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Assessment of organ motion during preoperative chemoradiotherapy for patients with adenocarcinoma of the rectum (AMPERE)

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Background

Patients diagnosed with locally advanced adenocarcinoma of the rectum are treated with concomitant chemoradiotherapy (CRT) according to national Danish guidelines¹, with the aim of reducing local recurrences^{2,3}. Depending on tumor location, this is a pre-operative procedure prior to total mesorectal excision (TME) or partial mesorectal excision (PME). Although the introduction of TME has significantly reduced the frequency of local recurrences⁴, the procedure is associated with a high risk of postoperative morbidity especially when combined with CRT. The morbidities most often reported include Low Anterior Resection Syndrome (LARS), sexual dysfunction and pain^{5,6}. Consequently, recent years have seen an increasing focus on other therapeutic approaches, such as “watch and wait”, where the aim is to treat some patients with definitive CRT alone. The success of these new approaches directly relies on the effectiveness of the radiotherapy treatment and thereby both on the level and the accuracy of the delivered dose to the clinical tumor volume (CTV). High precision treatment will also allow for smaller overall treatment volumes for standard treatment strategies, as detailed below.

In the past, treatment planning has exclusively been based on Computed Tomography (CT) scans. In recent years, introduction of the superior soft tissue contrast of magnetic resonance imaging (MRI) has supported improved visualization and delineation of gross tumour volume (GTV), CTV and organs at risk (OAR). In daily practice, delineation of treatment targets (GTV and CTV) and OAR is typically done on the treatment planning CT scan, with the supporting MRI co-registered to aid delineation. In radiotherapy, planning target volumes (PTV) are constructed by means of adding a population-based margin to the CTV to account for the random day-to-day variation in position and shape of the CTV. However, current practice is based on planning scans (CT and MR) from single point in time for delineation of both GTV, CTV and OAR (Figure 1c).

Multiple scans would allow for estimates of day-to-day variation of the GTV, CTV and OAR (Figure 1a+b). This would provide more correct margins for construction of populations based PTV and the possibility for individual patient based margins to account for the day-to-day variation of the specific GTV, CTV and OAR (Figure 1d). This may be even more important with the introduction of intensity modulated radiation therapy (IMRT) and advanced image guided radiation therapy (IGRT), as the administered dose is highly conformal and precisely delivered. Incorrect margins increase the risk of inadequate dose coverage of PTV and overdose of OAR – both potentially damaging.

Several studies have shown that anisotropic motion and shape variation of the rectum occurs during a CRT course⁷⁻⁹. These variations depend on the region of the CTV and also on the gender of the patient. In addition to the random day-to-day variation, systematic change in position and shape of both CTV and OAR may occur. Studies have shown an average reduction of the rectal volume of 57 % during radiotherapy treatment (RT), with almost all reduction occurring within the first 9 fractions¹⁰.

These studies support that a more detailed knowledge of organ motions and changes during treatment would allow for more correct PTV margins and an adaptive CRT approach. This could result in an improved dose coverage of the PTV or potentially sparing OARs. A sparing of OARs could facilitate a potential dose escalation to the GTV or CTV with a reduction in treatment toxicity.

