World J Surg (2010) 34:1609–1614
DOI 10.1007/s00268-010-0513-5

Preoperative Radiochemotherapy in T3 Operable Low Rectal Cancers: A Gold Standard?

Claudio Fucini · Filippo Pucciani · Claudio Elbetti · Riccardo Gattai · Antonio Russo

Published online: 6 March 2010

Abstract

Background Preoperative chemoradiation followed by total mesorectal excision (TME) has become a standard treatment of preoperatively staged T3 low rectal cancers in many institutions; however, a direct comparison of generalized preoperative versus selective adjuvant chemoradiation has never been assessed in a clinical practice setting.

Patients Over a 4-year period, 80 patients with T3 primary low adenocarcinoma of the rectum, judged operable at preoperative staging, were offered preoperative chemoradiation. Forty-seven patients (Group I) accepted the neoadjuvant treatment and 33 (Group II) preferred immediate surgery and postoperative chemoradiation if indicated.

Results Major postoperative complications occurred in 21% of Group I versus in 11% of Group II ($p = 0.3$) patients. After a mean follow-up of 92 months, the local recurrence rate was 4 and 9% ($p = 0.4$), metastasis rate was 30 and 24% ($p = 0.5$), 5-year survival probability was 0.79 (95% CI = 0.49–0.92) and 0.82 (95% CI = 0.70–1.00) (log-rank test, $p = 0.6$) for Group I and Group II, respectively.

Conclusions In T3 operable low rectal cancers, selective postoperative radiochemotherapy yielded similar long-term results regarding recurrence rate and survival as extended preoperative chemoradiation.

C. Fucini · F. Pucciani · C. Elbetti · R. Gattai
Department of Medical and Surgical Critical Care, Section of General and Oncological Surgery, University of Florence, Florence, Italy

A. Russo
Epidemiology Unit, CSPO, A.O.U. CAREGGI, Florence, Italy

C. Fucini (✉)
Patologia Chirurgica 3, Università degli Studi di Firenze, Viale Morgagni, 85, Florence, Italy
e-mail: claudio.fucini@unifi.it

Introduction

Complete removal of the rectum using total mesorectal excision (TME) is the treatment usually adopted for resectable rectal cancers less than 10 cm from the anal margin [1, 2]. Local recurrence rates of less than 10% and improved survival have been reported for locally invasive (T3) tumors following this procedure [3, 4]. To further reduce local recurrence and increase long-term survival, pre- or postoperative chemoradiation (RT + CHT) had been adopted as neoadjuvant or adjuvant treatment in locally advanced (AJCC/UICC stage II-T3/4N0 and stage III-N1/2) low rectal cancer [5–9]. A recent trial reported that preoperative chemoradiation combined with TME surgery has less morbidity and better control of the local recurrence rate than postoperative chemoradiation and without increased adverse effects [10]. Consequently, the neoadjuvant approach is increasingly adopted in many institutions despite the toxicity of chemoradiation, and in patients subjected to conservative procedures, the impairment of postoperative anorectal function remains matter of concern [11, 12].

There has been some criticism regarding the adoption of preoperative chemoradiation in preoperatively staged II cancers expressed by some authors [13, 14] since 18% of patients examined with endorectal ultrasound (ERUS) and magnetic resonance imaging (MRI) [10] are overstaged and therefore overtreated, and, in addition, T3N0 cancers with no involvement of mesorectal circumferential margin do not need neo- or adjuvant treatment [13, 14]. However, given that more than 22% of preoperatively staged T3 patients seem to have undetected mesorectal lymph node

involvement, other authors [15] contend that the extensive adoption of preoperative chemoradiation is appropriate as long as there is a reliable method of selecting patients who could benefit from this complementary treatment. In fact, clear-cut evidence of the advantages of preoperative chemoradiation in T3 operable rectal cancer either in stage II or III is still missing. A recent trial (MRC CR07 and NCIC-CTG C016, [16]) has evaluated the results of preoperative short-course radiotherapy (25 Gy/5F) versus postoperative chemoradiation limited to patients with involvement of circumferential resection margin. A reduction of local recurrence and an improvement in disease-free survival in the neoadjuvant arm of the study has been reported. Unfortunately, a similar trial examining preoperative chemoradiation versus selective adjuvant chemoradiation in subjects with T3 operable cancers is still absent.

