Endorectal brachytherapy boost after external beam radiotherapy in elderly or medically inoperable patients with rectal cancer: primary outcomes of the phase I HERBERT study

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Abstract

Purpose

This study evaluated toxicity and efficacy of the combination of external beam radiotherapy (EBRT) followed by high dose rate endorectal brachytherapy (HDREBT) boost in elderly and medically inoperable patients with rectal cancer.

Material and Methods

A phase I dose escalation study was performed. Treatment consisted of EBRT (13x3 Gy) followed by three weekly brachytherapy applications six weeks later. HDREBT dose started at 5 Gy per fraction, increasing with 1 Gy per fraction if dose limiting toxicity (DLT, defined as $\geq$ grade 3 proctitis < 6 weeks after HDREBT) occurred in ≤ 2 patients per dose level. The primary endpoint was the maximum tolerated dose, defined as one dose-level below the dose were three patients experienced DLT. Secondary endpoints were severe treatment-related late toxicity, clinical tumor response, freedom from local progression (FFLP) and local progression free and overall survival (L-PFS and OS).

Results

Thirty-eight patients with a median age of 83 years were included in the study. Thirty-two were evaluable for DLT and late toxicity and 33 for response evaluation. Maximum delivered dose was 8 Gy per fraction resulting in a recommended dose of 7 Gy per fraction. Response occurred in 29 of 33 patients (87.9%) with 60% complete response (CR). L-PFS and OS were 42% and 63% at two years. Patients with CR showed a significant improved L-PFS (60% at 2 yrs, p=0.006) and a trend in improved OS (80% at 2 yrs, p=0.11). Severe late toxicity occurred in 10/32 patients.

Conclusion

HDREBT after EBRT results in a high overall response rate, with improved local progression free survival for patients with a CR. The high observed rate of severe late toxicity requires further evaluation of the risks and benefits of a HDREBT boost.

Introduction

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

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

Contact-X-ray radiotherapy, 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 pre-operative treatment modality.(12, 13) Endorectal brachytherapy combined with EBRT in inoperable patients has only been described in 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 is to report both the primary outcome (maximum tolerated dose) and to evaluate tumor response, late toxicity and survival.

Material and methods

This study was performed at X and X. Patients were treated with EBRT, followed by three weekly HDREBT applications six weeks after EBRT (figure 1A). The primary outcome was the maximum tolerated HDREBT boost dose. A phase I dose escalation approach, based on an accelerated dose escalation design by Simon et al. was used.(17) Dose limiting toxicity (DLT) was specified as proctitis grade ≥ 3 occurring within 6 weeks after brachytherapy (CTCAE v3; 'stool incontinence or other symptoms interfering with ADL or operative intervention indicated').(18) Patients were entered in cohorts of six, starting at 5 Gy per fraction. Dose was increased with 1 Gy per fraction if no more than one patient experienced DLT. A dose level was expanded to nine patients if two patients experienced DLT. The maximum delivered dose was reached if three patients in one dose level experienced DLT. One dose level below this level is considered the maximum tolerated and recommended phase II 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 (FFLP), 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. Pre-treatment evaluation included digital rectal examination, endoscopy, MRI or (if contra-indicated) CT of the pelvis

and endorectal ultrasound (EUS) 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 > 2/3 of the rectal circumference was not allowed. Exclusion criteria were; prior pelvic radiotherapy, chemotherapy or surgery for rectal cancer, WHO score ≥ 3, life-expectancy of < 6 months and inability to undergo rectoscopy.

External beam radiotherapy

Patients received 39Gy EBRT (13x3 Gy, 4/week) 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-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 3D-conformal radiotherapy was required, but more advanced techniques as intensity modulated radiotherapy was allowed. Position verification could consist of either cone-beam-CT or megavolt/kilovolt orthogonal images. Dose distribution was in accordance to the recommendations of the International Commission on Radiation Units and Measurements (ICRU-62).

Brachytherapy

Brachytherapy equipment, treatment planning and positioning procedures were adapted from the McGill university center.(20) Prior to EBRT, endoluminal clips were inserted with a flexible recto-sigmoidoscope 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 semi-circular balloon was inflated over the applicator on the contralateral side. Delineation and treatment planning was 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 two 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, Wisconsin U.S.A) 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 hotspots in organs at risk (contralateral rectal wall, anal canal, vagina, bladder and bowel).

