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Lymphovascular invasion is a dominant risk factor for lymph node metastasis in T2 rectal cancer

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ABSTRACT

Background and study aims Surgical resection is standard treatment of T2 rectal cancer due to risk of concomitant lymph node metastases (LNM). Local resection could potentially be an alternative to surgical treatment in a subgroup of patients with low risk of LNM. The aim of this study was to identify clinical and histopathological risk factors of LNM in T2 rectal cancer.

Patients and methods This was a retrospective registry-based population study on prospectively collected data on all patients with T2 rectal cancer undergoing surgical resection in Sweden between 2009 and 2021. Potential risk factors of LNM, including age, gender, resection margin, lymphovascular invasion (LVI), histologic grade, mucinous cancer, and perineural invasion (PNI) were analyzed using univariate and multivariate logistic regression.

Results Of 1607 patients, 343 (21%) with T2 rectal cancer had LNM. LVI (odds ratio [OR] = 4.21, $P < 0.001$) and age < 60 years (OR = 1.80, $P < 0.001$) were significant and independent risk factors. However, PNI (OR = 1.50, $P = 0.15$), mucinous cancer (OR = 1.14, $P = 0.60$), histologic grade (OR = 1.47, $P = 0.07$) and non-radical resection margin (OR = 1.64, $P = 0.38$) were not significant risk factors for LNM in multivariate analyses. The incidence of LNM was 15% in the absence of any risk factor.

Conclusions This was a large study on LNM in T2 rectal cancer which showed that LVI is the dominant risk factor. Moreover, low age constituted an independent risk factor, whereas gender, resection margin, PNI, histologic grade, and mucinous cancer were not independent risk factors of LNM. Thus, these findings may provide a useful basis for management of patients after local resection of early rectal cancer.

Introduction

Organ-preserving strategies are gaining support in treatment of early colorectal cancer [1, 2]. It is now well-established that endoscopic methods of local resection, including flexible endoscopic resection and transanal endoscopic microsurgery, have a curative role in management of T1 colorectal cancer with favorable pathologic characteristics (low-risk T1) [3, 4]. In contrast, surgical resection has remained the treatment of choice for T2 colorectal cancer due to feared risk of lymph node metastasis (LNM). Overall, the rate of LNM in T2 rectal cancer is only 19% to 27%, which means that the great majority of patients have disease that is potentially amenable to local resection and they could avoid unnecessary surgery [5, 6, 7, 8, 9, 10, 11]. It is important to note that surgical resection of rectal cancer is associated with complications in 1 of 4 patients and a mortality rate

of 2% independent of T-stage [12]. Indeed, development of new methods, such as endoscopic full-thickness resection (EFTR) [13] and endoscopic intermuscular dissection [14], makes local resection of T2 rectal cancer feasible. It is well-known that pretherapeutic staging of lymph node status in early rectal cancer is notoriously difficult. Unfortunately, numerous studies have demonstrated that magnetic resonance imaging, computed tomography, and anorectal ultrasound have limited value in detecting pathologic lymph nodes in patients with early colorectal cancer [15, 16]. Thus, the major challenge is to identify the group of patients with T2 rectal cancer without or with low risk of having concomitant metastatic lymph nodes.

It is well-documented that certain histopathological features, such as lymphovascular invasion (LVI) and tumor budding, are important for risk of LNM in T1 rectal cancer [4]. However, there are limited data in the literature on histopathological risk factors for LNM in T2 rectal cancer. Studies that have addressed this topic in T2 rectal cancer show variable results and indicate that LVI [5], tumor budding [17, 18], high-grade tumor [19] and depth of invasion into muscularis propria [9, 20] can be important indicators of concomitant LNM. One reason for the variable results could be related to the fact that the number of patients in these studies is low, ranging between 72 and 346 [5, 8, 9, 17, 18, 19, 20]. Clinical factors also may contribute to increased risk of LNM in T2 rectal cancer. For example, a recent study reported that being younger is associated with increased risk of LNM in T1 colorectal cancer [3].

Based on these considerations, the aim of this study was to determine histopathological and clinical factors related to LNM in T2 rectal cancer in order to provide valid support for management of patients with early rectal cancer.

