Original Article

Predictors of Lymph Node Metastasis and Survival Outcomes in T1 Colorectal Cancer – A Retrospective Cohort Study

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Key Words
T1 colorectal cancer;
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Background. Colorectal cancer (CRC) is the third most prevalent and second deadliest malignancy worldwide. Lymph node metastasis (LNM) in submucosal invasive (T1) CRC, affecting 6-12% of cases, significantly worsens prognosis. Traditionally, LNM detection occurs post-operatively, influencing the choice between endoscopic resection (ER) and additional surgical resection (ASR). This study aims to identify LNM risk factors in T1 CRC and evaluate the impact of different treatment strategies on survival outcomes.

Methods. We conducted a retrospective review of 392 patients with T1 CRC treated at E-Da Hospital from January 2007 to December 2019. Patients underwent either ER alone, ER followed by ASR, or primary surgical resection. Data were collected on clinical and pathological characteristics, including tumor size, histological grade, and invasion status. Survival outcomes were analyzed using Kaplan-Meier curves and Cox regression for 5-year overall survival (OS) and disease-free survival (DFS).

Results. Our study found poor histological differentiation, positive resection margin and lymphovascular invasion as significant predictors of LNM. Survival analysis revealed no significant differences in 5-year OS and DSS among the three treatment groups: ER only (5-year OS: 88.4%), ER + ASR (93.8%), and primary surgery (89.4%). Similarly, disease-free survival rates were comparable across treatment modalities.

Conclusion. Poor histological differentiation, positive resection margin and lymphovascular invasion are key factors associated with LNM in T1 CRC. Treatment strategies, ranging from less to more invasive, do not significantly influence 5-year survival outcomes, suggesting that ER could be a viable option for selected patients. These findings highlight the need for personalized treatment plans based on individual LNM risk, pending further research and validation.

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Colorectal cancer (CRC) ranks as the third most prevalent cancer globally and stands as the second primary cause of mortality associated with malignancies.[1] The presence of lymph node metastasis (LNM) is associated with worse prognosis and is a critical factor in determining colon cancer stage.[2] The incidence of LNM in submucosal invasive (T1) CRC is approximately 6-12%.[3-6] The detection of lymph

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node metastasis has a major impact on treatment options and predicted outcomes in colorectal cancer patients.[7]

Historically, the presence of LNM in T1 CRC patients has been primarily determined post-operatively, leading to a potential divergence in treatment pathways. Endoscopic resection (ER) is regarded as a favorable treatment alternative for T1 CRC due to its less invasive nature compared to surgical resection.[8] Both the National Comprehensive Cancer Network and the Japanese guidelines endorse endoscopic resection (ER) as the recommended treatment for clinical stage T1 early CRC.[9,10] ER offers the benefits of organ preservation and functional improvement compared to radical surgery, and it is particularly advantageous for patients with suboptimal physical health.[11] However, previous studies have identified several high-risk factors associated with an increased incidence of LNM in T1 CRC, including poor differentiation, lymphatic invasion, tumor budding, and submucosal invasion depth exceeding 1000 μm.[12] Consequently, when these factors are detected following ER, radical surgery is generally recommended to ensure optimal patient outcomes. However, colorectal surgery is associated with an overall mortality rate of 1-5% and a morbidity rate of about 30%. Also, surgical resection may be complicated by adverse outcomes including frequent bowel movements, sexual dysfunction, and adhesions.[13,14] Therefore, the decision to perform ER or to proceed directly to surgical resection remains challenging.

The ambiguity surrounding the ideal treatment strategy is further compounded by the limited understanding of the risk factors and patient characteristics predisposing to LNM in T1 CRC. Many studies have focused on the unfavorable histological features of LNM.[6,15-17] Several retrospective studies have compared the long-term oncological outcomes of patients who underwent ER followed by surgery versus those who had surgery alone for T1 colorectal cancer.[5,18] These studies consistently found no significant differences in recurrence rates or long-term survival between the two groups, even after adjusting for potential confounding factors using propensity score matching or other statistical methods.[19-21] In our study, we also sought to investigate whether ER prior to surgery influences the outcomes of patients with T1 colorectal cancer, aiming to corroborate the findings of previous studies. A comprehensive investigation into these factors is crucial, not just for optimal treatment selection but also for enhancing our understanding of the disease's biology and progression.