In this article we examined the long-term results of a prospective observational study on a selected group of patients with T3 resectable low rectal cancer who were subjected, in a limited period of time, to preoperative chemoradiation or underwent selectively a more conventional treatment: immediate surgery followed by chemoradiation [17] when indicated.

Patients and methods

In a 4-year period (1997–2000) 80 patients with T3 resectable low rectal cancer measured by rigid rectoscopy at 10 cm or less from the anal margin were seen by the multidisciplinary oncologic team of our department. The median age was 63 years (range = 39–80 years). The tumors were deemed T3 cancers, resectable with curative intent with total mesorectal excision (TME), by means of clinical examination, abdominopelvic CT scan, endorectal sonography, chest X-ray, and at times by MRI with endorectal coil. No attempt was made to evaluate lymph node status. After explaining extensively the goals and the risk of neoadjuvant versus selective adjuvant treatment, preoperative chemoradiation was offered to all patients. Forty-seven patients [Group I, 28 men, mean age = 63 ± 9 (range = 45–77) years] accepted the neoadjuvant treatment, while 33 [Group II, 19 men, mean age = 64 (range = 39–80) years] preferred immediate surgery. Preoperative radiation therapy (RT) fields included the primary tumor, the adjacent lymph node drainage area in the pelvis, and the regional nodes along the superior hemorrhoidal vessels. The tumor dose was 45 Gy delivered in 25 daily doses of 1.8 Gy each. Chemotherapy consisted of fluorouracil (5-FU 375 mg/m^2 bolus daily for 5 days) and leucovorin (LV) (10 mg/m^2 daily for 5 days). The treatment was administered concurrently during the first 5 days and days 29–33 of radiation therapy.

Postoperative chemoradiation started 4–6 weeks after surgery with chemotherapy given for two cycles every 28 days at the same dosage reported above. After the two cycles of 5-FU plus LV, radiotherapy was initiated at a daily dose of 2 Gy over a period of 5 weeks (54 Gy).

All patients with positive nodes in both groups were scheduled to receive four extra cycles of postoperative chemotherapy.

The patients who received the neoadjuvant treatment had a new complete diagnostic workup before surgery was performed 6–9 weeks after completion of therapy. Forty-eight patients had an anterior resection with a coloanal anastomosis. Thirty-two patients had an abdominoperineal excision. All patients were enrolled in an institutional follow-up based on clinical examination, CEA monitoring, colonoscopy, and CAT scan of the abdomen and thorax to follow the progression of the disease. Median follow-up was 92 months (range = 84–132 months). Perioperative results, local recurrence rate, metastatic relapse, and cancer-specific and overall survival were examined for each group.

Statistical analysis

The distribution of individual characteristics of two treatment groups was evaluated by simple descriptive statistics and variable frequency and the distributions were compared using the Fisher exact test. The Wilcoxon rank-sum tests for unpaired data were performed for statistical evaluation of the significant difference between the two groups for continuous variables.

The index date for calculation of survival was defined as the date of primary treatment (RT + CHT or surgery). The observed survival was estimated using the Kaplan–Meier product limit method, and cumulative survival probability was calculated at 5 years, stratified according to treatment group. Differences were tested using the log-rank test. To assess the relative excess risk of death or recurrence according to treatment group and to control for confounding factors (age as a continuous variable, gender), proportional hazard models were fitted by computing the hazard ratio (HR) and the corresponding 95% confidence intervals (95% CI). The proportional assumption was examined with log–log survival plots or by adding time-dependent interaction terms into the model.

