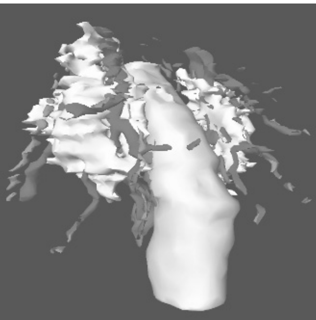
Local recurrence in rectal cancer : mechanisms of development, patterns of relapse and treatment options

Kusters, M.

Chapter 5



A comparison between the treatment of low rectal cancer in Japan and the Netherlands, with focus on the patterns of local recurrence

M. Kusters, G.L. Beets, C.J.H. van de Velde, R.G.H. Beets-Tan, C.A.M. Marijnen, H.J.T. Rutten, H. Putter, Y. Moriya

Annals of surgery 2009; 249(2):229-235

Abstract

Purpose: Differences exist between Japan and the Netherlands in the treatment of low rectal cancer. The purpose of this study is to analyze these, with focus on the patterns of local recurrence.

Methods: In the Netherlands 755 patients were operated by total mesorectal excision (TME) for low rectal cancer, 379 received preoperative radiotherapy (RT+TME). Applying the same selection-criteria resulted in 324 patients in the Japanese (NCCH) group, who received extended surgery consisting of a lateral lymph node dissection and a wider abdominoperineal excision. The majority received no (neo)adjuvant therapy. Local recurrence images were examined by a radiologist and a surgeon.

Results: 5-year local recurrence rates are 6.9% in the Japanese NCCH group, 5.8% in the Dutch RT+TME group and 12.1% in the Dutch TME group. Recurrence rate in the lateral pelvis is 2.2%, 0.8% and 2.7% in the Japanese, RT+TME group and TME group, respectively. The incidence of presacral recurrences was low in the NCCH group (0.6%), compared to 3.7% and 3.2% in the RT+TME and TME groups.

Conclusions: Both extended surgery and RT+TME result in good local control, as compared to TME alone. Preoperative radiotherapy can sterilize lateral extra-mesorectal tumor particles. A wider APR probably results in less presacral local recurrence. Comparison of the results is difficult because of differences in patient groups.

Introduction

The main purpose of curative surgical treatment for rectal cancer is en bloc excision of the primary tumor with its locoregional lymph nodes. It has been demonstrated that non-radical removal of the tumor leads to persistence of tumor cells, which contributes to the development of recurrent rectal cancer growth[1;2]. Local recurrence is known to cause severe morbidity.

With the Total Mesorectal Excision (TME) procedure the rectum with its primary lymphovascular field of drainage is removed as an intact package, by dissection under direct vision along pre-existing embryologically determined planes. Since its introduction the TME approach has led to striking results, reflected by lower local recurrence rates and improved survival, and has been advocated as being superior to conventional surgery[3;4].

However, the results of the TME technique for low tumors are not as good as for midrectal or higher tumors, with still a considerable local recurrence rate[5;6]. This is ascribed to the difficulty to obtain a wide circumferential margin (CRM) and the higher rate of perforations of the mesorectum and bowel wall, especially in the case of abdominoperineal resection (APR)[5;7;8].

In Western countries the addition of (neo)adjuvant therapy to improve the local recurrence rate has been well studied. Both short and long course of preoperative (chemo)radiation have shown to be effective[9-12]. However, it has also been shown that short-term radiotherapy can not prevent local recurrence development when advanced tumor growth or surgical failure results in a positive CRM[13].

In Japan extended surgery is the gold standard and the APR technique involves a wide perineal skin incision, together with resection of ischiorectal adipose tissue and the levator ani muscle[14], aiming for a wider circumferential tumor free margin than in a standard Western APR. However, in Japan the main focus is on the immediate harvesting of lymph nodes from the fresh specimen, which precludes assessment of the CRM at a later stage. Lateral Lymph Node Dissection (LLND), in which dissection of the iliac and obturator lymph nodes with the primary tumor is performed, is the standard treatment for advanced rectal cancer located at or below the peritoneal reflection[15;16]. It has been reported that local recurrence and survival rates have improved since the introduction of LLND and are known to be significantly better than in Western series with surgery only[15;17].

The question remains whether local recurrence can be prevented best by more frequent use of adjuvant (chemo)radiation or by more extended surgery. The aim of this study was to compare the patterns of local recurrence after TME surgery, TME surgery with short-term preoperative radiotherapy and Japanese extended surgery. The prospective databases of the Dutch TME trial and the National Cancer Center Hospital in Tokyo, with accurate follow-up, were used. The hypothesis is that recurrences in the lateral pelvic subsite would occur less often in the Japanese group than in the Dutch TME group, because the lateral lymph nodes are excised, with the mesorectum and perirectal fat tissue. In addition, the APR technique is more wide in Japan, also possibly leading to different patterns of recurrence in other pelvic subsites.

