Potential Causes of Stage Migration and Their Prognostic Implications in Colon Cancer: A Nationwide Survey of Specialist Institutions in Japan

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Objective: The actual status of stage migration in colon cancer that occurs in the procedure of preparing pathological specimens of lymph nodes has not been fully investigated.

Methods: A nationwide survey of specialist institutions for colon cancer treatment was conducted to clarify interinstitutional differences in processing surgical specimens. After categorizing 111 institutions on the basis of their practice of processing specimens, distribution of tumor stage and the recurrence status of 3294 colon cancer patients treated with the same level of lymphadenectomy were compared.

Results: Patients were diagnosed with lower tumor stages in non-teaching hospitals, in hospitals where lymph nodes were retrieved by less experienced clinicians and in hospitals in which lymph nodes were retrieved with procedures that preserved the planes of surgery around the primary tumor. However, the process of sectioning and embedding lymph nodes did not affect stage distribution. The average number of lymph nodes examined per case in each institute was 19.4. Institutional number of lymph nodes examined was not associated with node positivity but it did affect the substage in Stage III for number of lymph nodes examined ≥21. In contrast, none of the factors associated with stage migration caused interinstitutional differences in the recurrence status according to the tumor stage.

Conclusions: Considerable variety in the processing of surgical specimens existed even within one country, which could be a cause of stage migration in colon cancer. Better awareness of the clinical impact of the lymph node retrieval process is needed; an international guideline to standardize the treatment of surgical specimens might increase the value of tumor staging.

Key words: colon cancer — stage migration — pathological practice — lymph nodes — Will Rogers phenomenon

INTRODUCTION

Modern treatment strategies for colon cancer patients are determined on the basis of the tumor stage classification. Recent chemotherapy regimens are effective for preventing recurrence but may be harmful; this has increased the importance of sub-staging, as shown in the recent revision of the tumor-lymph node-metastasis (TNM) classification (1). An exact evaluation of the lymph node (LN) involvement status is essential for determining the appropriate post-operative
treatment strategy for colon cancer patients, and stage migration due to any cause directly prevents patients from receiving optimal treatment.

However, it is difficult to say that the actual status of stage migration that occurs in routine colon cancer treatment has been fully investigated, and the effect of stage migration on the prognostic outcome remains unclear. The variation in the number of LNs examined (NLNE) is well recognized as the cause of stage migration, and emphasis has been maintained on refining pathological practice to increase overall LN yield (2–4). We cannot gauge the significance of variations in the NLNE on the incidence of stage migration simply by analyzing the prognostic association of the NLNE at the patient level because the NLNE of individual patients is multifactorial (4–7). Although a number of reports have shown that a lower NLNE is associated with an unfavorable prognostic outcome in colorectal cancer (CRC) patients (8–16), a lower NLNE could be associated with not only insufficient LN sampling but also the quality of surgery (6,7,13,15), as well as patient factors, including poor host response against the tumor (5,17).

In addition, differences between institutions in their actual routine practice of processing surgical specimens, both in LN retrieval and post-LN retrieval stages, could be a cause of stage migration, but this issue has not been focused on.

Accordingly, a nationwide survey of specialist institutions belonging to the Japanese Society for Cancer of the Colon and Rectum (JSCCR) was conducted concerning the routine practices involved in processing resected specimens, nodal yields from resected specimens, stage distribution and prognostic outcome of colon cancer patients. In Japan, the level of LN dissection has been strictly defined on the basis of anatomical staging (18), and the concept of D3 dissection defined by the ligation level of the feeding artery and the length of bowel resection is well understood among practitioners (19).

Therefore, the causes of stage migration could be investigated without considering the bias of surgical factors in this study because all patients had undergone surgery with D3 dissection. In addition, we analyzed stage distribution and prognostic outcomes at the institutional level rather than the patient level to avoid the bias caused by patient factors.

In this study, we aimed to clarify the status of interinstitutional differences in processing surgical specimens and to identify techniques used in the process of preparing the LN specimens that cause stage migration. We also aimed to clarify how potential stage migration factors, including NLNE, affected the prognostic outcome in a population of patients treated at specialist institutions.