Results

Perioperative comparisons

Groups I and II were comparable with regard to gender, age, and the distribution of type of operation, i.e., abdominoperineal excision versus sphincter-sparing

Table 1 Distribution of clinical and demographic characteristics according to treatment group of 80 patients with rectal cancers classified primarily with ERUS as T3NxM0

	Preoperative chemoradiation (Group I) ($n = 47$)	Surgery ± postop chemoradiation (Group II) ($n = 33$)	p value[a]
Age at diagnosis (years) (mean ± SD)	63.1 ± 9.4	64.6 ± 12.7	0.6
Gender			
Male	28	19	
Female	19	14	0.8
Distance of distal margin of tumor from anal verge at diagnosis (cm) (mean ± SD)	7.1 ± −3.4	7.4 ± −3.0	0.5
Coloanal anastomoses[b]	27 [4]	21 [3]	0.5
Abdominoperineal excisions	20 (42%)	12 (36%)	
Local recurrences	2 (4%)	3 (9%)	0.3
Distant metastases	14 (30%)	8 (24%)	0.5
Alive	33 (70%)	24 (72%)	
Dead	14 (30%)	9 (28%)	0.5

[a] Fisher's exact test

[b] Number in *square brackets* is the number of excisions of the upper internal sphincter

(Table 1). All Group I patients completed the preoperative treatment despite the appearance of grade II and grade III toxicity (NCI scale) (skin, small bowel, hematological changes) in 12 of them. Forty patients were noted to have a clinical reduction of the tumor mass. Twenty Group II patients had surgery alone (13 men), 13 had postoperative chemoradiation because of lymph node involvement in 11 (N+) and/or infiltration or close proximity of the tumor edge to the lateral or distal margins of the specimen in 2.

In seven patients with anastomoses at the dentate line, the upper part of the internal sphincter was excised with the rectum. At surgery, all patients were considered locally cured. A temporary protective colostomy or ileostomy was performed at the time of surgery in all patients who underwent sphincter-sparing procedures and was closed 8-20 weeks later. In Group II patients the stoma was closed after the completion of adjuvant chemoradiation.

Postoperative pathologic features (TNM-UICC) of patients who had preoperative chemoradiation or primary surgery are given in Table 2. A complete pathologic remission of the tumor was observed in 12 (25%) of 47 and a partial response was observed in 8 patients of Group I, for a tumor downstaging rate of 42% (Table 2). All cancers of Group II were correctly staged as T3 at preoperative workup.

Microscopically clear surgical margins (radial, proximal, and distal) were obtained in 43 (91%) patients in Group I and in 30 (90%) of those who had primary surgery. All patients with invasion of the surgical margins in Group I had concomitant invasion of lymph nodes. Of the 33 patients who had primary surgery, 11 had pathologic positive lymph nodes, one with concomitant microscopic tumor invasion of the lateral section margins. All these patients received postoperative chemoradiation as well as two others with invasion limited to the lateral margins.

Table 2 Distribution of postoperative pathologic characteristics according to treatment group of 80 patients with rectal cancers classified primarily with ERUS as T3NxM0

	Preoperative chemoradiation *N* (%)	Primary surgery *N* (%)
TNM (pathological)		
T0	12 (25)	0
T1	0	0
T2	8 (17)	0
T3	27 (57)	33 (100)
Node+	12 (25)	11 (33)

Postoperative morbidity

One patient (2%) of Group I died postoperatively from a pulmonary embolism. Postoperative morbidity was 43% for Group I and 44% for Group II. Major complications, namely, complications requiring further surgery, intensive medical support, and prolonged hospital stay (>20 days), were slightly more frequent in Group I (21%) than in Group II (11%) ($p = 0.3$). The most frequent complication was anastomotic failure which occurred in 4 of 27 patients with coloanal anastomosis who received preoperative radiation and in 2 of 22 who had primary surgery (Table 3).

Acute grade III toxicity requiring temporary suspension of radiotherapy appeared in 4 of the 13 patients who received postoperative chemoradiation. In 8 of 12 (66%)

Table 3 Major postoperative complications observed in 12 patients by treatment group

N	Complication
Preoperative chemoradiation	
2	Intestinal obstruction[a]
2	Anastomotic failure with pelvic abscess
1	Anastomotic leakage evidenced after loop ileostomy closure[a]
1	J pouch necrosis[a]
2	Infection of perineal wound
Primary surgery	
2	Anastomotic leakage
1	Pancreatic fistula
1	Prolonged bladder dysfunction