Patients and methods

Study population

Patients were selected from the databases of the Dutch TME trial and of the National Cancer Center Hospital (NCCH) in Tokyo.

First a selection was made from a large prospective randomized multi-center study, the radiotherapy plus TME trial, in which 1530 Dutch patients were included between January 1996 and December 1999. This trial analyzed the effect of short-term preoperative radiotherapy (5 x 5 Gy) in patients operated with a total mesorectal excision (RT+TME), compared to patients with TME alone (TME)[10]. Inclusion criteria were the presence of a primary adenocarcinoma of the rectum, without evidence of metastatic disease at time of surgery and tumor location within 15 cm from the anal verge. Patients with other malignant diseases or with fixed tumors were excluded. Standardized techniques for surgery, radiotherapy and pathology were used[18]. Follow-up of all patients was conducted according to the trial protocol[18]. For the current study the following patients were excluded from the analysis: no resection (n = 37), distant metastasis at operation (n = 91) and no tumor at operation (n = 15).

Then, from the prospective database of the National Cancer Center Hospital (NCCH), Tokyo, a selection was made from January 1993 to April 2002, resulting in 923 consecutive patients operated for confirmed primary adenocarcinoma of the rectum. The patients underwent a LAR, Hartmann, APR or when a stage T4 tumor was suspected, pelvic exenteration. Surgery at the NCCH is performed according to the guidelines of the Japanese Research Society for Cancer of the Colon and Rectum[19]. Lateral lymph node dissection was performed in low rectal cancer, when based on preoperative evaluation or intra-operative findings, TNM stage II or III disease was suspected. A decision was made for each patient individually, based on the side and the extension of the tumor, whether a uni- or bilateral LLND was performed. Accurate documentation of lymph node status and localization was obtained, because all lymph nodes were dissected from the fresh specimen and their location and numbers were mapped in relation to the major arteries. Following that, the specimen and all lymph nodes were examined histopathologically. Follow-up of all patients consisted of thoracic CT, abdominal CT and pelvic CT-imaging every six months. For this study similar selection criteria were applied to the patients from the NCCH as for the TME trial patients, excluding the following patients: metastasis at the time of surgery (n = 134), other malignant diseases or double colorectal carcinoma (n = 62), fixed tumor during rectal examination (n = 15) and in situ carcinoma (n = 22).

The median follow-up of the Dutch RT+TME and TME patients alive was 7.0 years, of the Japanese NCCH patients 7.9 years.

Patient Selection

For both the Dutch and the Japanese groups patients with low rectal tumors were selected. To match the groups as closely as possible, two different definitions of low rectal tumors had to be interpreted. In the Dutch TME trial, low rectal cancer was defined as tumors of which the lower edge was within 5 cm of the anal verge as measured by endoscopy. In Japan, the peritoneal reflection is the most important landmark in defining the location of the tumor and 'low' rectal carcinoma is defined as a tumor of which the major part is located at or below the reflection[20]. The distance from the anal verge is often unreported. The anterior peritoneal reflection has been measured to be at 9 cm from the anal verge by intraoperative endoscopy[21]. With a mean tumor diameter of 4 cm in the Dutch TME trial, the distance between the lower border and the anal margin of the Japanese low cancers can thus be estimated as maximal 9-(4/2) = 7 cm. To match the tumors of the Japanese group we therefore selected tumors from 0 cm up to 7.0 cm from the anal verge in the Dutch groups. Using these criteria 324 Japanese patients were selected with rectal tumors at or below the peritoneal reflection and 755 patients from the Dutch database with tumors with the lower border from 0 cm up to 7.0 cm.

Definitions

In the Japanese group the total amount of harvested lymph nodes consisted of mesorectal lymph nodes, and when LLND was done, also the lateral lymph nodes. In the Dutch group the lymph node harvest consisted only of the mesorectal lymph nodes. The UICC 5th edition 1997 classification system was used for both groups to define TNM-staging. All patients who developed local recurrence, defined as any recurrence of rectal cancer in the small pelvis, were identified. Local recurrence was diagnosed either clinically, radiologically or histologically.

Methods

Analysis were made comparing three groups; the RT+TME group, the TME group and the NCCH group. For all locally recurrent patients the available preoperative images and the images at the time of discovery of the local recurrence were retrieved. A specialized oncologic radiologist (R.B.) and a surgeon (G.B.) reviewed the images together for both groups.

Examining the images, the site of the local recurrence was determined. The sites were classified into the following regions: lateral, presacral, perineal, anterior or anastomotic. The same borders for the respective sites were used as defined by Roels et al.[22]. When no images were available, the location of recurrence was classified using the radiology reports and clinical data. In one patient in the RT+TME group and in two patients in the NCCH group, insufficient information was provided to determine the location of recurrence with certainty.

