Recurrent glioblastoma in the era of molecular diagnostics: practice variation and practical implications

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Chapter 11

Summary and general discussion

Before we started writing this thesis, we had the idea that there was little uniformity in the treatment of recurrent glioblastoma, and there was a limited role for targeted therapies, let alone for routine WGS-based diagnostics. With this thesis, we aimed to assess practice variation (part 1), molecular diagnostics (part 2) and practical implications of whole genome sequencing (WGS, part 3) in adult patients with recurrent glioblastoma. By covering these subjects, we aimed to contribute to high-value care for these patients in the era of molecular diagnostics.

In **chapter 2** we showed that there is a lack of high-quality support in the literature for using mapping during glioma re-resection. Systematically reviewing the literature led to the finding that only 17% (10/58) of the included articles reported information about awake/asleep setting or intra-operative mapping during re-resection. Moreover, six out of these ten studies provided details on the use of mapping. Lastly, only one study compared overall survival in patients with awake re-resection versus patients with asleep re-resection. This study included patients with glioma World Health Organization (WHO) grade 3-4, and showed no significant difference in overall survival (hazard ratio 1.82, 95% confidence interval 0.99-3.34) or post-progression survival (hazard ratio 1.02, 95% confidence interval 0.58-1.8).[1] Overall, the main limitation of the current literature is that they are lacking to report details on intra-operative techniques or that they do not stratify between patient subgroups. Therefore, based on the results of our systematic review, a comprehensive evaluation of the prognostic impact of mapping-guided re-resection turned out to be difficult. However, the need of this is extra important since international guidelines provide little to no guidance when it comes to treatment decisions for recurrent glioma WHO grade 3-4.[2-4] A second important argument is the evidence in the newly diagnosed setting, in which intra-operative mapping has proven to contribute to better survival rates and fewer neurological deficits.[5-8] To rule out the possibility of undertreatment in patients with recurrent glioma, our study underlines the urgent need for future, well-designed studies addressing the beforementioned limitations. Fortunately, initiatives have been launched with international studies like the RECMAP study (NCT06273176) and the RECSUR study (NCT06283927).

In **chapter 3** we demonstrated that re-resection of recurrent glioblastoma is subject to practice variation both between and within Dutch neuro-oncology specialists. By presenting different cases of recurrent glioblastoma to neuro-oncology specialists and asking them the simple (main) question whether they would recommend a re-resection in the specific cases, we aimed to assess possible practice variation. The survey was filled out by 56 respondents, of which 15 (27%)

neurosurgeons, 26 (46%) neuro-oncologists, 2 (4%) medical oncologists, and 13 (23%) radiation oncologists. The results of this study were disconcerting. In the absence of unambiguous guidelines, we observed a relationship between preferred practice (whether to recommend a re-resection or not) and specialty. For instance, in one case 73% of the neurosurgeons recommended a re-resection compared to an opposite 73% of the radiation oncologists who not recommended a re-resection. Overall, in two of the four cases there appeared to be clinical equipoise, with neurosurgeons tending to recommend re-resection more frequently compared to the other specialists. Of note, practice variation was also seen within the same specialty, with one specialist recommending a re-resection because “gross-total resection is very well possible” while a colleague refrained from re-resection since “there is limited oncological benefit”, talking about the same lesion. As said, these results are worrisome but not surprising at the same time. Worrisome, because the survival benefit of re-resection[9] will be unequally allocated to patients, depending on a physician’s preference. Yet, health professionals agree on the need to reduce practice variation.[10] Simultaneously, our results are not quite surprising since the psychologist Daniel Kahneman already concluded that medicine is a ‘noisy’ profession (i.e. with unwanted variability of judgements) in which the interrater reliability could be powerfully reduced by guidelines.[11] We add that our results underline the crucial function of multidisciplinary tumor board discussion.

In **chapter 4** we illustrated that the abovementioned need for (inter)national guidelines on the treatment of recurrent glioblastoma is currently not met. Of the twelve European countries with national guidelines on the diagnosis and treatment of adult glioma (24% of the 50 European countries), nine provided any recommendations on the treatment of recurrent glioblastoma. Moreover, these recommendations differed profoundly from each other. Regarding the role of clinical trials in the recurrent setting, five (42%) of the available guidelines considered enrollment into clinical trial to be an option. It is important to note that the presence of guidelines should not become synonymous to good clinical practice. As seen in **chapter 3**, even in the presence of national guidelines remarkable differences in re-resection practice have been observed between neuro-oncology specialists. Thus, national guidelines do not necessarily rule out the phenomenon of practice variation. Similarly, the absence of national guidelines does not necessarily mean suboptimal practice, especially when considering the availability of international guidelines. More importantly, prioritizing the collection of evidence in the recurrent setting should precede the development of guidelines, since the increasing number of guidelines is currently not paralleled by an equal increase in evidence. Intensification of generation of more evidence should also discriminate between

practice variation that is unwanted and that which is not necessarily unwanted. Future research should investigate whether national guideline availability correlates with clinical outcomes and with sociodemographic characteristics and economic status of countries, in order to further study the impact and origins of unwanted (inter)national practice variation.

