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Original Article

ORIGINAL ARTICLE

Predictors of lymph-node metastasis in surgically resected T1 colorectal cancer in Western populations

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Abstract

Background: The risk of lymph-node metastasis (LNM) in T1 colorectal cancer (CRC) has not been well documented in heterogeneous Western populations. This study investigated the predictors of LNM and the long-term outcomes of patients by analysing T1 CRC surgical specimens and patients' demographic data.

Methods: Patients with surgically resected T1 CRC between 2004 and 2014 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Patients with multiple primary cancers, with neoadjuvant therapy, or without a confirmed histopathological diagnosis were excluded. Multivariate logistic-regression analysis was used to identify the predictors of LNM.

Results: Of the 22,319 patients, 10.6% had a positive lymph-node status based on the final pathology (nodal category: N1 9.6%, N2 1.0%). Younger age, female sex, Asian or African-American ethnicity, poor differentiation, and tumor site outside the rectum were significantly associated with LNM. Subgroup analyses for patients stratified by tumor site suggested that the rate of positive lymph-node status was the lowest in the rectum (hazard ratio: 0.74; 95% confidence interval: 0.63–0.86).

Conclusion: The risk of LNM was potentially lower in Caucasian patients than in API or African-American patients with surgically resected T1 CRC. Regarding the T1 CRC site, the rectum was associated with a lower risk of LNM.

Key words: T1 colorectal cancer; lymph-node metastasis; surveillance; epidemiology; end results database; overall survival

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Introduction

Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) were initially developed for the endoscopic resection of gastric tumors and then applied in Asia to treat early colorectal cancer (CRC) [1, 2]. Consistently, there has been a growing interest in adopting EMR/ESD as a curative therapy for T1 CRC in Western countries [3]. Although endoscopic resection has been associated with considerably less surgery-related morbidity and almost no post-operative mortality [4], problems associated with local treatment without regional lymph-node dissection have occurred in recent years. Therefore, patients with high risks of relapse and metastasis should undergo local resection under strict indications and intensive surveillance.

Advances in imaging techniques and high-definition colonoscopy such as magnifying chromoendoscopy and narrow-band imaging have resulted in the early optical detection of CRC [5, 6]. All submucosal invasions are generally grouped together as T1 CRC and removal of T1 CRC via EMR/ESD is increasingly performed in Western countries [7]. However, the primary risk associated with minimally invasive endoscopic therapies is lymph-node metastasis (LNM) [8, 9]. Given that LNM is strongly associated with distant metastasis development and poor prognosis, additional surgery involving lymph-node dissection is necessary for patients with high risks of LNM [10, 11]. Improvements in incidence of operative complications, mortality, and additional costs are limited with surgery. Nevertheless, ~90% of patients with T1 CRC did not develop LNM, suggesting that surgery in these patients leads to over-treatment. Methods to decrease the probability of unnecessary surgery and identify patients with high risks of LNM remain to be explored and developed [12, 13].

The management of early CRC remains controversial [14]. The National Comprehensive Cancer Network does not provide clear management guidelines for patients with T1 CRC. The majority of data regarding LNM in T1 CRC are based on Asian studies [11, 15]. Whether the standard criteria for EMR/ESD developed in Asia can be generalized to Western populations with T1 CRC has not been sufficiently examined. Furthermore, there is insufficient evidence regarding long-term outcomes of patients with surgically resected T1 CRC in heterogeneous Western populations [16]. Predictive factors such as lymphovascular invasion, tumor budding, and submucosal invasion depth are difficult to assess after endoscopic therapies [17]. Conversely, homogeneous patient and tumor characteristics might provide more appropriate indicators for the treatment of T1 CRC. Therefore, the association between clinicopathological characteristics of surgically resected specimens and the risk of LNM in patients with T1 CRC must be evaluated. The present study investigated the potential of commonly used but easily neglected clinicopathological characteristics combined with information on the patients' races and primary tumor sites to identify predictors of LNM. The purpose of this study was to establish an efficient treatment strategy for T1 CRC by analysing the tumor characteristics of surgically resected specimens from a large US national registry database—the Surveillance, Epidemiology, and End Results (SEER) database.

Patients and methods

Data source

In November 2016, we applied for and obtained research files from the SEER database of the National Cancer Institute; this database is a comprehensive source of population-based information covering 28% of the US population. Strict quality control is maintained by the SEER Quality Improvement program, which establishes standards for cancer registries and maintains these registries through continual monitoring, assessment, and education. We obtained permission to access the SEER database with the ID number 10947-Nov2016 via the Internet. This study was approved and reviewed by the Institutional Review Board of the Second Affiliated Hospital of Nanchang University (Jiangxi, China). This study was a retrospective analysis of publicly available de-identified data and was therefore exempted from requiring written informed consent.

