Endorectal Brachytherapy Boost After External Beam Radiation Therapy in Elderly or Medically Inoperable Patients With Rectal Cancer: Primary Outcomes of the Phase 1 HERBERT Study

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Summary

Elderly frail patients with rectal cancer not suitable for surgery are often treated with palliative radiation therapy with limited response duration. This dose-escalation study evaluated the maximum tolerated endoluminal brachytherapy dose after external beam radiation therapy. The recommended phase 2 brachytherapy dose is 7 Gy per fraction, and this

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Treatment resulted in a high overall response rate, with improved progression-free survival for patients with a complete response.

Introduction

The incidence of rectal cancer in elderly patients is increasing owing to screening and aging of the population (1, 2). Although total mesorectal excision (TME surgery) with or without preoperative radiation(chemo) therapy is the standard treatment for rectal cancer, the risk of surgical complications and postoperative mortality rises with increasing age and comorbidity. Postoperative complications occur in approximately 50% of patients older than 75 years, and 1-month postoperative mortality in patients aged 75 to 95 years with an American Society of Anesthesiology classification of II to IV ranges from 5.4% to 28.0%. At 6 months this results in an overall mortality of 13.4% in patients aged 75 to 85 years, increasing to almost 30% in patients aged 85 to 95 years (3). Because patients who are unfit for surgery are usually also unfit for chemotherapy, they are often offered palliative radiation therapy. However, there are indications that patients might benefit from a more radical approach using radiation therapy alone (4).

To achieve local control with radiation therapy alone, high doses are needed. With standard-dose external beam chemoradiotherapy (EBRT, 45-50 Gy) a complete pathologic response is observed in approximately 16% (5, 6). Dose-response analyses indicate that doses as high as 92 Gy (equivalent dose in 2 Gy per fraction [EQD2]) are needed to achieve a complete pathologic response in 50% of patients (7).

Contact x-ray radiation therapy, initially developed as monotherapy for small mobile tumors, can deliver high doses to the tumor surface and has been used in combination with EBRT in inoperable patients, with promising results (8-11). An alternative to contact X ray is high-dose-rate endorectal brachytherapy (HDREBT), which was originally developed as a preoperative treatment modality (12, 13). Endorectal brachytherapy combined with EBRT in inoperable patients has only been described in a few retrospective series (14-16). Little is known regarding the optimal dose and toxicity profile, and various treatment schedules have been used. The HERBERT study was designed to evaluate the maximum tolerated endoluminal brachytherapy dose after EBRT in inoperable rectal cancer patients, with the aim to provide durable local tumor control. The aim of this analysis was to report both the primary outcome (maximum tolerated dose) and to evaluate tumor response, severe treatment-related late toxicity, and survival.

Methods and Materials

This study was performed at the Netherlands Cancer Institute / Antoni van Leeuwenhoek Hospital, Amsterdam, and the Leiden University Medical Center. Patients were treated with EBRT, followed by 3 weekly HDREBT applications 6 weeks after EBRT (Fig. 1A). The primary outcome was the maximum tolerated HDREBT boost dose. A phase 1 dose-escalation approach, based on an accelerated dose-escalation design by Simon et al (17) was used. Dose-limiting toxicity (DLT) was specified as proctitis grade ≥3 occurring within 6 weeks after brachytherapy (Common Terminology Criteria for Adverse Events, version 3: “stool incontinence or other symptoms interfering with ADL or operative intervention indicated”) (18). Patients were entered in cohorts of 6, starting at 5 Gy per fraction. Dose was increased with 1 Gy per fraction if no more than 1 patient experienced DLT. A dose level was expanded to 9 patients if 2 patients experienced DLT. The maximum delivered dose was reached if 3 patients in 1 dose level experienced DLT. One dose level below this level is considered the maximum tolerated and recommended phase 2 dose. Additional patients were entered in this dose level to assure a safe toxicity profile.

Secondary endpoints were toxicity, clinical tumor response, freedom from local progression, local progression—free survival (L-PFS), and overall survival (OS). The study was approved by the medical ethics committees, and informed 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 (19).