HDREBT was performed using a microSelectron HDR afterloader (Elekta, Veenendaal, the Netherlands) with an Iridium-192 source. Verification of correct applicator positioning and determination of the indexer length was done by comparing the reference DRR from the planning-CT with anteroposterior and lateral radiographs, taken in treatment position.(20)

Follow up

Follow-up was done at two months, six months and yearly after HDREBT. Clinical tumor response was assessed on digital rectal examination and endoscopic evaluation and was classified in four categories; complete remission (CR), partial remission (PR; $\geq$30% decrease), stable disease (SD) and progressive disease (PD; $\geq$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 CTCAE v3. 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 v20.0. Baseline characteristics between dose levels were compared using the one-way ANOVA, Chi-square and Fisher's exact test. For reporting of dose limiting toxicity and severe late toxicity, descriptive statistics were

used. The Kaplan Meier method and log rank test were used for actuarial survival estimates. FFLP was defined as time from start of EBRT to local progression, with censuring at death or date of last follow-up. L-PFS and OS were was 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 (Figure 1B). Patient, tumor and treatment characteristics are shown in Table I. Nine patients were treated with 5 Gy per fraction, five 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 7Gy dose level after three DLTs were observed in the 8Gy dose level to assure safety. There were no statistically significant differences between patient characteristics in the different dose levels (web appendix A). CTV thickness at brachytherapy (median 1.0 cm) exceeded 2 cm in only two patients. A CTV D90 of >97% of the prescribed dose was achieved in 78% of patients.

The population consisted mainly of elderly patients (31/38 patients ≥ 75 years), and/or patients assessed as medically inoperable (29/38). Most patients had severe co-morbidity, with 31/38 patients classified as ASA III-IV. Almost all patients who were deemed medically operable but refused surgery were elderly (8/9 > 75 years).

One patient in the 5 Gy dose level and three in the 8 Gy dose level experienced dose limiting toxicity. Maximum tolerated dose was set at 7Gy. Details of DLT symptoms and subsequent course are summarized in Table II.

Response and Survival

At time of analysis 11/33 evaluable patients were alive with a median follow up of 30 months (range 21-86), of whom 8 were in complete remission at last follow-up. Clinical tumor response was observed in 29/33 patients (87.9%); 20 patients achieved CR and nine PR. A recurrence developed in 6/20 patients with CR, while 6/9 patients with PR showed progression. Seventeen patients (51 %) had a sustained response .

Median time to local progression was 9.3 months (range 4-32) and actuarial FFLP at 1, 2 and 3 years was 71%, 55 % and 44% respectively. Figure 2 shows the clinical tumor response and overall survival for evaluable patients (web appendix B; all patients per dose level). L-PFS rates at 1, 2 and 3 years were 63%, 42% and 20%, and corresponding OS rates were 81%, 63% and 26%, respectively, with a median overall survival of 33.2 months (95%CI 30.5-36.0).

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

Late toxicity

In total 27/32 patients had a response to treatment and were evaluable for analyses of late severe toxicity. Nine patients (33%) experienced grade 3 toxicity and one patient (4%) experienced grade 4 toxicity, these toxicities are detailed in Table III. In six 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 maximal tolerated and therefore recommended phase II dose was set at 7 Gy per fraction.

Overall response rate was 88%, with 60% of patients achieving CR. A sustained response was obtained in 51% patients. Severe late toxicity was seen in 10/32 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, overall survival was 63% at two 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 local progression free survival. Few retrospective series have used HDREBT or contact-X-ray therapy in combination with EBRT.(9-11, 14, 15, 21)

Corner et al. described a cohort of 52 inoperable patients (median age 82) treated with 6x6 Gy HDREBT or chemoradiation with a HDREBT boost of 2x6 Gy. HDREBT was prescribed at 1 cm from the applicator surface using a single channel applicator with optional shielding. CR was seen in 56% and PR in 27% of patients. Late toxicity occurred in six patients (three rectal ulcers, two strictures and one colovesical fistula). Median OS was 18 months.(15)

Aumock et al. reported the outcome of 199 patients with a T1-T3 tumor, treated with EBRT (45-48 Gy) and contact therapy (median surface dose: 60Gy in 2 fractions; range 45-120). 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 two patients required blood transfusion.(11)

A historical overview of all patients treated with contact-X-ray in France between 1980-2012 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 (13x3 Gy), with optional boost to 43 Gy, and 50 Gy (25x2 Gy). In case of incomplete response, additional interstitial BT or local resection was performed. Overall CR rate was 94% with a 3-year OS of 60%. Local recurrence occurred in 26/113

patients with a median time to recurrence of 16-17 months. Rectal bleeding was observed in 50-70% with grade 3 rectal bleeding in 10 patients.(10)

