Dose–time fractionation schedules of preoperative radiotherapy and timing to surgery for rectal cancer

Fu Jin, Huanli Luo, Juan Zhou, Yongzhong Wu, Hao Sun, Hongliang Liu, Xiaodong Zheng and Ying Wang

Abstract: Chemoradiotherapy (CRT) is extensively used prior to surgery for rectal cancer to provide significantly better local control, but the radiotherapy (RT), as the other component of CRT, has been subject to less interest than the drug component in recent years. With considerable developments in RT, the use of advanced techniques, such as intensity-modulated radiotherapy (IMRT) in rectal cancer, is garnering more attention nowadays. The radiation dose can be better conformed to the target volumes with possibilities for synchronous integrated boost without increased complications in normal tissue. Hopefully, both local recurrence and toxicities can be further reduced. Although those seem to be of interest, many issues remain unresolved. There is no international consensus regarding the radiation schedule for preoperative RT for rectal cancer. Moreover, an enormous disparity exists regarding the RT delivery. With the advent of IMRT, variations will likely increase. Moreover, time to surgery is also quite variable, as it depends upon the indication for RT/CRT in the clinical practices. In this review, we discuss the options and problems related to both the dose–time fractionation schedule and time to surgery; furthermore, it addresses the research questions that need answering in the future.

Keywords: IMRT, preoperative radiotherapy, rectal cancer, surgery, three-dimensional conformal radiotherapy

Introduction

Surgery is the cornerstone of curative therapy for rectal cancer, and combined-modality treatment is the recommended adjuvant, or neoadjuvant therapy. Multimodality therapy is often used for tumor downstaging or downsizing, anal sphincter, or other organ preservation, as well as improvements in local control (LC) or even overall survival (OS). Preoperative chemoradiotherapy (CRT) has been shown comparable or superior to postoperative treatment in terms of various end points,1–3 and preoperative radiation dose and time interval are significant predictors of the pathological complete response (pCR) rate and downstaging.4 However, different viewpoints exist regarding the optimal dose–time fractionation schedule of preoperative radiotherapy (RT) and time to surgery.

Conventionally, long-course RT (i.e. 1.8–2.0 Gy per day; total dose of 45–50.4 Gy), frequently combined with chemotherapy, has been the preferred approach for a majority of patients in most countries, particularly in the United States and in Southern Europe. Short-course RT (i.e. 5 Gy per day; total dose of 25 Gy) and surgery within the following week has been commonly used in Sweden and some other countries in Northern and Western Europe. Recently, short-course RT with delay to surgery has also been demonstrated a useful alternative to these two schedules.5 In fact, treatment differences exist even across institutions within the same country.6

Traditionally, preoperative RT has been delivered via three-dimensional conformal RT...
Local recurrence (LR) is a serious problem because it causes disabling symptoms and successful salvage of pelvic recurrence is rarely possible. Just 34 years ago, the LR risk was greatly reduced from 25% to 16% with the advent of postoperative RT, with anterior and posterior parallel opposed fields. In 2004, the German Rectal Cancer Study Group demonstrated improved LC and reduced toxicity when CRT with a three- or four-field technique was delivered preoperatively instead of postoperatively, and LR at 5 years was further reduced from 13% to 6%. In 2005, at a median follow up of 13 years, the Swedish rectal cancer trial eventually reported that LR was only 9% after short-course RT with immediate surgery. Therefore, preoperative RT/CRT for rectal cancer was found to be beneficial for reducing LR rates.

**The era of 3D-CRT**

Local recurrence (LR) is a serious problem because it causes disabling symptoms and successful salvage of pelvic recurrence is rarely possible. Just 34 years ago, the LR risk was greatly reduced from 25% to 16% with the advent of postoperative RT, with anterior and posterior parallel opposed fields.11 In 2004, the German Rectal Cancer Study Group demonstrated improved LC and reduced toxicity when CRT with a three- or four-field technique was delivered preoperatively instead of postoperatively, and LR at 5 years was further reduced from 13% to 6%.12 In 2005, at a median follow up of 13 years, the Swedish rectal cancer trial eventually reported that LR was only 9% after short-course RT with immediate surgery.13 Therefore, preoperative RT/CRT for rectal cancer was found to be beneficial for reducing LR rates.

**Conventional as well as hypo- and hyperfractionated RT strategies and time intervals**

During the last 2 decades, more modern trials have examined the most appropriate treatment schedule. Polish and Australian trials compared long-course CRT (28×1.8 Gy) and surgery 4–6 weeks later with short-course RT (5×5 Gy) and surgery within 7 days for cT3/T4 disease.14–16 No significant differences were observed in postoperative complications, LC, late toxicity, recurrence-free survival (RFS), disease-free survival (DFS), or OS; nevertheless, a significantly higher acute radiation toxicity was observed with long-course CRT. In 2017, the Stockholm III trial used three regimens: either short-course RT (5×5 Gy) with surgery within 1 week or after 4–8 weeks or 25×2 Gy with surgery after 4–8 weeks.5 No significant differences in local and distant recurrences or in RFS and OS were reported among the three different RT regimens. Compared with short-course RT with immediate surgery, postoperative complications were significantly reduced by delaying surgery; however, acute radiation-induced toxicities were seen in ~7% of these patients after much delay. In addition to a hypofractionated RT regimen (5×5 Gy), a hypofractionated RT schedule (30 Gy in 10 once-daily fractions) was tested in China to minimize side effects without compromising therapeutic efficacy.17 After a median follow up of 63.8 months, 5-year DFS and OS rates were 64.5% and 75.6% respectively. Moreover, grade ≥3 acute toxicity rates was only 1.2%, and the total grade ≥3 late RT toxicity rate was down to 2.7%.18

In order to verify the hypothesis that hyperfractionated accelerated radiotherapy (HART) may provide a favorable long-term outcome compared to hypofractionated RT, the pelvis was irradiated twice daily, with a minimal interfraction interval of 6h, and a total dose of 42 Gy was administered in doses of 1.5 Gy per fraction.19 Surgery was performed 1–2 weeks after RT. The results showed that the physical, emotional, and social functioning of long-term survivors were significantly better with HART; however, when compared with hypofractionated RT, there was no significant difference regarding LC and OS. In order to ensure that the overall treatment time was shorter than the proliferation delay Tₚ, set to 7 days,20 RT was delivered with a single fraction of 2.5 Gy twice daily (≥6h intervals) to a total dose of 25 Gy. Surgery was performed the following week.21 The clinical trial showed that LC was excellent in primarily resectable rectal cancer. Combined with S-1 as a radiosensitizer, this regimen of a 4-week delay in surgery also showed acceptable oncologic outcomes for T3 rectal cancer.22,23

There are many other dose fractionations of preoperative RT in addition to the above schedules. Figure 1(a, b) shows the most commonly used regimens.24–52 Here, a biologically effective dose
(BED) was calculated according to a linear-quadratic (LQ) model of radiation effect. BED was evaluated at the isocenter. In this model, $\alpha/\beta$ ratio of 10 was adopted for tumor tissue.20,53,54 Most of the regimens had larger BEDs of $\geq 30$ Gy. Meanwhile, the dose curves steepened and became concentrated for $d > 1$ Gy after the overall treatment time (OTT) was considered. If $\text{BED}_{3}/\text{BED}_{10}$ is used to represent the risk/benefit ratio of preoperative RT, 3–4 Gy per fraction using once-daily RT regimen or 2 Gy per fraction using twice/thrice-daily RT regimen might be optimal [Figure 1(c, d)]. In most centers, RT fractionation schedules and time to surgery are based on their clinical practice experiences. Given the different combination schemes of dose fractionation and time to surgery, a goal interval of 6–8 weeks is the most commonly used value in clinical trials [Figure 2(a)].5,15,17,18,21,24,27,28,31,32,34–36,38–42,44,46–48,50,52,55–94 Moreover, because of factors such as acute radiation reaction, there are some discrepancies between the goal intervals and true intervals.95 Despite limited samples, a linear correlation can be observed between them in Figure 2(b). In addition, because of the semi-Poisson distribution of the actual time interval,95 the mean values of goal time gaps are usually smaller than the median true time intervals [Figure 2(b)].5,18,21,24,32,36,38,41,43,44,46,47,52,56,61,70,73,74,79,80,82,90,91,93,96–108 It seems that surgery is usually performed early for most patients within a planned schedule.

Although the goals of preoperative RT/CRT are to minimize the recurrence risk, optimize survival, and avoid toxicity, different strategies have led to different outcomes. However, it is clinically relevant to wait for the highest degree of pathological response, as this helps to identify the optimal time to surgery and increases the chance of R0 resection. Moreover, patients might exhibit...
such favorable response that they become candidates for a watch-and-wait approach or local excision. Additionally, patients with a pCR might have better DFS and OS. Therefore, an enhanced radiation response is necessary for a better pathologic response after preoperative RT/CRT.