PATIENTS AND METHODS

Institutions Surveyed

A questionnaire survey to identify factors associated with stage migration in colon cancer patients was administered to 111 institutions belonging to JSCCR. These institutions included university hospitals, cancer centers and major regional hospitals all of which are core CRC treatment hospitals in Japan, and one or more of the leading CRC specialists were involved in the treatment. University hospitals and cancer center hospitals were treated as teaching hospitals (N = 53) and regional hospitals were treated as non-teaching hospital (N = 58) for analyses.

Contents of the Questionnaire Survey

The contents of the survey covers various items concerning the routine practice techniques performed for obtaining and preparing pathological LN specimens from surgical specimens of colon cancer. Representative questionnaire items (Fig. 1) were concerned with post-operative procedures used for LN retrieval, bowel sectioning, LN sectioning and LN embedding all of which were possibly associated with stage migration.

In addition, data on stage distribution and status of recurrence of a total of 3294 Stages II and III colon cancer patients were collected from these institutions. The average NLNE in each institution (institutional NLNE) obtained from 106 institutions (3047 patients) was also analyzed to determine its relevance to stage migration. T1- and T2-staged cancer patients were not included in this study. All patients had undergone curative-intent surgery with D3 lymphadenectomy (Fig. 1) in 2004 and were followed up for 5 years after surgery or until death.

Analyzes

The participating institutions were grouped on the basis of the type of post-operative procedure they used for processing the surgical specimens; the stage distribution, institutional NLNE and recurrence within 5 years after surgery were compared depending on the tumor stage. The Japanese stage classification defined by JSCCR was used for data collection; (18) this is the modified TNM staging system in which Stage III is divided into the following two subcategories on the basis of the LN status: IIIa for N1 and IIIb for N2 or positive findings in the central LNs (Fig. 2). The χ² test or the t-test was used to measure differences.

All patient data were anonymously collected from each institution, and the review board of JSCCR approved the study protocol.

Results

Status of Routine Practice for Processing Surgical Specimens in Japan

Personnel Engaged in LN Retrieval From Surgical Specimens

The survey disclosed that surgeons, not pathologists, retrieved LNs from resected colon cancer specimens in all institutions in Japan with a single exception (Table 1). In ~20% of the institutions surveyed, clinicians with <5 years of experience in clinical practice retrieved LNs from surgical specimens.
Figure 1. Differences in the routine practice for processing surgical specimens. The survey identified interinstitutional differences in the routine practice for processing surgical specimens. In this figure, the representative questionnaire items covering the processes used for lymph node (LN) retrieval, bowel sectioning, LN sectioning, and LN embedding are presented. Patterns of handling the planes of surgery around the primary tumor (A) and those of bowel sectioning (B) are thought to be possibly associated with the detection of metastatic LNs in the immediate area of the primary tumor. The LN sectioning process with or without gross inspection of metastasis (C) and patterns of LN embedding in processing different-sized LNs (D) is thought to be possibly associated with pathological detection of small LN metastasis.
LN Retrieval Procedure

LNs were retrieved from unfixed resection specimens in 107 institutions, while surgical specimens were fixed with formalin before LN retrieval in 4 institutions (Table 2). Regarding the management of fatty tissue around the primary tumor (Fig. 1A), the non-touch technique was used with the aim of evaluating the accurate radical surgical margin in 43 institutions, whereas the fatty tissue was removed to find LNs in the immediate area of the tumor in 62 institutions.

Procedure of Preparing Pathological Specimens of the Primary Lesion

None of the institutions adopted the whole-mount technique for bowel fixing; i.e. the bowel was opened first and then stretched on the board before fixation in all institutions. Various techniques were used in each institution (Table 2) to section the formalin-fixed bowel tissue containing the primary tumor (Fig. 1B).

Procedure of Preparing the Pathological LN Specimens

Multi-sectioning of formalin-fixed LNs for gross inspection of metastasis (Fig. 1C) was routinely performed in 26 institutions (Table 2). In 34 institutions, LNs were prepared with the intention that the cut surface included the hilum of the LN. There were interinstitutional differences in the technique of embedding LNs of varying sizes (Fig. 1D).

Figure 2. D3 LN dissection for colon cancer. D3 dissection is defined as systematic lymphadenectomy for pericolic, intermediate and central LNs. Pericolic LNs are located within 10 cm from the proximal and the distal margins of the primary tumor (LNs within 10 cm from the proximal margin of the tumor and those within 6 cm from the tumor for rectosigmoid cancer). Green, pericolic area; blue, intermediate area; red, central area.
Patients in teaching hospitals were diagnosed as having a more advanced tumor stage than those in non-teaching hospitals (Table 1). Patients were diagnosed with lower tumor stages in institutions that had personnel with limited experience in LN retrieval (Table 1) and in institutions that used the non-touch technique for maintaining the planes of surgery around the primary tumor (Table 2). In contrast, differences in procedures used for bowel sectioning, LN sectioning and LN embedding were not associated with differences in the distribution of tumor stage.