A final example of practice variation was seen in **chapter 5**. Here, the interlaboratory variation in next generation sequencing (NGS) of high-grade adult-type diffuse glioma in the Netherlands was surveyed. Our results showed that the composition of diagnostic NGS panels differed in each center, with numbers of genes in the different panels ranging from 12 to 523. Differences were more pronounced when tests are performed to find therapeutic targets in the case of recurrent disease: about half of the centers test for gene fusions and tumor mutational burden. Even though different centers most often end up with the same molecular information for the primary diagnosis after sequential, layered testing, this would be time and eventually cost consuming. In addition, the practice variation in the tests for therapeutic targets could reduce patient selection for potential trial participation when testing for targets is omitted.[12, 13] Without having studied the clinical impact of this practice variation, it is clear that in-house developed tests, standardized panels and routine application of broad gene panels all have their own advantages and disadvantages. Nevertheless, applying broad gene panels as a standard has the dual potential of refining the diagnostics and improving precision oncology.

In **chapter 6**, the protocol of the GLOW (GLioblastoma targeted treatment Option maximization by Wgs) study was presented. This prospective multicenter cohort study aims to investigate the feasibility, validity, utility and value of WGS for recurrent glioblastoma patients. This will allow for disclosure of potentially novel targets for therapy for these patients. Through collaboration of the Hartwig Medical Foundation and twelve Dutch centers, a total of 235 patients with a first glioblastoma recurrence will be included. This trial is registered under the identifier NCT05186064.

The interim results of the GLOW study were presented in **chapter 7**. After inclusion of the first 100 patients, a diagnostic success rate of 80% was found. Based on these 80 WGS reports, targeted therapy was initiated in 6 patients (7.5%). The following targeted therapies were initiated: abemaciclib (*CDK4/6* inhibitor), dacomitinib (*EGFR* inhibitor), entrectinib (*TRK/ROS1/ALK* inhibitor) and erlotinib (3x, *EGFR* inhibitor). The median duration on these experimental drugs was 1.76 months (interquartile range 1.44-2.14), with further progression and adverse events being reasons for discontinuation. Several factors for the poor targeted therapy initiation rate can

be identified. For instance, the clinical implementation of the WGS results was hampered by the prevalent physicians' opinion that upon recurrence, 'standard therapies' like lomustine and rechallenge temozolomide should be preferred. A considerable number of times, the WGS results were "preserved for potential future recurrence". A second major limitation for targeted therapy initiation in this recurrent glioblastoma population, was the following. Once the treating physician wanted to initiate experimental therapy, the DRUP (Drug Rediscovery Protocol) team was accessed and asked to disclose the specific drug for the specific patient. However, one of the criteria for participation in the DRUP is 'measurable disease' at the time of treatment initiation. Since maximal safe resection (i.e. cutting away all measurable disease) is the goal of neurosurgical intervention, our recurrent glioblastoma patients were then refused to participate in the DRUP. The latter made us prepare a DRUP-like program especially designed for glioma patients, to bridge the gap between treatment option identification and available therapies for this population. In the future, the results of this project, called glioblastoma individualized molecular treatment program (GLIMP), should also synergistically improve clinical implementation of WGS-based treatment option identification.

In **chapter 8**, the current clinical trial landscape was assessed to investigate the role of molecular biomarkers in trials on recurrent glioblastoma treatment. After screening the database ClinicalTrials.gov, we found that 76% (181/237) of the current studies did not include molecular criteria in the study design. In the remaining 56 studies, *EGFR* amplifications/mutations, *CDKN2A/B* or *C* deletion, *CDK4/6* amplification, and *RB* wildtype status were most frequently investigated, as were the corresponding drugs abemaciclib and ribociclib. Our study showed that the potential efficacy of targeted treatment is currently not yet translated into genome-driven trials in patients with recurrent glioblastoma. We therefore advocate an intensification of genome-driven trials in an attempt to provide more evidence for the (in)efficacy of targeted treatments and to bridge this knowledge gap. An excellent example is the N2M2 study, a phase I/IIa umbrella trial of molecularly matched targeted therapies.[14] The recently presented results of this N2M2 study (NCT03158389) show clinical activity of temsirolimus in patients demonstrating mTOR activation while palbociclib has no clinical activity in patients with *CDK4* amplification or *CDKN2A/B* codeletion. Currently, the acting on potentially druggable targets is challenged by target credentialing and validation, tumor heterogeneity and clinical trial design.[15] Efforts are needed to overcome these challenges and, as said, bridge the knowledge gap regarding genome-driven oncology in glioblastoma patients. The current lack of evidence and past results should not paralyze the exploration of new potentially actionable targets.

