

Towards diagnostic and therapeutic integration of advanced MR imaging in thoracic and neuro-oncology

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ADDENDUM

Valorisation

VALORISATION

SOCIAL RELEVANCE AND TARGET POPULATIONS

Globally, cancer is considered as the second most common cause of disease-related deaths. In 2012, cancer affected 14.1 million people, leading to 8.2 million deaths worldwide. Despite substantial advances in cancer therapy, successful treatment remains challenging due to the vast diversity and complexity of many cancer types. This thesis focused on patients with thoracic or brain cancer to improve in early diagnostics and cancer treatment, using non-invasive imaging techniques and image analyses. However, the findings of this thesis can be extrapolated to patients with other diseases and other tumour regions (e.g., head-and-neck, abdominal, and pelvic regions). Attributed to the global impact of cancer, improvements in clinical care will economically benefit the whole society as treatment will become more effective and consequently more cost efficient.

Since medical imaging is the cornerstone of modern cancer care, both in diagnostic radiology and therapeutic oncology, implementation of advanced MR imaging techniques, image analysis methods, and imaging modalities can have an enormous impact in clinical healthcare. Primarily, the patient would directly benefit from advances in medical imaging and subsequent increase in diagnostic accuracy (i.e., detecting and differentiating early disease development, tumour infiltration, and tumour metastases) and treatment accuracy (i.e., surgical resection, radiation dose delivery). In addition, MR images can be acquired in a non-invasive, patient-friendly manner without exposing the patient to a harmful, unnecessary ionising radiation dose. By further exploring the versatility of MRI, both high-quality anatomical and functional (PET-)MR images can be acquired to better understanding tumour biology and tumour characteristics related to treatment resistance. Ultimately, multiparametric insights could lead to improvements in current therapies and stimulate the development of individualized treatment strategies.

Selecting the most beneficial treatment-regime for an individual patient does not only aims to obtain the best patient outcome but also aims to maintain a high quality of life. Personalized healthcare therefore also has a social impact, affecting family, friends, and physicians involved in treatment decision-making. Clinical decision support systems based on multiparametric imaging and prediction models can assist physicians and patients in constructing the treatment option that is tailored to the needs and preferences of each individual patient.

To integrate innovative imaging modalities (i.e., UHF-MRI and PET/MRI) into oncology, retraining of radiologists, radiotherapists, and MR technicians is required.

Acquiring ECG-triggered mediastinal (PET-)MR images and UHF-MR images is not straightforward and often requires hands-on optimisation while acquiring images. Furthermore, the combined representation of nuclear PET-data with MR-data is relatively new to specialised MR technicians and radiologists. For UHF-MRI, expert knowledge is required to acquire and analyse complex anatomical and functional imaging (e.g., susceptibility-weighted imaging and mapping, phase-contrast imaging, CEST, MR spectroscopy, fMRI), making these techniques difficult to translate into daily clinical practice without additional training. Likewise, mediastinal (PET-)MR and UHF-MR images are rarely used in radiation oncology and retraining is needed to learn how to apply dedicated imaging protocols and deal with image-distorting artefacts and geometric integrity.

IMPACT ON CURRENT ACTIVITIES AND PRODUCTS

Based on the findings presented in Chapter 2, currently-available MRI techniques can be used to clinically assess mediastinal tumours and metastatic lymph nodes with overall high diagnostic accuracy. In radiation oncology, accurate evaluation of each individual lymph node can be used for state-of-the-art selective nodal irradiation. In addition, DWI and ADC-based radiomics analyses can be used to acquire complementary information to specify tumour heterogeneity as indicated in Chapter 7 and 8, respectively. These findings are an important source of information to be used in the development of clinical decision support systems.

In ^{18}F -FDG-PET/MR imaging, DWI could be decisive in nodal staging when the FDG-avid mediastinal nodes are doubted to be non-metastatic. Practical points of advice have been presented in Chapter 3 for implementing PET/MRI using a dedicated, patient-friendly protocol for thoracic anatomical imaging. By incorporating DWI in the same protocol, ^{18}F -HX4-PET/MRI has shown to visualise tumour hypoxia in oesophageal cancer and to detect early treatment responses.

The findings and practical workflow presented in Chapter 4 and 5 stimulate the use of anatomical UHF-MR images in neuro-oncology. UHF-MR images could supply radiologists with images that depict detailed neurologic malformations that could be the decisive factor for clinical interpretation (i.e., intracerebral tumour spread, tumour angiogenesis, and microbleeds). In addition, 7T MR images could be used for high-precision radiation treatment options in the central brain region. However, it is advised to optimise 7T-MR protocols for each specific clinical application and make the trade-off between image-quality and image integrity.

