Brachytherapy for rectal cancer

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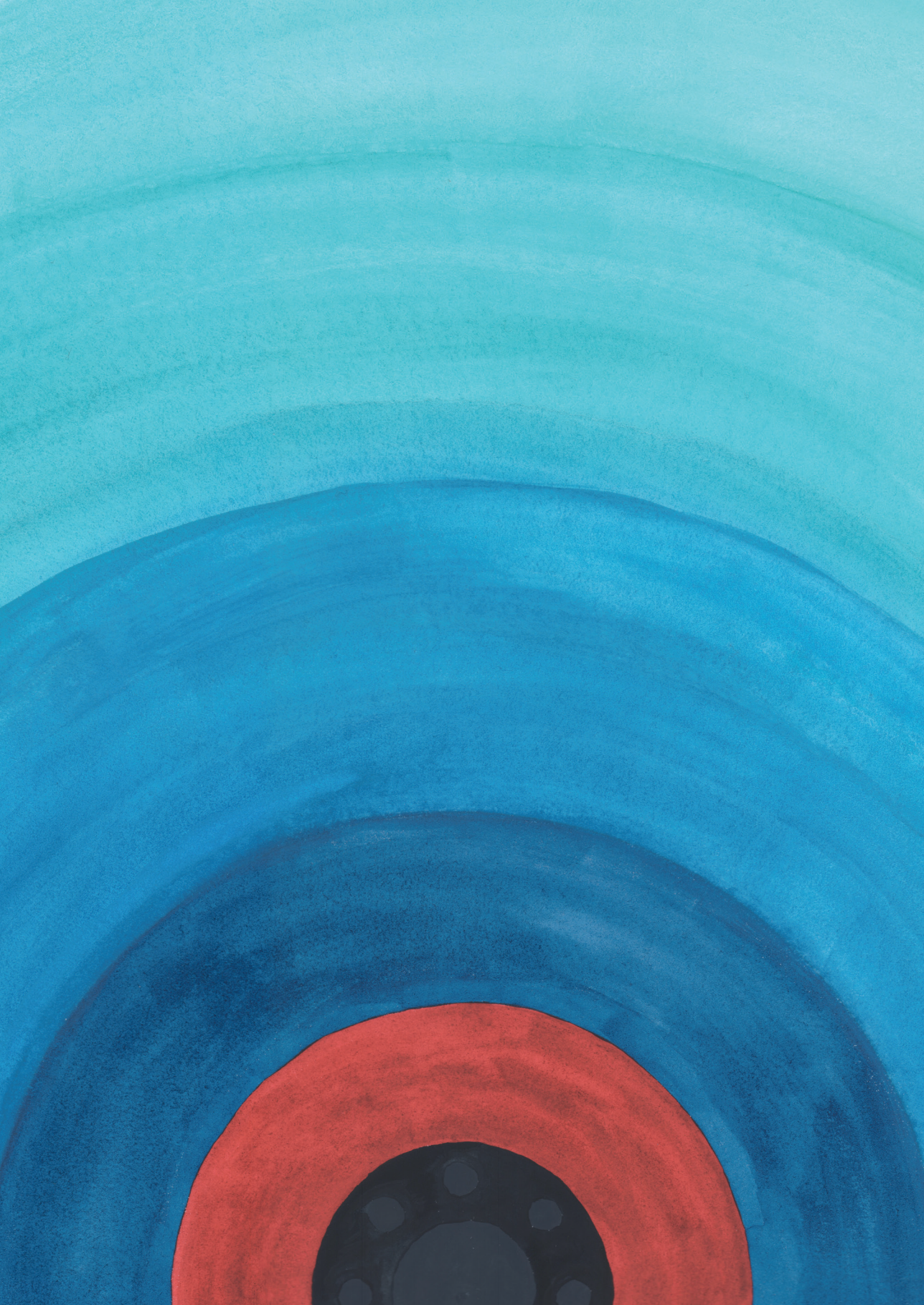

Chapter 8

Summary

8. SUMMARY

In this thesis, radical radiotherapy as an alternative to standard TME resection for elderly patients with rectal cancer is explored. As the population is aging, the incidence of rectal cancer is rising. And with increasing age, the burden of morbidity and postoperative mortality, associated with TME surgery, rises. Alternative treatment options for elderly patients are therefore urgently needed.