Patient selection

Patients with histologically verified adenocarcinoma of the rectum, stage cT2-4N0-1M0-1, who were unfit for or refused surgical treatment were eligible. Pretreatment evaluation included digital rectal examination, endoscopy, MRI or (if contra-indicated) CT of the pelvis, and endorectal ultrasound on indication. To allow adequate insertion of the
brachytherapy applicator, the tumor had to be within 15 cm of the anal verge and have a lumen of ≥2 cm. To avoid stenosis, tumor involvement of more than two-thirds of the rectal circumference was not allowed. Exclusion criteria were prior pelvic radiation therapy, chemotherapy or surgery for rectal cancer, World Health Organization score ≥3, life expectancy of <6 months, and inability to undergo rectoscopy.

**External beam radiation therapy**

Patients received 39 Gy EBRT (13 × 3 Gy, 4/wk) in the referring hospital. The clinical target volume (CTV) consisted of the gross tumor volume, rectum, mesorectum, and internal iliac and presacral lymph nodes. The cranial border was at the level of S2 to S3 in low-lying tumors or the promontory. Margin from CTV to planning target volume was 1 cm. Treatment was planned and delivered according to institutional guidelines. A minimum of CT-based 3-dimensional conformal radiation therapy was required, but more advanced techniques such as intensity modulated radiation therapy were allowed. Position verification could consist of either cone-beam CT or megavolt/kilovolt orthogonal images. Dose distribution was in accordance with the recommendations of the International Commission on Radiation Units and Measurements report 62.

**Brachytherapy**

Brachytherapy equipment, treatment planning, and positioning procedures were adapted from the McGill University Center (20). Before EBRT, endoluminal clips were inserted with a flexible rectosigmoidoscope at the proximal
and distal end of the tumor for delineation and position verification purposes. A flexible applicator (Oncosmart; Nucletron, Veenendaal, The Netherlands) of 2-cm diameter, with a central canal and 8 peripheral catheters, was inserted into the rectum. To fixate the applicator in the rectum and reduce dose to the contralateral wall, a semicircular balloon was inflated over the applicator on the contralateral side. Delineation and treatment planning were performed on a planning CT with applicator in situ, acquired before the first application. The CTV was defined as residual macroscopic tumor or scarring after EBRT and was delineated by 2 radiation oncologists. In case of discrepancy, consensus was sought for the definitive CTV. Delineation was performed in Pinnacle3, version 9.0 (Philips Medical Systems, Fitchburg, WI) and treatment planning with Oncentra Brachy (Elekta, Veenendaal, The Netherlands), using TG-43 dose calculation. The aim of treatment planning was complete coverage of the CTV by the 100% isodose, restricted to 2 cm from the applicator surface, avoiding hot spots in organs at risk (contralateral rectal wall, anal canal, vagina, bladder, and bowel).

High-dose-rate endorectal brachytherapy was performed using a microSelectron HDR afterloader (Elekta) with an 192Ir source. Verification of correct applicator positioning and determination of the indexer length was done by comparing the reference digitally reconstructed radiograph from the planning CT with anteroposterior and lateral radiographs, taken in treatment position (20).

Follow-up

Follow-up was done at 2 months, 6 months, and yearly after HDREBT. Clinical tumor response was assessed on digital rectal examination and endoscopic evaluation and was classified into 4 categories: complete remission (CR), partial remission (PR; ≥30% decrease), stable disease, and progressive disease (PD; ≥20% increase). Because of limited salvage options in this population, additional investigation such as MRI, biopsies, or imaging for detection of distant metastases were not routinely performed but were left at the discretion of the treating physician. Toxicity was scored according to the Common Terminology Criteria for Adverse Events, version 3. Late treatment-related toxicity was assessed in all patients with CR or PR >90 days after treatment, with censoring in case of progression.

Statistical analyses

Statistical analyses were performed with SPSS version 20.0 (IBM, Armonk, NY). Baseline characteristics between dose levels were compared using 1-way analysis of variance, χ² test, and Fisher exact test. For reporting of DLT and severe late toxicity, descriptive statistics were used. The Kaplan-Meier method and log-rank test were used for actuarial survival estimates. Freedom from local progression was defined as time from start of EBRT to local progression, with censoring at death or date of last follow-up. Local progression—free survival and OS were defined as time from start of EBRT to local progression or death of any cause and death of any cause, respectively.

