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Technological advances in radiotherapy of rectal cancer:

Opportunities and challenges

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Abstract

Purpose of review:

This review summarizes the available evidence for the use of modern radiotherapy techniques for chemoradiotherapy (CRT) for rectal cancer, with specific focus on intensity-modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT) techniques.

Recent findings:

The dosimetric benefits of IMRT and VMAT are well-established, but prospective clinical studies are limited, with phase I-II studies only. Recent years have seen the publication of a few larger prospective patient series as well as some retrospective cohorts, several of which include much needed late toxicity data. Overall results are encouraging, as toxicity levels – although varying across reports – appear lower than for 3D conformal radiotherapy. Innovative treatment techniques and strategies which may be facilitated by the use of IMRT/VMAT include simultaneously integrated tumour boost, adaptive treatment, selective sparing of specific organs to enable chemotherapy escalation, and non-surgical management.

Summary:

Few prospective studies of IMRT and VMAT exist, which causes uncertainty not just in regards to the clinical benefit of these technologies but also in the optimal use. The priority for future research should be subgroups of patients who might receive relatively greater benefit from innovative treatment techniques, such as patients receiving CRT with definitive intent and patients treated with dose escalation.

Keywords

Rectal cancer, chemoradiotherapy, intensity modulated radiotherapy, volumetric arc therapy, image guidance, adaptive radiotherapy

Introduction

Surgery is a mainstay of rectal cancer management, but radiotherapy plays an important role in neoadjuvant treatment, especially for locally advanced cases. Neoadjuvant radiotherapy and chemoradiotherapy (CRT) both reduce the risk of local recurrence, even with optimal surgical techniques (1–3). Consequently, standard clinical practice in many parts of the world is to treat locally advanced disease with long-course CRT, with delayed surgery after 6-12 weeks. The typical long-course CRT regimen consists of 45-50 Gy to the primary tumour and the regional lymph node stations, delivered over 5-6 weeks in daily 1.8-2.0 Gy fractions, with concomitant fluorouracil-based chemotherapy. However, neoadjuvant treatment strategies are increasingly individualised; in terms of treatment modality, radiotherapy dose and schedule, details of treatment technique, and choice of chemotherapy regimens (4). The rationale for use of CRT may also differ across patient groups: The majority of patients with locally advanced rectal cancer will be treated with CRT in order to lower the risk of local recurrence after surgery, but some patients are initially inoperable and the aim of CRT is to improve the probability of R0 resection. Additionally, an emerging subgroup of patient receive CRT with the purpose of minimizing the need for surgical interventions.

Radiotherapy for cancer has seen a technological revolution in the last decades. Modern radiotherapy techniques allow for delivery of highly conformal, inversely optimized treatment plans. Advances in imaging – including the use of computed tomography (CT) images for

treatment planning and on-board CT daily imaging – provide for high accuracy and precision in treatment delivery. Adaptive treatment strategies using multimodality magnetic resonance imaging (MRI) for target definition, plan adaptation, and response evaluation may be the next step forward.

In rectal cancer, these developments support individualisation of treatment planning and delivery, but also facilitate individualisation of treatment strategies, especially in terms of choice of radiotherapy dose. This review summarizes recently published evidence for the use of modern radiotherapy techniques for rectal cancer, with specific focus on intensity-modulated radiotherapy (IMRT) and arc therapy techniques, as well as adaptive treatment strategies.

Intensity modulated radiotherapy (IMRT) and volumetric arc therapy (VMAT)

Radiotherapy for rectal cancer initially used simple 2D treatment planning based on radiographs of bony pelvic structures. Treatment field configurations were either opposing fields or “box field” techniques, resulting in large volumes of normal tissue being irradiated. The introduction of computed tomography (CT)-based treatment planning allowed for direct identification and delineation of relevant target volumes in 3D. Combining CT-based planning with the use multi-leaf collimators (MLCs) facilitated 3D conformal radiotherapy (3D-CRT) with increased treatment accuracy and considerable reduction in normal tissue irradiation. Nonetheless, many of the lymph node targets in the pelvis are concavely shaped, and 3D-CRT techniques do not easily allow for sparing of the normal tissue contained in between those targets. For this reason, inverse planned treatment techniques, such as IMRT and VMAT (and the closely related tomotherapy technique) have increasingly been used for pelvic radiotherapy. These technologies are based on the delivery

of highly modulated dose fluence from multiple directions in order to limit high dose volumes outside the treatment target; they thus support the delivery of concavely shaped dose distributions. The main rationale behind these techniques is the reduction of dose to organs at risk with the expectation of lower radiation-induced early and late toxicity.