Statistical analysis

Statistical analysis was performed using SPSS package (SPSS 12.0 for Windows; SPSS Inc, Chicago, IL). Chi-square tests and one way ANOVA tests, Bonferroni corrected, were used to compare individual variables. The cancer-specific survival was defined as the time between rectal cancer surgery and death caused by cancer. Survival was estimated using the Kaplan-Meier method. Cox regression was used to asses differences in survival outcomes between groups; results are reported as hazard ratios with associated 95% confidence intervals. All P-values were two-sided and considered statistically significant at 0.05 or less. For local recurrence, cumulative incidences were calculated accounting for death as competing risk[23]. Similarly, cumulative incidences were calculated for subsite of local recurrence, with death and other types of local recurrence as competing risks, and for cancer-specific survival, with death due to other causes as competing risk. To account for possible confounding factors, multivariate analyses of local recurrence and cancer-specific survival were performed by first testing the effect of covariates in a univariate Cox regression. Covariates with trend-significant effects ($p < 0.10$) and group (RT+TME, TME, NCCH) were then selected for multivariate Cox regression.

Table 5.1 Patient characteristics and treatment details

	RT + TME **379 patients**	**TME** **376 patients**	**NCCH** **324 patients**	**p**
Sex				0.52
Male	244 (64)	234 (62)	215 (66)	
Female	135 (36)	142 (38)	109 (34)	
Age (years)				< 0.001
Mean (st.dev.)	64 (11)	64 (11)	58 (11)	
Type of resection				< 0.001
Low anterior resection	160 (42)	159 (42)	195 (60)	
Abdominoperineal resection	193 (51)	199 (53)	113 (35)	
Hartmann	24 (6)	15 (4)	3 (1)	
Pelvic exenteration	2 (1)	3 (1)	13 (4)	
Lymph node dissection				< 0.001
Standard TME	379 (100)	376 (100)	134 (41)	
Unilateral LLND	0	0	69 (21)	
Bilateral LLND	0	0	121 (38)	
Neoadjuvant therapy				< 0.001
Preoperative radiotherapy	379 (100)	0	0	
None	0	376 (100)	324 (100)	
Adjuvant therapy				< 0.001
Postoperative radiotherapy	3 (1)	52 (14)	5 (2)	
Postoperative chemotherapy	16 (4)	13 (3)	23 (7)	
None	360 (95)	315 (84)	297 (92)	

Values in parentheses are percentages

Results

Patient characteristics

Patient characteristics and treatment details are listed in Table 5.1. The age at operation of the Japanese patients was significantly lower than of the Dutch patients. In the Japanese group significantly more sphincter saving procedures had been performed, compared to the Dutch group. Lateral lymph node dissection was not performed in the Dutch patients, whereas 59% of the Japanese patients underwent unilateral or bilateral LLND.

Table 5.2 shows an overview of the pathology results of the Japanese and the Dutch groups. Early T-stage cancer was found significantly more in the Japanese group, while stage T3 and T4 cancer was found more in the Dutch. The average amount of harvested lymph nodes was 34 in Japanese group and 8 in the Dutch groups. The N-stages, whether lateral nodes were included or not, did not differ significantly. TNM-stage did not differ significantly between the groups.

The cancer-specific survival was higher in the Japanese extended surgery group than both in the Dutch TME group as in the Dutch RT+TME group (Figure 5.1a). The hazard ratios for death (95% CI) of the Dutch TME and RT+TME groups with respect to the Japanese group were 2.0 (1.2 - 3.3) and 1.7 (1.1 - 2.8), respectively.

Table 5.2 Pathologic results

	RT + TME 379 patients	**TME 376 patients**	**NCCH 324 patients**	**p**
Amount of lymph nodes resected				< 0.001
Mean (st.dev.)	7.3 (6.0)	9.3 (6.4)	33.7 (18.5)	
T-stage				< 0.001
T1	19 (5)	21 (6)	52 (16)	
T2	143 (38)	131 (35)	107 (33)	
T3	209 (55)	210 (56)	160 (49)	
T4	8 (2)	14 (4)	5 (2)	
N-stage			*/**	0.82/0.62
N0	244 (64)	229 (61)	198/192 (61/59)	
N1	80 (21)	82 (22)	75/80 (23/25)	
N2	55 (15)	64 (17)	51/52 (16/16)	
TNM-stage*				0.27
Stage I	129 (34)	123 (33)	125 (39)	
Stage IIa	111 (29)	100 (27)	72 (22)	
Stage IIb	4 (1)	6 (2)	1 (0)	
Stage IIIa	27 (7)	19 (5)	26 (8)	
Stage IIIb	53 (14)	63 (17)	49 (15)	
Stage IIIc	55 (15)	64 (17)	51 (16)	
Tumor size (cm)				0.09
Mean (st.dev.)	4.0 (1.6)	4.6 (1.7)	4.3 (2.1)	
Distal margin (cm)				0.46
LAR (st.dev.)	2.1 (1.5)	1.9 (1.7)	1.9 (0.9)	
APR (st.dev.)	4.3 (1.7)	4.1 (1.9)	4.2 (2.7)	

Values in parentheses are percentages
* on basis of mesorectal lymph nodes
** with extra positive lateral lymph nodes

