Original Article

Prognosis of T0 and T1 Colorectal Cancer Following Surgical Resection

Tzu-Chun Chen[1]
Chin-Hao Chang[2]
Tzung-Hsin Chou[1]
Ji-Shiang Hung[1]
John Huang[1]
Ben-Ren Lin[1]
Jin-Tung Liang[1]
[1]*Division of Colorectal Surgery, Department of Surgery,*
[2]*Department of Medical Reserach, National Taiwan University Hospital, Taipei, Taiwan*

Key Words
Early colorectal cancer;
Prognosis;
Lymph node metastasis

Purpose. The aim of this study was to analyze the lymph node metastasis status and prognosis in patients with T1 colorectal cancer treated by curative surgery. In addition, differences in survival between patients with T0 and T1 colorectal cancer were analyzed.
Methods. Cases of T0 and T1 colorectal adenocarcinoma treated by curative surgical resection between January 2001 and December 2013 at the National Taiwan University Hospital were identified. In total, 66 patients with T0 and 137 patients with T1 colorectal adenocarcinoma were included and the clinicopathologic data were reviewed.
Results. The rate of lymph node metastasis among cases of T1 colorectal cancer was 11.38%. There were no cases of lymph node metastasis in the T0 group. The risk of lymph node metastasis was significantly higher in poorly differentiated versus well-differentiated and moderately differentiated cancer ($p = 0.0231$). No statistically significant differences in long-term overall survival were observed in T1 colorectal cancer patients with negative versus positive lymph node status ($p = 0.6144$).
Conclusions. The outcome was excellent in T1 colorectal cancer patients who received radical surgical treatment, even in those patients with lymph node metastasis. In addition, there was no difference in the long-term overall survival between the T0 and T1 colorectal cancer patients.
[*J Soc Colon Rectal Surgeon* (*Taiwan*) *2014;25:134-140*]

The incidence of colorectal cancer is increasing rapidly in Taiwan, and it is currently the third most common cause of cancer death. In T1 colorectal cancer, invasion is limited to the submucosa. T1 colorectal cancer can be treated by local excision including endoscopic mucosal resection and endoscopic submucosal dissection, or by surgical resection.[1]

Local excision is more suitable in certain cases such as well-differentiated adenocarcinomas; T1 tumors less than 3 cm in diameter; tumors without lymphovascular invasion, budding, or sessile morphology; SM1 involvement (< 300 m from the muscularis mucosa); and tumors accessible for full-thickness excision with a 1-cm normal margin.[2-5] Additional surgical resection is recommended for patients with unfavorable factors because the lymph node metastasis (LNM) rate and cancer recurrence rate are higher in these circumstances.[6] The rate of LNM in cases of T1 adenocarcinoma is reported to be approximately 10%.[1,5,7] LNM is an independent risk factor for recurrence after surgical resection for T1 colorectal cancer.[1] However, the lymph node status cannot be assessed if the tumor is treated by local excision alone. Most previous studies assessed lymph node status in

Received: March 20, 2014. Accepted: September 22, 2014.
Correspondence to: Dr. Jin-Tung Liang, Division of Colorectal Surgery, Department of Surgery, National Taiwan University Hospital, No. 7, Chung-Shan South Road, Taipei, Taiwan. Tel: 886-2-2312-3456; Fax: 886-2-3393-8506; E-mail: jintung@ntu.edu.tw

T1 neoplasms to evaluate if further surgical treatment was needed. The aim of this study was to analyze the LNM status in patients with T1 colorectal cancer treated by curative surgical treatment at the National Taiwan University Hospital. We also analyzed the differences in survival between T0 and T1 colorectal cancer patients.