Multiple dose planning studies have examined whether the technical advances described above also result in improved treatment plans for rectal cancer patients. Overall, these studies have demonstrated that IMRT and VMAT treatment plans do indeed deliver significantly reduced dose to bowel, bladder, and bony structures in the pelvis (see e.g. (5–7)), even taking into account common uncertainties in treatment delivery, such as day-to-day variation in organ at risk positioning (8).

The theoretical rationale for the use of such highly conformal techniques is sound, and dose distribution improvements can clearly be achieved in clinical practice. However, the question remains as to whether this translates into clinical benefit for patients. The published evidence regarding this is more scarce (9). A number of prospective phase I and II studies have been conducted (10–26) using IMRT/VMAT for neoadjuvant treatment of rectal cancer, but many of them are based on very few patients. No randomized trials have been completed.

Late toxicity after IMRT / VMAT

Generally speaking, limiting treatment-induced toxicity may benefit patients in (at least) two ways: Lowering acute toxicity may allow for improved radiotherapy and chemotherapy compliance. Limiting late, chronic toxicity will improve patients' long term quality of life. For rectal cancer,

tolerability of standard, fluorouracil-based CRT is not a major problem, and thus introducing IMRT/VMAT in this context would conventionally aim at improving long term toxicity rates. Unfortunately, less than a handful of studies to date have presented data on late radiation-induced morbidity after highly conformal neoadjuvant radiotherapy. A recently published prospective Belgium study (21, 27) of tomotherapy for locally advanced rectal cancer enrolled 108 patients who received 46 Gy in 23 fractions to tumour and lymph node target volumes, with no concomitant chemotherapy (but escalated dose to the tumour, 55.2 Gy, for high risk patients). The absolute incidences of grade ≥3 late gastrointestinal and urinary toxicity were 9% and 4%, respectively, with a 13% rate of any grade ≥3 late toxicity. Thus there was non-negligible late toxicity, despite the use of highly conformal radiotherapy as neoadjuvant mono-therapy. The NRG Oncology Radiation Therapy Oncology Group 0822 study (25) treated 68 patients with IMRT and concomitant chemotherapy consisting of both capecitabine and oxaliplatin. Radiation dose was 45 Gy in 25 fractions, followed by a 3-dimensional conformal boost of 5.4 Gy in 3 fractions. Out of 42 patients evaluated for late toxicity, only one reported grade 3 non-haematological toxicity, likely related to the oxaliplatin rather than the radiotherapy. Grade $\geq$2 late non-hematologic toxicity was somewhat higher at 31%. Finally, a newly published German retrospective study compared patients treated with VMAT (n = 81) and 3DCRT (n = 107), all to 50.4 Gy in 28 fractions with concomitant 5-fluorouracil (28). Significantly less high-grade acute and late toxicity was seen in the patient cohort treated with VMAT – for late high grade toxicity, the incidences were 9% vs. 19% for VMAT and 3D-CRT, respectively.

Based on the data available, high grade late radiation-induced toxicity may not be completely avoidable, but could still be reduced compared to outcome after 3D-CRT. This makes sense from a

dosimetric perspective, given the considerable overlap between the lymph node target volumes and normal pelvic tissues: some volumes of normal tissue will always be irradiated to full prescription dose, irrespectively of the conformity of the radiotherapy treatment technique. However, data are very scarce and likely biased by improvement in surgical techniques over time. Additionally, the studies mentioned all considered physician-scored toxicity, which will very often show discrepancy with patient-experienced toxicity (29). There is a clear need for high quality studies measuring patient-reported outcomes using validated questionnaires.