Results

In total 38 patients were included between 2007 and 2013, of whom 32 were evaluable for toxicity endpoints and 33 for response analyses (Fig. 1B). Patient, tumor, and treatment characteristics are shown in Table 1. Nine patients were treated with 5 Gy per fraction, 5 with 6 Gy, 14 with 7 Gy, and 10 with 8 Gy per fraction. Differences in number of patients per dose level arise from including additional patients in a dose level if the follow-up for the primary endpoint was not yet reached. Additional patients were entered in the 7-Gy dose level after 3 DLTs were observed in the 8-Gy dose level to ensure safety. There were no statistically significant differences between patient characteristics in the different dose levels (Appendix E1; available online at www.redjournal.org). Clinical target volume thickness at brachytherapy (median, 1.0 cm) exceeded 2 cm.

<table>
<thead>
<tr>
<th>Table 1 Patient, tumor, and treatment characteristics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Characteristic</td>
</tr>
<tr>
<td>Total</td>
</tr>
<tr>
<td>Age (y), median (range)</td>
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<tr>
<td>Sex</td>
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<tr>
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<tr>
<td>Female</td>
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<tr>
<td>WHO score</td>
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<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
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<td>Comorbidities</td>
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<td>Anticoagulant use</td>
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<td>TNM classification</td>
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<td>T2N1M0</td>
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</tr>
<tr>
<td>T3N1M0</td>
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<tr>
<td>T3N2M0</td>
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<tr>
<td>Distance from anal verge (cm)</td>
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<td>0-5</td>
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<tr>
<td>5-10</td>
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<tr>
<td>10-15</td>
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<tr>
<td>Brachytherapy CTV, median (range)</td>
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<tr>
<td>Thickness (cm)</td>
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<td>Length (cm)</td>
</tr>
<tr>
<td>Volume (cm³)</td>
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<td>D90 (Gy)</td>
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</tbody>
</table>

Abbreviations: CTV = clinical target volume; WHO = World Health Organization.
in only 2 patients. A CTV D90 of \( >97\% \) of the prescribed dose was achieved in 78\% of patients.

The population consisted mainly of elderly patients (31 of 38 patients aged \( \geq 75 \) years) and/or patients assessed as medically inoperable (29 of 38). Most patients had severe comorbidity, with 31 of 38 patients classified as American Society of Anesthesiology III to IV. Almost all patients who were deemed medically operable but refused surgery were elderly (8 of 9 aged \( >75 \) years).

One patient in the 5-Gy dose level and 3 in the 8-Gy dose level experienced a DLT. Maximum tolerated dose was set at 7 Gy. Details of DLT symptoms and subsequent course are summarized in Table 2.

### Response and survival

At time of analysis, 11 of 33 evaluable patients were alive with a median follow-up of 30 months (range, 21-86 months), of whom 8 were in complete remission at last follow-up. Clinical tumor response was observed in 29 of 33 patients (87.9\%); 20 patients achieved CR and 9 PR. A recurrence developed in 6 of 20 patients with CR, whereas 6 of 9 patients with PR showed progression. Seventeen patients (51.5\%) had a sustained response.

Median time to local progression was 9.3 months (range, 4-32 months), and actuarial freedom from local progression at 1, 2, and 3 years was 71\%, 55\%, and 44\%, respectively. Figure 2 shows the clinical tumor response and OS for evaluable patients (Appendix E2; available online at www.redjournal.org; all patients per dose level). Local progression—free survival rates at 1, 2, and 3 years were 64\%, 42\%, and 20\%, and corresponding OS rates were 82\%, 63\%, and 27\%, respectively, with a median OS of 33.2 months (95\% confidence interval 30.5-36.0 months).

For patients with a complete response, L-PFS was significantly improved in comparison with those with no or partial response, which corresponded with a trend in improved OS (Fig. 3).

#### Late toxicity

In total, 28 of 32 patients had a response to treatment and were evaluable for analyses of late severe toxicity. Nine patients (33\%) experienced grade 3 toxicity, and 1 patient (4\%) experienced grade 4 toxicity; these toxicities are detailed in Table 3. In 6 patients, who all used anticoagulants, rectal bleeding grade 3 was observed. Four patients experienced severe rectal pain, which was caused by a deep ulcer at the tumor site.