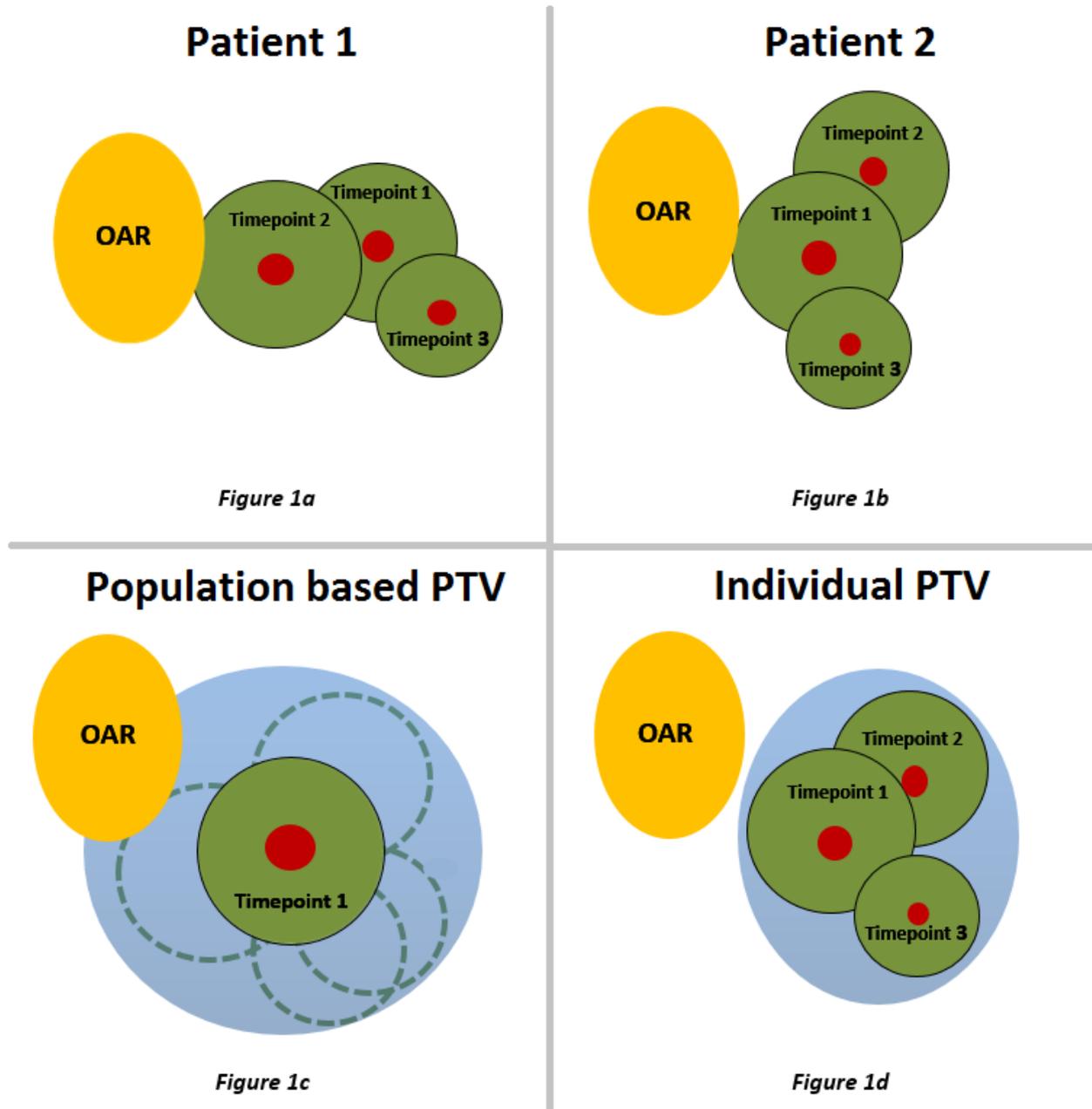


Figure 1: Construction of CTV-PTV margin. Yellow=OAR, Red=GTV, Green=CTV and Blue=PTV margin. Figure 1a and 1b illustrate the difference in motion of GTV/CTV for two different patients. Figure 1c shows a population based PTV margin taking into account target motion for both patients. Figure 1d shows the reduced margin using an individual margin construction.

The aim of this feasibility study is to address the impact on radiotherapy planning from systematic and random day-to-day variation in position and shape of the GTV and CTV in patients with rectum cancer using additional MRI scans before and during radiotherapy.

Previous studies of this problem have mainly been based on repeat kVCT or MVCT scans, i.e. without the superior soft tissue contrast from the MRI. Furthermore, the ability to introduce functional imaging, including diffusion-weighted imaging (DWI) and dynamic contrast-enhanced MRI (DCE-MRI), could provide

additional information regarding the OARs as well as GTV and CTV, including imaging-based assessment of treatment response and toxicity¹¹. This information along with morphological data could allow for comparative analysis of radiation dose distribution relative to e.g. local toxicity providing voxel- or area-based dose-response relationships¹²⁻¹⁴. By correlating the dose-response relationship with side effect registration it might be possible to predict the risk of local toxicity to OARs.

In this explorative study, patients will be MRI scanned at different time points (days) in the week prior to start of radiotherapy, in order to understand the day-to-day random variation in anatomy. Systematic changes in position and shape of the GTV and CTV during radiotherapy will be estimated using three additional MR-scans over the full course of treatment. Furthermore, annual follow-up scans will be performed with side effect assessments based on image analysis and side effect registration during and after completion of the RT course. The MRI scans will additionally be used to develop a MRI-based anatomy atlas for rectal cancer patient treatment volume delineation. All information provided by the scans will be analyzed retrospectively only. The information obtained will therefore not influence any patient treatment. However, the second-year follow-up scan will be evaluated on the same terms as a standard follow-up scan. Therefore, this can be seen as an additional check of the patient's condition. If there is a relapse of the disease, there may be changes in the patient's treatment course earlier than in standard follow-up scheme.