Treatment intensification driven by IMRT / VMAT

Many of the prospective studies conducted have focused on the combination of IMRT/VMAT with experimental chemotherapy regimens. The rationale is that use of highly conformal techniques will limit treatment-induce toxicity related to the local treatment, thus increasing the patient tolerance of more aggressive systemic treatment. The results of this strategy have been somewhat mixed (12, 16–19, 22, 25), although a number of studies report good tolerance of capecitabine and oxaliplatin delivered concomitantly with IMRT or VMAT. As an example, Arbea and colleagues conducted a phase II trial of 100 patients treated with concurrent capecitabine and oxaliplatin plus 47.5 Gy in 19-20 fractions (16) and observed grade 3 diarrhea in 9% of the patients. On the other hand, the multi-centre RTOG 0822 study treated patients with concomitant oxaliplatin in addition to capecitabine. The incidence of clinically significant acute gastrointestinal toxicity was considerable, despite careful optimization of treatment plans,: Thirty-five patients (51.5%) experienced acute grade ≥ 2 GI toxicity, out of which 12 patients (17.6%) experienced grade 3-4 diarrhea. Overall, while not uninteresting, these studies of CRT treatment intensification are hard to assess: They are mainly single centre, phase II studies, which are prone to selection bias.

One of the more innovative approaches in the context of treatment intensification is to exploit IMRT to spare active pelvic bone marrow in order to limit radiation-induced haematological toxicity. This approach has previously been investigated in gynaecological and anal cancer CRT (see e.g. (30, 31)), and normal tissue complication probability modelling studies suggest an interaction could exist between some types of chemotherapy and bone marrow irradiation (32). The last couple of years have seen a number of publications on the relationship between irradiated bone marrow and haematological toxicity in rectal cancer patients receiving neoadjuvant treatment (33, 34), including a prospective study of bone-marrow sparing IMRT combined with capecitabine and oxaliplatin (26). All patients on study received 50 Gy in 25 fractions, while active bone marrow as identified by MRI was contoured as an organ at risk and prioritized in the treatment plan optimization. Out of 35 patients, nine (25.7 %), six (17.1 %), one (2.9 %) and one (2.9 %) experienced acute Grade 2-4 leukopenia, neutropenia, anaemia and thrombocytopenia, respectively. This appears to be a promising approach for select patients, and might provide a rationale for the introduction of proton therapy in rectal cancer treatment (35, 36).

Another common approach using IMRT/VMAT in rectal cancer is to give a simultaneous integrated boost (SIB) to the primary tumour. A SIB is delivered by increasing slightly the daily treatment dose to the tumour compared to the elective volume. This allows for tumour dose escalation without extending the overall treatment time, and provides a treatment plan relatively robust to day-to-day variations in the positioning of the primary tumour volume. SIB techniques are challenging – although not impossible (37) – with 3D-CRT, and have hence gained in popularity after the introduction of IMRT and VMAT (see e.g. (15, 27)). The combination of SIB with adaptive

treatment strategies is a particularly exciting venue for research: The definition of the boost volume could e.g. be guided by response to induction chemotherapy, as investigated by Seierstad and colleagues (14), or by response part-way through the radiotherapy treatment course (20). The group at the San Raffaele Scientific Institute in Milan has done particularly interesting work, including investigation of the use of optimized treatment margins for safe delivery of an adaptive SIB during the second half of the treatment course (20, 38, 39).

Technological advances and organ-preservation strategies

Organ-preserving or non-surgical treatment strategies for localized rectal cancer have been subject to considerable attention in the last decade (40, 41). Many patients with low rectal cancers will be treated with abdominoperineal resection, resulting in a permanent stoma. Additionally, some elderly and those with major co-morbidity may not be candidates for radical surgery at all (42, 43). Most patients treated with neoadjuvant CRT will exhibit some degree of tumour regression at the end of treatment, and a sub-group will have complete response to treatment. Whether these patients need extensive surgery is the focus of intense debate and significant research efforts. This last year has seen considerable progress in the field with the publication of several prospective studies (44, 45) as well as a large retrospective series (46) of patients managed with no or limited surgery after CRT.