The first two studies show very similar response rates, in populations comparable to 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 two years. Most common late toxicity was rectal bleeding (7% grade 3).(28) This study shows the high potential of a non-surgical 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 to the present study. There are several possible explanations. First, the retrospective nature might have led to underreporting of toxicity. Secondly, 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 co-morbidity, with 65% of patients using anti-coagulants, 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 39Gy in 13 fractions (EQD2 46.8 Gy, $\alpha/\beta=3$) was selected, which is somewhat higher in comparison to 45Gy in 25 fractions (EQD2 43.2 Gy). On the other hand, this schedule appears safe in the extensive French experience.(10, 29) The brachytherapy dose was higher in the present study compared to 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 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 overall survival of 33 months was favorable compared to the series described by Corner et al. (median OS 18 months). A subgroup analysis excluding patients younger than 75 years found similar L-PFS and OS compared to the total population. When CR was achieved, a significant improvement was seen in L-PFS at two years (60% vs 15%) and a trend in OS (80% vs 46%). Overall survival was however not significantly improved due to other causes of death. The alternative treatment for our study population is palliative radiotherapy, which is effective for symptom palliation (56-100%), but with variable duration (1 to >44 months).(35) Complete clinical response after 40-60 Gy is reported in 30%, ranging from 49% in mobile tumors to 9% in fixed tumors, while 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 weighted against increased treatment burden and more toxicity in a population with limited overall survival.

A dose escalation design in radiotherapy 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 1-2 acute toxicity experienced severe late toxicity, indicating the limitation of this surrogate endpoint.

Another limitation is the difficulty of predicting CR based on endoscopy and digital rectal examination.(38, 39) Response assesment at first evaluation was often uncertain and additional assesments 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 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 co-morbidity. This suggests that patient selection might be at least as important in preventing severe toxicity as the delivered dose. Further correlation of patient, tumor and treatment characteristics with clinical outcomes will be performed in order 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 between EBRT with or without HDREBT with symptom relieve, patient reported quality of life and survival as the main endpoints.

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Figure legends

Figure 1: Study period (A) and flowchart (B)

HDRBT/BT: high dose rate brachytherapy, EBRT: external beam radiotherapy, FU: follow-up, DLT: dose limiting toxicity

1. Patient refused brachytherapy after a period of dehydration and hospital admission after EBRT
2. Patient died of cardiac arrest, not related to treatment
3. Two other patients deceased of pulmonary causes (not related to treatment), both had cCR based on endoscopies during treatment or autopsy and were included in response evaluation.
4. Patient was included in analyses of late toxicity.

Figure 2: Response and overall survival.

DLT: dose limiting toxicity; † diseased.

* Two patients received salvage surgery.

Figure 3: Overall and local progression free survival with sub-group 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 vs no complete response n=33
D. Overall survival: comparison complete response vs no complete response n=33

Table I. Patient, tumor and treatment characteristics

	n	%
Total	38	100%
Age (median range)	83	(57-94)
Gender		
▪ Male	21	55.3%
▪ Female	17	44.7%
WHO		
▪ WHO 0	4	11.8%
▪ WHO 1	15	44.1%
▪ WHO 2	15	44.1%
Co-morbidities		
▪ Cardiovascular co-morbidity	27	71.1%
▪ Pulmonary co-morbidity	12	31.6%
▪ Anticoagulant use	25	65.8%
TNM classification		
▪ T2N0M0	22	57.9%
▪ T2N1M0	1	2.6%
▪ T3N0M0	5	13.2%
▪ T3N1M0	8	21.1%
▪ T3N2M0	2	5.3%
Distance from anal verge		
▪ 0-5 cm	19	50.0%
▪ 5-10cm	13	34.2%
▪ 10-15cm	6	15.8%
Brachytherapy CTV	*median*	*range*
▪ Thickness (cm)	1.0	(0.4-3.0)
▪ Length (cm)	3.2	(1.8-6.4)
▪ Volume (cc)	7.1	(2.0-25.0)
▪ D90 (Gy)	7.1	(1.8-9.8)

Table II. Dose limiting toxicity

Dose level	Dose limiting toxicity	Severe late toxicity
5 Gy	Proctitis limiting ADL; Pain, frequency and fatigue	Yes*
8 Gy	Rectal bleeding; Hospital admission; blood transfusion	Yes*
8 Gy	Proctitis limiting ADL: Pain (opioids needed); rectal bleeding gr 2.	Yes*
8 Gy	Proctitis limiting ADL. Pain, tenesmus and frequency.	Censored; PD

ADL: Activities of daily living, gr: grade, PD; progressive disease.
* acute proctitis did not resolve < 90 days and was also scored as severe late toxicity (table III).