Hypothesis

Current standard treatment for rectal cancer in the department is based on a single planning CT and MRI-scan one week prior to treatment start. Follow-up scans are performed at one year and three years after completions of the RT course. The overall hypothesis is thus that the information from multiple additional MRI scans will allow for more precise, less toxic and more individualized treatment for rectal cancer. Specifically, performing additional MRI scans prior to, during and after treatment, and defining the GTV, CTV and OAR on each scan, will confirm or deny that:

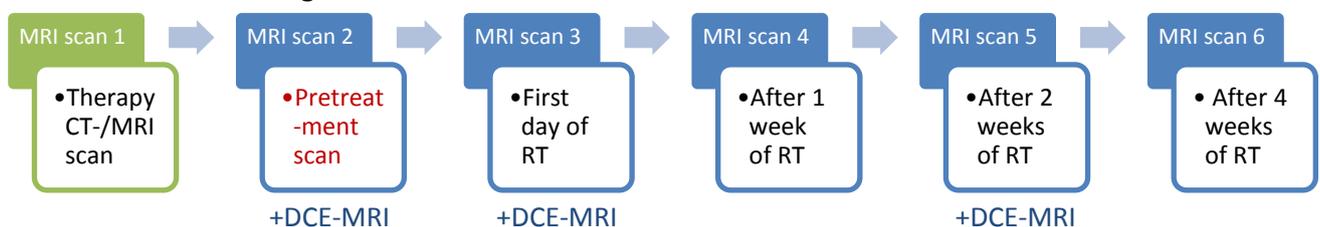
- Systematic and random changes in position and shape of the GTV, CTV and OAR can be characterized using additional MRI scans before and during radiotherapy.
- CTV-to-PTV margins for the patient group can be adapted, by characterizing systematic changes in position and shape of CTV during radiotherapy.
- An adaptive CRT strategy will facilitate dose escalation to the GTV without an increase in expected treatment toxicity.
- MRI scans providing morphological and functional data before, during and after CRT will provide information about treatment response and local toxicity.
- It is possible to correlate local toxicity information with registered side effects.

Method

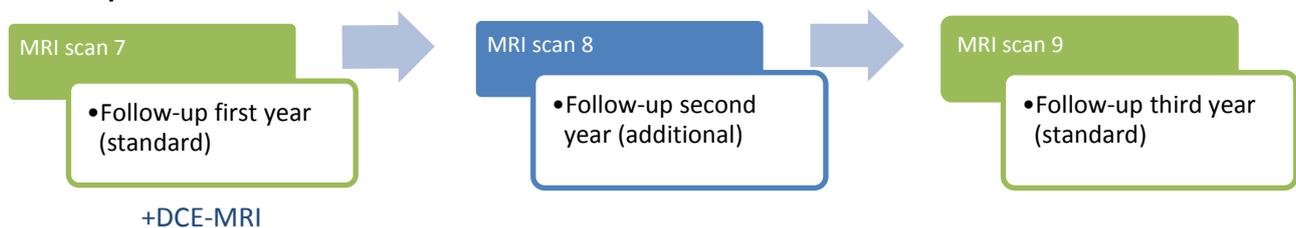
Patients will be scanned six times in addition to the standard MRI-scan appointments and follow-up: as part of the RT therapy scan, three-four days after therapy scan, on the first treatment day before the first radiotherapy treatment, after one, two and four weeks of RT, and an additional follow-up scan at two years after RT. DCE-MRI and DWI is not a part of the standard routine MRI-scans of rectal cancer patients in our

clinic. However, these are widely used modalities in other patient-groups e.g. prostate cancer. DCE-MRI will be performed in four of the nine appointments - two of the standard appointments and two of the additional. See overview below. The scans will be performed following the standard clinical setting; on a flat tabletop and with an empty bladder. Consistent with standard clinical routine the patients will receive an anti-peristaltic agent (Buscopan) prior to scanning, and receive a laxative if the rectal filling is too large. 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. The scan protocol will have an expected total scan time of 35 minutes, with total extra time needed in the clinic of 1 hour. Kidney function will be assessed prior to each contrast scan. The scans during radiotherapy treatment will be scheduled as an extension of the patients planned treatment course. Only two additional visits to the department is therefore needed (MRI scan 2 and 8).