Organ-preserving and/or non-surgical treatment strategies are rapidly gaining support and are increasingly used not only in prospective trials but also in routine clinical practice. They may change the role of radiotherapy in the management of rectal cancer, and this will increase the importance of conformal, accurate treatment delivery. There are indications that there exist dose-

response relationships for tumour regression (47) and local control after deferral of surgery (44, 48), and radiation dose-escalation may hence increase the proportion of patients who could be managed with no or limited surgery. This will require highly conformal techniques, likely with the use of SIB, in order to avoid excessive irradiation of normal tissue. A prospective study of high-dose CRT and non-surgical management treated 51 patients with low T2-3 rectal cancer with IMRT and SIB (60 Gy to the primary tumour, 50 Gy to elective nodal volumes, plus an additional 5 Gy endorectal brachytherapy boost): local control was high and the functional outcome good (44), providing an indication of what might be achievable with with modern, highly conformal techniques. Further studies are needed, especially to collect late toxicity, patient-reported quality-of-life, and functional outcome data to inform treatment plan optimization in the organ-preservation setting (29). Still, implementation of additional strategies may be needed in order to limit the high dose treatment volume, such as adaptive radiotherapy (20) or individualized treatment margins (49). It may also become relevant to consider new, less frequently studied organs at risk, such as the anal sphincter. Finally, research evaluation of additional chemotherapy, either prior to or following CRT (50, 51), would support further examination of bone-marrow sparing IMRT in this patient group.

Outstanding challenges for the use of IMRT and VMAT

Despite the many advances in conformal radiotherapy of rectal cancer, a number of challenges still exist. Inverse optimization of radiotherapy treatment plans requires reliable and consistent identification of target volumes as well as knowledge of relevant dose constraints for organs at risk. Multiple studies have reported large inter-observer variability of target delineation for rectal cancer (52, 53), but have fortunately also demonstrated that training, use of guidelines and

atlases, and multi-modal imaging can all improve delineation reliability. IMRT- and VMAT-based treatment has been shown to be sensitive to uncertainties in target volume definition (54, 55), underlining the need for delineation standardisation prior to implementation of conformal treatment techniques. Similarly, sufficient treatment margins must be used, if day-to-day variation in positioning and organ deformation is not to cause target under-dosage (56).

Considerable research effort within rectal cancer radiotherapy is focused on optimal utilization of MRI in the treatment process. Multi-modality MRI, including diffusion-weighted MRI, has shown promise for tumour delineation and response assessment (53, 57, 58) as well as for recurrence monitoring after definitive CRT (59). MRI-based treatment machines (combining Co-60 sources or linear accelerators with on-board MRI) have been recently released for clinical use or are going through the final stages of commercial development, respectively (60, 61). MRI is especially interesting as a modality for daily imaging for rectal cancer radiotherapy, as the primary tumour is challenging to visualize using on-board CT. MRI-guidance would allow for much more accurate daily delivery of dose-escalated treatments, but could potentially also be used for daily treatment adaptation.

To limit treatment-induced toxicity, an understanding of the relationships between dose distribution metrics and toxicity is needed to best utilize IMRT and VMAT techniques. In short, we need to know which dose constraints to use in the plan optimization process in order to produce a clinically optimal plan. However, the knowledge of dose-response and volume effects for normal tissue toxicity after CRT and surgery for rectal cancer is extremely limited. Some publications have studied acute toxicity, especially for bowel (62) and bladder (63), but dose plan factors affecting

late toxicity are not well understood, especially not for conformal treatments (64, 65). Some discrepancies in toxicity outcomes in the previously described studies could potentially be explained by variations in the plan optimization metrics used – some studies might have been conducted using treatments planned with suboptimal dose constraints.

Conclusions

IMRT and VMAT have shown promise for improving outcome for rectal cancer patients, but the published data are still limited. Dosimetric benefits have been demonstrated and many of the technical challenges have been solved, but careful quality assurance with regards to target delineation, margins and image guidance, and plan optimization constraints is needed prior to clinical implementation. Evaluation of clinical benefits in prospective clinical studies is still essential, especially in order to generate data on late toxicity using validated questionnaires. Such studies might want to focus on select groups of patients, who might be primary candidates for the use of these highly conformal, inversely planned treatment techniques. They include 1) patients with high risk of non-radical resections, i.e. very locally advanced cancers, where multi-level boost strategies might be much easier to implement using IMRT (14); 2) patients treated with aggressive chemotherapy regimens to limit acute toxicity; 3) patients aiming at organ preservation, e.g. patients who might avoid surgery due to very good tumour response.

Key points

- Dosimetric benefits of IMRT/VMAT for neoadjuvant treatment of rectal cancer are well-established.
- Studies demonstrating clinical benefits are limited to phase I/II, and late toxicity data are scarce.
- Primary candidates for future studies of highly conformal radiotherapy include patients with high risk of non-radical resections, patients treated with aggressive concomitant chemotherapy regimens, and patients aiming at organ preservation (e.g. “watch-and-wait” for clinical complete responders).