Patients and Methods

General information

Cases of T0 or T1 colorectal adenocarcinoma of the colon and rectum treated by curative surgical resection at the National Taiwan University Hospital between January 2001 and December 2013 were identified. Patients with synchronous colorectal cancer, those who received neoadjuvant chemotherapy and/or radiotherapy, those who were treated by transanal surgical excision, and those with tumors of non-glandular origin were excluded. In total 66 patients with T0 and 137 patients with T1 colorectal adenocarcinoma were included. In all patients, invasion was limited to the muscularis mucosa or the submucosa. Age, sex, tumor size, tumor location, and tumor morphology were recorded in these 203 patients. The patient pathological reports were reviewed and the TNM stage, invasion layer, histologic type, histologic grade, lymphovascular invasion, total number of nodes sampled, positive lymph node number, and mucinous component were assessed. The tumor locations included the right colon (cecum, ascending, and transverse colon), the left colon (splenic flexure, descending, and sigmoid colon), and rectum. Tumor morphology was classified into three groups: polypoid lesions; flat, sessile, and lateral spreading tumors; and depressed lesions.

Statistical analysis

The association between LNM and clinicopathologic variables was evaluated. The Student's t-test was used for continuous data and a chi-square test or Fisher's exact test was used for categorical data. Survival curves were generated by the Kaplan-Meier method. Univariate analysis was conducted using the log-rank test, and multivariate analysis, by the Cox regression hazards model. Statistical significance was defined at $p < 0.05$. The statistical analyses were performed using SAS 9.2 software (SAS Institute Inc., Cary, North Carolina, USA).

Results

The 203 patients included 108 men and 95 women, 34-93 years of age, with an average age of 64.4 years. The median number of lymph nodes removed by the surgical resection was 13 (range, 1-51). LNM was absent in 189 patients. In the 14 patients with LNM, the average number of malignant lymph nodes was 1.1, ranging from 1 to 2. Of the patients with LNM, 13 patients had 1 LNM, 1 patient had 2 LNMs, and no patients had 3 or more LNMs. All 14 patients with LNM had submucosal invasion. No cases of LNM were noted in the T0 group, and further analysis of the relationship between clinicopathologic features and LNM was limited to cases of T1 colorectal cancer. In total, 66 patients with T0 and 137 patients with T1 colorectal adenocarcinoma were included.

The clinicopathologic features in cases of T0 colorectal adenocarcinoma is shown in Table 1. The occurrence of LNM according to histopathologic features in the 137 cases of T1 colorectal adenocarcinoma is shown in Table 2. There were 41 patients with right colon cancer, 59 patients with left colon cancer, and 37 patients with rectal cancer. In the rectal cancer group, 6 patients (16.22%) had LNM. The frequency of LNM in the left colon cancer group was 6.78% (4/59), and that in the right colon cancer group was 9.76% (4/41). There was no statistical difference in the frequency of LNM between the three groups ($p = 0.3211$, Fisher's exact test).

The mean tumor size in cases of T1 colorectal cancer was 2.12 cm (range, 0.3-10 cm). LNM was noted in 1 patient with a tumor less than 1 cm (4.76%), in 7 patients with tumors of 1-2 cm (9.72%), and in 6 patients with tumors larger than 2 cm (13.95%). The tumor size cannot be identified in one patient without

Table 1. Clinicopathologic features and lymph node metastasis in cases of T0 colorectal adenocarcinoma

	Lymph node status	
	0: none (n = 66)	1: positive (n = 0)
Sex		
Female	28 (42.42%)	
Male	38 (57.58%)	
Age	62.83 ± 11.72	
Tumor size		
< 1 cm	11 (16.92%)	
1-2 cm	16 (24.62%)	
> 2 cm	38 (58.46%)	
Location		
Right colon	19 (28.79%)	
Left colon	29 (43.94%)	
Rectum	18 (27.27%)	
Grade		
Well	0 (0%)	
Moderately	21 (91.3%)	
Poorly	2 (8.7%)	
Mucinous		
Absent	63 (95.45%)	
Present	3 (4.55%)	
Morphology		
Polypoid	46 (70.77%)	
Flat, sessile, LST	14 (21.54%)	
Depressed	5 (7.69%)	
LVI		
Absent	3 (75%)	
Present	1 (25%)	

LST = lateral spreading tumors, LVI = lymphovascular invasion.

