Original Research Article

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 ☆

Laura Kairevičė [a,*], *Tadas Latkauskas* [b], *Algimantas Tamelis* [b], *Aleksandras Petrauskas* [c], *Henrikas Paužas* [b], *Tadas Žvirblis* [d], *Laimonas Jaruševičius* [a], *Žilvinas Saladžinskas* [b], *Dainius Pavalkis* [b], *Rasa Jančiauskienė* [a]

[a] *Department of Oncology and Hematology, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[b] *Department of Surgery, Medical Academy, Lithuanian University of Health Sciences, Kaunas, Lithuania*
[c] *Department of Chemotherapy with Day Care Unit, National Cancer Institute, Vilnius, Lithuania*
[d] *Vilnius University Hospital Santariškių Klinikos, Vilnius, Lithuania*

ARTICLE INFO

ABSTRACT

Background and objective: At present, there are common recommendations for treatment for stage II–III resectable rectal cancer patients: preoperative conventional chemoradiotherapy (CRT) with delayed surgery in 6–8 weeks or preoperative short-course radiotherapy (SCRT) followed by immediate surgery. The aim of this study was to compare overall survival (OS) and disease-free survival (DFS) in two treatment groups: preoperative SCRT and CRT both with delayed surgery plus adjuvant chemotherapy in CRT arm.
Materials and methods: A total of 150 patients were randomly assigned to two groups: 75 to CRT (preoperative conventional CRT, 50 Gy/25 fr with fluorouracil and leucovorin on the 1st and the 5th week of RT followed by TME surgery in 6–8 weeks and 4 cycles of adjuvant fluorouracil/leucovorin every 4 weeks; then follow-up) and 75 to SCRT (preoperative short-course RT, 25 Gy/5 fr followed by TME surgery in 6–8 weeks; then follow-up). The data of 140 patients (72 in CRT and 68 in SCRT group) were included in statistical analysis. Primary end points were OS and DFS.
Results: Median follow-up was 60.5 (range, 5–108) months. 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).

Conclusions: 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 versus SCRT.

1. Introduction

Preoperative short-course radiotherapy (SCRT), 25 Gy, 5 fractions, with immediate radical surgery (TME) and conventional chemoradiotherapy (CRT), 45–50 Gy, 1.8–2 Gy/fr, with concomitant 5-FU-based chemotherapy followed by radical TME surgery in 6–8 weeks are two main perioperative treatment strategies for locally advanced stage II–III resectable rectal cancer [1,2]; they are worldwide used in the daily clinical practice [3,4]. Trials have shown that CRT provides better local control than the same RT alone [1,2]. Besides, preoperative treatment (CRT or SCRT) also provides better local control, lower toxicity and better compliance compared to postoperative treatment [5,6]. However, a survival benefit was not found and until now, and there is no clear evidence which neoadjuvant treatment regimen is superior. The aim of the recent study was to evaluate and compare efficacy of two different standard and evidence-based treatment strategies: neoadjuvant SCRT plus surgery, as proposed by Pahlman et al. in the Swedish Rectal Cancer Trial in 1997 [7], Kapiteijn et al. in the Dutch trial in 2001 [8], and neoadjuvant conventional CRT plus surgery plus adjuvant fluorouracil-based chemotherapy, as proposed by Sauer et al. in the German trial in 2004 [5]. Design of the recent study was created in 2006, when these two treatment strategies were the standard ones. The hypothesis was raised that short-term RT with delayed surgery can induce downstaging and is at least effective as conventional CRT in terms of survival. Preoperative short-course RT with delayed surgery was quite a new approach in rectal cancer treatment in 2007.

2. Materials and methods

Our prospective randomized study was carried out from January 2007 until June 2013, in a single university center. Each patient provided written informed consent before participating in the study. The trial was approved by the regional biomedical ethics committees. The study is registered in the database of clinical trials (http://clinicaltrials.gov; Identifier: NCT00597311). The inclusion and exclusion criteria as well as pretreatment assessment were reported previously [9] and were similar to other clinical trials. The clinical staging was done according to the American Joint Committee on Cancer (AJCC) Cancer staging Manual, 6th edition and based on ERUS and/or pelvic CT and/or MRI findings for T and N categories and chest X-ray, abdominal ultrasound and/or CT for M category. Detailed baseline methods of staging, pathological findings

and staging (ypT, ypN, CRM, pCR, etc.), as well as information regarding surgical management, perioperative complications etc. are presented in recently published article by Latkauskas et al., 2016 [10].

2.1. Randomization

After screening, 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 fr, 5 Gy per fraction in 5 days following TME surgery after 6–8 weeks, then follow-up; or conventional chemoradiotherapy (CRT) with delayed surgery: RT 50 Gy/25 fr, 2 Gy per fraction over 5 weeks concomitant with fluorouracil (5-FU) and leucovorin (Lv) chemotherapy (5-FU 400 mg/m^2/day i/v 1 h infusion 1–4 days and Lv 20 mg/m^2/day bolus i/v injection 1–4 days) 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 i/v 1 h infusion 1–5 days) and Lv (20 mg/m^2/day bolus i/v injection 1–5 day) was started for 4 cycles every 4 weeks, then follow-up.

We used a simple randomization method with numbered opaque envelopes containing treatment allocations.

