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Peeters, K.C.M.J.

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Benchmarking the treatment of locally advanced rectal cancer: a comparative analysis of combined modality treatment with the Dutch randomized TME study

René A. Klaassen, Koen C.M.J. Peeters, Marleen J.E.M. Gosens, Harm J.T. Rutten, Hendrik Martijn, Gerard A.P. Nieuwenhuijzen, Hetty van der Berg, Iris D. Nagtegaal, Corrie A.M. Marijnen and Cornelis J.H. van de Velde

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ABSTRACT

Introduction

Objective of this article is to evaluate the current multimodality treatment for locally advanced rectal cancer (LARC) and to gain more insight in tumour biology.

Patients

A group of 201 single institution multimodality treated LARC patients with T4 and T3 tumours growing less than 2 mm from the mesorectal fascia were compared with a second group consisting of 316 patients with a T3 resectable rectal tumour, included in the Dutch TME trial.

Results

Overall survival after 3 years was not different (76% for TME, 67% for LARC, p = 0.071). Local recurrence rate (LR) was significantly lower in TME patients than in LARC patients at 3 years: 5% and 17% (p = 0.0001). In 83% of the LARC patients a negative circumferential resection margin could be realised, compared to 75% of the TME patients (p=0.037). Both circumferential margin status and lymph node status were important outcome parameters in both groups.

Conclusion

In both groups circumferential margin involvement and nodal positivity are independent prognostic factors in local control and survival. Outcome for a LARC patient is similar to resectable TME patients in absence of these factors. However, when chemoradiation did not result in achieving tumour regression and subsequent negative resection margins and negative lymph nodes, prognosis of LARC patients is significantly worse.

INTRODUCTION

For planning of surgical treatment, rectal carcinomas growing through the muscularis propria of the bowel wall (tumour invasion classification T3), are the most difficult group, since these are inhomogeneous. A large majority of these tumours present themselves as mobile at rectal examination. Mobility is considered a surrogate for the probability of freedom of involvement of the circumferential margin (CRM). These tumours can adequately be treated with short-term preoperative radiotherapy (5x5 Gy), followed by Total Mesorectal Excision (TME). However, a small proportion of T3 tumours infiltrate into or nearly into the circumferential fascia, and even with appropriate performed TME surgery free circumferential margins are not likely to be obtained. As these tumours are often less mobile at rectal examination, they are often referred to as being fixed. Fixity is a subjective measure, and cannot always be assessed properly. Infiltration into the vaginal septum or seminal vesicles may be underestimated at rectal examination and the same accounts for tumours out of the reach of the palpating finger. Large tumours may be over-staged merely due to their physical dimensions. The development of the Magnetic Resonance Imaging (MRI) has made it possible to distinguish a likely involved or free CRM (1, 2). In this paper locally advanced rectal cancer (LARC) refers to the close relation of the tumour to the circumferential margin based on MRI.

The treatment of patients with LARC is difficult. Short-term radiotherapy, followed by immediate surgery, does not result in down-staging of tumours (3) and is not effective in patients with a positive CRM (4). A positive CRM has been repeatedly showed to be one of the most important prognostic factors for local recurrence, next to invasion depth and nodal status in both mobile and LARC tumours (5-9). This has led to the development of neoadjuvant multimodality treatments with preoperative downsizing as main goal, in order to help the surgeon to achieve a radical resection.

Recently, several multimodality strategies have been investigated, but controversies remain to exist. At present, practice differs in Europe and in the USA, between countries in Europe, and even between institutions within the same country. It is obvious that current results are superior compared to historical controls. However, large differences in patient selections and treatment strategies make interpretation of the results difficult.

The current study compares the mobile or "not locally advanced" rectal cancer patients, treated with short-term radiotherapy with LARC patients, treated with long term (chemo)radiation. Prognosis, as well as known prognostic factors were compared.