Dose	Severe late toxicity (>90 days, maximum score)	Proctitis grade 3 < 6 wks	Response	Time *	Anticoagulant use
5 Gy	Grade 3: Proctitis limiting ADL *Symptoms:* Pain, frequency and fatigue *FU:* PD at 7 months, proctitis grade 2.	yes	PR	1 month†	Acenocoumarol
8 Gy	Grade 3: Rectal bleeding *Symptoms:* Hospital admission at 1 month; blood transfusion at 5 months. *FU:* PD at 9 months after HDREBT.	Yes	CR	1 month†	Carbasalate calcium
8 Gy	Grade 3: Proctitis limiting ADL *Symptoms*: Pain; opioids needed and rectal bleeding. FU: Improvement at 7 months (gr 1-2 bleeding persisted)	yes	PR	1 month†	Carbasalate calcium
5 Gy	Grade 3: Proctitis limiting ADL *Symptoms:* Pain and incontinence *FU:* Salvage surgery at 8 months for PD.	no	PR	2 months†	-
7 Gy	Grade 3: Rectal bleeding *Symptoms:* Blood transfusion at 5 months. *FU:* PD with severe rectal bleeding at 10 months.	no	PR	5 months	Phenprocoumon
7 Gy	Grade 3: Rectal bleeding *Symptoms:* Blood transfusion at 6 months (Hb 3.1) *FU:* Grade 1-2 proctitis	no	CR	6 months	Carbasalate calcium
7 Gy	Grade 3: Proctitis limiting ADL *Symptoms:* Urgency, frequency and tenesmus *Treatment:* Multiple medical interventions. *FU:* Gr 2 proctitis; PD at 21 months for which a palliative stoma	no	CR	8 months	-
7 Gy	Grade 4: Ulceration and rectocutaneous fistula *Symptoms:* Pain, fatigue, rectal bleeding (transfusion) *Treatment:* Specialized wound care and HBOT. *FU:* Slight improvement, but fistula persisted (gr 3)	no	CR	12 months	-
7 Gy	Grade 3: Rectal bleeding *Symptoms:* Blood transfusion at 19 months (Hb 3.5) *FU:* Grade 1 rectal bleeding	no	CR	19 months	Phenprocoumon
8 Gy	Grade 3; Rectal bleeding Symptoms: Blood transfusion at 21 months (possible interference of coecumtumor (Hb3.5). FU: Grade 1-2 rectal bleeding	no	CR	21 months	Phenprocoumon

*All time points in this table were calculated from end of treatment.

† Onset of grade 3 proctitis <90 days, but symptoms persisted >90 days.

ADL: activities of daily living, CR; complete response, PR; Partial response, PD; Progressive disease, FU; follow-up