Figure 5.1a Cancer-specific survival

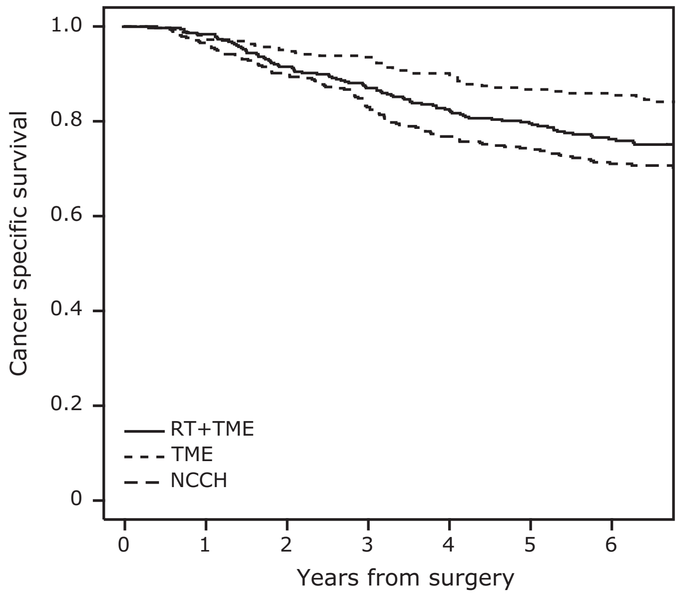


Figure 5.1b Local recurrence incidence

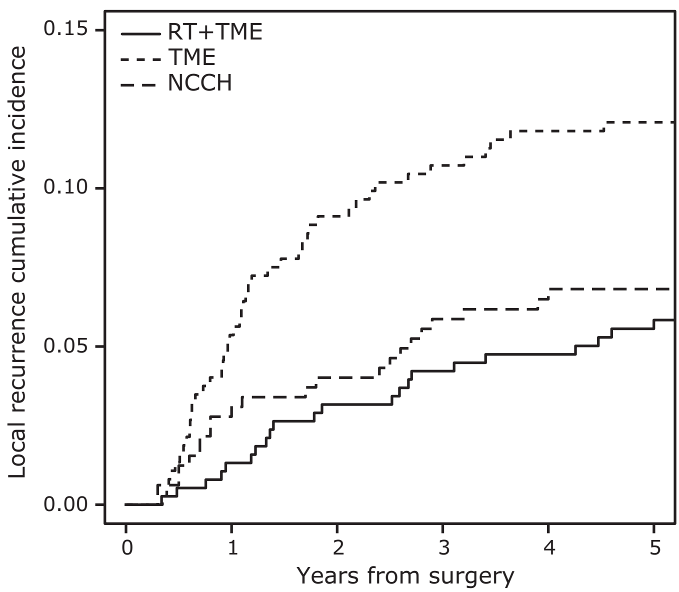


Table 5.3 Patterns of local recurrence

	Absolute number of LR (5-years percentage)			Relative distribution of LR*		
	RT + TME 379 pts	**TME 376 pts**	**NCCH 324 pts**	**RT+TME 24 pts**	**TME 46 pts**	**NCCH 23 pts**
presacral	14 (3.7%)	12 (3.2%)	2 (0.6%)	58%	26%	9%
lateral	3 (0.8%)	11 (2.7%)	8 (2.2%)	13%	24%	35%
anterior	4 (0.8%)	11 (3.0%)	1 (0.3%)	17%	24%	4%
anastomosis	2 (0.5%)	8 (2.1%)	5 (1.6%)	8%	17%	22%
perineum	0 (0%)	4 (1.1%)	5 (1.6%)	0%	9%	22%
unknown	1 (0%)	0 (0%)	2 (0.6%)	4%	0%	4%
	24 (5.8%)	**46 (12.1%)**	**23 (6.9%)**			
Hazard Ratio	1.0	1.6	1.0			
95% CI **	0.6-1.8	1.0-2.8				

* local recurrence per pelvic subsite, as a percentage of all local recurrences
** Hazard Ratio for local recurrence after multivariate analysis, with 95% CI as compared to the NCCH group

Local recurrence patients

23 patients (6.9% 5-years percentage) in the Japanese extended surgery group, 24 patients (5.8%) in the Dutch RT+TME group and 46 patients (12.1%) in the Dutch TME group were diagnosed with local recurrence (Table 5.3, Figure 5.1b). The hazard ratio for local recurrence (95% CI) of the Dutch TME group compared to the Japanese group was 1.6 (1.0 - 2.8). The hazard ratio (95% CI) of the Dutch RT+TME compared to the Japanese group was 1.0 (0.6 - 1.8). The mean time to local recurrence in the Japanese group is 2.1 years, 1.5 years in the TME-group and 2.6 years in RT+TME-group.