[a] Reoperation

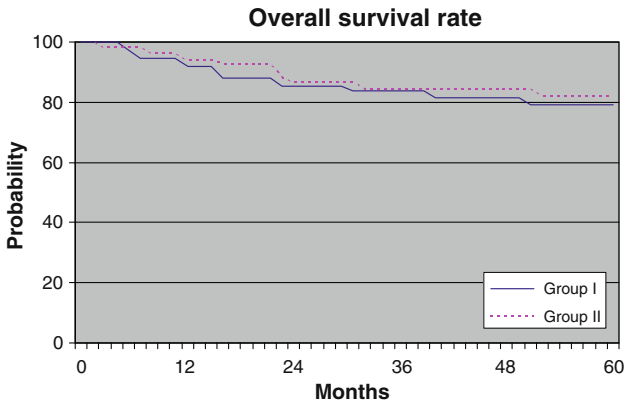

Fig. 1 Overall survival rate of Groups I and II

patients of Group I and in 8 of 11 of Group II scheduled for four postoperative extra cycles of chemotherapy, the treatment was stopped if the patient refused or there was appearance of grade IV hematologic toxicity.

Local recurrences and survival

Isolated local recurrences were registered in 2 of the 47 Group I patients 3 and 6 years respectively after the operation; both had clear section margins at operation. In 3 ($p = 0.3$) of the 33 Group II patients, recurrences (one isolated and two concomitant to metastatic relapse) had appeared respectively 6, 9, and 36 months after surgery. Among the patients who had immediate surgery, two recurrences were registered out of a total of 22 T3N0 tumors and one out of 11 T3N1 tumors. Recurrence occurred in one of the three patients with invasion of section margins.

Of the 80 patients followed for a mean of 92 months, 57 (71%) were still alive at the time of the evaluation. Metastatic disease as first relapse was observed in 14 of Group I and in 8 of Group II patients. Cumulative tumor relapses (metastatic and/or local) were therefore observed in 34 and 33% of patients of Group I and Group II, respectively (Table 1). Group I and Group II patients had a 5-year survival probability of 0.79 (95% CI = 0.49–0.92) and 0.82 (95% CI = 0.70–1.00), respectively (log-rank test, $p = 0.6$) (Fig. 1).

In multivariate analysis, adjusting for sex and age as continuous, Group I had a hazard ratio (HR) for death of 1.4 (95% CI = 0.5–4.1) when compared with Group II. Disease-free survival was also comparable (HR = 1.1, 95% CI = 0.3–4.4).

No differences in local recurrence, metastatic disease, disease-free survival, and overall survival were registered among subgroups of patients who had a complete pathologic response, those who were "downstaged," and those who were T3N0 after preoperative CT/RT. As expected, patients with pathologic N+ tumors had a significantly higher incidence of metastatic disease and worse survival than patients with N− cancers in both Group I and Group II. However, it must be noted that 11 Group I patients with positive nodes at surgery died of metastatic disease within 9–48 months. Only six patients in Group II with positive lymph nodes died of metastatic disease so far ($p = 0.04$).

Discussion

The aim of this study was to evaluate the effects of a neoadjuvant treatment with preoperative chemoradiation versus a selective postoperative approach in patients with clinically operable low rectal cancers preoperatively staged as T3. Despite the potential biases due to the small number of treated patients enrolled in a single center, the lack of formal randomization, and the self-selection for one of the two treatment groups, the results of this experience offer some points of reflection.

The patients evaluated had homogeneous characteristics and were staged by the same dedicated radiologist who performed the ERUS. The rate of complete pathologic response, "downstaging," or lymphatic invasion following preoperative chemoradiation was, in Group I patients, comparable to those reported in the literature [18–20], as was the rate of positive nodes in the immediate surgery group [10, 16]. Long-term relapse rate (local and metastatic) and survival were equivalent in the two groups. We did not observe a significant increase in the rate of sphincter-preserving operations after preoperative chemoradiation (Table 1). Toxicity from chemoradiation occurred in 25% of the patients who had preoperative treatment and in 30% of patients who had postoperative chemoradiation.

However, the latter represented only the 39% of operated subjects.