Early endpoints: pathologic tumor response
Several parameters have been considered to quantify tumor response, such as T (tumor size) and N (number of nearby lymph nodes) status downstaging and pCR. In China, a pCR rate of 4.5% and a downstaging rate of 70.2% were achieved using the 30 Gy protocol and surgery after 2 weeks. A high pCR rate of 11.8% was reported in the short-course RT-with-delay arm. A Polish trial showed an even higher pCR of 16.1% using conventional long-course CRT and surgery 4–6 weeks later. The tumor response could be further increased by the addition of specific chemotherapy regimens in preoperative setting.

Furthermore, a highly significant dose–response relationship was observed. For example, a trend toward increased pCR with higher doses was reported, with pCR being 15%, 23%, and 33% at 40 Gy, 46 Gy, and 50 Gy, respectively. Figure 3(a) also shows that increasing RT doses were associated with tumor response, but the incremental rates were different because of additional chemotherapy, and RT techniques, etc. However, if OTT was considered using this LQ model, the trends became very similar among some trials [Figure 3(b, c, d)]. Furthermore, improved response could be enhanced with intraoperative RT or with high-dose-rate γ-ray or contact X-ray brachytherapy boost.

Tumor regression takes time (median volume-halving time, 14 days). Several studies have previously demonstrated improved pCR after long time intervals (Table 1, longer intervals might not increase pCR in particular cohorts). The Korean Radiation Oncology Group found that pCR steadily increased after 5–6 weeks, escalated over 10% after 6–7 weeks, and peaked at 9–10 weeks for locally advanced rectal cancer. The downstaging rate increased steadily until 6–7 weeks and declined afterward. For patients with cT1-4N0-2M0-1, the highest pCR rates were observed at approximately 10–11 weeks from the end of long-course CRT. A waiting time exceeding 11 weeks might be associated with higher morbidity and a more difficult surgical resection because of tissue fibrosis and friability. After accounting for well-known confounders, such as comorbidities and tumor characteristics, an optimal threshold of 56 days (8 weeks) was determined after completion of neoadjuvant CRT for minimizing the risk of positive margins and maximizing pathologic downstaging.
Figure 3. Comparison of reported dose–response relationships between $BED_{10}$ and pCR. Studies on preoperative CRT were included if they were conducted to treat rectal cancer, comparing conventional dose with intensified dose. Data from eight comparative studies were analyzed. Logistic response curves fitted for each study. (a) $BED_{10}$ without OTT correction. $D_{50}$ (the dose required for 50% response) ranged from 68.3 to 108.0 Gy, and the normalized dose–response gradient $G_{50}$ at $D_{50}$ ranged from 0.87 to 2.42. (b, c, d, e) $BED_{10}$ with OTT correction: (b) three studies conducted by Hall, Kairevičė, and Rombouts showed very close results; $D_{50}$ was $59.0 \pm 13.5$ Gy, $58.8 \pm 19.0$ Gy, and $59.1 \pm 13.8$ Gy, but $G_{50}$ was $1.40 \pm 0.18$, $2.12 \pm 0.41$, and $1.56 \pm 0.21$, separately; (c) two studies performed by Mohiuddin and Wiltshire demonstrated that $D_{50}$ was $49.8 \pm 5.5$ Gy and $51.6 \pm 4.1$ Gy, and $G_{50}$ was $1.65 \pm 0.12$ and $1.78 \pm 0.10$; (d) Three groups also got the similar results. $D_{50}$ was $70.1 \pm 15.4$ Gy, $70.0 \pm 22.3$ Gy and $72.6 \pm 8.0$ Gy, and $G_{50}$ was $1.08 \pm 0.12$, $0.98 \pm 0.16$ and $1.03 \pm 0.07$, separately; and (e) No similar results were observed.

BED, biologically effective dose; OTT, overall treatment time, pCR, pathological complete response.
Table 1. Literature review.

| Study (year) | Study type | RT dose (Gy) | Chemotherapy | TME (yes/no) | Intervals (weeks) | Patients | Preoperative stages | Age (years) | Males (%) | pCR (%) | LR (%) | DFS (%) | OS (%) |
|-------------|------------|--------------|--------------|--------------|------------------|----------|---------------------|-------------|-----------|---------|--------|---------|--------|
| Francois et al.130 | Prospective | 13 × 3 | No | No | <2 | 99 | T2–4, N0–1 | 66 | 57.6 | 7.1 | 3 years: 9 | NR | 3 years: 78 |
| Stein et al.131 | Prospective | (25–30) × 1.8 | c.i. 5-FU + CPT-11 | Yes | 4–8 | 19 | T2–4, N0–1 | 51 | 74 | 21 | NR | NR | NR |
| Moore et al.132 | Retrospective | (26–28) × 1.8 | Bolus 5-FU/LV | No | <44 days | 82 | I–III | 59 | 63.4 | 12 | NR | NR | NR |
| Tran et al.133 | Retrospective | (25–30) × 1.8 | 5-FU | Yes | ≤44 days | 16 | II–III | 62 | 62 | 6 | NR | NR | NR |
| Veenhof et al.134 | Retrospective | 5 × 5 | No | Yes | <2 | 98 | T2–3, N0–1 | 67 | 65 | 0* | 5 years: 2 | 5 years: 74.6 | 5 years: 66.4 |
| Lim et al.135 | Retrospective | 28 × 1.8 | FL, CAP, or IC | No | 4–6 | 217 | T2–4 | 55* | 64 | 13.8 | NR | NR | NR |
| Tulchinsky et al.136 | Retrospective | (25–28) × 1.8 | 5-FU | Yes | ≤7 | 48 | II–III | 59* | 73 | 16.7* | 6 | NR | NR |
| Garcia-Aguila et al.137 | Prospective | (25–30) × 1.8 | 5-FU | Yes | >7 | 84 | III–IV | 66* | 64 | 34.5* | 4 | NR | NR |
| de Campos-Lobato et al.138 | Retrospective | 28 × 1.8 | 5-FU | Yes | <8 | 83 | T1–4, N0–2 | 54 | 76 | 16.2* | 3 years: 10.5* | 3 years: 75.3 | 3 years: 85.5 |
| Wolthuis et al.139 | Retrospective | 25 × 1.8 | 5-FU | Yes | <7 | 201 | T2–4, N0–2 | 64 | 62 | 15.9* | 5 years: 3 | NR | 5 years: 84 |
| Jeong et al.140 | Retrospective | 28 × 1.8 | 5-FU + LV | Yes | <8 | 105 | T1–4, N0–2 | 58 | 75 | 16.2 | 3 years: 7.8 | 3 years: 64.8 | 3 years: 90.2 |
| Sloothaak et al.141 | Retrospective | 25 × 2 or 28 × 1.8 | CAP or 5-FU ± oxaliplatin | Yes | <8 | 312 | T1–4, N0–2, M0–1 | 63 | 64 | 10.3* | NR | NR | NR |

(Continued)
| Study (year) | Study type | RT dose (Gy) | Chemotherapy | TME | Intervals (weeks) | Patients | Preoperative stages | Age (years) | Males (%) | pCR (%) | LR (%) | DFS (%) | OS (%) |
|-------------|------------|--------------|--------------|-----|------------------|---------|---------------------|------------|-----------|---------|--------|---------|--------|        |
|             |            |              |              |     |                  |         |                     |            |           |         |        |         |        |         |
| F Jin, H Luo et al. | journals.sagepub.com/home/tam | 7 | | | | | | | | | | | |
| Study type | RT dose (Gy) | Chemotherapy | TME | Intervals (weeks) | Patients | Preoperative stages | Age (years) | Males (%) | pCR (%) | LR (%) | DFS (%) | OS (%) |
|------------|-------------|--------------|-----|------------------|---------|---------------------|------------|-----------|---------|--------|---------|--------|        |
| Zeng96     | Retrospective | 25 x 2 | CAP | Yes | <7 | 111 | T2-4, N0-2 | 59 | 56 | 15.3* | 3 years: 12.9 | 3 years: 72.6 | 3 years: 89.0 |
|            |             |            |      |      | >7 | 122 | T2-4, N0-2 | 59 | 56 | 27.1* | 3 years: 4.8 | 3 years: 79.4 | 3 years: 94.5 |
| Calvo83    | Retrospective | 28 x 1.8 + 10-15 Gy IORT | Bolus 5-FU + LV | Yes | <6 | 136 | T2-4 | 66 | 67* | 8.8 | 5 years: 9.6 | 5 years: 69.9 | 5 years: 55.9* |
|            |             |            |      |      | >6 | 199 | T2-4 | 66 | 55* | 12.1 | 5 years: 5.5 | 5 years: 74.9 | 5 years: 70.4* |
| You140     | Retrospective | 25 x 2 | FOLFOX6 or XELOX | Yes | <7 | 139 | T1-4, N0-2 | 55 | 69 | 27.3* | 5 years: 74.7 | 5 years: 84.4 |
|            |             |            |      |      | >7 | 152 | T1-4, N0-2 | 56 | 71 | 29.6* | 5 years: 66.8 | 5 years: 75.3 |
| Mihmanlı141 | Retrospective | [25-28] x [1.8-2] | 5-FU | Yes | <8 | 45 | T2-4 | 54 | 71 | 8.9* | 6 years: 8.9 | 5 years: 55.3* | 5 years: 79.1* |
|            |             |            |      |      | >8 | 42 | T2-4 | 58 | 74 | 19.0* | 6 years: 7.1 | 5 years: 85.1* | 5 years: 94.4* |
| Akbar142   | Retrospective | 28 x 1.8 | XELOX | Yes | <=8 | 66 | T2-4, N0-2 | NR | 65 | 30 | 12 | 5 years: 66.7* | 5 years: 68.2 |
|            |             |            |      |      | >=8 | 93 | T2-4, N0-2 | NR | 68 | 33 | 25 | 5 years: 53.8* | 5 years: 54.3 |
| Macchia126 | Retrospective | NR | One or two drugs | Yes | <=6 | 300 | II-III | 66* | 60 | 12.6* | NR | NR | NR |
|            |             |            |      |      | >6 | 1598 | II-III | 65* | 64 | 23.0* | NR | NR | NR |
|            |             |            |      |      | >13 | 196 | II-III | 67* | 62 | 31.1* | NR | NR | NR |
| Couwen-berg125 | Retrospective | [25-28] x [1.8-2] | CAP | Yes | 3-6 | 479 | T1-4, N0-2 | 66.4 | 62.0 | 15.7 | NR | NR | NR |
|            |             |            |      |      | 7-8 | 1309 | T1-4, N0-2 | 63.5 | 65.8 | 13.9 | NR | NR | NR |
|            |             |            |      |      | 9-10 | 1668 | T1-4, N0-2 | 64.1 | 61.2 | 16.9* | NR | NR | NR |
|            |             |            |      |      | 11-12 | 1287 | T1-4, N0-2 | 64.3 | 63.0 | 15.6 | NR | NR | NR |
|            |             |            |      |      | 13-20 | 945 | T1-4, N0-2 | 64.4 | 63.6 | 16.8* | NR | NR | NR |
| Akgun124   | Prospective | 28 x 1.8 | 5-FU + LV | Yes | <=8 | 160 | T3-4, N+ | 60.4 | 59 | 10.0* | NR | NR | NR |
|            |             |            |      |      | >8 | 167 | T3-4, N+ | 61.7 | 57 | 18.6* | NR | NR | NR |

