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ORIGINAL ARTICLE

Effect of preoperative colonoscopic tattooing on lymph node harvest in T1 colorectal cancer

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Abstract
Objective This study aimed to identify the impact of preoperative colonoscopic tattooing (PCT) on lymph node harvest in T1 colorectal cancer patients.
Material and methods One hundred and forty-three patients were included who underwent curative resection and were diagnosed with T1 colorectal cancer. These patients were categorized into the tattooing group and the non-tattooing group depending on whether preoperative India ink tattooing was done. Clinicopathological findings and lymph node harvest were compared between the two groups.
Results The median number of lymph nodes examined was 18 in the tattooing group and 13 in the non-tattooing group ($p<0.001$). The rate of adequate lymph node harvest (retrieval of more than 12 lymph nodes) was higher in the tattooing group than that in the non-tattooing group (83.7 vs. 58.5 %, $p=0.002$). The PCT was significantly associated with adequate lymph node harvest in multivariate analysis (hazard ratio, 3.8; 95 % confidence interval, 1.5–9.2; $p=0.003$). Among the 40 patients who showed at least one carbon particle-containing lymph nodes, the positive lymph node rate was not different between carbon-containing LNs (0.9 %) and non-carbon-containing LNs (1.7 %).
Conclusions PCT was associated with higher lymph node yield in T1 colorectal cancer. It is questionable if tattooing has additional detection power as a sentinel lymph node mapping tool in T1 colorectal cancer.

Keywords Tattooing · Preoperative colonoscopy · Lymph node · T1 · Colorectal cancer

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Introduction

Preoperative colonoscopic tattooing (PCT) has been used as an effective tool for marking tumor sites in colorectal cancer [1]. It is sometimes confusing to identify tumor location by colonoscopy or abdominopelvic computed tomography due to the variable morphology and length of the colon. In the era of minimally invasive surgery, it is more difficult to identify the exact location of the tumor, especially in small-sized masses, by laparoscopic or robotic tactile sensation. However, in current practice, PCT is not used as a routine procedure before surgery. Spillage of India ink into the sterile abdomen could cause abdominal pain or abscess formation [2–4]. The peritoneal leakage rate after colonoscopic tattooing was reported to be 9.5 %, although mild peritonitis developed in only one case [5]. Because additional bowel preparation for tattooing is required for patients, the most common indication for PCT is to allow easy identification of a partially resected polypectomy site or a potentially undetectable lesion for planned surgical treatment.

In addition to localization by PCT, several authors recently reported that PCT could increase the number of nodes examined [6–8]. The reason for increased lymph node yield after tattooing was attributed to the fact that India ink-containing lymph nodes can be more easily detected by the surgeon or pathologist (Fig. 1) [6, 7]. Examination of an adequate number of nodes is crucial for accurate tumor stage discrimination in

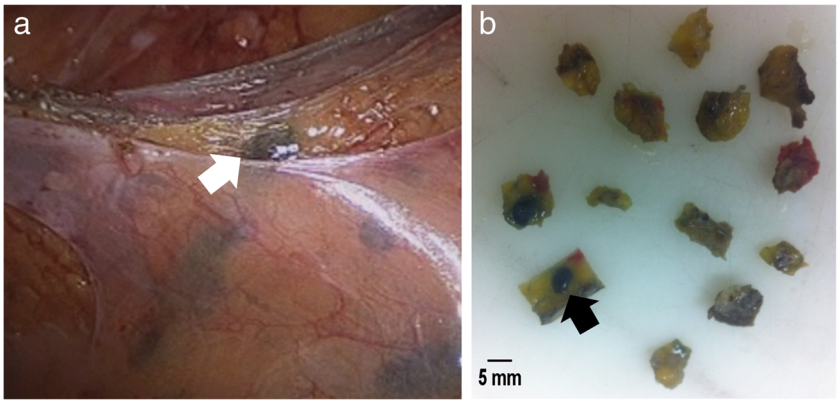

Fig. 1 Lymph node detection after tattooing. **a** Carbon particles are engulfed by macrophages in the lymph nodes which are therefore marked permanently. India ink-containing LNs could be more easily detected during the surgery (*white arrow*). **b** During the manual dissection of resected specimen after formalin fixation, some lymph nodes containing India ink from the preoperative tattooing could be easily detected (*black arrow*)