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Conflicts of interest

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References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

▪ of special interest

▪▪ of outstanding interest

1. Sebag-Montefiore D, Stephens RJ, Steele R, *et al.* Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. *Lancet*. 2009;373:811–820.

2. van Gijn W, Marijnen C a M, Nagtegaal ID, *et al.* Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol.* 2011;12:575–82.

3. Sauer R, Liersch T, Merkel S, *et al.* Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J. Clin. Oncol.* 2012;30:1926–33.

4. Valentini V, Glimelius B, Haustermans K, *et al.* EURECCA consensus conference highlights about rectal cancer clinical management: The radiation oncologist's expert review. *Radiother. Oncol.* 2013.

5. Guerrero Urbano MT, Henrys AJ, Adams EJ, *et al.* Intensity-modulated radiotherapy in patients with locally advanced rectal cancer reduces volume of bowel treated to high dose levels. *Int. J. Radiat. Oncol. Biol. Phys.* 2006;65:907–16.

6. Arbea L, Ramos LI, Martínez-Monge R, *et al.* Intensity-modulated radiation therapy (IMRT) vs. 3D conformal radiotherapy (3DCRT) in locally advanced rectal cancer (LARC): dosimetric

comparison and clinical implications. *Radiat. Oncol.* 2010;5:17.

7. Yu M, Lee JH, Jang HS, *et al.* A comparison of dosimetric parameters between tomotherapy and three-dimensional conformal radiotherapy in rectal cancer. *Radiat. Oncol.* 2013;8:181.

8. Nuyttens JJ, Robertson JM, Yan D, *et al.* The influence of small bowel motion on both a conventional three-field and intensity modulated radiation therapy (IMRT) for rectal cancer. *Cancer Radiother.* 2004;8:297–304.

9. ▪ Teoh S, Muirhead R. Rectal Radiotherapy - Intensity-modulated Radiotherapy Delivery, Delineation and Doses. *Clin. Oncol.* 2016;28:93–102.

Good general overview of clinical studies of IMRT / VMAT in rectal cancer, including discussion of technical challenges

10. Freedman GM, Meropol NJ, Sigurdson ER, *et al.* Phase I trial of preoperative hypofractionated intensity-modulated radiotherapy with incorporated boost and oral capecitabine in locally advanced rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2007;67:1389–93.

11. De Ridder M, Tournel K, Van Nieuwenhove Y, *et al.* Phase II study of preoperative helical tomotherapy for rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2008;70:728–34.

12. Aristu JJ, Arbea L, Rodriguez J, *et al.* Phase I-II trial of concurrent capecitabine and oxaliplatin with preoperative intensity-modulated radiotherapy in patients with locally advanced rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2008;71:748–55.

13. Ballonoff A, Kavanagh B, McCarter M, *et al.* Preoperative capecitabine and accelerated intensity-modulated radiotherapy in locally advanced rectal cancer: a phase II trial. *Am. J. Clin. Oncol.* 2008;31:264–70.

14. Seierstad T, Hole KH, Saelen E, *et al.* MR-guided simultaneous integrated boost in preoperative radiotherapy of locally advanced rectal cancer following neoadjuvant chemotherapy. *Radiother.*

Oncol. 2009;93:279–284.

15. Li J, Ji J, Cai Y, *et al.* Preoperative concomitant boost intensity-modulated radiotherapy with oral capecitabine in locally advanced mid-low rectal cancer: a phase II trial. *Radiother. Oncol.* 2012;102:4–9.

16. Arbea L, Martínez-Monge R, Díaz-González JA, *et al.* Four-Week Neoadjuvant Intensity-Modulated Radiation Therapy With Concurrent Capecitabine and Oxaliplatin in Locally Advanced Rectal Cancer Patients: A Validation Phase II Trial. *Int. J. Radiat. Oncol.* 2012;83:587–593.

17. Gasent Blesa JM, Garde Noguera J, Laforga Canales JB, *et al.* Phase II trial of concomitant neoadjuvant chemotherapy with oxaliplatin and capecitabine and intensity-modulated radiotherapy (IMRT) in rectal cancer. *J. Gastrointest. Cancer*. 2012;43:553–61.

