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REVIEW

Advancements in predicting outcomes in patients with glioma: a surgical perspective

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ABSTRACT

Introduction: Diffuse glioma is a challenging neurosurgical entity. Although surgery does not provide a cure, it may greatly influence survival, brain function, and quality of life. Surgical treatment is by nature highly personalized and outcome prediction is very complex. To engage and succeed in this balancing act it is important to make best use of the information available to the neurosurgeon.

Areas covered: This narrative review provides an update on advancements in predicting outcomes in patients with glioma that are relevant to neurosurgeons.

Expert opinion: The classical 'gut feeling' is notoriously unreliable and better prediction strategies for patients with glioma are warranted. There are numerous tools readily available for the neurosurgeon in predicting tumor biology and survival. Predicting extent of resection, functional outcome, and quality of life remains difficult. Although machine-learning approaches are currently not readily available in daily clinical practice, there are several ongoing efforts with the use of big data sets that are likely to create new prediction models and refine the existing models.

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Glioma; brain neoplasm; neurosurgery; prediction; personalised medicine

1. Introduction

Personalized treatment in oncology, where certain treatment options are better reserved for a selected group of patients, is highly dependent on classification and prediction. The goal is to reduce ineffective treatment, thereby removing unnecessary side-effects and costs, while maximizing the benefit for selected patients most likely to respond to the treatment. At present, biomarkers are important in neuro-oncology, but there is room for improvement in both predictive and prognostic capabilities [1–4]. In the WHO 2016 classification molecular markers were integrated to establish diagnoses, but they are also important prognostic markers [5]. For instance, most patients with lower-grade gliomas that are diagnosed with isocitrate dehydrogenase (*IDH*) wild-type tumors have a glioblastoma like prognosis [2–4]. The search for more precise molecular markers has been a popular approach in recent years, especially the prediction of treatment responses (e.g. one target, one treatment), but this task may be more complex than perhaps first perceived [6]. Intratumoral heterogeneity complicates this approach as tumor cells and tumor classes are neither homogenous throughout the entire lesion volume nor stable over time, and treatment related changes in molecular profiles might occur [7–12].

It is accepted that surgical decisions, including the surgical indication and planned extent of tumor removal, will affect risk and benefit in patients with glioma [13,14]. Surgical treatment is, by nature, highly personalized, and the complexity is clearly demonstrated in daily clinical practice by case selection for any given surgical strategy. The prediction techniques or models used should extend beyond pure surgical intuition whenever possible, as this is notoriously unreliable [15]. Still, many remain overly confident in their predictive capabilities. A pure biomarker approach in the absence of reliable and widely available liquid biopsies is of limited value in neurosurgical glioma management. Relevant outcomes for a neurosurgeon in patients with glioma may not be predicted by a traditional biomarker, and other means of foreseeing events are seemingly more appropriate. Here, we provide a narrative review on advancements in predicting outcomes in patients with glioma that are relevant to neurosurgeons.

1.1. Prediction of tumor subtype and grade based upon neuroimaging

Upon neurosurgical evaluation of a patient with glioma, a neuroradiological examination has been made. The foundation of brain tumor imaging is MRI, where T1w images with and without contrast agent, T2w images, and diffusion-weighted images are widely available. These images can provide useful predictions concerning tumor type and grade with evaluation of classic morphological features such as contrast enhancement, calcifications, and location within the brain [16]. To further increase diagnostic information the use of modern, metabolic and physiological techniques are increasingly employed. These

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Article highlights

- Accurate predictions and prognoses are needed to inform patients with glioma and this forms the foundation for shared decision making.
- 'Gut feeling' as a strategy for predicting outcome in patients with glioma is unreliable.
- Classical radiological markers for tumor biology and overall prognosis are still very useful but radiomics holds the potential for improved accuracy.
- Radiomics approaches may include hand-crafted features and classical statistical methods or deep learning.
- Effective use of big data will revolutionize how we acquire patient specific and relevant information. Ultimately, this holds the potential to improve predictions and prognostications in the future.