colorectal cancer. It is well known that patient prognosis in colorectal cancer is influenced by the retrieved number of lymph node [9–11] although the exact reason for this phenomenon remains unclear. Stage migration and the effect of extensive lymphadenectomy are suggested as possible explanations [6, 12]. Therefore, retrieval of more than 12 lymph nodes is recommended for adequate staging in colorectal cancer [9, 13].

The correct nodal staging evaluation is exceptionally important for T1 stage of colorectal cancer patients. If metastatic lymph nodes are not found, adjuvant chemotherapy would be missed on these understaged patients. It has not been thoroughly investigated if the effect of PCT on lymph node retrieval is still relevant in T1 stage of colorectal cancer.

Therefore, the aim of this study was to evaluate the impact of preoperative colonoscopic tattooing on lymph node retrieval especially in T1 colorectal cancer.

Material and methods

Eligibility

Using our prospectively collected database, we selected patients who underwent curative resection and were diagnosed with T1 colorectal cancer between January 2005 and April 2013. Excluded from the selection were patients who had undergone preoperative chemotherapy or radiotherapy, patients who were diagnosed with hereditary non-polyposis colorectal cancer (HNPCC) or familial adenomatous polyposis (FAP), patients who underwent transanal excision, patients who underwent emergency operation, and patients who were diagnosed as stage IV. In this study, we enrolled patients who underwent PCT using India ink; patients who underwent PCT using other materials such as methylene blue were also excluded.

The performed PCT was identified from the electronic medical record. Clinicopathological information for age; sex; tumor size; histologic grade; lymphovascular invasion; location of the primary tumor in the proximal colon (cecal, ascending, and transverse colon), distal colon (descending, sigmoid, and rectosigmoid colon), or rectum; pathologic nodal stage; and total number of lymph nodes examined were extracted from our database. Adequate lymph node harvest was defined as retrieval of more than 12 lymph nodes [6]. This study was approved by our Institutional Review Board.

Tattooing procedure

The tumor localization was marked by a gastroenterologist according to a standard protocol. Almost all tattooing were done 1 day before surgery. The lesion was tattooed with India ink for subsequent localization in the intraoperative setting. India ink solution was already sterilized before the procedure. An injection catheter was passed through the working channel of the endoscope. The injection needle was placed in the submucosa of the colon which was approximately 1 to 2 cm distal from the target lesion. To confirm the needle was placed in submucosa, not in the peritoneum, a small deposit of saline was injected. The syringe was replaced by one containing sterile India ink. Then, 0.5 to 1.0 mL of india ink was injected. This procedure was repeated until two or three sides of the lumen were tattooed.

Surgery and vessel ligation

All patients underwent curative resection based on standardized technique. In case of right-side tumors, if the tumor was located at the cecum or proximal portion of the ascending colon, the ileocolic vessels and the right branch of the middle colic vessels were transected. When the tumor was located at the hepatic flexure and proximal transverse colon, the middle colic vessels were ligated at their origin from the superior mesenteric vessels. For left-side tumors, inferior mesenteric

artery was ligated at the level of its origin from the aorta or just below the left colic artery.

Pathologic examinations and detection of carbon-containing lymph nodes

All mesenteric tissue was manually examined for lymph nodes. Fat clearing technique using chemicals was not applied. While performing manual dissection of specimen after formalin fixation, sometimes, lymph nodes harboring India ink could be detected easily (Fig. 1b). During the study periods, a single technician harvested lymph nodes of the resected specimens manually. After that, the pathologic examination was done by several pathologists. For this retrospective study, one experienced pathologist (HSP) reviewed the slides of all patients who underwent PCT. Carbon particle implementation in resected lymph nodes, which might originate from the preoperative India ink tattooing, was recorded for each patient.