18. Cubillo A, Hernando-Requejo O, García-García E, *et al.* A prospective pilot study of target-guided personalized chemotherapy with intensity-modulated radiotherapy in patients with early rectal cancer. *Am. J. Clin. Oncol.* 2014;37:117–21.

19. Zhu J, Gu W, Lian P, *et al.* A phase II trial of neoadjuvant IMRT-based chemoradiotherapy followed by one cycle of capecitabine for stage II/III rectal adenocarcinoma. *Radiat. Oncol.* 2013;8:130.

20. Passoni P, Fiorino C, Slim N, *et al.* Feasibility of an adaptive strategy in preoperative radiochemotherapy for rectal cancer with image-guided tomotherapy: boosting the dose to the shrinking tumor. *Int. J. Radiat. Oncol. Biol. Phys.* 2013;87:67–72.

21. ▪▪ Engels B, Platteaux N, Van den Begin R, *et al.* Preoperative intensity-modulated and image-guided radiotherapy with a simultaneous integrated boost in locally advanced rectal cancer: report on late toxicity and outcome. *Radiother. Oncol.* 2014;110:155–9.

Relatively large phase II trial of TomoTherapy used as mono-therapy for neoadjuvant treatment.

One of the very few studies to provide late toxicity data after modern radiotherapy for rectal cancer.

22. Zhu J, Liu F, Gu W, *et al.* Concomitant boost IMRT-based neoadjuvant chemoradiotherapy for clinical stage II/III rectal adenocarcinoma: results of a phase II study. *Radiat. Oncol.* 2014;9:70.

23. Huang M-Y, Chen C-F, Huang C-M, *et al.* Helical tomotherapy combined with capecitabine in the preoperative treatment of locally advanced rectal cancer. *Biomed Res. Int.* 2014;2014:352083.

24. Hernando-Requejo O, López M, Cubillo A, *et al.* Complete pathological responses in locally advanced rectal cancer after preoperative IMRT and integrated-boost chemoradiation. *Strahlentherapie und Onkol.* 2014;190:515–520.

25. Hong TS, Moughan J, Garofalo MC, *et al.* NRG Oncology Radiation Therapy Oncology Group 0822: A Phase 2 Study of Preoperative Chemoradiation Therapy Using Intensity Modulated Radiation Therapy in Combination With Capecitabine and Oxaliplatin for Patients With Locally Advanced Rectal Cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2015;93:29–36.

26. ▪ Jianyang W, Yuan T, Yuan T, *et al.* A prospective phase II study of magnetic resonance imaging guided hematopoietical bone marrow-sparing intensity-modulated radiotherapy with concurrent chemotherapy for rectal cancer. *Radiol. Med.* 2016;121:308–14.

Innovative study of bone-marrow sparing IMRT combined with capecitabine and oxaliplatin. The low haematological toxicity observed indicates that this might be a feasible strategy.

27. Engels B, Tournel K, Everaert H, *et al.* Phase II study of preoperative helical tomotherapy with a simultaneous integrated boost for rectal cancer. *Int. J. Radiat. Oncol. Biol. Phys.* 2012;83:142–8.

28. ▪ Dröge LH, Weber HE, Guhlich M, *et al.* Reduced toxicity in the treatment of locally advanced rectal cancer: a comparison of volumetric modulated arc therapy and 3D conformal radiotherapy. *BMC Cancer*. 2015;15:750.

Large retrospective series of patients treated with VMAT; with late toxicity reported using actuarial methods and compared to a similar group of patients treated with 3D-CRT.

29. Gilbert A, Ziegler L, Martland M, *et al.* Systematic Review of Radiation Therapy Toxicity Reporting in Randomized Controlled Trials of Rectal Cancer: A Comparison of Patient-Reported Outcomes and Clinician Toxicity Reporting. *Int. J. Radiat. Oncol. Biol. Phys.* 2015;92:555–67.

30. Liang Y, Bydder M, Yashar CM, *et al.* Prospective study of functional bone marrow-sparing intensity modulated radiation therapy with concurrent chemotherapy for pelvic malignancies. *Int. J. Radiat. Oncol. Biol. Phys.* 2013;85:406–14.

31. Bazan JG, Luxton G, Mok EC, *et al.* Normal tissue complication probability modeling of acute hematologic toxicity in patients treated with intensity-modulated radiation therapy for squamous cell carcinoma of the anal canal. *Int. J. Radiat. Oncol. Biol. Phys.* 2012;84:700–6.

