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REVIEW ARTICLE

Which is the best neoadjuvant (pre-surgery) chemoradiation regimen for locally advanced rectal carcinoma? Short or long course of radiation therapy? Do we have new data?

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Summary

Purpose: *Surgical resection is the cornerstone of curative treatment for rectal adenocarcinomas. For extensive invasive tumors, preoperative radiotherapy and chemoradiotherapy have been utilized to promote tumor regression in an attempt to convert a planned abdominoperineal resection to a sphincter-sparing surgical procedure. In order to find out which of the currently radiation therapy treatment regimen used preoperatively for rectal cancer is the best we conducted a comprehensive literature search.*

Methods: *We searched the Cochrane Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE database up to December 2018 for trials comparing the short and long term radiation therapy regimens for rectal carcinoma associated or not with chemotherapy.*

Results: *The search of the literature identified 38 papers related to the subject. After analysis and evaluation, 11 eligible trials were included for review. The optimal fractionation and timing of surgery in relation to radiotherapy was still controversial. Randomized trials showed that if surgery is delayed after 5×5 Gy and consolidation chemotherapy is added between 5×5 Gy and surgery, such a combination results in better short term overall survival and lower acute toxicity*

Conclusion: *Long-course radiotherapy with delay seems not to be different than short-course radiotherapy with delay, but prolongs substantially the treatment time.*

Key words: *long course, preoperative radiotherapy, randomized controlled trial, radio-chemotherapy, rectal cancer, short course*

Introduction

Colorectal cancer is the third most common cancer worldwide and the second or third most common cause of cancer-related deaths. One third of the cancers arise in the rectum, the rest in the colon and most cases are adenocarcinomas. For decades survival has been less favorable in rectal than in colon cancer, but this is no longer the case [1-4].

For rectal cancer, randomized trials have demonstrated superior local control, lower toxicity and better compliance of radiotherapy or radiochemotherapy administered before rather than after surgery [5-7]. Conventionally fractionated chemoradiation with delayed surgery or short course irradiation (25 Gy in 5 fractions) with immediate surgery are probably the most frequent approach in the preoperative treatment of patients with resectable rectal cancer [8-11]. Similar long term survival, local control and late morbidity have been reported for both these methods in non-comparative studies [12-14]. The benefit of the short course schedule is a lower rate of early toxicity than with chemoradiation [15-18]. In addition, short-course irradiation is less expensive and more convenient, especially in centres with a long waiting list. On the other hand, the use of high doses per fraction raises con-

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cern about late toxicity [19]. Conventionally fractionated chemoradiation might be better than the short-course radiation schedule at reducing local recurrences. Another advantage of chemoradiation is better sphincter preservation because the tumour bulk is reduced before surgery. However, there is no firm evidence to support this [20].

In order to response the question whether chemoradiation offers an advantage in sphincter preservation in comparison with 5x5 Gy schedule, and which regimen offers better results regarding long term survival, local control and late morbidity a comprehensive literature review was conducted.

Methods

The key words used for the search were: preoperative radiotherapy or radio-chemotherapy, short course, long course, rectal cancer, randomized controlled trials, comparison. A literature review was performed based on database search in: Cochrane Central Register of Controlled Trials, MEDLINE and EMBASE up to December 2018. The exclusion criteria were: 1) pre-clinical studies, 2) not English language and 3) studies with no comparison or randomization (Figure 1). The search of the literature identified 38 papers. Twenty-six publications were excluded after the study of their summaries, as they were not related to comparison or randomized controll between the short and long course of preoperative radiotherapy or radio-chemotherapy for rectal cancer. One paper was excluded since it was not English-written. Finally, 11 eligible trials were included for review.

Results

Bujko et al in 2004 [17] published the results of a randomized trial which aimed to verify whether preoperative conventionally fractionated chemoradiation offers an advantage in sphincter preservation in comparison with preoperative short term irradiation. Three hundred and twelve patients with resectable T3-4 rectal carcinoma without sphincter's infiltration and with a lesion accessible to digital rectal examination (DRE) were randomized into preoperative 5×5 Gy short term irradiation with subsequent total mesorectal excision (TME) performed within 7 days or chemo-radiation to a total dose of 50.4 Gy (1.8 Gy per fraction) concomitantly with two courses of bolus 5-fluorouracil and leucovorin followed by TME after 4-6 weeks. The authors found that the sphincter preservation rate

