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Short description of the project entitled

Characterization of patient specific PTV based on multiple MRI scans before and during treatment to obtain adaptive treatment strategy for dose escalation

Background

In radiotherapy, planned treatment volumes are typically constructed only once, at the start of treatment. Tumour (and relevant elective volumes) are outlined on baseline treatment planning imaging and a population-based margin is added to account for the random day-to-day variation in position and shape of the treatment volumes. However, this current practice is based on planning scans (CT and MR) from a single point in time for delineation of both the tumour volume and the organs at risk (OAR). Previous studies have shown that anisotropic motion and shape variation of the rectum occur during a CRT course [3,4]. In addition to the random day-to-day variation, systematic change in position and shape of both tumour volume and OAR may occur [5]. Furthermore, functional imaging (such as DWI) during the course of treatment may identify early response and hence potential treatment adaptation in terms of selective tumour boosting. By analysing multiple MRI scans before, during and after radiotherapy, it may be possible to optimize current treatment by providing individual treatment margins and/or adaptive treatment strategies, thereby delivering more precise and adaptive patient-based radiation treatments. An ongoing prospective imaging study in Aalborg (AMPERE, NCT03619668) will be examining these questions in patients with locally advanced rectal cancer.

The results found in this study will be validated on a national multi-center prospective imaging study initiated in Vejle (WW2, NCT02438839). The two protocols are both approved for secondary data analysis and will allow development and validation of an individualised, adaptive treatment strategy for rectal cancer radiotherapy.

Project aims:

Characterisation of patient specific PTV margins to obtain a more precise and accurate radiotherapy. To use an adaptive treatment strategy, to facilitate dose escalation to the tumour without an increase in expected treatment toxicity, ultimately providing better radiotherapy for the patients and supporting non-operative treatment strategies. Furthermore, the use of functional MRI for early tissue response, and hence the potential treatment adaptation of selective tumour boosting will be possible.

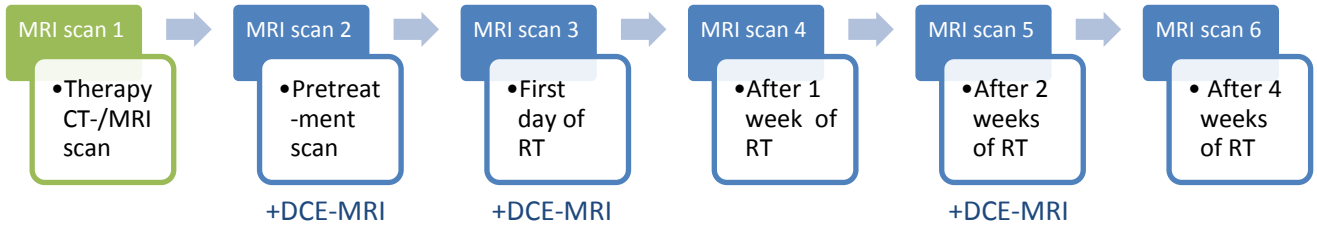
Patients and Methods:

AMPERE protocol:

Prospective sequential imaging study in patients treated with chemoradiotherapy for locally advanced rectal cancer; primary investigator: medical physicist Dennis Tideman Arp. Patients will be scanned six times in addition to the standard MRI-scan appointments and follow-up: as part of the RT therapy scan, three-four days after therapy scan, on the first treatment day before the first radiotherapy treatment, after one, two and four weeks of RT, and an additional follow-up scan at two years after RT (see figure 1). The MRI-scans consist of T2-weighted and diffusion-weighted sequences for anatomical analysis. The DCE-MRI will consist of

a dynamically acquired T1-weighted sequence. Furthermore, sequences for creation of pseudo CT images for dose calculation will be implemented.

