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ORIGINAL ARTICLE

Regional lymph node metastasis and locoregional recurrence of rectal carcinoma in the era of TNM surgery. Implications for treatment decisions

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Abstract
Background and aims For rectal carcinoma treated according to the concept of total mesorectal excision (TME surgery), the independent influence of regional lymph node metastasis on the locoregional recurrence risk is still in discussion. A reliable assessment of this risk is important for an individualised selective indication for neoadjuvant radio-/radiochemotherapy.
Methods Analysis of literature, especially of the last 20 years, and consideration of pathological and oncological basic research. Multivariate analysis of data of the Erlangen Registry of Colorectal Carcinoma.
Results The clinical assessment of the pretherapeutic regional lymph node status by the present available imaging methods is still unreliable. The analysis of the association between pretherapeutic regional lymph node status and locoregional recurrence risk has to be based on follow-up data of patients treated by primary surgery and has to be distinguished between patients treated by conventional and optimised quality-assured TME surgery, respectively. Data from Erlangen show an increase of the local recurrence risk for patients with at least four involved regional lymph nodes.
Conclusions For patients with at least four involved regional lymph nodes, a neoadjuvant radiochemotherapy may be indicated. However, today, the pretherapeutic diagnosis is uncertain and results in overtherapy in 40%. Thus, in case of positive lymph node findings by imaging methods, the benefits and risk of neoadjuvant therapy in such situations should always be discussed with the patient in the sense of informed consent and shared decision.

Keywords Local recurrence · Neoadjuvant treatment · Rectal carcinoma · Regional lymph node metastasis · TME (Total mesorectal excision) surgery

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Introduction

There is no discussion that for patients with rectal carcinoma, regional lymph node metastases (RLNM) are indicators of an increased risk of distant metastases. In contrast, the independent influence of RLNM on locoregional recurrence (LR) is still in discussion. In this context, it has to be differentiated according to type and quality of surgery (conventional or total mesorectal excision (TME) surgery), and the use of multimodal therapy has to be considered. In the following, 'TME surgery' is used for following the concept of total mesorectal excision for carcinomas of the middle and lower third and of partial mesorectal excision (PME) for carcinomas of the upper third, in each case with sharp dissection in the pelvis [1–3].

The subject of the association between the pretherapeutic regional lymph node status and the risk of LR directly influences the selection of patients for neoadjuvant treatment. Thus, this topic has practical clinical relevance, especially in the present time of general demand for a more selective and individualised indication for neoadjuvant

treatment, preventing under- as well as overtreatment [4–10]. In the following, the actual data of literature including new data from the Erlangen Registry of Colorectal Carcinoma (ERCRC) [11] will be analysed.

Preliminary remarks and definitions

In the description of the pretherapeutic regional lymph node status according to the rules of the TNM classification [12], it is distinguished between a clinical and a pathological classification (cN/pN). The clinical assessment of the pretherapeutic lymph node status is associated with uncertainty. The real situation is described by the results of the histopathological examination of the resection specimens, however, only in case of primary surgery. Following neoadjuvant treatment, the pathological examination of the regional lymph nodes describes the situation following neoadjuvant treatment (ypN); thus, in case of neoadjuvant treatment, the pretherapeutic lymph node status can be assessed only clinically (cN), but not pathologically.

Between Western Countries and Japan, there are differences in the anatomic subdivision of the rectum. In Japan, 'lower rectum' includes all tumours below the peritoneal reflection, corresponding to tumours of the middle and low third of the rectum, about <11–12 cm from the anal margin. In the Western countries, 'lower or low rectum' is used only for tumours of the lower third of the rectum (lower margin <6–7.5 cm from the anal margin).

Whether for analysis of the association between the pretherapeutic regional lymph node status and the risk of LR only patients with primary surgery or also patients with neoadjuvant treatment can be included depends on the reliability of the clinical diagnosis of RLNM. Thus, in the following, at first, the accuracy of the present imaging methods concerning regional lymph nodes will be discussed.

In the lymphatic spread of the rectal carcinoma, it has to be further distinguished between the predominant spread within the mesorectum upwards and the spread to lateral pelvic nodes. The latter will be discussed in a separate section.