Our objective was to evaluate the risk factors for lymph node metastasis in T1 colon cancer patients. We also compare survival outcomes, including 5-year overall (OS) and 5-year disease-free survival (DFS), between different treatment paradigms – endoscopic resection alone, ER with additional surgical resection and primary radical surgery.

Methods

We retrospectively reviewed the electronic medical records of all patients who were diagnosed with T1 CRC after endoscopic resection only, endoscopic resection followed by additional surgical resection and primary surgical resection in E-Da Hospital from January 2007 to December 2019. We retrieved information on age, sex, date of diagnosis, tumor stage, and treatment. The pathological reports contained data on tumor size, histological grade, resection margin, and lymphovascular invasion status. Tumor budding status and depth of submucosal invasion were not included in the pathological reports. Patients were excluded if they were lost to follow-up, or the pathology reports did not contain sufficient data or with stage IV disease. The patients were classified into three categories according to the treatment modalities (Fig. 1).

T1 CRC was defined according to the American Joint Committee on Cancer staging manual (8th edition[1]), as CRC invading the submucosa but not the muscularis propria. Location of the CRC was defined as from ascending colon to rectum. Therapeutic decision for lesions considered to be T1 CRC was done based on morphology, size, and location of the lesion. Endoscopic treatments, including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD), were applied based on the lesion characteristics and preference of the physician. Laparoscopic

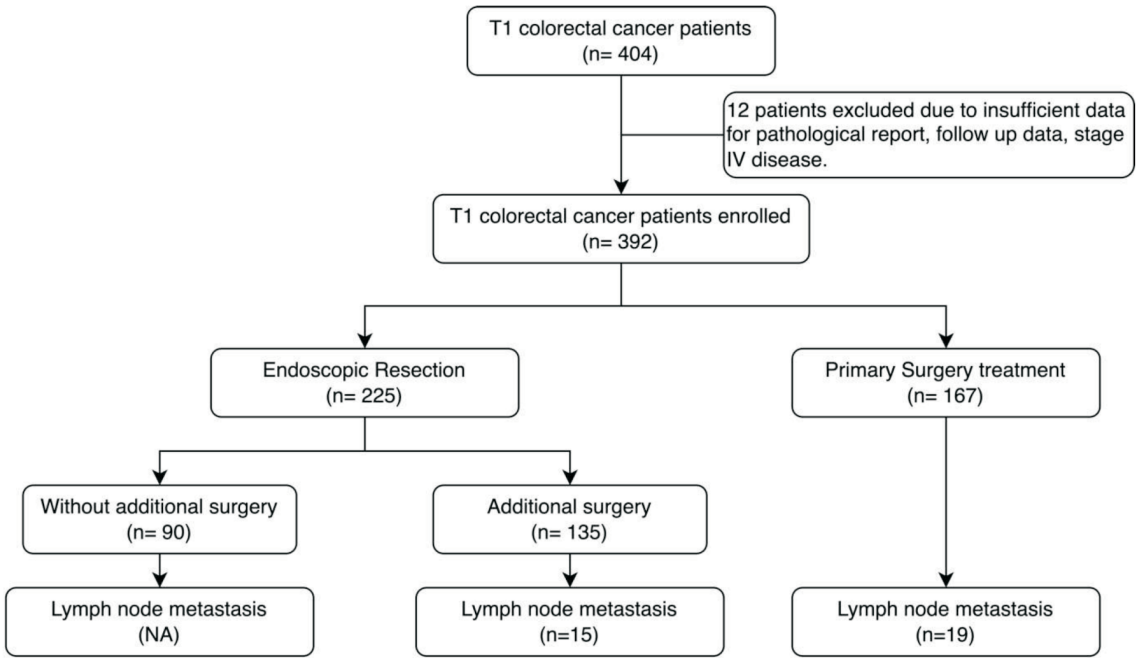

Fig. 1. Flow chart of patients' selection. NA, not applicable.

and open surgeries were performed by experienced colorectal surgeons. Primary surgery was done when the lesion was revealed as endoscopically unresectable by its size, surface pit pattern, or vascular pattern. The histological grade was categorized as well, moderately, or poorly differentiated. For the ER only group, resection margin, lymphovascular invasion were assessed based on the endoscopically resected specimen. In the primary surgery group, these factors were evaluated based on the surgically resected specimen. For the ER + ASR group, resection margin status was determined based on the endoscopically resected specimen, while lymphovascular invasion were assessed based on the surgically resected specimen. LNM was defined when at least one LN in the surgical specimen was positive.