Table 2. Univariate analysis of clinicopathologic features and lymph node metastasis in cases of T1 colorectal adenocarcinoma

	Lymph node status		*p*-value
	0: none (n = 123)	1: positive (n = 14)	
Sex			0.5152
Female	59 (47.97%)	8 (57.14%)	
Male	64 (52.03%)	6 (42.86%)	
Age	64.88 ± 12.35	67 ± 11.69	0.5413
Tumor size			0.499*
< 1 cm	20 (16.39%)	1 (7.14%)	
1-2 cm	65 (53.28%)	7 (50%)	
> 2 cm	37 (30.33%)	6 (42.86%)	
Location			0.3211*
Right colon	37 (30.08%)	4 (28.57%)	
Left colon	55 (44.72%)	4 (28.57%)	
Rectum	31 (25.2%)	6 (42.86%)	
Grade			0.0231*
Well	7 (6.31%)	2 (16.67%)	
Moderately	104 (93.69%)	9 (75%)	
Poorly	0 (0%)	1 (8.33%)	
Mucinous			1.0000*
Absent	116 (95.08%)	14 (100%)	
Present	6 (4.92%)	0 (0%)	
Morphology			0.5818*
Polypoid	82 (67.77%)	8 (57.14%)	
Flat, sessile, LST	17 (14.05%)	2 (14.29%)	
Depressed	22 (18.18%)	4 (28.57%)	
LVI			1.0000*
Absent	100 (88.5%)	12 (92.31%)	
Present	13 (11.5%)	1 (7.69%)	

LST = lateral spreading tumors, LVI = lymphovascular invasion.
* *p* value determined using Fisher's exact test.

LNM. There was no significant difference in the frequency of LNM according to tumor size ($p = 0.499$).

On morphological assessment, polypoid tumors were identified in 90 cases (8 were LNM positive); depressed lesions in 26 cases (4 were LNM positive); and flat, sessile, and lateral spreading tumors in 19 cases (2 were LNM positive). There were no significant differences in LNM status between groups ($p = 0.5818$).

Further, lymphovascular invasion ($p = 1.0000$) and presence of a mucinous component ($p = 1.0000$) were not associated with LNM status. The lymphovascular invasion data could not be found in the pathological reports of 11 patients in our study, and the mucinous component cannot be identified in one patient.

In contrast, with regard to histological grade, the rate of LNM in cases of poorly differentiated T1 colorectal adenocarcinoma was significantly higher than that in cases of well-differentiated and moderately differentiated tumors ($p = 0.0231$). These data could not be found in the pathological reports of 14 patients (12 with positive LMN and 2 with negative LMN) in our study.

The correlation of clinicopathologic features with the five-year overall survival rate is shown in Table 3. In univariate analysis, age was the only characteristic that significantly associated with five-year overall survival. No statistically significant differences in

Table 3. Univariate and multivariate analysis of the prognostic significance of clinicopathologic features in cases of T1 colorectal cancer

	Five-year overall survival rate	Univariate *p*-value[a]	Multivariate *p*-value[b]
Sex		0.4673	
Female	0.9692		
Male	0.9414		
Age		0.0079	0.9940
< 65	1.0000		
≥ 65	0.9041		
Tumor size		0.4213	
< 1 cm	1.0000		
1-2 cm	0.9577		
> 2 cm	0.9268		
Location		0.3043	
Right colon	0.9268		
Left colon	0.9483		
Rectum	1.0000		
Grade		0.7968	
Well	1.0000		
Moderately	0.9544		
Poorly	1.0000		
Mucinous		0.5896	
Absent	0.9525		
Present	1.0000		
Morphology		0.1046	
Polypoid	0.9663		
Flat, sessile, LST	1.0000		
Depressed	0.8745		
LVI		0.6265	
Absent	0.9540		
Present	0.9286		
Positive LN		0.5723	
Negative	0.9585		
Positive	0.9231		

LST = lateral spreading tumors, LVI = lymphovascular invasion, LN = lymph node.
[a] Log-rank test.
[b] Cox model.