Possibilities of clinical assessment of pretherapeutic regional lymph node status

With regard to the possibilities of pretherapeutic diagnosis of RLNM, it has to be distinguished between the lymph nodes in the mesorectum and the lateral pelvic lymph nodes.

The present clinical assessment of mesorectal lymph nodes is associated with considerable uncertainty [5, 8, 13, 14]. According to two meta-analyses [13, 15] and three systematic literature reviews [16–18], no significant differences between EUS, CT, and MRI with respect to staging the nodal status have been found (Table 1). However, in these reviews, exact information about the proportion of patients with neoadjuvant treatment and about the use of endorectal coil for MRI are partly missing.

High-resolution MRI employing pelvic phase-array coils is the best modality to evaluate the relation between tumour and fascia mesorectalis (the later plane of surgery and circumferential resection margin). Thus, today, MRI can be considered as the established modality of choice for preoperative staging and selection for neoadjuvant treatment [5, 8, 19, 20]. Near details of present day efficiency of MRI in the assessment of the pretherapeutic mesorectal lymph node status can be seen in Table 2. The pooled results are disappointing: positive predictive value only 63%, accuracy only 71%. A similar value for accuracy (380/502=76%) is reported from the National Cancer Center Hospital, Tokyo [21]. In this retrospective study (1988–2002, 817 patients) the lymph node status has been assessed by 'CT and/or MRI' and included for patients at or below the peritoneal reflection the lateral pelvic lymph nodes.

Summarising, it has to be stated that a reliable assessment of the pretherapeutic mesorectal regional lymph node status is not possible by the present imaging modalities [13, 14, 22].

An improvement in lymph node staging by the contrast agent ultrasmall super paramagnetic iron oxide-enhanced MRI was expected in future [8, 22–24]. However, this contrast medium is no more available at present. The results of the multi-slice (multi-detector row) CT (MDCT) seem to be similar to MRI [25–28]; however, the available data are limited.

The diagnosis of four or more involved mesorectal lymph nodes (cN2) is a further problem. Table 3 shows the results of four relevant studies (2000–2006, n=362). The pooled positive predictive value is only 60%. Forty percent of the positive findings are false, i.e., the results are near to purely coincidental values. Thus, the pretherapeutic MRI findings of cN2 cannot be considered as basis of an indication for neoadjuvant therapy.

The possibilities of clinical assessment of lateral pelvic lymph nodes could be studied only in Japan where patients with T3 and T4 rectal carcinomas below the peritoneal reflection (designated as lower rectal carcinoma according to the Japanese Society for Cancer of the Colon and Rectum, 1997) [29] have been treated by primary TME surgery with extended lateral pelvic lymphadenectomy (D3 lymphadenectomy) [3]. In a comparison between mesorectal and lateral pelvic lymph nodes [30], the results of MRI proved to be better for lateral than for mesorectal nodes: positive predictive value 56% (10/18) versus 46% (12/26), negative predictive value 91% (10/11) versus 81% (22/27), false positive findings 15% (8/53)

Table 1 Pretherapeutic assessment of regional mesorectal lymph node status by endorectal ultrasonography (EUS), computed tomography (CT) and magnetic resonance imaging (MRI)

Parameter/study type/author(s)/year	EUS	CT	MRI
A. Accuracy/systematic reviews			
Heriot et al. 1999 [16]	606/765=79.2% 95% CI: 76.3–82.1% variation: 62–88% (eight studies, 1989–1997)	80/123=65.0% 95% CI: 56.6–73.5% variation: 57–78% (three studies, 1981–1990)	207/289=71.6% 95% CI: 66.4–76.8% variation: 29–95% (11 studies, 1986–1997)
Kwok et al. 2000 [17]	1,504/2,031=74.0% 95% CI: 72.1–75.9% variation: 44–87% (36 studies, 1987–1997)	405/622=65.1% 95% CI: 61.4–68.9% variation: 35–100% (13 studies, 1981–1997)	323/436=74.0% 95% CI: 70.0–78.2% variation: 39–94% (14 studies, 1986–1997)
Skandarajah and Tjandra 2006 [18]	993/1438=69.1% 95% CI: 66.7–71.4% variation: 63–86% (eight studies, 1997–2006)[a]	Not given 95% CI: 62.3–71.2% variation: 47–89.5% (seven studies, 1997–2006)	291/436=66.7%
B. Diagnostic odds ratio/meta-analysis[b]			
Lahaye et al. 2005 [13]	8.83	5.86	6.53
C. Sensitivity and specifity/meta-analysis			
Bipat et al. 2004 [15]			
- Sensitivity	67% (95% CI: 60–73%)	55% (95% CI: 43–67%)	66% (95% CI: 54–76%)
- Specifity	78% (95% CI: 71–84%)	74% (95% CI: 67–80%)	76% (95% CI: 59–87%)