Patients (n = 150) who met the inclusion criteria were randomized to SCRT or CRT schedules, 75 patients in each arm. Eight patients (5.3%) were ineligible (withdrawal, not analyzed for DFS, due to metastases found during the operation (3 in CRT, 5 in SCRT group) (Fig. 1). Protocol violations were identified in 2 (1.5%) patients in the SCRT arm – they had no surgery (1 refused, 1 due to cardiac event), and also were not analyzed for DFS. No patients were lost to follow-up. All eligible patients were included in statistical analysis. OS was also calculated for all intent-to-treat (ITT) population (150 patients).

2.2. Irradiation technique

Patients randomized to short-course RT (5 Gy × 5 fr) received a total dose of 25 Gy over 5 consecutive days, from Monday to Friday. For patients, randomized to long-course RT, daily fractional dose was 2 Gy in 25 fractions over 5 weeks (total dose 50 Gy). Individual 3-dimensional dose planning with photon beam energy 15 MV and beam shaping with multileaves collimator (MLC) were used for all patients. RT technique arrangement was identical in the two treatment groups. The target volume included the primary tumor, adjacent lymph nodes and presacral region. The target volume extended from the top of the sacrum to 5 cm below the primary tumor. Laterally, it included pelvic sidewalls and internal iliac nodes.
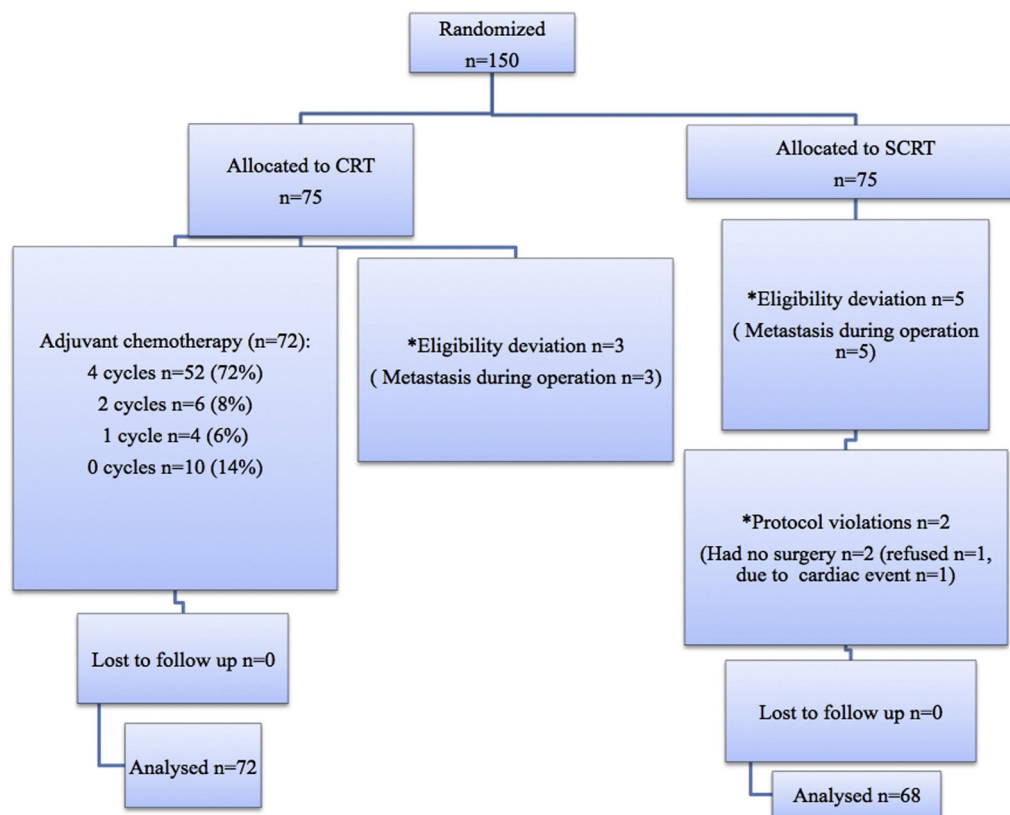
Figure 1 – Trial flowchart. *Not analyzed for DFS, because of never being tumor-free.

Posteriorly, the presacral lymph nodes and sacral hollow were covered. Anteriorly, an adequate margin was left to cover the tumor (including the posterior vaginal wall in women).

2.3. Follow-up

After treatment, follow-up visits were performed every 3 months for the first 2 years; later, every 6–12 months for at least 5 years. Evaluation consisted of physical examination, abdominal ultrasound, chest X-ray and colonoscopy. CT and/ or MRI were performed if there was suspicion of local or distant recurrence.

2.4. Statistical analysis

The trial was designed to test the non-inferiority of overall survival in the SCRT versus CRT group. Assuming equal trial groups, non-inferiority margin of hazard ratio of 0.8, 50% of event rate, 5% type I error, and 80% power, the sample size was estimated at least 138 subjects. Assuming the probability of dropouts in a range of 5–10%, we had to enroll at least 150 patients. Sample size calculations were done taking into account the recommendations from the educational book by Chow et al. [11].

Descriptive statistics were used to describe demographic patients' characteristics. The normality of the distribution was assessed using Kolmogorov–Smirnov test. The Student t-test was used to compare means of two independent quantitative data sets. The differences between independent two categorical data groups were evaluated by the Fisher exact test. Univariate logistic regression model was used to evaluate odds ratio for distant metastases. Survival trends were evaluated by Kaplan–Meier method. Log-rank test was used to evaluate difference between Kaplan–Meier curves. Risk factors for DFS and OS were assessed by univariate Cox regression analysis. Forest plots were drawn using Cox regression output. Disease free survival (DFS) was calculated as the time from the first day of treatment to the first date of disease progression or day of confirmed new tumor or death from any cause. Overall survival (OS) was calculated as the time from the first day of treatment to death from any cause. If during the last visit to clinician there was no evidence of disease progression or new tumor the date was confirmed as censored. A two-tailed P value less than 0.05 considered to be significant. Statistical analysis was performed using Statistical Analysis System (SAS) package version 9.2.

