Clinical Trial Note

Study protocol for an International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (T-REX study)

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Abstract

This is a prospective observational cohort study aiming to include 4000 patients with stages I to III colon cancer treated at 35 specialist institutions in Japan, South Korea, Germany, Russia, Lithuania and Taiwan. The anatomical distribution of lymph nodes and feeding arteries are investigated using surgical specimens according to pre-specified categorizing methods using intraoperative anatomical markings. Primary analyses are performed to identify the general principles of metastatic lymph node distribution in terms of its relation to the location of the primary tumor and feeding arteries. Secondary analyses will be used to estimate prognostic outcomes according to bowel resection length and central radicality and will be used to evaluate the quality of resected surgical specimens. Through in-depth lymph node mapping, standardized criteria for the definite area of 'regional' lymph node resection in routine surgical procedures can be identified, which is expected to contribute to international standardization in colon cancer surgery (ClinicalTrials.gov NCT02938481).

Key words: lymphadenectomy, bowel resection margin, lymph node mapping, D3 dissection, complete mesocolic excision

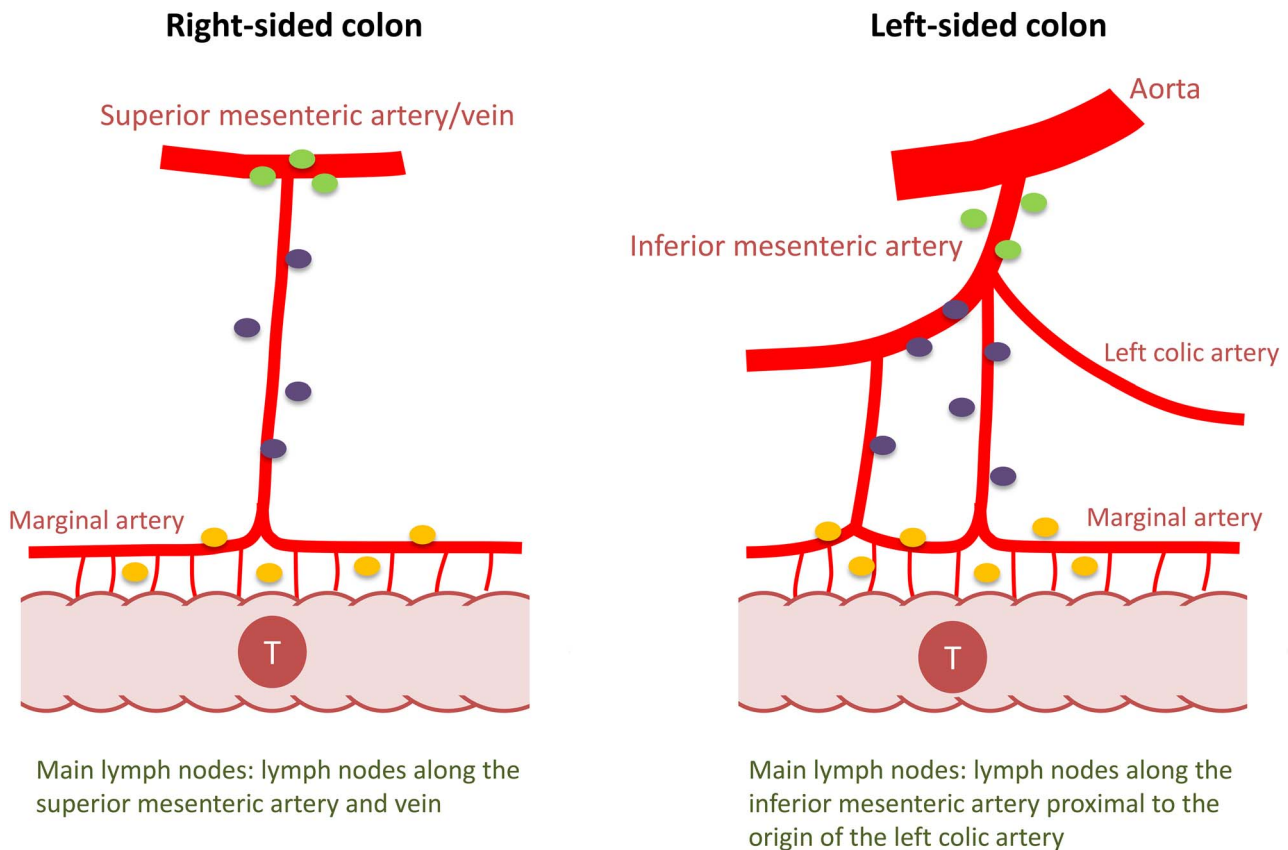**Pericolic lymph nodes**   **Intermediate lymph nodes**   **Main lymph nodes**