32. Bazan JG, Luxton G, Kozak MM, *et al.* Impact of chemotherapy on normal tissue complication probability models of acute hematologic toxicity in patients receiving pelvic intensity modulated radiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2013;87:983–91.

33. Yang TJ, Oh JH, Apte A, *et al.* Clinical and dosimetric predictors of acute hematologic toxicity in rectal cancer patients undergoing chemoradiotherapy. *Radiother. Oncol.* 2014:13–16.

34. Wan J, Liu K, Li K, *et al.* Can dosimetric parameters predict acute hematologic toxicity in rectal cancer patients treated with intensity-modulated pelvic radiotherapy? *Radiat. Oncol.* 2015;10:162.

35. Wolff HA, Wagner DM, Conradi L-C, *et al.* Irradiation with protons for the individualized treatment of patients with locally advanced rectal cancer: a planning study with clinical implications. *Radiother. Oncol.* 2012;102:30–7.

36. Colaco RJ, Nichols RC, Huh S, *et al.* Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal

cancer. *J. Gastrointest. Oncol.* 2014;5:3–8.

37. Jakobsen A, Mortensen JP, Bisgaard C, *et al.* Preoperative chemoradiation of locally advanced T3 rectal cancer combined with an endorectal boost. *Int. J. Radiat. Oncol. Biol. Phys.* 2006;64:461–5.

38. Maggiulli E, Fiorino C, Passoni P, *et al.* Characterisation of rectal motion during neo-adjuvant radiochemotherapy for rectal cancer with image-guided tomotherapy: Implications for adaptive dose escalation strategies. *Acta Oncol. (Madr).* 2012;51:318–324.

39. ▪ Raso R, Scalco E, Fiorino C, *et al.* Assessment and clinical validation of margins for adaptive simultaneous integrated boost in neo-adjuvant radiochemotherapy for rectal cancer. *Phys. Medica*. 2015;31:167–172.

Interesting technical paper, descriping a novel adaptive boost strategy.

40. Habr-Gama A, Perez RO, Nadalin W, *et al.* Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. *Ann. Surg.* 2004;240:711–7; discussion 717–8.

41. Habr-Gama A, Gama-Rodrigues J, São Julião GP, *et al.* Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. *Int. J. Radiat. Oncol.* 2014;88:822–8.

42. Rutten HJT, den Dulk M, Lemmens VEPP, *et al.* Controversies of total mesorectal excision for rectal cancer in elderly patients. *Lancet Oncol.* 2008;9:494–501.

43. Smith FM, Rao C, Oliva Perez R, *et al.* Avoiding radical surgery improves early survival in elderly patients with rectal cancer, demonstrating complete clinical response after neoadjuvant therapy: results of a decision-analytic model. *Dis. Colon Rectum*. 2015;58:159–71.

44. ▪▪ Appelt AL, Pløen J, Harling H, *et al.* High-dose chemoradiotherapy and watchful waiting for

distal rectal cancer: a prospective observational study. *Lancet. Oncol.* 2015;16:919–27.

Prospective study of watch-and-wait strategy for clinical complete responders after high-dose CRT. Demonstrated that dose-escalation for organ-preservation might be feasible using highly conformal radiotherapy.

45. ▪▪ Garcia-Aguilar J, Renfro LA, Chow OS, *et al.* Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. *Lancet. Oncol.* 2015;16:1537–46.

Prospective study of CRT and limited, organ-preserving surgery; showed that this approach can be implemented in a multi-centre setting.

46. ▪ Renehan AG, Malcomson L, Emsley R, *et al.* Watch-and-wait approach versus surgical resection after chemoradiotherapy for patients with rectal cancer (the OnCoRe project): a propensity-score matched cohort analysis. *Lancet. Oncol.* 2016;17:174–83.

Large retrospective cohort study of clinical complete responders after CRT undergoing observation; with patients matched to a surgically managed cohort. Reported oncological outcomes in observation cohort comparable to the surgery cohort.

47. Appelt AL, Pløen J, Vogelius IR, *et al.* Radiation dose-response model for locally advanced rectal cancer after preoperative chemoradiation therapy. *Int. J. Radiat. Oncol. Biol. Phys.* 2013;85:74–80.