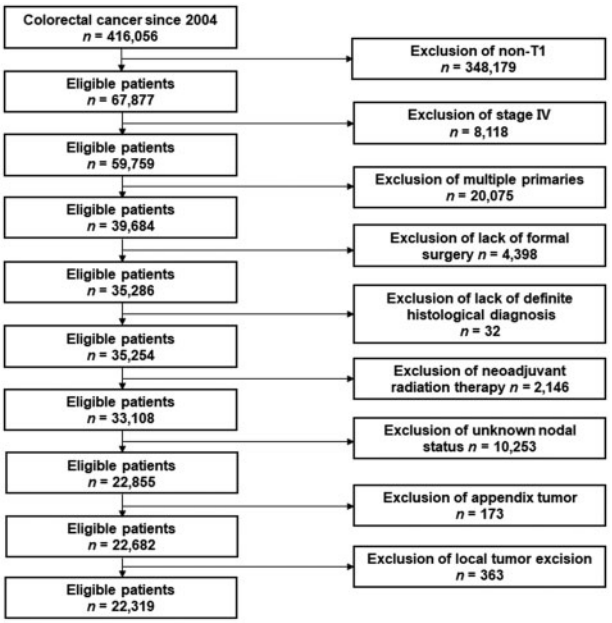

Figure 1. Patients were obtained using a selection flow sheet.

This study included patients with surgically resected (codes 30–32, 40–41, 51–52, 55, 57, 60–61, 65–66, 70, 80), histologically confirmed American Joint Committee on Cancer (AJCC) T1 CRC diagnosed between January 2004 and December 2014. A total of 363 patients received photodynamic therapy, electrocautery, cryosurgery, laser ablation, laser excision, curette, and fulguration, whereas the remaining patients received wedge or segmental resection, partial proctectomy, total proctectomy, or total proctocolectomy. As shown in Figure 1, patients with stage IV or multiple primary tumors or those who have received neoadjuvant radiation therapy were excluded.

Classification of T1 colorectal cancer

Tumor site, grade, and histology were coded according to the International Classification of Diseases for Oncology, version 3. Tumor stage was coded according to the AJCC tumor–node–metastasis staging system, 7th edition [18].

Statistical analysis

One-way ANOVA with the Student–Newman–Keuls *post hoc* test was used to compare the differences in continuous data and chi-squared test was used to compare the differences in categorical data. Multivariate logistic regression was used to identify factors predicting a positive lymph-node status. Statistical analyses were performed using the IBM SPSS software for Windows,

Table 1. Characteristics of the patients and prevalence of lymph-node metastasis in T1 colorectal cancer

Characteristic	Total ($n = 22,319$)	N0 ($n = 19,952$, 89.4%)	N1 ($n = 2,136$, 9.6%)	N2 ($n = 231$, 1.0%)
Age at diagnosis (years)				
Mean age	64.7	65.0	62.5	62.6
Age (years)				
≤40	511	437 (85.5%)	62 (12.1%)	12 (2.3%)
41–60	7,942	6,933 (87.3%)	919 (11.6%)	90 (1.1%)
>60	13,866	12,582 (90.7%)	1,155 (8.3%)	129 (0.9%)
Sex				
Male	11,438	10,289 (89.9%)	1,025 (9.0%)	124 (1.1%)
Female	10,881	9,663 (88.8%)	1,111 (10.2%)	107 (1.0%)
Tumor site				
Proximal colon	8,977	8,144 (90.7%)	755 (8.4%)	78 (0.9%)
Distal colon	10,478	9,173 (87.5%)	1,172 (11.2%)	133 (1.3%)
Rectum	2,662	2,447 (91.9%)	196 (7.4%)	19 (0.7%)
Unknown	202	188 (93.1%)	13 (6.4%)	1 (0.5%)
Race				
Caucasian	17,646	15,868 (89.9%)	1,600 (9.1%)	178 (1.0%)
African-American	2,463	2,152 (87.4%)	288 (11.7%)	23 (0.9%)
Asian-Pacific Islander	1,953	1,698 (86.9%)	227 (11.6%)	28 (1.4%)
American Indian	121	113 (93.4%)	6 (5.0%)	2 (1.7%)
Unknown	136	121 (89.0%)	15 (11.0%)	0 (0)
Grade				
Grade I	4,315	4,022 (93.2%)	276 (6.4%)	17 (0.4%)
Grade II	13,933	12,385 (88.9%)	1,399 (10%)	149 (1.1%)
Grade III/IV	1,650	1,286 (77.9%)	307 (18.6%)	57 (3.5%)
Unknown	2,421	2,259 (93.3%)	154 (6.4%)	8 (0.3%)

version 19.0 (IBM Corporation, Armonk, NY, USA). A *P*-value of <0.05 was considered statistically significant.