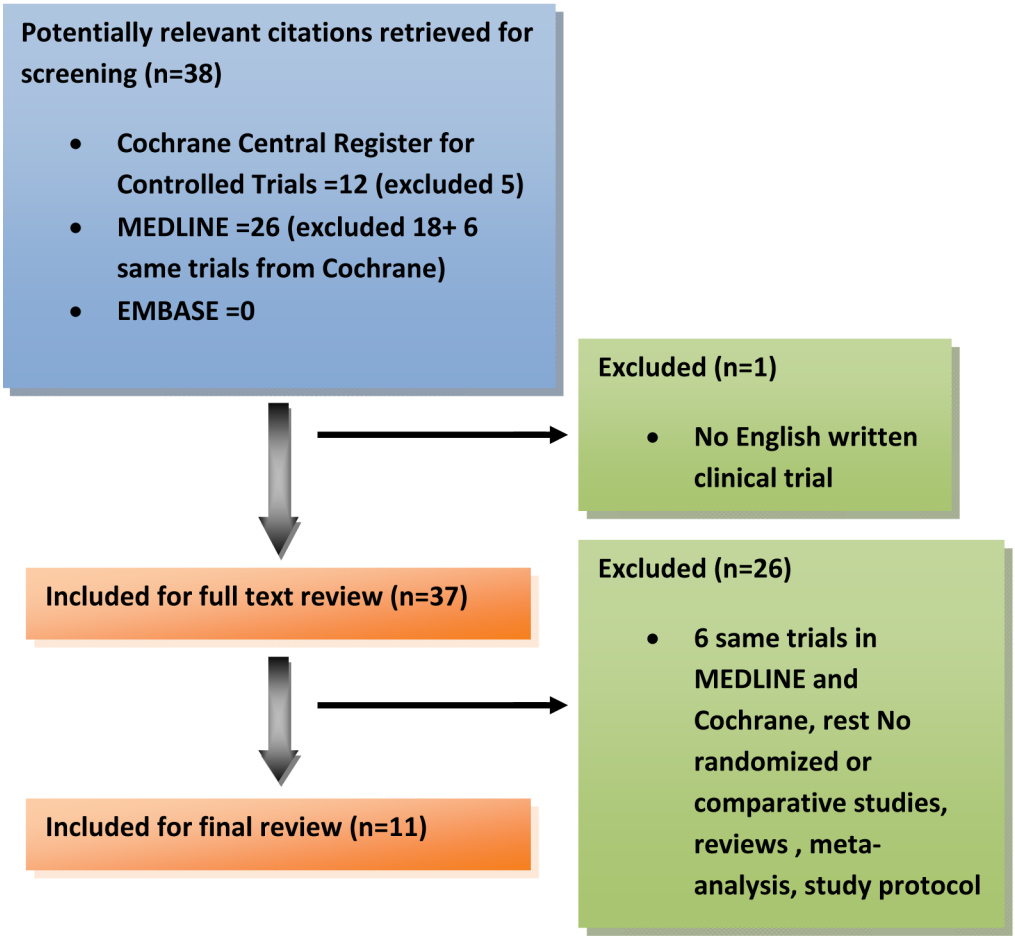

Figure 1. Results of the literature research and studies included for analysis.

was 61% in the 5×5 Gy arm and 58% in the radiochemotherapy arm, (p=0.57) and the tumor was 1.9 cm smaller on average (p<0.001), among patients treated with chemo-radiation compared with the short term schedule. The conclusion of the study was that, despite significant downsizing, chemo-radiation did not result in increased sphincter preservation rate in comparison with short term preoperative radiotherapy.

The same Polish Colorectal Study Group consisted of Bujko et al [21] published in 2006 the long term results of the above mentioned randomized trial aimed to compare survival, local control and late toxicity in the two treatment groups. Three hundred and twelve patients with clinical stage T3 or T4 resectable rectal cancer were enrolled. The results have shown that early radiation toxicity was higher in the chemo-radiation group (18.2 vs 3.2%; p<0.001). The actuarial 4-year overall survival (OS) was 67.2% in the short course group and 66.2% in the chemo-radiation group (p=0.960). Disease-free survival (DFS) was 58.4 vs 55.6% (p=0.820), crude incidence of local recurrence was 9.0 vs 14.2% (p=0.170) and severe late toxicity was 10.1 vs 7.1% (p=0.360), respectively. The conclusion of the study was that neoadjuvant chemo-radiation did not increase survival, local control or late toxicity compared with short course radiotherapy alone.

Latkauskas et al in 2012 [22] presented the early results of a randomized trial which aimed to compare the downstaging achieved after long course chemo-radiotherapy (chRT) and short term radiotherapy (sRT) followed by delayed surgery. Eighty-three patients with resectable stage II and III rectal adenocarcinoma were randomized to receive long course radiotherapy (50Gy/25fractions, 1.8-2Gy per fraction over 5 weeks) with chemotherapy (400 mg/m^2 5-Fluorouracil, 20 mg/m^2 Leucovorin) during the first and last week of radiotherapy followed by surgery after 6 weeks or short term radiotherapy with delayed surgery (radiotherapy 25Gy/5fractions, 5Gy per fraction over 5 days followed by surgery after 6 weeks). The results showed that R0 resection (resection with negative margins) rate was 91.3% in the chRT and 86.5% in the sRT group (p=0.734). Sphincter preservation rates were 69.6 vs 70.3% (p=0.342) and postoperative complication rates were 26.1 vs 40.5% (p=0.221). There were more patients with early pT stage [pT0 (complete pathological response) and pT1] in the chRT group [21.8 vs 2.7% (p=0.03)] and more patients with pT3 disease in the sRT group [75.7 vs 52.2% (p=0.036)]. There were no differences in pN stage and lymphatic or vascular invasion in either group. The study concluded that long course preoperative chemo-radiation resulted in greater statistically significant tumor downsizing and downstaging compared with short term radiation, but there was no difference in the R0 resection rates. Postoperative morbidity was similar in both groups.