Right-sided colon

Superior mesenteric artery/vein

Marginal artery

T

Main lymph nodes: lymph nodes along the
superior mesenteric artery and vein

Left-sided colon

Aorta

Inferior mesenteric artery

Left colic artery

Marginal artery

T

Main lymph nodes: lymph nodes along the
inferior mesenteric artery proximal to the
origin of the left colic artery

Figure 1. Lymph node classification in colon cancer. According to the *Japanese Classification of Colorectal Carcinoma (2nd English edition)*, lymph nodes were classified into pericolic, intermediate and main lymph nodes. Note that different anatomical landmarks are used to determine main lymph nodes depending on the primary tumor location (i.e. main lymph nodes are those along the superior mesenteric artery/vein for tumors in the right-sided colon or those located along the inferior mesenteric artery proximal to the origin of the left colic artery in the left-sided colon). (Reprinted with permission from "Japanese D3 Dissection" by Hideki Ueno and Kenichi Sugihara in Surgical Treatment of Colorectal Cancer (ISBN 978-981-10-5142-5; Springer Nature Singapore Pte Ltd. 2018))

Introduction

Although standardization of surgical procedures is expected to improve oncological long-term outcomes (1), there is a great deal of international variation in colon cancer surgery, especially in terms of the length of bowel resection and central radicality. For example, studies have reported that the length of resected bowel specimens in Japan is approximately half that of resected specimens from specialist institutions in Western countries such as Germany (2).

In addition, from an international viewpoint, there are various anatomical landmarks of central radicality that vary by country; these include the middle of the colic arteries (3), the superior mesenteric vein/artery (4), and the extramesenteric lymph nodes over the head of the pancreas and along the gastroepiploic arcade (1). The resection margin of the bowel and central radicality are significantly associated with patients' oncologic outcomes after surgery. There are a number of possible reasons for such noticeable international differences in surgical procedures.

First, although the optimal extent of bowel resection in colon cancer surgery is largely determined by how one defines *regional* pericolic lymph nodes, which should be removed in routine practice because of the risk of harboring metastatic disease in the pericolic

area, there are no standardized criteria for regional pericolic lymph nodes. Second, central lymph node dissection, a surgical procedure that characterizes both complete mesocolic excision (CME) and Japanese D3 dissection, has recently attracted the attention of colorectal surgeons as a high-quality surgery to treat colon cancer; however, its surgical indication has not been confirmed. Third, although ethnic differences in physique are widely recognized, whether there are ethnic differences in the distribution of lymph nodes and feeding arteries has not been studied. This information should be clarified to estimate whether globally standardized surgical procedures for colon cancer can be successfully achieved.

An international symposium 'Standardization of Surgical Treatment of Colon Cancer' was organized by Prof. Sugihara with support by Translational Research Center for Medical Innovation (TRI) in Tokyo, Japan, in 2013. At this symposium, researchers from the USA, Europe and Asia presented their surgical procedures and treatment outcomes to discuss standardization of surgical procedures. As a result, it was recognized that an international collaborative study with a common study protocol was to be made in order to establish scientific evidence for the optimal resection margin of the bowel and anatomical landmarks of central radicality in colon cancer surgery.

