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

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Chapter 1

General introduction and outline

"We have done everything we could, and at this point there is nothing more we can do for you." Giving a patient a message like this will promptly take the patient's hope – physicians should therefore never say anything like this. More importantly, the second part of this phrase is invalid either way. Actually, there is always something a physician could do for the patient, for instance regarding symptom management or palliative care. Therefore, this is one of the most valuable lessons a physician must keep in mind, especially while caring for the sickest of the sick. Indeed, this thesis is about the sickest of the sick: patients with a recurrent glioblastoma. And for these patients, the current challenge is to prove the first part of the phrase (i.e. the 'everything-part') wrong as well by redefining 'everything'. Now, whole genome sequencing (WGS) is not standard-of-care for patients with a glioblastoma. This thesis partly focusses on the feasibility and potential benefit of WGS in patients with a recurrent glioblastoma. Diagnostically speaking, WGS is very close to 'doing everything'. Patients with such a dismal prognosis like patients with a recurrent glioblastoma tend to have, ultimately deserve physicians whose goal is to go the extra mile. Physicians who are open to acknowledge and reduce unwanted practice variation. Who are eager to consider diagnostics and treatments that are not (yet) standard-of-care. And who take ethical considerations into account while caring for their patients on their precarious journey.

GLIOBLASTOMA

Glioblastoma, the most common glial primary brain tumor, is almost always lethal. In the Netherlands, every year approximately 1000 patients are diagnosed with this heterogeneous disease.(1) According to the most recent taxonomy, the term glioblastoma refers to an isocitrate dehydrogenase (*IDH*) wildtype tumor that is classified World Health Organization (WHO) grade 4.(2) Symptomatology depends on the affected brain location(s) and thus include a wide range of possible neurologic deficits like headache, nausea, muscle weakness, speech deficits, new onset of epileptic seizures, vision problems or neuropsychological symptoms.(3) Standard treatment for patients with newly diagnosed glioblastoma consists of maximal safe surgical resection followed by postoperative radiotherapy with concomitant and adjuvant temozolomide chemotherapy.(4, 5) Despite this intensive treatment scheme, the prognosis of this incurable disease remains poor with a median survival of less than fifteen months.(6) Moreover, the benefit from temozolomide is only pronounced in patients with a tumor with methylation of the O6-methylguanine-DNA methyltransferase (MGMT) promoter.(7) Unfortunately, the tumor almost inevitably recurs.

SEMANTIC DISCUSSION

One can debate the proper formulation of ‘recurrence’ of the glioblastoma. Some people favour ‘relapse’ or ‘regrowth’ instead, since the infiltrative growth pattern of glioblastoma makes complete (i.e. on microscopic level) surgical resection impossible. Consequently, the glioblastoma never went away after initial treatment and can therefore, strictly seen, not recur. In literature, however, ‘recurrence’ and its conjugations are by far the most common terms, followed by ‘relapse’ and ‘regrowth’. More importantly, these semantics do not hamper the consensus on the clinical meaning: disease progression characterised by new signs of vital tumor tissue on clinical and/or radiological examination after initial antitumor treatment, ultimately confirmed by histopathological analysis. For uniformity, ‘recurrence’ and its conjugations will be used throughout this thesis.

RECURRENT GLIOBLASTOMA

In the recurrent setting, evidence on the best treatment strategy becomes scarce and highly relies on individual patient characteristics. As the guideline of the European Association for Neuro-Oncology (EANO) states, ‘standard-of-care treatments for patients with recurrent glioblastoma are not well-defined.’(5) Only a small number of 20-30% of the patients with well-localized tumors are eligible for re-resection, commonly with a symptomatic lesion seen not earlier than six months after initial resection.(5) In general, this selected group of patients may have a survival benefit from re-resection, especially when adjuvant treatment will follow the surgical procedure.(8, 9) However, given that patient-specific factors such as Karnofsky Performance Status (KPS), extent of resection, and radiological findings impact the survival benefit as well, the decision whether or not to perform a re-resection is everything but straightforward.(10-15) When it comes to systemic treatment, nitrosoureas or retreatment with temozolomide are most commonly used, with limited progression-free survival rates at six months (15-20%) and objective response rate of less than 10%.(16-20) Patients with a methylated MGMT promoter may benefit from a temozolomide rechallenge, from lomustine or even from the combination of both.(21-23) Outside of the European Union, bevacizumab has been approved for recurrent glioblastoma.(24, 25) The European evidence-based opinion, however, is that there is no survival benefit of bevacizumab for the treatment of recurrent glioblastoma.(5, 26, 27) Some patients undergo re-irradiation, which may result in local disease control in a proportion of patients.(28-32) However, a second

course of radiotherapy is not always feasible due to the hazards of cumulative (cognitive) neurotoxicity.

