgery and treatment. More data shows that patients after brain tumor surgery suffer from cognitive disabilities and as a consequence decreased quality of life [290, 354-356]. One study investigating the HRQoL in elderly patients that had received surgical treatment for meningioma suggests that the HRQoL were more significantly related to Karnofsky performance scale and comorbidities, perhaps due to decreased possibility of rehabilitation with a previous burden of disease [356].

The decision-making process and surgical dilemma for asymptomatic meningiomas appears even more complicated in the light of these possible consequences. To be able for the individual patients to make an informed decision, information regarding possible both physical and cognitive impairment must be presented.

5.2.2 Treatment strategies for asymptomatic meningiomas

Meningioma is the most common intracranial tumor, and a more and more common incidental finding, possibly due to the increased age of the population in general and increase availability of CT and MRI scans [357-361]. The discovery of an incidental intracranial meningioma poses an ethical dilemma whether to treat actively with surgery or to continue with active surveillance with follow-up MRI scans [103]. Studies on follow-up on incidental meningiomas showed that approximately a third of the meningiomas grew [362, 363] and features associated with slow or no growth of meningioma includes calcification, low T2 MRI signal and higher age of patient [364, 365].

Choosing the right treatment strategy for asymptomatic meningiomas can be challenging due to the possible risks with surgical intervention and in the majority of cases a slow growth, if none at all. The main recommendation by the EANO for asymptomatic meningiomas is observation with MRI with contrast 6 months after radiological diagnosis and if the patient remain asymptomatic continue with annual MRI scans, and surgery should be offered if symptoms arise or signs of radiological growth [91]. Although, some clinical and radiological factors have been shown to be associated with a higher proliferative potential which should be taken into consideration, such as male gender, recurrence, absence of calcification [320, 366]. This group should possibly be followed more closely or even be offered surgical treatment as some studies have showed that asymptomatic meningiomas have a lower rate of complication postoperatively [367].

5.2.3 Postoperative adjuvant treatment in WHO grade II and III meningiomas

The use of radiotherapy is shown to be beneficial for patients with higher grade meningiomas, although there is an ongoing debate regarding the role of early radiotherapy in atypical meningiomas. Since the last revision of WHO classification system in 2016 the characteristic of brain invasion is now considered a hallmark of atypical (i.e. WHO grade II) meningioma [2]. Not only is there different approaches to the detection of brain invasion, the change in histological criteria will probably lead to increased amount of patients

meningiomas diagnosed as atypical [66]. Further stratifications through DNA methylation and identification of molecular markers such as *TERT* promotor mutation can provide more robust classification to identify those with more aggressive biology despite benign histological evaluation [67].

5.2.4 Return to work

Having an employment is not only valuable for the society but plays an important role for the individual [368]. Both predictors for working capacity postoperatively and large-scale studies in the area have been lacking. It is estimated that 60% of adults survive their cancer, and that these survivors suffer from a range of problems such as fatigue, cognitive impairment and complications related to radio- and chemotherapy [369].

A large population-based study from Germany studied the return to work in patients diagnosed with breast, colorectal, or prostate cancer [370]. 90% of the patients returned to work during the first two years. Furthermore, 17% reduced their working hours and 6% of the patients left their work due to their cancer diagnosis within five years of their RTW.

When studying literature regarding RTW for patients with intracranial lesions frequency of return seems to vary depending on type. Patients after surgery for pituitary adenomas showed that the surgical technique (microsurgical or endoscopic) did not influence the work capacity in the long-term, as 72.3% of patients after microsurgery and 78.4% after endoscopic surgery returned to work after a median sick leave period of 6 weeks [371]. 10% of working age patients in microsurgery group went on permanent sick leave, compared to 13% of the group undergoing endoscopy, majority of patients being female.

Glioma patients show similar percentages as meningioma patients in regards to return to work; 52% of patients were working one year after surgery and 63% after two years [280]. Lower functional status and previous sick leave does also seem to influence RTW, as in patients with meningioma. Interestingly, patients with incidental low-grade glioma return to work to a larger extent, 91.2% returned to their employment within one year after surgery

[281]. Perhaps due to lesser of tumor burden in patients with asymptomatic glioma and smaller tumor lesions [372].

The RTW after meningioma surgery is impaired both one year after index date where 49.3% had returned to work and after two years where 57.3% of the patients had returned to work, compared to 84.3% of the unique, paired controls two years after index date [287]. Even with the limitations of not being a randomized study or that the controls were not patients with meningioma not undergoing surgery, it's a comparative study which presents real-world and objective data regarding the ability to return to work for these patients. Since both retaining work and RTW has been shown to have a large impact on the quality of health, this should be considered in a preoperative setting, especially in asymptomatic patients with meningioma [373-375].

The impact of rehabilitation is unknown in patients undergoing surgical treatment for intracranial lesions, but rehabilitation with focus on return to work would be optimal in younger patients with better long-term prognosis. For such patients to be able to regain work capacity would be of significant value [376].

5.3 Register-based studies (Paper II-IV)

5.3.1 Registries as a data source for research

Sweden as a country has a long history of national registries and a system of unique personal identify numbers which makes it possible to link data from different registries to a unique individual. There are a large number of different registries that can be used for clinical research. Registries with data from clinical and administrative databases are useful to be able to include large number of patients, which is useful in the neurosurgical field where patient cohorts tends to be smaller. In addition, registry-based research is especially important in the field of neurosurgery due to the fact that large variations in clinical practices exist [95, 377].

