Original Article

A Retrospective Analysis of Lymph Node Distribution in pT1 Colorectal Adenocarcinoma

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Key Words
pT1 colorectal cancer;
Lymph node metastasis;
Lymph node dissection

Purpose. pT1 colorectal cancer carries approximately 10% risk of lymph node metastasis. Surgical resection is indicated for pT1 tumors bearing risk factors. In present study, we aimed to clarify the pattern of lymph node metastasis in pT1 colorectal cancer and wish to provide suggestions of lymph node dissection level.
Methods. The consecutive pT1 colorectal patients undergoing elective surgery from 1999 to 2019 were analyzed retrospectively. Clinical data including clinicopathological features, degree of lymph node metastasis and recurrence sites were reviewed.
Results. A total of 1020 cases were enrolled. Nearly half of the tumors were located in left-sided colon. Among all cases, 928 were stage I disease, 89 had stage III disease, and 3 had stage IV disease.
Regarding the distribution pattern, the N1 stage accounted for the majority of patients with node positive disease. Of the 92 cases with lymph node metastasis, 82 cases had level I disease, 7 had level II and 3 had level III disease. Cases with positive level III lymph nodes were associated with a significantly higher ratio of N2 and M stage.
Conclusions. The majority of cases with pT1 with lymph node metastasis belonged to N1 stage. Presence of level III lymph node metastasis was found in both the colon and rectum and were related with a significant higher ratio of N2 stage and M stage. D2 dissection will be suggested for the majority of cases, but if distant metastasis or image-found high-level lymph node metastasis is present, D3 dissection should be considered.

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The invasion depth is positively correlated with the risk of lymph node metastasis (LNM) in colorectal cancer (CRC). Previous studies reported that the pT1 invasion depth in CRC carries approximately 10% risk of LNM.[1,2] The local endoscopic excision procedure of colonoscopy, such as Endo-Mucosal resection (EMR) and endoscopic submucosal dissection (ESD), has become more prevalent in clinical practice. Surgical resection is indicated for pT1 tumors bearing risk factors suggested in many guidelines.[3] For locally excised pT1 tumor, researchers have emphasized investigating LNM risk factors to carefully select candidates for surgical resection. Tumors with unfavorable differentiation, deep submucosal invasion, lymphatic or vascular invasion, unfree resection margin, or higher degree of tumor budding are risk factors found with LNM. Otherwise, surgical resections were not suggested for tumors without these factors.[2,4] As

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for the level of surgical resection and lymph node dissection (LND) based on the Japanese Society for Cancer of the Colon and Rectum (JSCCR), D2 dissection for pT1 will be required, instead of usually suggesting a more radical D3 dissection.[5] However, performing a comprehensive analysis of the tumor status is often difficult preoperatively and can not be confirmed before surgical resection.[6] Those who would benefit from more extensive LND thus may be hard to identify based on current guideline. Therefore, the present study aimed to clarify the patterns of pT1 CRC's LNM and wished to provide the suggestion of LND level accordingly.

Materials and Method

Patients

We retrospectively enrolled cases from the prospectively maintained database of our department from 1999 to 2019. Initially, consecutive 1,061 cases who underwent elective surgical resection with pathologically confirmed pT1 colorectal adenocarcinoma were obtained. Surgical resection was performed either as the primary or additional treatment after endoscopic resection. All enrolled cases did not receive neoadjuvant therapy. The pathological staging was assessed using the 7th American Joint Committee on Cancer tumor necrosis metastasis system.[7]

Exclusion criteria were as follows: synchronous cancer with more advanced T stage, familial adenomatous polyposis, and missing data. Then, a total of 1,020 cases were included in the final analysis (Fig. 1). Clinical data (e.g., clinicopathological features, LNM distribution and recurrence sites) were reviewed. The study was reviewed and approved by the Institutional Review Board of Taipei Veterans General Hospital (IRB-TPEVGH: 2022-09-004CC).