*p < 0.05.
5-FU, 5-fluorouracil; CAP, capecitabine; c.i., continuous infusion; CPT-11, irinotecan; DFS, disease-free survival; FL, 5-fluorouracil + leucovorin; FOLFOX6, oxaliplatin + leucovorin + 5-FU; IORT, intraoperative radiotherapy; LR, local recurrence; LV, leucovorin; mFOLFOX-6, modified FOLFOX-6; IC, irinotecan + capecitabine; N, number of nearby lymph nodes stage; NR, not reported; OS, overall survival; pCR, pathological complete response; RT, radiotherapy; T, tumor size stage; TME, total mesorectal excision; XELOX, oxaliplatin + capecitabine.
Long-term endpoints: LC and survival

After a median follow up of 11 years, the German CAO/ARO/AIO-94 trial reported that 10-year LR and OS rates were 7.1% and 59.6%, respectively, using 50.4 Gy in 28 fractions. After a median follow up of 12 years, the TME trial finally reported that 10-year LR and OS rates were 5% and 48% respectively, with short-course RT. The effect of RT on LC persisted, as well as the absence of a survival benefit. Nevertheless, it significantly improved survival in patients with a pCR, downstaging, or a negative circumferential margin.

Early systematic reviews concluded that preoperative RT at a BED of >30 Gy reduced LR risk and improved OS, and that no significant difference was observed in outcomes for different time intervals between conventional neoadjuvant CRT and surgery. Moreover, higher doses increased LR reduction. A linear dose–response effect of BED was seen on the risk reduction of LR, and an exponent correlation was detected between LR and BED (Figure 4). Each 1 Gy increase in BED would reduce LR rates by 1.36–1.72%; hence, it was proposed that a BED of approximately 68.8–73.5 Gy would be needed to achieve 100% LC.

In contrast to the linear effect of BED on reduction in LR, the effects of BED on DFS and OS were not linear due to considerable heterogeneities. After dose escalation with three dose levels of 40 Gy, 46 Gy and 50 Gy, 2-year actuarial LR-free survival rates were 72%, 90%, and 89%, respectively; DFS rates were 62%, 84%, and 78%, respectively; OS rates were 72%, 94%, and 92%, respectively. A statistically significant increase in survival was seen with doses of ≥46 Gy, but there was no difference in survival between doses of 46 Gy and 50 Gy. However, after a long follow up of 11.9 years, patients with a concomitant dose boost (52.5 Gy) exhibited higher rates of 10-year OS than those for whom a conventional approach was used (45 Gy; 71.6% versus 62.4%).

As a radiation sensitizer, chemotherapy may augment RT. It may also sterilize circulating micrometastases and impede disease progression and distant organ involvement. Prolongation of DFS and OS are ultimately expected. However, previous studies have demonstrated that a combination of preoperative RT and preoperative, with or without postoperative fluorouracil-based chemotherapy, would only further increase LC, without showing any significant differences in DFS and OS. However, it might benefit patients with a tumor 10–15 cm from the anal verge in terms of DFS. Recently, the final results of the German CAO/ARO/AIO-94 trial showed that DFS at 3 years could be improved after adding oxaliplatin to fluorouracil-based neoadjuvant CRT for patients with cT3–4 rectal cancer. However, this trial had serious methodological shortcomings. Although the benefits of chemotherapy on DFS are limited, as shown by the published data, current guidelines continue recommending a chemotherapy course because there is no sufficient evidence to conclude there is no absolute benefit of chemotherapy.

Figure 4. Comparison of reported dose–response relationships between BED_{10} and LR.

(a) The linear regression model fitted for risk reduction of LR as a function of BED_{10}. (b) Exponent curves fitted for LR versus BED. BED, biologically effective dose; LR, local recurrence; RT, radiotherapy; ndf, the number of degrees of freedom; p0, the fitting parameter; Prob, probability.
Preoperative CRT can induce serious side effects such as diarrhea, urinary tract infection, sexual dysfunction, and secondary malignancies. Meanwhile, toxicities and complications related to RT have also increased with the greater use of neoadjuvant CRT. The impact of RT on sexual, urinary, and anal functions has been documented in many previous trials, although surgery is likely to be the major factor. However, in 2019, a prospective study demonstrated that neoadjuvant CRT for lower rectal cancer did not affect postoperative urinary function, treatments, the timing, and evaluation methods vary largely among these trials. Direct investigations of the effect of RT dose on the anorectal function have been reported recently; a higher RT dose to anal sphincter complex tends to worsen the long-term anorectal function.

Furthermore, many trials demonstrated that there were no significant differences in severe late toxicity and quality of life with short-course RT with immediate surgery, and conventionally fractionated CRT with delayed surgery; however, CRT clearly increased the grade 3–4 acute toxicity. A recent retrospective analysis revealed that a dose boost did not increase the grade ≥ 2 chronic toxicity after neoadjuvant CRT. Interestingly, the Radiation Therapy Oncology Group (RTOG) trial 0012 compared hyperfractionated radiation (55–60 Gy) with once-daily radiation (50–55 Gy) and also found the similar acute and late toxicities. Regarding the effect of timing intervals on toxicity, although the Stockholm III trial revealed that acute toxicity was only <1% after RT with immediate surgery compared with 5–7% after RT with delay, it is possible that these toxicities were obscured by early postoperative complications.

The addition of chemotherapy to preoperative RT has a sound radiobiological rationale, but will simultaneously increase grade III and IV acute toxicities. In a study, gastrointestinal (GI) toxicity was more frequently observed in the CRT group than in the RT-alone group (28.1% versus 12.9%, respectively); a consequence of the increased toxicity was that the patients could not receive the full treatment or they experienced interruptions that could have a negative impact on outcomes. At present, no statistical difference was reported in late toxicity between the preoperative RT and CRT groups.

In summary, moderate RT dose escalation using the 3D-CRT technique and appropriate chemotherapy administration might be effective. The optimal time interval depends on clinical endpoints. There still remains a scope for the optimization of RT/CRT schedules. Although there is conflicting evidence because of various factors, strategies with the potential to improve outcomes, while reducing toxicities, are needed to guide future designs.

The era of IMRT
Early in 1993, MacFarlane and colleagues reported that total mesorectal excision (TME) instead of conventional surgery had led to substantial improvements in morbidity and survival. It is hoped that improvements in RT techniques will further reduce LR and adverse events, and increase the survival. As an innovative technique, IMRT allows conformal dose distribution in the target while sparing the bladder and bowels. It is of critical importance for accurate target determination and strict dose–volume constraints. With the integration of image guidance and IMRT, both a more precise definition of target volume and accurate irradiation are allowed. Organ motion with changes in shape, size and position can be observed; a small target margin can be applied, consequently reducing potential toxicity. Using a synchronous integrated boost (SIB) technique, the dose per fraction can be further increased to the primary tumor while shortening the treatment time. However, adequate quality controls of procedures are always required.