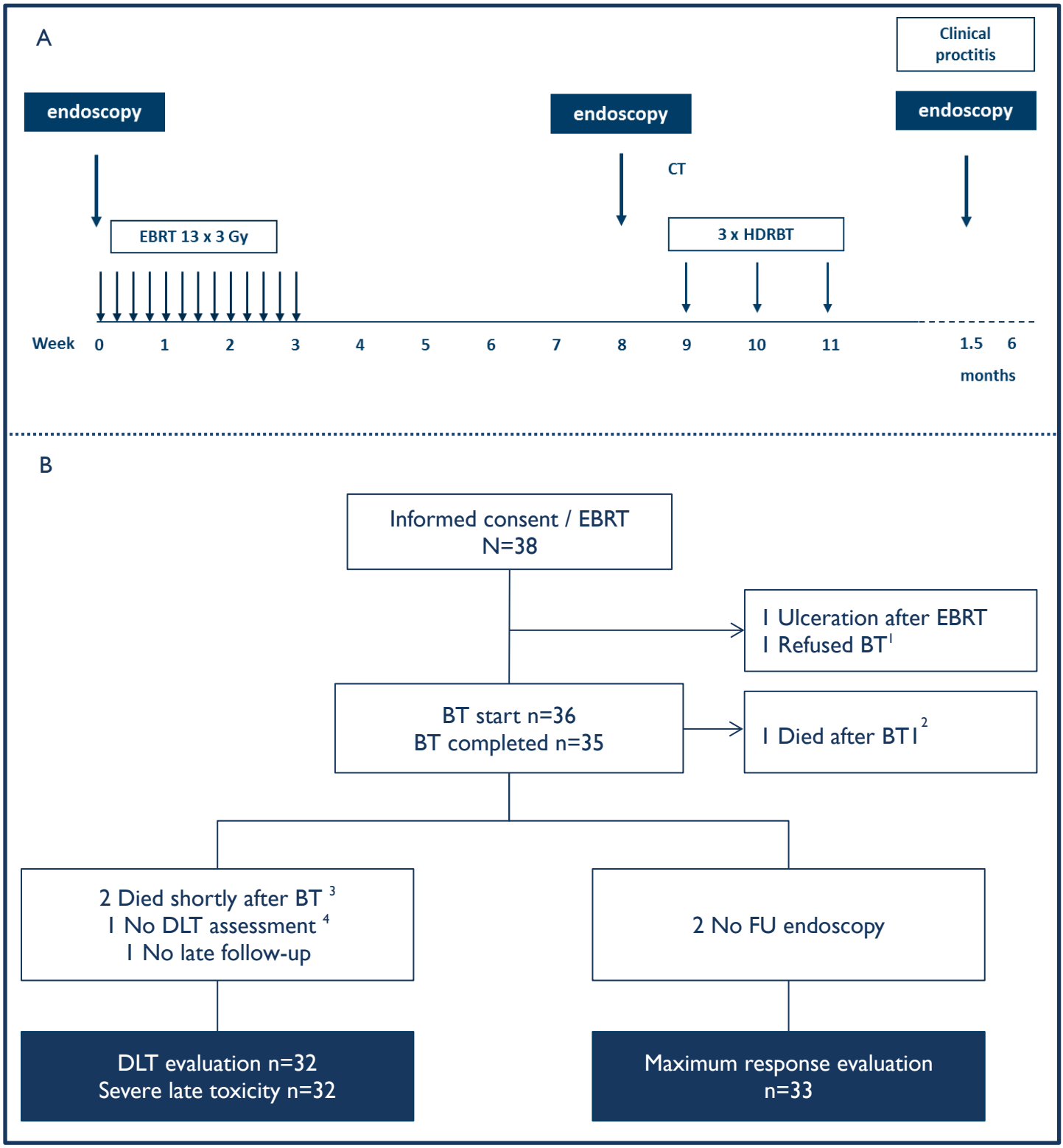

Figure 1: Study period (A) and flowchart (B)

HDRBT/BT: high dose rate brachytherapy, EBRT: external beam radiotherapy, FU: follow-up, DLT: dose limiting toxicity

1. Patient refused brachytherapy after a period of dehydration and hospital admission after EBRT
2. Patient died of cardiac arrest, not related to treatment
3. Two other patients deceased of pulmonary causes (not related to treatment), both had cCR based on endoscopies during treatment or autopsy and were included in response evaluation.
4. Patient was included in analyses of late toxicity.