In 2016 the same group of Latkauskas et al [23] published the updated results of their randomized trial which aimed to compare the downstaging achieved after long course chemo-radiotherapy (chRT) and short term radiotherapy (sRT) followed by delayed surgery. In this updated trial 140 patients diagnosed with stage II-III rectal cancer between 2007 and 2013 were included. The patients were randomized to one of the two arms as in the previous trial. Primary endpoints of this trial were downstaging and pathological complete response rate. Secondary endpoints were local recurrence rate and OS. The results have shown that pathological complete response was found in 3 (4.4%) cases after sRT and 8 (11.1%) after chRT (p=0.112). Downstaging (stage 0 and I) was observed in 21 (30.9%) cases in the sRT group vs. 27 (37.5%) cases in chRT group (p=0.409). Median follow-up time was 39.7 months (range 4.9-79.7). Three-year OS was 78% in the sRT group vs 82.4% in the chRT group (p=0.145), while DFS differed significantly: 59% in the sRT group vs 75.1% in the chRT group (p=0.022). Hazard ratio of cancer progression for sRT patients was 1.93 (95% CI: 1.08-3.43) compared to chRT patients. The conclusion of the study was that 3-year DFS was better in the chRT group comparing with the sRT group with no difference in OS.

The Trans-Tasman Radiation Oncology Group Trial 01.04 published in 2012 by Ngan et al [24] was a randomized trial which aimed to compare the local recurrence rate between short course and long course neoadjuvant radiotherapy for rectal cancer. In this trial 323 patients with ultrasound- or magnetic resonance imaging-staged T3N0-2M0 rectal adenocarcinoma within 12 cm from anal verge were randomly assigned to receive short course radiotherapy (162 patients) or long course chemo-radiotherapy (161 patients). Short course radiotherapy consisted of 25 Gy in 5 fractions administered in 1 week, followed by surgery 3 to 7 days later. Six monthly courses of 5-Fluorouracil (5-FU; 425 mg/m^2) and folinic acid (20 mg/m^2) administered daily for 5 days started 4 to 6 weeks after surgery. Long course chemo-radiotherapy consisted of a total of 50.4 Gy in 28 fractions over 5 weeks and 3 days with continuous infusional 5-FU 225 mg/m^2 per day, administered 7 days per week for the duration of radiation. Surgery followed 4 to 6 weeks after chemo-radiotherapy. Four monthly courses of the same chemotherapy as for short course patients started 4 to 6 weeks post surgery. The results showed that 3-year local

recurrence rates were 7.5% for short course and 4.4% for long course (difference, 3.1%; 95% CI, -2.1 to 8.3; p=0.24). For distal tumors (<5 cm), 6 of 48 short course patients and one of 31 long course patients experienced local recurrence (p=0.21). Five-year distant recurrence rates were 27% for short course and 30% for long course (log-rank p=0.92; hazard ratio [HR] for long course:short course, 1.04; 95% CI, 0.69 to 1.56). OS rates at 5 years were 74% for short course and 70% for long course (log-rank p=0.62; HR, 1.12; 95% CI, 0.76 to 1.67). Late toxicity rates were not substantially different (Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer G3-4: short course, 5.8%; long course, 8.2%; p=0.53). The authors concluded that 3-year local recurrence rates between short and long course were not statistically significantly different. Long course may be more effective in reducing local recurrence for distal tumors. No differences in rates of distant recurrence, recurrence-free survival, OS, or late toxicity were detected.

Ansari et al [25] from the same research group published recently in 2017 the results of the above Trans-Tasman Radiation Oncology Group Trial 01.04 regarding acute adverse events (AEs), postoperative complication rates and perioperative mortality when comparing preoperative short course and long course regimens in the management of resectable low T3 rectal cancer included in analysis. A hundred percent of short course patients and 93% of long course patients received the preoperative planned radiotherapy. There was no 30-day operative mortality. A statistically significant higher percentage of at least 1 AE occurred in the long group (short group, 72.3%; long group, 99.4%; p<0.001). There were significant differences in favor of short course for grade 3 AE: radiation dermatitis (0% vs 5.6%, p=0.003), proctitis (0% vs 3.7%, p=0.016), nausea (0% vs 3.1%, p=0.029), fatigue (0% vs 3.7%, p=0.016) and grade 3/4 diarrhea rates (1.3 vs 14.2% p<0.001). No statistically significant differences in surgical complication rates were seen (short course 53.2 vs 50.4% long course, p=0.68), although permanent stoma (38.0 vs 29.8%, p=0.13) and anastomotic breakdown (7.1 vs 3.5%, p=0.26) rates favored long course with perineal wound complications (38.3 vs 50.0%, p=0.26) in favor of short course. The authors concluded that long course patients had significantly higher AEs compared with short course with no statistically significant differences in postoperative complications. There were clinical trends in permanent stoma rates and anastomotic leaks in favor of long course but with an increased perineal wound breakdown rate.