Patients and methods

Patients

All data were derived from the Swedish Colorectal Cancer Registry (SCRCR), a national quality registry containing prospectively collected data on rectal cancers from 1995 and colon cancers from 2007. SCRCR includes patient data, tumor characteristics, surgical treatment, complications, histopathology, oncologic therapy and follow-up data. During the study period, the coverage compared to the compulsory Swedish Cancer Registry was 99% for rectal cancer and the validity was reported as high [21].

Inclusion and exclusion criteria

Data on all patients treated with surgical resection for nonsynchronous pathology-verified T2 rectal cancer between February 2009 and May 2021 were included in the study. Exclusions criteria were metastatic disease, neoadjuvant treatment, local resection, unknown lymph node status, and missing data. Thus, all patients receiving neoadjuvant treatment were excluded because that treatment likely affects the stage of tumors and reduces LNM.

Clinicopathological variables

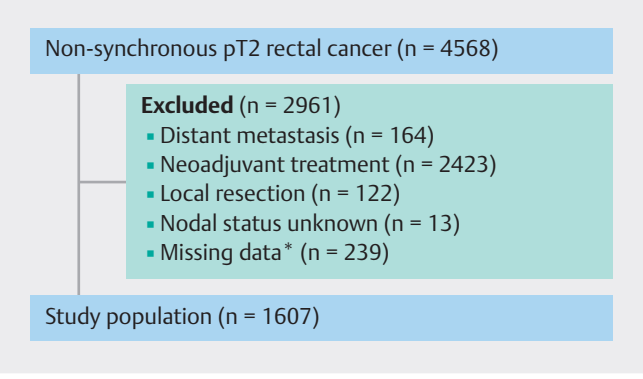
Age, gender, histologic grade, LVI, perineural invasion (PNI), mucinous cancer, and resection margin (R0/R1/Rx) were analyzed as potential risk factors of LNM. LVI was determined by morphological appearance and immunostaining was not used in most cases. Tumor budding and size were not included in SCRCR during the study period. Histologic differentiation was classified according to World Health Organization guidelines and the Vienna classification, which uses the least differentiated component grade for differentiation (low-grade cancer [well and moderate differentiation] and high-grade [poor differentiation] cancer) [22]. Resection margins refers to both lateral and vertical borders. The study population was further analyzed regarding low- and high-risk tumors based on risk factors identified in the multivariate analyses.

Statistical analysis and missing data

Statistical analyses were performed with SPSS (IBM) version 28. Univariate and multivariate logistic regression was used to investigate the relationship between potential risk factors and LNM. The Hosmer-Lemeshow test was performed for goodness of fit. Proportion of LNM was given as percentage and continuous variables were reported with median and range. X^2-test was used when comparing low- and high-risk groups. To account for missing data, a multiple imputation model using Mersenne twister number generator with 20 imputations was performed. For sensitivity reasons, the imputed data were compared with complete case analyses. We used 95% confidence intervals and $P < 0.05$ was considered significant.

Ethics

This study was carried out in accordance with the ethical principles of the Declaration of Helsinki. Approval by the Regional Ethical Review Board, Lund University (2023–01159–01) was granted prior to the study. Data retrieved from SCRCR were coded and patient anonymity was guaranteed.



▶ **Fig. 1** Overview of study population. *Missing data on metastatic disease, neoadjuvant treatment and type of operation.

▶ **Table 1** LNM in T2 rectal cancer.

	Total (%)		LNM (% of total)	
Gender		1607	(100.0%)	343
▪ Male	902	(56.1%)	201	(22.3%)
▪ Female	705	(43.9%)	142	(20.1%)
Age (y)				
▪ < 60	233	(14.5%)	67	(28.8%)
▪ ≥ 60	1374	(85.5%)	276	(20.1%)
Histologic grade				
▪ Low-grade	1455	(90.5%)	293	(20.1%)
▪ High-grade	139	(8.6%)	46	(33.1%)
▪ Missing	13	(0.8%)	4	(30.8%)
LVI				
▪ Absent	1320	(82.1%)	219	(16.6%)
▪ Present	245	(15.2%)	115	(46.9%)
▪ Missing	42	(2.6%)	9	(21.4%)
PNI				
▪ Absent	1468	(91.4%)	303	(20.6%)
▪ Present	66	(4.1%)	28	(42.2%)
▪ Missing	73	(4.5%)	12	(16.4%)
Mucinous cancer				
▪ Absent	1445	(89.9%)	307	(21.2%)
▪ Present	108	(6.7%)	29	(26.9%)
▪ Missing	54	(3.4%)	7	(13.0%)
Resection margin				
▪ R0	1578	(98.2%)	336	(21.3%)
▪ R1	12	(0.7%)	4	(33.3%)
▪ Rx	5	(0.3%)	1	(20.0%)
▪ Missing	12	(0.7%)	2	(16.7%)

LNM, lymph node metastasis; LVI, lymphovascular invasion; PNI, perineural invasion.