Results of trials on neoadjuvant treatments carried out in the TME era [10, 21] demonstrated that the main relevant oncologic effect of this approach is a significant reduction of local recurrence rate. This reduction, however, is not always accompanied by a decrease in the number of metastases and, more important, by an increase in survival or disease-free survival when compared with surgery alone or postoperative chemoradiation. This is difficult to explain if we think that, as reported in a classic study on the natural history of the operated rectal cancer [22], 25% of patients with recurrent disease will die from the effects of local recurrence alone. Some authors [21] explain this apparent incongruity of the results as being a result of the small number of local recurrences registered in both arms of their trial (5.6 vs. 10.9%); indeed in another study [10], the difference in the number of local recurrences was not so small (6 vs. 13%), and the survival curves at 5 years were very similar. Other explanations seem to be warranted.

In our experience 20% of patients who underwent neoadjuvant treatment had positive lymph nodes at surgery. As already reported by others [20, 23, 24], the persistence of positive lymph nodes after chemoradiation is tied to a high rate of metastatic failure and subsequent death. In fact, the outcome of our node-positive (N+) patients after chemoradiation was significantly worse than that of patients with positive nodes in the surgery alone group; remarkably, when it occurred, metastatic disease appeared earlier and with a more aggressive behavior in N+ patients post-chemoradiation than in N+ patients post-surgery alone. In one trial [25], the outcome of N+ patients after a short course of preoperative radiotherapy was better than that of persistent N+ patients after preoperative chemoradiation. In the German experience [10], where we must presume a similar distribution of the worst cancers in the two arms of the trial, mortality from cancer in patients who had a relapse was higher in those subjects who had been subjected to the neoadjuvant approach. These data suggest that preoperative chemoradiation could act as a selection tool for the worst cancers, but conversely it could also have a detrimental effect by negatively influencing survival.

In conclusion, from our experience and from an analysis of the data from the literature, it appears that there is no clear-cut evidence of a real benefit of preoperative chemoradiation for the ultimate cure (overall and disease-free survival) of T3 rectal tumors. Until reliable biological markers of sensitivity to chemoradiation [26] are developed and their role as prognostic tools established, in an era where TME for rectal cancer has obtained wide application, the extensive adoption of preoperative chemoradiation in patients with operable cancer should be critically re-examined in a randomized trial similar to the MRC CR07 and NCIC-CTG C016 trial [16]. At the moment, the selective radiochemo postoperative approach maintains its merit since it reduces the number of subjects who will experience the morbidity reported by the German trial with the extensive postoperative approach and the number of patients with long-term anorectal dysfunction [11]. Preoperative chemoradiation should be reserved for use in very low T3/T4 cancers in patients who refuse a terminal abdominal stoma or in T3 cancers with deep infiltration of the mesorectum seen at preoperative MRI, where the achievement of a satisfactory lateral margin with a standard TME could be uncertain.

Acknowledgment This work was funded by the Local Research Budget of the University of Florence.

Disclosures All authors disclose any financial and personal relationships with other people or organizations that could inappropriately influence their work. No potential conflicts of interest include employment, consultancies, stock ownership, honoraria, paid expert testimony, patent applications/registrations, and grants or other funding.

References

1. MacFarlane JK, Ryall RD, Heald RJ (1993) Mesorectal excision for rectal cancer. Lancet 20:457–460
2. Leo E, Belli F, Baldini MT et al (1994) New perspective in the treatment of low rectal cancer: total rectal resection and coloendoanal anastomosis. Dis Colon Rectum 37:S62–S68
3. Berger A, Tiret E, Cunningham C et al (1999) Rectal excision and colonic pouch-anal anastomosis for rectal cancer: oncologic results at five years. Dis Colon Rectum 42:1265–1271
4. Rullier E, Zerbib F, Laurent C et al (1999) Intersphincteric resection with excision of internal anal sphincter for conservative treatment of very low rectal cancer. Dis Colon Rectum 42:1168–1175
5. Boulis-Wassif S, Gerard A, Loygue J et al (1984) 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 53:1811–1818
6. Higgins GA, Humphrey EW, Dwight RW et al (1986) Preoperative radiation and surgery for cancer of the rectum. Veterans Administration Surgical Oncology Group Trial II. Cancer 58:352–359
7. Shumate CR, Rich TA, Skibber JM et al (1993) Preoperative chemotherapy and radiation therapy for locally advanced primary and recurrent rectal carcinoma. A report of surgical morbidity. Cancer 71:3690–3696
8. Minsky B, Cohen A, Enker W et al (1994) Preoperative 5-fluorouracil, low-dose leucovorin, and concurrent radiation therapy for rectal cancer. Cancer 73:273–280
9. Hyams DM, Mamounas EP, Petrelli N et al (1993) A clinical trial to evaluate the worth of preoperative multimodality therapy in patients with operable carcinoma of the rectum: a progress report of National Surgical Breast and Bowel Project Protocol R-03. Dis Colon Rectum 40:131–139