Sidedness definition

Right-sided colon cancer was defined as a tumor arising from the cecum to the transverse colon, whereas left-sided colon cancer was located at the splenic flexure of the colon to rectosigmoid colon. The LND level and lymph node location groups were classified according to Japanese Classification of Colorectal Car-

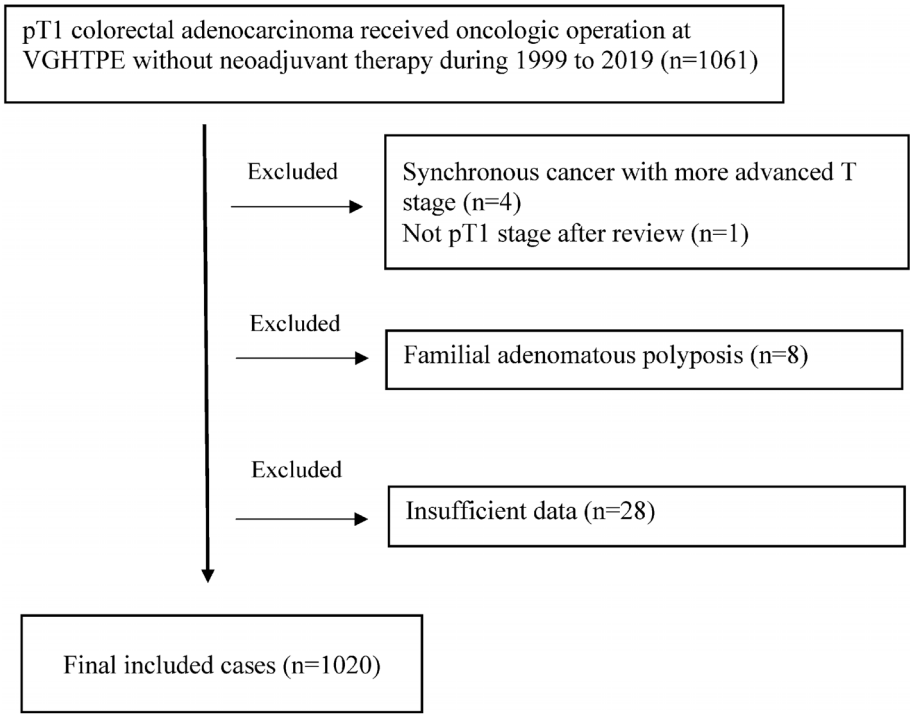

Fig. 1. Flow chart of selection of all cases included in the analyses.

cinoma and were described briefly as follows: Level I is LNM within paracolic area, defined as extension within 10 cm on both the oral and anal sides of the tumor, with lateral extension limited along marginal arteries, or LNM within pararectal area, defined as extension within 10 cm on the oral side and 3 cm on the anal side of the tumor above the peritoneal reflection, and 2 cm on the anal side of the tumor below it. Level III is defined as LNM at the roots of superior mesenteric artery or inferior mesenteric artery. Level II is LNM located between the area of level I and level III. Level IV is LNM beyond the regional nodes as described above. We didn't perform lateral dissection in patients included in our study.[8]

Statistical analysis

The statistical analyses were performed using the Statistical Package for the Social Sciences Version 23.0 (SPSS, Inc, Chicago, IL). Student's t-test was used for continuous variables whereas Chi-square test and Fisher's exact test were used for categorical variables in univariate analysis.

Results

Clinicopathological characteristics of all cases with pT1 disease

Table 1 summarizes the clinicopathological characteristics of all cases. Among the 1020 consecutive cases included in this study, the median age was 64.1 (range, 55.8-73.5) years. The median follow-up was 68 (range, 39-114) months. Half of the tumors were located in the left-sided colon (49.3%). The median number of lymph nodes harvested was 12 (range, 9-17). Among all patients, 928 (91%) cases were stage I disease, 89 (8.7%) had stage III disease, and 3 (0.3%) had stage IV disease.