Statistical analysis

All calculations and analysis were performed using the SPSS software package version 20.0 (SPSS Inc., Chicago, IL). The differences in clinicopathological features between the tattooing group and the non-tattooing group were analyzed using the two-sided Pearson chi-square test or Fisher's exact test for categorical variables and with a Student's t test for continuous variables. Factors with a p value less than 0.1 in univariate analysis were entered into multivariate analysis. Factors associated with adequate lymph node harvest were analyzed by logistic regression analysis. A p value <0.05 was considered to indicate significance.

Results

A total of 143 patients were available for analysis. Forty-nine of whom (34.2 %) underwent preoperative colonoscopic tattooing (tattooing group). Other patients were categorized into non-tattooing group.

There was no difference in gender, age, body mass index (BMI), carcinoembryonic antigen, lymphovascular invasion, histologic grade, or operation type between the tattooing and the non-tattooing groups. The percentage of distal colon cancer patients was higher in the tattooing group and that of the rectal cancer patients was higher in the non-tattooing group ($p<0.001$). The mean tumor size was larger in the non-tattooing group than that in the tattooing group (1.9 vs. 1.3 cm, $p<0.001$). The node positive rate was 14.3 % in the tattooing group and 13.8 % in the non-tattooing group, which showed no significant difference (Table 1).

The median number of lymph nodes retrieved was significantly larger in the tattooing group than that in the non-tattooing group (18 vs. 13, $p<0.001$). This trend was consistently observed in the rectal cancer group ($p=0.005$) and in the overall colon cancer group ($p=0.020$). However, in subgroup analysis of the proximal colon, there was no difference in the number of retrieved lymph nodes between the two groups ($p=0.926$) (Table 2).

Overall, 96 patients (67.1 %) showed an adequate lymph node harvest. The rate of adequate lymph node harvest was significantly higher in the tattooing group than that in the non-tattooing group (83.7 vs. 58.5 %, $p=0.002$). In subgroup analysis, adequate lymph node harvest rate was higher in the rectal cancer group and the distal colon cancer group ($p=0.044$, $p=0.001$) (Fig. 2).

For adequate lymph node harvest, age and PCT were found to be significant factors on univariate analysis. Both remained significant on multivariate analysis (age: hazard Ratio, 0.3; 95 % confidence interval, 0.1–0.8; $p=0.023$, PCT: HR, 3.8; 95 % CI, 1.5–9.2; $p=0.003$, respectively) (Table 3).

Among 49 patients who underwent PCT, 40 patients (81.6 %) had at least one lymph node containing carbon particle. For other 9 patients, there was no lymph node containing carbon particle. Thus, the detection rate of carbon particle after PCT was 81.6 % (40/49). In the subgroup analysis of 40 patients who showed carbon-containing LNs, the median number of LNs per person was 13 (range 2–37). A total of 993 lymph nodes were retrieved. Among them, 527 LNs (53 %) were shown to contain carbon particles. There were five carbon-containing LNs among a total of 13 metastatic LNs (38.4 %). The positive rate was 0.9 % in carbon-containing LNs and 1.7 % in non-carbon-containing LNs (Table 4).

Discussion

This study demonstrated that preoperative colonoscopic tattooing (PCT) was associated with an increased number of lymph nodes examined in T1 colorectal cancer. In addition, this could increase the rate of adequate lymph nodes harvested, which was defined as retrieval of more than 12 lymph nodes.