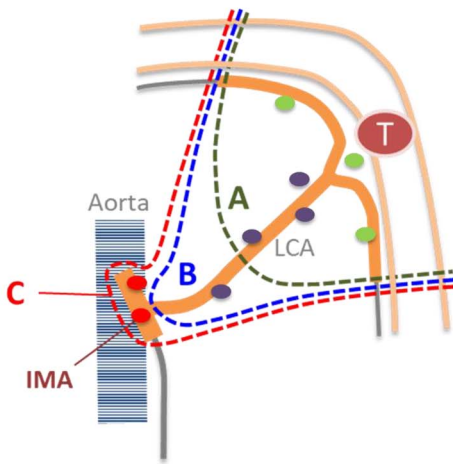## Ileocolic/right colic artery (ICA/RCA) area
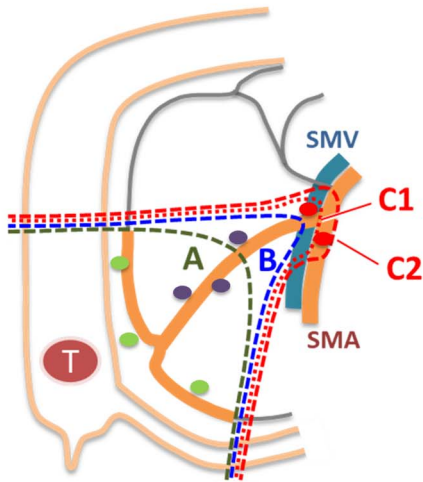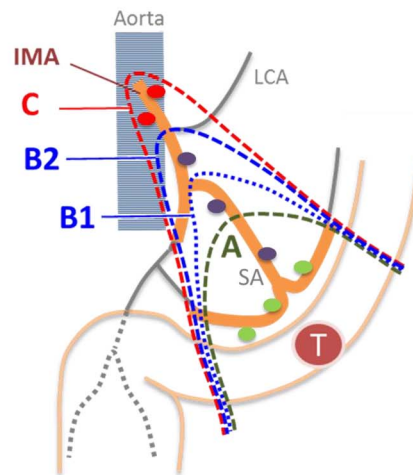
Middle colic artery (MCA) area
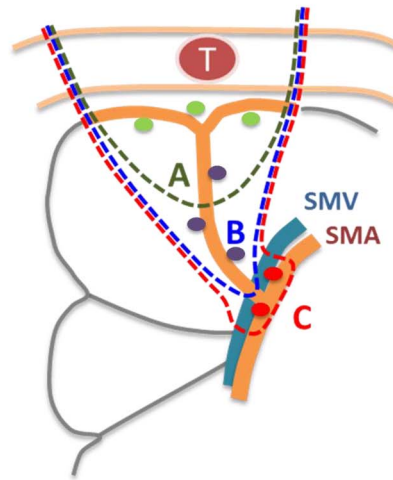
Levels of central radicality

A ▎ at the middle of the colic artery
B ▎ at the origin of the colic artery (no exposure of the SMA/SMV)
C ▎ Level B with lymphadenectomy around the origin of the colic artery
  C1: to the left side of the SMV
  C2: to the left side of the SMA [in the ICA/RCA area]

Left colic artery (LCA) area

Sigmoid artery (SA) area

Levels of central radicality

A ▎ at the middle of the colic artery
B ▎ at the origin of the colic artery
  B1: at the origin of the SA
  B2: at the level of the LCA [in the SA area]
C ▎ at the origin of the IMA