We analyzed the baseline characteristics of all patients by treatment method. The primary outcomes were clinical and pathological characteristics associated with lymph node metastasis. The patients were followed up according to the institutional protocol. Follow-up visits were scheduled every 3 months for the first 2 years, every 6 months for the next 3 years, and annually thereafter. Overall survival (OS) was defined as the time from the date of radical surgery (for the ER + ASR and primary surgery groups) or the date of endoscopic resection (for the ER only group) to the date of death from any cause or the last follow-up. Disease-free survival (DFS) was defined as the time from the date of radical surgery (for the ER + ASR and primary surgery groups) or the date of endoscopic resection (for the ER only group) to the date of recurrence, death from any cause, or the last follow-up. The secondary outcomes were 5-year OS and 5-year DFS, between different treatment paradigms – endoscopic resection with or without subsequent radical surgery versus primary radical surgery.

Quantitative variables are presented as means ± standard deviations (SDs) and qualitative variables as frequencies with percentages. We compared baseline characteristics using one-way ANOVA and the Pearson chi-squared test for continuous and categorical variables, respectively. Kaplan-Meier curves were drawn to compare recurrence-free survival and OS among treatment methods, and statistical significance was calculated using the log-rank test. Cox's regression analysis was performed to identify variables independently related to LNM. Parameters with p values < 0.05 in univariate analysis were included in multivariate analysis. Hazard ratios (HRs) with 95%

confidence intervals (CIs) were calculated. Logistic regression (univariate and multivariate) analyses were performed to identify LNM-related factors in patients who underwent endoscopic resection followed by additional surgical resection and primary surgery. Parameters with p values < 0.05 in univariate analysis were again included in multivariate analysis. Odds ratios (ORs) with 95% CIs were derived. SPSS software for Windows was used for all analyses (ver. 18.0; SPSS Inc. Chicago, IL, USA). A p value < 0.05 was considered statistically significant.

Results

Baseline characteristics of all patients

A total of 404 T1 CRC cancer patients were identified of which 12 were excluded due to: insufficient data for pathological report (n = 4); follow up data (n = 6), stage IV disease (n = 2) (Fig. 1). The remaining 392 cases of T1 CRCs constitute the study population with a mean age of 63.3 years. The gender distribution showed a predominance of men (61%). In evaluating the follow-up duration, the median duration varied across the groups, with the primary surgery group having the longest median duration of 57.5 months (IQR: 25.25-75.25), followed by the ER + ASR group with 59.0 months (IQR: 11.0-83.0), and the ER only group with 67.0 months (IQR: 29.0-97.0). A Kruskal-Wallis test revealed a statistically significant difference in follow-up durations across the groups ($p \leq 0.001$). The mean tumor size differed among the three treatment groups. Patients in the primary surgery group had the largest mean tumor size at 22.17 mm (SD: 12.7), while those in the ER only and ER + ASR groups had smaller mean tumor sizes of 15.92 mm (SD: 10.6) and 15.64 mm (SD: 10.6), respectively. The histology grade was predominantly well + moderate differentiated across all groups, accounting for 97% of the total cases. Our study also evaluated the resection margins and lymphovascular invasion, where significant differences were observed in the resection margins ($p < 0.001$) and lymphovascular invasion ($p = 0.09$). In terms of location, the majority of tumors were located in the colon (65%), and there was a notable difference in sidedness, with 75% of tumors being on the left side, which was statistically significant ($p = 0.02$) (Table 1). Upon further analysis of the recurrence rates among the three groups (ER only, ER + ASR, and pri-

