Local recurrence in rectal cancer : mechanisms of development, patterns of relapse and treatment options

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Chapter

7

Results of European pooled analysis of IORT containing multimodality treatment for locally advanced rectal cancer: adjuvant chemotherapy prevents local recurrence rather than distant metastase

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Under review

Abstract

Background: The purpose of this study is to analyze the pooled results of multimodality treatment of locally advanced rectal carcinoma (LARC) in four major treatment centers with particular expertise in intra-operative radiotherapy (IORT).

Patients and methods: 605 patients with LARC who underwent multimodality treatment up to 2005 were studied. The basic treatment principle was preoperative (chemo)radiotherapy, intended radical surgery, IORT and elective adjuvant chemotherapy. In uni- and multi-variate analyses risk factors for local recurrence (LR), distant metastases (DM) and overall survival (OS) were studied.

Results: Chemoradiotherapy lead to more downstaging and complete remissions than radiotherapy alone ($p < 0.001$). 42% of the patients received adjuvant chemotherapy, independent of TNM-stage or radicality of the resection. LR rate, DM rate and OS were 12.0%, 29.2% and 67.1%, respectively. Risk factors associated with LR were no downstaging, lymph node positivity, margin involvement and no postoperative chemotherapy. Male gender, preoperatively staged T4-disease, no downstaging, lymph node positivity and margin involvement were associated with a higher risk for DM. A risk model was created to determine a prognostic index for individual patients with LARC.

Conclusions: Overall oncologic results after multimodality treatment of LARC are promising. Adding adjuvant chemotherapy to the treatment can possibly improve LR rates.

Introduction

The introduction and acceptance in surgical practice that the rectum should be removed within its enveloping mesorectal fascia has led to a decline in local recurrence (LR) rate in rectal cancer treatment.[1] A direct inverse relation between tumor distance to the mesorectal fascia and LR has been established; a distance of 1 mm or less is associated with a high LR rate[2;3]. In this study locally advanced rectal cancer (LARC) is defined by the high probability of circumferential margin involvement. The patients described have a threatened or involved mesorectal fascia (T3+ or T4 tumors) assessed by CT or MR imaging.

Preoperative radiotherapy has been used to facilitate surgical resection by downsizing LARC. Still, in many patients areas at risk will remain, but normal tissue tolerance limits the dose of preoperative radiotherapy[4]. Chemotherapy has been added to the preoperative radiotherapy to overcome dose limitations and to enhance the tumorcidal effect of the neoadjuvant treatment[5].

Another approach to overcome dose limitations is to apply intra-operative radiotherapy (IORT) boost to a specific area[6]. IORT allows the deliverance of a radiation boost, biologically comparable to an additional 30 to 40 Gy fractionated irradiation, to a well-defined volume under direct vision, with a possibility to shield or remove dose-sensitive structures. However, the IORT equipment is expensive and the logistics are complex. Furthermore, non-metastasized LARC is not very common. Therefore in Europe a few centers implemented this type of combination therapy. In this paper the long-term results of IORT multimodality treatment have been pooled and analysed in four major IORT expert centers[6-9].

Concerning adjuvant treatment, adjuvant chemotherapy has come to widespread use in colon cancer treatment[10;11]. However, during the observed period there was no consensus among clinicians whether the use of chemotherapy should be standard in LARC. The four studied centers dealt differently with the implementation of adjuvant chemotherapy, creating the opportunity to analyse the effect in a large cohort of patients. Especially as adjuvant chemotherapy in LARC patients is being accepted gradually in Europe, this study is one of the few occasions to analyze the effect of adding adjuvant chemotherapy to the multimodality treatment of LARC.

Patients and Methods

Patients

Four major referral centers for LARC have been involved in IORT since the early nineties of the last century. The centers are the University Hospital Gregorio Marañón Madrid (GMM), the Catholic University of the Sacred Heart Rome (SHR), the University of Heidelberg (UKH), and the Catharina Hospital Eindhoven (CHE). The patients of the four centers have been pooled from the beginning of their IORT-program until 2005. Patients with preoperative distant metastases were excluded from this study, leaving 605 patients for analyses. Median follow up time for surviving patients was 56 months (range 10 - 164).