### Discussion

The aim of this study was to evaluate tolerability and effectivity of HDREBT after EBRT in elderly or medically inoperable patients with rectal cancer. In this dose-escalation study, the maximum tolerated and therefore recommended phase 2 dose was set at 7 Gy per fraction. Overall response rate was 88\%, with 61\% of patients achieving CR. A sustained response was obtained in 52\% of patients. Severe late toxicity was seen in 10 of 32 patients, of which rectal blood loss, associated with the use of anticoagulants, was most frequently observed. In this population of mainly elderly and medically inoperable patients, OS was 64\% at 2 years, with a median OS of 33 months.

The HERBERT study is, to our knowledge, the first prospective dose-finding study evaluating toxicity, response, and survival after a combination of HDREBT and EBRT. Results indicate that this treatment is feasible in medically inoperable patients with a T2-T3 tumor and can provide durable L-PFS. Few retrospective series have used HDREBT or contact x-ray therapy in combination with EBRT (9-11, 14, 15, 21).

Corner et al (15) described a cohort of 52 inoperable patients (median age, 82 years) treated with 6 \( \times \) 6 Gy HDREBT or chemoradiation with a HDREBT boost of 2 \( \times \) 6 Gy. High-dose-rate endorectal brachytherapy was prescribed at 1 cm from the applicator surface using a single channel applicator with optional shielding. Complete response was seen in 56\% and PR in 27\% of patients. Late toxicity occurred in 6 patients (3 rectal ulcers, 2 strictures, and 1 colovesical fistula). Median OS was 18 months (15).

Aumock et al (11) reported the outcome of 199 patients with a T1-T3 tumor treated with EBRT (45-48 Gy) and contact therapy (median surface dose, 60 Gy in 2 fractions; range, 45-120 Gy). Excellent control was achieved in T1 (100\%) and mobile T2 (85\%) lesions, and a CR was seen in 58\% of patients with a fixed T2 or T3 tumor. Transitory proctitis occurred in 19 patients, of whom 2 patients required blood transfusion (11).

A historical overview of all patients treated with contact X ray in France between 1980 and 2012 describes a subgroup of 120 patients with T2-T3 tumors treated with contact X ray followed by (chemo)radiation. Median contact X ray surface dose was 85 Gy in 3 fractions, and EBRT schedules used were 39 Gy (13 \( \times \) 3 Gy), with optional...
boost to 43 Gy, and 50 Gy (25 × 2 Gy). In case of incomplete response, additional interstitial brachytherapy or local resection was performed. The overall CR rate was 94%, with a 3-year OS of 60%. Local recurrence occurred in 26 of 113 patients, with a median time to recurrence of 16 to 17 months. Rectal bleeding was observed in 50% to 70%, with grade 3 rectal bleeding in 10 patients (10).

The first 2 studies show very similar response rates, in populations comparable to that in our study. The third study was performed in slightly younger patients, and treatment was intensified when necessary, resulting in higher response rates.

In the last decade, dose escalation in rectal cancer has also been a topic of interest in patients with locally advanced rectal cancer and in organ-preservation strategies (21-28). A recent study showed excellent results after combined EBRT (60 Gy; simultaneous integrated boost) with an endorectal brachytherapy boost (5 Gy) in patients with T2-3 rectal cancer. A CR rate of 78% was observed in 51 evaluable patients, with a sustained response of 52% at 2 years. Most common late toxicity was rectal bleeding (7% grade 3) (28). This study shows the high potential of a nonsurgical approach in well-selected fit patients. This approach with intensified chemoradiotherapy and optional salvage surgery is, however, not feasible in our population.