48. Appelt AL, Jakobsen A. Radiation Techniques for Increasing Local Control in the Non-Surgical Management of Rectal Cancer. *Curr. Colorectal Cancer Rep.* 2015;11:267–274.

49. Nijkamp J, Marijnen C, van Herk M, *et al.* Adaptive radiotherapy for long course neo-adjuvant treatment of rectal cancer. *Radiother. Oncol.* 2012;103:353–9.

50. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, *et al.* Watch and Wait Approach Following Extended Neoadjuvant Chemoradiation for Distal Rectal Cancer. *Dis. Colon Rectum*. 2013;56:1109–

1117.

51. Garcia-Aguilar J, Chow OS, Smith DD, *et al.* Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: a multicentre, phase 2 trial. *Lancet Oncol.* 2015;16:957–966.

52. Fuller CD, Nijkamp J, Duppen JC, *et al.* Prospective randomized double-blind pilot study of site-specific consensus atlas implementation for rectal cancer target volume delineation in the cooperative group setting. *Int. J. Radiat. Oncol. Biol. Phys.* 2011;79:481–9.

53. Burbach JPM, Kleijnen J-PJ, Reerink O, *et al.* Inter-observer agreement of MRI-based tumor delineation for preoperative radiotherapy boost in locally advanced rectal cancer. *Radiother. Oncol.* 2016;118:399–407.

54. Lobefalo F, Bignardi M, Reggiori G, *et al.* Dosimetric impact of inter-observer variability for 3D conformal radiotherapy and volumetric modulated arc therapy: the rectal tumor target definition case. *Radiat. Oncol.* 2013;8:176.

55. Mavroidis P, Giantsoudis D, Awan MJ, *et al.* Consequences of anorectal cancer atlas implementation in the cooperative group setting: radiobiologic analysis of a prospective randomized in silico target delineation study. *Radiother. Oncol.* 2014;112:418–24.

56. Nijkamp J, Swellengrebel M, Hollmann B, *et al.* Repeat CT assessed CTV variation and PTV margins for short- and long-course pre-operative RT of rectal cancer. *Radiother. Oncol.* 2012;102:399–405.

57. Joye I, Deroose CM, Vandecaveye V, *et al.* The role of diffusion-weighted MRI and (18)F-FDG PET/CT in the prediction of pathologic complete response after radiochemotherapy for rectal cancer: a systematic review. *Radiother. Oncol.* 2014;113:158–65.

58. Martens MH, van Heeswijk MM, van den Broek JJ, *et al.* Prospective multicenter validation

study of MRI volumetry for response assessment after preoperative chemoradiation in rectal cancer: can the results in literature be reproduced? *Int. J. Radiat. Oncol.* 2015.

59. Lambregts DMJ, Lahaye MJ, Heijnen LA, *et al.* MRI and diffusion-weighted MRI to diagnose a local tumour regrowth during long-term follow-up of rectal cancer patients treated with organ preservation after chemoradiotherapy. *Eur. Radiol.* 2015.

60. Wooten HO, Green O, Yang M, *et al.* Quality of Intensity Modulated Radiation Therapy Treatment Plans Using a ^{60}Co Magnetic Resonance Image Guidance Radiation Therapy System. *Int. J. Radiat. Oncol. Biol. Phys.* 2015;92:771–8.

61. Lagendijk JJW, Raaymakers BW, van Vulpen M. The Magnetic Resonance Imaging-Linac System. *Semin. Radiat. Oncol.* 2014;24:207–209.

62. Yang TJ, Oh JH, Son CH, *et al.* Predictors of acute gastrointestinal toxicity during pelvic chemoradiotherapy in patients with rectal cancer. *Gastrointest. Cancer Res.* 2013;6:129–36.

63. Appelt AL, Bentzen SM, Jakobsen A, *et al.* Dose-response of acute urinary toxicity of long-course preoperative chemoradiotherapy for rectal cancer. *Acta Oncol.* 2015;54:179–86.

64. Viswanathan AN, Yorke ED, Marks LB, *et al.* Radiation dose-volume effects of the urinary bladder. *Int. J. Radiat. Oncol. Biol. Phys.* 2010;76:S116–22.

65. Kavanagh BD, Pan CC, Dawson LA, *et al.* Radiation dose-volume effects in the stomach and small bowel. *Int. J. Radiat. Oncol. Biol. Phys.* 2010;76:S101–7.