Maastricht University

Multiparametric image modelling

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MAIN AIMS AND OUTCOMES

The standard treatment for patients with locally advanced rectal cancer is chemo-radiotherapy (CRT) followed by surgical resection. In a minority of patients (±20%) the tumour completely disappears as a result of CRT. In these "complete responders" surgery may be avoided. This "watch-and-wait" approach has been shown to result in similar survival outcomes as surgery, but with considerably better functional outcome and quality of life. It is impossible to know upfront which patients will achieve a complete response after CRT. If we could predict how well patients will respond to CRT beforehand, this may create opportunities to further personalize and optimize neoadjuvant treatment, for example by intensifying CRT in patients likely to response, ultimately aiming to increase complete response rates and offer more patients the chance of organ-preservation.

This thesis focuses on investigating the role of different medical imaging techniques and image analysis tools in predicting neoadjuvant treatment response. In addition to 'anatomical' imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI), there are to date several 'functional' or 'molecular' imaging techniques available that can help us visualize biological tumor properties such as cell structure (diffusion weighted imaging (DWI)), tumor perfusion/angiogenesis (dynamic contrast enhanced imaging (DCE)), or metabolic tumor activity (positron emission tomography (PET)). In addition, novel image post-processing tools such as Radiomics can help us to study the detailed imaging phenotype of a tumour lesion on a pixel-per-pixel level, providing us with new insights into for example underlying tumor heterogeneity (i.e. texture analysis). Quantitative parameters derived from functional imaging and image post-processing can be used as imaging biomarkers of disease which in turn may be used to predict clinical outcomes such as treatment response. Although promising results have been reported for various imaging biomarkers in previous studies, evidence mainly comes from small single-center studies focusing on a single imaging or post-processing technique at a time. Results are conflicting and little is known about the complementary value of combining parameters acquired using different imaging techniques, an approach commonly referred to as "multiparametric imaging". With this thesis we set out to investigate the value of multiparametric imaging to predict response to chemoradiotherapy in rectal cancer, to identify the best predictive imaging biomarkers and evaluate how these should best be combined with other clinical information such as the radiological tumour stage. In addition we have explored whether it is feasible to build prediction models that are reproducible when using heterogeneous multicenter data from everyday clinical practice.

Chapter 2 summarized the role of diffusion-weighted imaging – one of the most commonly used functional imaging techniques in oncology – for the clinical management of rectal cancer, including its role for prediction of response. In Chapters 3 and 4 the information from anatomical (MRI, CT), functional (DWI, PET) and image post-processing techniques (e.g. texture analysis) was combined into a 'multiparametric' imaging model to predict response. Best performance was achieved when combining imaging features derived from MRI with clinical staging variables; the added value of PET and CT was limited. In Chapter 5, we investigated how imaging parameters derived from multicenter data – i.e. from MRI scans acquired in different institutions – are affected by variations in scanner hardware, scan protocols, radiologists and image analysis software. We found that functional DWI parameters and more advanced (complex) imaging features are more affected by variations between centers. For this reason we chose to include mainly simpler and better reproducible parameters to develop our clinical response prediction model described in Chapter 6. In this model (similar to the models, described in Chapters 3 and 4) clinical radiological staging variables such as the tumour (T-) and nodal (N-) stage had the highest predictive value, particularly when staging was performed by experienced radiologists using current state-of-the-art clinical guideline criteria. Quantitative imaging parameters contributed little in the multicenter setting, despite efforts to account for data variations between centers.

RELEVANCE

The results presented in this thesis are relevant for future studies that are aimed at developing image-based clinical prediction models. Lessons learned from our multicenter data analyses in Chapters 5 and 6 can offer guidance on how to handle data variations that are inherently present when dealing with everyday clinical imaging data derived from multiple institutions. Though heterogeneous data will always remain part of the clinical reality, efforts should be taken towards further protocol harmonization and standardization.

The results of this thesis are also relevant for the clinical management of rectal cancer patients. Our literature review presented in Chapter 2 can serve as a quick reference for clinicians on the pros and cons of using DWI to help guide clinical treatment management. From Chapters 3 and 4 we have learned that PET/CT does not seem to have any added value when combined with clinical and MRI variables in the setting of pre-treatment response prediction, indicating that there is currently no

incentive to include PET/CT in the primary staging work up of rectal cancer. Finally, the results from Chapters 3, 4 and 6 consistently demonstrate the importance of clinical radiological staging variables as predictors of response. Chapter 6, however, also showed that the predictive performance of these staging variables was dependent on the experience level of the radiologist performing the staging and on whether staging was performed using state-of-the-art staging guidelines. These result highlight the importance of having dedicated radiologists involved in rectal cancer management, and also underscore the importance of dedicated radiological teaching and training, and investment in clinical guideline implementation.

TARGET POPULATION

The results of this thesis are relevant to several groups. Although this thesis focused specifically on rectal cancer, the impact of multicenter imaging variations on multiparametric imaging modelling and lessons learned on how to handle these can also be translated to other organs and outcomes. These findings are thus important for all researchers focused on multiparametric image model development.
Our findings are also relevant for radiologists performing rectal cancer staging, as well as other clinicians dealing with the management of rectal cancer. Our results describe the current role and limitations of imaging to help predict neoadjuvant treatment response. Though the predictive performance of our multicenter model in Chapter 6 was too low to base actual clinical decision making on, the search for biomarkers continues and should be expanded to other fields. If imaging can be integrated with other clinical biomarkers to build stronger clinical prediction models of response, these models could be used as decision support tools to help further personalize treatment in rectal cancer and optimize treatment outcomes.

ACTIVITIES

The results of this thesis have been presented to a wide audience at both national and international conferences, and have been published in peer-reviewed journals. The paper publication of Chapter 3 was awarded the European Radiology ESGAR award 2020. Lessons learned from this thesis are incorporated into follow-up projects on multicenter data modelling to predict other clinical outcomes and investigating other target organs. Moreover, the large multicenter dataset that was acquired as

part of this thesis has been further expanded and is currently being used in several ongoing collaborative international projects focusing on optimizing the diagnostic performance of imaging for the staging and response evaluation of rectal cancer patients. The current thesis and results of these future studies may serve as a basis for future guideline updates.