Figure 2. Schematic of the levels of central radicality in the T-REX study. Three categories of lymphadenectomy are provided for central radicality according to pre-specified anatomical landmarks. Subclassifications are provided for level C in tumors located in the ileocolic and right colic artery area and for level B in tumors located in the sigmoid artery area.
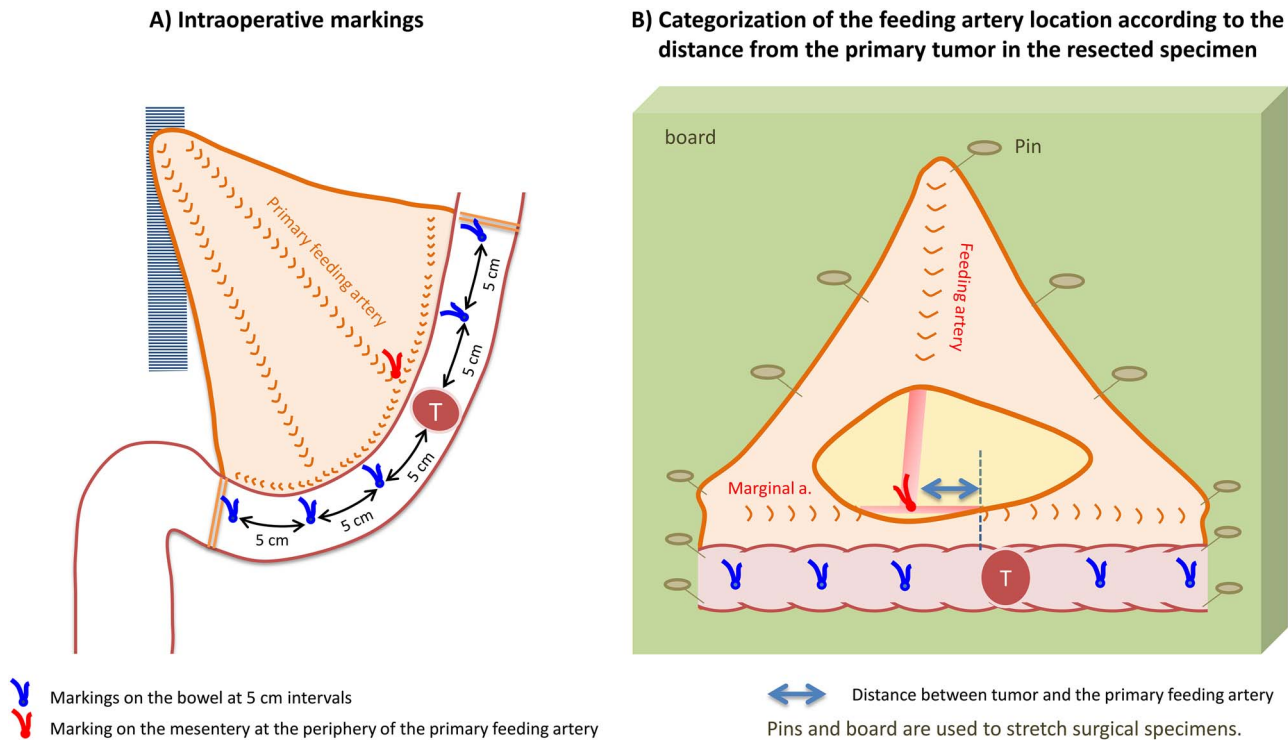
A) Intraoperative markings

B) Categorization of the feeding artery location according to the distance from the primary tumor in the resected specimen

Markings on the bowel at 5 cm intervals

Marking on the mesentery at the periphery of the primary feeding artery

Distance between tumor and the primary feeding artery

Pins and board are used to stretch surgical specimens.

Figure 3. Intraoperative markings and identification of feeding arteries in resected specimens. Intraoperative markings on the bowel at 5 cm intervals make 11 pericolic segments: i.e. primary tumor area; $0 < D \leq 5$ cm (proximal/distal sides); $5 < D \leq 10$ cm (proximal/distal sides); $10 < D \leq 15$ cm (proximal/distal sides); $15 < D \leq 20$ cm (proximal/distal sides) and 20 cm $< D$ (proximal/distal sides). The location of feeding arteries and pericolic lymph nodes are classified according to these segments.

Based on such clinical situations in the field of colon cancer, the International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer (T-REX study) was conducted by the Japanese Society for Cancer of the Colon and Rectum (JSCCR). In this study, the actual distribution of the metastatic nodes in the pericolic, intermediate, and main lymph nodes (Fig. 1) and its association with the location of the primary tumor and feeding artery will be elucidated. The primary purpose of the study is to establish an international consensus on the extent of bowel resection and appropriate central lymphadenectomy in colon cancer surgery based on an in-depth analysis of lymph node mapping.