Table 1. Baseline characteristics of all patients

Variables	Total (N = 392)	ER only (N = 90)	ER + surgery (N = 135)	Primary surgery (N = 167)	*p*-value
Age (years), mean (SD)	63.3 (10.82)	63.7 (10.35)	61.4 (10.36)	65.1 (10.7)	0.01
Gender, *n* (%)					0.82
Men	240 (61%)	53 (58%)	85 (62%)	102 (61%)	
Women	152 (39%)	37 (42%)	50 (38%)	65 (38%)	
Follow up duration (months)					≤ 0.001
Median (IQR)	60.0 (20.0-90.0)	57.5 (25.25-75.25)	59.0 (11.0-83.0)	67.0 (29.0-97.0)	
Tumor size (mm), mean	18.49 (12.0)	15.92 (10.6)	15.64 (10.6)	22.17 (12.7)	0.01
Histology grade (%)					
Well + moderately	383 (97%)	89 (98%)	129 (95%)	165 (98%)	0.12
Poor	9 (3%)	1 (2%)	6 (5%)	2 (2%)	
Resection margin (+)	54 (14%)	11 (12%)	41 (31%)	2 (1.2%)	< 0.001
Lymphovascular invasion (+)	29 (7%)	2 (2%)	11 (8%)	16 (9%)	0.09
Location, *n* (%)					0.08
Colon	256 (65%)	47 (52%)	97 (72%)	112 (67%)	
Rectum	136 (35%)	43 (48%)	38 (28%)	55 (33%)	
Sidedness					0.02
Right side	100 (25%)	10 (11%)	36 (27%)	54 (32%)	
Left side	292 (75%)	80 (89%)	99 (73%)	113 (68%)	
Recurrence	14 (3.6%)	6 (6.6%)	2 (1.4%)	6 (3.6%)	0.12
Lymph node metastasis, *n* (%)	34 (8.7%)	NA	15 (11%)	19 (11%)	0.04

mary surgical resection), we found that while the overall comparison did not yield a statistically significant difference, pairwise comparisons revealed some interesting findings. The *p*-value for the comparison between the ER only group and the ER + ASR group was 0.04, indicating a significant difference in recurrence rates. However, the *p*-values for the comparisons between the ER only group and the primary surgical resection group ($p = 0.26$) and between the ER + ASR group and the primary surgical resection group ($p = 0.25$) did not reach statistical significance. Furthermore, in the ER only group, local recurrence accounted for 50% (3/6) of all recurrence cases, while in patients who underwent surgical treatment, local recurrence accounted for only 12.5% (1/8) of all recurrence cases.

Clinicopathologic characteristics and factors associated with lymph node metastasis

Table 2 presents the clinicopathologic characteristics of patients with (N = 34) and without (N = 268) lymph node metastasis (LNM). While age, tumor location, tumor size, and resection method (ER + ASR or primary surgery) did not show significant differences between the two groups, histology grade ($p < 0.001$), resection margin ($p = 0.01$), lymphovascular invasion ($p < 0.001$), and tumor sidedness ($p = 0.04$) exhibited substantial variance. The well + moderate histology grade was more prevalent in the group without LNM (99%), while positive resection margin, presence of lymphovascular invasion, and left-sided tumors were more common in the LNM group.

In the univariate analysis, poor histology grade, positive resection margin, presence of lymphovascular invasion, and left sidedness were significantly associated with LNM. However, in the multivariate analysis, only poor histology grade (OR 28.62, 95% CI 3.38-214.92, $p = 0.002$), positive resection margin (OR 8.02, 95% CI 1.78-36.10, $p = 0.007$), and presence of lymphovascular invasion (OR 60.28, 95% CI 17.36-209.37, $p < 0.001$) remained significantly associated with LNM, while sidedness lost its significance ($p = 0.18$).

Table 2. Univariate and multivariate analysis for factors associated with lymph node metastasis in patient received surgical treatment for T1 CRC (ER + ASR, primary surgery)

Variables	With LNs metastasis (N = 34)	Without LNs metastasis (N = 268)	Univariate *p*-value	Multivariate	
				OR (95% CI)	*p*-value
Age (years), mean (SD)			0.15		
< 60 years	22 (65%)	139 (52%)			
> 60 years	12 (35%)	129 (48%)			
Gender, *n* (%)			0.46		
Men	23 (68%)	164 (61%)			
Women	11 (32%)	104 (39%)			
Location, *n* (%)			0.93		
Colon	22 (65%)	187 (70%)			
Rectum	12 (35%)	81 (30%)			
Tumor size (mm), mean			0.89		
< 2 cm	15 (44%)	115 (43%)			
> 2 cm	19 (56%)	153 (57%)			
Histology grade (%)			< 0.001	28.62 (3.38-214.92)	0.002
Well + moderately	6 (18%)	265 (99%)			
Poor	28 (82%)	3 (1%)			
Resection margin (+)	11 (32%)	43 (16%)	0.01	8.02 (1.78-36.10)	0.007
Lymphovascular invasion (+)	17 (50%)	10 (3%)	< 0.001	60.28 (17.36-209.37)	< 0.001
Sidedness			0.04		0.18
Right side	5 (20%)	85 (32%)			
Left side	29 (80%)	183 (68%)			
Resection method, *n* (%)			0.94		
ER + ASR	15 (44%)	120 (45%)			
Primary surgery treatment	19 (56%)	148 (55%)			