Distribution pattern of LNM

The N and M status of all patients is shown in Table 2. Of the 89 cases with stage III disease, two had isolated cancer nodule (N1c) without LNM. The location of solitary isolated cancer nodule was analyzed as LNM grouping. Regarding the LNM pattern, the N1 stage (93.5%) accounted for the majority of the 92 patients with LNM (89 stage III; 3, stage IV). All cases with distant metastatic disease were limited to one metastatic site at the time of diagnosis. The comparison among different LNM levels is shown in Table 3. As for the LNM pattern, 82 (89.1%) had level I disease, 7 (7.6%) had level II, and 3 (3.3%) had positive level III lymph nodes. Cases with positive level III

Table 1. Clinicopathological characteristics of all patients with pT1 disease

Characteristic	n = 1020
Age (years)	
Mean ± SD	64.5 ± 12.0
Median + IQR	64.1 (55.8-73.5)
Gender	
Male	594 (58.2%)
Female	426 (41.8%)
Tumor sidedness	
Right-sided	213 (20.9%)
Left-sided	503 (49.3%)
Rectum	304 (29.8%)
Pre-op CEA level*	
≤ 5 ng/ml	918 (92.8%)
> 5 ng/ml	71 (7.2%)
TNM staging	
I	928 (91%)
III	89 (8.7%)
IV	3 (0.3%)
Tumor size (cm)#	
Mean ± SD	2.3 ± 13
Median + IQR	2 (1.5-3)
Dissection level	
Level I	201 (19.7%)
Level II	369 (36.2%)
Level III	450 (44.1%)
Numberof harvested lymph nodes	
Mean ± SD	13.5 ± 7.3
Median + IQR	12 (9-17)
< 12	391 (38.3%)
≥ 12	629 (61.7%)

SD = standard deviation; IQR = interquartile range; CEA = carcinoembryonic antigen.

* Thirty-one patients lacked of record of pre-operative CEA level.

Twenty-one patients lacked of record of tumor size.

Table 2. Distribution of pT1 patients with node positive disease

Features	TNM staging		
	Stage I (%) n = 928	Stage III (%) n = 89	Stage IV (%) n = 3
N stage			
N0	928 (100%)	0	0
N1a	0	53 (59.6%)	0
N1b	0	30 (33.7%)	1 (33.3%)
N1c	0	2 (2.2%)	0
N2a	0	4 (4.5%)	1 (33.3%)
N2b	0	0	1 (33.3%)
M stage			
M0	928 (100%)	89 (100%)	0
M1	0	0	3 (100.0%)
Positive level of lymph nodes			
Level I	0	81 (91.0%)	1 (33.3%)
Level II	0	7 (7.9%)	0
Level III	0	1 (1.1%)	2 (66.7%)

Table 3. Metastasis pattern of pT1 patients with node positive disease

Features	Level of positive lymph nodes			*p*
	Level I [c] (%) n = 82	Level II [d] (%) n = 7	Level III [e] (%) n = 3	
Tumor size (cm)				0.45
Mean ± SD [a]	2.5 ± 1.9	2.7 ± 1.7	3.9 ± 1.6	
Median + IQR [b]	2 (1.5-2.9)	2 (1.1-4)	3	-
Number of harvested lymph nodes				0.95
Mean ± SD	14.5 ± 7.0	14.1 ± 6.2	13.3 ± 2.3	
Median + IQR	13 (11-17)	13 (7-20)	12	-
Dissection level				0.54
Level I	15 (18.3%)	0	0	
Level II	22 (26.8%)	3 (42.9%)	0	
Level III	45 (54.9%)	4 (57.1%)	3 (100%)	
N stage				*< 0.01*
N1	79 (96.3%)	7 (100%)	0	
N2	3 (3.7%)	0	3 (100%)	
M stage				*< 0.01*
M0	81 (98.8%)	7 (100%)	1 (33.3%)	
M1	1 (1.2%)	0	2 (66.7%)	
Sidedness				0.91
Right side [f]	13 (15.9%)	2 (28.6%)	0	
Left side [g]	45 (54.9%)	3 (42.9%)	2 (66.7%)	
Rectum [h]	24 (29.3%)	2 (28.6%)	1 (33.3%)	

Italics value indicates statistical significance at $p < 0.05$.