Results

Demographic characteristics

Of the 416,056 patients with CRC in the SEER database, we finally included 22,319 patients. Of these, 17,646 (79.1%) were Caucasian, 2,463 (11.0%) were African-Americans, 1,953 (8.8%) were Asian-Pacific Islanders (APIs), and 121 (0.5%) were AI (Table 1). In the 22,319 patients, the median number of harvested lymph nodes was 13, 19,952 (89.4%) patients were node-negative (N0), and 2,367 (10.6%) patients were node-positive (N1, 2,136 [9.6%]; N2, 231 [1.0%]). The mean age of the patients at diagnosis of the disease at all stages and in the LNM group was 64.7 and 62.5 years, respectively, and the patients with LNM at diagnosis were significantly younger ($P < 0.001$ for all comparisons). The LNM rate at diagnosis varied in race, age, sex, tumor site, and tumor grade. Additional details regarding patient demographics and tumor characteristics are summarized in Table 1.

Relationship between patient characteristics and lymph-node positivity

To estimate the potential correlation between LNM and various clinicopathological characteristics, we used multiple logistic-regression models of patient-based analysis. Age, sex, race, tumor grade, and tumor site were found to be significantly associated with LNM. Patients aged ≤40 years (hazard ratio [HR] 1.57, 95% confidence interval [CI] 1.21–2.03) were more likely to develop LNM than patients aged ≥61 years. The LNM rate was higher in African-American (HR 1.29, 95% CI 1.13–1.47) and API patients (HR 1.27, 95% CI 1.10–1.47) than in Caucasian patients. The LNM rate was higher in patients with grade II (HR 1.70, 95% CI 1.49–1.94) and grade III/IV (HR 3.92, 95% CI 3.31–4.63) tumors than in patients with grade I tumors. In subgroups stratified by tumor site, the rate of a positive lymph-node status was the lowest in the rectum (HR 0.74, 95% CI 0.63–0.86) than in other parts of the colon.(all $P < 0.050$; Table 2).

Discussion

In the present study, we found a LNM rate of 10.6% in patients with surgically resected T1 CRC. The mean age of patients with LNM at diagnosis was significantly lower than that of patients without LNM. Meanwhile, patients aged ≤40 years were more likely to develop LNM than patients of other age groups. When the subgroups were stratified by tumor site, it was found that the group with rectal cancer (RC) had the lowest rate of a positive lymph-node status. Another notable finding of our study was that LNM rates varied among different races in a heterogeneous Western population. Caucasian patients with T1 CRC potentially had a lower risk of LNM than APIs or African-American patients.

The requirement for additional radical surgery is mainly based on the histopathological predictors of LNM. The following pathological indicators have been recommended by the European Society of Gastrointestinal Endoscopy and the Japanese Society for Cancer of the Colon and Rectum: lymphovascular invasion, grade 2 or 3 tumors budding at the deepest point of tumor invasion, submucosal invasion depth ≥1,000 pm, and poorly differentiated adenocarcinoma [19–21]. We found that undifferentiated carcinomas, such as signet-ring-cell carcinomas and mucinous adenocarcinomas, were associated with a high incidence of LNM. This finding was in line with those reported by previous studies indicating that patients with grade III/IV tumors have a higher rate of LNM than patients with grade I/II tumors [22–24]. Unfortunately, we were unable to extract

Table 2. Predictors of positive lymph-node status in T1 colorectal cancer according to multivariate logistic regression

Covariate	HR (95% CI)	P-value
Sex		
Male	1 (Reference)	
Female	1.14 (1.04–1.24)	0.040
Race		
Caucasian	1 (Reference)	
African-American	1.29 (1.13–1.47)	<0.001
Asian-Pacific Islander	1.27 (1.10–1.47)	0.001
American Indian	0.63 (0.31–1.29)	0.480
Age at diagnosis (years)		
≤40	1.57 (1.21–2.03)	0.001
41–60	1.40 (1.28–1.53)	<0.001
≥61	1 (Reference)	
Grade		
Grade I	1 (Reference)	
Grade II	1.70 (1.49–1.94)	<0.001
Grade III+ IV	3.92 (3.31–4.63)	<0.001
Tumor site		
Proximal colon	1 (Reference)	
Distal colon	1.31 (1.20–1.45)	<0.001
Rectum	0.74 (0.63–0.86)	<0.001

information regarding tumor budding and lymphatic-vessel invasion from the SEER database in this study.