PRACTICE VARIATION

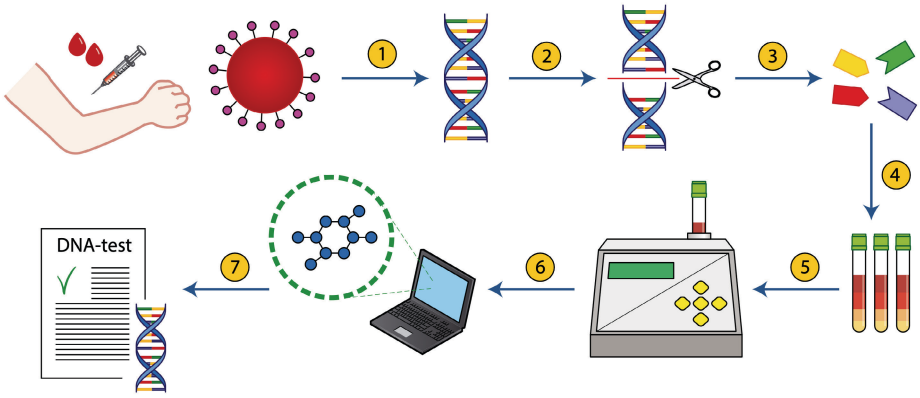
Practice variation in medicine has been studied before and is a well-known phenomenon.(33, 34) Likewise in neuro-oncology, practice is subject to variation, for instance in mapping procedures in glioma surgery, neuroimaging after glioblastoma surgery, or perioperative laboratory testing.(35-37) Despite the need to reduce practice variation in medicine, health professionals are not sure about the feasibility of such a reduction.(38) Generally, two main factors can be identified to explain the variability in treatment decisions: the lack of guidelines/large prospective studies, and the concept of noise. Both are covered by Kahneman et al., who described noise as the 'unwanted variability of judgements' with the property that the true answer may be even unknowable.(39) Kahneman also concluded that medicine is a noisy profession in which the interrater reliability could be powerfully reduced by guidelines.(40) In the absence of clear guidelines on recurrent glioblastoma treatment, one should be aware of the risk of unwanted practice variation. Simultaneously, randomized or prospective clinical trials are urgently needed and should also contribute to the development of evidence-based guidelines on the treatment of recurrent glioblastoma.

GENOME SEQUENCING

The entire human genome was first cataloged in 2001, after thirteen years of international effort.(41) Nowadays, the turnaround time of sequencing and analyzing the entire genome is normally within five to ten days. Ever since that first complete genome sequencing more than two decades ago, genome sequencing is increasingly integrated into clinical practice, with reduction of costs and increase of availability as a result. Started with diagnostic applications, genome sequencing is currently used for therapeutic strategies as well. Theoretically, fighting cancer by treating at DNA level holds great promise for individualized therapy. In a heterogenetic disease like glioblastoma, WGS will provide all molecular information through a single test within a reasonable time of one to two weeks *(Figure 1).* The potential of WGS in the area of personalized medicine for patients with cancer has been demonstrated before, with high sensitivity and precision to detect molecular alterations.(42, 43)

The actionability of a given molecular alteration is based on information in public knowledgebases, including the Clinical Knowledgebase (CKB), Oncology Knowledge Base (OncoKB) or the Clinical Interpretation of Variants in Cancer (CIViC). It can be split by evidence levels according to stablished classification levels, including the six level ESCAT (ESMO Scale for Clinical Actionability of molecular Targets) classification.(44) According to the ESCAT classification, treatment based on hypothetical targets should only be considered in the context of early clinical trials. To demonstrate that such hypothesized treatments are effective, downstream clinical studies are required. These trials should also investigate and link pharmacodynamics to the clinical utility of the targeted therapy, since not all drugs will effectively cross the blood-brain barrier. A successful example of molecular therapy is dabrafenib/trametinib in patients with progressive *BRAF* p.V600E mutant gliomas.(45)

Figure 1. A simplified overview of the process of whole genome sequencing (WGS).