Results of meta-analyses and systematic literature reviews including at least two imaging methods. Most of the patients are treated by primary surgery, but no exact information about the proportion of patients with neoadjuvant treatment given. MRI using endorectal coil excluded so far as information is given

[a] Studies between 1986 and 1996 excluded

[b] The diagnostic odds ratio (DOR) is a measure for the diagnostic performance of a test, which combines sensitivity and specifity into one measure [88]. The larger the DOR, the better the test discriminates between patients with and without the target disorder

versus 26% (14/53) and overall accuracy 83% (44/53) versus 64% (34/53). Only the last difference is statistically significant (p=0.046).

In this context, it has to be emphasised that an involvement of lateral pelvic lymph nodes is in most cases associated with positive mesorectal lymph nodes: Sugihara et al. [31]: 103/129 (80%) and Ueno et al. [32]: 31/41 (76%).

Regional lymph node metastasis and the risk of locoregional recurrence

The following deals with the problem whether absence or presence of regional lymph node metastasis (N0 or N1,2) has an independent influence on the risk of LR (the impact of the number of involved lymph nodes is discussed in the following section). In this respect, it is essential to distinguish between conventional and optimised and quality-assured TME surgery.

As shown above, the pretherapeutic clinical assessment of the regional lymph node status is uncertain. Thus, a reliable analysis of the association between pretherapeutic regional lymph node status and the risk of LR is possible only by using the histopathological assessment of the pretherapeutic regional lymph node status, i.e., the pN status after primary surgery (without neoadjuvant treatment) describing the pretherapeutic situation.

Following conventional surgery, the different frequency of LR for pN0 and pN1,2 patients is proven for a long time already [33–39].

For the actual optimised TME surgery, a correlation between pN and LR seems unlikely for theoretical reasons. The TME surgery is characterised by the complete removal of the lymphatic drainage upwards as a package limited by fascias, thus, regional lymph nodes—except, lateral pelvic nodes (see below)—do not remain as origin of LR.

For patients treated by primary surgery following the concept of TME, two publications include relevant multivariate analyses dealing with the influence of pN0 and pN1,2, respectively, on the risk of LR. In both studies, the LR rates for pN0 and pN1,2 were not different. In the largest study [40] (n=686), the crude LR rate for all patients was 7%, the hazard ratios compared to pN0=1.0 were for pN1 1.5 (95% CI, 0.8–3.1) and for pN2 1.4 (95%

Table 2 Pretherapeutic diagnosis of involved regional mesorectal lymph nodes (cN1,2) by high-resolution MRI employing pelvic phased-array coils/review of the literature 1999–2009

Authors, year	*n*	Negative PV	Positive PV	False positive findings	Accuracy
Kim et al. 2000 [89]	217	45/61 (74%)	91/156 (58.3%)	63/217 (30.0%)	136/217 (62.7%)
Botterill et al. 2001 [90][a]	61	29/41 (71%)	18/20 (90%)	2/61 (3%)	47/61 (77%)
Gagliardi et al. 2002 [91]	26	10/14 (71%)	8/12 (67%)	4/26 (15%)	18/26 (69%)
Brown et al. 2003 [92][b]	98	50/57 (88%)	33/41 (80%)	8/98 (8%)	83/98 (85%)
Matsuoka et al. 2003 [93]	10	8/8 (100%)	1/2 (50%)	1/10 (10%)	9/10 (90%)
Branagan et al. 2004 [94]	40	14/18 (78%)	13/22 (59%)	9/40 (23%)	27/40 (68%)
Oberholzer et al. 2005 [95]	17	6/9 (67%)	5/8 (63%)	3/17 (18%)	11/17 (65%)
Arii et al. 2006 [30][c]	53	22/27 (81%)	12/26 (46%)	14/53 (26%)	34/53 (64%)
Ferri et al. 2006 [96]	29	8/9 (89%)	9/20 (45%)	11/29 (38%)	17/29 (59%)
Kim et al. 2006 [97][d]	30	17.3/17.7 (98%)	10.7/12.3 (87%)	1.6/30 (5%)	28/30 (93%)
Adeyemo a. Hutchinson 2009 [98]	29	17/19 (89%)	6/10 (60%)	4/29 (14%)	23/29 (79%)
Total	610	226.3/280.7 (80.6%)	206.7/329.3 (62.8%)	122.6/610 (20.1%)	433/610 (71.0%)
95% CI (%)		75.8–85.1	57.7–68.1	17.0–23.3	67.4–74.6
Variation		67–100%	45–90%	3–38%	59–93%

