

Original Article

Ex vivo intra-arterial methylene blue injection in the operation theater may improve the detection of lymph node metastases in colorectal cancer[☆]

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ABSTRACT

Introduction: Lymph node (LN) assessment after colorectal cancer resection is fundamentally important for therapeutic and prognostic reasons. LN positivity is an indication for adjuvant treatment. This study aimed to investigate whether immediate postoperative intra-arterial methylene blue (MB) injection (MBI) into colorectal cancer specimens by a surgeon in the operating room could improve the rate of total LN and metastatic LN recovery for pathological examination.

Materials and methods: Seventy-three consecutive patients prospectively enrolled between January 2011 and December 2013 were assigned to the methylene blue (MB)-stained group and compared with 107 controls in the unstained group.

Results: The median number and range values of metastatic LNs, the number of LNs <0.5 cm, the total number of LNs harvested, and the number of cases with LN metastasis were significantly different between the MB-stained and MB-unstained groups ($p = 0.016$, $p = 0.010$, $p = 0.025$, and $p = 0.006$ respectively).

Conclusions: Immediate MBI (fresh, unfixed samples) by a surgeon in the operating room may result in a significant increase in the number of metastatic LNs diagnosed and the number of cases with positive LNs. Shifting of the injection from the pathology laboratory to the operation theater would be a good alternative whenever the operation theater is not the area located as the pathology department.

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Introduction

Lymph node (LN) assessment after colorectal cancer resection is fundamentally important for therapeutic and prognostic reasons. LN positivity is an indication for adjuvant treatment. Many studies have shown that patients with a higher number of examined LNs have a higher survival rate after colon resection than patients with a lower number of examined LNs [1–6].

In 2007, the National Quality Forum suggested harvesting a minimum of 12 LNs as the standard quality indicator for colon

cancer specimens [7]. Despite these recommendations, it has been reported that this minimum number of LNs are not detected or examined in 75% of all colorectal specimens [8,9]. Markl et al. proposed a novel technique that involves *ex vivo* intra-arterial injection of methylene blue (MB) dye, which allows the detection of small LNs in resected colorectal cancer specimens [10–12]. They showed that *ex vivo* MB injection (MBI) can dramatically increase the number of LNs detected, but not the number of metastatic LNs. In this previous study, intra-arterial MBI was performed immediately in the pathology department (fresh, unfixed samples) or within 4 h (after formalin fixation), mostly by a pathologist. We hypothesized that the time delay involved in specimen transportation from the operating room to the pathology department, together with tissue fixation itself, might affect the results of the study. The aim of our study was to investigate whether immediate postoperative intra-arterial MBI of colorectal specimens by a surgeon in the operating room would improve total LN and metastatic LN recovery for

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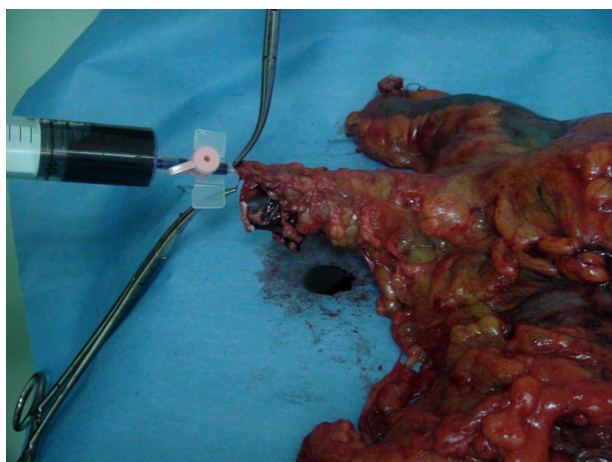


Fig. 1. Ex vivo methylene blue injection into superior rectal artery of rectal resection.



Fig. 2. Rectosigmoid colectomy specimen, transverse section after methylene blue injection.

pathological examination. We assumed that harvesting more LNs could lead to the identification of more nodal metastases and help avoid understaging.

Materials and methods

We prospectively enrolled 73 consecutive patients with colorectal cancer between January 2011 and December 2013, and assigned them to the MB-stained group. All colorectal cancer specimens received and registered between January 2007 and December 2010 served as controls, assigned to the unstained group ($n = 107$).