The third randomized controlled trial of Polish Colorectal Study Group was published in 2013 by Bujko et al [26] and presented an interim analysis of comparison of two neoadjuvant therapies for unresectable rectal cancer. In this study 97 patients with cT3 or cT4 or locally recurrent rectal cancer without distant metastases were randomly assigned to receive short course radiation therapy (5x5 Gy) and 3 courses of FOLFOX4 chemotherapy (group I) or long course radiation therapy 50.4 Gy delivered in 28 fractions given simultaneously with 5-FU, leucovorin and oxaliplatin chemotherapy (group II). After completion of chemo-radiation the patients were operated and the interval between the start of radiation and surgery was the same (12 weeks) in both groups. The results showed that grade III+ acute toxicity was observed in 26% of patients in group I and in 25% in group II. There were two toxic deaths, both in group II. The microscopically radical resection (primary endpoint) rate was 73% in group I and 71% in group II. Overall and severe postoperative complications were recorded in 27 and 9% of patients vs. 16 and 7%, respectively. Pathological complete response was observed in 21% of the patients in group I and in 9% in group II. The authors managed to show that the interim analysis revealed no major differences in acute toxicity and local efficacy between the two evaluated strategies.

In 2016 the mature results of the abovementioned trial were presented by Bujko et al [27]. Five hundred and fifteen patients were eligible for analysis (261 in group I and 254 in group II). The results showed that preoperative treatment acute toxicity was lower in group I than in group II (p=0.006); any toxicity being, respectively, 75 vs 83%, grade III-IV 23 vs 21% and toxic deaths 1 vs 3%. R0 resection rates (primary endpoint) and pathological complete response rates in groups I and II were, respectively, 77 vs 71%, p=0.07, and 16 vs 12%, p=0.17. The median follow-up was 35 months. At 3 years, the rates of OS and DFS in groups I and II were, respectively, 73 vs 65% (p=0.046, and 53 vs 52%, p=0.85), together with the cumulative incidence of local failure and distant metastases being, respectively (22 vs 21%, p=0.82, and 30 vs 27%, p=0.26). Postoperative and late complications rates in group I and II were, respectively, 29 vs 25% (p=0.18, and 20 vs 22%, p=0.54). The conclusion was that no differences were observed in local efficacy between 5×5 Gy with consolidation chemotherapy and long course chemo-radiation. Nevertheless, an improved OS and lower acute toxicity favored the 5×5 Gy schedule with consolidation chemotherapy.

The Stockholm III randomized trial was published in 2015 by Pettersson et al [28] and aimed

to investigate the impact of short course radiation therapy in tumor downstaging in patients with operable rectal cancer if surgery was performed after an interval of 4-8 weeks. The patients were randomized to receive either short course radiotherapy (5x5 Gy) with immediate surgery or the same short course radiotherapy with surgery delayed 4-8 weeks or long course radiotherapy (50 Gy/25 fractions) with surgery delayed 4-8 weeks. A hundred and twenty patients were randomized to the long course radiation therapy and were not analyzed in the present study. A total of 462 of 545 randomized patients who received short course radiation therapy with immediate or delayed surgery had specimens available for reassessment. At pathological assessment, the circumferential margin (CRM) was defined as positive if the tumor involved the CRM or was 1mm or less from the margin. It was judged to be negative if the distance from the tumor to the margin exceeded 1 mm. The Dworak system was used for the assessment of tumor regression: grade 0, no regression; grade 1, dominant tumor mass with obvious fibrosis and/or vasculopathy; grade 2, dominantly fibrotic changes with few tumor cells or groups (easy to find); grade 3, very few (difficult to find microscopically) tumor cells in fibrotic tissue with or without mucous substance; grade 4, no tumor cells, only fibrotic mass (total regression or response). The analysis has shown that there were statistically significant differences in distributions between the randomization arms regarding tumor stage and ypT category; both were lower in patients randomized to short course radiation-delay. Nodal status did not differ significantly between the groups. There were differences in the rate of complete pathological response: 11.8% in the short course radiation-delay arm compared with 1.7% for short course radiation-immediate. There was also a significant difference in tumor regression grade according to Dworak between the two groups (p<0.001). Thirty-four patients (14.9%) in the short course radiation-delay group had grade 3 or 4 tumor regression compared with 6 (2.6%) in the short course radiation-immediate arm. Positive circumferential resection margins were uncommon (6.3%) and rates did not differ between the two treatment arms. The authors have concluded that short course radiation therapy induces tumor downstaging if surgery is performed after an interval of 4-8 weeks.