Treatment

In Table 7.1 the similarities and differences between the centers are shown. Over the years the adjuvant and neoadjuvant treatment schemes have changed within each center. However, the basic treatment principle: preoperative radiotherapy, followed by resection and an IORT boost, remained constant. In all the centers IORT was delivered as an electron boost during open surgery. The IORT dose and energy was comparable in all centers and was typically in range from 10 to 12.5 Gy, the energies ranged from 8 to 12 MEV and the most used diameter of the bevelled applicator was 6 cm. The preoperative radiotherapy-dose was typically in the range of 45 to 50.4 Gy in fractions from 1.8 to 2.0 Gy. The use of additional chemotherapy to preoperative radiotherapy was not introduced at the same time at all centers. That all four centers have gradually accepted the use of preoperative chemoradiotherapy and adjuvant chemotherapy for their patients, based on 5 FU schemes, leaves sufficient control patients who did not have chemotherapy.

Statistical analysis

Statistical analysis was performed using SPSS package (SPSS 16.0 for Windows; SPSS Inc, Chicago, IL). T-tests and chi-square tests were used to compare individual variables. Local recurrence (LR) rate, distant metastases (DM) rate, cancer-specific survival (CSS) and overall survival (OS) were estimated using the Kaplan-Meier method. CSS was

Table 7.1 Patients and treatment in the different centers

	All n = 605	**GMM n = 141**	**SHR n = 113**	**UKH n = 150**	**CHE n = 201**	**p**
Mean age, years (range)	62 (22-86)	63 (26-82)	61 (22-80)	59 (30-81)	62 (36-86)	0.018
Mean follow-up, months (range)	62 (10-164)	53 (17-107)	74 (18-164)	60 (10-133)	64 (21-157)	< 0.001
Gender						0.612
Female	216 (36)	47 (33)	43 (38)	49 (33)	77 (38)	
Male	389 (64)	94 (67)	70 (62)	101 (67)	124 (62)	
Clinical T-stage						< 0.001
T3+	431 (71)	126 (89)	91 (81)	125 (83)	89 (44)	
T4	174 (29)	15 (11)	22 (19)	25 (17)	112 (56)	
Preoperative treatment						< 0.001
Only radiotherapy	220 (36)	0 (0)	53 (47)	95 (63)	72 (36)	
Chemoradiotherapy	385 (64)	141 (100)	60 (53)	55 (37)	129 (64)	
Type of surgery						< 0.001
Non-sphincter saving	291 (48)	56 (40)	42 (37)	91 (61)	102 (51)	
Sphincter saving	314 (62)	85 (60)	71 (63)	59 (39)	99 (49)	
Postoperative chemotherapy						< 0.001
Yes	254 (42)	100 (71)	20 (18)	112 (75)	22 (11)	
No	351 (58)	41 (29)	93 (82)	38 (25)	179 (89)	

GMM Hospital Universitario Gregorio Maranon, Madrid; SHR University of the Sacred Heart, Rome; UKH University of Heidelberg, Heidelberg; CHE Catharina Hospital, Eindhoven

defined as the time between rectal cancer surgery and death caused by rectal cancer. Differences were assessed using the Log-Rank test. P-values were two-sided and considered statistically significant at a value of 0.05 or less. For determination of risk factors, first univariate analyses were performed by analyzing the effect of the covariates in a univariate Cox regression, stratifying for treatment center. Then, covariates with trend-significant effects ($p < 0.10$) were selected for multivariate analysis, stratifying for treatment centers, using stepwise Cox proportional hazards regression modeling. Both forward and backward stepwise regression was used and a two-sided p-value of less than 0.05 was considered significant. A baseline prognostic model for prognostic factors was created by using the beta-values per variable after multi-variate analysis. Consequently, for each prognostic index group a survival curve was made using the Kaplan-Meier method.