Results

A total of 4568 patients with nonsynchronous T2 rectal cancer were identified in the SCRCR. A total of 2961 patients were excluded due to distant metastases (n = 164), neoadjuvant treatment (n = 2423), endoscopic resection (n = 22), unknown lymph node status (n = 13), transanal endoscopic microsurgery (n = 82), local resection (n = 18) and missing data on metastatic disease, neoadjuvant treatment and type of operation (n = 239) (▶ **Fig. 1**). The final study population consisted of 1607 patients with T2 rectal cancers treated with surgical resection (▶ **Fig. 1**), including 902 males (56.1%) and 705 females (43.9%) with a median age of 72 years (range 25–96).

Risk factors for LNM

LNM was identified in 343 patients (21.3%) with T2 rectal cancer. The median number of analyzed lymph nodes was 22. Incidence of LNM was 46.9% (115/245) when LVI was present and 16.6% when LVI was absent (▶ **Table 1**). Incidence of LNM was about the same, regardless of whether LVI was the only risk factor present (43.8%, 60/137) (▶ **Table 2**) or if LVI was combined with additional risk factors (▶ **Table 1**). The proportion of LNM was 40.0% (8/20) when PNI was the only risk factor (▶ **Table 2**) and 42.2% (28/66) in cases in which PNI was combined with other risk factors (▶ **Table 1**). High-grade cancer and mucinous cancer were associated with 33.1% (46/139) and 26.9% (29/108) incidence of LNM, respectively (▶ **Table 1**). In the absence

▶ **Table 2** Proportion of LNM with only one or no significant risk factors present.

	Total (n)	LNM (%)
LVI*	60/137	43.8%
PNI	8/20	40.0%
Mucinous cancer	8/38	21.1%
High-grade tumor	10/51	19.6%
Age at diagnosis (y) < 60*	33/162	20.3%
Resection margin (R1/Rx)	1/8	12.5%
No significant risk factors	171/1122	15.2%

*Significant risk factor.
LNM, lymph node metastasis; LVI, lymphovascular invasion; PNI, perineural invasion.

of other risk factors, LNM incidence dropped to 19.6% (10/51) for high-grade cancer and 21.1% (8/38) for mucinous cancer (▶ **Table 2**). Incidence of LNM was 20.1% (276/1374) and 28.8% (67/233) in patients aged ≥ age 60 years < age 60 years, respectively (▶ **Table 1**). LNM proportion was 15% (165/1083) in the absence of any risk factor (▶ **Table 2**).

Univariate and multivariate analysis

High-grade cancer, LVI, PNI, and age < 60 years were identified as statistically significant risk factors in univariate analysis (▶ **Table 3**). In multivariate analysis, LVI (odds ratio [OR] 4.21, $P < 0.001$) and age < 60 years (OR 1.80, $P < 0.001$) were identified as independent risk factors for LNM, whereas high-grade cancer (OR 1.47, $P = 0.07$) and PNI (OR 1.50, $P = 0.15$) were not significant risk factors (▶ **Table 3**). Moreover, incidence of LNM was 15.2% (171/1122) in patients aged ≥ 60 years and 24.2% (48/198) in patients aged < 60 years, in the absence of LVI.

▶ **Table 3** LNM according to potential risk factors.

