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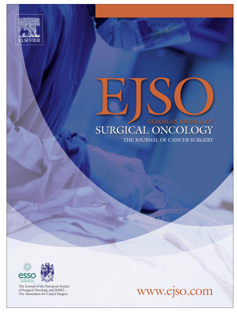

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Original Article

Patterns of local recurrence in rectal cancer; a study of the Dutch TME trial

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Abstract

Aim of the study: In patients from the Dutch TME trial patterns of local recurrence (LR) in rectal cancer were studied. The purpose was to reconstruct the most likely mechanisms of LR and the effect of preoperative radiotherapy.

Methods: 1417 patients were analyzed; 713 were randomized into preoperative radiotherapy and total mesorectal excision (RT+TME), 704 into TME alone. Of the 114 patients with LR, the subsites of LR were determined and related to tumor and treatment factors.

Results: Overall 5-year LR-rate was 4.6% in the RT+TME group and 11.0% in the TME group. Presacral local recurrences occurred most in both groups. Radiotherapy reduced anastomotic LR significantly, except when after low anterior resection (LAR) distal margins were less than 5 mm. Abdominoperineal resection (APR) mainly resulted in presacral LR. Even after resection with a negative circumferential resection margin, LR rates were high. 30% of the patients had advanced tumors, which resulted in 58% of all LRs. Lateral LR comprised 20% of all LR. Presacral LR resulted in a poor prognosis, in contrast to anterior or anastomotic LRs with a relatively good prognosis.

Conclusions: RT reduces LR in all subsites and is especially effective in preventing anastomotic LR after LAR. APR surgery mainly results in presacral LR, which may be prevented by a wider resection. In the TME trial many advanced tumors were included, rather requiring chemoradiotherapy in stead of RT. Currently, with good imaging techniques, better selection can take place. Especially lateral LR might be a problem in the future.

Key words

Local recurrence; rectal carcinoma; abdominoperineal resection; low anterior resection; distal margin; preoperative radiotherapy

Introduction

Optimal local control is an important goal in the treatment of rectal cancer. Since the introduction of the total mesorectal excision (TME) local control has improved drastically, with further improvement through the addition of preoperative radiotherapy [1;2]. In the Dutch TME trial, surgeons were trained in TME-surgery by workshops and tutorials in order to achieve optimal surgical quality. Although locally advanced tumors were supposed to be excluded, only fixed tumors at rectal examination could be identified, since routine imaging was not mandatory at that time [2]. However, histological evaluation of the circumferential resection margins (CRM) suggested that a substantial proportion of advanced tumors had been included [3]. Suspected CRM involvement, T4 disease and massive lymph node involvement, all risk factors for local recurrence, can currently be well identified by preoperative MR imaging [4;5]. In the presence of these risk factors, nowadays a long course of neo-adjuvant (chemo)radiation would be given in order to achieve downsizing and downstaging before surgery [6]. The purpose of this study is to analyze the patterns of local recurrence in the TME trial, reconstructing the most likely mechanisms of local recurrence and the effect of preoperative radiotherapy.

Patients and methods

Patients

Patients were selected from a large prospective randomized multi-center study that 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). Inclusion criteria were primary adenocarcinoma of the rectum, without evidence of metastatic disease 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 [2].

For the current study only the Dutch patients were selected and the following patients were excluded from the analysis: ineligible patients (n = 50), no resection (n = 37) and no tumor at operation (n = 26), leaving 1417 patients for analysis.

Methods

All patients with a local recurrence, defined as any rectal cancer recurrence in the small pelvis, were identified. Local recurrence was diagnosed either clinically, radiologically or histologically. All patients with a local recurrence were studied individually. Sources of information additional to the standard trial database items were the operative report, the histological report, specimen photographs when available, initial preoperative imaging when available, imaging of the local recurrences, and the clinical history and follow up after the diagnosis of the local recurrence. The data were reviewed case by case by a team consisting of 2 radiologists, 1 radiation oncologist and 2 surgeons.