The incidence of recurrence was lower in Stage IIIb patients treated at teaching hospitals than in patients treated at non-teaching hospitals; this difference was marginally significant (32.7 vs. 41.6%, \(P = 0.06\)). However, none of the other factor associated with interinstitutional differences in stage distribution caused a significant interinstitutional difference in the incidence of recurrence in patients having the same tumor stage.

### Impact of the Institutional NLNE on Stage Distribution and Oncological Outcome

The average NLNE in 3047 patients analyzed in this study was 20.0. The average institutional NLNE in 106 institutions was 19.4, and the NLNE in each institution was 12 or more in 91 (85.8%) institutions. There were several cutoff values in the institutional NLNE (i.e. 21–23) for which a greater NLNE was associated with a higher ratio of patients classified as...
Stage IIIb to those classified as Stage IIIa (Table 3). However, the status of recurrence of the same tumor stage did not differ between the two groups of institutions assessed using any institutional NLNE cutoff value.

STAGE DISTRIBUTION AND ONCOLOGICAL OUTCOME ACCORDING TO THE INSTITUTIONAL TERTILE

When institutions were ranked on the basis of the institutional NLNE and then classified into three evenly sized groups, we found that the proportion of patients classified as Stages IIIa and IIIb differed between the combined first + second tertile group and the third tertile group. In contrast, no significant difference was observed in the proportion of patients classified as Stages II and III among the three groups (Table 4).

There was no significant difference in the recurrence status of patients classified as having the same tumor stage among the three tertile groups (Table 4).

DISCUSSION

Significant interinstitutional variability in the NLNE has been demonstrated (20), and attention has recently been focused on whether the institutional NLNE could be a measure of the quality of colon cancer care (12,21). There have been some attempts to identify the hospital characteristics associated with differences in the institutional NLNE (4,22,23), and some studies have reported that teaching hospitals were more likely to have a high LN examination rate (21,24,25). Pathologists belonging to the multidisciplinary team were shown to be associated with high median LN yields (6), and the increased resources available for providing quality multidisciplinary cancer care in academic centers were considered to be a possible reason for the greater LN yield in teaching hospitals (25).

Similar to previous studies (21,24,25), teaching hospitals were significantly correlated with increased NLNE in this study, and we found that patients were more likely to be diagnosed with more advanced tumor stages in teaching hospitals than in non-teaching hospitals. In addition, patients were diagnosed as having a lower tumor stage in institutions where less experienced doctors were in charge of LN retrieval. These findings indicate that stage migration may result from investigator factors related to the process of LN retrieval that are presumably associated with the skill of the investigators involved and their awareness of the importance of NLNE for accurate tumor staging.

From this nationwide survey of specialist institutions in Japan, we found that there were some interinstitutional differences in the routine practice of processing surgical specimens. For example, with regard to the management of fatty tissue around the primary tumor, manual dissection is routinely performed in some institutions, whereas the non-touch technique is used in other institutions. The results of this study indicated that the non-touch technique could be a cause of understaging, although the technique allows accurate pathological evaluation of the plane of surgery, which reflects the quality of surgery for colon cancer (26). On the other hand, a significant bias in stage distribution was not associated with interinstitutional differences in the post-LN retrieval process such as sectioning of formalin-fixed LNs and their embedment.

Although we have an international tumor staging system (1,27), there have been few attempts to create a standardized practical manual for processing surgical specimens. There are
some descriptions for the optimal processing of surgical specimens in the Japanese CRC staging manual (18). For example, it is recommended that the hilum of LN be identified and LNs be dissected in the plane through the hilum for pathological examination; it is also recommended that LNs be dissected in multiple planes with the aim of identifying metastatic areas. However, we failed to find any significant factor that improved the identification of LN metastasis in routine practice. A practical manual for processing surgical specimens should be evidence-based and well balanced between the required effort and effectiveness of detection of LN metastasis, and a standardized practical manual based on such a concept will contribute to accurate stage classification and optimal survival as a consequence of appropriate selection of post-operative treatment.