Point: IMRT improves clinical endpoints
Multiple retrospective studies have shown that preoperative IMRT or volumetric-modulated arc therapy (VMAT, arc-based IMRT) is associated with a clinically significant reduction in GI or genitourinary (GU) toxicity, with or without improvement in LC compared with 3D-CRT. Furthermore, these modalities can potentially prevent delays in time to surgery and reduce hospitalizations, emergency department visits, and treatment breaks. However, no significant differences were noted in tumor responses, DFS and OS.

Furthermore, several prospective studies have shown encouraging results. Preoperative IMRT with an SIB [46 + 55.2 (Gy) in 23 fractions] was
Therapeutic Advances in Medical Oncology 12

The grade $\geq 3$ late GI and GU toxicity was 9% and 4%, respectively; 5-year LC and OS were 97% and 68%, respectively. These values were in line with the results after preoperative CRT. \(^{12,151}\) In order to reach the best loco–regional control and to prevent systemic relapse, RT and chemotherapy are usually integrated. A Turkish study adopted hypofractionated RT (33 Gy/10 fractions), with concurrent oral capecitabine. Surgery was scheduled 6–8 weeks after the end of CRT; 11.5% of patients had pCR, and no grade 3–4 toxicity was observed. \(^{173}\) Another phase II trial studied IMRT (47.5 Gy in 19/20 fractions) in combination with capecitabine and oxaliplatin (CAPEX). TME was scheduled 4–6 weeks after the CRT. A pCR was observed in 13% of patients, and major response in 48%, which seemed to translate into improved outcomes such as LC of 100%, DFS of 84%, and OS of 87%, after a median follow up of 55 months.\(^{47}\)

Moreover, preoperative IMRT with an SIB without dose escalation [41.8 $\times$ 46.2/48.4 (Gy) in 22 fractions], with concomitant capcitabine, was tested. Surgery was performed 6–8 weeks later. The rate of grade $\geq 3$ acute toxicity was 2.4%. A total of 25.5% patients achieved pCR, with 2-year LC, DFS, and OS rates of 100% for these patients.\(^{92}\) If dose was escalated with an SIB [46 $\times$ 57.5 (Gy) in 23 fractions], and concomitant with capcitabine, surgery was planned around 8 weeks. A total of 30.6% of patients could achieve pCR with quite acceptable toxicity profiles.\(^{44}\) At a median follow up of 38.2 months, the similar treatment schemes [45 $\times$ 55 (Gy) in 25 fractions, capcitabine, surgery 8 weeks later] resulted in 2-year DFS and OS of 90% and 90%, respectively, with a high pCR rate of 35%.\(^{41}\)

To obtain a better tumor response, elevating treatment dose has been considered a feasible method. Preoperative capcitabine and IMRT with an SIB [45 $\times$ 55 (Gy) in 25 fractions] were used and TME followed 6 weeks later. The crude pCR rate was up to 38%, with 50% achieving downstaging.\(^{91}\) Recently, a near-total neoadjuvant approach was tested using multiagent chemotherapy, that is, sequential short-course IMRT (5 $\times$ 5 Gy) and FOLFOX (fluorouracil, leucovorin calcium, and oxaliplatin) followed by TME. A higher T downstaging of 75% and a superior 3-year DFS rate of 85% were observed compared with conventional neoadjuvant CRT (41% and 68%, respectively).\(^{94}\)

The role of preoperative IMRT in rectal cancer remains to be determined at this juncture. Moreover, the addition of different chemotherapy and different treatment sequences confound it more. CRT-to-surgery interval also affects these clinical endpoints in the era of IMRT.\(^{178}\) More trials with the prospective aim to further explore the efficiency of preoperative IMRT are expected.

Meanwhile, the limitations and potential difficulties inherent to IMRT, that is, dose inhomogeneity and integral dose, must be considered. Patient selection is of utmost importance. IMRT is also technically challenging, because the oncological outcomes are highly dependent on accurate target determination and dose–volume parameters. Careful quality assurance with regards to target delineation, image guidance, and plan optimization constraints is needed prior to treatment.

Using the SIB technique, two different doses per fraction are usually delivered in two different target regions, that is, a two-target approach. Neoadjuvant chemotherapy prior to preoperative RT/CRT gives us a chance to induce tumor regression, which allows the dose to the macroscopic postchemotherapy tumor to be increased by several additional Gy using the third targets. Additionally, a dynamic target could be generated within the frame of adaptive RT to accompany dose escalation. Also, it appears promising to harness functional imaging to guide dose to

Counterpoint on IMRT and corresponding deliberation

Although preoperative IMRT has shown improved oncological outcomes, conflicting results are constantly being published. A retrospective study has demonstrated that IMRT was associated with worse R0 resection rates and sphincter preservation, without any differences in pathologic downstaging, unplanned readmission, or long-term OS.\(^{179}\) A prospective phase II study used VMAT-SIB [45 $\times$ 57.5 (Gy) in 25 fractions] and two-drug chemotherapy CAPOX. Radical resection was performed 8 weeks after treatment. Although a very high tumor response was achieved, an acute toxicity rate of 44% was also recorded.\(^{50}\) RTOG 0822 studied IMRT (25 $\times$ 1.8 Gy), followed by a boost (3 $\times$ 1.8 Gy) using 3D-CRT with concurrent CAPOX. Surgery was performed 4–8 weeks after CRT. A grade $\geq 2$ GI toxicity rate of 51.5% occurred preoperatively, which substantially exceeded the target rate of 28%.\(^{177}\)
subvolumes of the target with a high tumor load and de-escalate dose to low-risk volumes.

In summary, trimodality therapy for rectal cancer inherently has uncertainties: treatment sequence, timing, and duration of the various modalities. Many treatment paradigms have been tested, such as surgery ± adjuvant RT/CRT, and preoperative RT/CRT/chemotherapy ± surgery ± CRT (Figure 5). However, until now, most fractionation schedules in preoperative RT have been empirical and based on the outcome of clinical trials. Fractionation schedules and the time interval are rather homogeneous across various institutions. Given patient selection and other treatment interventions, one cannot accurately assess whether and to what extent they influence clinical outcomes. If a radiobiological response model for fractionation is established on the basis of previous clinical studies, the controversy regarding dose fractionation schedules and time interval may disappear.

In addition, with the widespread standardization of surgery, diversification of drug, and precision of RT, the specific modality will be eliminated or used more sufficiently for a subset of patients, such as a ‘watch and wait’ strategy after preoperative RT/CRT, neoadjuvant chemotherapy only, and multidrug CRT. The priority for future research should be subgroups of patients who might receive relatively greater benefit from innovative treatment techniques. Moreover, with the development of technology and change in people’s
understanding, the optimal regimen will also constantly change. These studies will be critical to further implementation of precision medicine through maximizing clinical outcomes, while minimizing associated toxicities.

New era: particle RT such as proton and heavy ions

Particle RT has recently garnered great attention. It can deliver radiation with a highly conformal dose distribution while maintaining minimal excess dose to normal tissues. Additionally, it is coupled with various biological advantages, especially for heavy-ion beam, such as a lack of oxygen effect and less cell cycle-related radiosensitivity. It enables treatment of diseases that are inaccessible with conventional RT, for example, postoperative recurrence of rectal cancer.

A recent report has shown that patients were treated with 73.6 GyE (physical dose multiplied by relative biological effectiveness) in 16 fractions using carbon ion. The 5-year LC rate was 88% and survival was 59%. These figures are higher than those with photon RT. Moreover, particle RT might be further optimized by dose escalation or hypofractionation. Given a high rate of distant metastases in most studies, concurrent and adjuvant systemic therapies should also be investigated.

Acknowledgements

Fu Jin and Huanli Luo contributed equally to this work. The authors thank the following colleagues for their assistance and advice in this study: Shi Li, Xia Tan, Xianfeng Liu, Xia Huang, Qicheng Li, Mingsong Zhong, Han Yang, Chao Li, Yanan He, Xiumei Tian, Da Qiu, Guanglei He, Li Yin, Guang Li, and Bo Li. The interim findings on relationships between biologically effective dose and pathological complete response, and local recurrence were presented at the ESMO as a poster. The poster’s abstract was published in Annals of Oncology (2019) 30 (suppl_9):ix30-ix41.10.1093/annonc/mdz421.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work is supported by the National Natural Science Foundation of China under grant no. 11575038 and 11805025.

Conflict of interest statement

The authors declare that there is no conflict of interest.

Supplemental material

Supplemental material for this article is available online.

References

1. 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: 1926–1933.

2. 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.

3. Song JH, Jeong JU, Lee JH, et al. Preoperative chemoradiotherapy versus selective postoperative chemoradiotherapy for stage II-III resectable rectal cancer: a meta-analysis of randomized controlled trials. Radiat Oncol 2017; 35: 198–207.

4. Hall MD, Schultheiss TE, Smith DD, et al. Effect of increasing radiation dose on pathologic complete response in rectal cancer patients treated with neoadjuvant chemoradiation therapy. Acta Oncol 2016; 55: 1392–1399.

