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Supplementary Material

Appendix 1: Trial design

Figure a1: Overview of trial design.
Appendix 2: Radiotherapy

External beam radiotherapy

All patients were treated with intensity modulated radiotherapy (IMRT) using a concomitant boost technique. Delineation and treatment planning was performed according to the national guidelines of the Danish Colorectal Cancer Group at the time, with minor modifications.

Radiotherapy treatment planning was based on computed tomography (CT) scans (2.5-3 mm slice thickness) of the pelvis (upper L4 to free air under the anus), with water as peroral contrast. Magnetic resonance imaging (MRI) scans were used to aid target delineation. Patients were scanned and treated in the supine position.

Target delineation

The following treatment volumes were delineated:
- CTV-T: Tumour clinical target volume. Consisted of tumour as well as rectum at the same level, with any pathologically enlarged regional glands included in the volume.
- CTV-N: Lymph node clinical target volume. Contained the mesorectal, presacral and lateral pelvis region, including presacral, rectalis superiore, rectalis mediane, iliaca interna, obtural lymph nodes; defined as being from the a. iliaca communis bifurcation till 2 cm below tumor's distal limit or corresponding to anus. The following definitions were used for CTV-N delineation:
  - Lateral pelvis and upper presacral region: Proximal border at the bifurcation of the common iliac artery into the external and internal iliac artery. Distal border where the obturator artery enters the obturator canal. Ventral border following the internal iliac vessels in the proximal part of the volume, and the obturator vessels after the bifurcation. Dorsal border at the os sacrum in the proximal part of the volume, and the piriformis muscle in the distal part. Lateral border at the psoas muscle in the proximal part of the volume, and the bony structures of the pelvis in the distal part.
  - Mesorectal and lower presacral region: Proximal border where the inferior mesenteric artery bifurcates into the superior rectal artery and the sigmoid artery. Distal border at the levator ani. Ventral border at the mesorectal fascia, the prostate / seminal vesicles or the uterus / vagina. Dorsal border at the os sacrum or the coccyx.

Margins were added to account for internal motion and positioning uncertainties:
- ITV-T / ITV-N: Internal target volumes, consisting of CTV-T / CTV-N with a 5 mm margin, corrected for bony structures.
- PTV-T / PTV-N: Planning target volumes, consisting of ITV-T / ITV-N with a 5 mm margin.

Organs at risk

Bladder, bowel and femoral heads were considered organs at risk during treatment planning.
- Bladder: Entire bladder was delineated, including the urine compartment
- Bowel: The entire “peritoneal cavity” (representing the ”potential” intestinal volume) were delineated along the peritoneal wall, avoiding large vessels, bladder and musculature. The upper border was the CT slice where the L5 discus stopped; though always at least 2 cm cranially for the CTV-E.
- Femoral heads: The bone outline was marked corresponding to the femoral heads and including collum chirurgicum.

Dose prescription and target coverage requirements

Treatment was planned as concomitant boost treatments, with an average dose of 60 Gy to the PTV-T and 50 Gy to the PTV-N, delivered in 30 fractions. The following dose coverage requirements were used:
- 100% of the CTV-T to receive at least 95% of the prescribed dose
- 98% of the PTV-T and the PTV-N to receive at least 95% of the prescribed dose.
- 100% of the PTV-T and the PTV-N to receive at least 90% of the prescribed dose.
- Dose maximum 107% of 60 Gy
- No more than 2% of the PTV-N outside of the PTV-T to receive more than 107% of 50 Gy.

Dose constraints to organs at risk
Target coverage was always prioritized over dose to organs at risk in treatment planning. However, the following dose constraints were aimed for:

- **Bladder**: Volume receiving 45 Gy and above below 75%.
- **Bowel**: Volume receiving 40 Gy and above below 400 cm$^3$, volume receiving 50 Gy and above below 300 cm$^3$.
- **Femoral heads**: Volume receiving 50 Gy and above below 95%.

**Treatment**

Treatment was given once-daily at weekdays, i.e. 5 fractions per week. Overall treatment time was kept at six weeks as far as possible, with a maximum of seven weeks. Cone beam CT was used for position verification for the first three treatment fractions and once weekly thereafter.

**Brachytherapy boost**

The intracavitary brachytherapy boost was delivered as a high dose rate treatment, using an Ir-192 source. The cylindrical applicator had a 2 cm diameter, a single, central channel, and the option of inserting lead shielding into ¼, ½ or ¾ of the circumference to protect the uninvolved part of the rectal mucosa.

A single fraction of 5 Gy was prescribed at a distance of 1 cm from the applicators surface along the length of the applicator to cover the entire length of the tumour.

Tumour extent for brachytherapy treatment planning was assessed in one of two ways:

- Based on clips placed proximally and distally from the tumour prior to brachytherapy, and positioning of clips relative to applicator determined from orthogonal x-rays. This was done for the first 35 patients treated on trial.
- Based on MRI scan of treatment volume with applicator in place, with tumour delineated on MRI. This was done for the final 16 patients treated on trial.