Because not every elderly patient is frail and not every frail patient is elderly, a one-size-fits-all approach does not suffice. Multiple factors have to be considered and it is therefore strongly advised to consult the geriatric department for a comprehensive geriatric assessment. Generally, patients can then be divided into four categories: (1) fit patients; (2) medium-fit patients, at surgical risk; (3) frail patients, in whom radical surgery is contraindicated and (4) very frail patients, in whom only palliative care is indicated. In fit patients, standard treatment is advised, but adjustments to the standard treatment can be made to minimise the toxicity. For example, the use of short course radiotherapy instead of chemoradiotherapy or reduction of the electively treated volume in external beam radiotherapy to lower toxicity. In medium-fit patients, further adjustments can be made to reduce treatment morbidity and in case of a clinical (near) complete response, a watch-and-wait strategy or local excision could be favoured to TME surgery. The group at high surgical risk might benefit from radical radiotherapy. And the last group, for which there is no curative intent, should be treated with a short palliative radiotherapy schedule in an attempt to alleviate symptoms.

As is clear from the above, understanding and predicting toxicity in these frail patients is extremely important. Therefore, a better understanding of dose-response effects for toxicity in external beam radiotherapy (Chapter 2) and for brachytherapy (Chapter 4 and 5) is needed. Knowing the chances of a complete response and associated risk of toxicity of a brachytherapy boost (Chapter 3 and 5) would allow us to discuss the risks and benefits with patients in shared decision making. Further improvements in the brachytherapy technique (Chapter 6 and 7) will increase the efficacy and reduce toxicity, optimising both response and tolerability of a HDREBT boost in rectal cancer.

CHAPTER 2

The bowel or small bowel have always been considered to be the main limiting organs at risk for external beam radiotherapy in rectal cancer and reliable and practical dose constraints are therefore needed. Contouring of individual small bowel loops (SBL) is often regarded as the gold standard for dose-response analyses, but is very time consuming and disregards the day-to-day variation. Two widely used less time consuming and more motion-robust alternatives are the bowelbag following EMBRACE guidelines (EMBRACE-BB) and bowelbag following RTOG

guidelines (RTOG-BB). In Chapter 2, these contouring methods were compared in a cohort of 157 locally advanced rectal cancer patients treated with chemoradiotherapy and factors associated with acute and late gastrointestinal toxicity were evaluated.
A statistically significant dose-response correlation could not be detected for any of the defined bowel delineations. Risk of acute toxicity was, however, clearly increased in patients with prior abdominal surgery, whereas concurrent chemoradiotherapy was the single most important risk factor for severe late gastrointestinal toxicity.
The volume of the EMBRACE-BB was approximately 2-3 times the volume of the small bowel loops and showed a strong linear correlation to the volume of SBL (rho = 0.9). The volume of the RTOG-BB was approximately a factor of 6 larger with a lower correlation (rho = 0.5-0.7).
Based on a literature review, a dose constraint for the volume of individual small bowel loops receiving 15 Gy (SBL V15) of 164 cc is proposed for acute grade 2-3 gastrointestinal toxicity. Using the correlation of SBL with EMBRACE-BB from the current analysis (EMBRACE-BB (V15) = SBL(V15) x 1.69 + 78.4), a constraint of 350 cc for EMBRACE-BB V15 is suggested as an alternative.

CHAPTER 3 - 5

In chapters 3, 4 and 5 the results of the HERBERT study are presented. The HERBERT study was a feasibility study, evaluating the efficacy and tolerability of an HDR endorectal brachytherapy boost after external beam radiotherapy in elderly frail patients with rectal cancer. The study was designed as a brachytherapy boost dose escalation study which started with 3×5 Gy, six weeks after EBRT (13×3 Gy, 4/wk) and increased with 1 Gy per fraction in every next dose level. Dose-limiting toxicity was defined as proctitis grade 3 (CTCAEv3) occurring within six weeks after brachytherapy. Secondary endpoints were toxicity, clinical tumour response, freedom from local progression, local progression free survival (L-PFS) and overall survival (OS). Brachytherapy was performed with a flexible applicator with eight channels and treatment planning was based on a planning CT acquired prior to the first brachytherapy application. The clinical target volume was defined as the residual tumour or scarring at time of brachytherapy and delineation on the CT was assisted by the baseline MRI, endoscopy images and clips positioned at the proximal and distal end of the tumour. The 100% isodose was prescribed to the radial margin of the CTV with a restriction of 400% within the applicator.
In total, 38 patients with cT2-3N0-1 rectal cancer were included between 2007 and 2013. Thirty-two were evaluable for toxicity endpoints and 33 for response analyses. Patients were elderly with a median age of 83 and most had severe co-morbidity: 76% of patients were deemed medically inoperable. Dose-limiting toxicity occurred in the 8 Gy dose level, resulting in a maximum tolerated dose of 7 Gy per fraction. Almost 90% of patients had a response to treatment with a complete response (cCR) in 61%. After a median FU of 30 months, 52% had a sustained response to treatment. Median time to local progression was 9.3 months and actuarial freedom from local

progression at 1, 2 and 3 years was 71%, 55% and 44% respectively. Survival was limited due to the nature of the population, but in patients with a complete response to treatment, a significant benefit in local progression free survival and trend for overall survival was observed. At two years the local progression free survival was 60% vs. 15% (p=0.006) and the overall survival was 80% vs. 46% in cCR vs. non-cCR patients (p=0.11) After an update with a median FU of 43.7 months, the overall survival benefit also was significant (p=0.01) (unpublished).