In our daily practice, the tumor size measured at preoperative examination and tumor location might be the most important factors in deciding whether to use PCT. As we expected, mean tumor size of the tattooing group was smaller than that of the non-tattooing group. The rate of PCT performed in the rectal cancer group was only 13 %, which was lower than that in the colon cancer group (proximal colon group—39 %, distal colon group—55 %, $p<0.001$). In the case of rectal cancer, rigid sigmoidoscopy can detect tumor location in the operation theater; thus, PCT might be limitedly applied in these patients. Among colon cancer patients, the correct tumor

Table 1 Patient baseline characteristics

Variables		Tattooing group (N=49) N (%)	Non-tattooing group (N=94) N (%)	p
Gender	Male	33 (67.3)	59 (62.8)	0.587
	Female	16 (32.7)	35 (37.2)	
Age (year)	≤70	41 (83.7)	74 (78.7)	0.479
	>70	8 (16.3)	20 (21.3)	
BMI (kg/m^2)	Mean (SD)	23.5 (2.6)	24.0 (3.0)	0.348
CEA (ng/mL)	Mean (SD)	2.0 (1.4)	2.2 (1.5)	0.336
Tumor location[b]	Proximal colon	11 (22.4)	17 (18.1)	<0.001
	Distal colon	30 (61.2)	24 (25.5)	
	Rectum	8 (16.3)	53 (56.4)	
Tumor size (cm)	Mean (SD)	1.3 (0.5)	1.9 (1.0)	<0.001
Specimen length (cm)	Mean (SD)	18.6 (7.8)	18.4 (7.6)	0.896
Nodal stage	N (−)	42 (85.7)	81 (86.2)	0.941
	N (+)	7 (14.3)	13 (13.8)	
Lymphovascular invasion	Positive	3 (6.1)	6 (6.4)	0.464[a]
	Negative	43 (87.8)	75 (79.8)	
	Unknown	3 (6.1)	13 (13.8)	
Histologic grade[c]	G1	16 (32.7)	33 (35.1)	0.552[a]
	G2	31 (63.3)	60 (63.8)	
	G3	2 (4.1)	1 (1.1)	
Operation type	Open	7 (14.3)	27 (28.7)	0.054
	MIS	42 (85.7)	67 (71.3)	

BMI body mass index, CEA carcinoembryonic antigen, *LN* lymph node, *MIS* minimally invasive surgery included laparoscopy surgery and robotic surgery

[a] Fisher's exact test

[b] Tumor location; Proximal colon: ascending colon–transverse colon; Distal colon: descending colon–sigmoid colon

[c] Histologic grade; G1—well differentiated, G2—moderately differentiated, G3—poorly differentiated

location is more important in the distal colon than the proximal colon. While performing a right hemicolectomy, the dissection plane was less dependent on tumor location. In the case of distal colon cancer, surgical treatment options such as left hemicolectomy or anterior resection are more dependent on tumor location. In addition, the precise tumor location is clinically important not only in deciding the adequate proximal and distal resection margins but also in deciding whether to perform splenic flexure mobilization. In our practice, splenic flexure mobilization was not a routine procedure [14, 15]. Thus, PCT was most frequently used in cases of distal colon cancer.

Table 2 Comparison of median retrieved lymph node numbers according to preoperative colonoscopic tattooing

			Tattooing group	Non-tattooing group	p
Colon and rectal cancer	Overall	N	49	94	
		Median (range)	18 (4–47)	13 (1–46)	<0.001
Colon cancer	Overall	N	41	41	
		Median (range)	16 (4–44)	12 (1–46)	0.020
	Proximal colon	N	11	17	
		Median (range)	22 (6–38)	19 (7–46)	0.926
	Distal colon	N	30	24	
		Median (range)	16 (4–44)	10 (1–26)	<0.001
Rectal cancer		N	8	53	
		Median (range)	22 (13–47)	14 (2–32)	0.005