5-year overall survival and disease-free survival

Fig. 2 illustrates the 5-year overall survival (OS) curves for patients undergoing different treatment strategies, namely ER only and ER + ASR, primary surgery. The 5-year OS was 88.4% for patients treated with ER only, 93.8% for those treated with ER + ASR, and 89.4% for primary surgery. The difference in survival between the three treatment strategies was not statistically significant ($p = 0.09$).

Fig. 3 illustrates the 5-year disease-free survival rates among patients subjected to different treatment modalities: ER only, and ER + ASR, primary surgery. The analysis revealed a 5-year disease-free survival rate of 95.3% for patients in the ER only group, 96.7% for those in the ER + ASR and 94.6% for the primary surgery group. The *p*-value of 0.29 indicates that there is no statistically significant difference in disease-free survival between the two treatment strategies over a five-year period.

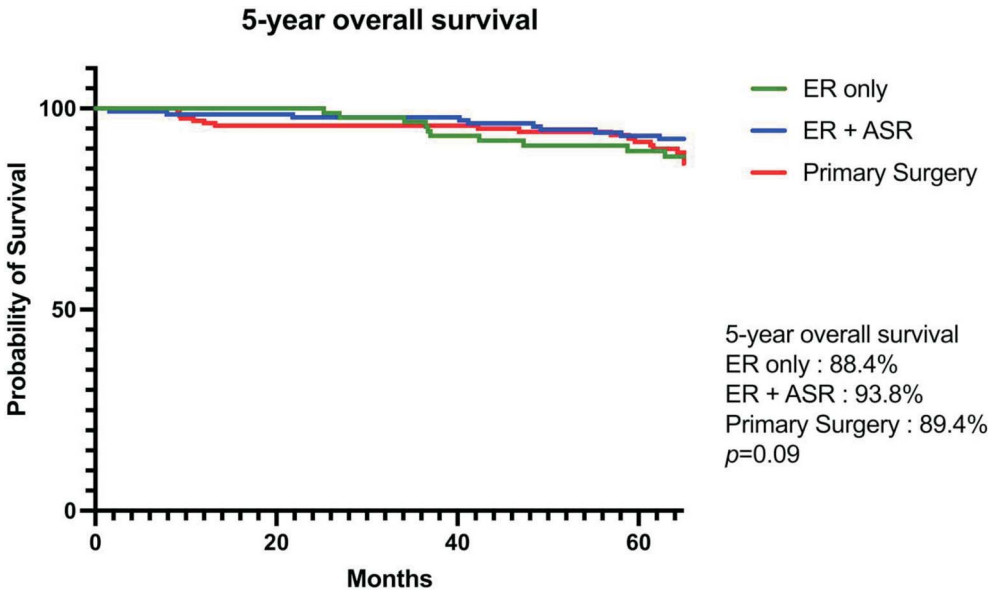

Fig. 2. 5-year overall survival.