PATIENTS AND METHODS

LARC group

The Catharina Hospital in Eindhoven is a national referral centre for rectal cancer patients in whom a R0 resection is not likely to be obtained. Multimodality treatment of patients with primary locally advanced rectal cancer is applied since 1994 (10). This study group consists of 201 consecutive patients with locally advanced primary rectal adenocarcinoma treated in the Catharina Hospital Eindhoven between 1994 and 2004. Patients presenting with a rectal tumour infiltrating into the mesorectal fascia or within proximity of less than 2 mm on MRI were eligible. Most of these tumours were referred as being fixed at rectal examination. Sometimes fixity was established by bimanual palpation during a staging laparotomy. All patients had biopsy-proven rectal adenocarcinoma. Patients with recurrent rectal cancer and distant metastasis at first presentation were excluded. The data were collected prospectively. Mean age was 62,1 years (36-86 years), 122 patients were male and 79 female. Median follow up of the survivors in this group was 36 months. The first 71 patients were treated with long course of preoperative radiotherapy consisting of 50,4 Gy (1,8 Gy fraction). Later, chemotherapy was added to the radiotherapy. In 109 patients daily bolus injections 5FU 350 mg/sqm and leucovorin 20 mg/sqm were administered two hours before irradiation in the first and fifth week of irradiation. In 2003 21 patients received a continuous scheme: 825 mg capecitabine/sqm bid every irradiation day and oxaliplatin 50 mg/sqm every first day of each irradiation week, total irradiation dose 45 Gy/1.8 Gy fractions in five weeks. After 6-8 weeks patients underwent radical surgery. During this surgery intraoperative radiotherapy (IOERT; 10-15 Gy) was applied as a boost at the area of risk. Details about this procedure were published before (10). Standard pathological analysis was performed on all rectal resection specimens.

TME study group

Data from patients included in the Dutch TME trial were the basis of this study. The TME trial is a large prospective randomized multicentre trial that compared short term (5x5 Gy) preoperative radiotherapy and TME surgery with TME surgery alone which has been extensively described (11, 12). Informed consent had been obtained from all included patients and the medical ethics committees of all participating hospitals have approved the trial.

For the current study, data of the eligible Dutch patients in the trial as described earlier were analyzed (11) . The following patients were excluded from the analysis: no resection, tumour left behind, distant metastases at operation, TNM stage IV and no tumour at operation. For the current analysis, patients with pT1 or pT2 tumours were also excluded. Of the remaining patients only those who were randomized to the arm with 5x5 Gy preoperative irradiation (n=316) acted as benchmark, since these patient represent optimal standard treatment in the Netherlands. Mean age was 63,2 years (26-88 years), 214 patients were males and 102 were

females. Accrual for the TME study was from 1995 until 2005 and the mean follow up of the survivors at the time of analysis was 58 months

Statistics

Patient characteristics were compared using the chi-square test. Prognosis (overall survival (OS), distant metastasis free survival (MFS) and local recurrence free survival) were calculated, using the Kaplan-Meier method. Log rank testing was used to compare these different patient groups. The starting point for the analyses of survival and recurrence was the day of surgery.

Multivariate proportional hazard regression analysis (Cox regression) was performed to identify independent risk factors for the primary outcome variables, using the parameters with a p-value of less than 0.05 in the univariate analysis. A prognostic model for the outcome parameters was built, incorporating the significant variables. Data have been analysed with SPSS statistical software.

RESULTS

Univariate survival analysis

Table 1 shows the survival characteristics of CRM involvement, lymph node involvement and surgical procedure in the LARC population and irradiated patients of the TME trial. In T3-LARC and T4-LARC patients a similar outcome was observed in all investigated variables, therefore LARC patients will be reported as one group.

Prognosis in both patient populations was similar for OS en MFS (figure 1). However, the local recurrence rate (LR) was significantly lower in TME patients than in LARC patients at 3 years: 5% versus 17% ($p = 0.0001$). In contrast, more positive CRMs were present in the TME group (25% versus LARC 17%, $p = 0.037$). In patients with negative margins, local recurrence rates were 2% (TME) versus 10% (LARC); in patients with positive margins 14% (TME) versus 53% (LARC), $p < 0.0001$. Figure 2 shows the influence of positive margins on local recurrence for both the TME and LARC patients. Nodal status was an important prognostic parameter. In patients with negative lymph nodes local recurrence rates after 3 years were 3% (TME) versus 12% (LARC, $p = 0.004$). In patients with positive nodes: 7% (TME) versus 28% (LARC, $p = 0.0007$). Development of metastases and overall survival were predicted by nodal status as well, but there were no differences between both patient populations (figure 3).