Patients and methods

Study type and ethical issues

The T-REX study is an international, multicenter, prospective, obser-vational, cohort study that collects clinical and pathological data to assess the metastatic lymph node distribution and identify the optimal length of bowel resection and central radicality for colon cancer management.

This study was conducted in accordance with the Declaration of Helsinki, as amended on October 22, 2008, by the 59th World Medical Association General Assembly in Seoul (https://www.wma.net/wp-content/uploads/2018/07/DoH-Oct2008.pdf).

The final study protocol, including the final version of the subject information and consent forms, were approved in writing by the Ethics Committee of the JSCCR and the Investigational Review Board of each institution. Patients are included in the T-REX study only after written informed consent has been obtained.

Sample size setting

One of the important investigations in the T-REX study is the sub-population analysis, including the analysis of metastatic lymph node distribution according to T stage, for which stages T1, T2, T3, T4a and T4b, respectively, account for 17%, 13%, 56%, 8% and 6% in patients with colon cancer (5). The sample size calculation depended on the number of patients that should be included in the smallest population sub-set, i.e. the T4b population. On the basis of the consensus of opinion among the investigators, the number of patients included as the smallest population was determined to be ~200. Consequently, the target sample size of the T-REX study is 4000, which allows for a margin of error of 1% in the T4b population.

Patients included

Patients with colon cancer of preoperative stage I, II or III, who received potentially curative surgery at participating institutions (Table 1), are recruited between 30 May 2013, and 31 December 2018. The patient enrollment was initially started on 30 May 2013, only in Japan and then started internationally on 22 January 2015. The data of patients registered until 30 May2013, which include only those of Japanese patients, will be analyzed together with the international data. The inclusion criteria are as follows: (1) histologically proven colon adenocarcinoma; (2) pathological stage I, II or III; (3) potentially curative surgery; and (4) informed consent for observational data collection. Based on the protocol, the following patients are excluded from the study: (1) patients with Tis (mucosal cancer), (2) patients with multiple colon cancers, and (3) patients with preoperative adjuvant therapy.
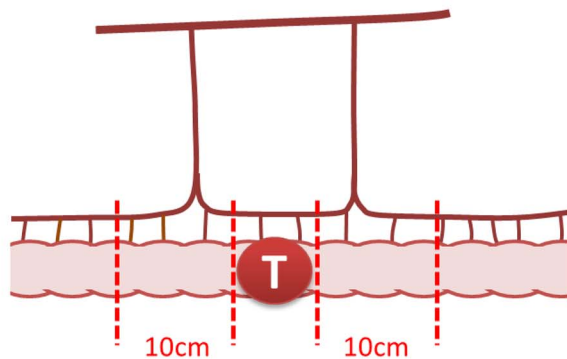
Type **I**. There is a feeding artery below the primary tumor.
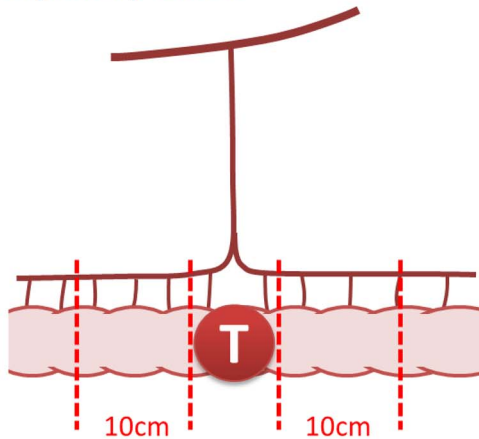
Type **II**. There is only one feeding artery within 10 cm of the primary tumor.
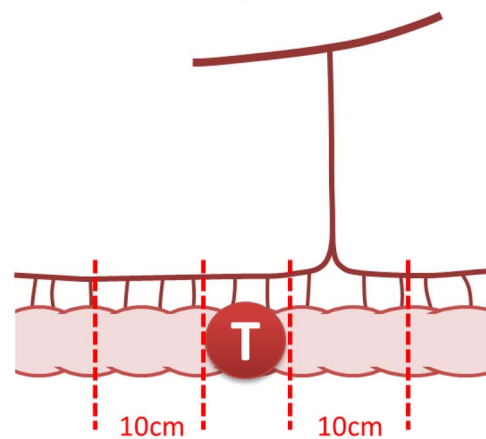
Type **III**. There are two feeding arteries within 10 cm of the primary tumor.