IMPACT ON FUTURE ACTIVITIES AND PRACTICE

Although promising results have been presented in this thesis, further academic research is needed to stimulate the integration of (PET-)MRI in thoracic and UHF-MRI neuro-oncology. In future research, innovative MR sequences need to be revised for mediastinal imaging, together with advanced methods to compensate for respiratory and cardiac motion. In addition, the diagnostic value of mediastinal (PET-)MR needs to be investigated and dedicated protocols need to be validated in direct comparison to PET/CT, with histopathological validation. Nevertheless, the presented protocols and practical suggestions of this thesis could have an impact on current radiation treatment. For instance, novel MR-LINAC systems (e.g., ViewRay MRIdian linac and Elekta Unity) could benefit from our imaging protocols as real-time soft-tissue image feedback is used to visualise tumour mobility, related to cardiac and respiratory motion, and improve the precision of radiation dose delivery.

Before PET/MRI can be fully integrated in radiation oncology, however, specific modifications are required to ensure reproducible patient positioning (e.g., flat table overlay, coil bridges) and the generation of accurate photon attenuation correction templates. Moreover, this thesis argues that tumour-specific protocols combining PET-tracers beyond ^{18}F -FDG with dedicated MRI sequences (incl. DWI) will soon become valuable tools to fully exploit the diagnostic potential of PET/MRI. However, there is still a lack of evidence defining key clinical applications and demonstrating the cost-effectiveness of PET/MR and need to be investigated further. Nevertheless, hybrid imaging modalities have a unique potential as a theragnostic tool by using PET-tracers labelled with radiopharmaceuticals or radiolabelled antibodies. In addition, the ability to detect hypoxic regions and correlate anatomical and cellular changes by ^{18}F -HX4-PET/MRI paves the way for personalized anti-cancer treatment, as presented in Chapter 6. By selecting patients with hypoxic tumours prior to treatment, a window-of-opportunity arises wherein attempts to reduce tumour hypoxia could be made by enhancing the susceptibility of hypoxic cells to anti-cancer treatment and/or targeting hypoxic tumour cells (e.g., boosted radiation dose painting, hypoxia-activated prodrugs). Consequently, further development of PET/MR tracers and hypoxia targeted agents spikes the interest of health care companies, stimulating further research.

In radiation oncology and neurosurgery, advanced visualisation of organs-at-risk, microvasculature, and tumour infiltration along white matter tracts could benefit target volume definition. the risk applying 7T MRI in RTP is clinically manageable in, but limited to, central brain regions that display high image quality and spatial accuracy. In peripheral regions, however, the anatomically-optimised 7T sequences did not meet the requirements of geometrical accuracy for RTP. This implies that

dedicated 7T MRI scan protocols need to be optimised for the specific clinical usage in diagnostic radiology or in radiation therapy. To apply UHF-MRI in thoracic regions, new multi-channel excitation coils are being introduced to provide precise control over the RF field distribution to enable high-quality imaging even over large volumes.

Lastly, MR radiomics analyses provide unique insight in tumour heterogeneity by extracting quantitative phenotypic features from ADC maps. Open access has been permitted to the datasets used in Chapter 8 and is publicly available for further research. Based on ADC-based radiomics, prediction models can be developed and are the focus of future research. Some examples from the MAASTRO Clinic research group are already available on www.predictcancer.org. However, MR radiomics is not yet ready to be translated into daily clinical practice and further standardization of quality-assured DWI protocols are needed for multicentre validation. One step towards standardization includes the radiomics quality score (RQS) initiative.

PLANNING AND REALISATION

Transcending stand-alone MRI, the future of imaging lies in smartly combining different imaging modalities and parametric imaging techniques to gain comprehensive insights in tumour biology that could ultimately lead to individualised anti-cancer treatment. With the increasing amount of data available, analysis methods are required that can manage multiple scans and can combine the knowledge.

In radiation oncology, UHF-MR images might improve delineation of the gross tumour volume (GTV) by visualizing tumour microvascularization. Therefore, a future clinical study (NCT02062372) has been designed to investigate this potential and evaluates the value of 7T-image guided biopsies.

Hybrid PET/MRI has also gained interest for precise target volume delineation on anatomical MR images, for defining biological target (sub-)volumes based on hypoxia imaging, as well as for monitoring treatment response. The study presented in Chapter 7 was part of an ongoing clinical trial (NCT02233387) investigating the potential of ^{18}F -HX4 PET in patients with oesophageal, cervical, prostate, glioblastoma, rectum cancer or brain metastases. The benefit of boosting specific radioresistant parts of the tumour is still under clinical evaluation. MAASTRO Clinic is participating in a prospective phase II PET-Boost trial in patients with non-small cell lung cancer (NCT01024829).