	Univariate analysis			Multivariate analysis		
	OR	95 % CI	*P* value	OR	95 % CI	*P* value
Gender						
▪ Male	1.00	Ref		1.00	Ref	
▪ Female	0.88	0.69–1.12	0.30	0.83	0.65–1.07	0.16
Age at diagnosis (y)						
▪ ≥ 60	1.00	Ref		1.00	Ref	
▪ < 60	1.61	1.17–2.20	< 0.03	1.80	1.29–2.50	< 0.001
Histologic grade						
▪ Low-grade	1.00	Ref		1.00	Ref	
▪ High-grade	1.96	1.35–2.85	< 0.001	1.47	0.92–2.18	0.07
LVI						
▪ Absent	1.00	Ref		1.00	Ref	
▪ Present	4.48	3.34–5.92	< 0.001	4.21	3.03–5.56	< 0.001
PNI						
▪ Absent	1.00	Ref		1.00	Ref	
▪ Present	2.77	1.68- 4.55	< 0.001	1.50	0.93–2.96	0.15
Mucinous cancer						
▪ Absent	1.00	Ref		1.00	Ref	
▪ Present	1.36	0.87–2.12	0.18	1.14	0.67–1.81	0.60
Resection margin						
▪ R0	1.00	Ref		1.00	Ref	
▪ R1/Rx	1.56	0.55–4.42	0.40	1.64	0.54–4.93	0.38

LNM, lymph node metastasis; OR, odds ratio; CI, confidence interval; LVI, lymphovascular invasion; PNI, perineural invasion.

▶ **Table 4** Low- and high-risk groups according to outcome in multivariate analyses.

	Total (n)	LNM (n)	*P* value
Low-risk*	1122	171 (15%)	< 0.001
High-risk†	32	19 (59%)	

*Low-risk: Perineural invasion, gender, resection margin (R1/Rx). histologic grade, mucinous subtype or age at diagnosis ≥ 60 years.
†High-risk: LVI present and age at diagnosis < 60 years.
LNM, lymph node metastasis; LVI, lymphovascular invasion.

Low- and high-risk groups

We identified a low- and high-risk group based on results of the multivariate analysis. The low-risk group compromised patients aged ≥ 60 years without LVI, 15.2% of whom (171/1122) had LNM (▶ **Table 4**). The high-risk group consisted of patients with LVI who were aged < 60 years and LNM was present in 59.4% of this group (19/32) (▶ **Table 4**).

Missing data

All 1607 included cases had information on LNM. Multiple imputation was performed to account for missing data about risk factors (▶ **Table 1**). In total, 1475 cases (91.8%) had complete data for all variables. Sensitivity analyses (complete case analyses) were made and showed no difference in significance between the nonimputed (n = 1475) and imputed (n = 1607) data when comparing results of univariate and multivariate analyses.

Discussion

Surgical resection remains the cornerstone of management of patients with T2 rectal cancer due to risk of concomitant LNM [4]. The main reason for studying clinicopathological risk factors for LNM in T2 rectal cancer is to identify cases with low risk of LNM that are suitable for local resection. This is especially important knowing that the number of early rectal cancers will increase as a result of implementation of screening programs in the future [23].

Risk of LNM is a major obstacle for using methods of local resection in patients with T2 rectal cancers. This study demonstrates that the overall incidence of LNM in T2 rectal cancer is 21%, which is within the lower range of previous studies (19%-27%) [5, 6, 8, 24, 25]. This means that nearly 80% of these patients undergo potentially unnecessary surgery. It is well-known that morbidity and mortality is significant in patients undergoing rectal cancer surgery and ranges between 30% and 50% and 2% and 12%, respectively [12, 26, 27]. Moreover, almost 40% of these patients suffer from sexual, urinary, or bowel dysfunction after rectal cancer surgery [28]. In addition to transanal endoscopic microsurgery, new developments in endoscopic resection methods, such as EFTR [13] and endoscopic intermuscular dissection [14], allow R0 resection of T2 rectal cancer. Thus, identification of T2 rectal cancer with low risk of LNM suitable for local resection is challenging but also of great benefit for individual patients. Current imaging methods are not reliable for staging LNM in patients with rectal cancer [29, 30]. For example, a recent study showed that magnetic resonance imaging (MR) erroneously staged 74% of cases with LNM as node negative, and inversely, the majority of cases staged with MRI as having LNM, were in fact, node negative [15]. Thus, considering the difficulties in staging lymph node status in early rectal cancer, postresection analysis of histological risk factors could be a useful way to select patients for conservative management or salvage surgery after local resection. In this context, it is important to note that salvage surgery does not compromise oncologic outcome compared with primary surgery in patients with early rectal cancer [31, 32, 33].