Included only are studies without neoadjuvant therapy or with neoadjuvant therapy in less than 10% of patients. Kim et al. 2007 [25] was not included because patients of this publication are included in Kim et al. 2006 [97].

[a] Neoadjuvant short-course radiotherapy in one out of 61 patients

[b] Neoadjuvant long-course radiotherapy in six out of 98 patients

[c] Lateral pelvic lymph node findings excluded

[d] Average of three observers

PV predictive value

CI, 0.6–3.4; p=0.49). In the study of Ross et al. [41] (212 patients after exclusion of 17 patients with distant metastasis, in 11 patients=5.2% neoadjuvant radiotherapy), the crude LR rates were 16/112=14% for pN0 and 10/100=10% for pN2 (p=0.41).

Other multivariate analyses of the association between pN status and LR in patients treated by primary TME surgery refer to selected subgroups, e.g., stage II patients treated by anterior resection alone [42] or pT1 and 2 patients only [43] or patients treated by intersphincteric resection only [44] and are, for the general question of the indication for neoadjuvant treatment, not relevant. The same applies to the study of Eriksen et al. [45] because the multivariate analysis includes only 1,676 (67.6%) of 2,480 pT3 patients, namely, those with known circumferential resection margin (CRM) status; thus, the results cannot be considered as representative for all pT3 patients. The multivariate study of Bufalari et al. [46] cannot be considered relevant because of the very limited number of patients (n=73).

Recently Fujita et al. [21] reported the treatment results for 817 patients with rectosigmoid, rectal and anal carcinomas, clinical stage II and III. A multivariate analysis performed for pretherapeutic clinical factors only showed the pretherapeutic clinical assessment of regional lymph nodes (including lateral pelvic nodes in rectal carcinomas at and below the peritoneal reflection; cN+) as statistically significant factor affecting LR. This study is questionable because of insufficient technique in carrying out the residual tumour (R) classification (only one block histologically examined), missing data on the circumferential resection margin (CRM) status, missing differentiation between rectosigmoid, rectal and anal canal carcinomas in

Table 3 Pre-operative MRI-diagnosis of more than three involved regional mesorectal lymph nodes (cN2)/review of literature 1999–2009

Authors, year	*n*	Positive predictive value
Kim et al. 2000 [89]	217	26/54 (48%)
Brown et al. 2003 [92]	98	10/10 (100%)
Oberholzer et al. 2005 [95]	17	3/3 (100%)
Kim et al. 2006 [97][a]	30	3.3/4 (83%)
Total	362	42.3/71 (60%)
95% CI		48–71%
Variation		48–100%

MRI studies with endorectal coils were not included. In one study [92], there were six out of 98 patients with neoadjuvant long-course radiotherapy while in all other studies primary surgery. Kim et al. 2007 [25] is not included because patients of this publication are included in Kim et al. 2006 [97]

[a] Average of three observers

the multivariate analysis and the limitation of the multivariate analysis to clinical factors only. Thus, for the problem under discussion this study cannot be considered.

Summarising, it can be stated that there are no reliable data indicating that in patients treated by optimised TME surgery, any involvement of regional lymph is associated with an increased LR rate and requires neoadjuvant or adjuvant radiotherapy.