5. Erlandsson J, Holm T, Pettersson D, et al. Optimal fractionation of preoperative radiotherapy and timing to surgery for rectal cancer (Stockholm III): a multicentre, randomised, non-blinded, phase 3, non-inferiority trial. Lancet Oncol 2017; 18: 336–346.

6. Morris EJ, Finan PJ, Spencer K, et al. Wide variation in the use of radiotherapy in the management of surgically treated rectal cancer across the English national health service. Clin Oncol (R Coll Radiol) 2016; 28: 522–531.

7. Jacobs BL, Zhang Y, Schroek FR, et al. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. JAMA 2013; 309: 2587–2595.

8. Nutting CM, Morden JP, Harrington KJ, et al. Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial. Lancet Oncol 2011; 12: 127–136.
9. Chun SG, Hu C, Choy H, et al. Impact of intensity-modulated radiation therapy technique for locally advanced non-small-cell lung cancer: a secondary analysis of the NRG oncology RTOG 0617 randomized clinical trial. *J Clin Oncol* 2017; 35: 56–62.

10. Yang Y, Feng L, Wang Y, et al. A dosimetric analysis of preoperative intensity-modulated and image-guided radiation therapy with and without simultaneous integrated boost for locally advanced rectal cancer. *Technol Cancer Res Treat* 2015; 14: 557–563.

11. Gastrointestinal Tumor Study Group. Prolongation of the disease-free interval in surgically treated rectal carcinoma. *N Engl J Med* 1985; 312: 1465–1472.

12. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. *N Engl J Med* 2004; 351: 1731–1740.

13. Folkesson J, Birgisson H, Pahlman L, et al. Swedish rectal cancer trial: long lasting benefits from radiotherapy on survival and local recurrence rate. *J Clin Oncol* 2005; 23: 5644–5650.

14. Buijk K, Nowacki MP, Nasierowska-Guttmejer A, et al. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. *Br J Surg* 2006; 93: 1215–1223.

15. Ngan SY, Burmeister B, Fisher RJ, et al. Randomized trial of short-course radiotherapy versus long-course chemoradiation comparing rates of local recurrence in patients with T3 rectal cancer: Trans-Tasman Radiation Oncology Group trial 01.04. *J Clin Oncol* 2012; 30: 3827–3833.

16. Ansari N, Solomon MJ, Fisher RJ, et al. Acute adverse events and postoperative complications in a randomized trial of preoperative short-course radiotherapy versus long-course chemoradiotherapy for T3 adenocarcinoma of the rectum: Trans-Tasman Radiation Oncology Group trial (TROG 01.04). *Ann Surg* 2017; 265: 882–888.

17. Zhan T, Gu J, Li M, et al. Intermediate-fraction neoadjuvant radiotherapy for rectal cancer. *Dis Colon Rectum* 2013; 56: 422–432.

18. Zhu XG, Li JL, Li XF, et al. Two-week course of preoperative radiotherapy for locally advanced rectal adenocarcinoma: 8 years’ experience in a single institute. *Am J Clin Oncol* 2017; 40: 266–273.

19. Wziętek I, Kryj M, Idasiak A, et al. Randomized clinical trial on hyperfractionated versus hypofractionated preoperative radiotherapy for rectal cancer: long term outcomes including quality of life assessment. *Int J Radiat Oncol Biol Phys* 2014; 90: S21.

20. Colorectal Cancer Collaborative Group. Adjuvant radiotherapy for rectal cancer: a systematic overview of 8,507 patients from 22 randomised trials. *Lancet* 2001; 358: 1291–1304.

21. Widder J, Herbst F, Dobrowsky W, et al. Preoperative short-term radiation therapy (25 Gy, 2.5 Gy twice daily) for primary resectable rectal cancer (phase II). *Br J Cancer* 2005; 92: 1209–1214.

22. Beppu N, Matsubara N, Kakuno A, et al. Feasibility of modified short-course radiotherapy combined with a chemoradiosensitizer for T3 rectal cancer. *Dis Colon Rectum* 2015; 58: 479–487.

23. Beppu N, Kimura F, Aihara T, et al. Patterns of local recurrence and oncologic outcomes in T3 low rectal cancer (≤ 5 cm from the anal verge) treated with short-course radiotherapy with delayed surgery: outcomes in T3 low rectal cancer treated with short-course radiotherapy with delayed surgery. *Ann Surg Oncol* 2017; 24: 219–226.

24. Derdel J, Mohiuddin M, Kramer S, et al. Is dose/time fractionation important in treating rectal cancer? *Int J Radiat Oncol Biol Phys* 1985; 11: 579–582.

25. Glimelius B, Grönberg H, Järhult J, et al. A systematic overview of radiation therapy effects in rectal cancer. *Acta Oncol* 2003; 42: 476–492.

26. Sanghera P, Wong DW, McConkey CC, et al. Chemoradiotherapy for rectal cancer: an updated analysis of factors affecting pathological response. *Clin Oncol (R Coll Radiol)* 2008; 20: 176–183.

27. Guckenberger M, Saur G, Wehner D, et al. Comparison of preoperative short-course radiotherapy and long-course radiochemotherapy for locally advanced rectal cancer. *Strahlenther Onkol* 2012; 188: 551–557.

28. Ortholan C, Romestaing P, Chapet O, et al. Correlation in rectal cancer between clinical tumor response after neoadjuvant radiotherapy and sphincter or organ preservation: 10-year results of the Lyon R 96-02 randomized trial. *Int J Radiat Oncol Biol Phys* 2012; 83: e165–e171.

29. Viani GA, Stefano EJ, Soares FV, et al. Evaluation of biologic effective dose and
30. Vestermark LW, Jensen HA and Pfeiffer P. High-dose radiotherapy (60 Gy) with oral UFT/ folinic acid and escalating doses of oxaliplatin in patients with non-resectable locally advanced rectal cancer (LARC): a phase I trial. *Acta Oncol* 2012; 51: 311–317.

31. Burbach JP, den Harder AM, Intven M, et al. Impact of radiotherapy boost on pathological complete response in patients with locally advanced rectal cancer: a systematic review and meta-analysis. *Radiother Oncol* 2014; 113: 1–9.

32. Ceelen W, Boterberg T, Pattyn P, et al. Neoadjuvant chemoradiation versus hyperfractionated accelerated radiotherapy in locally advanced rectal cancer. *Ann Surg Oncol* 2007; 14: 424–431.

33. Glimelius B. Neo-adjuvant radiotherapy in rectal cancer. *World J Gastroenterol* 2013; 19: 8489–8501.

34. Hartley A, Ho KF, McConkey C, et al. Pathological complete response following pre-operative chemoradiotherapy in rectal cancer: analysis of phase II/III trials. *Br J Radiol* 2005; 78: 934–938.

35. Idasiak A, Galwas-Kliber K, Behrendt K, et al. Pre-operative hyperfractionated concurrent radiochemotherapy for locally advanced rectal cancers: a phase II clinical study. *Br J Radiol* 2017; 90: 20160731.

36. Lorchel F, Peignaux K, Créhange G, et al. Preoperative radiotherapy in elderly patients with rectal cancer. *Gastroenterol Clin Biol* 2007; 31: 436–441.

37. Suwinski R, Taylor JM and Withers HR. Rapid growth of microscopic rectal cancer as a determinant of response to preoperative radiation therapy. *Int J Radiat Oncol Biol Phys* 1998; 42: 943–951.

38. Brooks S, Glynne-Jones R, Novell R, et al. Short course continuous, hyperfractionated, accelerated radiation therapy (CHART) as preoperative treatment for rectal cancer. *Acta Oncol* 2006; 45: 1079–1085.

39. Lee JH, Kim JG, Oh ST, et al. Two-week course of preoperative chemoradiotherapy followed by delayed surgery for rectal cancer: a phase II multi-institutional clinical trial (KROG 11-02). *Radiother Oncol* 2014; 110: 150–154.

40. 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.

41. Tey J, Leong CN, Cheong WK, et al. A phase II trial of preoperative concurrent chemotherapy and dose escalated intensity modulated radiotherapy (IMRT) for locally advanced rectal cancer. *J Cancer* 2017; 8: 3114–3121.

42. Parekh A, Truong MT, Pashtan I, et al. Acute gastrointestinal toxicity and tumor response with preoperative intensity modulated radiation therapy for rectal cancer. *Gastrointest Cancer Res* 2013; 6: 137–143.

43. But-Hadzic J, Anderluh F, Brecelj E, et al. Acute toxicity and tumor response in locally advanced rectal cancer after preoperative chemoradiation therapy with shortening of the overall treatment time using intensity-modulated radiation therapy with simultaneous integrated boost: a phase 2 trial. *Int J Radiat Oncol Biol Phys* 2016; 96: 1003–1010.

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

45. Wang L, Li ZY, Li ZW, et al. Efficacy and safety of neoadjuvant intensity-modulated radiotherapy with concurrent capcitabine for locally advanced rectal cancer. *Dis Colon Rectum* 2015; 58: 186–192.