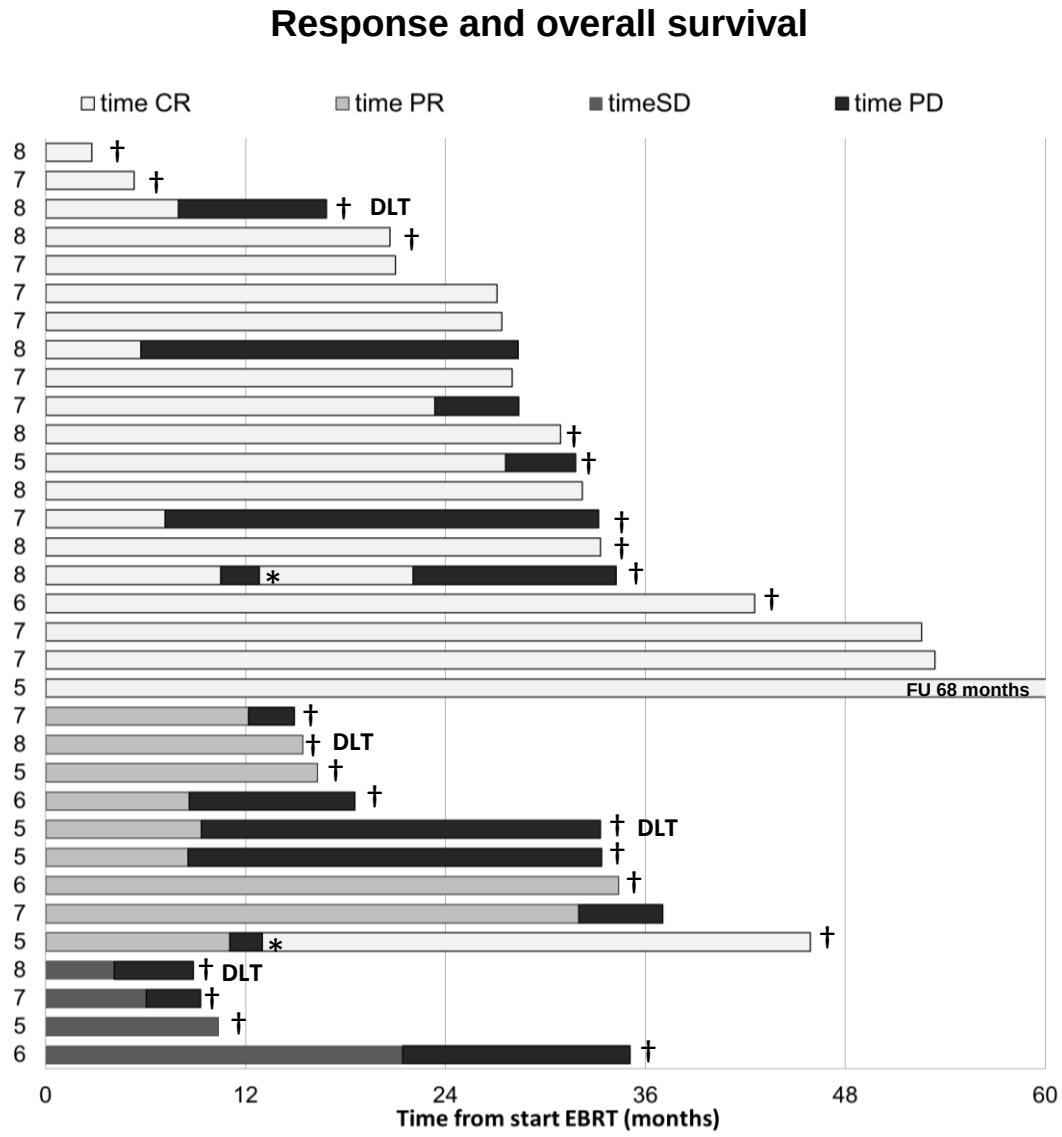

Figure 2: Response and overall survival.

DLT: dose limiting toxicity; † diseased.

* Two patients received salvage surgery.