Type of surgery and location of the tumour:

With a tumour below 5 cm from the anal verge 20% of the patients underwent a low anterior resection (LAR) and 80% an abdomino-perineal resection (APR). Irrespective the location of the tumour AP resected specimens showed significantly more positive circumferential margins (31% versus 15%, $p<0.0001$). When TME patients were compared to LARC patients, the

Table 1. Kaplan-Meier (log-rank) Univariate calculated 3 year survival analysis

			Overall survival			Local recurrence			Distant metastasis free survival		
	TME	LARC	TME	LARC		TME	LARC		TME	LARC	
	n	n	3yr % (n)	3yr % (n)	*p*	3yr % (n)	3yr % (n)	*p*	3yr % (n)	3yr % (n)	*p*
All patients	316	201	76% (232)	67% (75)	0.0706	5% (227)	17% (73)	0.0001#	69% (191)	67% (59)	0.2337
CRM neg	238	167	81% (188)	74% (66)	0.1103	2% (184)	10% (65)	0.0096#	77% (162)	70% (54)	0.0519
CRM pos	78	34	60% (44)	40% (9)	0.1180	14% (43)	53% (8)	0.0000#	44% (29)	51% (6)	0.9844
p			0.0000#	0.0002#		0.0001#	0.0000#		0.0000#	0.0143#	
LAR	220	97	77% (166)	69% (35)	0.1968	2% (163)	18% (34)	0.0000#	72% (138)	62% (27)	0.0601
APR	96	90	73% (66)	70% (33)	0.3293	12% (64)	15% (32)	0.5811	63% (53)	69% (25)	0.9694
p			0.7149	0.7015		0.0022#	0.8138		0.2905	0.5735	
pN neg	166	132	84% (135)	75% (52)	0.0999	3% (131)	12% (51)	0.0042#	85% (120)	77% (41)	0.0611
pN pos	150	69	67% (97)	54% (23)	0.0629	7% (96)	28% (22)	0.0007#	52% (71)	49% (18)	0.2319
p			0.0000#	0.0025#		0.0044#	0.0163#		0.0000#	0.0000#	

CRM: circumferential resection margin, LAR: low anterior resection, APR: abdomino-perineal resection, pN: pathological lymph node status, # significant (log rank < 0.05)

latter had significantly less positive margins after APR (43% vs 19%, p=0.0001). In contrast, after LAR there was no significant difference between the two patient groups (LARC 10% vs TME 17%, p= 0.133). Overall survival and metastases-free survival were similar in both treatment groups, if stratified for surgical technique. However, LR-rate for LAR patients was much lower in TME patients than in LARC patients: at 3 years 2% versus 18% (p=0.000).

Multivariate analysis.

Table 2 summarizes the results of the Cox regression multivariate analysis. The location of the tumour and the type of operation showed no longer prognostic value. Nodal status, CRM and patient population remained important factors for prognosis.

Based on these results we created four prognostic groups for each patient population (table 3, figures 4a, 4b, 4c). These figures illustrate the good prognosis of LARC patients in case of a negative CRM and negative lymph nodes. The TME patients with both positive lymph nodes and a positive CRM show a poor prognosis, just like the LARC patients with these characteristics.