Endoscopic resection and radical surgery were both optional approaches to treat T1 CRC. Radical surgery could completely remove the tumor and regional lymph nodes. Radical surgery in the rectum is more likely to result in leakage, sexual and urinary dysfunctions, and other operative complications than local resection [25]. Undoubtedly, transanal local resection of early RC has unique advantages owing to its lower perioperative complications and mortality rates than those of traditional total mesorectal excision for RC. As novel minimally invasive RC therapies, transanal resection and transanal endoscopic microsurgery are expected to be widely used for local excision of early RC in clinical practice [26].

Recently, accumulating evidence has demonstrated significant differences in clinicopathological characteristics, anatomic structures, embryological origins, and genetic-mutation profiles among the proximal colon, distal colon, and rectum [27]. However, the impact of primary tumor sites on the risk of LNM in patients with T1 CRC remains controversial. In the present study, a subgroup analysis was conducted on the primary tumor sites, which were divided into three groups: the proximal colon, distal colon, and rectum. Notably, the lowest rate of a positive lymph-node status rate was observed in the rectum group. This result did not draw a similar conclusion to that reported by several other studies that found a more frequent occurrence of LNM in the rectum [28, 29]. The patient cohorts of previous retrospective studies were small and included more tumors in the lower third of the rectum, which is the possible reason for this discrepancy. Further prospective research is warranted to investigate the association between primary tumor sites and LNM of T1 CRC.

The present study had certain limitations and strengths. Patients who cannot be cured by endoscopic resection would possibly undergo radical surgery. Consequently, the inclusion criteria for the patient cohorts were easily skewed, with less frequent presentation of patients with diseases at relatively early stages. However, the SEER database is one of the largest registries that allowed the comparative analysis of T1 CRC. To the best of our knowledge, this was the most comprehensive population-based study that evaluated the predictors of T1 CRC through the analysis of commonly used but easily neglected clinicopathological characteristics.

In conclusion, the present study demonstrated that Caucasian patients potentially have a lower risk of LNM than APIs or African-American patients. Regarding the T1 CRC site, patients with RC had a lower risk of LNM than those colonic cancer. Clinicians must consider these commonly used but easily neglected clinicopathological characteristics when establishing therapeutic guidelines and making treatment decisions for patients with T1 CRC.

Authors' contributions

C.H.Y., Z.Z., T.C.Z., and H.L. conceived of and designed this study. T.C.Z. and C.G.H. collected and assembled the data. C.H.Y., Z.Z., and H.L. analysed and interpreted the data. Z.Z., H.L., and F.X.T. drafted the manuscript. C.H.Y., Z.Y.L., and P.D. prepared the figures and tables. All authors read and approved the final manuscript.

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Conflicts of interest

None declared.

References

1. Huang C, Huang RX, Xiang P *et al*. Current research status of endoscopic submucosal dissection for colorectal neoplasms. *CIM* 2012;**35**:158–64.
2. Tanaka S, Terasaki M, Kanao H *et al*. Current status and future perspectives of endoscopic submucosal dissection for colorectal tumors. *Dig Endosc* 2012;**24**:73–9.
3. Uraoka T, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection in Japan and Western countries. *Dig Endosc* 2012;**24**:80–3.
4. De Ceglie A, Hassan C, Mangiavillano B *et al*. Endoscopic mucosal resection and endoscopic submucosal dissection for