Table 3. Impact of the NLNE on stage distribution

<table>
<thead>
<tr>
<th>Institutional NLNE</th>
<th>No. of institutes</th>
<th>No. of patients</th>
<th>No. of patients according to tumor staging system</th>
<th>P value</th>
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<td></td>
<td></td>
<td></td>
<td>Stage II</td>
<td>Stage IIa</td>
</tr>
<tr>
<td>&lt;12</td>
<td>15</td>
<td>336</td>
<td>170 (50.6)</td>
<td>123 (36.6)</td>
</tr>
<tr>
<td>≥12</td>
<td>91</td>
<td>2711</td>
<td>1520 (56.1)</td>
<td>845 (31.2)</td>
</tr>
<tr>
<td>&lt;13</td>
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<td>455</td>
<td>245 (53.8)</td>
<td>157 (34.5)</td>
</tr>
<tr>
<td>≥13</td>
<td>86</td>
<td>2592</td>
<td>1445 (55.7)</td>
<td>811 (31.3)</td>
</tr>
<tr>
<td>&lt;14</td>
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<td>761</td>
<td>424 (55.7)</td>
<td>244 (32.1)</td>
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<tr>
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<td>77</td>
<td>2286</td>
<td>1266 (55.4)</td>
<td>724 (31.7)</td>
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<tr>
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<td>663 (31.4)</td>
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<td>548 (56.1)</td>
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<td>658 (33.0)</td>
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<td>1161 (55.0)</td>
<td>696 (33.0)</td>
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<tr>
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<td>29</td>
<td>935</td>
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<td>272 (29.1)</td>
</tr>
<tr>
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<td>2294</td>
<td>1267 (55.2)</td>
<td>744 (32.4)</td>
</tr>
<tr>
<td>≥24</td>
<td>25</td>
<td>753</td>
<td>423 (56.2)</td>
<td>224 (29.7)</td>
</tr>
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</table>

Although race and ethnicity were reported to be irrelevant for NLNE evaluation (3,28), these are some differences between Western countries and Japan that could explain the higher LN examination rate observed in this study. First, all patients had undergone D3 dissection with central vascular ligation in our population, whereas lower-level ligation is more likely to be popular in most Western countries (29,30), performed in Western countries (22,23,25); however, this was not the case in the present study. This might be explained by differences in the NLNE in the population. The mean NLNE per patient was reported to range from 11 to 14 for Stages II and III CRCs in Western countries such as the USA (3,16), UK (20) and New Zealand (15), whereas the corresponding figure was as high as 20, and the proportion of institutions with NLNE ≥12 reached 86% in the population analyzed in this study.
although we can find an exceptional instance in Germany (19). In addition, in Japan, LNs are retrieved from unfixed resection specimens by surgeons, as disclosed in this study, who thereafter carefully map the retrieved LNs according to their location.

We found that there were significant interinstitutional differences in the proportion of patients classified in each subgroup of Stage III when the cutoff point for the institutional NLNE was ≥21. Our findings indicate that understaging from Stage III to Stage II can be avoided by obtaining an NLNE of 12 recommended by some staging systems and guidelines (1,18,29); however, higher-level NLNE could still be required for more accurate staging which will aid an appropriate selection of adjuvant chemotherapy regimen. Theoretically, strong stage migration causes alterations in survival outcomes in each stage, a type of effect known as the Will Rogers phenomenon (31). As shown above, stage migration actually occurred in our population, but none of the stage migration factor (i.e. hospital, investigator involved in LN retrieval and NLNE) was identified to be significantly linked to this phenomenon. Therefore, we assume that the impact of stage migration factors on the prognostic outcome could be limited under the circumstance where a relatively favorable NLNE is maintained. The only limitation of this study was that it was a retrospective evaluation; a prospective study would be required to prove our findings.

In conclusion, emphasis should continue to be placed on refining the routine practice of retrieving LNs. Even if the standard NLNE of 12 is achieved, modern tumor staging requires a higher level of NLNE for accurate classification of tumors. In addition, this study clarified that considerable interinstitutional differences in the manner of treating surgical specimens, which could be a cause of stage migration, existed even in a cohort of specialist institutions within one country. The establishment of an international guideline to standardize the treatment of surgical specimens may enhance the value of tumor stage classification.

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Conflicts of interest statement

None declared.

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