The same Stockholm Colorectal Cancer Study Group recently published the updated results of their Stockholm III randomized trial [29]. The article was published in Lancet Oncology in 2017 by Erlandsson et al and the primary endpoint was time to local recurrence calculated from the date of randomization to the date of local recurrence in three groups of patients already mentioned in the previous study. In this trial between October 1998, and January 2013, 840 patients were recruited and randomized; 385 patients in the three-arm randomization, of whom 129 patients were randomly assigned to short course radiotherapy, 128 to short course radiotherapy with delay, and 128 to long course radiotherapy with delay, and 455 patients in the two-arm randomization, of whom 228 were randomly assigned to short course radiotherapy and 227 to short course radiotherapy with delay. In patients with any local recurrence, median time from date of randomization to local recurrence in the pooled short course radiotherapy comparison was 33.4 months (range 18.2-62) in the short course radiotherapy group and 19.3 months (range 8.5-39.5) in the short course radiotherapy with delay group. Median time to local recurrence in the long course radiotherapy with delay group was 33.3 months (range 17.8-114.3). Cumulative incidence of local recurrence in the whole trial was 8 of 357 patients who received short course radiotherapy, 10 of 355 who received short course radiotherapy with delay, and 7 of 128 who received long course radiotherapy (HR vs short course radiotherapy: short course radiotherapy with delay 1.44 (95% CI 0.41-5.11); long course radiotherapy with delay 2.24 (0.71-7.10; p=0.48), both deemed non-inferior. Acute radiation-induced toxicity was recorded in one patient (<1%) of 357 after short course radiotherapy, 23 (7%) of 355 after short course radiotherapy with delay, and 6 (5%) of 128 patients after long course radiotherapy with delay. The frequency of postoperative complications was similar between all arms when the three-arm randomization was analyzed (65;50% of 129 patients in the short course radiotherapy group; 48;38%) of 128 patients in the short course radiotherapy with delay group; 50;39%) of 128 patients in the long course radiotherapy with delay group). Odds ratio (OR) vs short course radiotherapy: short course radiotherapy with delay 0.59 (95% CI 0.36-0.97), long course radiotherapy with delay 0.63 (95% CI 0.38-1.04), p=0.075. However, in a pooled analysis of the two short course radiotherapy regimens, the risk of postoperative complications was significantly lower after short course radiotherapy with delay than after short course radiotherapy (144;53% of 355 vs 188;41% of 357; OR 0.61 (95% CI 0.45-0.83) p=0.001). The authors have concluded that delaying surgery after short course radiotherapy gives similar oncological results compared with short course radiotherapy with immediate surgery. Long course radiotherapy with delay is similar to both short course radiotherapy regimens, but prolongs the treatment time substantially. Although radiation-

Table 1. Randomized controlled trials comparing the different preoperative radiation therapy or radio-chemotherapy regimens in rectal cancer

Author, journal, year of publication	*Number of patients*	*Randomized arms*	*Endpoints of the trial*	*Results*
Bujko K. et al [17], Radiotherapy and Oncology, 2004	312 patients with resectable T3-4 rectal carcinoma	-**Arm 1**: 5×5 Gy preoperative RT given in one week and with surgery performed within 7 days (155 patients) -**Arm 2:** chRT, 50.4 Gy /28 fr/1.8 Gy fr concomitantly with two courses of 5-fluorouracil and leucovorin and with operation performed 4-6 weeks later (157 patients)	If chRT is superior in sphincter preservation than short course radiation	The sphincter preservation rate was 61% in the 5×5 Gy arm and 58% in the chRT arm, (P=0.57)
Bujko K. et al [21], British Journal of Surgery, 2006	312 patients with resectable T3-4 rectal carcinoma	-**Arm 1:** 5×5 Gy preoperative RT given in one week and with surgery performed within 7 days (155 patients) -**Arm 2:** chRT, 50.4 Gy /28 frs/1.8 Gy fr concomitantly with two courses of 5-fluorouracil and leucovorin and with operation performed 4-6 weeks later (157 patients)	Evaluation of: long term survival, incidence of local recurrence, distant metastases, late toxicity	Early radiation toxicity was higher in the chRT group (18.2 vs 3.2%; P<0.001). The actuarial 4-year OS was 67.2% in the RT group and 66.2% in the chRT group (P=0.960). DFS was 58.4 vs 55.6% (P=0.820), LR was 9.0 vs 14.2% (P=0.170) and SLT was 10.1 vs 7.1% (P=0.360), respectively
Latkauskas T. et al [22], Colorectal Disease, 2012	83 histologically confirmed stage II and III rectal cancer less than 15 cm from the anal verge	-**Arm 1:** chRT: RT 50Gy / 25fr, 1.8-2Gy /fr over 5 weeks with chemotherapy 5-Fu / Lv (400 mg/m^2 5-Fluouracil, 20 mg/m^2 Leucovorine) during the first and last week of RT (surgery after 6 weeks) (46 patients) -**Arm 2:** Short term RT with delayed surgery: RT: 25Gy / 5fr, 5Gy/fr over 5 days (surgery after 6 weeks) (37 patients)	To evaluate the downstaging achieved after short course RT compared with that after conventional long course chRT.	There were more patients with early pT stage [pT0 (complete pathological response) pT1] in the chRT group [21.8% vs 2.7% (P=0.03)] and more patients with pT3 disease in the short term RT group [75.7% vs 52.2% (P=0.036)].
Latkauskas T. et al [23], BMC cancer, 2016	140 histologically confirmed stage II and III rectal cancer less than 15 cm from the anal verge	-**Arm 1:** chRT: RT 50Gy / 25fr, 1.8-2Gy /fr over 5 weeks with chemotherapy 5-Fu / Lv (400 mg/m^2 5-Fluouracil, 20 mg/m^2 Leucovorine) during the first and last week of RT (surgery after 6 weeks) (72 patients) -**Arm 2:** Short term RT with delayed surgery: RT: 25Gy / 5fr, 5Gy/fr over 5 days (surgery after 6 weeks) (68 patients)	Primary endpoints of this trial were downstaging and pathological complete response rate. Secondary endpoints were LR rate and OS.	No difference in pathological complete response rate (P=0.112), No difference in downstaging effect (P=0.409), No difference in 3-years OS (P=0.145),but DFS significantly better in chRT group (P=0,022)
Ngan SY et al [24], Journal of Clinical Oncology, 2012	323 patients with histologically confirmed rectal adenocarcinoma, with lower borders within 12 cm of the anal verge; ultrasound- or magnetic resonance imaging (MRI) -staged T3 disease	-**Arm 1:** Short course RT: 25 Gy/5 daily fr/5 Gy/fr surgery 3 to 7 days later. Adguvant chemotherapy six monthly courses of fluorouracil (425 mg/m^2) and folinic acid (20 mg/m^2) administered daily for 5 days 4 to 6 weeks after surgery (162patients) -**Arm 2:** Long course chRT: 50.4 Gy /28 fr/1.8 Gy/fr over 5 weeks and 3 days with continuous infusional Fluorouracil 225 mg/m^2 daily for the duration of radiation. Surgery followed 4 to 6 weeks after chRT. Same adjuvant chemotherapy as in Arm 1, four monthly courses 4 to 6 weeks post surgery (161 patients)	Primary and point to compare the LR, rate. Secondary endpoints: distant recurrence, relapse-free survival, OS, or late toxicity rate between short course and long course neoadjuvant RT for rectal cancer	No statistically difference between the two Arms regarding primary and secondary end points