Pre-treatment and during treatment:



Follow-up:

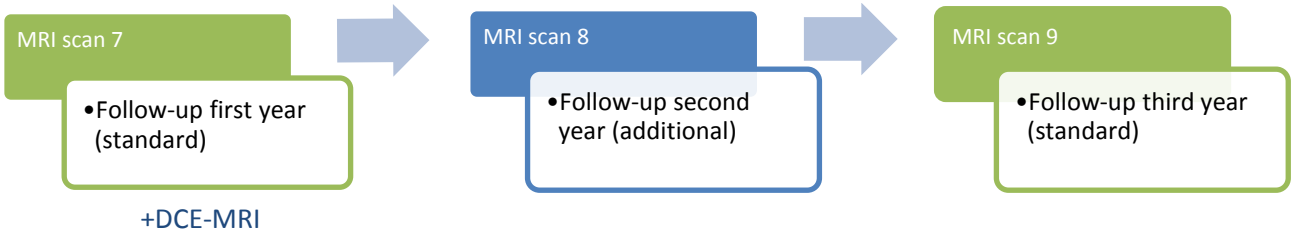


Figure 1: Green indicate scans which are part of standard management; blue indicate MRI scans which are specific to this study. DCE-MRI: dynamic contrast-enhanced MRI.

WW2 protocol:
This prospective trial, conducted under Danish Colorectal Cancer Group, examines non-operative management of early rectal cancer, treated with dose escalated chemoradiotherapy. Multi-parametric MRI scans are performed at the following time points:

- Before enrollment (disease grading)
- Before start of treatment (baseline and dose planning)
- 2 weeks after start of radiation treatment (assessment of early response)
- 6 (and potentially 12) weeks after end of treatment (response evaluation)
- Before each follow-up visit

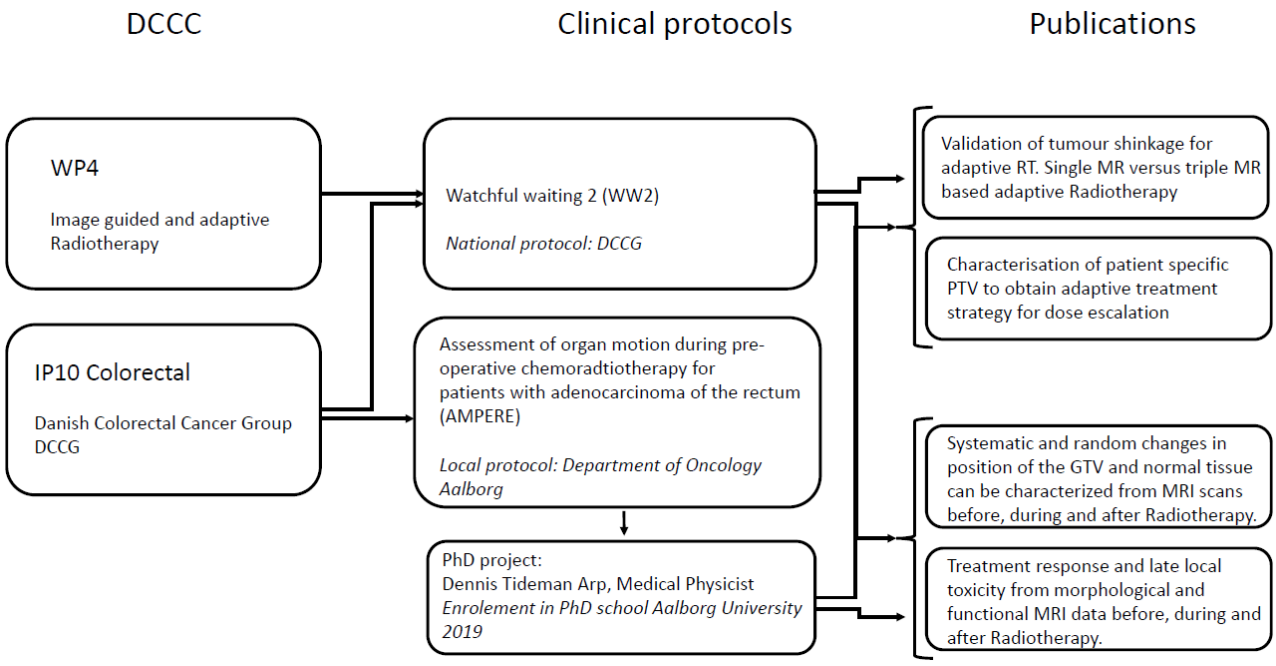
MRI before start of treatment and after 2 weeks of treatment are performed at the treating department of oncology/radiotherapy. All other MRI scans have been performed at the participating departments of radiology according to local guidelines. Currently, 83 patients are enrolled in the WW2 protocol, across three Danish centres (Vejle, Aalborg, Rigshospitalet). Total planned enrolment is 104 patients, with expected completion in first quarter of 2019. Confirmation has been given by the trial steering committee that data from all trial patients will be made available for secondary analysis in the current PhD project. Collection of imaging data from the three participating centres, via the national DICOM database, will form part of the project.