[a] SD = standard deviation. [b] IQR = interquartile range. [c] Level I = Pericolic/perirectal. [d] Level II = Intermediate. [e] Level III = Main. [f] One patient has level I and II lymph nodes metastasis. [g] One patient has level I and II lymph nodes metastasis; one patient has level I and III lymph nodes metastasis; one patient has level II and III lymph nodes metastasis. [h] One patient has level I, II and III lymph nodes metastasis.

lymph nodes were associated with a significantly higher ratio of N2 stage ($p < 0.01$) and M stage ($p < 0.01$). The ratio of patients receiving D1, D2 or D3 LND and tumor sidedness were not significantly different between patients with positive level I, II or III lymph nodes.

Recurrence pattern of pT1 disease

The recurrence pattern of all patients is shown in Table 4. Overall, the recurrence rate was 2.3% (23/1017). Cases with N+ had a significantly higher recurrence rate than those without (6.7% vs. 1.8%, $p = 0.01$). The N+ group had a significantly higher ratio of lung metastasis while no significant difference was found regarding the ratio of liver metastasis between N+ and N– groups. Notably, only two cases had local recurrence (LR) (0.2%), and both of them belonged to the N– group.

Discussion

The present study is a preliminary report evaluating the distribution and recurrence patterns of LNM in pT1 CRC. In our study, 9% of pT1 patients were found to have LNM with 93.5% of them belonged to N1 disease. The overall recurrence rate was 2.3%. Cases with N+ had a significantly higher recurrence rate than those without. While 89.1% of patients with LNM were level I disease, our data still demonstrated that for pT1 CRC, the possibility of level III LNM exists in both the colon and rectum. It is at a very low ratio although the risk exists. Among three cases with level III LNM in this study, two were located at the sigmoid colon and one at the upper rectum. For all three, the pathology of initial resections has been reviewed and confirmed to be pT1 by our specialized pathologist. This LNM pattern is inconsistent with that of the JSCCR, revealing no incidence of level III LNM in pT1 colon cancer.[5] While all three cases belonged to N2 disease, two of them were found to have distant metastasis at the time of diagnosis. This shows that D3 dissection is required for some very few cases with pT1 to achieve LR free. At least, D3 is suggested for patients with distant metastasis.

Some may argue that not all cases underwent D3 dissection in our series. Hence, the LNM condition has not been well investigated. However, among all patients with pN+, no one has LR after surgical resection including those with Level III LNM. It is indirect evidence that proved no positive LNM was left behind locally. Ironically, the only two cases with LR were noted in pN– cases with rectum cancer.

With respect of the risks of high level LNM in pT1 patients, a cohort study by Kobayashi et al. also reported the possibilities of main LNM or distant LNM with the presence of clinical evidence of extensive node metastasis.[8] Their conclusions were similar with that of JSCCR's report. For clinically T1 and node-negative CRC, D1 LND was the optimal strategy, whereas, for clinically T1 and node-positive CRC, D2 LND appeared optimal. In these two reports, whether patients with distant metastasis were included remains unclear because the detailed staging was not revealed, but positive LNM at level IV LN was indeed included in their series. There is another intriguing point that positive level IV LNM existed in their series but without cases of positive level III. Somehow, this evidence matches our interpretation that a high level LNM might exist in a very rare possibility. In this study, we did not match our preoperative image surveys to the pathological LNM pattern. Further analysis will be performed to provide more accurate suggestions regarding surgical radicality.

Table 4. Recurrence pattern of all patients with pT1 disease

Recurrence site	Node positive (%) n = 92	Node negative (%) n = 928	*p*
Recurrence	6 (6.5%)	17 (1.8%)	*0.01*
Local recurrence	0	2 (0.2%)	-
Distant metastasis	6 (6.5%)	16 (1.7%)	*0.01*
Liver	2 (2.2%)	10 (1.1%)	0.3
Lung	4 (4.3%)	6 (0.6%)	*0.01*
Other metastatic sites	1 (1.1%)	5 (0.5%)	0.43
Local recurrence + Distant metastasis	0	1 (0.1%)	-

Italics value indicates statistical significance at $p < 0.05$.