3. Results

From January 2007 to June 2013, 150 patients were enrolled into the study, and 10 patients were ineligible due to the reasons mentioned above. Initial data on 83 patients, included between 2007 and 2010, were reported previously in 2011 [9]. Patient characteristics (n = 140) in two groups at randomization were similar and well balanced (Table 1).

Table 1 – Patient and tumor characteristics according to treatment received.			
Characteristic	SCRT (n = 68)	CRT (n = 72)	P
Age, years	65.6 ± 9.51	63.1 ± 10.13	0.141
Gender, n (%)			
Male	43 (63.2)	49 (68.1)	0.597
Female	25 (36.8)	23 (31.9)	
ASA, n (%)			
1	1 (1.5)	1 (1.4)	0.802
2	32 (48.5)	31 (43.1)	
3	33 (49)	40 (55.5)	
Period from the end of neoadjuvant therapy to surgery, days			
Clinical stage, n (%)	48.0 ± 12.51	47.1 ± 8.57	0.626
II	16 (23.5)	15 (20.8)	0.839
III	52 (76.5)	57 (79.2)	
Clinical T category, n (%)			
cT2	6 (9)	4 (6)	0.075
cT3	56 (82)	52 (72)	
cT4	6 (9)	16 (22)	
Clinical N category, n (%)			
cN0	22 (32)	21 (29)	0.502
cN1	33 (49)	31 (43)	
cN2	13 (19)	20 (28)	
Tumor distance from anal verge, n (%)			
<5 cm	34 (50)	30 (41.7)	0.584
5–10 cm	29 (42.6)	37 (51.4)	
11–15 cm	5 (7.4)	5 (6.9)	

Values are mean ± standard deviation, unless indicated otherwise. ASA, American Society of Anesthesiologists; physical status classification system.

Table 2 – Results of postoperative histological examination.			
	SCRT (%), n = 68	CRT (%), n = 72	P
Complete response	3 (4.4)	8 (11.1)	0.293
I stage – T1,2N0M0	18 (26.5)	19 (26.4)	
II stage – T3,4N0M0	22 (32.4)	27 (37.5)	
III stage – T1-4N + M0	25 (36.7)	18 (25)	

3.1. Local and distant recurrences

Median follow-up of the patients was 60.5 (range 5–108) months. During that time, local recurrence rate was 7% (5 patients) in CRT (n = 72) and 6% (4 patients) in RT (n = 68) group, with no statistical difference between the groups. Three patients in CRT group and 3 patients in SCRT group had both distant metastases and local relapse.

Distant metastasis rate was 16 (22%) after CRT (n = 72) and 21 (31%) after SCRT (n = 68) with no statistical significance between the groups. Odds ratio for distant metastases for SCRT patients was 1.564 (95% CI, 0.733–3.335) if compare to CRT patients. The hazard ratio (HR) for cancer progression (distant and local) for SCRT patients was 1.88 (95% CI, 1.132–3.122, P = 0.015) compared to CRT patients.

3.2. Disease free and overall survival

Disease free survival (DFS) was statistically significant different in CRT and SCRT groups (P = 0.013). Five years DFS was 67% and 45% in CRT and SCRT, respectively (Fig. 2).

Overall survival (OS) at 5 years was 79% in CRT (n = 72) and 62% in SCRT (n = 68) group, and this difference was also statistically significant (P = 0.015; HR = 2.05; 95% CI, 1.13–3.70; P = 0.017) (Fig. 3).
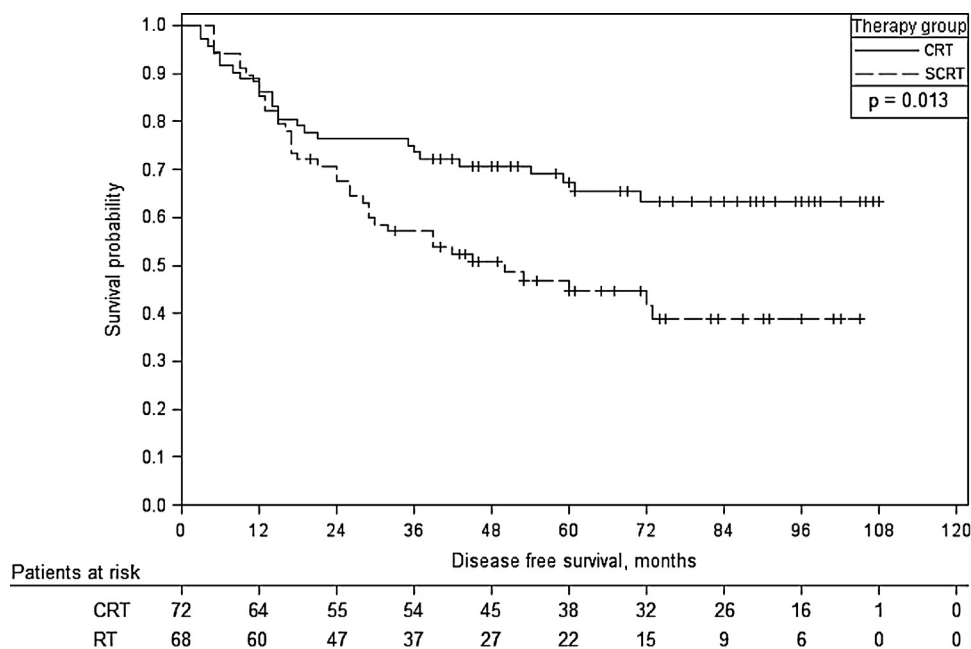
The pathological complete response rate (Table 2) was 4.4% after SCRT and 11% after CRT. Downstaging to ypT0, T1 and T2 was observed in almost 31% of cases in SCRT group and 37.5% cases in CRT group, but there were no significant differences between the groups.