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Author, journal, year of publication	*Number of patients*	*Randomized arms*	*Endpoints of the trial*	*Results*
Ansari N et al [25], Annals of Surgery, 2017	322 patients with histologically confirmed rectal adenocarcinoma, with lower borders within 12 cm of the anal verge; ultrasound- or magnetic resonance imaging (MRI) -staged T3 disease	-**Arm 1:** Short course RT: 25 Gy/5 daily fr/5 Gy/fr surgery 3 to 7 days later. Adjuvant chemotherapy six monthly courses of fluorouracil (425 mg/m^2) and folinic acid (20 mg/m^2) administered daily for 5 days 4 to 6 weeks after surgery (161patients) -**Arm 2:** Long course chRT: 50.4 Gy /28 fr/1.8 Gy/fr over 5 weeks and 3 days with continuous infusional Fluorouracil 225 mg/m^2 daily for the duration of radiation. Surgery followed 4 to 6 weeks after chRT. Same adjuvant chemotherapy as in Arm 1, four monthly courses 4 to 6 weeks post surgery (161 patients)	To evaluate acute AE postoperative complication rates and perioperative mortality between short course and long course neoadjuvant RT for rectal cancer	Significant differences in favor of short course for grade 3 AE: radiation dermatitis (0% vs 5.6%, P=0.003), proctitis (0% vs 3.7% P=0.016), nausea (0% vs 3.1%, P=0.029), fatigue (0% vs 3.7%, P=0.016) and grade 3/4 diarrhea rates (1.3%vs 14.2%, P<0.001). No differences in surgical complication rates (short course 53.2 vs 50.4% long course, p=0.68)
Bujko K. et al [26], Radiotherapy and Oncology, 2013	97 patients with fixed cT3 or cT4 or locally recurrent rectal cancer without distant metastases	-**Arm 1:** Short course RT 5X 5 Gy and 3 courses of FOLFOX4 chemotherapy (49 patinets) -**Arm 2:** Long course RT 50.4 Gy/28 fr/1.8 Gy/fr simultaneously with 5-Fluorouracil, leucovorin and oxaliplatin chemotherapy (48 patients) Surgery 12 weeks from the begging of RT in both Arms	primary endpoint: rate of microscopically radical resection (R0), secondary and points: acute toxicity and complete response rate	The R0 rate was 73% in Arm 1 and 71% in Arm 2. Grade III+ acute toxicity: 26% in Arm 1 and 25% in Arm 2. Overall and severe postoperative complications were recorded in 27% and 9% of patients vs. 16% and 7%, respectively. Pathological complete response was observed in 21% of the patients in Arm 1 and in 9% in Arm 2
Bujko K. et al [27], Annals of Oncology, 2016	515 patients with fixed cT3 or cT4 or locally recurrent rectal cancer without distant metastases	-**Arm 1:** Short course RT 5X 5 Gy and 3 courses of FOLFOX4 chemotherapy (261 patients) -**Arm 2:** Long course RT 50.4 Gy/28 fr/1.8 Gy/fr simultaneously with 5-Fluorouracil, leucovorin and oxaliplatin chemotherapy (254 patients) Surgery 12 weeks from the begging of RT in both Arms	primary endpoint: rate of microscopically radical resection, secondary and points: acute toxicity and complete response rate	-R0 rates and pathological complete response rates in Arm 1 and Arm 2 were, respectively, 77% vs 71%, P=0.07, and 16% vs 12%, P=0.17. -Preoperative treatment acute toxicity was lower in Arm 1 than in Arm 2, P=0.006; 3-years OS and DFS in Arm 1 and Arm 2 were, respectively, 73% vs 65%, P=0.046, and 53% vs 52%, P=0.85, -Postoperative and late complications rates in Arm 1 and Arm 2 were, respectively, 29% vs 25%, P=0.18, and 20% vs 22%, P=0.54.
Pettersson D. et al [28], The British Journal of Surgery, 2015	462 patients with primary rectal cancer, defined as an adenocarcinoma within 15 cm of the anal verge, and judged to be resectable	-**Arm 1:** short course RT (5x5 Gy) with immediate surgery (234 patients) -**Arm 2:** same short course RT with surgery delayed 4-8 weeks (228 patients)	To compare the pathological outcomes in the two short course RT randomization arms with a special focus on T (tumor) and N (nodes) categories, involved resection margins and tumor regression.	-Rate of complete pathological response significant batter in the short course RT-delay arm, (11.8 % vs. 1.7 %). -Significant difference in tumor regression grade according to Dworak between the two groups (P<0.001) in favor of short course RT-delay arm,(14.9 % vs. 2.6 %) - Positive circumferential resection margins were uncommon and rates did not differ between the two treatment arms