Examining the images and data, the location of the recurrence was classified into one of the following subsites:

- Presacral: predominantly midline, in contact with sacral bone

- Anterior: predominantly midline, involving bladder, uterus, vagina, seminal vesicles or prostate
- Anastomotic: after low anterior or low Hartmann, at the staple line
- Lateral: pelvic sidewall, immediately behind posterior ischiac spine, in the obturator lymph node compartment or along iliac vessels
- Perineal: perineum, anal sphincter complex with surrounding perianal and ischiorectal space

Although the distal margin for the low anterior resections and low Hartmann's was prospectively recorded, the database did not contain reliable information on the completeness of the mesorectum distally. For the patients with a local recurrence the operative reports were studied to define whether the distal mesorectum was transsected below the tumor, or if a distally complete mesorectal excision was performed.

Statistical analysis

Statistical analysis was performed using SPSS package (SPSS 12.0 for Windows; SPSS Inc, Chicago, IL). T-tests and chi-square tests were used to compare individual variables. Survival was estimated using the Kaplan-Meier method. 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 local recurrence, cumulative incidences were calculated accounting for death as competing risk [7]. Similarly, cumulative incidences were calculated for subsite of local recurrence, with death and other types of local recurrence as competing risks, and for survival, with death due to other causes as competing risk.

Results

Clinical and pathological characteristics

Clinical and pathological characteristics are listed in Table 1. Low tumor location, abdominoperineal resection (APR) surgery, higher TNM stage and involvement of the circumferential resection margin are associated with local recurrence, as previously reported [8]. After a median follow-up of 7.0 years (range 2.5-9.8) 114 of the 1417 patients developed a local recurrence; 36 patients in the RT+TME group (5-year 4.6% LR-rate) and 78 patients in the TME group (5-year 11.0% LR-rate).
The mean time to local recurrence is 2.6 years in RT+TME group and 1.5 years in the TME group. Nineteen of 36 patients (55%) in the RT+TME group had distant metastases at the time of local recurrence diagnosis. This was in 32 of 78 (41%) patients in the TME group ($p = 0.264$). If distant metastases diagnosed within 1 month of local recurrence diagnosis were also considered as occurring simultaneously, distant metastases rate was 74% in the RT+TME group and 40% in the TME group ($p = 0.004$) [9].

Patterns of local recurrence

The subsites of local recurrence are presented in Table 2. Presacral local recurrences (Figure) occurred most in both randomisation groups (5-year local recurrence rate RT+TME: 2.0% and TME: 3.6%). There was a significant difference between the two randomisation arms in the anastomotic subsite, with 0.7% 5-year local recurrence in the RT+TME group and 2.7% in the TME group ($p = 0.003$). Lateral local recurrences comprised about 20% of all local recurrences.

Surgical aspects

Type of surgery

In patients undergoing a LAR or Hartmann procedure, 67 of 981 developed a local recurrence (5-year 7.8% LR-rate). In contrast, 47 of 389 patients who underwent an APR developed a local recurrence (5-year 11.7% LR-rate). In LAR patients, the majority of the recurrences was anastomotic 24/67 (36%) or presacral 19/67 (28%). In APR patients, presacral recurrences presented most often 21/47 (45%).

CRM involvement

In total, 267 patients had a positive CRM on pathology examination. Of those, 46 developed a local recurrence, indicating that CRM involvement is not the only factor explaining the occurrence of local relapses. Twenty-nine of the 267 patients (10.9%) with a positive CRM had a T1 or T2 tumor, suggesting that suboptimal surgery played a role in the occurrence of those relapses. In these 29 patients local recurrence rate was 12.4% after 5 years, whereas this was 23.6% in T3 or T4 tumors with a positive CRM ($p = 0.217$). Forty-one percent of these 29 patients had undergone a LAR, 59% had undergone an APR. In tumors operated by LAR with a negative CRM, local recurrence rate was 3.5% in N0 tumors and 12.5% in N+ tumors ($p < 0.001$). Similarly for tumors operated by APR with a negative CRM, local recurrence rate was 2.0% in N0 tumors and 18.0% in N+ tumors ($p <0.001$).