colorectal lesions: a systematic review. *Crit Rev Oncol Hematol* 2016;**104**:138–55.
5. Puig I, Lopez-Ceron M, Arnau A *et al.* Accuracy of the narrow-band imaging international colorectal endoscopic classification system in identification of deep invasion in colorectal polyps. *Gastroenterology* 2019;**156**:75–87.
6. Backes Y, Moss A, Reitsma JB *et al.* Narrow band imaging, magnifying chromoendoscopy, and gross morphological features for the optical diagnosis of T1 colorectal cancer and deep submucosal invasion: a systematic review and meta-analysis. *Am J Gastroenterol* 2017;**112**:54–64.
7. Bartel MJ, Brahmbhatt BS, Wallace MB. Management of colorectal T1 carcinoma treated by endoscopic resection from the Western perspective. *Dig Endosc* 2016;**28**:330–41.
8. Belderbos TD, Leenders M, Moons LM *et al.* Local recurrence after endoscopic mucosal resection of nonpedunculated colorectal lesions: systematic review and meta-analysis. *Endoscopy* 2014;**46**:388–402.
9. Kim B, Kim EH, Park SJ *et al.* The risk of lymph node metastasis makes it unsafe to expand the conventional indications for endoscopic treatment of T1 colorectal cancer: a retrospective study of 428 patients. *Medicine (Baltimore)* 2016;**95**:e4373.
10. Miyachi H, Kudo SE, Ichimasa K *et al.* Management of T1 colorectal cancers after endoscopic treatment based on the risk stratification of lymph node metastasis. *J Gastroenterol Hepatol* 2016;**31**:1126–32.
11. Yoda Y, Ikematsu H, Matsuda T *et al.* A large-scale multicenter study of long-term outcomes after endoscopic resection for submucosal invasive colorectal cancer. *Endoscopy* 2013;**45**:718–24.
12. Overwater A, Kessels K, Elias SG *et al.* Endoscopic resection of high-risk T1 colorectal carcinoma prior to surgical resection has no adverse effect on long-term outcomes. *Gut* 2018;**67**:284–90.
13. Tanaka S, Asayama N, Shigita K *et al.* Towards safer and appropriate application of endoscopic submucosal dissection for T1 colorectal carcinoma as total excisional biopsy: future perspectives. *Dig Endosc* 2015;**27**:216–22.
14. Saitoh Y, Inaba Y, Sasaki T *et al.* Management of colorectal T1 carcinoma treated by endoscopic resection. *Dig Endosc* 2016;**28**:324–9.
15. Suh JH, Han KS, Kim BC *et al.* Predictors for lymph node metastasis in T1 colorectal cancer. *Endoscopy* 2012;**44**:590–5.
16. Patel N, Patel K, Ashrafian H *et al.* Colorectal endoscopic submucosal dissection: systematic review of mid-term clinical outcomes. *Dig Endosc* 2016;**28**:405–16.
17. Bianco F, De Franciscis S, Belli A; on behalf of the Italian Society of Colo-Rectal Surgery (SICCR) Cancer Group *et al.* T1 colon cancer in the era of screening: risk factors and treatment. *Tech Coloproctol* 2017;**21**:139–47.
18. Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010;**17**:1471–4.
19. Ferlitsch M, Moss A, Hassan C *et al.* Colorectal polypectomy and endoscopic mucosal resection (EMR): European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline. *Endoscopy* 2017;**49**:270–97.
20. Pimentel-Nunes P, Dinis-Ribeiro M, Ponchon T *et al.* Endoscopic submucosal dissection: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. *Endoscopy* 2015;**47**:829–54.
21. Watanabe T, Itabashi M, Shimada Y; Japanese Society for Cancer of the Colon and Rectum *et al.* Japanese Society for Cancer of the Colon and Rectum (JSCCR) Guidelines 2014 for treatment of colorectal cancer. *Int J Clin Oncol* 2015;**20**:207–39.
22. Caputo D, Caricato M, La Vaccara V *et al.* T1 colorectal cancer: poor histological grading is predictive of lymph-node metastases. *Int J Surg* 2014;**12**:209–12.
23. Nakadoi K, Oka S, Tanaka S *et al.* Condition of muscularis mucosae is a risk factor for lymph node metastasis in T1 colorectal carcinoma. *Surg Endosc* 2014;**28**:1269–76.
24. Saraste D, Gunnarsson U, Janson M. Predicting lymph node metastases in early rectal cancer. *Eur J Cancer* 2013;**49**:1104–8.
25. Kidane B, Chadi SA, Kanters S *et al.* Local resection compared with radical resection in the treatment of T1N0M0 rectal adenocarcinoma: a systematic review and meta-analysis. *Dis Colon Rectum* 2015;**58**:122–40.
26. De Graaf EJ, Doornebosch PG, Tollenaar RA *et al.* Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. *Eur J Surg Oncol* 2009;**35**:1280–5.
27. Minoo P, Zlobec I, Peterson M *et al.* Characterization of rectal, proximal and distal colon cancers based on clinicopathological, molecular and protein profiles. *Int J Oncol* 2010;**37**:707–18.
28. Aytac E, Gorgun E, Costedio MM *et al.* Impact of tumor location on lymph node metastasis in T1 colorectal cancer. *Langenbecks Arch Surg* 2016;**401**:627–32.
29. Gschwantler M, Kriwanek S, Langner E *et al.* High-grade dysplasia and invasive carcinoma in colorectal adenomas: a multivariate analysis of the impact of adenoma and patient characteristics. *Eur J Gastroenterol Hepatol* 2002;**14**:183–8.