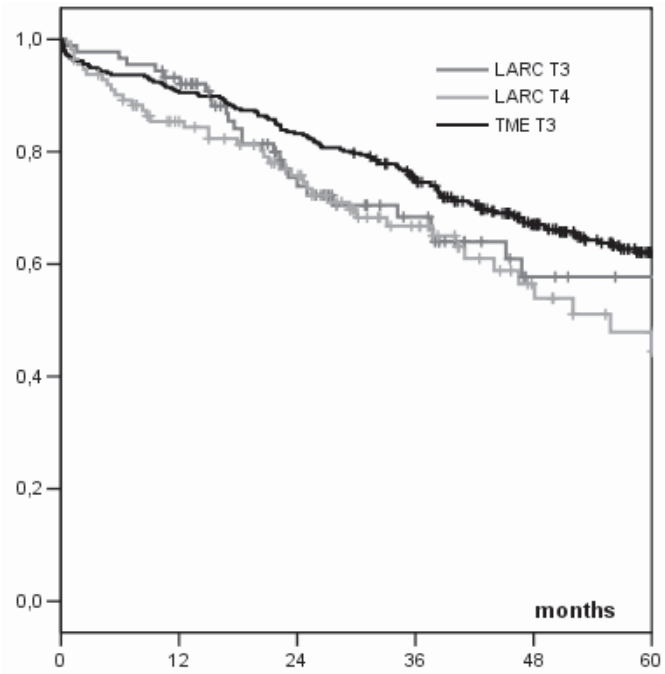

fig. 1	0	12	24	36	48	60	months
TME T3	316	288	264	232	166	98	at risk
	100	91	84	76	67	62	% surv
LARC T3	89	81	48	32	16	13	at risk
	100	93	75	68	58	58	% surv
LARCT4	112	86	67	43	22	15	at risk
	100	85	76	67	56	48	% surv
						p=0,630	log rank

Figure 1. Kaplan-Meier: Overall survival for the different patient populations.
No difference is observed between T3 and T4 LARC tumours. TME treated patients show the same survival as LARC patients (p = 0.630)

DISCUSSION

We demonstrated that in a group of locally advanced rectal carcinomas with a poor pre-treatment prognosis the majority of cases will end up with a prognosis comparable to mobile T3 tumours. The applied multimodality treatment resulted in a relatively low percentage of CRM positive cases (17%). Survival rate in CRM negative LARC tumours are similar to the results in TME treated mobile rectal tumours after preoperative radiotherapy.

In recent years the treatment of mobile, or primary resectable, rectal cancer has improved dramatically. The hypothesis that the introduction of TME surgery would result in an improvement of overall survival (13) in addition to improved local control, was confirmed in the Dutch

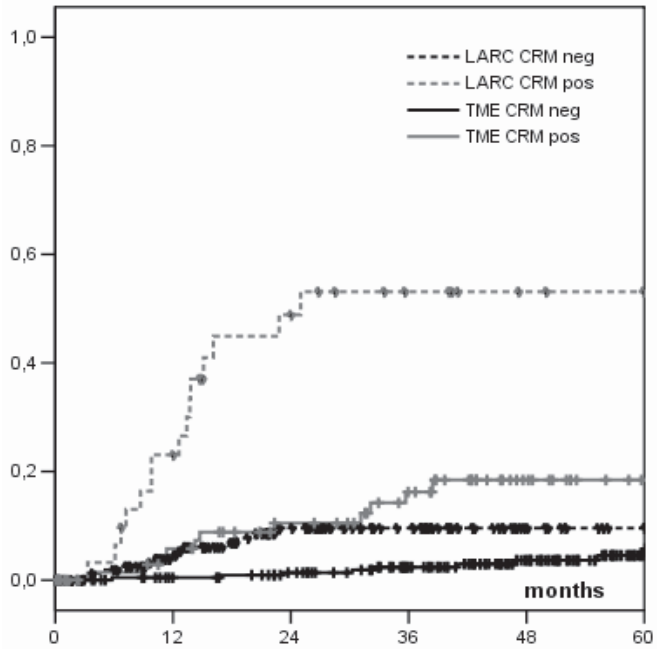

fig. 2	0	12	24	36	48	60	months
TME	238	220	208	184	140	81	at risk
CRM neg	0	0	1	2	4	5	% LR
TME	78	64	53	43	24	14	at risk
CRM pos	0	6	10	14	18	18	% LR
LARC	167	135	91	65	36	26	at risk
CRM neg	0	4	10	10	10	10	% LR
LARC	34	23	13	8	3	2	at risk
CRM pos	0	23	49	53	53	53	% LR

p=0,000 log rank

Figure 2. Kaplan-Meier: Local recurrence in both patient population in relation to circumferential margin involvement