Results

Effect of treatment modalities

For preoperatively staged T3+ carcinomas 42% received preoperative chemoradiotherapy; for T4 cancers this was 78% ($p < 0.001$). Any downstaging was achieved in 31% of the patients treated with preoperative radiotherapy and in 59% of the patients with preoperative chemoradiotherapy ($p < 0.001$). Complete remission occurred in 4% and 11% of patients treated with preoperative radiotherapy and preoperative chemoradiotherapy, respectively ($p < 0.001$). Radicality of the resection was not dependent of whether downstaging had occurred or not ($p = 0.18$). Lymph nodes (LN) were positive in 41% of the patients after preoperative radiotherapy and in 30% after preoperative chemoradiotherapy ($p = 0.008$). In patients treated with preoperative chemoradiotherapy the distance of the lower tumor border to the anus was not different from the patients treated with preoperative radiotherapy, but the type of surgery turned to more sphincter saving procedures after preoperative chemoradiotherapy ($p < 0.001$). The administration of adjuvant chemotherapy was independent of margin positivity ($p = 0.07$) and TNM-stage ($p = 0.13$).

Local and distant recurrence

Overall, 61 patients developed LR (12.0% 5-year LR rate). After uni- and multi-variate analysis (Tables 7.2 and 7.3) the risk factors associated with LR were no downstaging, LN positivity, margin involvement and no adjuvant chemotherapy. In Figure 7.1 LR rates after multi-variate analysis are shown for the factor postoperative chemotherapy. In the patients who received adjuvant chemotherapy, LR rate was 5.5% and 12.0% in the patients who did not ($p = 0.026$). When any downstaging had been achieved by preoperative treatment, LR rate after adjuvant chemotherapy was 5.6%, not significantly different from the 8.1% LR rate without adjuvant chemotherapy ($p = 0.087$). Adjuvant chemotherapy improved LR rates from 21.6% to 12.3% in patients with tumors in which no downstaging had occurred after preoperative treatment ($p = 0.031$). Irradical surgery resulted in a LR rate of 45.1% in 5 years, while this was 9.5% after radical surgery ($p <$

Table 7.2 Uni-variate analysis

	Local recurrence			Distant metastasis			Overall survival		
	HR	**CI**	**p**	**HR**	**CI**	**p**	**HR**	**CI**	**p**
Age			0.985			0.748			0.000
Up to 69 years	1.00			1.00			1.00		
70 years or older	0.99	0.55-1.81		0.94	0.65-1.36		1.78	1.34-2.37	
Gender			0.483			0.025			0.028
Female	1.00			1.00			1.00		
Male	1.21	0.71-2.07		1.47	1.05-2.05		1.40	1.04-1.88	
Tumor distance from anus			0.968			0.627			0.301
≤ 5 cm	1.00			1.00			1.00		
≥ 5.1 cm	1.01	0.60-1.69		1.08	0.79-1.48		1.16	0.88-1.54	
Clinical T-stage			0.396			0.039			0.426
T3+	1.00			1.00			1.00		
T4	1.28	0.72-2.27		1.45	1.02-2.06		1.14	0.83-1.58	
Preoperative treatment			0.520			0.961			0.005
Only radiotherapy	1.00			1.00			1.00		
Chemoradiotherapy	0.83	0.47-1.47		1.01	0.71-1.44		0.62	0.44-0.86	
Type of surgery			0.436			0.962			0.216
Non-sphincter saving	1.00			1.00			1.00		
Sphincter saving	1.23	0.74-2.04		0.99	0.73-1.35		0.84	0.64-1.11	
Any downstaging			0.001			0.000			0.001
Yes	1.00			1.00			1.00		
No	2.77	1.55-4.93		1.91	1.38-2.65		1.61	1.21-2.14	
N-stage			0.000			0.000			0.000
N0	1.00			1.00			1.00		
N+	2.95	1.77-4.93		2.68	1.97-3.64		2.31	1.75-3.05	
Margin involvement			0.000			0.001			0.000
No	1.00			1.00			1.00		
Yes	6.19	3.49-10.9		2.14	1.39-3.31		2.43	1.67-3.53	
Postop. chemotherapy			0.052			0.608			0.002
Yes	1.00			1.00			1.00		
No	1.99	0.99-3.99		1.11	0.74-1.67		1.79	1.23-2.60	

0.001). In patients with positive margins, LR rate was 23.8% in patients who had adjuvant chemotherapy and 57.4% in patients who had not (p = 0.030).