Our study identified LVI as an independent and dominant risk factor of LNM in T2 rectal cancer. This finding is line with other studies reporting LVI as an independent risk factor for LNM in T2 rectal cancer. However, one study did not find LVI to be an independent risk factor for LNM in T2 rectal cancer [5, 9, 17, 25, 34]. This discrepancy may be related to the relatively few patients (n = 72) in the previous study [17].

The present study contained 1607 patients and represents the largest study on risk factors for LNM in T2 rectal cancer in the literature. Notably, our data suggest that the risk of LNM was 47% when LVI was present and only 17% when LVI was absent, independent of other risk factors. Thus, LVI is a significant risk factor to consider in the process of deciding whether to recommend conservative management or salvage surgery after local resection of T2 rectal cancer. This notion is also supported by a previous report showing that the rate of LNM in T2 rectal cancer in the absence of LVI is only 9% [6]. In general, PNI is considered to be an indicator of tumor aggressiveness, although its role in predicting LNM in early colorectal cancer is elusive [5, 8, 35]. Herein, PNI was found to be significant in univariate analysis but not in multivariate analysis. This could be related to the fact that incidence of PNI was only 4% in the present study, increasing the risk of type 2 error. The literature is complex and contradictory on the role of PNI as risk factor for LNM in T2 rectal cancer. For example, one study showed that PNI is not an independent risk factor [8] whereas another investigation reported that PNI is an independent risk factor for LNM in T2 rectal cancer [35]. Nonetheless, considering that the incidence of LNM was 40% when PNI was the only risk factor present, it cannot be excluded that PNI could also be an important risk factor of LNM in T2 rectal cancer. Histologic grade, resection margin, mucinous cancer, and gender were not significant risk factors according to the multivariate analyses in our study. Interestingly, we observed that younger age (< 60 years) was an independent risk factor for LNM in T2 rectal cancer, suggesting that tumors that develop early in life are more aggressive than those that develop later in life. This notion is supported by two previous studies reporting that low age is an independent risk factor for LNM in T2 rectal cancer [9, 36]. It is interesting to note that the risk of LNM was nearly 60% in patients younger than age 60 years with LVI. Traditionally, depth of invasion has been considered to be a risk factor for LNM in T1 colorectal cancer, although more recent studies and a meta-analysis have demonstrated that depth of submucosal invasion is not an independent risk factor for LNM in T1 colorectal cancer [3, 37, 38]. A

few studies have examined the impact of depth of invasion into muscularis propria (circular versus longitudinal muscle layer) on LNM in T2 rectal cancer and found that LNM risk is low in tumors with invasion limited to the circular layer and high in cases with invasion into the longitudinal muscle of the muscularis propria [9, 20, 34]. In fact, invasion limited to the circular muscle was associated with a LNM risk of 8% to 15%, which is similar to T1 cancers [9, 34]. In contrast, LNM risk in tumors invading the longitudinal muscle was as high as 22% to 28%, which is close to the risk observed in T3 cancers [9, 34]. Thus, T2 rectal cancers with superficial invasion limited to the circular muscle layers appear to be feasible to manage with local resection in selected cases. Considering this, it is tempting to suggest that endoscopic intermuscular dissection, in which tumors are resected together with the circular muscle layer, may be a suitable method to use in further studies of local resection of T2 rectal cancer [14].

One strength of this study was the large population-based sample size of prospectively collected data. In fact, to our knowledge, this was the largest study of clinicopathological risk factors for LNM in T2 rectal cancer in the literature, which helps to make the multivariate analysis more robust herein. Nonetheless, there are also some limitations to our study. First, the study design was retrospective, which could introduce some selection bias. In addition, tumor budding was not included in this registry and, therefore, it could not be analyzed in the present study. Another limitation is that lymphatic and vascular invasion were not evaluated separately.

Conclusions

Taken together, these findings demonstrate that only 1 of 5 patients with T2 rectal cancer has LNM, indicating that the great majority would potentially benefit from local resection. In fact, this is the largest investigation of clinicopathological risk factors for LNM in T2 rectal cancer showing that LVI and younger age are significant risk factors for tumor spread to lymph nodes. In particular, it was found that LVI is a dominant risk factor that should be considered in the decision process about salvage surgery after local resection of T2 rectal cancer.

Conflict of Interest

The authors declare that they have no conflict of interest.

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