Distal margin

To investigate the influence of the distal margin on the occurrence of local recurrences, local relapses were stratified for distal margin and lymph node involvement by treatment arm in Table 3. TME alone in node positive disease resulted in considerable local recurrence rates when the distal margin was 2 cm or shorter. In node negative disease local recurrence rates were not significantly different for the separate margin groups. Radiotherapy resulted in small numbers of local recurrence, except when distal margins were less than 5 mm. For the patients with a local recurrence after LAR or Hartmann procedure, in 25 of 67 (37%) the distal mesorectum was transsected below the tumor, in 33 (49%) a distally complete mesorectal excision was performed, and in 9 (13%) it was unknown whether a complete or a partial mesorectal excision had been performed. In both partial and complete excision mean distal margin was 2.7 cm.

Tumor aspects

To evaluate the effect of radiotherapy on local recurrences mainly caused by surgery-related factors or mainly due to biological tumor factors, a hypothetical division was made. Patients with tumors mainly caused by biological agressive tumor behaviour were considered as patients with risk factors. The following factors were considered risk factors: TNM stage IV disease, T4 tumor, N2 disease (4 or more involved lymph nodes) or a positive CRM in T3 or T4 disease. All other patients were considered as patients without risk factors. In those patients suboptimal surgery possibly played a role in the aetiology of the local recurrence. For patients without risk factors, the 5-year local recurrence rate was 5.1%, whereas this figure was 21.0% for patients with risk factors ($p < 0.001$).

In retrospect, 421 patients (30%) had at least one of the above-mentioned risk factors (IV stage: 87, T4: 51, N2: 236, CRM+: 267). Of those 421, 204 patients received RT+TME and 215 patients underwent TME only. The 5-year local recurrence rate was 17.0% and 24.6% respectively, indicating that the addition of short-term preoperative RT still resulted in an unacceptable high number of recurrences in this group. Sixty-six out of 114 local recurrences (58%) occurred in patients with risk factors; 23 (35%) were presacral, 18 (27%) were lateral, 14 (21%) were anterior and the remaining 11 were located in other areas. In 39 of these 66 (59%) the local recurrence occurred simultaneously with distant metastases.

Forty-eight out of 114 local recurrences (42%) occurred in patients without risk factors. For patients without risk factors, 5-years LR-rates were 2.3% for the RT+TME group and 7.9% for the TME group ($p < 0.001$). Interestingly, in this group, a large percentage of the recurrences occurred in the anastomosis 18/48 (38%), whereas the percentage of presacral recurrences 17/48 (35%) was similar. Compared to the group of patients with risk factors, lateral recurrences were seen in only 10% (5/48). In 12 of these 48 (25%) the local recurrence appeared simultaneously with distant metastases.

Survival

Overall survival after local recurrence diagnosis per randomisation arm, stratified for subsite, is presented in Table 4. Overall survival is lower after local recurrence in the RT+TME group, compared to the TME group. The prognosis for anastomotic and anterior recurrences is generally better than for presacral and lateral recurrences.

Discussion

The present study aimed at reconstructing the mechanisms of local recurrence and to analyze the effect of short-term preoperative radiotherapy through studying the details of all patients with local relapse in the TME trial. Since this trial preoperative imaging, preoperative therapy, surgery and adjuvant treatment modalities have changed, but still these new data give insight in local recurrence genesis and help understanding how to prevent local relapse in current rectal cancer treatment.

We have shown that presacral local recurrences are the most common type of local recurrence and have a poor prognosis in general. Anastomotic and anterior recurrences have a relatively good prognosis.