46. Myerson RJ, Tan B, Hunt S, et al. Five fractions of radiation therapy followed by 4 cycles of FOLFOX chemotherapy as preoperative treatment for rectal cancer. *Int J Radiat Oncol Biol Phys* 2014; 88: 829–836.

47. 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 Biol Phys* 2012; 83: 587–593.

48. Arbea L, Díaz-González JA, Subtil JC, et al. Patterns of response after preoperative intensity-modulated radiation therapy and capcitabine/oxaliplatin in rectal cancer: is there still a place for ecoendoscopic ultrasound? *Int J Radiat Oncol Biol Phys* 2011; 81: 439–444.

49. 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: 728–734.

50. Picardi V, Macchia G, Guido A, et al. Preoperative chemoradiation with VMAT-SIB.
in rectal cancer: a phase II study. Clin Colorectal Cancer 2017; 16: 16–22.

51. Lupattelli M, Matrone F, Gambacorta MA, et al. Preoperative intensity-modulated radiotherapy with a simultaneous integrated boost combined with Capecitabine in locally advanced rectal cancer: short-term results of a multicentric study. Radiat Oncol 2017; 12: 139.

52. Alongi F, Fersino S, Mazzola R, et al. Radiation dose intensification in pre-operative chemoradiotherapy for locally advanced rectal cancer. Clin Transl Oncol 2017; 19: 189–196.

53. Joo JH, Park JH, Kim JC, et al. Local control outcomes using stereotactic body radiation therapy for liver metastases from colorectal cancer. Int J Radiat Oncol Biol Phys 2017; 99: 876–883.

54. Kinj R, Bondiau PY, Francois E, et al. Radiosensitivity of colon and rectal lung oligometastasis treated with stereotactic ablative radiotherapy. Clin Colorectal Cancer 2017; 16: e211–e220.

55. Rödel C, Graeven U, Fietkau R, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomised phase 3 trial. Lancet Oncol 2012; 13: 679–687.

56. Zhao L, Bai C, Shao Y, et al. A phase II study of neoadjuvant chemoradiotherapy with oxaliplatin and Capecitabine in rectal cancer. Cancer Lett 2011; 310: 134–139.

57. Fernández-Martos C, Aparicio J, Bosch C, et al. Preoperative uracil, tegafur, and concomitant radiotherapy in operable rectal cancer: a phase II multicenter study with 3 years’ follow-up. J Clin Oncol 2004; 22: 3016–3022.

58. Beppu N, Kobayashi M, Matsubara N, et al. Comparison of the pathological response of the mesorectal positive nodules between short-course chemoradiotherapy with delayed surgery and long-course chemoradiotherapy in patients with rectal cancer. Int J Colorectal Dis 2015; 30: 1339–1347.

59. Myerson RJ, Genovesi D, Lockett MA, et al. Five fractions of preoperative radiotherapy for selected cases of rectal carcinoma: long-term tumor control and tolerance to treatment. Int J Radiat Oncol Biol Phys 1999; 43: 537–543.

60. Sato T, Ozawa H, Hatate K, et al. A phase II trial of neoadjuvant preoperative chemoradiotherapy with S-1 plus irinotecan and radiation in patients with locally advanced rectal cancer: clinical feasibility and response rate. Int J Radiat Oncol Biol Phys 2011; 79: 677–683.

61. Read TE, McNevin MS, Gross EK, et al. Neoadjuvant therapy for adenocarcinoma of the rectum: tumor response and acute toxicity. Dis Colon Rectum 2001; 44: 513–522.

62. Panagiotopoulou IG, Parashar D, Qasem E, et al. Neoadjuvant long-course chemoradiotherapy for rectal cancer: does time to surgery matter? Int Surg 2015; 100: 968–973.
71. 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.

72. Huang CM, Huang MY, Tsai HL, et al. An observational study of extending FOLFOX chemotherapy, lengthening the interval between radiotherapy and surgery, and enhancing pathological complete response rates in rectal cancer patients following preoperative chemoradiotherapy. *Therap Adv Gastroenterol* 2016; 9: 702–712.

73. Medical Research Council Rectal Cancer Working Party. Randomised trial of surgery alone versus radiotherapy followed by surgery for potentially operable locally advanced rectal cancer. *Lancet* 1996; 348: 1605–1610.

74. Chan AK, Wong AO, Langevin J, et al. Preoperative chemotherapy and pelvic radiation for tethered or fixed rectal cancer: a phase II dose escalation study. *Int J Radiat Oncol Biol Phys* 2000; 48: 843–856.

75. Kairevičė L, Latkauskas T, Tamelis A, et al. Preoperative long-course chemoradiotherapy plus adjuvant chemotherapy versus short-course radiotherapy without adjuvant chemotherapy both with delayed surgery for stage II-III resectable rectal cancer: 5-year survival data of a randomized controlled trial. *Medicina (Kaunas)* 2017; 53: 150–158.

76. Taher AN, El-Baradie MM, Nasr AM, et al. Locally advanced rectal carcinoma: preoperative radiotherapy versus postoperative chemoradiation, 10-year follow-up results of a randomized clinical study. *J Egypt Natl Canc Inst* 2006; 18: 233–243.

77. Duncan W, Smith AN, Friedman LS, et al. The evaluation of low dose pre-operative X-ray therapy in the management of operable rectal cancer; results of a randomly controlled trial. *Br J Surg* 1984; 71: 21–25.

78. Klenova A, Parvanova V, Georgiev R, et al. Preoperative radiotherapy in rectal cancer: treatment results of three different dose regimens. *J BUON* 2006; 11: 161–166.

79. Wiltshire KL, Ward IG, Swallow C, et al. Preoperative radiation with concurrent chemotherapy for resectable rectal cancer: effect of dose escalation on pathologic complete response, local recurrence-free survival, disease-free survival, and overall survival. *Int J Radiat Oncol Biol Phys* 2006; 64: 709–716.

80. Boulis-Wassif S, Gerard A, Loygue J, et al. Final results of a randomized trial on the treatment of rectal cancer with preoperative radiotherapy alone or in combination with 5-fluorouracil, followed by radical surgery. Trial of the European organization on research and treatment of cancer gastrointestinal tract cancer cooperative group. *Cancer* 1984; 53: 1811–1818.

81. Ciammella P, Ruggieri MP, Galeandro M, et al. Short-course preoperative radiotherapy combined with chemotherapy in resectable locally advanced rectal cancer: local control and quality of life. *Radiol Med* 2013; 118: 1397–1411.

82. Pettersson D, Holm T, Iversen H, et al. Preoperative short-course radiotherapy with delayed surgery in primary rectal cancer. *Br J Surg* 2012; 99: 577–583.

83. Calvo FA, Morillo V, Santos M, et al. Interval between neoadjuvant treatment and definitive surgery in locally advanced rectal cancer: impact on response and oncologic outcomes. *J Cancer Res Clin Oncol* 2014; 140: 1651–1660.

84. Du D, Su Z, Wang D, et al. Optimal interval to surgery after neoadjuvant chemoradiotherapy in rectal cancer: a systematic review and meta-analysis. *Clin Colorectal Cancer* 2018; 17: 13–24.

85. Martin ST, Heneghan HM and Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. *Br J Surg* 2012; 99: 918–928.

86. Foster JD, Jones EL, Falk S, et al. Timing of surgery after long-course neoadjuvant chemoradiotherapy for rectal cancer: a systematic review of the literature. *Dis Colon Rectum* 2013; 56: 921–930.

87. Stuuyck C, Wegge M and Bulens P. Moderate dose escalation with volumetric modulated arc therapy improves outcome in rectal cancer. *Acta Oncol* 2017; 56: 1501–1506.

88. Nguyen NP, Ceizyk M, Vock J, et al. Feasibility of image-guided radiotherapy for elderly patients with locally advanced rectal cancer. *PLoS One* 2013; 8: e71250.

89. 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: 1389–1393.

90. 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: 142–148.
91. 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: 264–270.

92. But-Hadzic J and Velenik V. Preoperative intensity-modulated chemoradiation therapy with simultaneous integrated boost in rectal cancer: 2-year follow-up results of phase II study. *Radiol Oncol* 2018; 52: 23–29.

93. Yamashita H, Ishihara S, Nozawa H, et al. Comparison of volumetric-modulated arc therapy using simultaneous integrated boosts (SIB-VMAT) of 45 Gy/55 Gy in 25 fractions with conventional radiotherapy in preoperative chemoradiation for rectal cancers: a propensity score case-matched analysis. *Radiat Oncol* 2017; 12: 156.

94. Markovina S, Youssef F, Roy A, et al. Improved metastasis- and disease-free survival with preoperative sequential short-course radiation therapy and FOLFOX chemotherapy for rectal cancer compared with neoadjuvant long-course chemoradiotherapy: results of a matched pair analysis. *Int J Radiat Oncol Biol Phys* 2017; 99: 417–426.

95. Sun Z, Adam MA, Kim J, et al. Optimal timing to surgery after neoadjuvant chemoradiotherapy for locally advanced rectal cancer. *J Am Coll Surg* 2016; 222: 367–374.

