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Tattooing improves the detection of small lymph nodes and increases the number of retrieved lymph nodes in patients with rectal cancer who receive preoperative chemoradiotherapy: A randomized controlled clinical trial

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ABSTRACT

Background: In rectal cancer who received chemoradiotherapy, the number of Lymph nodes (LNs) required remains unclear. We conducted a randomized controlled trial to determine whether preoperative tattooing increases the number of LNs and enhances the detection rate of metastatic LNs.

Methods: Eighty patients with rectal cancer who received chemoradiotherapy were randomly assigned to receive no tattooing (C group) or to receive tattooing (T group).

Results: The number of LNs was significantly higher in the T group (13.3 ± 7.4 , mean \pm SD) than in the C group (8.8 ± 5.9 , $p < 0.001$), however, the number of positive LNs did not differ (0.5 ± 1.3 vs. 0.5 ± 1.1 , $p = 0.882$). The long-axis diameter of LNs was significantly smaller in the T group than in the C group (3.4 ± 1.8 vs. 3.9 ± 2.3 mm, $p < 0.001$), however, the long-axis diameter of positive LNs did not differ.

Conclusions: Tattooing increased the number of retrieved LNs by 51%, however, there was no increase in the number of positive LNs.

A short summary: In patients with rectal cancer who received preoperative chemoradiotherapy, tattooing increased the number of retrieved lymph nodes, however, it did not increase the number of positive lymph nodes.

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1. Introduction

Patients in whom many lymph nodes (LNs) are retrieved have been reported to have good outcomes in colorectal cancer without distant metastasis.^{1–3} In colon cancer, the retrieval of at least 12 LNs has been recommended to ensure accurate staging of disease.^{4,5}

Preoperative chemoradiotherapy is the international standard treatment for locally advanced rectal cancer. Chemoradiotherapy has been reported to reduce LN size⁶ and to decrease the number of retrieved LNs.^{7–12}

Consequently, 12 or more LNs are retrieved in only 20% of patients with locally advanced rectal cancer who receive preoperative chemoradiotherapy.⁸ The number of retrieved LNs required for accurate staging of disease remains unclear.

Preoperative endoscopic tattooing for colorectal cancer has been shown in some studies to increase the number of retrieved LNs, while other studies have not. These were all retrospective studies. The influence of tattooing on the number of retrieved LNs thus remains unclear.

We therefore conducted a prospective randomized, controlled clinical trial to evaluate the effects of preoperative tattooing on the number of retrieved LNs in patients with locally advanced rectal cancer who preoperatively received chemoradiotherapy.

2. Methods

2.1. Patients

We enrolled patients with clinical stage II or III, histologically confirmed adenocarcinoma of the middle or lower rectum who were scheduled to receive preoperative chemoradiotherapy and radical surgery in Tokai University Hospital. Patients were excluded

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from the study if they had a history of surgery for colorectal cancer, if they underwent a colostomy before chemoradiotherapy, or if they were scheduled to undergo laparoscopic surgery.

Patients were randomly assigned not to undergo tattooing (control, C group) or to undergo tattooing (T group). A minimization method was incorporated in the randomization to adjust baseline imbalance between the two groups in sex.

This study was conducted with the approval of the ethics committee of Tokai University (11R-004). All patients gave written informed consent before randomization. The study was registered with the University Hospital Medical Information Network (UMIN) (UMIN000016268).

2.2. Tattooing

Commercial Indian ink sterilized by autoclaving at 120 °C for 20 min was used for tattooing (KAIMEI & Co., Ltd., Saitama, Japan). In the T group, 0.1 mL of Indian ink was submucosally injected by the saline test injection technique¹⁷ into 2 sites distal to the tumor under colonoscopic guidance on the day before surgery.