Not only does registries offer large patient samples and information regarding the surgical treatment, it also provides information regarding trends, costs and information regarding complications of surgical treatment. Although, the quality of the registries depends on what is reported to the registry, both how well the registry forms are answered and that the level of coverage is consistent and adequate. Limitations also include those inevitable related to registry-based studies, such as limited details and that missing data is almost impossible to complete. The factor of subjective interpretation of variables (e.g. postoperative hematoma defined as symptomatic) is another caveat with registries, compared to more objective variables ch as VTE or reoperation. The lack of long-term data is another limitation in regards to neurological deficit postoperatively. The evaluation of postoperative deficit from surgeon may not be as sensitive as patient reported deficit some suggest [378].

For follow-up other registries can be used to connect unique patients with registries, such as matching patients with registries for sick leave with prescriptions, e.g. antiepileptic medication. Ongoing work with linking registries to study prescription of medications would be helpful to validate the data in registries and provide real-world information with higher precision regarding individual patients.

5.4 Strengths and limitations

Studies based on registries possesses strengths in the possibility to collect large number of patients with rare diagnosis, making research in these groups possible. Data to the SBTR is reported in a standardized and continuous fashion in a recent time period in a population-based setting. Due to the organization of regional health care, the patients who experience major postoperative complication in need of neurosurgical care are treated at the same department and therefore likely to be reported to the registry.

Limitations of studies based on registries are typically related to lack of detailed clinical data, both related to radiology and biology (such as molecular markers), and no possibility to complete the missing data. In paper II radiological data regarding contrast enhancement, being a prognostic factor in low-grade gliomas, would have been useful in the analyses. The registry has also been lacking data on patients not undergoing surgery where a wait-and-see approach is selected. In paper III we lacked long-term data regarding the neurological deficit, a variable not included in the registry. The variables of postoperative complications such as postoperative hematoma are subject to interpretation, creating possible discrepancies in the data reported to the registry.

6 Main conclusions

- The radiological marker T2-FLAIR mismatch sign is a non-invasive sign with seemingly good specificity for *IDH*-mutated astrocytomas, but with limited sensitivity. The main value seems to be as an imaging marker with only limited clinical importance beyond this, although microcystic content could be an explanation for the image pattern.

- Age in relation to treatment and outcome after surgery for LGG is scarcely studied in the older population. The findings suggest a cut-off age at 50 years to select high-risk patients. Additionally, elderly patients (60 years and older) seem to tolerate surgery in similar fashion to their younger counterparts, although shows increase in neurological deficit postoperatively and mortality one year after surgery compared to patients younger than 60 years.

- A substantial portion undergoing meningioma surgery experience a complication, even among the asymptomatic patients. When benchmarking the current postoperative risks after meningioma surgery in Sweden the risks are in line with relevant literature. Asymptomatic patients do not suffer from complication in similar extent, but a significant part of the asymptomatic patients suffer from neurological deficit in the short-term after surgery.

- Return to work after medical and surgical treatment is of great importance for the individuals and for the society as a whole. When studying the patterns of sick leave in patients undergoing surgery for intracranial meningioma data shows a significant reduced rate of RTW among patients after meningioma surgery compared with five unique matched controls. Factors associated with increased risk of sick leave included history of depression, higher tumor grade, neurological deficit postoperatively and sick leave in the year prior to the surgical treatment.

7 Future perspectives

Assessment of molecular markers in a non-invasive way through artificial intelligence (AI) will aid in the further development in the area. AI is useful in both the field of radiology and pathology due to the possibility of pattern recognition, but can also be used to predict pure clinical outcome such as functional decline after surgery [379].

Non- and minimally invasive markers are up-and-coming in the diagnosis of LGG. Although not yet implemented in clinical practice, further research in the field of radiomics and circulating tumor DNA and RNA in both blood plasma and CSF will probably result in the future implementation of these markers for diagnosis and follow-up of both response to therapy and to detect possible progression.

The molecular markers of *IDH* mutational status and status of 1p/19q codeletion have revolutionized diagnosis and subsequent treatment patterns in patients with LGG. Other molecular markers such as *TERT*, *AXTR*, *p53*, *EGFR* and *CDKN2A* are probably involved in the gliomagenesis, although their clinical impact is not yet fully known. The rising importance of molecular markers and the genetic landscape of tumors, will lead to important stratification of patients. Future research will have to be based on more refined subgroups in order to better investigate response to treatment, and perhaps paving the way for newer targeted, individualized therapies. New therapeutic possibilities, such as drugs targeting *IDH*, show promise and at a later stage may constitute a much-needed supplement to the current options of the radio-, chemo-, and brachytherapy available today.

DNA methylation is proven to be a robust, reliable tool revealing clinically relevant subgroups in a variety of tumor types, and this tool is expected to be better integrated with clinical practice, especially in diagnosing the more difficult and rare tumor types.

The Swedish Brain Tumor Registry (SBTR) has undergone a change to the CNS-registry, which also includes patients diagnosed on radiological criteria after the date 2018-01-01, in addition to the patients undergoing surgery. The registry is including patients with tumors in both brain and spinal cord with

pathological, cytological or radiological diagnosis. The register now contains richer diagnosis, specific clinical data, up to data molecular data, standardized data on complications, quality of life and adds data for each treatment (e.g. a reoperation for tumor recurrence) providing better longitudinal data. This revision will better serve its purpose as a quality registry, but will also improve research through the possibility to establish natural course and more. Linking registries with for instance information regarding medications from prescriptions and self-report system to improve follow-up data on health-related quality of life to would improve research in a patient centered perspective.

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Appendix