96. Zeng WG, Zhou ZX, Liang JW, et al. Impact of interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer on surgical and oncologic outcome. *J Surg Oncol* 2014; 110: 463–467.

97. Shinvani AT, Small W Jr, Stryker SJ, et al. Preoperative chemoradiation for rectal cancer: results of multimodality management and analysis of prognostic factors. *Am J Surg* 2007; 193: 389–393; discussion 393–394.

98. Kim SY, Hong YS, Kim DY, et al. Preoperative chemoradiation with cetuximab, irinotecan, and capecitabine in patients with locally advanced resectable rectal cancer: a multicenter phase II study. *Int J Radiat Oncol Biol Phys* 2011; 81: 677–683.

99. Avalone A, Delrio P, Pecori B, et al. Oxaliplatin plus dual inhibition of thymidilate synthase during preoperative pelvic radiotherapy for locally advanced rectal carcinoma: long-term outcome. *Int J Radiat Oncol Biol Phys* 2011; 79: 670–676.

100. Gunther JR, Chadha AS, Shin US, et al. Preoperative radiation dose escalation for rectal cancer using a concomitant boost strategy improves tumor downstaging without increasing toxicity: a matched-pair analysis. *Adv Radiat Oncol* 2017; 2: 455–464.

101. De Campos-Lobato LF, Geisler DP, Da Luz Moreira A, et al. Neoadjuvant therapy for rectal cancer: the impact of longer interval between chemoradiation and surgery. *J Gastrointest Surg* 2011; 15: 444–450.

102. Guckenberger M, Wulf J, Thalheimer A, et al. Prospective phase II study of preoperative short-course radiotherapy for rectal cancer with twice daily fractions of 2.9 Gy to a total dose of 29 Gy–long-term results. *Radiat Oncol* 2009; 4: 67.

103. Beppu N, Matsubara N, Noda M, et al. The timing of surgery after preoperative short-course S-1 chemoradiotherapy with delayed surgery for T3 lower rectal cancer. *Int J Colorectal Dis* 2014; 29: 1459–1466.

104. Rullier E, Rouanet P, Tuech JJ, et al. Organ preservation for rectal cancer (GRECCAR 2): a prospective, randomised, open-label, multicentre, phase 3 trial. *Lancet* 2017; 390: 469–479.

105. Kaytan-Saglam E, Balik E and Saglam S. Delayed versus immediate surgery following short-course neoadjuvant radiotherapy in resectable (T3N0/N+) rectal cancer. *J Cancer Res Clin Oncol* 2017; 143: 1597–1603.

106. Bae BK, Kang MK, Kim JC, et al. Simultaneous integrated boost intensity-modulated radiotherapy versus 3-dimensional conformal radiotherapy in preoperative concurrent chemoradiotherapy for locally advanced rectal cancer. *Radiat Oncol* 2017; 35: 208–216.

107. Huang CM, Huang MY, Tsai HL, et al. A retrospective comparison of outcome and toxicity of preoperative image-guided intensity-modulated radiotherapy versus conventional pelvic radiotherapy for locally advanced rectal carcinoma. *J Radiat Res* 2017; 58: 247–259.

108. 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.

109. Marijnen CA. Organ preservation in rectal cancer: have all questions been answered? *Lancet Oncol* 2015; 16: e13–e22.

110. Maas M, Nelemans PJ, Valentini V, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol* 2010; 11: 835–844.
111. Abdel-Rahman O, Kumar A, Kennecke HF, et al. Impact of duration of neoadjuvant radiation on rectal cancer survival: a real world multi-center retrospective cohort study. *Clin Colorectal Cancer* 2018; 17: e21–e28.

112. Pettersson D, Lörinc E, Holm T, et al. Tumour regression in the randomized Stockholm III trial of radiotherapy regimens for rectal cancer. *Br J Surg* 2015; 102: 972–978; discussion 978.

113. Gérard JP, Azria D, Gourgou-Bourgade S, et al. Comparison of two neoadjuvant chemoradiotherapy regimens for locally advanced rectal cancer: results of the phase III trial ACCORD 12/0405-Prodige 2. *J Clin Oncol* 2010; 28: 1638–1644.

114. Engineer R, Mohandas KM, Shukla PJ, et al. Escalated radiation dose alone vs. concurrent chemoradiation for locally advanced and unresectable rectal cancers: results from phase II randomized study. *Int J Colorectal Dis* 2013; 28: 959–966.

115. Mohiuddin M, Regine WF, John WJ, et al. Preoperative chemoradiation in fixed distal rectal cancer: dose time factors for pathological complete response. *Int J Radiat Oncol Biol Phys* 2000; 46: 883–888.

116. Valentini V, Coco C, Cellini N, et al. Ten years of preoperative chemoradiation for extraperitoneal T3 rectal cancer: acute toxicity, tumor response, and sphincter preservation in three consecutive studies. *Int J Radiat Oncol Biol Phys* 2001; 51: 371–383.

117. 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.

118. Rombouts AJM, Hugen N, Verhoeven RHA, et al. Tumor response after long interval comparing 5x5Gy radiation therapy with chemoradiation therapy in rectal cancer patients. *Eur J Surg Oncol* 2018; 44: 1018–1024.

119. Díaz-González JA, Calvo FA, Cortés J, et al. Prognostic factors for disease-free survival in patients with T3-4 or N+ rectal cancer treated with preoperative chemoradiation therapy, surgery, and intraoperative irradiation. *Int J Radiat Oncol Biol Phys* 2006; 64: 1122–1128.

120. Chuong MD, Fernandez DC, Shridhar R, et al. High-dose-rate endorectal brachytherapy for locally advanced rectal cancer in previously irradiated patients. *Brachytherapy* 2013; 12: 457–462.

121. Buckley H, Wilson C and Ajithkumar T. High-dose-rate brachytherapy in the management of operable rectal cancer: a systematic review. *Int J Radiat Oncol Biol Phys* 2017; 99: 111–127.

122. Dhadda AS, Zaitoun AM and Bessell EM. Regression of rectal cancer with radiotherapy with or without concurrent capcitabine–optimising the timing of surgical resection. *Clin Oncol (R Coll Radiol)* 2009; 21: 23–31.

123. Kuan FC, Lai CH, Ku HY, et al. The survival impact of delayed surgery and adjuvant chemotherapy on stage II/III rectal cancer with pathological complete response after neoadjuvant chemoradiation. *Int J Cancer* 2017; 140: 1662–1669.

124. Akgun E, Caliskan C, Bozbiyik O, et al. Randomized clinical trial of short or long interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg* 2018; 105: 1417–1425.

125. Couwenberg AM, Intven MPW, Hoendervangers S, et al. The effect of time interval from chemoradiation to surgery on postoperative complications in patients with rectal cancer. *Eur J Surg Oncol* 2019; 45: 1584–1591.

126. Macchia G, Gambacorta MA, Masciocchi C, et al. Time to surgery and pathologic complete response after neoadjuvant chemoradiation in rectal cancer: a population study on 2094 patients. *Clin Transl Radiat Oncol* 2017; 4: 8–14.

127. Kwak YK, Kim K, Lee JH, et al. Timely tumor response analysis after preoperative chemoradiotherapy and curative surgery in locally advanced rectal cancer: a multi-institutional study for optimal surgical timing in rectal cancer. *Radiother Oncol* 2016; 119: 512–518.

128. Sloothaak DA, Geijsen DE, van Leersum NJ, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg* 2013; 100: 933–939.

129. Lefevre JH, Mineur L, Kotti S, et al. Effect of interval (7 or 11 weeks) between neoadjuvant radiochemotherapy and surgery on complete pathologic response in rectal cancer: a multicenter, randomized, controlled trial (GRECCAR-6). *J Clin Oncol* 2016; 34: 3773–3780.

130. Francois Y, Nemoz CJ, Baulieux J, et al. Influence of the interval between preoperative radiation therapy and surgery on downstaging and on the rate of sphincter-sparing surgery for rectal cancer: the Lyon R90-01 randomized trial. *J Clin Oncol* 1999; 17: 2396–2402.

131. Stein DE, Mahmoud NN, Anné PR, et al. Longer time interval between completion
of neoadjuvant chemoradiation and surgical resection does not improve downstaging of rectal carcinoma. *Dis Colon Rectum* 2003; 46: 448–453.

132. Moore HG, Gittleman AE, Minsky BD,* et al.* Rate of pathologic complete response with increased interval between preoperative combined modality therapy and rectal cancer resection. *Dis Colon Rectum* 2004; 47: 279–286.

133. Tran CL, Udani S, Holt A,* et al.* Evaluation of safety of increased time interval between chemoradiation and resection for rectal cancer. *Am J Surg* 2006; 192: 873–877.

134. Veenhof AA, Kropman RH, Engel AF,* et al.* Preoperative radiation therapy for locally advanced rectal cancer: a comparison between two different time intervals to surgery. *Int J Colorectal Dis* 2007; 22: 507–513.

135. Lim SB, Choi HS, Jeong SY,* et al.* Optimal surgery time after preoperative chemoradiotherapy for locally advanced rectal cancers. *Ann Surg* 2008; 248: 243–251.