In this study we demonstrate that preoperative radiotherapy reduces local recurrences in all subsites and is especially effective in preventing in anastomotic recurrences. In addition, we found that short-term preoperative radiotherapy reduces the number of recurrences caused by a too short distal margin. Abdominoperineal resection mainly resulted in presacral local recurrences; even after resection with a negative circumferential resection margin, local relapse rate was high. Further, suboptimal selection and inclusion of many ‘advanced tumours’ in the TME trial is likely to be a factor most recurrences.

Low anterior resection

Apart from presacral recurrences, anastomotic recurrences are relatively frequent, especially in non-irradiated LAR patients. Table 3 suggests that node positive patients who did not undergo radiotherapy require a larger distal margin (more than 2 cm) than node negative patients, where a margin of 1 cm seems sufficient.

A complicating factor in analyzing the sphincter-saving procedures in the TME trial is that a total mesorectal excision down to the pelvic floor was not mandatory and surgeons were allowed to transsect the mesorectum 5 cm below the tumor. Unfortunately, it is unclear what proportion of the patients received a partial mesorectal excision in stead of a TME. However, the difference between node positive and node negative patients suggests that the risk is not so much in intramural spread as

in intramesorectal spread, since it is unlikely that node positive disease results in more extensive intramural spread.

Chinese histological studies have reported that distal intramural spread is seen in about only 5% of rectal cancer patients, usually within 1 cm of the lower edge of the tumor [10-12]. Koh et al [13], examining the distribution of mesorectal lymph nodes based on imaging and histopathology, hardly found any lymph nodes distal to the tumor. This in contrast to an anatomical cadaver study of Perez et al [14], who found lymph nodes up to the distal third of the mesorectum. However, several studies reported distal mesorectal spread in 10-15% of rectal cancer patients, usually within 2-3 cm and more often in the form of small mesorectal deposits than involved nodes [10-12].

Probably, the risk for mesorectal tumor deposits is larger in node positive than in node negative patients. Therefore, surgeons should be aware that in node positive patients a transsection of the mesorectum closer to the tumor carries a risk of leaving small tumor deposits behind. This should be kept in mind when for some reason a patient is not receiving preoperative radiotherapy; then a mesorectal transsection of 5 cm below the tumor is a wise precaution in these patients. But still, radiotherapy can prevent anastomotic recurrences, except when distal margins are less than 5 mm.

Abdominoperineal resection

APR-surgery has shown poor results in several reports, with higher local recurrence rates than after low anterior resections [15]. In this study, APR-surgery mainly resulted in presacral local recurrences. It is known from the TME trial, that APR is associated with higher CRM involvement [3]. We previously speculated that tumor spill from these positive margins might cause these presacral local recurrences through force of gravity [16].

Anatomical and radiological studies show that in the lowest part of the rectum the mesorectum tapers and terminates at the pelvic floor [17]. If a tumor is located in the distal third of the rectum, the surrounding mesorectum is very thin, especially on the ventral side [18]. Near the anal margin the visceral fascia (covering the mesorectum) blends with the parietal fascia (covering the levator ani muscle), forming the corrugator muscle, which separates the internal from the external sphincter. At

this level a tumor that extends only a few millimeters beyond the muscular bowel wall is at risk for a positive margin when following the normal resection plane.

Even when negative margins are achieved, these low tumors seem to behave differently compared to proximal tumors. In this study, as much as 18.0% of the CRM-negative N+ tumors operated by APR developed a local recurrence. Apparently, in these low tumors tumor particles still seem to be left behind even when the circumferential margin seems sufficient, causing local recurrences at various subsites. Possibly, during surgery tumor cells are pushed into the lateral lymph flow routes during surgery, leaking back into the surgical volume after the resection [19].

A wide APR, resecting the complete levator ani muscle, might provide better local control of low tumors [16;20]. Japanese surgeons advocate the lateral lymph node dissection. Another option, favored by Japanese and Western surgeons, is chemoradiation prior to surgery in low T3 tumors, as if they are true locally advanced disease [21]. This has been reported to result in downstaging and even sometimes the possibility for sphincter-saving surgery [21]. It also addresses the small tumor particles that are apparently left behind in patients without involved margins, be it in lateral nodes or somewhere else.