images are nowadays often used in research where data are used beyond the qualitative evaluations [17]. Radiomics refer to the use of quantitative features extracted from images and a milestone proof-of-concept publication was published in 2014 in other types of cancer [18]. These handcrafted features are selected for either traditional statistical methods or deep-learning algorithms. Finally, a 'black box' strategy using deep learning for image analyses are also explored. MRI of a tumor (and its surroundings) captures more of the disease compared to focal tissue samples. Given the heterogenous nature of gliomas, it is likely that imaging may both correlate well with, and even supplement, a biomarker approach. For instance, a 1 cm superficial *IDH* mutated WHO grade II astrocytoma probably holds a different prognosis than a molecular apparently similar 7 cm lesion not amendable to gross total removal. Also, anaplastic astrocytoma (by definition lacking histological necrosis) with radiological necrosis exhibits prognosis similar to glioblastoma [19]. Finally, we acknowledge that many of the below-mentioned techniques are available only at a limited number of centers, or are used mainly in research and not yet validated or readily available in clinical practice.

In a classical glioblastoma, with ring-like enhancement and central necrosis there is usually little problem with grading prediction. This is a more difficult task in patients with no or non-specific contrast enhancement. Oligodendrogliomas may, for instance, demonstrate faint and patchy uptake, despite being WHO grade II [16]. To address the problem in non-enhancing lesions PET evaluations have gained increased interest. The amino-acid tracer [F-18]Fluoroethyltyrosine (FET) has demonstrated promising results in non-enhancing gliomas where increased uptake is strongly associated with high-grade glioma (HGG) as determined by histopathology [20]. Three patterns were recognized where no uptake corresponded to WHO grade II gliomas and homogenous or heterogeneous uptake (i.e. a hot spot) indicated HGG. This has practical implications since a heterogeneous uptake may be at risk of sampling bias, and thus FET-PET may be used to guide biopsy targets in non-enhancing gliomas. Finally, in non-enhancing gliomas the FET-PET uptake may add independent prognostic information [21–23]. Nevertheless, one recent systematic review indicates that there is yet no clear-cut role for amino-acid PET for the neurosurgeon in the management of patients with glioma due to inconsistencies and heterogeneous data [24].

Other techniques that may be used to detect anaplastic foci are MR spectroscopy and diffusion kurtosis imaging. MR spectroscopy has demonstrated pathological ratio of Choline/N-acetylasperate and Choline/Creatine in non-enhancing gliomas, with hot spot using chemical shifts can be utilized to detect anaplastic foci in order to avoid undergrading and misclassification [25]. Diffusion kurtosis imaging was able to discriminate between grade II and III gliomas with area under the curve (AUC) of 0.82 [26]. The benefit of these techniques relies on the availability also outside PET centers, lower costs, and no exposure to radiation for the patient. Newer techniques of MR spectroscopy detecting 2-hydroxyglutarate, the oncometabolite produced by the *IDH* mutation, is promising in terms of detecting *IDH* mutant gliomas [27–29].

Glioma subtyping is highly relevant to patients with lower-grade gliomas (i.e. WHO grade II and III). These patients are divided further into astrocytomas *IDH* wild-type or *IDH* mutated and oligodendrogliomas where both *IDH* mutation and 1p19q codeletion are present [2,5]. These are now recognized as different tumor entities, but the classification also holds prognostic information. There are no perfect qualitative MRI markers for molecular subclassification, but the T2-FLAIR mismatch sign is highly indicative of *IDH* mutant astrocytoma [30–32]. The predictive performance of the mismatch sign can be improved by implementing more advanced sequences such as regional cerebral blood volume and diffusion-weighted imaging [33].

A rapidly developing field of research is the use of noninvasive radiomics features for brain tumor classification. Radiomics is based on the extraction of large amounts of quantitative data from medical images using data-characterization algorithms to detect features and patterns that are not easily detectable to the human eye. There are now many papers in the field of glioma subclassification, demonstrating promising results reaching beyond the standard (semi)qualitative image analyses [34–40]. The approach with radiomics has proven powerful also for the task of glioma grading [41]. The newest development is the introduction of deep-learning in glioma diagnostics where images have been used directly or with handcrafted radiomic features [42–47]. Results from these studies are highly encouraging, and it is likely that these quantitative and artificial intelligence-based methods will assist and further refine prediction of brain tumor diagnoses in the near future.

We have discussed grading and subtyping, but these approaches may also be used for other prognostic and predictive radiogenomic information (e.g. *MGMT* methylation, predicting response to chemotherapy in patients with glioblastoma) [48–53]. Identification of predictive markers (radiological or tissue based) where response to certain therapies can be foreseen is much needed. However, such refinement will not represent a substantial progress unless therapeutic options also increase. Even today with MGMT methylation status as a useful marker for response to temozolomide, the absence of treatment alternatives often does not lead to tailored treatment.