In this study, D3 dissection was performed in 47.4% of cases with right-sided colon tumors, 41.5% of left-sided colon tumors, and 46.2% of rectal tumors. Compared with Kobayashi et al.'s series, our study comprises a higher LND ratio. Despite the T1 impression of the tumor preoperatively, maybe higher dissection had been favored by our surgeons. This study spanned a very long range of collection time. The recurrence rate of our cases is comparable with theirs. Showing that treatment quality had been adequately maintained throughout the long collection period.[1,9] Indeed, the distribution ratios of LNM are very similar between these two series. In our study, only two cases with pN- developed LR at 13 and 33 months postoperatively, and both are large-sized rectal cancers. It is clear that the retained LN was not the cause of LR. Instead, tumor spillage intraoperatively was highly suspected as the cause. Therefore, technical issues regarding the dissection of rectal cancer of larger tumors should be very careful to prevent any tumor tissue spillage. Collectively, we agreed that optimal dissection level should be based on meticulous image examinations and intraoperative findings. Higher LND (i.e., level III dissection) should be considered for clinical N2 and M1 disease.

On the other hand, prognosis of pT1 colon cancer has been reported to be much better than that of pT3 and pT4.[10,11] Early and adequate treatment is crucial to achieving good results. Kotake et al. reported only 0.78% of pT2 cases were accompanied by the main LNM and concluded that no influence on overall survival was found in the group receiving D3 dissection.[12] Since multiple studies had reported that the submucosal invasion depth was correlated with LNM risk,[6,13] the actual metastatic risk in pT1 cancer can be reasonably suggested to be lower than pT2. Each treatment should be weighed based on risks associated with benefits before making decisions. Averagely speaking, the surgical risk has been low in current surgeries.

The present study has the strength of a relatively large and homogenous patient group but several limitations should still be acknowledged. First, this is a retrospective and single-institutional study. Selection bias thus may be hardly avoidable. Secondly, the pathological features and microsatellite status were not included.

To conclude, the majority of cases with pT1 with LNM belonged to the N1 stage. Although the incidence was very rare, level III LNM was found in both the colon and rectum. Precise pre-operative evaluation is crucial. D2 dissection will be suggested for the majority of patients, but if distant metastasis or image-found high-level LNM is present, D3 dissection should be considered.

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原　著

T1 大腸直腸腺癌淋巴結型態的回溯性分析

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目的　約略 10% 的 T1 分期大腸直腸癌會伴隨著淋巴結轉移。對於帶有危險因子的 T1 分期腫瘤目前建議施行手術。這篇研究希望能瞭解在 T1 分期大腸直腸癌中，淋巴結轉移的分布，並藉此提供有關淋巴結廓清手術範圍的建議。

方法　研究收錄自 1999 年至 2019 年接受選擇性手術，且病理分期為 T1 分期的大腸直腸癌病人來進行回溯性分析。回顧項目包括臨床病理特徵、淋巴結轉移的範圍及復發部位等。

結果　研究共收錄 1020 例，其中近半為左側腫瘤。癌症分期部分，928 例為第一期癌症，89 例為第三期癌症，3 例為轉移性癌症。在 92 例有淋巴結轉移的病例中，多數為 N1 分期。其中 82 例為 level I 的淋巴結轉移， 7 例為 level II 的淋巴結轉移，3 例為 level III 的淋巴結轉移。在 level III 淋巴結轉移的病例中，N2 分期或有遠端轉移的比例顯著較高。

結論　在 T1 分期的大腸直腸癌病例中，若伴隨有淋巴結轉移則多數屬 N1 分期。在此研究中大腸癌或直腸癌的病例皆有發現到 level III 的淋巴結轉移，且這些病例為 N2 分期或有遠端轉移的比例顯著較高。對於多數的 T1 分期的大腸直腸癌，建議施行 D2 範圍淋巴結廓清手術。然而若發現遠端轉移或影像上存在深層淋巴結轉移的證據，則應該考慮施行 D3 範圍的淋巴結廓清手術。

關鍵詞　T1 分期大腸直腸癌、淋巴結轉移、淋巴結廓清手術。