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Author, journal, year of publication	*Number of patients*	*Randomized arms*	*Endpoints of the trial*	*Results*
Erlandsson et al [29], Lancet Oncology, 2017	840 patients with primary rectal cancer, defined as an adenocarcinoma within 15 cm of the anal verge, and judged to be resectable	385 patients randomized in 3 Arms: -**Arm 1:** short course RT (5×5 Gy) with immediate surgery (129 patients) -**Arm 2:** same short course RT with surgery delayed 4-8 weeks (129 patients) -**Arm 3:** long course radiotherapy (25×2 Gy) with surgery after 4-8 weeks (128) 455 patients randomized in 2 Arms: -**Arm 1:** short course RT (5×5 Gy) with immediate surgery (228 patients) -**Arm 2:** same short course RT with surgery delayed 4-8 weeks (227 patients)	The primary endpoint was time to local recurrence, - Secondary endpoints: acute radiation toxicity and postoperative complications	-No difference in three arms regarding oncological results -Although radiation-induced toxicity was seen after short course RT with delay, postoperative complications were significantly reduced compared with short course RT
Kairevice L. et al [30], Medicina, 2017	150 patients with stage II-III resectable rectal	-**Arm 1:** RT 25 Gy/5 fr, 5 Gy/fr in 5 days and surgery after 6-8 weeks, (75 patients) -**Arm 2:** RT 50 Gy/25 fr, 2 Gy/fr concomitant with fluorouracil and leucovorin following by surgery after 6-8 weeks; then within 8 weeks period adjuvant chemotherapy of 5-Fuorouracil and Leucovorin was started for 4 cycles every 4 weeks (75 patients)	To compare OS and DFS in two treatment groups	-The 5-year DFS was 67% in the chRT group and 45% in the short course RT group (P=0.013) -The 5-year OS was 79% and 62% in the chRT and short course RT groups, respectively (P=0.015)

ChRT: chemo-radiotherapy, RT: radiation therapy, Fr: fractions, OS: overall survival, DFS: disease-free survival, LR: local recurrence, SLT: severe late toxicity, AE: adverse events, FOLFOX4: 2-h infusion of 85 mg/m^2 of oxaliplatin on day 1, given simultaneously with 200 mg/m^2 of leucovorin through a Y catheter. Next, a bolus of 400 mg/m^2 5-Fluorouracil followed by 600 mg/m^2 of 5-Fluorouracil in a 22-h continuous infusion every 14 days, vs.: versus.

induced toxicity was seen after short course radiotherapy with delay, postoperative complications were significantly reduced compared with short course radiotherapy. The final authors' suggestion was that short course radiotherapy with delay to surgery is a useful alternative to conventional short course radiotherapy with immediate surgery.