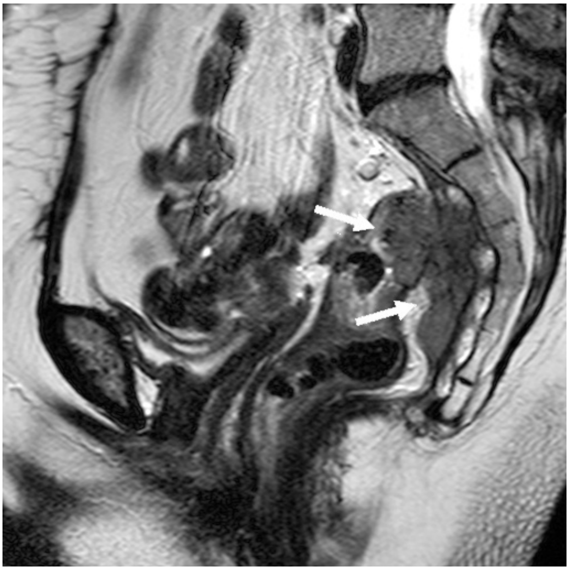
In the Japanese patients with local recurrence, 11 patients (48%) had distant metastases before or at the time of local recurrence diagnosis. In the Dutch TME patients with local recurrence this was the case in 9 patients (20%), in the RT+TME local recurrence patients in 13 (54%). When distant metastases diagnosed within one month of local recurrence diagnosis were considered as being simultaneous, these distant metastases rates were 62%, 30% and 88% for the Japanese, Dutch TME and Dutch RT+TME local recurrence patients, respectively. At the time of last follow up or death 95%, 77% and 88% had metastases in the respective groups.

Patterns of Local Recurrence

In Table 5.3 the patterns of local recurrence for the three groups are shown.
Presacral recurrences (Figure 5.2) occurred in 3.7% of the RT+TME patients and in 3.2% of the TME patients. In the Japanese group only 0.6% of the patients developed presacral recurrence. When only looking at the patients operated by APR or PE, 5-year local recurrence rates in the presacral subsite were 6.5% in the RT+TME group, 4.4% in the TME group and 1.8% in the Japanese group.

In this study the lateral recurrence (Figure 5.3) rate in the non-irradiated TME group is 2.7%, comprising 24% of all local recurrences. The hazard ratio of lateral recurrence in the RT+TME group (0,8%) vs. the TME group (2.7%) is significantly different from zero (HR = 5.3, 95% CI 0.6 - 43.9) after multivariate analysis. In the Japanese group 2.2% developed local recurrence in the lateral pelvic subsite, not differing significantly from the Dutch groups. When T3 and T4 tumors only are selected, similar trends were observed.

Figure 5.2 MR image of presacral local recurrence



Sagittal MR image of locally recurrent mass in the presacral subsite

Figure 5.3 MR image of lateral recurrence

Transverse MR image of local recurrence in the extra-mesorectal region (lateral subsite), highly suggestive of local relapse from nodal metastasis in the lateral lymph nodes

Circumferential Resection Margin and Lateral Lymph Nodes

In the Dutch TME-group 23% (88/376) of the patients showed CRM involvement on pathological examination. Of these CRM-positive patients, the 5-year local recurrence percentage was 33%. In the CRM-negative cases, this was 9%. In the RT+TME-group 20% (77/379) of the patients showed CRM involvement. Of these CRM-positive patients, the 5-year local recurrence rate was 25%. In the CRM-negative cases, 3% developed local recurrence in 5 years, versus 9% in the TME-group (HR = 0.4, 95% CI 0.2 - 0.8).

Of the Japanese group it is not possible to report on CRM involvement; the immediate harvesting of lymph nodes from the fresh specimen precludes assessment of the CRM at a later stage. For the 190 patients operated by unilateral- or bilateral LLND, the 5-year local recurrence rate was 36% in the lateral node positive patients and 7% in the lateral negative patients (HR = 6.4, 95% CI 2.6 - 15.7).

Discussion

We compared Western and Japanese treatment results, looking at the patterns of local recurrence. The Japanese group differs from the Dutch groups in that the patients received extended surgery consisting of a lateral lymph node dissection and a wider APR.

The main limitation of the present study is the difficult comparison of the group of Japanese patients with the group of Dutch patients. There are many sources of potential bias, such as non-randomization and upstaging, as described previously[24]. The Japanese patients are younger and have tumors with lower T-stage, although differences in local recurrence are still significant after multivariate analysis. Lymph node yield is much higher in the Japanese patients, which is probably due to differences in pathological examination methods[17]. The differences in survival are undoubtedly more related to these differences than to any treatment effect. The definition and measurement of distal rectal cancer is different in the two countries, and although we tried to match the two groups as closely as possible, one or the other group may contain more distal tumors. The findings of the present study and the interpretation of the results therefore require some caution. Notwithstanding these limitations, the present study can give insight in the merits of the approaches and the mechanism of preventing local recurrences.