Pre-treatment and during treatment:



Follow-up:



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.

The GTV, CTV and OAR will be delineated separately on CT and all MRI-scans. Using a rigid bony anatomy based method, the MRI-scans will be registered to CT scan, to allow a comparison of the position and shape variations of the volumes. Side effect registration will be performed at MRI scans 1, 6, 7 and 9 and consist of CTCAE (ver.4), LARS score and EORTC quality of life questionnaires (QLQ-C30 and QLQ-CR29).

Endpoints

Endpoints relevant to this study are:

- Characterization of the systematic and random changes in position and shape of GTV, CTV and OAR.
- Estimation of change in CTV-to-PTV margins, as found by characterizing systematic changes in position and shape of CTV during radiotherapy.
- Estimation of the dose escalation to the GTV and/or a reduction in treatment toxicity facilitated by an adaptive CRT.

- Image-based assessment of treatment response and local toxicity using morphological and functional data, based on MRI scans from before, during and after CRT.
- A correlation is found between local toxicity assessment and side effect registrations.

Inclusion and exclusion criteria

Approximately 25 patients are annually referred to the department of oncology for standard preoperative chemoradiotherapy for rectal cancer. Inclusion period is expected to be from June 2018 to June 2020; all patients referred in this time period fulfilling the criteria below will be offered participation in the study.

Inclusion criteria: Patients >18 years referred to standard chemoradiotherapy for locally advanced rectal cancer.

Exclusion criteria:

- Prior surgery in pelvic minor region
- Pacemaker
- Neurostimulator
- Other non MR-compatible implants
- Pregnancy
- Incapable of undergoing MRI
- Incapable of understanding the patient information
- Allergic to contrast agent
- Contraindication for Buscopan
- Reduced renal function (GFR < 50 ml/min)

Patients who cannot tolerate the contrast used for DCE-MRI (due to allergies, contraindications for Buscopan or reduced renal function (GFR < 50 ml/min)) will still be offered inclusion in the study, but without the contrast-based MRI scans.

Benefits and Risks

The MRI examination is not associated with any exposure to ionizing radiation and there are no additional risks involved in comparison to a standard clinical MRI scan with contrast administration. The patient is equipped with earplugs for noise reduction and a manual alarm, which always can be activated during the scans. The total MR examination consists of multiple scans cf. the methods section. The patient will have to spend additional time in the clinic to undergo the MRI scans. All scans will be placed as conveniently as possible to accommodate the patient clinical schedule.

DCE-MRI is not a part of the standard routine MRI-scans of rectal cancer patients in our clinic, and therefore introduce an added inconvenience and small risk. However, these are widely used modalities in other patient-groups e.g. prostate cancer. The DCE-MRI sequence requires the use of intra-venous administered contrast agents using a cannula (venflon). The cannula is placed by the radiographer prior to the MRI scan, using standard sterile technique. This can be associated with mild discomfort and there is a

low risk of infection around the injection-area. Mild to modest side effects occur in about 2% of the patients. Possible side effects include skin itch, heating sensation, nausea and very rarely vomiting. In about 1 of 1 million patients severe hypersensitivity have fatal consequences, as a result of a collapse of the circulatory system. The department has an established procedure in case of anaphylactic events during use of contrast. This procedure includes an on-call clinician, who will respond promptly to any severe side effects. In less than 1% of the patients renal function may be affected, but this risk will be minimized by performing a blood test of renal function prior to the use of contrast agent.

By participating in the trial, the patients will not necessarily have any clinical benefits. All image analysis will be performed retrospectively, however the additional follow-up scan at second year will be reviewed by a radiologist and therefore a relapse could be detected sooner. The study will foremost contribute to clinical development and research of the use of modern radiological imaging techniques for image-guided radiation therapy.

Statistics

This is an exploratory study. There will be a feasibility check after 14 patients: If the results at this point suggest that the imaging schedule can be adhered to and that a reasonably proportion of eligible patients are willing to participate, the study will continue and is expected to include 25 patients during the inclusion period. If the study has included more than 25 patients before the inclusion period has ended, the study will be closed. If fewer than 25 patients have been included within the inclusion period, the study will be reevaluated. The patients will, in addition to the main analysis, be divided into two sets of subgroups for secondary analysis:

- Gender: women vs. men
- Tumor location (height): High/mid vs. low

Assuming that 50 % of all eligible patients accept participation in the protocol, 25 patients can realistically be enrolled in the proposed time frame and will provide enough information that each subgroup can be analyzed separately as well as together.