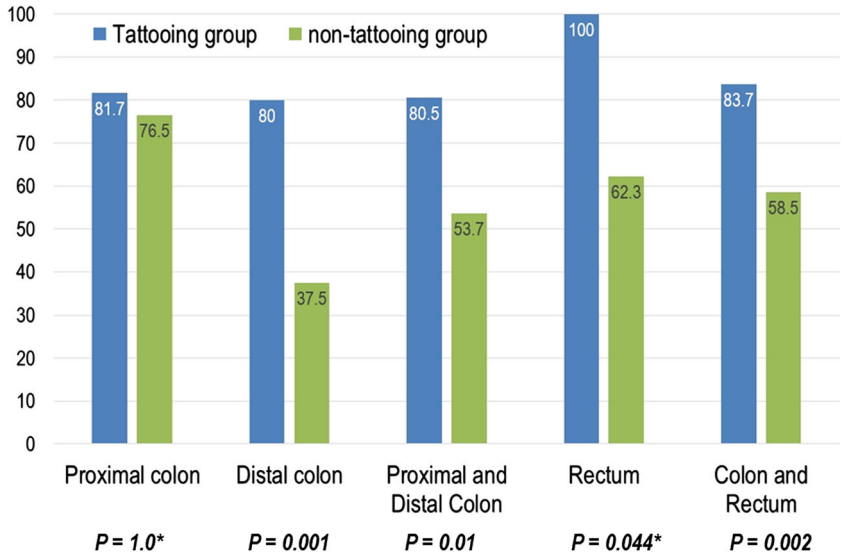

Fig. 2 Comparison of adequate lymph node harvest (≥12 retrieved lymph nodes) ratio between tattooing group and non-tattooing group according to specific location of the tumor; *Fisher's exact test

In our data, the median number of retrieved lymph nodes and the rate of more than 12 retrieved lymph nodes were higher in the tattooing group than that in the non-tattooing group. According to recently published studies, preoperative tattooing increased the number of lymph nodes examined [6–8]. A possible explanation for this finding is easier discrimination of lymph nodes containing carbon particles during surgery or pathologic examination. Bartels et al. reported that the surgeons expanded the surgical dissection plane when they encountered visible pigmented LNs out of the planned area in two cases [7]. However, we believe that two cases might be too few to impact overall increased LN numbers, although it is uncertain if there were additional such cases. Our retrospective study was also unable to identify such cases. Therefore, it is difficult to confirm if the increased number of lymph nodes after tattooing was due to the enlarged dissection plane by carbon particle-containing LNs detected during surgery. Regarding the possibility of increased LN numbers during pathologic examination, standardization of pathologic review is very important to support the hypothesis. It is well known that the number of lymph nodes examined is dependent on the individual pathologist [16, 17]. In our hospital, all of the manual lymph nodes harvest after the colorectal surgery had been performed by one specialized pathology technician during the study period. This is the reason why we do not include the pathologist as one of the possible variables in determining lymph node harvest, which might be one of the strengths of our study. Therefore, our results support the hypothesis of easier identification of carbon-containing lymph nodes during pathologic examination.

Several authors reported the possibility of tattooing as a useful tool for sentinel lymph node mapping [7, 18]. Recently, Yan et al. reported the endoscopic submucosal injection of 1 mL carbon nanoparticles suspension at the tumor site is feasible to detect sentinel lymph nodes in clinically T1–2 colorectal cancers [19]. In this concept, our data indicated that the detection rate of PCT was 81.6 %. However, among the 40 patients who showed at least one carbon particle-containing lymph nodes, the positive lymph node rate was similar between carbon-containing LNs (0.9 %) and non-carbon-containing LNs (1.7 %). It is questionable if tattooing has additional detection power as a sentinel LN mapping tool in T1 colorectal cancer. However, it should be mentioned that the median number of carbon-containing LNs per each person in our study (median 13, range 2–27) was higher than that in previous reports (median 5–6) [7, 18]. Further large-scale studies are warranted to reveal the true impact of tattooing as a sentinel lymph node mapping tool.