In this study extended surgery, as performed in the National Cancer Center Hospital in Japan, results in good local control (5-year LR percentage of 6.9%). This is significantly less than after TME-surgery alone, which showed 12.1% local recurrence. Preoperative radiotherapy plus TME-surgery also results in good local control (5.8%). The better local control is also reflected in fact that the recurrences develop later when radiotherapy is given (2.6 years postoperatively) or more extended surgery is performed (2.1 years), compared to the 1.5 years after TME surgery. The high percentage of distant metastases at time of local recurrence diagnosis after RT+TME or extended Japanese surgery can also be seen as a marker of good local control, because now mainly patients with the worst disease get local recurrence, as if local recurrence is a sign of systemic disease.

The Japanese wider perineal resection is likely to result in less positive margins than in standard perineal resections, where the ‘coning in’ is probably responsible for the high percentage of 23% involved margins in standard TME. Almost one out of four of these margin positive patients developed a local recurrence in this study. Unfortunately, pathology techniques differ between Japan and the Netherlands, making it impossible to draw firm conclusions on CRM involvement in the Japanese group. It has been described that recurrence rates after abdominoperineal resections (APR) are far worse than after anterior resections (AR). Even the pioneer of TME surgery, professor Heald, reported local recurrence in only 5% of cases ten years after AR, but in his patients who underwent an APR, the local recurrence rate was as high as 36%[25]. Heald and co-workers recently published an anatomical and radiological study, in which they observed that in the lowest part of the rectum the mesorectum tapers and terminates at the pelvic floor[26]. Also Nagtegaal et al.[5] concluded that following the mesorectum downward along the sphincter muscles is associated with increased occurrence of positive CRM. In the TME trial perforations in the anal canal were described, stressing the need for a more extended approach[8;27]. Holm et al. recently reported on extended abdominoperineal resection, showing a low risk of CRM involvement[28]. It could be suggested that a wider perineal approach has a major contribution to good local control.

In the Dutch TME trial presacral recurrences were the most common type of recurrences. This was also reported in a large overview reported by Roels et al.[22]. It is intriguing that this type of recurrence was uncommon in the Japanese group. The exact pathogenesis of presacral recurrences has been puzzling, as it is the easiest plane of dissection of a rectal cancer operation with often a wide margin of mesorectal fat. One could hypothesize that presacral recurrences result from implants of tumor cells originating from positive margins or tears or perforations at the tumor site. Through the force of gravity these implants would occur most often in the midline in the low/mid presacral area. Seventy-five percent of the presacral recurrences develop after APR surgery in the Dutch group and radiotherapy apparently cannot sterilize these tumor particles. If this hypothesis were to be correct, presacral recurrences would occur less often with surgical techniques that avoid tumor spill, such as the wider perineal resections in the Japanese group. But of course this theory remains speculative.

The effect of the application of uni- or bilateral LLND on prevention of lateral recurrence is questionable. In the Japanese group 2.2% developed local recurrence in the lateral pelvic subsite, not differing significantly from the Dutch groups. In this study the lateral recurrence rate in the non-irradiated TME-group is 2.7%, comprising 24% of all local recurrences. The difference in lateral recurrence in the RT+TME group (0.8%) vs. the TME group (2.7%) shows that radiotherapy plays a significant role in the reduction of local recurrence in the lateral pelvic subsite. Further, the significant lower local recurrence rate of CRM-negative RT+TME patients compared to CRM-negative TME-patients suggests the sterilization of tumor deposits outside the mesorectum. Only few reports are published about local recurrence in the lateral pelvis. In the overview report of Roels et al.[22] 6% of all patients and 21% of the patients with local recurrence had a relapse in the lateral pelvic subsite. Also Kim et al.[29] reported recently that even after preoperative chemoradiotherapy combined with TME 24 of 366 (6.6%) patients with stage T3 or T4 tumors up till 8 cm from the anal verge developed lateral recurrence. Syk et al.[30] reported only two of the 33 recurrent tumors originating from lateral pelvic lymph nodes in a population based cohort. However, the study did not focus on low rectal tumors only and might be biased because patients who had a R1-resection or short distal resection margin were excluded. In the current report only low rectal tumors were studied and incomplete resection was not an exclusion criterion.

In the choice between more extensive surgery or preoperative radiotherapy as a means to improve the local recurrence rate, the morbidity associated with the treatment plays a major role. Patients who undergo radiotherapy have been shown to have an increased risk of sexual dysfunction and incontinence. In the Dutch TME trial 76% of the TME and 67% of the RT+TME male patients who were previously sexually active were still active[31]. For female patients, these figures were 90% and 72%, respectively. Preoperative radiotherapy resulted in more erection and ejaculation problems in males and vaginal dryness and pain during intercourse in females. Fecal incontinence was observed in 51.3% of the RT+TME patients, as compared to 36.5% in the TME patients. Regarding the lateral lymph node dissection, before nerve-sparing surgery, sexual dysfunction was present in as many as 96% of the patients[32]. LLND with nerve-sparing techniques 50-75% of the males are reported to be sexually active, although ejaculation is often compromised[33;34]. Urinary function is maintained well, but there are no reports on fecal continence. Although in Japan nerve-sparing techniques in LLND surgery are used to minimize damage the autonomic nervous system in the pelvis[15;35], most Western surgeons feel that in western patients, with a higher body mass index, nerve preserving techniques are more difficult and will lead to an excess morbidity. There is one report on results in 9 Western patients with locally advanced rectal cancer operated by LLND and ANP, with 1 patient with erection dysfunction and 1 patient suffering from retrograde ejaculation[36]. Currently, the National Cancer Center Hospital in Tokyo coordinates a multi-center randomized clinical trial comparing conventional TME vs. LLND in patients with low rectal carcinoma, addressing the questions of survival benefit and morbidity. The inclusion of about 600 patients will be completed in the end of 2009.