Kairevice et al in 2017 [30] published the 5-year survival data of a randomized controlled trial. In this trial 150 patients with stage II-III resectable rectal cancer were randomly assigned to one of two treatment arms: short course preoperative radiotherapy (SCRT) with delayed surgery, RT 25 Gy/5 fractions, 5 Gy per fraction in 5 days following TME (total mesorectal excision) after 6-8 weeks, then follow-up; or conventional chemoradiotherapy (CRT) with delayed surgery: RT 50 Gy/25 fractions, 2 Gy per fraction over 5 weeks concomitant with fluorouracil (5-FU) and leucovorin (Lv) chemotherapy (5-FU 400 mg/m^2/day iv 1 h infusion, days 1-4 and Lv 20 mg/m^2/day bolus iv injection days 1-4) on the 1st and 5th week of RT following TME surgery after 6-8 weeks; then within 8 weeks period adjuvant chemotherapy of 5-FU (400 mg/m^2/day iv 1 h infusion days 1-5) and Lv (20 mg/m^2/day bolus iv injection days 1-5) was started for 4 cycles every 4 weeks, then follow-up. The aim of this study was to compare OS and DFS in these two treatment groups. Median follow-up was 60.5 months (range, 5-108). The results have shown that the 5-year DFS was 67% in the CRT group (n=72) and 45% in the SCRT group (n=68) (p=0.013; HR=1.88; 95% CI, 1.13-3.12; p=0.015). The 5-year OS was 79% and 62% in the CRT and SCRT groups, respectively (p=0.015; HR=2.05; 95% CI, 1.13-3.70; p=0.017). The 5-year OS for intent-to-treat (ITT) population (n=150) was 78% in the CRT and 58% in the SCRT group (p=0.003; HR=2.28; 95% CI, 1.30-4.00; p=0.004). In conclusion the 5-year DFS and OS were significantly better in the CRT than the SCRT group. For ITT population, OS was also significantly better after CRT vs SCRT.

The results of the randomized trials are summarized in Table 1.

Discussion

It is known from the literature that preoperative radiotherapy reduces the risk of local recurrence after surgery for rectal cancer by more than 50%, even with optimized TME [6-11]. Nowadays, conventionally fractionated long course radiotherapy (5 fractions of 1.8-2 Gy per week during 5-6 weeks), most often in combination with chemotherapy, represent the predominant treatment in most countries. Short course radiotherapy (5 fractions of

5 Gy in 1 week [5×5 Gy]), and surgery within the following week is commonly used in Sweden and in some other countries in northern and western Europe. However, the optimal fractionation and timing of surgery in relation to radiotherapy is still controversial [31].

The randomized trials have shown that when comparing short course preoperative radiation therapy with immediate surgery to long course preoperative chemo-radiation for rectal cancer the results are similar regarding distant recurrence, recurrence-free survival, OS, and late toxicity. Moreover, despite significant downsizing, chemo-radiation did not result in increased sphincter preservation rate in comparison with short term preoperative radiotherapy [17,21,24,25]. Regarding the downstaging effect of short course radiotherapy, two short courses of preoperative radiotherapy regarding the time to surgery (immediately vs delayed) were compared in the Stockholm III randomized trial. Besides the fact that, no major differences were found between the two regimens regarding oncological results, the authors concluded that short course radiation therapy can induces tumor downstaging if surgery is performed after an interval of 4-8 weeks of radiation therapy [28,29].

Additionally, several trials compared the downstaging effect achieved after long course chemo-radiotherapy and short course radiotherapy followed by delayed surgery and found that long course preoperative chemo-radiation resulted in greater statistically significant tumor downsizing and downstaging compared with short course radiation, but there was no difference in the R0 resection rates [22]. Besides that, 3-year DFS was better in chemo-radiotherapy group comparing with short course radiotherapy group with no difference in OS [23] or more recently the 5-year DFS and OS were significantly better in the chemo-radiotherapy group than the short course radiotherapy group when adjuvant chemotherapy was added to the chemo-radiotherapy arm [30]. It is believed that such results in the last trial conducted by Kairevice et al are expected because in the short course radiotherapy group no chemotherapy was given at all whereas in the long course radiotherapy the chemotherapy was given as neoadjuvant as well as adjuvant.

Finally, based on the potentially tumor downstaging effect of short course radiation therapy when the surgery is delayed it was believed that if consolidation chemotherapy is added between 5×5 Gy and surgery, such a combination might thereby be superior to long course chemoradiation. Moreover, a possible benefit of short course radiotherapy with delay is that upfront chemotherapy can be given to patients with a high risk of distant metastases during the waiting time after the end of radiotherapy. This concept has been studied in the recently closed RAPIDO trial [32] and in a recently published Polish trial [27]. Results from the RAPIDO trial are not yet available but the Polish trial reported improved tolerability and improved survival after short course radiotherapy followed by consolidation chemotherapy compared to conventional chemoradiotherapy. The present aim in rectal cancer treatment must be to maintain a low rate of local recurrence, minimise the risk of early and late treatment toxicity and postoperative complications, and to address the problem of distant disease. This might be achieved with short course radiotherapy with delay and chemotherapy in the period between radiotherapy and surgery.

Conclusion

To conclude, short course radiotherapy with surgery delayed for 4-8 weeks might have certain advantages over immediate surgery in rectal cancer treatment. Oncological outcomes seem similar to short course radiotherapy with surgery within a week; acute radiation toxicity is observed but the postoperative complications are significantly fewer. Long course radiotherapy with delay seems to be no different than short course radiotherapy with delay, but prolongs the treatment time substantially. Additionally, short course radiotherapy followed by consolidation chemotherapy and delayed surgery improved tolerability and survival compared to conventional chemoradiotherapy. Therefore, short-course radiotherapy with consolidation chemotherapy can be considered as an effective option for preoperative management in very advanced rectal cancer, especially in countries with long waiting lists for radiotherapy.

Conflict of interests

The authors declare no conflict of interests.

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