10. Sauer R, Becker H, Hohenderberg W et al (2004) Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 351:1731–1740
11. Lim JF, Tjandra JJ, Hiscock R et al (2006) Preoperative chemoradiation for rectal cancer causes prolonged pudendal nerve terminal motor latency. Dis Colon Rectum 49:12–19
12. Pollack J, Holm T, Cedermark B et al (2006) Long-term effect of preoperative radiation therapy on anorectal function. Dis Colon Rectum 49:345–352
13. Craven I, Sebag-Montefiore D (2007) Is there a role for radiotherapy in operable rectal cancer? Clin Oncol 19:687–692
14. Kachnic LA, Hong TS, Ryan DP (2008) Rectal cancer at the crossroads: the dilemma of clinically staged T3, N0, M0 disease. J Clin Oncol 20:350–351
15. Guillem JG, Díaz-González JA, Minsky BD et al (2008) cT3N0 rectal cancer: potential overtreatment with preoperative chemoradiotherapy is warranted. J Clin Oncol 20:368–373
16. Sebag-Montefiore D, Stephens RJ, Steele R et al (2009) Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet 373(9666): 811–820
17. O'Connel M, Martenson JA, Wieand HS et al (1994) Improving adjuvant therapy for rectal cancer by combining protracted-infusion fluorouracil with radiation therapy after curative surgery. N Engl J Med 331:502–510
18. Mohiuddin M, Hayne M, Regine WF et al (2000) Prognostic significance of postchemoradiation stage following preoperative chemotherapy and radiation for advanced/recurrent rectal cancer. Int J Radiat Oncol Biol Phys 48:1075–1080
19. Garcia-Aguilar J, Hernandez de Anda E, Sirivongs P et al (2003) A pathologic complete response to preoperative chemoradiation is associated with lower recurrence and improved survival in rectal cancer patients treated by mesorectal excision. Dis Colon Rectum 46:298–304
20. Ruo L, Tickoo S, Klimstra DS et al (2002) Long term prognostic significance of extent of rectal cancer response to preoperative radiation and chemotherapy. Ann Surg 236:75–81
21. Peeters KC, Marijnen CA, Nagtegaal ID et al (2007) The TME trial after a median follow-up of 6 years: increased local control but no survival benefit in irradiated patients with resectable rectal carcinoma. Ann Surg 246:693–701
22. Welch JP, Donaldson GA (1979) The clinical correlation of an autopsy study of recurrent colorectal cancer. Ann Surg 189:496–502
23. Janian NA, Crane C, Feig BW et al (2001) Improved overall survival among responders to preoperative chemoradiation for locally advanced rectal cancer. Am J Clin Oncol 24:107–112
24. Theodoropoulos G, Wise WE, Padmanabhan A et al (2002) T level downstaging and complete pathologic response after preoperative chemoradiation for advanced rectal cancer result in decreased recurrence and improved disease-free survival. Dis Colon Rectum 45:895–903
25. Bujko K, Michalski W, Kepka L et al (2007) Polish Colorectal Study Group. Association between pathologic response in metastatic lymph nodes after preoperative chemoradiotherapy and risk of distant metastases in rectal cancer: An analysis of outcomes in a randomized trial. Int J Radiat Oncol Biol Phys 67:369–377
26. Okonkwo A, Musunuri S, Talamonti M et al (2001) Molecular markers and prediction of response to chemoradiation in rectal cancer. Oncol Rep 3:497–500