Although not an imaging modality, similar information can become available from liquid biopsies. In addition to providing information on tumor diagnosis, liquid biopsies would also

be useful for disease monitoring [54,55]. With a molecular profile that reflects the 'parent tumor' the surgical approach can be adapted. The most radical adaption would be to bypass the need for biopsies in cases not suitable for any meaningful resection.

Finally, we acknowledge that many combined techniques, for instance using several advanced MRI parameters or MRI and PET parameters can probably be used to further improve performance of noninvasive diagnostics.

1.2. Prediction of extent of resection

Prior to the routine of early postoperative MRI following surgery for infiltrating gliomas, neurosurgeons were far from calibrated in their estimation of extent of resection [56,57]. In the study by Shaw *et al.,* it was demonstrated that 41% of patients had a residual low-grade glioma >1 cm in diameter following what was reported as a gross-total resection [56]. In modern glioma surgery, a myriad of surgical adjuncts can assist in detection of tumor remnants, with best evidence for intraoperative MRI and 5-aminolevulinic acid [13,58]. Even without these tools, it is also likely that neurosurgeons at present are better calibrated due to the constant feedback of postoperative imaging, however there are little data on this. In a single surgeon experience a significant learning curve in estimation of extent of resection was demonstrated, and insular lesions were particularly difficult to predict quantitatively [59]. Another recent series on prediction of extent of resection demonstrated only moderate reliability of surgeons' estimates in patients with glioblastoma [60].

As surgical experience takes time to gather patients taking part in the learning curve may suffer from inaccurate estimates leading to suboptimal surgical decision-making. Also, estimations of achievable extent of resection are presumably even more inaccurate *preoperatively* compared to the situation in the final stage of the operation. In glioblastoma, what is considered resectable varies significantly even between experienced neurosurgeons (see Figure 1), although the majority vote correlated well with clinical outcome [61]. In non-enhancing gliomas Hendriks *et al.* used neurosurgeons with different level of experience and there was a slight overestimation of tumor removal [62]. Interestingly, cumulative knowledge from historical data as an unbiased alternative outperformed the neurosurgical experts. Thus, to help us select patients for meaningful surgical resections, it may be wise to use historical data from a broad expert panel or extensive databases to provide unbiased best estimates. In line with this, it has been created so-called resection probability maps [62–64]. Ius *et al.* demonstrated the 'minimal common brain' with functional guided resection stop due to conflict with regions that were considered not to be compensated functionally if damaged [64]. Creating such maps may also be a transparent way of comparing surgical teams and calibrating inappropriate deviations in surgical practice [63,65]. Nevertheless, despite effects of treatment variation, patient-related factors may be more important for outcome than treatment related factors in patients with glioblastoma provided the current treatment options [66]. Also, there are more factors than tumor location that affect the extent of surgical resection. For example, among many factors, the tissue texture, color and consistence, degree of neovascularization and perivascular and subependymal growth, and border delineation of the lesion could affect surgical extents of resection in a given location. Perhaps important tissue-related factors that affect resectability could be predicted by radiomics approaches in the future.

Another factor that relates to the presumed availability for extensive surgery is the prediction of function within or in the near surroundings of the tumor. There are several noninvasive methods available to provide this information, although it should be emphasized that these methods are only estimates and should not be taken as proof of function (or proof of absence of function). The functions most frequently evaluated in clinical practice are motor, language or visual function.