Patients at risk										
CRT	72	64	55	54	45	38	32	26	16	1	0
RT	68	60	47	37	27	22	15	9	6	0	0

Figure 2 – Five-year disease-free survival (n = 140) according to treatment received.
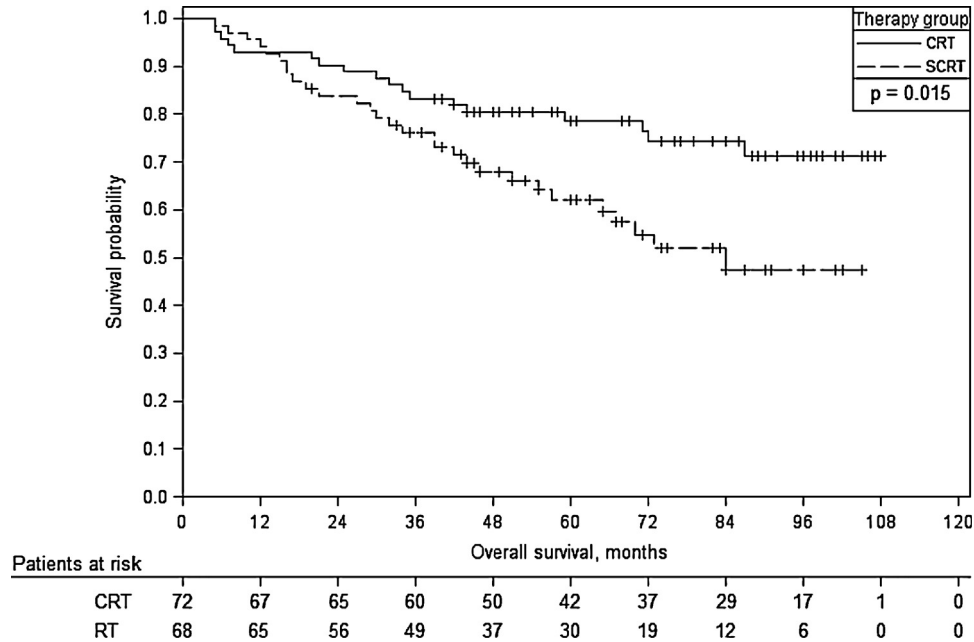
Figure 3 – Five-year overall survival (n = 140) according to treatment received.

OS for the ITT population, all 150 patients, at 5 years was 78% in the CRT (n = 75) and 58% in SCRT group (n = 75) (Fig. 4) and this difference was statistically significant (P = 0.003; HR = 2.28; 95% CI, 1.30–4.00; P = 0.004). DFS analysis of all 150 patients was not possible, because 10 patients were never free of disease: metastases were found in 8 patients during the operation, and 2 patients were not operated at all.

3.3. Forest plot analysis for DFS and OS

Figs. 5 and 6 show Forest plot analyses with HRs for patients who received preoperative CRT compared with those who received preoperative SCRT in terms of DFS and OS. For almost all subgroups of patients, the HR increases after CRT, it shows, that CRT was more beneficial compared to SCRT in terms of DFS and OS. The strongest difference of risk for developing
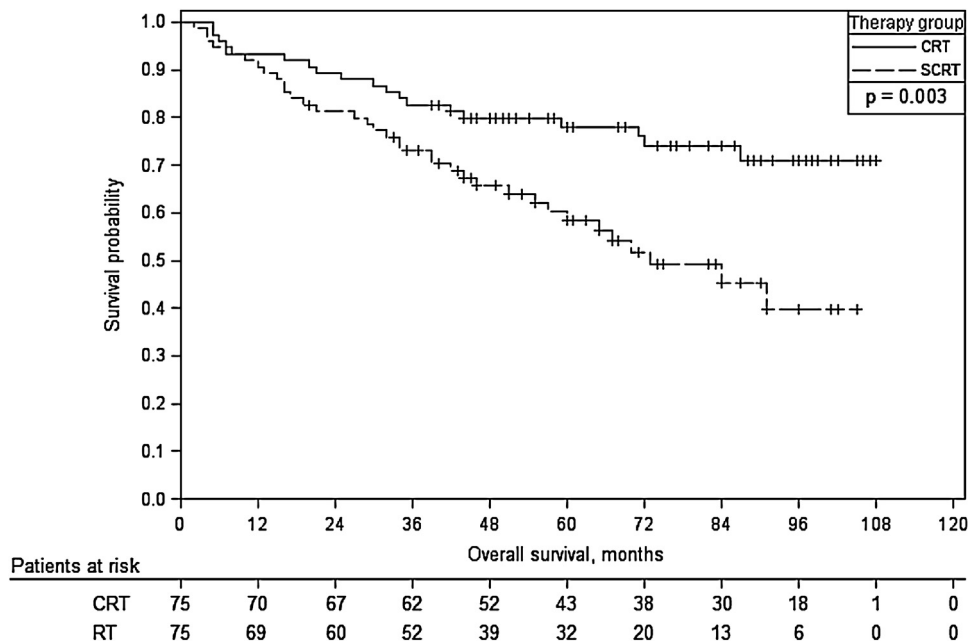