All studies observed a lower rate in severe late toxicity compared with the present study. There are several possible explanations. First, the retrospective nature might have led to underreporting of toxicity. Second, favorable criteria for contact X ray include tumors with a limited diameter (<3 cm), leading to smaller irradiated volumes. In addition, the high rate of comorbidity, with 65% of patients using anticoagulants, might result in a higher risk of severe rectal bleeding. Furthermore, the total biologic equivalent doses differ between studies. In the HERBERT study, an EBRT schedule of 39 Gy in 13 fractions (EQD2 46.8 Gy, α/β = 3) was selected, which is somewhat higher in comparison with 45 Gy in 25 fractions (EQD2 43.2 Gy). On the other hand, this schedule seems to be safe in the extensive French experience (10, 29). The brachytherapy dose was higher in the present study compared with other HDR series and prescribed to the circumferential CTV margin, instead of 1 cm from the applicator. However, besides tumor thickness, air or feces can increase the distance between the applicator and the circumferential margin of the CTV, hampering optimal coverage. During the course of the study, being aware of the high applicator surface dose when planning at 2 cm, an additional constraint of 400% at the applicator surface was added. In contact X ray, a dose of 30 Gy to the surface results in approximately 10 Gy at 1-cm depth (30), which is more comparable to the HDR dose in

Fig. 2. Response and overall survival. Abbreviations: CR = complete response; DLT = dose-limiting toxicity; PD = progressive disease; PR = partial response; SD = stable disease. *Two patients received salvage surgery. †Deceased.
this cohort. However, the treatment volume with contact therapy is often smaller, and no dose is delivered to the contralateral wall. Future use of additional balloon spacing, shielding, daily image guidance, and MRI during brachytherapy can further improve conformal dose delivery, with increased sparing of organs at risk (31-34).

Overall survival is difficult to interpret in this mainly elderly population with severe comorbidity. A median OS of 33 months was favorable compared with the series described by Corner et al (15) (median OS 18 months). A subgroup analysis excluding patients younger than 75 years found similar L-PFS and OS compared with the total population. When CR was achieved, a significant improvement was seen in L-PFS at 2 years (60% vs 15%) and a trend in OS (80% vs 46%). Overall survival was, however, not significantly improved owing to other causes of death. The alternative

Fig. 3. Overall survival (OS) and local progression–free survival (PFS) with subgroup analyses for patients with a complete response. (A) Local progression–free survival (n = 33). (B) Overall survival (n = 38). (C) Local progression–free survival: comparison complete response versus no complete response (n = 33). (D) Overall survival: comparison complete response versus no complete response (n = 33). Abbreviation: CI = confidence interval.
treatment for our study population is palliative radiation therapy, which is effective for symptom palliation (56%-100%) but with variable duration (1 to >44 months) (35). Complete clinical response after 40 to 60 Gy is reported in 30%, ranging from 49% in mobile tumors to 9% in fixed tumors, whereas a sustained response is rare (78% recurrence after CR) (36). However, the value of a more durable response with a brachytherapy boost has to be weighed against increased treatment burden and more toxicity in a population with limited OS.

A dose-escalation design in radiation therapy has clear limitations because evaluation of late toxicity requires long-term follow-up. Acute proctitis was used as a surrogate for late toxicity (37). Although all patients with DLT developed severe late toxicity, also patients with grade 1 to 2 acute toxicity experienced severe late toxicity, indicating the limitation of this surrogate endpoint.

Another limitation is the difficulty of predicting CR on the basis of endoscopy and digital rectal examination (38, 39). Response assessment at first evaluation was often uncertain, and additional assessments over time usually clarified the course of disease. Biopsies or MRI were only performed if there were clinical implications.

In conclusion, HDREBT after EBRT offers a high response rate of almost 90%, with approximately 60% CR and a significantly improved L-PFS in patients with a CR. However, a high rate of grade 3 toxicity was observed, with a clear correlation to comorbidity. This suggests that patient selection might be at least as important in preventing severe toxicity as the delivered dose. Further correlation of patient,