It has to be pointed out that following neoadjuvant treatment patients with RLNM (ypN+) represent a negative selection of the pretherapeutically lymph node positive patients, namely no (or not sufficiently) responding patients. For these patients, the proportion of pretherapeutically lymph node positive patients (cN+) remains unknown because the clinical assessment of lymph node metastasis is not sufficiently reliable (see previous discussion). The statistically significant correlation between ypN and LR after neoadjuvant radiochemotherapy (Rödel et al. [47]; n=344) and neoadjuvant long-course radiotherapy (Larsen et al. [48]; n=204), respectively, is not relevant for the question of indications for neoadjuvant treatment because from this correlation cannot be concluded to an association between the pretherapeutic lymph node status and the LR rate.

Number of involved regional lymph nodes and the risk of locoregional recurrence

A different prognosis, depending on the number of involved regional lymph nodes (1–3 versus ≥4), has already been described in the mid of the last century [49, 50] and was the reason for the subdivision of lymph node positive patients in the Dukes' stages C1 and C2 and the (p)N1 and (p)N2 categories of the TNM classification. Moran et al. [51] confirmed the higher LR rates in cases of pN2 with data on conventional surgery without neoadjuvant treatment.

In the registry of the Norwegian Rectal Cancer Project [40], the risk of LR in patients treated by primary TME surgery was for pN1 and pN2 nearly identical (see previous discussion). In contrast, in the multivariate analysis of Ross et al. [41], a significant increase of the LR rate depending on the number of involved regional lymph nodes has been reported. However, further details, especially with regard to the cut-off value, are missing.

In a univariate analysis, Cecil et al. [52] demonstrated that following (low) anterior resection according to the principles of TME surgery and 'only minimal' use of neoadjuvant radiotherapy, the crude LR in patients with more than eight involved regional lymph nodes increases significantly in comparison with patients with no lymph node metastasis and 1–8 involved nodes: 3/13(23%) versus 13/457(2.8%; p=0.008).

Because of these inconsistent data, the relationship between number of involved regional lymph nodes and the risk of locoregional recurrence was analysed on the basis of the data of the ERCRC from a time period with use of primary TME surgery (without neoadjuvant therapy) in the vast majority of patients, i.e., January 1, 1986 to January 31, 1995. Inclusion criteria, patients' characteristics, LR rates and the results of uni- and multivariate analysis of risk factors for LR are presented in Table 4. While there is no statistically significant difference between pN0 and pN1, there are highly significant differences (p<0.001) between pN1 and pN2 in the multivariate analysis too. Correspondingly, in view of locoregional recurrence risks, a subdivision between pN0,1 and pN2 is preferable because this subdivision results in the highest difference of the locoregional recurrence rates: 10.3% versus 33.5% (p<0.001).

From the data presented in Table 4, one may conclude that in case of extensive lymph node metastasis (involvement of four or more lymph nodes, N2) the risk of locoregional recurrence is about 30% and thus, a neoadjuvant radio-/radiochemotherapy is indicated. However, it has to be taken into consideration that in such patients, the prognosis is determined in the first place by the high risk of distant metastasis. Moreover, there is the problem of pretherapeutic diagnosis of N2 by imaging. As shown in Table 3, the positive predictive value is at present only 60%. Thus, the pretherapeutic clinical finding cN2 cannot be considered as certain basis for an indication for neoadjuvant radiotherapy. However, in this situation, the patient is to be included in the decision (see further discussion).

Problems of lateral pelvic lymph nodes

The predominant and typical lymphatic drainage of the rectum is directed upwards in the mesorectum to the nodes along the superior rectal and inferior mesenteric arteries. In addition, there is a lateral lymphatic drainage to the lateral lymph node compartment. The latter has been studied predominantly in Japan where an extended lateral pelvic lymph node dissection (pelvic side wall dissection, D3 dissection) has been performed routinely for years. According to the JSCCR [29] the lateral nodes include: (1) middle rectal root nodes (lateral to the pelvic nerve plexus); (2) internal iliac nodes; (3) obturator nodes; (4) median and lateral sacral nodes; (5) external iliac nodes; (6) common iliac nodes and (7) aortic bifurcation nodes. According to the TNM classification [12], involvement of the stations 1–4 is classified as regional lymph node metastasis, of stations 5–7 as distant metastasis.