In **chapter 9**, the genetic predisposition to adult glioblastoma based on whole genome sequencing analysis was studied. In an unselected cohort of 98 patients, pathogenic germline variants (PGVs) were observed in 11% (11/98) of the patients. PGVs were found in the following genes: *BRCA1*, *MSH6*, *PMS2, TP53, NF1* and *SUFU*. In eight of these patients (73%) causality was supported by a second (somatic) event and/or a matching genome-wide mutational signature. Our study showed that germline predisposition does also play a role in the development of adult glioblastoma (as is more commonly known for pediatric gliomas), with mismatch repair deficiency being the main mechanism. This finding might have some consequences and can be integrated in the discussion about the application of WGS-based diagnostics. First, several of these PGVs were in predisposition genes that are increasingly important for (targeted) therapy selection.[16-19] Second, most of the PGVs found in our study are currently not tested for in most of the Dutch laboratories, as we have seen in **chapter 5**. Our findings do also underline the importance of genetic counseling prior to germline testing, with specific attention for mismatch repair gene deficiencies, as recommended in the EANO guideline on molecular testing of gliomas in adults.[12] As the use of comprehensive tumor genetic and genomic diagnostic test continues to grow, the detection of PGVs is occurring more frequently than previously expected.[20, 21] Thus, comprehensive tumor genetic and genomic profiling for glioblastoma patients requires an integrated approach that facilitates appropriate referral to clinical geneticists.

In **chapter 10**, the challenges related to informed consent procedures and data sharing regarding WGS in (recurrent) glioblastoma were discussed. The increased use of WGS in neuro-oncology for diagnostic and research purposes necessitates a renewed conservation about informed consent procedures and about governance structures for sharing personal health data, illustrated by the findings from **chapter 9**. There is currently no consensus on how to obtain informed consent for WGS in this population. In this chapter, we analyzed the formats and contents of frameworks suggested in literature. Since (recurrent) glioblastoma is characterized by the rarity of the disease, extremely poor prognosis and impact on cognitive abilities, we suggested that the informed consent procedure should be tailormade for these patients. A combined model of specific and tiered consent was proposed, and in parallel, the development of meta-governance solutions should be prioritized to facilitate widespread use of genomic data and international collaborations.[22] It is important to understand how patient characteristics influence patient preferences in receiving WGS findings, which in turn could influence categorization based on relevance in tiered consent.

FUTURE DIRECTIONS

Taking the evidence from **chapters 2 to 10** together, we conclude that the journey of a patient with recurrent glioblastoma is subject to practice variation in diagnostics and treatments, in which the clinical implementation of WGS results in the context of precision oncology has currently little support from treating physicians, accompanied by some ethical objections that need to be considered. Another important conclusion is that routine WGS-based diagnostics might help the (future) patient, since WGS – which was proven fast and feasible in our population – has a great potential to not only create a lot of new knowledge about the biology of glioblastomas, but also to unravel novel targets for treatment.

The results of this thesis lead to the following future directions. First, we endorse future studies on the survival benefit of re-resection and the development of prediction models to be able to better discriminate which individual patients will benefit from (mapping-guided) re-resection. This could reduce practice variation in re-resection and might further improve the concept of precision oncology. Simultaneously, while the costs continue to decrease, routine WGS-based diagnostics should gain more prominence upon glioblastoma recurrence. The advantages of WGS are multiple, with the uniformity and completeness on the diagnostic hand, and the accumulation of tumor specific knowledge on the scientific hand. To facilitate access to targeted therapies for recurrent glioblastoma patients, we are eager to initiate the beforementioned GLIMP study in the near future. We are convinced that these patients deserve equal changes, acknowledging the specific characteristics and associated hurdles in this entity. To this end, a second project we are about to start is charting the neuro-oncology specialists' individual attitudes and beliefs towards clinical implementation of WGS-based therapies. What are the ideas, thoughts and assumptions behind the reluctance to prefer targeted therapy over 'standard' treatment? Finally, more molecularly matched targeted therapy trials are urgently needed to collect target specific evidence for efficacy, as some recent successful stories in other glioma populations were published.[23, 24]

This thesis was started with the statement that "there is actually always something a physician can do for the patient", referring to symptom management and palliative care. At the end of this thesis, we may now conclude that 'doing everything' in terms of diagnostics and treatments should be redefined once WGS and WGS-based treatments become clinical practice. Fortunately, science is characterized by curiosity and not by cynicism, therefore leaving us hopeful for the future in which new and effective treatments for recurrent glioblastoma patients will be discovered. A long way might be ahead, yet the potential is all the greater.

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