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Endorectal brachytherapy

Evaluation of clinical and endoscopic toxicity after external beam radiotherapy and endorectal brachytherapy in elderly patients with rectal cancer treated in the HERBERT study

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ABSTRACT

Introduction: The HERBERT study evaluated a high-dose-rate endorectal brachytherapy boost (HDREBT) after EBRT in medically inoperable/elderly patients with rectal cancer. The response-rates are promising but not without risk of toxicity. The current analysis provides a comprehensive overview of patient reported, physician reported and endoscopically observed toxicity.

Material and methods: A brachytherapy dose finding study was performed in 38 inoperable/elderly patients with T2-T4N0-1 rectal cancer. Patients received EBRT (13×3 Gy) followed by three weekly HDREBT applications (5–8 Gy). Toxicity was assessed via three methods: patient and physician (CTCAEv3) reported rectal symptoms and endoscopically. Wilcoxon's signed rank test, paired t-test and Spearman's correlation were used.

Results: Patient reported bowel symptoms showed a marked increase at the end of EBRT and two weeks after HDREBT. Acute grade 2 and 3 proctitis occurred in 68.4% and 13.2% respectively while late grade 2 and $\geq$3 proctitis occurred in 48% and 40%. Endoscopic evaluation mainly showed erythema and telangiectasia. In three patients frank haemorrhage or ulceration occurred. Most severe toxicity was observed 12–18 months after treatment.

Conclusion: For elderly patients with rectal cancer, definitive radiotherapy can provide good tumour response but has a substantial risk of toxicity. The potential benefit and risks of a HDREBT boost above EBRT alone must be further evaluated.

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Radiotherapy for rectal cancer is mainly used as preoperative treatment in combination with total mesorectal excision (TME) with the aim of reducing the risk of local recurrence. Although rectal cancer has been regarded as relatively radio-resistant, complete pathologic response after standard neo-adjuvant chemoradiotherapy is observed in approximately 16% [1,2]. In selected centres, with a dedicated watch and wait approach after chemoradiation, complete clinical response rates can be as high as 34–49% due to specific selection criteria [3,4]. Dose–response analyses indicate that higher complete response rates can be achieved with increased radiation doses in rectal cancer [5]. As a result, there is growing interest in organ preservation, avoiding radical TME-surgery altogether.

To increase the chance of a complete response, dose escalation is necessary. This can be achieved by combining external beam radiotherapy (EBRT) with either an EBRT boost or a more locally applied treatment like contact-X-ray or brachytherapy. The last two have been used for small T1/T2 tumours as definitive treatment [6–8] whereas an EBRT boost has mainly been investigated in the preoperative setting in more advanced tumours with the purpose of increasing radical resection rates and sphincter preservation [9]. A combination of EBRT with either contact-X-ray or high dose rate endoluminal brachytherapy (HDREBT) boost has been offered to patients who were medically unfit for surgery as an alternative to palliative treatment [10–12]. However, still little is known about the most optimal dose, and the toxicity profile of this combined external and internal radiotherapy approach.

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The HERBERT study was designed to evaluate the feasibility of adding a HDREBT boost to external beam radiotherapy with the aim to provide durable local tumour control in elderly/medically inoperable patients with rectal cancer. Patients received 39 Gy EBRT in 13 fraction followed by three weekly HDREBT applications using a dose escalation design. The primary endpoint was acute dose limiting toxicity defined as physician reported proctitis grade 3 (CTCAEv3) within 6 weeks after brachytherapy; secondary endpoints included response, survival and toxicity. Although the primary results showed promising response rates of almost 90% and a safe acute toxicity profile in dose levels $\leq$ 7 Gy per fraction, there was considerable late toxicity with approximately one-third of patients experiencing proctitis grade 3 during follow up [13]. Little has been reported on toxicity of endorectal brachytherapy. The aim of the current analysis is to provide a comprehensive overview of the observed toxicity in the HERBERT study using patient and physician reported clinical toxicity and endoscopically observed toxicity.

Material and methods

The HERBERT study, designed as a phase I dose escalation study, was performed at the Leiden University Medical Center and the Netherlands Cancer Institute. Patients with histologically verified adenocarcinoma of the rectum, stage cT2-4N0-1M0-1, who were unfit for or refused surgical treatment were eligible. Details of the study design and methods have been described previously [13]. The study was approved by the medical ethics committee in both centres and informed oral and written consent was obtained from all patients before treatment. The study was registered with the Dutch Central Committee on Research Involving Human Subjects; registration No. NL17037.031.07 [14].