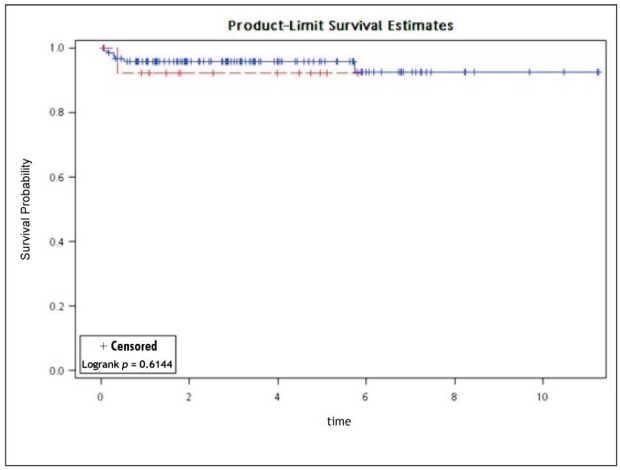

Fig. 1. Long-term overall survival curves of T1 colorectal cancer patients with positive versus negative lymph node status. Solid line: negative lymph node status; dashed line: positive lymph node status.

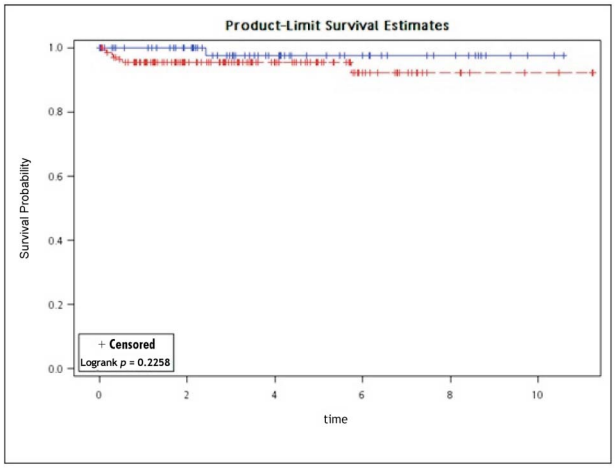

Fig. 2. Long-term overall survival curves of patients with T0 versus T1 colorectal adenocarcinoma. Solid line: T0 colorectal cancer; dashed line: T1 colorectal cancer.

overall survival were observed in T1 colorectal cancer patients with positive versus negative LNM (p = 0.6144, Fig. 1) or in patients with T0 versus T1 colorectal cancer (p = 0.2258, Fig. 2).

Discussion

The incidence of colorectal cancer is increasing rapidly in Taiwan, and it is the third leading cause of cancer mortality. Invasion is limited to the submucosa in T1 colorectal cancer and it can be treated with local excision including endoscopic mucosal resection and endoscopic submucosal dissection, or surgical resection.[1] Local excision is best performed when specific conditions are met.[2-5]

The rate of LNM is approximately 10% in cases of T1 colorectal adenocarcinoma[1,4,7] and LNM is an in-

dependent risk factor for recurrence after surgical resection in these cases.[1] Additional surgical resection is recommended for patients with unfavorable prognostic factors because the LNM rate and cancer recurrence rate are increased under these conditions.[6] Most previous studies assessed lymph node status in T1 neoplasms to determine if further surgical treatment is needed in these cases. We analyzed the possible risk factors for LNM in cases of T1 colorectal cancer to determine further treatment strategies.

The rate of LNM in T1 colorectal cancer is approximately 10%.[4,7] In our study, there were 14 patients with LNM, all of which showed submucosal invasion. In 66 patients with invasion limited to the mucosa, there was no LNM. The rate of LNM in our T1 colorectal cancer cohort was 11.38% (14/137), consistent with previous studies.