<table>
<thead>
<tr>
<th>Dose</th>
<th>Severe late toxicity (&gt;90 d, maximum score)</th>
<th>Proctitis grade 3 &lt;6 wk</th>
<th>Response</th>
<th>Time (mo)*</th>
<th>Anticoagulant use</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 Gy</td>
<td>Grade 3: Proctitis limiting ADL&lt;br&gt;Symptoms: Pain, frequency, and fatigue&lt;br&gt;FU: PD at 7 mo, proctitis grade 2</td>
<td>Yes</td>
<td>PR</td>
<td>1 †</td>
<td>Acenocoumarol</td>
</tr>
<tr>
<td>8 Gy</td>
<td>Grade 3: Rectal bleeding&lt;br&gt;Symptoms: Hospital admission at 1 mo; blood transfusion at 5 mo&lt;br&gt;FU: PD at 9 mo after HDREBT</td>
<td>Yes</td>
<td>CR</td>
<td>1 †</td>
<td>Carbasalate calcium</td>
</tr>
<tr>
<td>8 Gy</td>
<td>Grade 3: Proctitis limiting ADL&lt;br&gt;Symptoms: Pain; opioids needed, and rectal bleeding&lt;br&gt;FU: Improvement at 7 mo (gr 1-2 bleeding persisted)</td>
<td>Yes</td>
<td>PR</td>
<td>1 †</td>
<td>Carbasalate calcium</td>
</tr>
<tr>
<td>5 Gy</td>
<td>Grade 3: Proctitis limiting ADL&lt;br&gt;Symptoms: Pain and incontinence&lt;br&gt;FU: Salvage surgery at 8 mo for PD</td>
<td>No</td>
<td>PR</td>
<td>2 †</td>
<td>-</td>
</tr>
<tr>
<td>7 Gy</td>
<td>Grade 3: Rectal bleeding&lt;br&gt;Symptoms: Blood transfusion at 5 mo&lt;br&gt;FU: PD with severe rectal bleeding at 10 mo</td>
<td>No</td>
<td>PR</td>
<td>5</td>
<td>Phenprocoumon</td>
</tr>
<tr>
<td>7 Gy</td>
<td>Grade 3: Rectal bleeding&lt;br&gt;Symptoms: Blood transfusion at 6 mo (Hb 3.1)&lt;br&gt;FU: Grade 1 to 2 proctitis</td>
<td>No</td>
<td>CR</td>
<td>6</td>
<td>Carbasalate calcium</td>
</tr>
<tr>
<td>7 Gy</td>
<td>Grade 3: Proctitis limiting ADL&lt;br&gt;Symptoms: Urgency, frequency, and tenesmus&lt;br&gt;Treatment: Multiple medical interventions&lt;br&gt;FU: Gr 2 proctitis; PD at 21 mo for which a palliative stoma</td>
<td>No</td>
<td>CR</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>7 Gy</td>
<td>Grade 4: Ulceration and rectocutaneous fistula&lt;br&gt;Symptoms: Pain, fatigue, rectal bleeding (transfusion)&lt;br&gt;Treatment: Specialized wound care and HBOT&lt;br&gt;FU: Slight improvement, but fistula persisted (gr 3)</td>
<td>No</td>
<td>CR</td>
<td>12</td>
<td>-</td>
</tr>
<tr>
<td>7 Gy</td>
<td>Grade 3: Rectal bleeding&lt;br&gt;Symptoms: Blood transfusion at 19 mo (Hb 3.5)&lt;br&gt;FU: Grade 1 rectal bleeding</td>
<td>No</td>
<td>CR</td>
<td>19</td>
<td>Phenprocoumon</td>
</tr>
<tr>
<td>8 Gy</td>
<td>Grade 3: Rectal bleeding&lt;br&gt;Symptoms: Blood transfusion at 21 mo (possible interference of coecum tumor (Hb 3.5)&lt;br&gt;FU: Grade 1 to 2 rectal bleeding</td>
<td>No</td>
<td>CR</td>
<td>21</td>
<td>Phenprocoumon</td>
</tr>
</tbody>
</table>

* All time points in this table were calculated from end of treatment.
† Onset of grade 3 proctitis <90 days, but symptoms persisted >90 days.

**Abbreviations:** ADL = activities of daily living; CR = complete response; FU = follow-up; Hb = hemoglobin; HBOT = Hyperbaric oxygen therapy; HDREBT = high-dose-rate endorectal brachytherapy; PD = progressive disease; PR = partial response.
tumor, and treatment characteristics with clinical outcomes will be performed, to improve future patient selection and treatment objectives. Future studies should focus on weighing the risks and benefits of a brachytherapy boost in elderly and/or inoperable patients. A proposed study design would be to randomize patients to EBRT with or without HDREBT, with symptom relief, patient-reported quality of life, and survival as the main endpoints.

References