2.3. Neoadjuvant chemoradiotherapy

Preoperative radiotherapy was performed with 18 MeV X-ray beams delivered by a linear accelerator (Clinac 2100C, Varian Medical Systems, Inc., Palo Alto, CA, USA), using a four-field technique. Patients received 1.8 Gy of radiotherapy daily to a total dose of 45 Gy. Oral uracil-tegafur (UFT, 300 mg/m², Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) plus leucovorin (75 mg, Taiho Pharmaceutical Co., Ltd.) or oral S-1 (80 mg/m², Taiho Pharmaceutical Co., Ltd.) was used concurrently. We reported the detail method of chemoradiotherapy previously.^{18,19}

2.4. Surgery

Total mesorectal excision was performed 6–8 weeks after the completion of radiotherapy. The inferior mesenteric artery was ligated at its aortic origin. Lateral LN dissection was not performed in any patient. The proximal resection margin was at least 5 cm from the tumor margin. The distal resection margin was 3 cm from the tumor margin in the middle rectum and 2 cm from the tumor margin in the lower rectum. Extent of distal resection of the mesorectum was determined according to the report by Hida et al.²⁰ All surgical procedures were performed by 4 or 5 staff members, consisting of 2 or 3 colorectal staff surgeons (SS, TS, AT, KO, or GS) and 1 or 2 members of the surgical team.

2.5. Pathological procedures

In Japan, surgeons dissect the surgical specimen and identify LNs. Pathologists examine all of the specimens which are considered to be candidates for LNs. One of the members of the colorectal surgical team dissected the resected specimens in the operating room within 30 min after excision. LNs were identified by direct inspection and manual palpation after closely slicing the mesorectum and sigmoid mesentery. Retrieved LNs were fixed in 3.7% formalin and were submitted to the Department of Pathology. Pathologists examined all specimens considered candidate LNs. LNs were sliced to obtain the maximal cut surface and were stained with hematoxylin and eosin. Fat clearance methods were not used in any patient. The tumor regression grade (TRG) system²¹ was used to evaluate the histologic response to chemoradiotherapy.

2.6. Measurement of LN size and evaluation of ink uptake by LNs

The long-axis diameter of the LNs was measured, and ink uptake by the LNs was evaluated using specimens stained with hematoxylin and eosin. Pathological slides were prepared with the use of a digital camera, and the long axis of the LNs was measured using a computer digitizer (ImageJ 1.47, National Institutes of Health, Bethesda, MD, USA).

2.7. Assessment

The primary endpoints were the number of LNs retrieved, the number of LNs negative for metastasis, and the number of LNs positive for metastasis. Secondary endpoints were LN size and the proportion of LNs with ink uptake (tattooed LNs). Patients in the T group were subdivided into 2 groups: patients who had no LNs with ink uptake (T group without tattooed LNs) and patients who had at least 1 LN with ink uptake (T group with tattooed LNs).

2.8. Statistical analysis

Data are presented as the means \pm SD for continuous variables and as frequencies (%) for categorical variables. Differences between groups were compared with the use of Fisher's exact test or the chi-square test for categorical variables and the Mann-Whitney *U* test or Kruskal-Wallis test for continuous variables. Univariate and subsequent multivariable linear regression was used to identify independent predictors of a higher number of retrieved LNs. Baseline variables with $p < 0.10$ in univariate analysis were included in the multivariable models. In all statistical analyses, a two-sided value of $p < 0.05$ was considered to indicate statistical significance. Statistical calculations were performed using JMP, ver. 11 software (SAS Institute Inc., Cary, NC, USA).

We previously reported that the mean number of retrieved LNs was 9 ± 6 in patients with rectal cancer who received preoperative chemoradiotherapy.⁶ Previous retrospective studies have found that tattooing increases the number of retrieved LNs by 3–5.^{13–15} On the basis of these results, we assumed that the mean number of LNs would be 9 in the C group and that the difference between the groups in the mean number of LNs would be 4, with a standard deviation of 6, an alpha error of 0.05, and a beta error of 0.2. We therefore estimated that 36 patients would be required per group. In addition, we assumed that 10% of patients would drop out of the study. Enrollment was therefore stopped when 40 participants had been enrolled in each group. Analysis was by intention-to-treat.

This study was approved by the ethics committee of Tokai University (11R-004). The study was registered with the University Hospital Medical Information Network (UMIN) (UMIN000016268).

3. Results

3.1. Patient enrollment

From April 2010 through March 2014, a total of 80 patients were enrolled. Forty patients were assigned to the C group, and 40 were assigned to the T group. In the T group, all 40 patients underwent tattooing on the day before surgery. There were no tattooing-related complications. All 80 patients completed preoperative chemoradiotherapy and underwent radical surgery.

3.2. Patient characteristics

Patient characteristics were well balanced between the groups (Table 1). LN metastasis was found in 9 patients (23%) in the C group

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