In the Japanese literature 1998–2008, the frequency of lateral lymph node metastasis in rectal carcinoma is

Table 4 Dependence of locoregional recurrence risk on the regional lymph node status in rectal carcinoma patients treated by primary TME surgery in curative intent. Data from the Erlangen Registry of Colorectal Carcinoma (ERCRC)

Patients group	*n* (%)	Actuarial 5year locoregional recurrence rate (%; 95% CI)	Statistical analysis (*p*)		
			Univariate	Multivariate	
				(a) pN0 versus pN1,2	(b) pN0,1 versus pN0
Total	553	14.6 (11.5–17.7)	–	–	–
Age (years) ≤65	360 (65.1)	15.3 (11.4–19.2)	(0.269)	–	–
>65	193 (34.9)	13.3 (8.2–18.4)			
Gender					
Male	307 (55.5)	15.9 (11.6–20.2)	(0.577)	–	–
Female	246 (44.5)	12.9 (8.8–17.2)			
Tumour <6cm	230 (41.6)	19.6 (14.1–25.1)	0.003	0.025	0.017
site[a] 6–16cm	323 (58.4)	11.2 (7.7–15.7)			
Surgical APE	143 (25.9)	18.9 (12.2–25.6)	0.061	(0.764)	(0.667)
Procedure SS	410 (74.1)	13.1 (9.6–16.6)			
R R0	547 (98.9)	14.5 (11.4–17.6)	(0.453)	–	–
R1	6 (1.1)	33.3 (0–86.6)			
Grading G1,2	472 (85.4)	13.1 (10.0–16.2)	0.009	(0.146)	(0.165)
G3,4	81 (14.6)	24.2 (14.0–34.4)			
pT pT1,2	179 (32.4)	8.7 (4.4–13.0)	0.008	(0.131)	(0.241)
pT3,4[b]	374 (67.3)	17.7 (13.6–21.8)			
pN					
(a) pN0	303 (54.8)	8.4 (5.3–11.5)	<0.001	0.001	–
pN1,2[c]	250 (45.2)	22.9 (17.2–38.6)			
b) pN0,1	438 (79.2)	10.3 (7.4–13.2)	<0.001	–	<0.001
pN2[d]	115 (20.8)	33.5 (23.7–43.3)			

Inclusion criteria

- Solitary invasive rectal carcinoma (invasion at least to submucosa, distal tumour margin 16 cm or less from anal margin, measured with rigid rectosigmoidoscope, not related to familial adenomatous polyposis, ulcerative colitis or Crohn's disease
- No other previous or synchronous malignant tumour except squamous and basal cell carcinoma of the skin and carcinoma in situ of the cervix uteri
- Primary (low) anterior resection or abdominoperineal excision according to the principles of TME surgery
- No neoadjuvant radio(chemo)therapy (2 pat. with neoadjuvant radiotherapy and 11 patients with neoadjuvant radiochemotherapy not included)
- Surgery January 1, 1986 to December 31, 1995
- Surgery in curative intent: no remaining macroscopic tumour (R0,1)
- No distant metastasis (M0)
- No postoperative letality (26 pat. not included)
- Tumour status known (9 pat. not included)

Follow-up time: median 44 months (range 1–270 months). Postoperative adjuvant therapy: total 42 (7.6%), radiotherapy 11 (2.0%), chemotherapy 3 (0.5%), radiochemotherapy 28 (5.1%). Methods: log-rank test to compare the rates of locoregional recurrences, Cox regression analysis to identify independent risk factors for locoregional recurrence

[a] Distance between distal tumour margin and anal margin/linear anocutanea

[b] A 5-year locoregional recurrence rates for pT1 (n=41) 2.5(0–7.4)%; for pT2 (n=138) 10.6 (5.3–15.9)%; for pT3 (n=340) 16.1 (12.0–20.2)% and for pT4 (n=34) 35.7 (17.3–54.1)%. Differences—pT1 versus pT2, p=0.057; pT2 versus pT3, p=0.166 and pT3 versus pT4, p=0.021

[c] Significant difference of locoregional recurrence rates between pN1 (n=135; 14.8 [8.6–21.0]%) and pN2 (n=115; 33.5 [23.7–43.3]%), univariate p<0.001 and multivariate p<0.001