LNM was not observed any of the T0 colorectal neoplasms in our study. Thus, we only analyzed the clinicopathologic features of T1 colorectal cancer patients for the risk of LNM. Nakadoi et al. found that LNM was found in 41 (8.22%) of 499 cases. The rate of LNM was significantly high in lesions featuring poorly differentiated/mucinous adenocarcinoma, submucosal invasion > 1800 mm, vascular invasion, and high-grade tumor budding.[8] Poorly differentiated colorectal cancer was identified as risk factor for LNM in cases of T1 colorectal cancer in our study; however, other possible risk factors such as lymphovascular invasion were not identified as significant. Wang et al. found that the diagnosis of vascular invasion may differ between pathologists and also by staining method. The difference may also be attributed to the difficulty in the pathologic identification of vascular invasion as tissue retraction around tumor foci may mimic vascular invasion.[7] Lastly, the difference may be attributable to the missing data on lymphovascular invasion; these data could not be found in the pathological reports of 11 patients in our study.

Kobayashi et al. demonstrated that LNM and histological grade were independent risk factors for recurrence following curative resection for T1 colorectal cancer.[1] They found that even with nodal involvement, the 5-year overall survival rate of patients with T1 colon cancer was greater than 90% and the prognosis after curative resection for T1 colon cancer did not differ between patients with and without LNM. The authors hypothesized that the positive prognosis might depend on the number of LNMs. In their study, most of the stage III patients with T1 colorectal cancer were had N1 disease. In another study, Kobayashi et al. demonstrated that none of the clinicopathologic features examined were associated with overall survival, and the 5-year survival rates for patients with and without LNM were 100% and 96.0%, respectively ($p = 0.69$).[4] In our study, age was the only clinicopathologic feature that was associated with the five-year survival rate in univariate analysis. The prognosis after curative resection for T1 colon cancer did not differ between patients with and without LNM. In our study, 14 patients had LNM. The average number of malignant lymph nodes was 1.1, ranging from 1 to 2. The lymph node status of all patients was N1.

There was no statistically significant difference in long-term overall survival between patients who had positive LNM and those with negative LNM among patients with T1 colorectal cancer. This is likely due to the excellent prognosis of T1 colorectal cancer patients who underwent radical surgery regardless of their nodal status.

LNM was not detected in cases of T0 colorectal neoplasms in our study. Furthermore, we found no statistically significant difference in long-term overall survival between patients with T0 versus T1 colorectal cancer.

However, there were limitations in our study. The median number of lymph nodes removed by the surgical resection was 13 (range, 1-51). The number of lymph nodes removed by the surgery ranged from 1 to 36 in T0 colorectal neoplasm. In this part, it did not influence our result because there was no lymph node metastasis in T0 colorectal neoplasm. However, the number of lymph nodes removed by surgical resection ranged from 1 to 51 in T1 colorectal cancer. This may be due to that surgeons may performed less lymph node dissection in early colorectal cancer when they estimated there was no lymph node metastasis. The number of lymph nodes less than six was found in 21 patients, and one of them had positive lymph node.

The few number of lymph nodes may downgrade the tumor stage (from N2 to N1 or N0) and cause the different result in the relation of clinicopathologic features and lymph node metastasis in cases of T1 colorectal adenocarcinoma. But as mentioned earlier, the rate of LNM in our T1 colorectal cancer cohort was 11.38% (14/137) in our study, consistent with previous studies. Besides, the average number of harvested lymph node was 11.5 in T1 colorectal cancer with positive lymph node, and it was 13.5 in T1 colorectal cancer with negative lymph node. The average of harvested lymph node in T1 colorectal cancer with negative node was more than the number in T1 patients with negative node. We supposed that the survival will be not different in T1 colorectal cancer patients with positive versus negative LNM or in patients with T0 versus T1 colorectal cancer even though few lymph node dissection in some patients.

Conclusion

T1 colorectal cancer patients who underwent radical surgery had satisfactory outcomes regardless of the presence of LNM. In addition, there was no statistically significant difference in long-term overall survival between patients with T0 versus T1 colorectal cancer.

Acknowledgment

The authors would like to acknowledge the Taiwan Clinical Trial Bioinformatics and Statistical Center, Training Center, and Pharmacogenomics Laboratory (founded by the National Research Program for Biopharmaceuticals [NRPB] at the National Science Council of Taiwan; NSC 102-2325-B-002-088) for statistical assistance and the Department of Medical Research at the National Taiwan University Hospital.