Study 1 (based on AMPERE data)

- Delineation of GTV, CTV (and OAR) separately on CT and all MRI-scans.
- Geometric analysis of GTV and CTV to characterise systematic and random changes in position and shape.
- Create individual patient specific radiation treatment margin based on these analyses.
- Calculate an adaptive margin to evaluate the impact on the treatment with radiotherapy and if this will allow dose escalation to the tumour without an increase in expected treatment toxicity.

Study 2 (based on national multi-center data)

- Validation of tumour shinkage for adaptive RT: using WW2 data for early stage patients and data from the prospective Vejle protocol for patients with locally advanced cancer.
- Establishment of an adaptive RT approach for tumour shrinkage from the AMPERE data (three MRI scans during RT). The WW2 (single MRI scan during RT) will be used to validate the adaptive RT and to investigate the need for additional MRI scans during the course of RT.
- Examination of an adaptive treatment approach based on functional MRI from the AMPERE protocol; with diffusion-weighted aspects to be validated in national and Vejle data.



Planned publications:

1: Characterization of patient specific PTV to obtain adaptive treatment strategy for dose escalation.

2: Systematic and random changes in position of the GTV and normal tissue can be characterized from MRI scans before, during and after radiotherapy.

3: Treatment response and late local toxicity from morphological and functional MRI data before, during and after radiotherapy.

4: Adaptive Radiotherapy for colorectal cancer from a single MRI. Do multiple MRI scans during RT provide additional knowledge for tumour shrinkage adaptive RT?

Participating centers:
Vejle Hospital, Department of Oncology
Aalborg University Hospital, Department of Oncology/Medical Physics
Rigshospitalet, Department of Oncology
Bispebjerg Hospital, Department of Radiology

Clinical and national impact:
Current treatment of rectal cancer is highly effective with respect to local tumour control, but also carries a substantial late morbidity burden for patients. This is especially the case for patients treated with combined chemoradiotherapy and surgery. By improving the quality of rectal cancer radiotherapy, through individual treatment margins and adaptive treatment strategies more patients may be treated with chemoradiotherapy as the national primary treatment modality. This has the potential to spare patients for the severe morbidities associated with surgery, as well as the need for stomas.

Ethical considerations:
Both protocols used in this project are approved by the regional ethics committees, including data sharing and analysis. The WW2 protocol group has approved the use of protocol data for the exploratory studies initiated in this project. The project is conducted in accordance with the approved protocols and applicable legislation, and complies with the principles of the fifth version of the Helsinki Declaration.

References:
1. Lambregts DMJ. Organ saving treatment after chemoradiotherapy for rectal cancer - MRI as a selection tool. Universitaire Pers Maastricht; 2013. p. 1–158.

2. Beets-Tan RGH, Beets GL. MRI for assessing and predicting response to neoadjuvant treatment in rectal cancer. Nat Rev Gastroenterol Hepatol. 2014 Aug; 11(8):480–8.

3: Nijkamp, J. et al., 2012, 'Repeat CT assessed CTV variation and PTV margins for short- and long-course pre-operative RT of rectal cancer', Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology, vol. 102, no. 3, pp. 399-405.

4: Nuyttens, J.J. et al. 2002, 'The variability of the clinical target volume for rectal cancer due to internal organ motion during adjuvant treatment', International journal of radiation oncology, biology, physics, vol.53, no. 2, pp. 497-503.

5: Robbe Van den Begin, Jean-Paul Kleijnen, Benedikt Engels, Marielle Philippens, Bram van Asselen, Bas Raaymakers, Onne Reerink, Mark De Ridder & Martijn Intven (2018) Tumor volume regression during pre-operative chemoradiotherapy for rectal cancer: a prospective observational study with weekly MRI, Acta Oncologica, 57:6, 723-727.