5-Year DM rate was 29.2%. Male gender, preoperatively staged T4-disease, no downstaging, LN positivity and margin involvement were associated with a higher risk for DM (Tables 7.2 and 7.3). Adjuvant chemotherapy did not influence distant metastasis rate, as shown in Figure 7.2 (p = 0.608).

Table 7.3 Multi-variate analysis

	Local recurrence			Distant metastasis			Overall survival		
	HR	**CI**	**p**	**HR**	**CI**	**p**	**HR**	**CI**	**p**
Age									0.000
Up to 69 years		n.a.			n.a.		1.00		
70 years or older							1.82	1.36-2.44	
Gender						0.000			0.019
Female		n.a.		1.00			1.00		
Male				1.58	1.13-2.21		1.43	1.06-1.93	
Clinical T-stage									
T3+		n.a.		1.00				n.a.	
T4				2.02	1.42-2.86				
Preoperative treatment									0.267
Only radiotherapy		n.a.			n.a.		1.00		
Chemoradiotherapy							0.82	0.57-1.17	
Any downstaging			0.019			0.000			0.049
Yes	1.00			1.00			1.00		
No	2.04	1.12-3.72		1.99	1.40-2.83		1.35	1.00-1.82	
N-stage			0.001			0.000			0.000
N0	1.00			1.00			1.00		
N+	2.48	1.45-4.24		2.36	1.74-3.22		2.37	1.78-3.16	
Margin involvement			0.000			0.034			0.000
No	1.00			1.00			1.00		
Yes	4.67	2.58-8.44		1.68	1.08-2.61		2.01	1.37-2.95	
Postop. chemotherapy			0.026						0.002
Yes	1.00				n.a.		1.00		
No	2.38	1.11-5.11					1.90	1.27-2.85	

HR; hazard ratio, CI; confidence interval, p; p-value

Survival

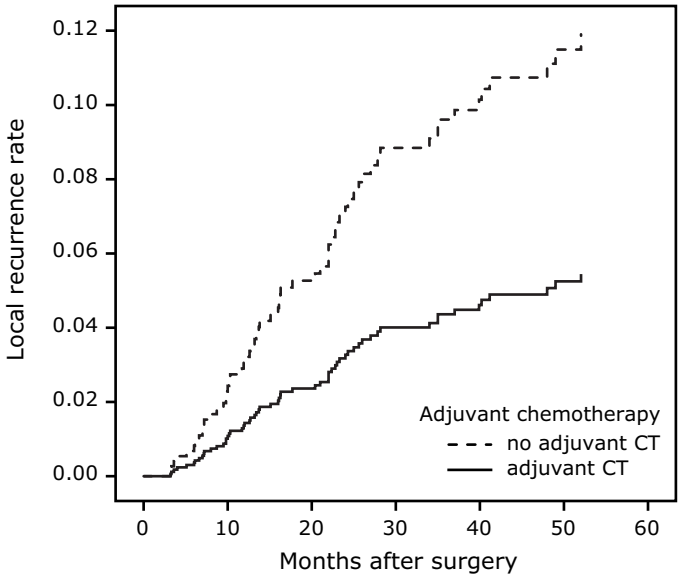
OS was 67.1% after 5 years. Risk factors for death were age older than 70 years, male gender, no downstaging, LN positivity, margin involvement and no adjuvant chemotherapy (Tables 7.2 and 7.3). Postoperative death within three months after surgery was 5.3% in patients aged 70 years or older, compared to 1.8% in patients younger than 70 years (p = 0.020). Excluding the patients who died within three months from the analysis still resulted in lower OS in the elderly patients. However, this was mainly due to other causes of death than cancer, as CSS was not significantly different in elderly, compared to younger patients (p = 0.897). CSS was 73.5% after 5 years; significant risk factors after multi-variate analysis were male gender, LN positivity and margin involvement.