Figure 4 – Five-year overall survival for ITT population (n = 150) according to treatment received.
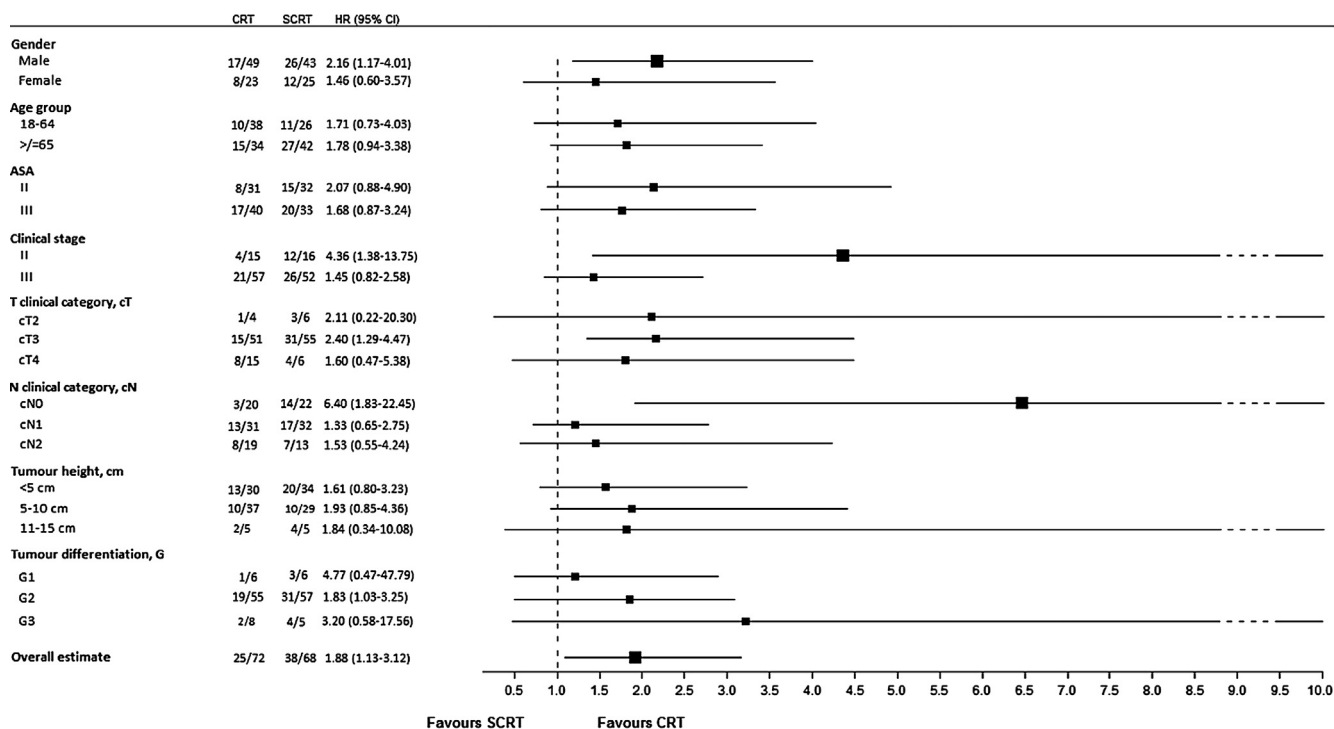
Figure 5 – Forest plot analysis of DFS according to treatment received.
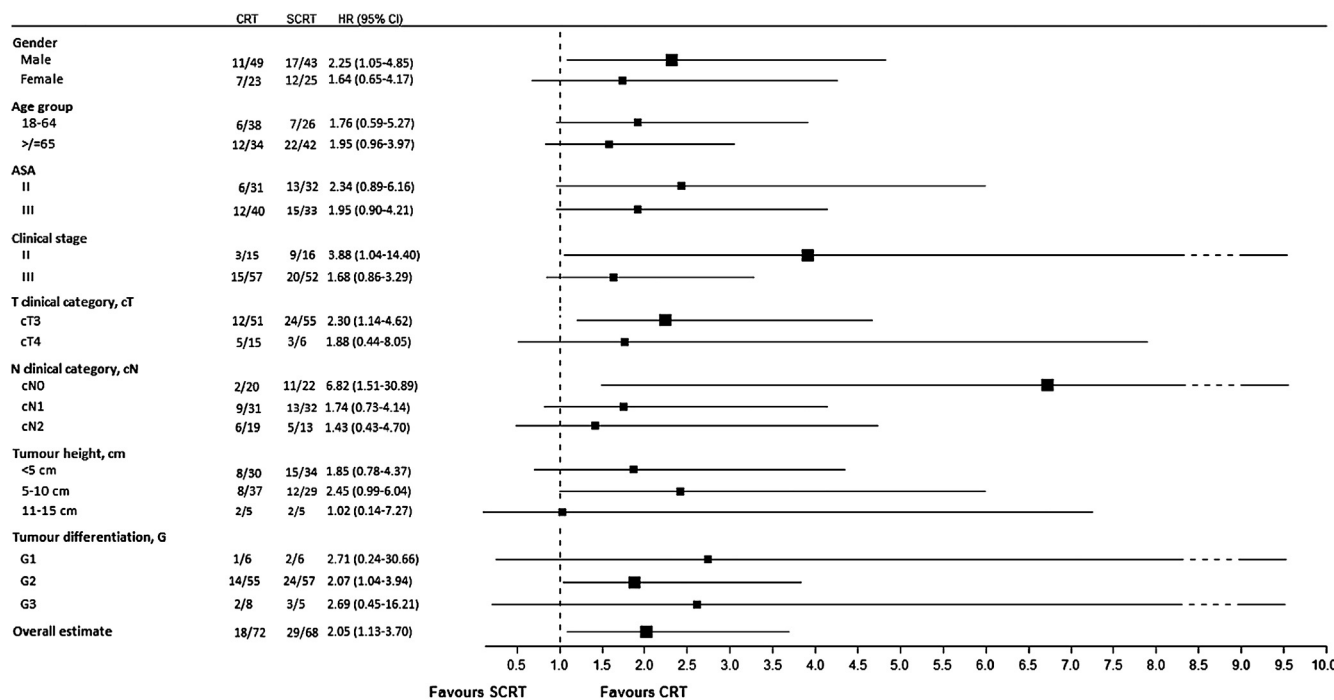