Treatment

Patients were treated with 39 Gy EBRT, delivered in 13 fractions of 3 Gy, 4 days a week followed by three weekly HDREBT applications of 5–8 Gy per fraction. Details on EBRT and HDREBT were previously described [13]. In brief, for HDREBT a flexible applicator (Oncosmart®, Elekta, Veenendaal, The Netherlands) of 2 cm diameter, with 8 peripheral catheters and an inflatable semi-circular balloon, was used. The clinical target volume (CTV) was defined as residual macroscopic tumour or scarring after EBRT which was delineated on a planning-CT scan with the applicator in situ prior to the first brachytherapy application. The aim of treatment planning was complete coverage of the CTV by the 100% isodose. The 100% isodose was restricted to 2 cm from the applicator surface with no hotspots allowed in the surrounding organs. During the course of the study an additional constraint of 400% isodose within the applicator surface was added. HDREBT was performed using a microSelectron HDR afterloader (Elekta, Veenendaal, the Netherlands) with an Iridium-192 source.

Endpoints

Toxicity was assessed using three methods: patient reported symptoms as assessed with questionnaires, clinical proctitis scored by the treating physician according to NCI Common Toxicity Criteria of Adverse Events (CTCAE v3), and endoscopic images of the tumour site and the contralateral rectal wall.

Questionnaires were sent to all patients at 13 time points; at baseline, weekly during EBRT, two and four weeks after EBRT, weekly during HDREBT and two weeks, two months, six months and one year after brachytherapy. The used questionnaire is based on the symptoms mentioned in the RTOG/EORTC GU and GI toxicity scoring systems and has been previously used in studies on toxicity after radiotherapy for prostate cancer (Web Appendix A) [15,16]. Symptoms concerning pain with stools, painful abdominal cramps/urge, tenesmus, mucus discharge, faecal incontinence and bowel function as a general problem were scored in a four point Likert scale; 1. no, not at all; 2. yes, a little; 3. yes, quite a bit; 4. yes, very much. Use of pads for incontinence or soiling and rectal blood loss were scored as 1. no, not at all; 2. yes, 1–2 days a week; 3. yes, more than 2 days a week; 4. yes, every day. Additional questions on bowel function included; faecal consistency, frequency of stools per day and use of medication or dietary changes for bowel symptoms.

Clinical acute dose limiting toxicity (proctitis grade 3 CTCAEv3 within 6 weeks after brachytherapy) was prospectively scored. Additional proctitis scores (CTCAEv3) were collected retrospectively from patient charts. Proctitis grade 1: rectal discomfort, intervention not indicated, grade 2; symptoms not interfering with activities of daily living (ADL); medical intervention indicated, grade 3; stool incontinence or other symptoms interfering with ADL; operative intervention indicated, grade 4; Life threatening consequences (e.g., perforation) [17]. Scores were collected for all time points corresponding to the questionnaires and additionally yearly during further follow-up. The maximum score for each time point was used. For example, the maximum score between 1 and 3 months was assigned to time point 2 months, the maximum score between 3 and 9 months for time point 6 months, the maximum score between 9 and 18 months the time point of 1 year etc.

Late faecal incontinence, rectal bleeding and rectal pain were additionally scored as separate symptoms (CTCAEv3). Maximum score occurring more than 90 days after treatment was documented. Patients with progressive disease were excluded for late proctitis, incontinence, rectal bleeding and rectal pain.

Endoscopic assessment at tumour site was scored by C.M. and E. R. in a 5 point scale; 0. erythema/scarring; 1. superficial ulcer; 2. deep ulcer; 3. very deep ulcer; 4. evident tumour mass (see Fig. 1A). Endoscopic toxicity at the contralateral wall was scored using the endoscopic proctitis assessment scale by Khan et al.; 0. normal mucosa; 1. mild erythema; 2. diffuse erythema and punctate haemorrhage; 3. frank haemorrhage and 4. ulceration (see Fig. 1B) [18].

Endoscopic assessment was done at baseline, prior to brachytherapy, 2 and 6 months after brachytherapy and yearly during follow-up. For correlation of CTCAE with endoscopic toxicity, the CTCAE score at time of endoscopy was used.

Statistical analyses

Statistical analyses were performed with SPSS version 23.0 (IBM, Armonk, NY) and R version 3.3.2 (R Foundation, Vienna, Austria). Median follow-up was calculated using the Kaplan–Meier method. Time was calculated from start of EBRT to last date of clinical follow-up. Descriptive statistics were used for reporting of observed toxicity. Wilcoxon's signed rank test and paired t-test were used for evaluation of patient reported outcomes at different time points. Correlation of patient reported bowel symptoms, proctitis (CTCAEv3) and endoscopic toxicity was assessed using Spearman's correlation. Patient level bootstrapping was applied to correct for multiple measurements per patient. For correlation of CTCAE proctitis with patient reported symptoms a scale was used including questions concerning painful defecation, cramps, tenesmus, mucus, incontinence, blood loss and bowel function as a general problem (Cronbach's alpha = 0.83). To correct for multiple testing, a p-value of <0.01 was considered significant.

Patients who did not receive HDREBT were censored for all analyses from six weeks after EBRT. Patients with stable disease (SD) or progression (PD) were censored for late toxicity ($\geq$90 days after brachytherapy), starting one month prior to documented SD