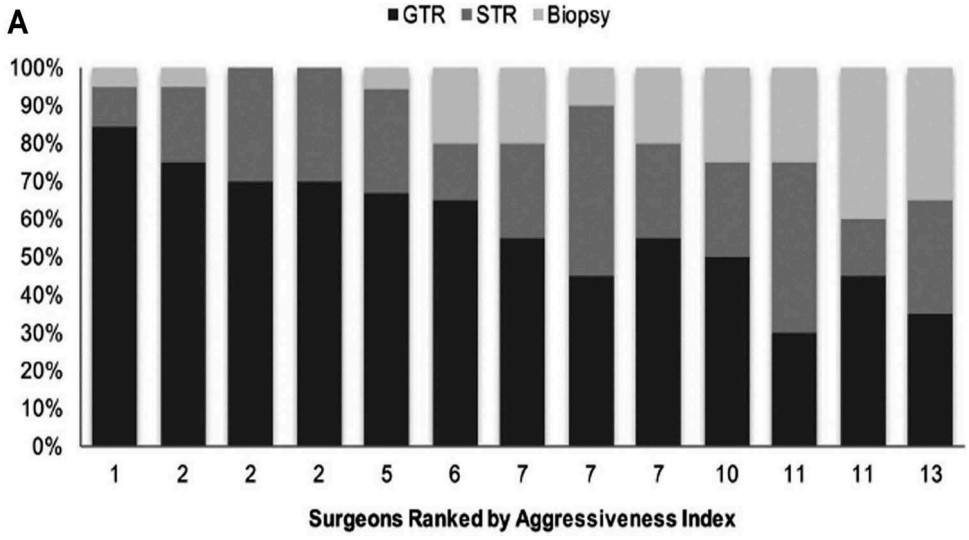

Figure 1. Experienced neurosurgeons providing recommended surgical strategy in 20 cases, demonstrating significant variability. The surgeons are ranked left-to-right with higher 'aggressiveness' to the left.

Sonabend AM et al. [61] by permission of Oxford University Press

Diffusion tensor imaging (DTI) based tractographies have been found useful by several groups in providing anatomical knowledge of larger fiber tracts and the relation to the tumor as this may assist in planning of procedure and surgical strategy [67,68]. Navigated transcranial magnetic stimulation (nTMS) have been found useful primarily for motor localization, and may be used as seeding points for DTI [69–71].

Functional MRI (fMRI) is a reasonable noninvasive alternative to the WADA test for establishing language lateralization [72–74]. For precise localization of language, fMRI has only moderate sensitivity and specificity and is by many considered unreliable [75].

The abovementioned methods of identification of function may also influence the accuracy of prediction of neurological deficits, although postoperative functional outcome and quality of life is presumably also largely influenced by factors beyond these more 'basic' brain functions (that are more easily monitored).

1.3. Prediction of functional status

Surgeons often base their treatment decisions upon glioma location [76,77]. Karnofsky Performance Status (KPS) or similar crude scales are often used to assess gross functional status [78]. Such functional scales have repeatedly been reported as prognostic factors in management of patients with glioma [79–81]. For surgeons, it is particularly important to note that a decline in functional status following surgery is linked to impaired survival [82–84]. As treatment is not curative, and in the case of high-grade gliomas not very effective in terms of prolonging life, functional status is very important. However, surgeons tend to be overly optimistic if asked to predict their patients' functional levels postoperatively [85]. Scoring systems for assessing the risk of functional deterioration may be a way to advance [77]. However, while the physical functional status in patients with cancer outside of the brain are associated to the burden of disease, functional levels in brain cancer may be more associated with eloquent tumor locations. If less aggressive treatment is given in presumed eloquent locations, the reduced survival associated with functional impairment may also in some cases be a self-fulfilling prophecy. Also, the conventional functional scales put much emphasis on the patients' physical abilities, while mental or cognitive abilities are often overlooked. Thus, a one-dimensional focus on eloquent brain regions associated with risk of physical functional impairment may not always be in the patients' interest. Shared decision-making, making patients' part of the difficult treatment decisions may be feasible in some patients, especially if considering planned deficits [86–88]. Predicting impact and course of such deficits and the consequences for quality of life is still very difficult.

Another aspect of outcome prediction for neurosurgeons is the use of the intraoperative acquired information in relation to postoperative deficit. Several publications highlight that many patients recover substantially during the first 3 months following surgery [89–91]. Since functional status is highly correlated to motor function we use this as an example below, although detection and intraoperative avoidance of other functions are equally relevant. The prediction of functional status may be improved if using neurophysiological motor monitoring. For instance, Seidel *et al.* demonstrated the motor function recovery in relation to the motor evoked potential, where an irreversible signal reduction or even worse, a complete signal loss, holds the most severe prognosis as demonstrated in Figure 2 [91].