In a prognostic model the prognostic index for each individual patient was calculated by this formula:

Prognostic index = (*Age over 70 years* > Yes: 0.60, No: 0) + *(Male gender* > Yes: 0.36, No: 0) + (*Any downstaging* > Yes: 0, No: 0.30) + (*LN positivity* > Yes: 0.86, No: 0) + (*Margin positivity* > Yes: 0.70, No: 0) + (*Adjuvant chemotherapy* > Yes: 0, No: 0.64)

In Figure 7.3 OS according to prognostic index categories are shown. The differences between the groups were significant ($p < 0.001$).

Figure 7.1 Local recurrence rate after cox regression analysis

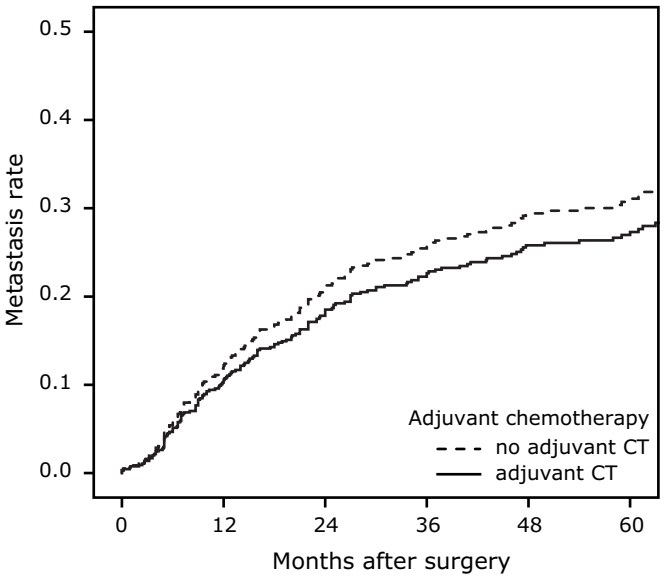


P-value between curves = 0.026

Discussion

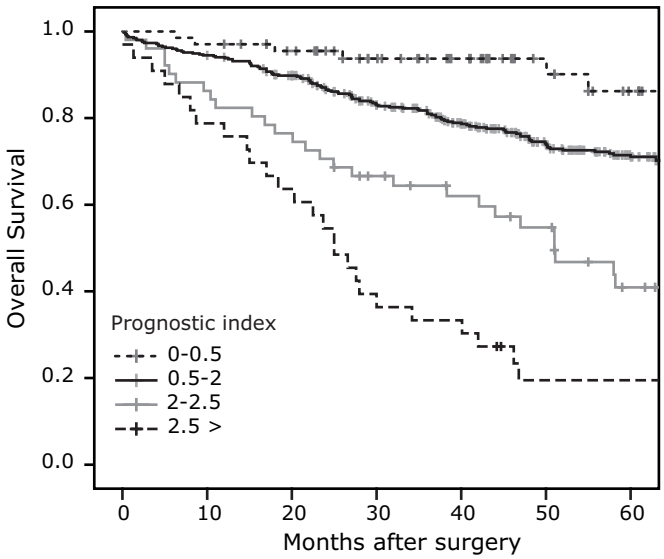
In this study the long-term results of individual patient data of four major centers practicing IORT containing multimodality treatment in locally advanced rectal cancer (LARC) were pooled. The advantage of a pooled analysis is that sufficient numbers of patients with adequate follow up can be studied, to reach the power necessary for conclusions. However, the risk is that due to different selection mechanisms an uncontrolled bias may be introduced. An incomplete or inconsistent dataset constitutes a potential threat to a meaningful analysis. The four hospitals in this paper that have pooled their results are considered reference centers for the treatment of LARC. The use of multimodality treatment has been studied in a prospective manner over the years. Therefore, the centers share the basic treatment principles and have complete and

Figure 7.2 Metastasis rate after cox-regression analysis



P-value between curves = 0.608

Figure 7.3 Overall survival according to prognostic index group



p = 0.000

(Between --+-- and —+— line: p = 0.144, —+— and —+— line: p = 0.000, —+— and --+-- line: p = 0.000)

Prognostic index = (Age over 70 years > Yes: 0.60, No: 0) + (Male gender > Yes: 0.36, No: 0) + (Any downstaging > Yes: 0, No: 0.30) + (LN positivity > Yes: 0.86, No: 0) + (Margin positivity > Yes: 0.70, No: 0) + (Adjuvant chemotherapy > Yes: 0, No: 0.64)

concise data. But still, the results have to be interpreted with caution.