TME trial (12). Local control was further improved by the introduction of 5 times 5 Gy preoperative radiotherapy. This combination resulted in very low local recurrence rates; in fact, local recurrence does not contribute significantly to mortality anymore. From subgroup analyses it became clear that prognosis of patients with an involved CRM is significantly worse (14). Locally advanced patients are by definition patients with a visceral mesorectal fascia exposed to the threat of tumour involvement. TME surgery in those patients, even after short course of preoperative irradiation, will inevitably lead to a high percentage of irradical resections and

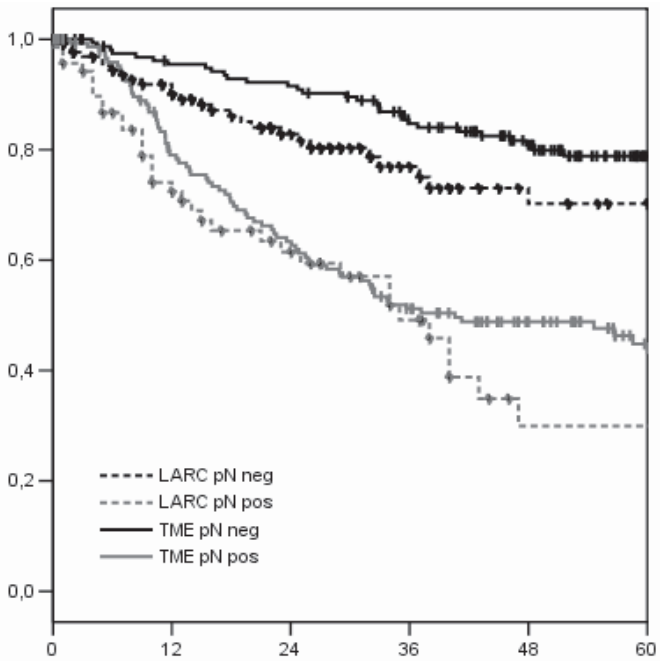

fig. 3	0	12	24	36	48	60	months
TME	166	147	141	120	95	54	at risk
pN neg	100	96	92	85	82	79	%meta
TME	150	115	90	71	52	30	at risk
pN pos	100	81	64	52	49	45	%meta
LARC	132	103	68	41	26	20	at risk
pN neg	100	92	83	77	73	70	%meta
LARC	69	45	31	18	6	6	at risk
pN pos	100	74	61	49	30	30	%meta

P=0,0000 log rank

Figure 3. Kaplan-Meier: Metastatic free survival in both patient populations, in relation to lymph node status

subsequent higher local recurrence rate (12, 15). In this study a multimodality treatment for patients with locally advanced rectal cancer was benchmarked against a comparable group of patients from the TME study. The only difference was the initial estimation of the circumferential margin.One of the primary questions of the current study was, whether the use of multimodality treatment could reduce the number of irradical resections and subsequently contribute to an improved outcome.In both groups circumferential margin involvement is an important predictor of local recurrence. Long course preoperative radiotherapy effectively lowers the rate of positive surgical margins. In fact, in these patients the *a priori* high risk on a

Table 2. Cox regression Multivariate analysis

	Overall survival			**Local recurrence**			**Distant metastasis**		
	HR	95% CI	*p*	HR	95% CI	*p*	HR	95% CI	*p*
CRM neg	1			1			1		
CRM pos	2.13	1.54-2.93	0.000[#]	4.50	2.41-8.41	0.000[#]	2.39	1.71-3.34	0.000[#]
LAR	1			1			1		
APR	1.01	0.74-1.38	0.935	1.35	0.72-2.52	0.346	1.08	0.77-1.50	0.671
pN neg	1			1			1		
pN pos	1.93	1.44-2.59	0.000[#]	2.48	1.32-4.66	0.005[#]	3.10	2.23-4.32	0.000[#]
TME	1			1			1		
LARC	1.50	1.09-2.06	0.013[#]	3.75	2.00-7.02	0.000[#]	1.49	1.06-2.09	0.020[#]