The intracavitary brachytherapy boost was delivered in the final week of external beam treatment. No external radiotherapy treatment was given on the brachytherapy treatment day.
Appendix 3: Response assessment

Final evaluation of tumour response to CRT was six weeks after treatment completion. Patients were allocated to observation if they had no signs of remaining disease, as assessed by clinical examination, endoscopy with biopsies, MRI, and CT.

Endoscopies & biopsies

The strategy of including endoscopy with biopsies was chosen following the results of a previous study, reported at the European Multidisciplinary Colorectal Cancer Congress in Nice, 2010. Ink tattoos surrounding the tumour were placed in the rectal wall at baseline. At least four biopsies were performed at predefined areas within the ink-marked area at 3, 6, 9 and 12 o’clock, and if necessary at point of interest. If an ulcer or erosion persisted they were taken at the edge (at the potentially invasive front).

A small number of patients had unusually good response to the CRT, with no clear target for biopsies at the evaluation six weeks after treatment. For those patients, negative biopsies at week six of treatment were used as evidence of no remaining local disease. See Table a1 below for an overview of biopsy results in weeks 4, 6, and 6 weeks after end of treatment.

Visual inspection of the primary tumour site was performed by endoscopy. A typical patient with evident clinical complete response would have only a small, white scar remaining in the rectal wall; however, a superficial erosion/ulceration was accepted, as long as there were no palpable tumor and negative biopsies.

Tumour regrowth in the rectal lumen was detected by endoscopy during follow-up. Typically, early recurrence presented as a gradually increasing ulceration and firmness of the surrounding tissues. Late recurrence was often initiated by the appearance and gradual growth of adenomatous hyperplasia developing into polypoid tissue growth within or just outside the ink marked area, or by appearance of an increasingly deep and firm ulceration and palpable tumor mass.

Biopsies were performed during follow-up if suspicious lesions in the rectal wall were detected at endoscopy; generally at least two biopsies were taken from or near the centre of the lesion.

MRI and CT

MRI was based on standard institutional preoperative imaging for rectal cancer patients. Diffusion weighted imaging sequences became institutional standard for preoperative patients about half way through the trial, at which point these were included in the evaluation MRI session as well.

Magnetic resonance imaging was primarily used to evaluate the status of regional lymph nodes after CRT. Suspect lymph nodes were considered malignant if their diameter was >5mm. No heterogeneity criteria were used. While primary tumour regression would be reported by the radiologist, and would thus be available to support response evaluation, this was not the purpose of MRIs at this time point, and no patient was allocated to surgery solely due to unclear response of primary tumour on MRI. “Magnetic resonance imaging tumour regression grade” (mTRG) was not in use as a reporting instrument at the time of the trial.

Thorax and abdomen was evaluated for metastatic disease using standard CT imaging.
Table a1: Biopsies during and after treatment

<table>
<thead>
<tr>
<th>Time point</th>
<th>Biopsy results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Week 4 of treatment</strong></td>
<td></td>
</tr>
<tr>
<td>- Remaining tumour cells</td>
<td>23 (45%)</td>
</tr>
<tr>
<td>- No remaining tumour cells</td>
<td>23 (45%)</td>
</tr>
<tr>
<td>- ND</td>
<td>5 (10%)</td>
</tr>
<tr>
<td><strong>Week 6 of treatment</strong></td>
<td></td>
</tr>
<tr>
<td>- Remaining tumour cells</td>
<td>15 (29%)</td>
</tr>
<tr>
<td>- No remaining tumour cells</td>
<td>33 (65%)</td>
</tr>
<tr>
<td>- ND</td>
<td>3 (6%)</td>
</tr>
<tr>
<td><strong>6 weeks after end of treatment</strong></td>
<td></td>
</tr>
<tr>
<td>- Remaining tumour cells</td>
<td>6 (12%)</td>
</tr>
<tr>
<td>- No remaining tumour cells</td>
<td>39 (76%)</td>
</tr>
<tr>
<td>- ND</td>
<td>6 (12%)</td>
</tr>
</tbody>
</table>

ND: Not done. Typical reasons for not performing biopsies were either bleeding (two patients at week 6, one patient 6 weeks after the end of treatment) or no remaining lesion to biopsy (one patient at week 6, four patients at 6 weeks after end of treatment).
Appendix 4: Participating centres

**Vejle Hospital, Vejle, Denmark**

Principle investigator: John Pløen, MD  
*Number of patients:* 38 (out of those, 20 patients were originally referred from outside surgical departments, but were screened for eligibility in the department in Vejle).

**Aalborg University Hospital, Aalborg, Denmark**

Principle investigator: Frank S. Jensen, MD  
*Number of patients:* 9

**Bispebjerg University Hospital, Copenhagen, Denmark**

Principle investigator: Henrik Harling, DMSc  
*Number of patients:* 8