Risk factors

An involved or close circumferential resection margin (CRM) has repeatedly been confirmed as one of the most important risk factors for local recurrence [3]. In the TME trial CRM-positivity was 17% and even as much as 30% after an abdominoperineal resection [22]. CRM involvement results in a high local recurrence rate, even if the tumor was a T1 or T2 stage tumor. In this study 89.1% of CRM-positivity occurred in T3 or T4 tumors, indicating that it is mainly attributable to adverse tumor factors and not so much to bad surgery. In most cases, a long course of neo-adjuvant (chemo)radiation, rather than a short-course of radiotherapy, can probably downstage these tumors and lead to better results [6]. Thus, nowadays, with good imaging and preoperative discussion in a multidisciplinary team, a positive margin is probably more a sign of inadequate surgical technique rather than unrecognized advanced disease [23].

Apart from the CRM, T4 tumors, massive lymph node involvement (N2 disease) and synchronous metastases can be considered as a sign of aggressive tumor biology. Although difficult to prove, short-

term preoperative radiotherapy may be insufficient to prevent local recurrences in this subgroup. We therefore analyzed patients without risk factors resulting in a hypothetical 5-year LR-rate of 2.0% for the RT+TME group and 7.2% for the TME group. We realize this post-factum distinction between 'risk factors' and 'no risk factors' is a hypothetical approach that may be due to subjective interpretation. However, it gives insight in the outcomes and patterns of local recurrence for current practice, where good preoperative imaging is available. Nowadays it would be unlikely that these 'more advanced' tumors would be only subjected to a short course of preoperative radiotherapy.

Lateral disease

Although the main lymphatic flow is upward in the mesorectum, involvement of lateral nodes outside the mesorectum does occur. This has been studied in detail by Japanese surgeons who have documented that in low rectal cancer in general there is a 10% chance of involved lateral nodes. In advanced distal cancer this percentage is even 15-20% [24-26]. In the TME trial lateral local recurrences represent about 20% of all local recurrences, a figure in accordance with an overview of Roels et al [27]. We can conclude that lateral disease is responsible for a considerable amount of local relapse. We previously analyzed only low rectal tumors, when lateral lymph node spread is especially present, and noticed a significant difference between the RT+TME and TME arms. Thus, radiotherapy can probably sterilize lateral tumor particles in most of the cases [16].

A problem however arises if positive lateral lymph nodes are not included in the radiation target volume, as in intensity modulated radiation therapy (IMRT). In contrast to the TME trial, in which the lateral lymph nodes were probably always irradiated, smaller areas only receive a high dose of local radiotherapy in IMRT, not including the lateral areas if they are not suspected to be involved.

Finally, once local recurrence has occurred, almost all RT+TME patients develop distant metastases within one year and few survive for two years. This can be explained by the fact that patients who develop local relapse after RT+TME, are a selection of patients with more aggressive disease [9]. In TME-patients anastomotic local recurrences seem to behave more as true local disease, compared to local recurrences in the other subsites, also mentioned by other authors [28;29]. As a consequence,

although these recurrences may appear 'easier' to resect, because of the higher chances of cure they should be treated with a maximal curative intent, including neoadjuvant treatment and surgery in an expert centre. In this study centrally situated recurrences were treated surgically more often than peripheral tumors and were less often metastasized, possibly explaining the better prognosis of these tumors.

Concluding, a short course preoperative radiotherapy prevents local recurrence in all subsites and is especially effective in preventing anastomotic recurrences. Surgical technique and attention to distal margin can play a role in preventing local recurrences. Abdominoperineal resection surgery mainly results in presacral local recurrences, which may be prevented by a wider resection. The majority of the recurrences however are related to the advanced nature of the disease, which can nowadays be identified with modern imaging techniques and consequently be treated with neoadjuvant chemoradiation.