Step 1: DNA extraction from blood and tumor tissue. Step 2 and 3: fragmentation and amplification of the DNA. Step 4: adding chemicals to sequence the DNA. Step 5: replication of the DNA fragments and sequencing preparation. Step 6: reading of the DNA fragments (sequencing) and processing the sequencing information. Step 7: building the WGS report.

ETHICS IN NEURO-ONCOLOGY

The increased use of (broad) genome sequencing in neuro-oncology necessitates a renewed conversation about informed consent procedures. There is currently no consensus on how to obtain informed consent for WGS in patients with (recurrent) glioblastoma. Notwithstanding, it is the physician's moral duty to ensure that the patient understands both the potentials and downsides of genome sequencing.

For instance, since WGS analysis requires not only tumor DNA but also a control DNA sample (e.g. from blood) to discriminate somatic mutations (tumor sample) from germline mutations (control sample), unravelling the germline DNA potentially reveals genetic predisposition. This knowledge might be relevant for patients and their relatives, and the question whether the disease runs in the family is often an important question in the consulting room. Therefore, the potential consequences of the germline analysis must be kept in mind and should be discussed with patients before WGS diagnostics are performed. Regarding these 'unsolicited findings', it is important to be aware of the patient's right not to know, as it applies to family members as well.(46) Finally, patients should be made aware of the fact that, despite the therapeutic potential following WGS, the analysis itself does not impact individual outcomes.

Next to ethical considerations regarding informed consent procedures, the governance structures for sharing personal health data should be adapted to (broad) genome sequencing too. For instance, WGS generates extensive data on the genomic alterations in the cancer cells, as well on normal cells. This data is per definition highly personal and therefore require strict regulations. In the European Union, data handling is safeguarded by the General Data Protection Regulation (GDPR).(47) The recurrent glioblastoma population is characterized by its vulnerability and, in case of cognitive impairments, abstract themes such as data sharing warrant extra meticulous communication. Indeed, physicians have the responsibility to explain details about the benefits and risks of WGS in an accurate and understandable manner.(48) Notwithstanding the increasing role of molecular diagnostics, the abovementioned considerations should frame the shared decision making process between physician and patient.

AIMS AND OUTLINE OF THIS THESIS

In **part I** of this thesis, we study several aspects of **practice variation**. First, we review the literature on mapping-guided re-resection in recurrent glioma (**chapter 2**). In **chapter 3** we study the practice variation in re-resection between neuro-oncology specialists in the Netherlands. In international guidelines, recommendations for the treatment of recurrent glioblastoma are limited. In **chapter 4**, we investigate the availability of national guidelines and recommendations throughout Europe. Once a re-resection is planned, this offers the opportunity to expand the histopathological analysis with molecular tissue analysis to look for treatment targets. We study the

current practice of genome sequencing in **chapter 5**, in the primary as well as in the recurrence setting.

In **part II** of this thesis, we describe the role of **molecular diagnostics** to personalize and optimize systemic treatment for patients with a recurrent glioblastoma. To uniform practice and to maximize treatment options, we present the protocol of our prospective, nationwide trial on complete genome diagnostics in recurrent glioblastoma patients in **chapter 6**. We describe the results of the interim analysis of this study in **chapter 7**. Since it is important to study new targeted treatments in the context of available clinical trials, we review the current clinical trial landscape in **chapter 8**.

Part III of this thesis covers some **practical implications**. Applying whole genome sequencing potentially reveals genetic predisposition to glioblastoma. Therefore, we study the prevalence of pathogenic germline variants in **chapter 9**. In **chapter 10**, we provide an ethical framework analysis of obtaining informed consent for whole genome sequencing.

Finally, we summarize and discuss the findings of these studies in **chapter 11** and provide future directions.

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