Glioma surgery remains a delicate balancing act between achieving maximal tumor resection and inducing new deficits, and the tolerance for adverse events often depends on expected tumor classification and grade, prognosis, and available time for convalescence and rehabilitation. Knowledge about risks is of great interest for patients, but also for predicting chance of net gain from surgery. In patients with glioblastoma there is a poor prognosis and limited time for rehabilitation, hence complications and neurological deficits should be avoided [82,83,92]. Currently, it is difficult to compare complication rates across studies as there is considerable variation in patient selection (i.e. external validity),

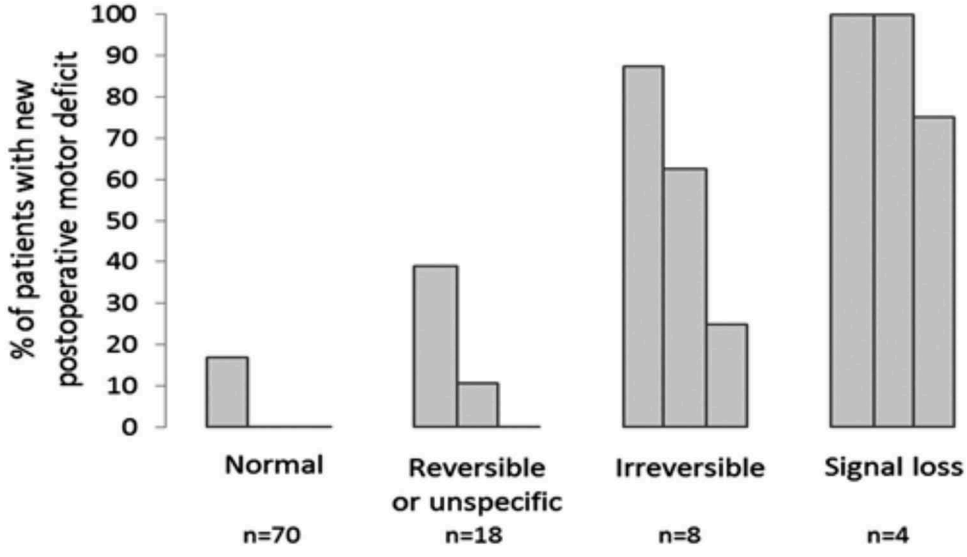

Figure 2. New postoperative motor deficits in relation to MEP signal alterations. Motor function at first postoperative day *(left bar)*, at discharge *(center bar)*, and at the 3-month postoperative *(right bar)*. With permission from reference [91].

classification of outcomes, and follow-up time following surgery. Population-based and standardized registration of all patients who undergo glioma surgery providing a sampling less hampered by case selection and publication bias should therefore be encouraged [93,94].

1.4. Prediction of quality of life

As opposed to functional status with a one-dimensional focus, quality of life (QoL) is a multidimensional construct including physical, psychological, emotional and social domains. It is assessed from the patients' perspective, and thereby account for their own subjective evaluation of health. In patients with cognitive impairment, patient-reported outcomes may not always be entirely valid or reliable, and this remains a challenge [95]. Other challenges with QoL data are unfavorable patient selection and missing data. Still, QoL data is rightly getting increased attention and accurate predictions of QoL following treatment would be much appreciated.

However, questions remain about what we actually are able to predict. Individual changes in generic overall quality of life after glioma surgery are frequently seen, perhaps reflecting the potency for both symptom relief and adverse effects [92,96,97]. However, findings are heterogeneous, and reliable identification of predictive factors remains difficult. At baseline it seems like larger tumors have worse QoL [98], however this has not been found to be a significant factor in longitudinal studies [96,99]. New or worsened neurological deficits after surgery seem to have a negative impact on QoL in the short term [99], but the impact of tumor location on overall QoL is perhaps lower than frequently believed [100,101]. It is sometimes easier to acknowledge the function of the 'dominant' hemisphere since language is readily screened bedside. This may explain the neurosurgical tradition of respecting this 'dominant' function, but when it comes to patients and QoL such a distinction cannot be made, and in the preoperative setting a right-sided location has actually been associated with worse QoL [98]. According to a novel strategy with QoL maps, using the cumulative knowledge gathered from previous patients experiences, the central region seems prone to negative changes in QoL 1 month after surgery [101]. However, which brain functions that are most important to patients probably depend upon timing of assessment and the QoL may change with adaptation to their new situation due to a 'response shift' [102]. In general, knowledge about the impact of various deficits on long-term quality of life is still lacking. Thus, a prediction of for instance a worst-case scenario of QoL based upon procedural risk is still not possible from a scientific point of view.

