Technological innovations in diagnosis and treatment of glioblastoma

Impact paragraph

Gliobastoma (GBM) represents the most common and aggressive primary brain cancer in adults, accounting for approximately 75% of malignant brain tumors. GBM has an estimated annual incidence of around approximately 2 in 10,000 people in the European union. Without treatment the median survival time for these patients is around 4.5 months and even with extensive treatment that includes surgery, chemotherapy and radiation therapy, the median survival is only 15 months. Since the Stupp-protocol has become standard of care after its publication in 2005, no significant survival improvement has been achieved for this combination treatment comprising radiotherapy and concomitant chemotherapy with temozolomide (TMZ). This outlook needs to be improved and requires three fundamental conditions to be fulfilled:

1. The ability to identify the full extent of this highly invasive tumour. This is impossible with the currently available diagnostic tools.
2. The improvement of the efficacy of the available treatment modalities and the development of new therapeutic options.
3. An improved prediction of the benefits and toxicities of the available treatments for individual patients. Due to the nature of this disease, the ability of both physician and patient to make an informed choice, taking into account the potential treatment outcome and side effects versus quality of life, is an essential part of defining patient tailored treatment plans.

In order to create advancements in these three areas this thesis focussed on the following objectives:

1. Review the current and novel diagnostic imaging methods and techniques used to predict treatment response.
2. Investigate the technical feasibility of incorporating 7 T MRI into neurosurgical navigation and radiation treatment planning (RTP) systems, and determine the recommended phase II dose for Chloroquine (CQ) in combination with concurrent chemo(TMZ)-radiotherapy in patients with a newly diagnosed GBM.
3. Investigate the optimization of decision support systems to improve treatment outcome prediction.

This thesis focussed on diagnostic methods and therapeutic interventions by three means: (1) through the analysis of images with radiomics and the "Non-invasive Gliobastoma Testing" (NIGT) platform, (2) through the potential of implementing 7 T MRI in radiotherapy practice, and (3) through the addition of CQ to the standard of care treatment.

In **Chapters 2 and 3** decision support systems for GBM were investigated. There is a clear need for improved decision support systems as the number of patients with a GBM is expected to increase the coming years due to the ageing population.

Moreover, as a growth in therapeutic options is anticipated there is a clear need for treatments that are better tailored to patients' individual tumor and preferences. The availability of increasing amounts of data such as clinical characteristics, semantic features, radiomics and molecular markers enables the development of novel decision support systems through the development of treatment outcome prediction models. These models can be used to estimate probabilities for treatment benefits and risks (i.e. side effects) in individual patients and thereby permit a patient individualized approach. To enable physicians to use all of these tools in actual clinical practice, Chapter 2 describes how the currently available non-invasive prognostic and predictive techniques can be combined together to form a comprehensive decision support tool: the NIGT platform. The goal of this platform is to predict and monitor treatment responses in patients with GBM. It allows physicians to fully capture the complexity and heterogeneity of the tumor and enables selection of the most optimal treatment. As both the diagnostic and therapeutic options for GBM continue to expand, such as the radiomics-based prediction model as described in Chapter 3, these techniques can be integrated in the NIGT platform. In a later stage, the tool can also be modified and be made available to patients. In order to give physicians and patients access to this support system, it will be published on the website https://www.cancerdata.org/ through which it will made publicly available and can be applied during the consultations with radiation oncologists to support the treatment decision-making process. This will assist both physicians and patients to make the best decision for the patient's personal situation, an ability relevant to all cancer patients, but even more so to GBM patients considering the careful balance between quantity- and quality-of-life.

The studies described in **Chapters 4 and 5** regarding 7 T MRI were the first to investigate its possible implementation for improved diagnosis and therapy targeting of GBM into clinical practice. These studies identified susceptibility artefacts and quantified geometrical distortions present in 7 T MR images. The studies also showed that there are still some technical challenges to overcome before 7 T MRI can be clinically implemented for neuro-oncological RTP. Further research to determine the full clinical value of 7 T MRI for the treatment of GBM is required, and the image quality of 7 T MRI needs further improvement. Medical technology companies such as Siemens, together with for instance the ultra-high-field MR imaging center Scannexus B.V. in Maastricht, are working on the latter. The research presented in this thesis demonstrates that the integration of high quality and geometrically reliable 7 T anatomical MR images into neurosurgical navigation and RTP systems is technically feasible and safe. The recommendations from these studies can be implemented within clinical (radiation oncology) practice.

A potential avenue to improve the efficacy of existing GBM treatments was investigated through the phase I study presented in **Chapter 6**. There has been mounting preclinical evidence of the efficacy of CQ for autophagy inhibition in cancer. CQ is

a readily available, generic drug which could be added almost immediately to the standard treatment of GBM with limited toxicity and with minimal financial impact. Although CQ has previously been combined with radiotherapy and chemotherapy in GBM, the presented phase I study is the first to combine CQ with the current standard of care treatment according to the Stupp-protocol. The study demonstrates limited toxicity in combination with this standard treatment and supports further research into the clinical effectiveness of CQ.

Based on the (pre)clinical work including the work described in Chapter 6 an orphan drug designation was granted for CQ for the treatment of glioma in the EU in November 2014 (EU/3/14/1377) and in the US in May 2015 (Request number: 15-4750). This provides a 10-year market exclusivity for CQ within the EU and the US. Orphan drugs are generally approved faster than drugs without orphan designation. Furthermore, the orphan designation results in fee reductions for protocol assistance and follow-up, pre-authorization inspections, new applications for market authorization and post-authorization activities for small and medium-sized enterprises.

Although GBM may appear histologically identical, the prognosis and response to therapy may be dependent on tumor biomarkers. Over the past ten years several predictive and prognostic biomarkers in GBM have been identified such as MGMT promotor methylation and mutations of IDH 1 and 2. Their value has been confirmed in more recent prospective studies. However, patient selection based on tumor biomarkers is only slowly being implemented into clinical practice. Preclinical data have shown that the addition of CQ to standard treatment is potentially most effective in *EGFRvIII* expressing and hypoxic tumors. The identification of predictive biomarkers may improve patient survival and reduce toxicity in non-responding patients in a cost-effective manner. In the proposed phase II trial as described in the **Future Perspectives** section of this thesis both the effect of CQ on survival as the value of *EGFRvIII* in identification of patients who respond to CQ treatment will be established. The phase II study is summarised in the following video: *https://youtu.be/H3W2wD8Pjsc*. The high unmet need for improved treatment for GBM and the absence of other effective treatment options position CQ close to market introduction.

In summary, the work described in this thesis has explored several new approaches that hold the potential to improve the overall survival in the treatment of patients with GBM. The promising results achieved give rise to further investigate their clinical, scientific and societal impact and judge their value on their respective merits.