Conflict of interest statement

There were no conflicts of interest

There were no sources of funding

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Table 1 Clinicopathologic characteristics

	All patients		Patients with local recurrence	
	LR- ***N = 1303***	***LR+*** ***N = 114***	***RT+*** ***N = 36***	***RT-*** ***N= 78***
Age (yrs)				
Median (range)	65 (26-83)	65 (23-92)	62 (26-82)	66 (43-83)
Sex				
Male	837 (64)	69 (61)	23 (64)	46 (59)
Female	466 (36)	45 (39)	13 (36)	32 (41)
Distance from anus				
< 5 cm	387 (30)	48 (42)	20 (56)	28 (36)
5 – 10 cm	529 (40)	47 (41)	10 (28)	37 (47)
> 10 cm	386 (30)	19 (17)	6 (16)	13 (17)
Resection type				
APR	389 (30)	47 (41)	18 (50)	45 (58)
LAR	843 (65)	61 (54)	16 (44)	29 (37)
Hartmann	71 (5)	6 (5)	2 (6)	4 (5)
T-stage				
T1	79 (6)	0 (0)	-	-
T2	447 (34)	15 (13)	5 (14)	10 (12)
T3	735 (56)	90 (79)	28 (78)	62 (80)
T4	42 (4)	9 (8)	3 (8)	6 (8)
N-stage				
N0	800 (61)	29 (26)	10 (28)	19 (24)
N1	306 (24)	46 (40)	12 (33)	34 (44)
N2	197 (15)	39 (34)	14 (39)	25 (32)
CRM				
Negative	1082 (83)	68 (60)	17 (47)	51 (65)
Positive	221 (17)	46 (40)	19 (53)	27 (35)

Values in parenthesis are percentages
LR = local recurrence
RT = preoperative radiotherapy

Table 2 Subsites of local recurrence

	RT+ ***N = 713***	***RT-*** ***N = 704***
Presacral	15 (2.0)	25 (3.6)
Lateral	9 (1.1)	14 (1.9)
Anterior	6 (0.7)	14 (1.9)
Anastomosis	5 (0.7)	19 (2.7)
Perineum	0 (0)	4 (0.6)
Unknown	1 (0.1)	2 (0.3)
TOTAL	**36 (4.6)**	**78 (11.0)**

Values in parenthesis are 5-year LR-rates, by competing risks analysis
RT = preoperative radiotherapy

Table 3 Local recurrence rate according to distal margin and lymph node status

	RT-			**RT+**		
Distal Margin	***N0***	***N+***		***N0***	***N+***	
0 – 5 mm	5.6	30.0		11.8	28.6	
6 – 10 mm	8.8	34.6		0	0	
11 – 20 mm	4.6	29.7		0	7.2	
> 21 mm	5.5	8.6		1.7	5.8	
TOTAL	**5.6**	**19.4**	**<0.001**	**1.7**	**9.3**	**<0.001**

In LAR and Hartmann procedures. Values are 5-year local recurrence percentages

Table 4 Overall survival after local recurrence diagnosis

	RT+ ***N = 36***	***RT-*** ***N = 78***
Presacral	6.7 (1/15)	29.5 (8/25)
Lateral	0 (0/9)	14.4 (2/14)
Anterior	33.3 (2/6)	38.5 (5/14)
Anastomosis	20.0 (1/5)	52.6 (10/19)
Perineum	n.a.	0 (0/4)
Unknown	0 (0/1)	50.0 (1/2)
ALL	**11.1 (4/36)**	**33.0 (25/78)**

Values are overall survival percentages at two years after LR diagnosis

Figure MR Image of a presacral local recurrence


C: 220.9, W: 383.9
Seq: SE
Slice: 3 mm
Pos: 89.1
TR: 12670.1
TE: 120
AC: 6
L
FFS
FoV: 180 mm
Image no: 28
Image 28 of 52
P
- + 1(40)
52
L
1
A4
F