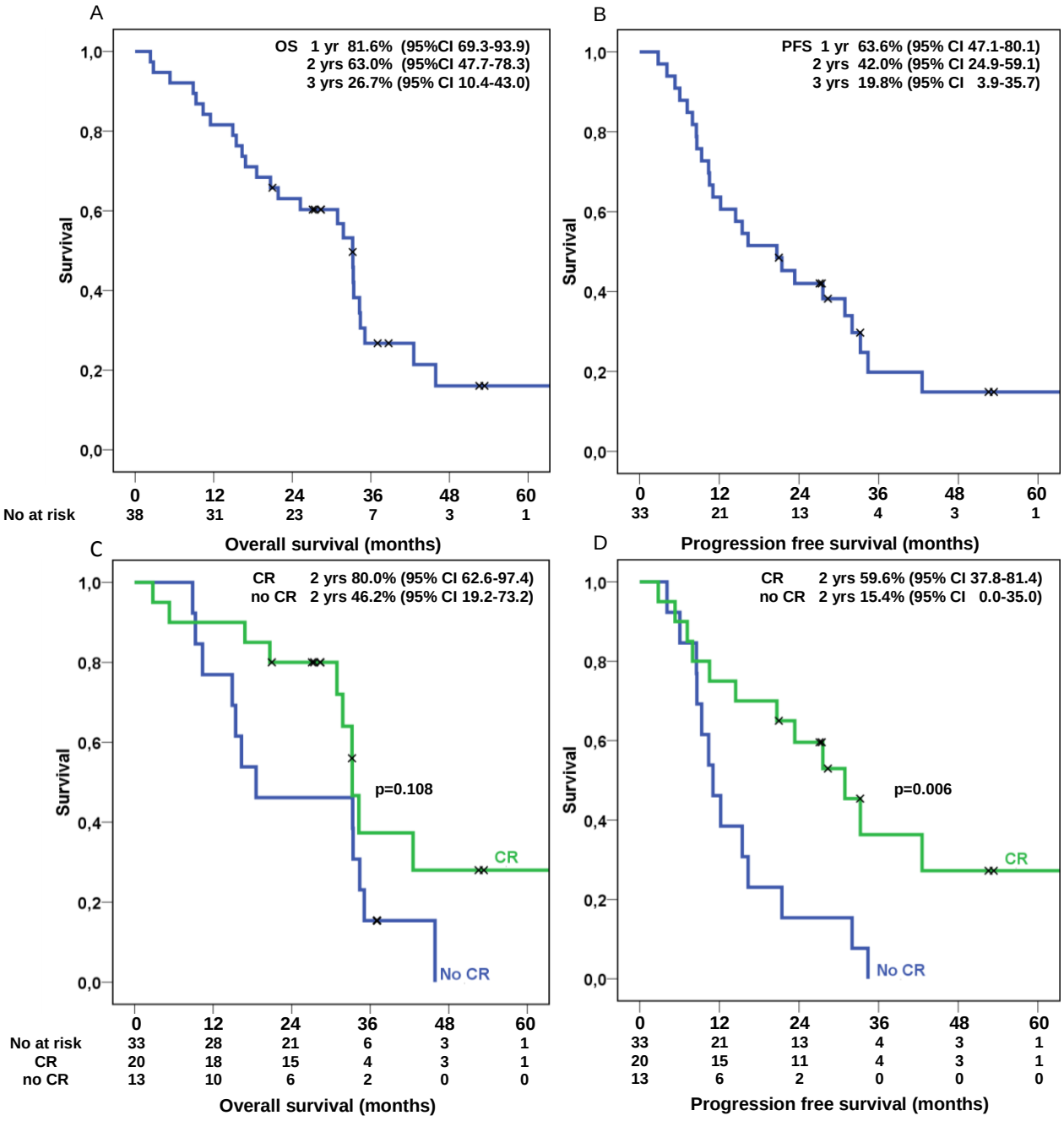

Figure 3: Overall and local progression free survival with sub-group analyses for patients with a complete response.

A. Overall survival N=38
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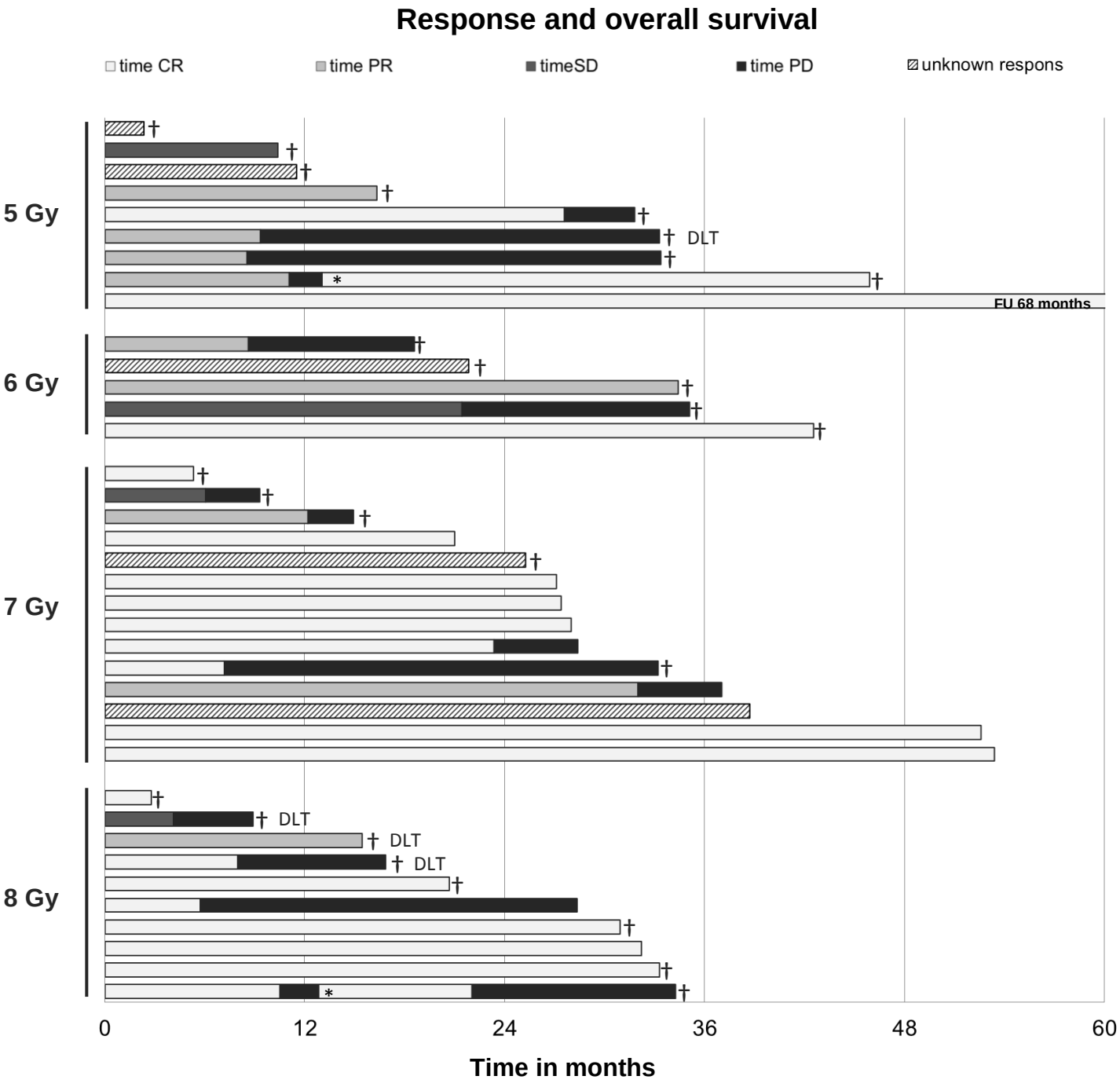
Web appendix A: Patient and tumor and treatment characteristics per dose level.