MRI is currently considered as the most reliable in staging rectal cancer. Preoperative MRI modalities are further improving and techniques are developed to distinguish better between non-metastatic and metastatic lymph nodes, by for example lymph node specific contrast enhancement[37]. With present day MRI sometimes patients are identified with clearly involved or suspected lateral lymph nodes. As often preoperative chemoradiation is the choice of treatment in these cases, it is doubtful whether the lateral lymph nodes can be fully sterilized. Also, the risk for disseminated disease is high and prognosis is unfavorable for lateral lymph node positive patients. For these patients it may be wise to consider a combination of treatments: neoadjuvant chemoradiation, a lateral lymph node dissection and possibly even systemic therapy.

In conclusion, both extended surgery and preoperative radiotherapy with standard TME surgery result in good local control in the treatment of distal rectal cancer, as compared to TME alone.

Reference List

1. Rao AR, Kagan AR, Chan PM, Gilbert HA, Nussbaum H, Hintz BL. Patterns of recurrence following curative resection alone for adenocarcinoma of the rectum and sigmoid colon. Cancer 1981; 48(6):1492-1495.
2. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986; 2(8514):996-999.
3. Martling A, Holm T, Johansson H, Rutqvist LE, Cedermark B. The Stockholm II trial on preoperative radiotherapy in rectal carcinoma: long-term follow-up of a population-based study. Cancer 2001; 92(4):896-902.
4. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet 1986; 1(8496):1479-1482.
5. Nagtegaal ID, van de Velde CJ, Marijnen CA, van Krieken JH, Quirke P. Low rectal cancer: a call for a change of approach in abdominoperineal resection. J Clin Oncol 2005; 23(36):9257-9264.
6. Gunderson LL, Sargent DJ, Tepper JE, Wolmark N, O'Connell MJ, Begovic M et al. Impact of T and N stage and treatment on survival and relapse in adjuvant rectal cancer: a pooled analysis. J Clin Oncol 2004; 22(10):1785-1796.
7. Quirke P. Training and quality assurance for rectal cancer: 20 years of data is enough. Lancet Oncol 2003; 4(11):695-702.
8. Den Dulk M, Marijnen CA, Putter H, Rutten HJ, Beets GL, Wiggers T et al. Risk factors for adverse outcome in patients with rectal cancer treated with an abdominoperineal resection in the total mesorectal excision trial. Ann Surg 2007; 246(1):83-90.
9. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997; 336(14):980-987.
10. Kapiteijn E, Marijnen CA, 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(9):638-646.
11. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med 2004; 351(17):1731-1740.
12. Gerard A, Buyse M, Nordlinger B, Loygue J, Pene F, Kempf P et al. Preoperative radiotherapy as adjuvant treatment in rectal cancer. Final results of a randomized study of the European Organization for Research and Treatment of Cancer (EORTC). Ann Surg 1988; 208(5):606-614.
13. Marijnen CA, Nagtegaal ID, Kapiteijn E, Kranenbarg EK, Noordijk EM, van Krieken JH et al. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: report of a multicenter randomized trial. Int J Radiat Oncol Biol Phys 2003; 55(5):1311-1320.
14. Moriya Y. Chapter 12: Importance of lymphatic spread. In: Rectal Cancer Surgery, Optimisation, Standardisation, Documentation. Edited by Soreide and Norstein. Pages 153-164. Springer-Verlag Berlin and Heidelberg GmbH & Co. 1997.
15. Moriya Y, Sugihara K, Akasu T, Fujita S. Importance of extended lymphadenectomy with lateral node dissection for advanced lower rectal cancer. World J Surg 1997; 21(7):728-732.
16. Yano H, Moran BJ. The incidence of lateral pelvic side-wall nodal involvement in low rectal cancer may be similar in Japan and the West. Br J Surg 2008; 95(1):33-49.
17. Steup WH. Chapter 6: Historical comparison Japanese data NCCH; Comparison between Japan and the Netherlands. Thesis: Colorectal cancer surgery with emphasis on lymphadenectomy. Pages 83-100. 1994. ISBN: 90-9007890-8
18. Kapiteijn E, Kranenbarg EK, Steup WH, Taat CW, Rutten HJ, Wiggers T et al. Total mesorectal excision (TME) with or without preoperative radiotherapy in the treatment of primary rectal cancer. Prospective randomised trial with standard operative and histopathological techniques. Dutch ColoRectal Cancer Group. Eur J Surg 1999; 165(5):410-420.
19. General rules for clinical and pathological studies on cancer of the colon, rectum and anus. Part I. Clinical classification. Japanese Research Society for Cancer of the Colon and Rectum. Jpn J Surg 1983; 13(6):557-573.