At later follow-up after surgery, patients with higher tumor grades have worse quality of life than patients with lower tumor grades [96]. In patients with high-grade glioma tumor progression has been shown to reduce QoL significantly [92,103,104]. This corresponds to the observation that QoL have been demonstrated to be better and more stable after gross-total resection, but the findings are not adjusted for case-mix and should be interpreted with some caution [92,96,105]. In patients with low-grade glioma and stable disease of at least 1 year following surgery, the lack of seizure control is associated with reduced QoL [106]. In the longer-term LGG patients with stable disease have compromised QoL similar to other cancer patients, with the addition of neurocognitive complaints and seizures [107]. These findings corroborates literature on seizures in general, where seizure freedom is associated with improvement in QoL [108]. This information is important for neurosurgeons treating patients with LGG, since achieving extensive resections are important for seizure control [109].

Altogether, the available evidence supports the strategy of opting for extensive surgical resections whenever safely possible to achieve tumor and seizure control. These factors have repeatedly been associated with QoL in patients with high- and low-grade gliomas, respectively.

1.5. Prediction of survival based upon clinical factors prior to tissue diagnosis

For patients with low-grade glioma, there are two widely utilized clinical prognostic scores, the EORTC/Pignatti score [110] and the UCSF/Chang score [79]. The risk factors according to the EORTC score are age ≥40 years, astrocytoma histology, largest diameter ≥6 cm, tumor crossing midline and presence of deficit prior to surgery. Prior to surgery, the histopathology is not known, and the morphological criteria does not fit into the current classification system, making this score of lesser relevance. Of note, a small series demonstrated that when *IDH* mutational status is considered, the EORTC score provides limited prognostic information [111].

The UCSF score is a true preoperative score where patients receive a score between zero and four, with one point given per risk factor. In this scoring system age >50, KPS < 90, eloquent location and largest tumor diameter >4 cm are considered risk factors. The UCSF score has also been validated in an independent large multi-center study [81]. The prognostic impact of the age cut off of 50 years has also been reported to be better than 40 years in a population based study, likely reflecting the chance of having *IDH* wild-type astrocytoma increases with age [112,113].

In patients with glioblastoma the recursive partitioning analysis (RPA) score including age, functional status, mental status, tumor location and surgical procedure (biopsy versus resection) as key variables have proven useful in prognostication [114–116]. Interestingly, an adapted version of the influential clinical RPA from 1993 still proved robust in the temozolomide era including age, WHO performance status, cognitive status and surgical procedure [117]. A recent integrated molecular and clinical prognostic model confirmed the important role of MGMT, and age was the only clinical variable of importance beyond MGMT [118]. This new model was particularly strong in separating groups when treated with radio- and chemotherapy.

Radiological features harbor significant potential in survival prediction and radiomics will likely play an increasing role. For low-grade glioma, the growth velocity is strongly linked to

prognosis [119,120]. Speed of growth may also be a prognostic factor in glioblastoma [121]. Similarly, nodular enhancing focus despite not being anaplastic by histology, and progressive contrast enhancement are negative prognostic factors in LGG [122]. However, one recent study in the molecular era has indicated that prognostic capabilities of contrast enhancement is most important in *IDH* mutant astrocytomas [123]. Slower growth as determined by volumetric measurement has also been linked to long-term survival in patients with glioblastoma [121]. Despite being a powerful and seemingly robust prognostic factor, volumetric measurements are still not routine in clinical practice [124–126]. Automatic segmentation based upon artificial neural networks is likely the way to proceed, and this method has recently demonstrated to be better than the classical bidimensional criteria in determination of tumor burden/progression in patients with glioma [127].

2. Expert opinion

Predicting the course of disease and outcomes with different treatments is key for the patient and for creating a foundation for shared decision-making. As demonstrated in this review, there are many aspects of outcome that can be considered for a neurosurgeon caring for patients with glioma. We have summarized some of the useful tools in Table 1.

For a neurosurgeon, the use of reliable noninvasive tools would be helpful. Although traditional neuroimaging features can be useful, the field of radiomics is much more promising. In terms of classification and prognostication, radiomics will likely outperform traditional neuroimaging features. More validation studies within the field of radiomics and the development of a streamlined work-flow suitable for clinical use should allow us to inform patients more accurately [18,36,37,51].

