Tumor heterogeneity in glioblastoma

Addenda

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Despites decades of pre-clinical and clinical research, the standard-of-care treatment for patients with glioblastoma (GBM) has remained relatively unchanged and prognosis remains poor. Currently, novel approaches to study cancer biology, growth, progression and treatment effectiveness are of great relevance to identify novel treatment options and ultimately increase patients' survival. As cancer is still one of the leading causes of mortality worldwide continuous research to improve patients' outcome is of great importance. Furthermore, the societal impact of cancer including the large economic burden its treatment modalities and overall morbidity pose calls for a more effective and efficient approach towards cancer treatment.

The work in this thesis describes novel methods to study tumor heterogeneity in GBM using either imaging techniques or pre-clinical research models. Even though the studies in this thesis focus on GBM, its findings can also be extrapolated to all other types of solid cancers.

Clinical relevance

Inter- and intratumoral heterogeneity has gained a lot of attention over the past decade as a major determinant in cancer relapse and treatment resistance. In this light, the paradigm is now shifting from a one-treatment-fits-all approach towards a personalized medicine approach which takes into account genetic profiles (i.e. Mammaprint score) and specific tumor characteristics (i.e. HER2-status for targeted therapy or tumor proportion score for PDL-1 expression for immune checkpoint inhibitors). The great improvement that we have observed in cancer treatment due to these approaches shows that accounting for inter- and intratumoral heterogeneity is of great clinical relevance in order to move the field forward.

This thesis describes different methods to study tumor heterogeneity in GBM. These approaches can aid into a more accurate prediction of the most effective treatment option to provide a patients' best chances of survival. On the other hand, this also has the potential to predict whether a patient is not going to respond to a certain treatment preventing needless adverse events and subsequent loss of quality of life.

Gain for society

The findings described in this study, though focused on GBM, can be extrapolated towards other types of cancers. Being able to improve understanding about tumor heterogeneity will ultimately benefit cancer patients in general. This will also aid in more optimal treatment selection with higher chances of success regarding prolonging survival and improve quality of life. Cancer treatment and morbidity poses a large burden on the health care system and is accountable for a major part of health care costs. Especially the newer treatment options come with high costs which leads to the ethical question of how much money society is able and willing to spend for sometimes only a small benefit in survival. This has recently become a major topic for debate as also in The Netherlands we reach the limits of the health care costs society can account for. Therefore, more accurate prediction of useful treatment options leading to less morbidity and treatment costs related to ineffective treatment options are important for society as a whole, not only from a patients' point of view but also from a societal and economical view.

Improvement in health care

In line with what is said before, an improved understanding of tumor heterogeneity can both improve cancer survival as well as decrease cancer morbidity. This is relevant in health care as the morbidity that comes with the toxicity of anti-cancer treatment also poses a large burden on the already overloaded health care system.

Novelty of the concept

Both quantitative and qualitative imaging analysis and cancer organoids are not novel concepts but have been getting more attention over the past years. Even though these concepts are not new, they still hold limitations which withholds them from actual clinical implementation.

This thesis further explores these concepts and critically reviews their current limitations. Though promising, we believe that several obstacles still have to be overcome before these concepts can be implemented into clinical practice. Important overall aspects include standardization and thorough validation of the methods that are used in order to be universally applicable and to be able to make an actual impact on the way cancer is being researched, diagnosed and ultimately treated.

Road to the market

The research presented in this thesis does not directly hold market value in a commercial sense. Commercial services are already available concerning both imaging texture analysis and organoids but are currently limited to a research setting. Further development is a major topic of research across the globe. Exploring more complex organoid (and other three-dimensional) models including multiple cell types present in the tumor, and further optimization of imaging analysis, progressing into artificial intelligence and deep learning, will increase the clinical applicability of these techniques and paves the road for further commercial development.

Concluding remarks

Tumor heterogeneity is a major determinant in cancer relapse and treatment resistance, not only in GBM but in all types of cancer. The approaches described in this thesis are of relevance towards the clinical, society and the health care system. Further development of these techniques is a major research topic worldwide and will aid in progression to the market and clinical implementation.