Personal privacy

Personal information regarding the subjects are protected under the "Personal Data and Health Law". The project will be reported to the "Data Protection Agency", through the Regions' framework notification system. Individual patient records are reviewed to assess whether the patient is a possible candidate to be included in the project. If the health professional who has treated the patient gives permission (see Health Law § 46 paragraph. 1 and 3) the patient will be informed about the project. Patients will be asked for consent for their data, in completely anonymized form, to be used for follow-up studies, which may include sharing the data with collaborators in Denmark and abroad.

From patient records, information will be obtained regarding:

- Patient age
- Gender
- Tumor height
- Clinical TNM stage
- ypTNM

- Type of surgery
- R0-resection
- Tumor regression grade
- Prior relevant disease
- Prior or current medication
- Status at baseline scan
- Pathological description of biopsy and surgical specimen
- Diagnostic images
- Treatment history
- Radiotherapy doseplans
- Acute and late toxicity
- Follow-up information regarding tumour control and survival

Finances

Members of the project group are financed via their employment at their departments at Aalborg University Hospital. The MRI-scans are provided by The Department of Medical Physics. No external financial support to the project members are given for the purpose of conducting this study.

Remunerations and other benefits

Participants will not receive any remunerations.

Recruitment of participants

All subjects need to be referred to standard chemoradiotherapy for locally advanced rectal cancer. The patients are informed about the project by the attending physician in the oncology department. During the preliminary consultation in the oncology department, it is clearly stated that the project is a health science research project aimed at improving the knowledge about internal movement of the rectum and surrounding organs, with the aim of improving the accuracy of delivering radiation therapy.

Patients are enrolled on trial on the basis of verbal and written information. At the first appointment in the department, the doctor informs about the study and the patient receives the written information. At the second appointment, any questions can be answered and the patient may subsequently give written consent for study participation. The information provided must include the purpose of the study, the risks, benefits and disadvantages. Patients are allowed at least 24 hours to consider their decision and must be informed that they may withdraw their consent at any time. Time will also be allowed for asking questions. The patient has the right to an assessor or observer. Informed consent must be obtained before any study-related procedure. The signed, dated consent form will be stored in a locked room and is available for audit and inspection at any time.

Publication of trial results

All data will be pseudo-anonymized when used for publications. The final data is expected to be published in international journals and presented at scientific conferences in accordance with the Vancouver rules. The results will be disseminated through public lectures and popular science post. The results from this protocol will be published, whether they are positive, negative or inconclusive. First author on articles directly related to the hypotheses of the protocol is the investigator. First authors of derivative works of the

protocol are allocated to the persons devising the idea for the work and manages the task (concept, protocol application, database manager, data processing, analysis and manuscript). Co-authorship is assigned according to the Vancouver rules, but these rules may be waived if the persons are not active, and/or the project is handed over to another person at a later date.

Ethics

The project is conducted in accordance with the approved protocol and applicable legislation, and complies with the principles of the fifth version of the Helsinki Declaration. The information concerning subjects is protected by the "Law concerning the processing of personal data" and Health Act, Section 3 concerning patients' rights. The project requires approval by the local research ethics committee (north / middle) and the Data Protection Agency. Data from the trial is kept for 15 years after completion. The trial is initiated when approved by the Ethics Committee for the Northern Region.

This study is an explorative step into making CRT the definitive treatment modality and sparing the patient for the morbidities associated with surgery. The subjects will not have any immediate benefits of participation in this study, unless the extra second-year follow-up scan shows relapse of the disease leading to an change in treatment course. The results have the potential to make future radiotherapy treatments of rectal cancer patient more precise with less side effects and will provide important information regarding the organ motion during preoperative CRT. The risk for the patient is described in the "Benefits and Risks"-section. The patient is not exposed to any ionizing radiation, but the use of contrast agents in the DCE-MRI does add a small risk and inconvenience to the patient. The main inconvenience to patients is the time commitment, but this has been sought minimized by scheduling scans in relation to standard appointments. The overall risks, discomforts and side-effects are assessed to be acceptable compared to the potential benefits of the project (and future secondary research projects).

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