Today shared decision-making concerning the risk and benefit ratio of the surgical strategy is often a division of unknowns. The benefits in terms of survival is largely dependent on the diagnosis and the obtained resection [128–130]. The prediction of functional status postoperatively has proven difficult to obtain, and there does not exist a widely accepted tool for this purpose. We are then left with a 'gut feeling' in many instances, although this is known to be notoriously unreliable even for simpler tasks.

For predicting quality of life and for complex brain functions like mental health, memory, personality, and executive function the knowledge about the impact of various treatment decisions is even more limited. A radiomics approach could predict both the molecular diagnosis and other tissue-related factors affecting resectability. Also, the use of a probability map for functional status or QoL may improve decision-making and help educate patients. For both approaches, large amounts of neuroimaging data need to be linked to other data sources (i.e. molecular and clinical/patient reported outcomes).

Finally, certain prognostic factors have been consistent across time periods and study designs (e.g. age and functional status). Nevertheless, we think the time for development of new simple clinical prognostic scores has passed. In the near future, true-integrated solutions with imaging, clinical factors, and biomarkers will either refine current models or create completely new ones, with the result of improved prediction and prognostication. The amount of data integrated in such models indicate that data needs to be handled automatically.

In general, we firmly believe that integrated big-data approaches outlined above could facilitate evidence-based personal medicine in neuro-oncological surgery. If clinicians were able to easily search a database of a large set of patients treated for the same type of tumor with the same tumor location, the same radiological appearance, and same clinical prognostic factors, statistical profiles of the risk and benefits associated with various treatment decisions could be made to guide decision-making in future patients.

Although big data creates new opportunities and machine learning holds potential for improved accuracy in prediction and prognostication, especially with the use of medical imaging, there are some problems [131]. Ensuring effective de-identification and privacy with increasing amount and complexity of data is a challenge when data sharing for sufficient amount of cases is needed in many instances [132–134]. Since data routinely is heterogeneous one barrier is related to standardization of data into a common format, and united efforts are needed since data sharing across institutions and countries frequently are needed [134]. Finally, there are issues related to ethical and legal aspects that needs to be handled before implementation, e.g. who should be held responsible in cases with erroneous prediction by the model.

3. Five-year view

A barrier in choosing the best approach is the overwhelming amount of data available, so many choose in-house tradition and yesterday's solutions. The potential is huge for tailored treatment based upon improved prediction in patients with glioma and we believe that, in particular, big-data and machine learning will play a crucial role. However, there is currently a huge technology gap in what is possible in a research setting and what is actually done in regular clinical

Table 1. Summary of tools for outcome prediction that may be of value to neurosurgeons in patients with glioma.

	LGG	HGG	Usefulness	Example references
'Gut feeling'	-	-	Notorious unreliable	[15,59–61,85]
FET PET	+	-	Anaplasia, prognosis in non-enhancing tumors	[20–24]
MR spectroscopy	+	-	Anaplasia, *IDH* mutation	[25,27–29]
Radiomics	+	+	Noninvasive detection of biomarkers, prognosis	[30–41,49–53]
Milan complexity score	(+)	(+)	To predict functional status following surgery	[77]
Motor evoked potential	+	+	Primarily to avoid motor deficit, but also to predict prognosis of postop motor deficit	[91]
Clinical factors and survival	+UCSF score	+RPA	Simple models with good prognostic performance	[79,81,114–118]
Machine learning	++	++	Not available in clinic. Radiomics, prediction and prognostication	[42–47]

practice. The implementation of even simpler novel methods that significantly alter work flows are seemingly impossible to implement at times. For instance, volumetric measurements of gliomas are consistently reported to be superior to traditional measurements, however very few centers have this as a clinical routine [126,127,135,136].

To bridge the gap in medicine and in neurosurgical practice we believe that new members of our teams are needed [137]. For instance, technicians, programmers, engineers, and computer scientists are needed for data curation/standardization, algorithm development, data visualization and by this achieve safe and streamlined integration suitable for clinical use. The frequent reductionism and single factor focus seen in much prognostic research is problematic. Sole focus on key clinical factors, a few imaging features, or a few molecular factors is unlikely to provide true progress. To fully capture the disease and to move the field forward we need to integrate different sources with rich information.

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Declaration of Interest

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