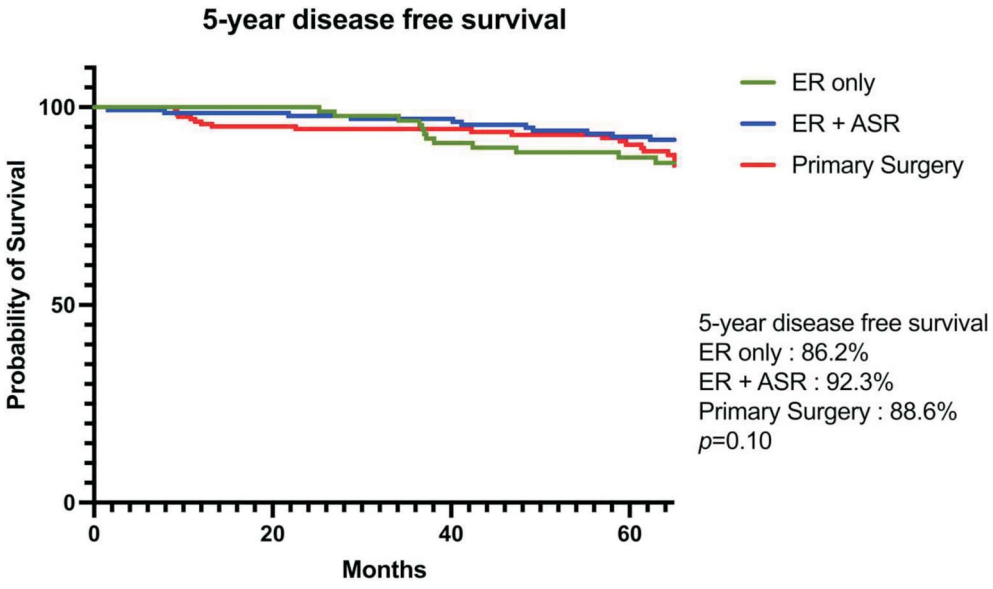

Fig. 3. 5-year disease-free survival.

Discussion

Our retrospective analysis highlights that poor histological differentiation and lymphovascular invasion are significant predictors of lymph node metastasis in T1 colorectal cancer, with these factors maintaining their prognostic value in multivariate analysis. These findings underscore the importance of these variables in the risk stratification for potential LNM. Furthermore, our findings suggest that the selected treatment strategy — endoscopic resection (ER) only, ER followed by additional surgical resection (ER + ASR), or primary surgical resection — did not significantly impact the 5-year overall and disease-specific survival, suggesting that less invasive approaches might be appropriate for carefully selected patients without compromising survival outcomes.

The criteria for pursuing additional surgical resection following endoscopic removal of T1 colorectal cancer have been established in guidelines internationally. A comparison of curative standards for T1 CRC endoscopic resection across different guidelines reveals a consensus on the importance of several key factors. The American Society for Gastrointestinal Endoscopy (ASGE) guidelines and the National Comprehensive Cancer Network (NCCN) guidelines in the United States both emphasize the significance of lymphovascular invasion, histological grade, depth of submucosal invasion, and tumor budding.[22,23] Similarly, the European Society of Gastrointestinal Endoscopy (ESGE) guidelines consider lymphovascular invasion, histological grade, and depth of submucosal invasion as crucial factors.[24,25] The Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines also include all four factors,[26] while the Chinese guidelines focus on lymphovascular invasion, histological grade, and depth of submucosal invasion.[27] The Korean guidelines align with the American and Japanese guidelines, considering all four factors.[9] This comparison highlights the international recognition of these key pathological features in guiding treatment decisions for T1 colorectal cancer, supporting the validity of our study's focus on these factors and their impact on lymph node metastasis and survival outcomes. Should histopathological analysis of the excised specimen reveal any of the subsequent features, it is advised to proceed with surgical resection accompanied by lymph node dissection: (1) extent of invasion into the submucosa; (2) lymphovascular invasion; (3) the presence of poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma; (4) evidence of tumor budding.

Many studies have identified lymphovascular invasion as the strongest indicator of lymph node metastasis. Odds ratio ranging from 4.4 to 10.19.[28-30] Although lymphovascular invasion is a critical risk factor, its detection is hindered by significant variability in interpretation among pathologists. There are reports in the literature of low agreement between observers when assessing lymphovascular invasion.[31] In the near future, standardization of staining methods and diagnostic criteria should become a global requirement while also bearing in mind cost-effectiveness.

Histological grade is also stated as a risk factor in several studies.[32-34] In our study, compared with well and moderately differentiated carcinoma, the LNM risk of poor-differentiated and undifferentiated cancer rose to approximately 28.62 (p = .002). Consistent with previous findings in T1 CRC.[35,36]

In our study, we did not find a significant association between tumor size and lymph node metastasis in either univariate or multivariate analysis. However, some studies have reported a correlation between larger tumor size and increased risk of LN metastasis in T1 colorectal cancer.[34,37-40] It is important to note that these studies relied on data from the United States Surveillance, Epidemiology, and End Results (SEER) database, and their findings have not been consistently validated in other databases or populations. Future research should aim to clarify the relationship between tumor size and LN metastasis in T1 colorectal cancer using data from diverse populations and databases to provide a more comprehensive understanding of this potential risk factor.