Patient characteristics	**5Gy**	**6Gy**	**7Gy**	**8Gy**	**total**	
	n=9	n=5	n=14	n=10	n=38	p-value
	n (%)	n (%)	n (%)	n (%)	n (%)	
Age (median/ range)	81 (57-93)	87 (69-94)	82 (63-91)	83 (72-91)	83 (57-94)	0.55
Gender						
male	6 (66.7)	2 (40.0)	7 (50.0)	6 (60.0)	21 (55.3)	0.78
female	3 (33.3)	3 (60.0)	7 (50.0)	4 (40.0)	17 (44.7)	
ASA-score						
II	1 (11.1)	0 (0.0)	1 (7.1)	5 (50.0)	7 (18.4)	0.09
III	8 (88.9)	5 (100)	12 (85.7)	5 (50.0)	30 (78.9)	
IV	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (2.6)	
WHO performance						
WHO 0	1 (16.7)	0 (0.0)	2 (15.4)	1 (10.0)	4 (11.8)	0.41
WHO 1	1 (16.7)	3 (60.0)	8 (61.5)	3 (30.0)	15 (44.1)	
WHO 2	4 (66.7)	2 (40.0)	3 (23.1)	6 (60.0)	15 (44.1)	
Co-morbidities						
Cardio Vascular no	2 (22.2)	1 (20.0)	5 (35.7)	3 (30.0)	11 (28.9)	0.87
yes	7 (77.8)	4 (80.0)	9 (64.3)	7 (70.0)	27 (71.1)	
Pulmonary no	7 (77.8)	4 (80.0)	8 (57.1)	7 (70.0)	26 (68.4)	0.68
yes	2 (22.2)	1 (20.0)	6 (42.9)	3 (30.0)	12 (31.6)	
Anticoagulant use no	4 (44.4)	2 (40.0)	4 (28.6)	3 (30.0)	13 (34.2)	0.86
yes	5 (55.6)	3 (60.0)	10 (71.4)	7 (70.0)	25 (65.8)	
Tumor Characteristics						
TNM classification						
T2N0M0	7 (77.8)	1 (20.0)	7 (50.0)	7 (70.0)	22 (57.9)	0.33
T2N1M0	0 (0.0)	0 (0.0)	1 (7.1)	0 (0.0)	1 (2.6)	
T3N0M0	0 (0.0)	2 (40.0)	1 (7.1)	2 (20.0)	5 (13.2)	
T3N1M0	2 (22.2)	2 (40.0)	3 (21.4)	1 (10.0)	8 (21.1)	
T3N2M0	0 (0.0)	0 (0.0)	2 (14.3)	0 (0.0)	2 (5.3)	
Distance from anal verge						
0-5 cm	3 (33.3)	3 (60.0)	5 (35.7)	8 (80.0)	19 (50.0)	0.20
5-10cm	5 (55.6)	2 (40.0)	5 (35.7)	1 (10.0)	13 (34.2)	
10-15cm	1 (11.1)	0 (0.0)	4 (28.6)	1 (10.0)	6 (15.8)	
Brachytherapy CTV	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)	
Volume (cc)	9.6 (2.0-25.0)	7.2 (4.7-9.6)	6.4 (2.0-20.0)	7.1 (3.6-14.8)	7.1 (2.0-25.0)	0.67
Max thickness (cm)	1.1 (0.7-3.0)	1.1 (0.8-1.4)	1.0 (0.4-1.7)	1.0 (0.7-1.6)	1.0 (0.4-3.0)	0.30
Length (cm)	3.4 (2.1-5.2)	3.6 (2.4-4.0)	2.8 (2.2-4.1)	2.9 (1.8-6.4)	3.1 (1.8-6.4)	0.72
D90 (Gy)	6.7 (1.8-8.3)	6.6 (4.7-9.8)	6.8 (4.3-8.7)	8.2 (5.0-9.8)	7.1 (1.8-9.8)	0.13

Web appendix B



Response and overall survival arranged by dose level.

All 38 patients are included in this figure. DLT: dose limiting toxicity; † diseased.

* Two patients received salvage surgery.