CRM: circumferential resection margin, LAR: low anterior resection, APR: abdomino-perineal resection, pN: pathological lymph node status, HR: hazard ratio, 95% CI: 95% confidential interval, [#] significant (p< 0.05)

Table 3. Hazard ratio Circumferential resection margin and lymph node status combined

	TME group				**LARC group**			
	CRM neg		**CRM pos**		**CRM neg**		**CRM pos**	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Overall survival								
pN neg	1		0.98	0.46-2.09	1		2.94 [##]	1.37-6.30
pN pos	1.41	0.91-2.18	4.40 [##]	2.80-6.89	2.06 [#]	1.19-3.56	3.95 [##]	2.00-7.83
Local recurrence								
pN neg	1		0.00 [*]		1		5.23 [##]	1.71-16.01
pN pos	1.16	0.31-4.32	10.52 [##]	3.60-10.75	1.49	0.49-4.55	11.20 [##]	4.40-28.48
Distant metastasis								
pN neg	1		1.26	0.518	1		2.19	0.82-5.83
pN pos	2.44 [##]	1.48-4.03	8.64 [##]	5.18-14.44	2.71 [##]	1.49-4.94	4.20 [##]	1.97-8.95

CRM: circumferential resection margin, pN: pathological lymph node status, HR: hazard ratio, 95% CI: 95% confidential interval, [#] p<0.05, [##] p<0.01, [*] no events (n=30)

positive CRM was lowered to a level significantly lower than in TME patients (17% versus 25%). The importance of a negative surgical margin is highlighted by the finding that prognosis for survival is equal to TME patients with negative margins.

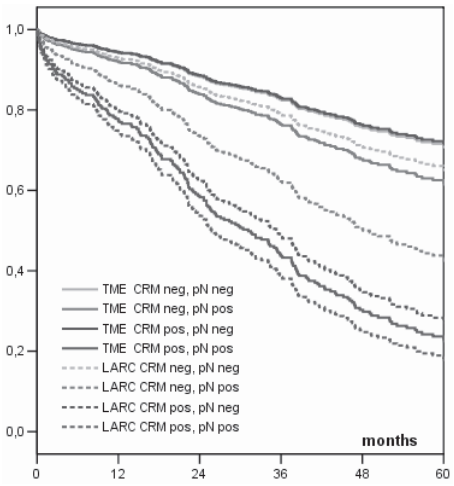

Figure 4a. Cox regression: overall survival, categorized in treatment, margin and lymphnodes

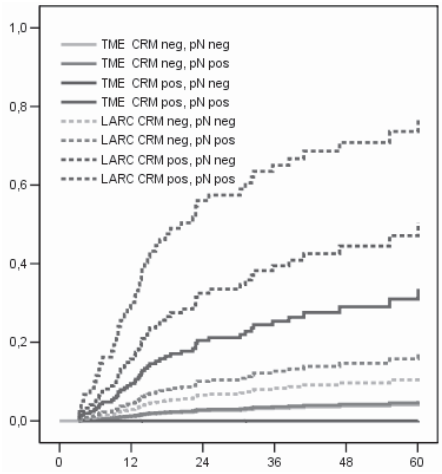

Figure 4b. Cox regression: local recurrence, categorized in treatment, margin and lymphnodes

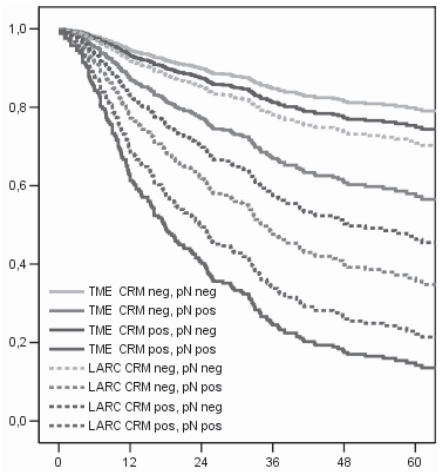

Figure 4c. Cox regression: metastatic free survival, categorized in treatment, margin and lymph nodes