Figure 6 – Forest plot analysis of OS according to treatment received.

disease progression occurred in males, clinical stage II, cT3, cN0 category patients who showed a significantly higher risk after preoperative SCRT compared to preoperative CRT with an overall estimate (HR = 1.88; 95% CI, 1.13–3.12; P = 0.015). The strongest difference of risk for death occurred also in males, and in patients with clinical stage II, cT3, cN0 and G2 categories, which showed significantly higher risk after preoperative SCRT compared with preoperative CRT (overall estimate HR = 2.05; 95% CI, 1.13–3.70; P = 0.017).

4.   Discussion

Indirect comparison shows that neoadjuvant SCRT and conventional CRT for locally advanced stage II–III resectable rectal cancer could give similar results in terms of local control [7,8,12–14], toxicity, adverse effects [12–14] and survival [7,14]. SCRT is considered to have the advantage over CRT that it allows rapid treatment with high compliance for patients who are frail, elderly and with comorbidities which preclude 5-fluorouracil-based chemotherapy [4].

Several meta-analyses compared these two different preoperative treatment regimens – SCRT and conventional CRT: there was no difference in DFS, OS, but CRT resulted in significantly higher pathological complete response rate, lower local recurrence rate and higher acute toxicity [15–17]. According the results of our trial, DFS, OS were better in CRT plus adjuvant FU/Lv arm comparing with SCRT and with those observed in some other trials. The main explanations for this could be a positive effect of chemotherapy, both neoadjuvant and adjuvant, and good compliance to the treatment. The compliance for the neoadjuvant CRT schedule was 69.2% in the Polish trial [18,19]. Eighty four per cent of patients received concurrent FU in preoperative long-course CRT (LC) arm in the TTROG Trial 01.04 [20]; adjuvant chemotherapy completed 85% of short-course RT (SC) and 86% of LC patients. Compliance was really high in our study: all 150 (100%) patients received planned neoadjuvant treatment both in short-term RT and in long-term CRT arm; 72% (52 of 72 eligible patients in CRT arm) completed all 4 cycles of adjuvant FU/Lv, 8% (6 of 72 patients) completed 2 cycles and 6% (4 of 72) completed 1 cycle of adjuvant FU/Lv. No adjuvant chemotherapy was administered to 14% of the patients (10 of 72 eligible patients in CRT arm). Compliance to preoperative treatment was excellent; to postoperative, rather good.

Initial results from the EORTC 22921 Trial [21] showed that FU-based chemotherapy preoperatively or postoperatively after neoadjuvant RT had no significant effect on survival as it has on local control. But the rate of adherence to preoperative CRT was 82%, and to postoperative chemotherapy only 42.9%. Long-term results from the same trial [22] show, that adjuvant FU-based chemotherapy does not affect DFS and OS, and, in the authors' opinion, this was due to poor adherence to adjuvant chemotherapy and not preserved dose-intensity over all the cycles. Long-term results from the Stockholm III trial [23] are awaited as well since there were reported only initial results concerning compliance, surgical procedures, pathological findings and perioperative complications.

Other clinical trials [24,25] with 5-FU based chemotherapy and meta-analyses (5-FU+/-oxaliplatin, OXA) [26–28] also failed to demonstrate a significant benefit of adjuvant chemotherapy in terms of OS and DFS. In the PROCTOR-SCRIPT trial [24], compliance to all planned chemotherapy cycles was 73.6%, very similar to recent study, but in the I-CNR-RT trial [25] only 58.4% of patients received cycles 3 to 6. There are two main lines going through these meta-analyses and individual trials, which can explain why the endpoints were not met: poor or low adherence to the treatment (EORTC 22921 trial, I-CNR-RT trial, CHRONICLE [29] trial) and the small

sample size and/or poor accrual, which then can translate into the lack of statistical power (CHRONICLE, EORTC 22921, I-CNR-RT, PROCTOR-SCRIPT trials). Besides, the latter three studies – EORTC 22921, Italian and Dutch – had long accrual periods, and this could have an influence on diagnostic procedures, RT and surgical techniques, as well as on survival results, with the improvement over time.

Studies that reported the overall adherence to postoperative chemotherapy as good or excellent (78–92% and more) have shown significant differences in survival between the arms [30–32]. However, these trials did not include an observation arm; however, at least we can generally understand from them that chemotherapy works when it is applied. Activity of OXA was also tested in several other clinical trials in neoadjuvant [33–36] setting and as induction chemotherapy [37]. Unfortunately, adding OXA to FU-based preoperative chemotherapy did not improve local control, DFS or OS, but added significant toxicity in most studies.