[d] No significant difference of locoregional recurrence rates between pN0 (n=303; 8.4 [5.3–11.5]%) and pN1 (n=135) 14.8 [8.6–21.0]%), univariate p=0.055 and multivariate p=0.166

APE abdominoperineal excision, *SS* sphincter-saving surgery: (low)anterior resection, *R* residual tumour classification

reported as about 10% (Mori et al. [53]: 40/906=4.4%; Takahashi et al. [54]: 57/632=9.0%; Koda et al. [55]: 35/265=13.2% and Sugihara et al. [31]: 129/930=13.8%, pooled value 261/2733=9.5%, 95% CI 8.4–10.7%). Not included in these figures are cases with immunohistochemical findings of tumour cells only [56–58] because the prognostic relevance of such findings is not proven.

The most important risk factors for lateral node metastases are the tumour site (tumours below the peritoneal reflection, especially tumours with a distal margin ≤4 cm [59] or ≤6.5 cm from anal margin [54] and involvement of mesorectal nodes [31, 54, 60]. Other factors are direct involvement of the circumferential resection margin by tumour [58, 61], G3,4 [59], cT3,4/pT2-4, tumour diameter ≥4 cm and female gender [31].

For rectal carcinomas ≤8 cm from the anal margin, a score for the estimation of the risk of lateral lymph node metastasis has been published by Ueno et al. [59]. Three risk factors are considered: distal margin of tumour 4 cm or less from the anal margin, histological type other than adenocarcinoma G1 or 2 and involvement of mesorectal lymph nodes. The frequencies of lateral lymph node metastasis are 3% (1/34) for zero, 8% (10/120) for one, 33% (24/73) for two and 60% (6/10) for three risk factors, respectively.

In patients with cT3,4 carcinomas below the peritoneal reflection, since many years in Japan, an extended lateral pelvic lymph node dissection has been performed; since the early 1990s, with pelvic autonomic nerve preservation [53, 62–66].

This Japanese strategy found no acceptance in western countries because

- in comparison with TME surgery, the benefit of additional extended lateral pelvic lymph node dissection for survival could not be proven;
- increased long-term urinary and sexual dysfunction;
- longer operation time and
- increased blood loss [5, 67–71].

Today, in Europe, for low cT3,4 carcinomas neoadjuvant radio-/radiochemotherapy generally is used [9, 72–77]. This is increasingly accepted as an alternative to extended lateral pelvic node dissection in Japan too [21, 55, 59, 78–80].

Implications for the indication to neoadjuvant therapy

For a long time, regional lymph node metastases have been considered as independent factor not only for distant metastases, but also for LR. This has changed in the era of TME surgery. Today, in case of careful and quality-assured TME for middle and lower rectal carcinoma and PME for upper rectal carcinoma, an increased risk for LR cannot be assumed for each patient with regional lymph node metastasis.

Frequently, all patients with clinically positive regional lymph nodes are treated with neoadjuvant radio-/radiochemotherapy as proposed by many actual guidelines. In the USA, it has been recommended to treat T1,2 tumours with clinically diagnosed regional lymph node metastasis by primary surgery [81]. This has been accepted in the last actualisation of the German guidelines [76] too.

Today, increasingly, the indication for neoadjuvant treatment is based on MRI. In this case, the regional lymph node status is usually not considered [45, 72, 75, 77, 82–84].

Recent data, limited so far (Table 4), show that involvement of four or more regional lymph nodes (N2) is an independent risk factor for LR in TME surgery too. Thus, an indication for neoadjuvant radiotherapy may be concluded. This is in agreement with the assessment of N2 as a poor prognostic factor and the use of neoadjuvant chemoradiation for such patients [8, 23, 73, 74, 85]. Future clinical trials should be based on a more differentiated indication of neoadjuvant treatment in stage III diseases with detailed documentation of lymph node findings in the imaging diagnosis.

However, there is the problem that with today's available imaging methods, the involvement of four or more regional lymph nodes can preoperatively be diagnosed only with 60% certainty (Table 3). In this case, neoadjuvant radiotherapy is in 40% overtreatment associated with considerable late adverse effects. Thus, this situation is a typical example for the requirement to discuss risks and benefits with the patient [86, 87]. A differentiated shared discussion in the sense of an informed consent should take place in any such case.

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