The predilection for LN metastasis in left-sided colorectal cancers could be attributed to biological differences in tumor behavior or to variations in the lymphatic drainage patterns between the two sides. Previous studies have suggested differences in genetic and molecular profiles between right- and left-sided colo-

rectal cancers, which may influence their metastatic potential.[41-43] In our study left-side colorectal cancer was significantly associated with LNM in univariate, but not in multivariate analysis, and hence only a dependent risk factor in our study. Numerous research papers have categorized colorectal cancer tumors based on their anatomical position as either left- or right-sided,[34,44-47] consistently finding that T1 CRCs on the left side (10.8% to 12.0%) have a markedly higher incidence of lymph node metastasis (LNM) compared to those on the right (4.8% to 5.4%). Collectively, these findings suggest that the location of the tumor could serve as an indicator for the likelihood of LNM in T1 CRC.

Furthermore, our findings suggest that the selected treatment strategy — endoscopic resection (ER) only, ER followed by additional surgical resection (ER + ASR), or primary surgical resection — did not significantly impact the 5-year overall and disease-free survival.

Our investigation into T1 colorectal cancer treatment outcomes is strengthened by the lengthy follow-up and rigorous multivariate analysis, underscoring the importance of histological differentiation and lymphovascular invasion in predicting lymph node metastasis. The study's retrospective design, however, introduces selection bias and limits our control over confounders, including the absence of data on tumor budding and submucosal invasion depth. Despite these constraints, our results highlight critical areas for future prospective research and may inform clinical practice pending further validation.

Conclusion

Our retrospective study assessed 392 T1 colorectal cancer patients across various treatments. While robust in its longitudinal scope, the exclusion of data on tumor budding and submucosal invasion depth marks a limitation due to the retrospective nature of the study. The investigation nonetheless provided a thorough examination of clinical and pathological factors relative to lymph node metastasis and survival outcomes.

Key findings indicate that poor histological differentiation and lymphovascular invasion are significant predictors of lymph node metastasis, with implications for risk stratification and treatment selection in T1 CRC. The survival analysis revealed no substantial differences in 5-year outcomes across treatment modalities, questioning the necessity of more invasive treatments in certain cases.

Future research should employ prospective designs to incorporate broader risk factors, including tumor budding and depth of invasion. This approach could refine the understanding of treatment impacts on T1 CRC and improve patient-specific care through more nuanced risk assessments and therapeutic strategies.

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原　著

T1 結直腸癌淋巴結轉移預測因子及存活率分析 — 回顧性研究

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背景　大腸直腸癌 (CRC) 是全球第三大流行病和第二大致命惡性腫瘤。黏膜下浸潤性 (T1) CRC 中有約 6-12% 的案例中伴隨淋巴結轉移 (LNM)，是否有淋巴結轉移顯著著影響病人的預後。在 T1CRC 的治療策略中，內視鏡切除 (ER) 和手術切除皆是可行的方案。本研究旨在確定 T1 CRC 中的 LNM 危險因素，並評估不同治療策略對存活結果的影響。

方法　我們對 2007 年 1 月至 2019 年 12 月在義大醫院治療的 392 例 T1 CRC 患者進行回顧性分析。患者接受單純 ER、ER 後額外手術切除 (ASR) 或直接手術切除。收集臨床和病理特徵的數據，包括腫瘤大小、組織學分化和侵襲狀態。使用 Kaplan-Meier 曲線和 Cox 回歸分析 5 年總存活 (OS) 和無病存活率 (DFS) 的存活結果。

結果　我們的研究發現不良的組織學分化、組織邊緣發現癌細胞和淋巴侵襲是 LNM 的重要預測因子。存活分析顯示，三個治療組的 5 年 OS 和 DFS 沒有顯著差異：單純 ER (5 年 OS：88.4%)、ER + ASR (94.1%) 和直接手術切除 (89.4%)。不同治療方式在無病存活率亦無統計學上顯著差異。

結論　在本研究中，不良的組織學分化、組織邊緣發現癌細胞和淋巴侵犯是 T1 大腸直腸癌 LNM 的關鍵因素。不同的治療策略不會顯著影響 5 年存活結果。

關鍵詞　T1 大腸直腸癌、淋巴結轉移、危險因子、存活結果。