Our study is small and this is one of its biggest limitations; on the other hand, patients' characteristics were well balanced between the groups. Data on positive pathological lymph nodes in recent study – 25 (36.8%) cases in the SCRT group and 18 (25%) cases in CRT group ($P > 0.05$) – could suggest that there was an imbalance in the original nodal status between SCRT and CRT arm or it could be due to the positive chemotherapy effect. There were also less metastases found during the operation in CRT arm comparing to SCRT, 3 (4%) and 5 (6.6%), respectively, which can also reflect the impact of absence of chemotherapy and 6–8 weeks interval from end of 5×5 RT schedule till surgery in SCRT arm, during which metastatic dissemination is likely to proceed. The differences between all these comparatives were not statistically significant. Other explanation for metastases and imbalance between positive lymph nodes in different treatment arms could be inadequate initial stating, and this also should be taken into account. Analysis of the literature by Hermanek et al. shows that clinical imaging is uncertain and results in over-staging as well as over-therapy in 40% [38]. A pooled international analysis of six institutions by Guillem et al. showed that in 41 of 188 patients (22%) originally clinically staged as cT3N0, pathological analysis of the resected specimen following preoperative chemoradiotherapy revealed ypN+, although another 18% of patients may be overstaged and therefore overtreated [39]. Thus inadequate imaging and staging is one of the limitations in many randomized clinical studies.

5.   Conclusions

These two different regimens – preoperative short-course RT and conventional CRT – as independent and evidence-based different treatment schedules are widely used all over the world. Despite the fact that our study is small, it confirmed the efficacy of systemic chemotherapy in the treatment of locally advanced rectal cancer as well as the importance of the compliance to the treatment, what is clear from the survival results in the CRT plus adjuvant FU/Lv arm. Our findings might give additional insight into the treatment of resectable stage II–III rectal cancer patients.

Conflict of interest

The authors declare no conflict of interest.

REFERENCES

[1] Glimelius B, Tiret E, Cervantes A, Arnold D, on behalf of the ESMO Guidelines Working Group. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2013;24(Suppl 6):vi81–8.

[2] Valentini V, Aristei C, Glimelius B, Minsky BD, Beets-Tan R, Borras JM, et al. Multidisciplinary Rectal Cancer Management: 2nd European Rectal Cancer Consensus Conference (EURECA-CC2). Radiother Oncol 2009;92:148–63.

[3] Glimelius B. Neo-adjuvant radiotherapy in rectal cancer. WJG 20th Anniversary Special Issues (5): colorectal cancer. World J Gastroenterol 2013;19(46):8489–501.

[4] Glynne-Jones R. Commentary on Latkauskas et al.. Colorectal Dis 2011;14:294–301.

[5] Sauer R, Becker H, Hohenberger W, Rödel C, Wittekind Ch, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004;351:1731–40.

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

[7] Swedish Rectal Cancer Trial, Cedermark B, Dahlberg M, Glimelius B, Påhlman L, Rutqvist LE, Wilking N. Improved survival with preoperative radiotherapy in resectable rectal cancer. N Engl J Med 1997;336:980–7.

[8] Kapiteijn E, Marijnen CAM, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001;345:638–46.

[9] Latkauskas T, Pauzas H, Gineikiene I, Janciauskienė R, Juozaityte E, Saladzinskas Z, et al. Initial results of a randomized controlled trial comparing clinical and pathological dowstaging of rectal cancer after preoperative short-course radiotherapy or long-term chemoradiotherapy, both with delayed surgery. Colorectal Dis 2011;14:294–301.

[10] Latkauskas T, Pauzas H, Kairevice L, Petrauskas A, Saladzinskas Z, Janciauskiene R, et al. Preoperative conventional chemoradiotherapy versus short-course radiotherapy with delayed surgery for rectal cancer: results of a randomized controlled trial. BMC Cancer 2016;16:927. http://dx.doi.org/10.1186/s12885-016-2959-9

[11] Chow SC, Shao J, Wang H. Sample size calculations in clinical research. Comparing Time-to-Event Data. 2nd ed. Boca Raton: Chapman & Hall; 2008. p. 163–86.

[12] Widder J, Herbst F, Dobrowsky W, Schmid R, Pokrajac B, Jech B, 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;92:1209–14.

[13] Radu C, Berglund A, Pahlman L, Glimelius B. Short-course preoperative radiotherapy with delayed surgery in rectal cancer – a retrospective study. Radiother Oncol 2008;87:343–9.

[14] Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005;23:5644–50.

[15] Ceelen W, Fierens K, Van Nieuwenhove Y, Pattyn P. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer: a systematic review and meta-analysis. Int J Cancer 2009;124:2966–72.

[16] Latkauskas T, Paskauskas S, Dambrauskas Z, Gudaityte J, Saladzinskas S, Tamelis A, et al. Preoperative chemoradiation vs radiation alone for stage II and III resectable rectal cancer: a meta-analysis. Colorectal Dis 2010;12:1075–83.

[17] De Caluwe L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer (Review). The Cochrane Collaboration The Cochrane Library 2013;Issue 2.

[18] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bębenek M, Pudełko M, et al. Sphincter preservation following preoperative radiotherapy for rectal cancer: report of a randomized trial comparing short-term radiotherapy vs. conventionally fractionated radiochemotherapy. Radiother Oncol 2004;72:15–24.

[19] Bujko K, Nowacki MP, Nasierowska-Guttmejer A, Michalski W, Bebenek M, Kryj M. Long-term results of a randomized trial comparing preoperative short-course radiotherapy with preoperative conventionally fractionated chemoradiation for rectal cancer. Br J Surg 2006;93:1215–23.