The overall results of the pooled analysis demonstrate that the basic treatment principle was successful, with a local recurrence (LR) rate of 12.0%, a distant metastasis (DM) rate of 29.2% and an overall survival (OS) of 67.1%. This treatment principle consisted of preoperative radiotherapy, followed by surgical resection, which was extended if necessary to obtain free surgical margins, and consequently the application of IORT. This basic scheme has been modulated by the addition of chemotherapy to the preoperative irradiation (preoperative chemoradiotherapy) and administration of adjuvant chemotherapy to a part of the patients.

In uni- and multivariate analyses three independent factors influenced oncologic results in terms of LR, DM and OS majorly, namely downstaging, lymph node (LN) status and margin involvement. This study showed that downstaging was more often achieved after preoperative chemoradiotherapy than after preoperative radiotherapy, justifying the switch to preoperative chemoradiotherapy in the four treatment centers. The fact that only specialized treatment centers were analyzed, may be the explanation that downstaging did not significantly improve radicality of the resections in this cohort of patients. Preoperative LN status could not be assessed adequately when no MR images were available, so this variable was not taken into consideration. However, pathological LN status seems to be affected by preoperative chemoradiotherapy, as LN positivity was significantly lower after preoperative chemoradiotherapy, even when these were more clinical T4 tumors. Further, as margin involvement has been repeatedly confirmed as a major factor influencing treatment results[3;12;13], adequate multi-disciplinary treatment planning is essential to prevent irradical surgery. The risk model allows determination of prognosis in individual patients with LARC. As risk factors accumulate, death occurs in up to 80% of the patients after 5 years, so more aggressive adjuvant treatment modalities should be considered seriously in patients with a high prognostic index.

The role of adjuvant chemotherapy in rectal cancer is still subject of debate and research in several European countries. It is known that adherence to adjuvant chemotherapy is generally poor. However, this study is strongly in favour of the use of adjuvant chemotherapy. Local recurrence rate seems to be improved significantly, with a reduction in local recurrence of 6.5% after adjuvant chemotherapy. This would mean a number needed to treat of 100/6.5 = 16 patients, to prevent one case of local recurrence. A striking finding was that adjuvant chemotherapy even effectively reduced the development of local recurrence when surgical margins were positive or when no downstaging had occurred after preoperative treatment. Although we did not find an improvement in cancer specific survival after adjuvant chemotherapy, gradually evidence is increasing that adjuvant chemotherapy can improve survival[14-16] and local recurrence rates[17], at least in a selected group of rectal cancer patients. This turns the adagio up side down that adjuvant chemotherapy does not penetrate into fibrotic tissue in the operation field. This phenomenon may cast a new light on the multimodality treatment with IORT, followed by adjuvant chemotherapy. One could contemplate that high dose local radiotherapy sensitized the operation field for subsequent adjuvant chemotherapy.

Surprisingly the development of distant metastasis was not prevented by adjuvant chemotherapy. LARC in this study is biologically characterized by local growth without the

development of early distant metastasis. Maybe these tumors represent a genotype relatively insensitive to the usual adjuvant chemotherapy used for prevention of distant metastasis. Further molecular research is needed to elucidate this finding. Another explanation may be the late administration of adjuvant chemotherapy. From the time of diagnosis to the actual delivery of adjuvant chemotherapy it takes more than 5 months, but this is even longer when complications occur.

Concluding, the four studied centers have improved their survival and local recurrence rates by the use of their basic treatment approach in LARC. The first step in this approach is to administer preoperative chemoradiotherapy in order to downstage the tumor and facilitate surgical resection. Adjuvant chemotherapy could lower the chance of local recurrence in the vast majority of patients. It is tempting to assume that a high dose local radiotherapy plays a role in the increased potential of adjuvant chemotherapy to prevent local relapses.

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