Chapter 4 describes a comprehensive overview of patient-reported, physician-reported and endoscopically observed toxicity. The endoscopy images were assessed for changes to the normal rectal wall and to the tumour site, which were analysed separately. Both physician- and patient-reported toxicity showed a clear increase in the third week of EBRT and two weeks after brachytherapy reducing to baseline values between EBRT and brachytherapy and two months after brachytherapy. Maximum proctitis score during this period was grade 2 in 68% and grade 3 in 13%. The patients with grade 3 acute proctitis showed ongoing toxicity for more than three months and experienced severe late proctitis as well. In total, severe late proctitis was observed in 10 patients (crude risk in evaluable patients 40%, actuarial risk at one year 23%).

Endoscopic evaluation of the normal rectal wall mainly showed erythema and telangiectasia. In three patients, frank haemorrhage or ulceration occurred 12-18 months after treatment. At the tumour site, deep ulceration occurred in 42% of patients with a complete or partial response.

Chapter 5 evaluates the association of patient-, tumour- and dosimetric parameters with tumour response and toxicity. Tumour volume at diagnosis showed a strong association with clinical complete response. Patients with a baseline tumour volume < 20 cc had a 2-year sustained response rate of 74% compared to only 25% for patients with baseline tumour volume > 20 cc ($p = 0.007$). Also, tumours that showed no volume reduction after external beam radiotherapy (n=4) had a poor response to the brachytherapy boost. No dose-response correlation was observed between prescribed dose to the CTV (D90/D98) and clinical tumour response.

Brachytherapy CTV (D90/98) was however correlated with acute and late proctitis. In addition, CTV volume, CTV width and high dose regions in the CTV (D1cc/D2cc) were associated with ulceration at the tumour site. Deep ulceration occurred in 7/9 (78%) of patients with a CTV D2cc > 14 Gy per fraction and in 3/18 (17%) patients with a CTV D2cc < 14 Gy per fraction ($p = 0.002$).

In conclusion, the HERBERT study shows that HDREBT is feasible in elderly rectal cancer patients with promising responses, but with considerable risk of toxicity. Patients with tumours < 20 cc at baseline, who respond well to EBRT are the best candidates for a brachytherapy boost. To limit the risk of toxicity a D2cc < 14 Gy per fraction is advised.

CHAPTER 6

A side study of the HERBERT study, the Repeat CT study, is reported in Chapter 6. In 11 patients, treated with an endorectal brachytherapy boost, additional CT scans were made at time of the second and third brachytherapy application. The treatment plan used for the brachytherapy boost (based on the planning CT scan acquired prior to the first brachytherapy application) was projected on the CT scans of the 2nd and 3rd application. A sufficient dose coverage was observed with the use of the first treatment plan in only 12/22 scans. In two cases, a significant improvement could be made by replanning, but in the remaining eight of 22 situations an intervention would have been necessary to correct applicator-balloon setup or to remove remaining air and/or faeces between the CTV and the applicator. This demonstrates that a single treatment plan, as was used in the HERBERT study, results in suboptimal dose distributions. Repeat CT scanning should therefore be the minimal standard of practice in HDREBT.

CHAPTER 7

The preferred imaging modality for contouring a rectal tumour is MRI. In the HERBERT study, MR imaging was not feasible because of artefacts caused by the endoluminal clips. Further improvement in the HDREBT technique could be facilitated by replacing the clips used in the HERBERT study with gold fiducials. The REMARK study was therefore initiated as part of a larger project for MRI-guided brachytherapy for rectal cancer. In this study, technical success rate and safety of four fiducial types were evaluated (Visicoil 0.5/0.75; Cook and Gold Anchor). Two endoscopic ultrasound (EUS)-guided placement strategies were used (in the tumour/rectal wall vs. in the mesorectum around the tumour). Twenty patients undergoing neoadjuvant external beam radiotherapy participated and in total, 64 fiducials were placed. After a median time of 17 days after placement (range 7-47 days), a total of 42/64 (66%) fiducials were still present (55% intratumoral vs. 90% mesorectal fiducials, P=0.009). There was no relevant difference in technical success rate of the different fiducial types. Based on the current analyses, placement of fiducials in the mesorectum is preferred.