References

1. Kobayashi H, Mochizuki H, Morita T, Kotake K, Teramoto T, Kameoka S, et al. Characteristics of recurrence after curative resection for T1 colorectal cancer: Japanese multicenter study. *J Gastroenterol* 2011;46:203-11. doi: 10.1007/s00535-010-0341-2
2. Okabe S, Shia J, Nash G, Wong WD, Guillem JG, Weiser MR, et al. Lymph node metastasis in T1 adenocarcinoma of the colon and rectum. *J Gastrointest Surg* 2004;8:1032-9. doi: 10.1016/j.gassur.2004.09.038
3. Benizri EI, Bereder JM, Rahili A, Bernard JL, Vanbiervliet G, Filippi J, et al. Additional colectomy after colonoscopic polypectomy for T1 colon cancer: a fine balance between oncologic benefit and operative risk. *Int J Colorectal Dis* 2012; 27:1473-8. doi: 10.1007/s00384-012-1464-0
4. Kobayashi H, Higuchi T, Uetake H, Iida S, Ishikawa T, Ishiguro M, et al. Resection with en bloc removal of regional lymph node after endoscopic resection for T1 colorectal cancer. *Ann Surg Oncol* 2012;19:4161-7. doi: 10.1245/s10434-012-2471-7
5. Nascimbeni R, Nivatvongs S, Larson DR, Burgart LJ. Long-term survival after local excision for T1 carcinoma of the rectum. *Dis Colon Rectum* 2004;47:1773-9. doi: 10.1007/s10350-004-0706-9
6. Chok KS, Law WL. Prognostic factors affecting survival and recurrence of patient with pT1 and pT2 colorectal cancer. *World J Surg* 2007;31:1485-90. doi: 10.1007/s00268-007-9089-0
7. Wang HS, Liang WY, Lin TC, Chen WS, Jiang JK, Yang SH, et al. Curative resection of T1 colorectal carcinoma: risk of lymph node metastasis and long-term prognosis. *Dis Colon Rectum* 2005;48:1182-92. doi: 10.1007/s10350-004-0935-y
8. Nakadoi K, Tanaka S, Kanao H, Terasaki M, Takata S, Oka S, et al. Management of T1 colorectal carcinoma with special reference to criteria for curative endoscopic resection. *J Gastroenterol Hepatol* 2012;27:1057-62. doi: 10.1111/j.1440-1746.2011.07041.x

原　著

T0 及 T1 大腸直腸癌術後之預後

陳姿君[1]　張晉豪[2]　周宗興[1]　洪基翔[1]　黃約翰[1]　林本仁[1]　梁金銅[1]

[1]國立台灣大學醫學院附設醫院　外科部　大腸直腸外科

[2]國立台灣大學醫學院附設醫院　醫學研究部

目的　本研究之目的對於及 T1 大腸直腸癌之淋巴結轉移情況進行分析。同時分析 T0 及 T1 大腸直腸癌病人在存活上之差異。

方法　收集於西元 2001 年 1 月至 2013 年 12 月間，T0 及 T1 大腸直腸癌於台大醫院進行根治性手術治療之病患。總共包括 203 名病患，其中包括 66 位 T0 大腸直腸癌及 137 位 T1 大腸直腸癌病人，針對其臨床及病理特性進行分析。

結果　對於 T1 大腸直腸癌其淋巴結轉移機率為 11.38%，在 T0 大腸直腸癌並無發現淋巴結轉移之現象。分化不良之 T1 大腸直腸癌為淋巴結轉移之風險因子。另外，在 T1 大腸直腸癌中，有無淋巴結轉移在存活上並無統計上之差異。

結論　在 T1 大腸直腸癌其預後很好，有淋巴結轉移與無淋巴結轉移之存活率並無明顯差異。除此之外，對於 T0 及 T1 大腸直腸癌之存活率亦無統計上之差異。

關鍵詞　早期大腸直腸癌、預後、淋巴節轉移。