There are several limitations to this retrospective study design. First, in our cohort, 33 % of patients had an inadequate lymph node harvest (less than 12 retrieved lymph nodes). Nash et al. reported that 96 % of specimens had more than 12 harvested lymph nodes among 152 colon cancer patients. This high rate may be explained partially by the second dissection of specimen if less than 12 LNs were obtained in first dissection [8]. In this cohort, second dissection was not a routine procedure. Although, the low yield in this cohort might help to discriminate the number of harvest LNs between the tattooing group and the non-tattooing group, this hypothesis need validation by a different study design. Second, the rate of PCT performed was different according to colon cancer and rectal cancer. However, in subgroup analysis including colon cancer patients, PCT was still independently associated with adequate lymph node harvest in multivariate analysis (data not shown). Third, it is uncertain why an increased number of lymph nodes examined after tattooing was not demonstrated in the proximal colon cancer group. It was reported that the average number of retrieved lymph nodes in the right-side colon cancer group was higher than that in the left-side colon cancer group [20]. Our data are similar to previous results. Although the effect of increased lymph node harvesting after

Table 3 Factors associated with adequate lymph node harvest (≥12 retrieved lymph nodes)

Variables		Univariate analysis		Multivariate analysis	
		N (%)	*p*	HR (95 % CI)	*p*
Gender	Male	57 (62.0)	0.095	1	0.076
	Female	39 (76.5)		2.0 (0.9–4.7)	
Age (year)	≤70	83 (72.2)	0.013	1	0.023
	>70	13 (46.4)		0.3 (0.1–0.8)	
BMI (kg/m^2)	<25	59 (64.8)	0.465		
	≥25	37 (71.2)			
CEA (ng/mL)	<5	91 (66.9)	1.0[a]		
	≥5	5 (71.4)			
Tumor location[b]	Proximal colon	22 (78.6)	0.282		
	Distal colon	33 (61.1)			
	Rectum	41 (67.2)			
Tumor size (cm)	<2	56 (62.2)	0.140		
	≥2	40 (75.5)			
Specimen length (cm)	<21	65 (63.1)	0.116		
	≥21	31 (77.5)			
LN group	Node negative	84 (68.3)	0.608		
	Node positive	12 (60)			
Lymphovascular invasion	Positive	5 (55.6)	0.640[a]		
	Negative	81 (68.6)			
	Unknown	10 (62.5)			
Histologic grade[c]	G1	28 (57.1)	0.154[a]		
	G2	66 (72.5)			
	G3	2 (66.7)			
Surgeon	A	18 (66.7)	0.448[a]		
	B	44 (72.1)			
	C	29 (59.2)			
	D	5 (83.3)			
Preoperative tattooing	No	55 (57.3)	0.002	1	0.003
	Yes	39 (83)		3.8 (1.5–9.2)	

BMI body mass index, *CEA* carcinoembryonic antigen, *LN* lymph node

[a] Fisher's exact test

[b] Tumor location; Proximal colon: ascending colon–transverse colon; Distal colon: descending colon–sigmoid colon

[c] Histologic grade; G1—well differentiated, G2—moderately differentiated, G3—poorly differentiated

Table 4 Lymph node status in patients who had carbon-containing LNs (*N*=40)

Parameters		No
Median number of carbon-containing LNs per specimen		13 (2–37)[a]
Rate of carbon-containing LNs	Among total LNs	527/993 (53 %)
	Among metastatic LNs	5/13 (38.4 %)
	Among nonmetastatic LNs	522/980 (53.2 %)
Rate of metastatic LNs	Among total LNs	13/993 (1.3 %)
	Among carbon-containing LNs	5/527 (0.9 %)
	Among non carbon-containing LNs	8/466 (1.7 %)

LN lymph node

[a] Range

PCT might be neutralized by the higher lymph node yield in the proximal colon cancer group, further investigation with a large sample size is necessary to address the limitations and unanswered questions of our study.

In conclusion, our study demonstrated that preoperative colonoscopic tattooing is associated with increased number of lymph nodes examined in T1 colorectal cancer. Preoperative colonoscopic tattooing could be a considerable option to increase the retrieved number of lymph nodes in T1 colorectal cancer especially in low median lymph node harvest cohort.

Conflict of interest The authors declare that they have no competing interests.

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