136. Tulchinsky H, Shmueli E, Figier A,* et al.* An interval > 7 weeks between neoadjuvant therapy and surgery improves pathologic complete response and disease-free survival in patients with locally advanced rectal cancer. *Ann Surg Oncol* 2008; 15: 2661–2667.

137. Garcia-Aguilar J, Smith DD, Avila K,* et al.* Optimal timing of surgery after chemoradiation for advanced rectal cancer: preliminary results of a multicenter, nonrandomized phase II prospective trial. *Ann Surg* 2011; 254: 97–102.

138. Woltuis AM, Penninckx F, Haustermans K,* et al.* Impact of interval between neoadjuvant chemoradiotherapy and TME for locally advanced rectal cancer on pathologic response and oncologic outcome. *Ann Surg Oncol* 2012; 19: 2833–2841.

139. Jeong DH, Lee HB, Hur H,* et al.* Optimal timing of surgery after neoadjuvant chemoradiation therapy in locally advanced rectal cancer. *J Korean Surg Soc* 2013; 84:338–345.

140. You KY, Huang R, Zhang LN,* et al.* Tailored selection of the interval between neoadjuvant chemoradiotherapy and Surgery for locally advanced rectal cancer: analysis based on the pathologic stage or chemoradiation response. *J Cancer Res Clin Oncol* 2015; 141:719–728.

141. Mihmanli M, Kabul Gurbulak E, Akgun IE,* et al.* Delaying surgery after neoadjuvant chemoradiotherapy improves prognosis of rectal cancer. *World J Gastrointest Oncol* 2016; 8: 695–706.

142. Akbar A, Bhatti AB, Niazi SK,* et al.* Impact of time interval between chemoradiation and surgery on pathological complete response and survival in rectal cancer. *Asian Pac J Cancer Prev* 2016; 17: 89–93.

143. Van Gijn W, Marijnen CA, 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: 575–582.

144. Keskin M, Bayraktar A, Sivirikoz E,* et al.* Sparing sphincters and laparoscopic resection improve survival by optimizing the circumferential resection margin in rectal cancer patients. *Medicine (Baltimore)* 2016; 95: e2669.

145. Patel A, Green N, Sarmah P,* et al.* The clinical significance of a pathologically positive lymph node at the circumferential resection margin in rectal cancer. *Tech Coloproctol* 2019; 23: 151–159.

146. Wong RK, Tandan V, De Silva S,* et al.* Preoperative radiotherapy and curative surgery for the management of localized rectal carcinoma. *Cochrane Database Syst Rev* 2007; 2: CD002102.

147. Petrelli F, Sgroi G, Sarti E,* et al.* Increasing the interval between neoadjuvant chemoradiotherapy and surgery in rectal cancer: a meta-analysis of published studies. *Ann Surg* 2016; 263: 458–464.

148. Glimelius B, Isacsson U, Jung B,* et al.* Radiotherapy in addition to radical surgery in rectal cancer: evidence for a dose-response effect favoring preoperative treatment. *Int J Radiat Oncol Biol Phys* 1997; 37: 281–287.

149. Suwinski R, Wzietek I, Tarnawski R,* et al.* Moderately low alpha/beta ratio for rectal cancer may best explain the outcome of three fractionation schedules of preoperative radiotherapy. *Int J Radiat Oncol Biol Phys* 2007; 69: 793–799.

150. Petrelli F, Trevisan F, Cabiddu M,* et al.* Total neoadjuvant therapy in rectal cancer: a systematic review and meta-analysis of treatment outcomes. *Ann Surg*. Epub ahead of print 15 July 2019. DOI: 10.1097/ SLA.0000000000003471.

151. Bosset JF, Collette L, Calais G,* et al.* Chemotherapy with preoperative radiotherapy in rectal cancer. *N Engl J Med* 2006; 355: 1114–1123.

152. Breugom AJ, Smeets R, Bosset JF,* et al.* Adjuvant chemotherapy after preoperative (chemo) radiotherapy and surgery for patients with rectal cancer: a systematic review and meta-analysis of individual patient data. *Lancet Oncol* 2015; 16: 200–207.
153. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 2017; 28: iv22–iv40.

154. National Comprehensive Cancer Network. NCCN clinical practice guidelines in oncology: rectal cancer. Version 3, https://nccn.org. (2017, accessed 1 June 2017).

155. Jin F, Luo HL, Zhou J, et al. Cancer risk assessment in modern radiotherapy workflow with medical big data. Cancer Manag Res 2018; 10: 1665–1675.

156. Tiv M, Puyraveau M, Mineur L, et al. Long-term quality of life in patients with rectal cancer treated with preoperative (chemo-)radiotherapy within a randomized trial. Cancer Radiother 2010; 14: 530–534.

157. Pucciarelli S, Del Bianco P, Efficace F, et al. Patient-reported outcomes after neoadjuvant chemoradiotherapy for rectal cancer: a multicenter prospective observational study. Ann Surg 2011; 253: 71–77.

158. Peeters KC, van de Velde CJ, Leer JW, et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients–a Dutch colorectal cancer group study. J Clin Oncol 2005; 23: 6199–6206.

159. Herman JM, Narang AK, Griffith KA, et al. The quality-of-life effects of neoadjuvant chemoradiation in locally advanced rectal cancer. Int J Radiat Oncol Biol Phys 2013; 85: e15–e19.

160. Huang M, Lin J, Yu X, et al. Erectile and urinary function in men with rectal cancer treated by neoadjuvant chemoradiotherapy and neoadjuvant chemotherapy alone: a randomized trial report. Int J Colorectal Dis 2016; 31: 1349–1357.

161. Bruheim K, Guren MG, Dahl AA, et al. Sexual function in males after radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys 2010; 76: 1012–1017.

162. Contin P, Kulu Y, Bruckner T, et al. Comparative analysis of late functional outcome following preoperative radiation therapy or chemoradiotherapy and surgery or surgery alone in rectal cancer. Int J Colorectal Dis 2014; 29: 165–175.

163. Hirata Y, Nozawa H, Kawai K, et al. The influence of neoadjuvant chemoradiation for lower rectal cancer on urinary function. Asian J Surg 2019; 42: 731–739.

164. Van der Sande ME, Hupkens BJP, Berbee M, et al. Impact of radiotherapy on anorectal function in patients with rectal cancer following a watch and wait programme. Radiother Oncol 2019; 132: 79–84.

165. Badakhshi H, Ismail M, Boskos C, et al. The role of concomitant radiation boost in neoadjuvant chemoradiotherapy for locally advanced rectal cancer. Anticancer Res 2017; 37: 3201–3205.

166. Ceelen WP, Van Nieuwenhove Y and Fierens K. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev 2009; 2: CD006041.

167. De Caluwé L, Van Nieuwenhove Y and Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. Cochrane Database Syst Rev 2013; 2: CD006041.

168. Fiorica F, Cartei F, Licata A, et al. Can chemotherapy concomitantly delivered with radiotherapy improve survival of patients with resectable rectal cancer? A meta-analysis of literature data. Cancer Treat Rev 2010; 36: 539–549.

169. MacFarlane JK, Ryall RD and Heal RJ. Mesorectal excision for rectal cancer. Lancet 1993; 341: 457–460.

170. Ng SY, Colborn KL, Cambridge L, et al. Acute toxicity with intensity modulated radiotherapy versus 3-dimensional conformal radiotherapy during preoperative chemoradiation for locally advanced rectal cancer. Radiother Oncol 2016; 121: 252–257.

171. 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.

172. De Bari B, Franzetti-Pellanda A, Saidi A, et al. Neoadjuvant chemoradiotherapy delivered with helical tomotherapy under daily image guidance for rectal cancer patients: efficacy and safety in a large, multi-institutional series. J Cancer Res Clin Oncol 2019; 145: 1075–1084.

173. Jabbour SK, Patel S, Herman JM, et al. Intensity-modulated radiation therapy for rectal carcinoma can reduce treatment breaks and emergency department visits. Int J Surg Oncol 2012; 2012: 891067.

174. 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: 155–159.

175. Kaplan SO, Akbörü H, Tabak SD, et al. Hypofractionated preoperative chemoradiotherapy in locally advanced rectal cancer: preliminary results. *Turk J Oncol* 2019; 34: 21–26.

176. Sun Z, Adam MA, Kim J, et al. Intensity-modulated radiation therapy is not associated with perioperative or survival benefit over 3D-conformal radiotherapy for rectal cancer. *J Gastrointest Surg* 2017; 21: 106–111.

177. 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.

178. Chang H, Jiang W, Ye WJ, et al. Is long interval from neoadjuvant chemoradiotherapy to surgery optimal for rectal cancer in the era of intensity-modulated radiotherapy? A prospective observational study. *Onco Targets Ther* 2018; 11: 6129–6138.

179. Yamada S, Kamada T, Ebner DK, et al. Carbon-ion radiation therapy for pelvic recurrence of rectal cancer. *Int J Radiat Oncol Biol Phys* 2016; 96: 93–101.