Patients were included if they were scheduled to undergo curative resection of any part of the colon or upper rectum for histologically proven adenocarcinoma. Patients who received palliative treatment, emergency resections, or neoadjuvant treatment were excluded from the study. The specimens were analyzed by pathologists in the Department of Pathology at the Umraniye Education & Research Hospital in Istanbul, Turkey. MBI was successfully performed in all cases. Immediately after resection, a surgeon in the operating room used appropriately sized catheters (16–20 G) to cannulate the main artery or arteries of fresh and unfixed specimens in the MBI-stained group (Fig. 1). The arteries were injected with 10–20 mL MB dye (50 mg MB in 5 mL distilled water, diluted with 0.9% NaCl solution in a 1:3 ratio). Success of the injection was determined during the procedure by the observation of instant blue staining of the specimens. Following conventional formalin fixation for approximately 48 h, macroscopic and subsequent conventional preparation was performed in the laboratory, and specimens were examined microscopically. The primary tumors were located, and representative pieces were secured for histologic examination. The mesenteric fatty tissue was sliced, visually examined, and palpated (Fig. 2). The conventional LN dissection used for the control group comprised an optional secondary dissection in cases with insufficient LN harvest. The following data were collected and analyzed for this study: demographic, surgical, pathological (including T and P stage), number of LNs harvested, number of positive LNs, smallest LN diameter, smallest metastatic LN diameter, largest metastatic LN diameter, number of LNs <0.5 cm in diameter, number of metastatic LNs <0.5 cm in diameter, and number of pN(+) cases.

Statistical analysis

The significance of differences was determined by using the Yates continuity correction test, Pearson chi-squared test, and Fisher exact test. Values of $p \leq 0.05$ were considered statistically significant.

Results

There were 73 patients in the MBI group and 107 patients in the control group. Patient characteristics are summarized in Table 1. The 2 groups were fairly well balanced. There were no significant differences in characteristics such as sex, age, tumor location, pathologic stage, histologic grade, perineural invasion (NI) or lymphatic invasion (LI) although vascular invasion (VI) was significantly higher in the MBI group than in the control group. In our study, a colorectal surgeon from the multidisciplinary team operated on all patients from both groups. MBI performed by the surgeon in the operation theater did not influence the operation time. It took only a few minutes.

There were significant differences between the MBI and the control group in the median number and range values of metastatic LNs (0.0, 0–26 [mean, 1.89 ± 3.80 LNs] vs. 0.0, 0–20 [mean, 1.34 ± 3.38 LNs]; $p = 0.016$), number of LNs <0.5 cm in diameter (15.0, 2–47 [mean, 16.36 ± 9.41 LNs] vs. 12.0, 1–46 [mean, 13.30 ± 8.61 LNs]; $p = 0.010$), the total number of LNs harvested (22.0, 3–65 [mean, 24.48 ± 12.99 LNs] vs. 17.0, 3–84 [mean, 21.49 ± 13.76 LNs]; $p = 0.025$), and the number of pN(+) cases (47.9% vs 28.0%; $p = 0.006$) (Table 2). All cases of MBI and control group were the basis for the rate calculation of mean positive LNs. The smallest LN diameter, number of LNs <0.5 cm in diameter, smallest metastatic LN diameter, largest metastatic LN diameter, and adequacy of harvested LNs were not significantly different between the 2 groups.

Discussion

In 2007, the National Quality Forum endorsed the guideline that a minimum of 12 LNs should be collected after colon resection as indicators of surgery quality [7]. However, large descriptive studies have reported that this minimum number of LNs are not collected and examined in up to 75% of patients [8,9]. In our study, the control group showed better results than those reported for the previous 2 studies, with only 19.6% of the patients having fewer than 12 nodes examined. The application of *ex vivo* arterial MBI decreased this rate to 12.3%, which was a marked improvement.

Many studies have shown that arterial MBI is a simple method that can improve LN harvest in colorectal cancer. However, past studies have also shown that increasing the number of examined LNs does not increase the number of metastases that are detected [10,11,13–16]. Markl et al. [11] concluded that the MBI technique guarantees adequate histopathological LN staging in virtually all cases of colorectal cancer; therefore, it is an extremely

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