20. Steup WH, Moriya Y, van de Velde CJ. Patterns of lymphatic spread in rectal cancer. A topographical analysis on lymph node metastases. Eur J Cancer 2002; 38(7):911-918.
21. Najarian MM, Belzer GE, Cogbill TH, Mathiason MA. Determination of the peritoneal reflection using intraoperative proctoscopy. Dis Colon Rectum 2004; 47(12):2080-2085.
22. Roels S, Duthoy W, Haustermans K, Penninckx F, Vandecaveye V, Boterberg T et al. Definition and delineation of the clinical target volume for rectal cancer. Int J Radiat Oncol Biol Phys 2006; 65(4):1129-1142.
23. Putter H, Fiocco M, Geskus RB. Tutorial in biostatistics: competing risks and multi-state models. Stat Med 2007; 26(11):2389-2430.
24. Havenga K, Enker WE, Norstein J, Moriya Y, Heald RJ, van Houwelingen HC et al. Improved survival and local control after total mesorectal excision or D3 lymphadenectomy in the treatment of primary rectal cancer: an international analysis of 1411 patients. Eur J Surg Oncol 1999; 25(4):368-374.
25. Heald RJ, Moran BJ, Ryall RD, Sexton R, MacFarlane JK. Rectal cancer: the Basingstoke experience of total mesorectal excision, 1978-1997. Arch Surg 1998; 133(8):894-899.
26. Salerno G, Sinnatamby C, Branagan G, Daniels IR, Heald RJ, Moran BJ. Defining the rectum: surgically, radiologically and anatomically. Colorectal Dis 2006; 8 Suppl 3:5-9.
27. Nagtegaal ID, van de Velde CJ, van der WE, Kapiteijn E, Quirke P, van Krieken JH. Macroscopic evaluation of rectal cancer resection specimen: clinical significance of the pathologist in quality control. J Clin Oncol 2002; 20(7):1729-1734.
28. Holm T, Ljung A, Haggmark T, Jurell G, Lagergren J. Extended abdominoperineal resection with gluteus maximus flap reconstruction of the pelvic floor for rectal cancer. Br J Surg 2007; 94(2):232-238.
29. Kim TH, Jeong SY, Choi DH, Kim DY, Jung KH, Moon SH et al. Lateral Lymph Node Metastasis Is a Major Cause of Locoregional Recurrence in Rectal Cancer Treated with Preoperative Chemoradiotherapy and Curative Resection. Ann Surg Oncol 2007.
30. Syk E, Torkzad MR, Blomqvist L, Ljungqvist O, Glimelius B. Radiological findings do not support lateral residual tumour as a major cause of local recurrence of rectal cancer. Br J Surg 2006; 93(1):113-119.
31. Marijnen CA, van de Velde CJ, Putter H, van den BM, Maas CP, Martijn H et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2005; 23(9):1847-1858.
32. Hojo K, Sawada T, Moriya Y. An analysis of survival and voiding, sexual function after wide iliopelvic lymphadenectomy in patients with carcinoma of the rectum, compared with conventional lymphadenectomy. Dis Colon Rectum 1989; 32(2):128-133.
33. Kyo K, Sameshima S, Takahashi M, Furugori T, Sawada T. Impact of autonomic nerve preservation and lateral node dissection on male urogenital function after total mesorectal excision for lower rectal cancer. World J Surg 2006; 30(6):1014-1019.
34. Mori T, Takahashi K, Yasuno M. Radical resection with autonomic nerve preservation and lymph node dissection techniques in lower rectal cancer surgery and its results: the impact of lateral lymph node dissection. Langenbecks Arch Surg 1998; 383(6):409-415.
35. Moriya Y, Sugihara K, Akasu T, Fujita S. Patterns of recurrence after nerve-sparing surgery for rectal adenocarcinoma with special reference to loco-regional recurrence. Dis Colon Rectum 1995; 38(11):1162-1168.
36. Di Matteo G, Peparini N, Maturo A, Di Matteo FM, Zeri KP, Redler A et al. Lateral pelvic lymphadenectomy and total nerve sparing for locally advanced rectal cancer in Western patients. Panminerva Med 2001; 43(2):95-101.
37. Lahaye MJ, Engelen SM, Kessels AG, de Bruine AP, von Meyenfeldt MF, van Engelshoven JM et al. USPIO-enhanced MR imaging for nodal staging in patients with primary rectal cancer: predictive criteria. Radiology 2008; 246(3):804-811.