Nodal status in TME and LARC patients are different entities. Whereas in TME patients the initial nodal status is recognised, in LARC patients an unknown number will have had positive nodes that have been sterilized due to the neoadjuvant therapy. In this case, pN0 consists of an heterogeneous group of patients who were initially node negative and patients whose metastatic tumours responded well to treatment. In all patients, node positivity was associated with a higher local recurrence risk. However, node positive LARC patients had a significantly higher risk than their TME counterparts. This might be explained by the presence of non-responders in the node positive LARC group. These patients have a worse prognosis due to the therapy-resistance in addition to their lymph node status. Another possible explanation for the higher risk of local recurrence in more advanced stages of nodal involvement was

published by Steup and Fujita (16, 17). They demonstrated a positive correlation between nodal stage and lateral nodal involvement. A higher local recurrence rate in node positive LARC patients, especially in the midrectal segment, where most of the lateral nodes reside in the obturator fossa, suggest a higher nodal stage contributing to the development of local recurrence originating in this lateral nodal depot. Indirectly, the absence of this phenomenon in low rectal cancer may support the theory that low tumours do not drain preferably in the lateral lymph nodes. The differences between lymph node positive LARC and TME patients with respect to the development of local recurrence reflects the higher stage of the LARC patients.

Another interesting point is the prognostic value of CRM involvement in node negative T3 patients. In the patients treated with short-term radiotherapy (TME group), no local recurrence occurred during follow up, whereas LARC patients have a high chance on local recurrence (HR 5.23, p<0,00001). This suggests that 5 x 5 Gy effectively prevents local recurrences in positive margin patients without nodal disease, but not in CRM+ patients with nodal metastases. This conclusion is supported by the fact that in the control arm of the TME study without 5x5 Gy preoperative irradiation local recurrence rate equal was in node negative and node positive patients. In addition, it underlines that LARC patients who still have a positive CRM after chemoradiation are poor responders and have a very poor prognosis.

Above mentioned demonstrates that both circumferential margin and nodal status play an important role in the local control after rectal cancer surgery. With this regard, mobile and advanced rectal cancers obey to the same rules. Success of multimodality treatment for advanced rectal cancer depends on how well these primary unfavourable variables are controlled. Our results demonstrate that outcome for a LARC patient is similar to TME patients when these unfavourable parameters have been controlled by chemoradiation. The key role in recent progress in the treatment of locally advanced rectal cancer is the cooperation between the different modalities. Several multimodality strategies have been developed and evaluated. Due to lack of randomised trials, there are still controversies in what treatment and especially which sequence offers the best survival. However, some agreement seems to be present: at this moment long-term radiotherapy (50 Gy) with concomitant fluoroucil (5-FU) based chemotherapy is becoming the most used neoadjuvant therapy (18-20).

Last years preoperative combined adjuvant therapy has gained acceptance as standard therapy in favour of postoperative regimens (21-24). Key factor in this development is the improved possibility of preoperative imaging and thus staging (25, 26).

CONCLUSION

Insight into the tumour biology of progressing rectal cancer has been gained by the comparison of the response to two different treatment strategies. The interaction between two

independent variables i.e. positive circumferential surgical margin and positive lymph nodes and its relevance for the development of local recurrence is obvious. Another observation was, that local recurrences, at least partly could be explained as metastatic disease in the lateral lymph node compartment. The question that remains to be answered is whether further intensification of neoadjuvant local or more attention to systemic treatment will help to control this type of recurrence. Especially in low rectal cancer, 5x5 Gy preoperative irradiation followed by immediate surgery cannot prevent a relatively high positive circumferential margin rate (27). In more advanced T3 and T4 cases long course neoadjuvant treatment (LCNT) effectively reduces the number of positive margins, and therefore LCNT may also play an important role in T3 low rectal cancer. Selection for either treatment requires high-resolution preoperative imaging. Overall LCNT is able to restrain progressing rectal cancer. In the future, the isolated local recurrence without the development of distant metastatic disease will be very rare. Most patients will develop distant metastatic disease and one out of three will die of metastatic disease. The focus of upcoming studies also will have to include proper patient selection for adjuvant treatment.

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