[20] Ngan SY, Burmeister B, Fisher RJ, Solomon M, Goldstein D, Joseph D, 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;30:3827–33.

[21] Bosset JF, Collette L, Calais G, Mineur L, Maingon Ph, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006;355:1114–23.

[22] Bosset JF, Calais G, Mineur L, Maingon Ph, Stojanovic-Rundic S, Bensadoun RJ, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: long-term results of the EORTC 22921 randomized study. Lancet Oncol 2014;15:184–90.

[23] Pettersson D, Cedermark B, Holm T, Radu C, Pahlman L, Glimelius B, et al. Interim analysis of the Stockholm III trial of preoperative radiotherapy regimens for rectal cancer. Br J Surg 2010;97:580–7.

[24] Breugom AJ, Van Gijn W, Muller EW, Berglund A, Van den Broek CBM, Fokstuen T, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo) radiotherapy and total mesorectal excision: a Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. Ann Oncol 2015;16:200–7.

[25] Sainato A, Cernusco LNV, Valentini V, De Paoli A, Maurizi ER, Lupattelli M, et al. No benefit of adjuvant Fluorouracil Leucovorin chemotherapy after neoadjuvant chemoradiotherapy in locally advanced cancer of the rectum (LARC): long term results of a randomized trial (I-CNR-RT). Radiother Oncol 2014;113:223–9.

[26] Breugom AJ, Swets M, Bosset JF, Collette L, Sainato A, Cionini L, 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;16:200–7.

[27] Bujko K, Glynne-Jones R, Bujko M. Does adjuvant fluoropyrimidine-based chemotherapy provide a benefit for patients with resected rectal cancer who have already received neoadjuvant radiochemotherapy?. A systematic review of randomized trials. Ann Oncol 2010;21:1743–50.

[28] Bujko K, Glimelius B, Valentini V, Michalski W, Spalek M. Postoperative chemotherapy in patients with rectal cancer receiving preoperative radio(chemo)therapy: a meta-analysis of randomized trials comparing surgery ± a fluoropyrimidine and surgery + a fluoropyrimidine ± oxaliplatin. Eur J Surg Oncol 2015;41:713–23.

[29] Glynne-Jones R, Counsell N, Quirke P, Mortensen N, Maraveyas A, Meadows HM, et al. Chronicle: results of a randomized phase III trial in locally advanced rectal cancer after neoadjuvant chemoradiation randomizing postoperative adjuvant capecitabine plus oxaliplatin (Xelox) versus control. Ann Oncol 2014;25:1356–62.

[30] Rödel C, Liersch T, Becker H, Fietkau R, Hohenberger W, Hothorn T, et al. Preoperative chemoradiotherapy and postoperative chemotherapy with fluorouracil and oxaliplatin versus fluorouracil alone in locally advanced rectal cancer: initial results of the German CAO/ARO/AIO-04 randomized phase 3 trial. Lancet Oncol 2012;13:679–87.

[31] Rödel C, Graeven U, Fietkau R, Hohenberger W, Hothorn T, Arnold D, et al. Oxaliplatin added to fluorouracil-based preoperative chemoradiotherapy and postoperative chemotherapy of locally advanced rectal cancer (the German CAO/ARO/AIO-04 study): final results of the multicenter, open-label, randomized, phase 3 trial. Lancet Oncol 2015;16:979–89.

[32] Hong YS, Nam BH, Kim KP, Kim JE, Park SJ, Park YS, et al. Oxaliplatin, fluorouracil, and leucovorin versus fluorouracil and leucovorin as adjuvant chemotherapy for locally advanced rectal cancer after preoperative chemoradiotherapy (ADORE): an open-label, multicenter, phase 2, randomized controlled trial. Lancet Oncol 2014;15:1245–53.

[33] Aschele C, Cionini L, Lonardi S, Pinto C, Cordio S, Rosati G, et al. Primary tumor response to preoperative chemoradiation with or without oxaliplatin in locally advanced rectal cancer: pathologic results of the STAR-01 Randomized Phase III Trial. J Clin Oncol 2011;29:1–8.

[34] Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, 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;28:1638–44.

[35] Gerard JP, Azria D, Gourgou-Bourgade S, Martel-Laffay I, Hennequin C, Etienne PL, et al. Clinical Outcome of the ACCORD 12/0405-Prodige 2 Randomized Trial in rectal cancer. J Clin Oncol 2012;30:4558–65.

[36] O'Connell MJ, Colangelo LH, Beart RW, Petrelli NJ, Allegra CJ, Sharif S, et al. Capecitabine and oxaliplatin in the preoperative multimodality treatment of rectal cancer: surgical end points from National Surgical Adjuvant Breast and Bowel Project Trial R-04. J Clin Oncol 2014;32:1927–34.

[37] Fernandez-Martos C, Pericay C, Aparicio J, Salud A, Safont MJ, Massuti B, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, locally advanced rectal cancer: Grupo Cancer de Recto 3 Study. J Clin Oncol 2010;28:859–65.

[38] Hermanek P, Merkel S, Fietkau R, Rödel C, Hohenberger W. Regional lymph node metastasis and locoregional recurrence of rectal carcinoma in the era of TME [corrected] surgery: implications for treatment decisions. Int J Colorectal Dis 2010;25:359–68.

[39] Guillem JG, Díaz-González JA, Minsky BD, Valentini V, Jeong SY, Rodriguez-Bigas MA, et al. cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. J Clin Oncol 2008;26:368–73.