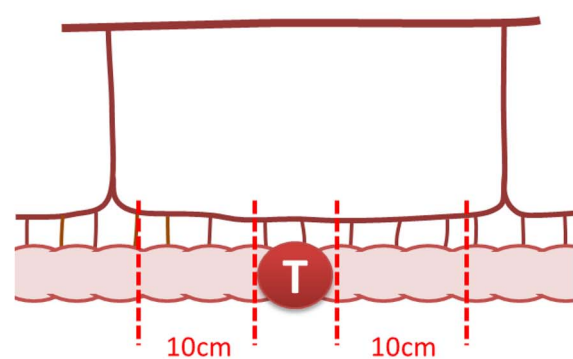## Type **IV**. There is no feeding artery within 10 cm of the primary tumor.

Figure 4. Patterns of feeding artery distribution. According to the *Japanese Classification of Colorectal Carcinoma (2nd English edition)*, the pattern of feeding artery distribution is classified into four based on the distance of the first and second feeding arteries from the primary tumor.

Parameters collected

All clinicopathological information is collected via the electronic data capture system, eClinical Base (eCB®) administered by the TRI. The data collected included patient characteristics (age, sex, height, body weight and tumor location); surgery-related factors (year and month of surgery, operation type, intraoperative marking method, length of bowel resected, level of central radicality [Fig. 2], operation time and estimated blood loss and morbidity and mortality); feeding artery information (the location of the first and second feeding arteries, distance from the primary tumor [Fig. 3] and pattern of feeding artery distribution [Fig. 4]); pathological information (timing of lymph node retrieval, depth of tumor invasion (pT), tumor grade, residual tumor, circumferential margin involvement and lymph node distribution status [Fig. 5]); and adjuvant chemotherapy information (Table 2). Prognostic information (year and month of last follow-up, prognostic outcome, year and month of recurrence and recurrence site) will be collected at 4 years after the last patient registration (January 2023). Photographs of resected surgical specimens are collected, and their quality will be assessed by central review as described below.

Intraoperative procedure (surgical process)

This study does not regulate the level of lymph node dissection or the bowel resection length. Retrieved lymph nodes are grouped as pericolic, intermediate or main lymph nodes (Fig. 1). This study provides the original classification for the level of central radicality, which is categorized into three levels (A, B and C) according to the extent of lymphadenectomy of intermediate and main lymph nodes (Fig. 2).

Prior to bowel resection, the distance from the closest tumor edge is measured in the natural state, and the points at 5, 10, 15 and 20 cm from the proximal and distal edge of the tumor are respectively marked on the bowel wall with a stitch (Fig. 3). This procedure yields 11 pericolic segments (primary tumor area; $0 < $ distance from the edge of the primary tumor $(D) \leq 5$ cm; $5 < D \leq 10$ cm; $10 < D \leq 15$ cm; $15 < D \leq 20$ cm; and 20 cm $< D$), which are used to categorize the location of pericolic lymph nodes and feeding arteries.

Postoperative procedure (pathological process)

Photographs of resected surgical specimens. High-resolution digital color photographs are taken on fresh specimens immediately after resection, including anterior and posterior views adjacent to a metric scale for calibration (Fig. 6). All photographs are submitted to the University of Leeds where morphometric analysis and surgical specimen grading of the dissection plane based on the presence and extent of any identifiable mesocolic defects will be made by one of the authors (N.W.) according to a method previously reported (6, 7).

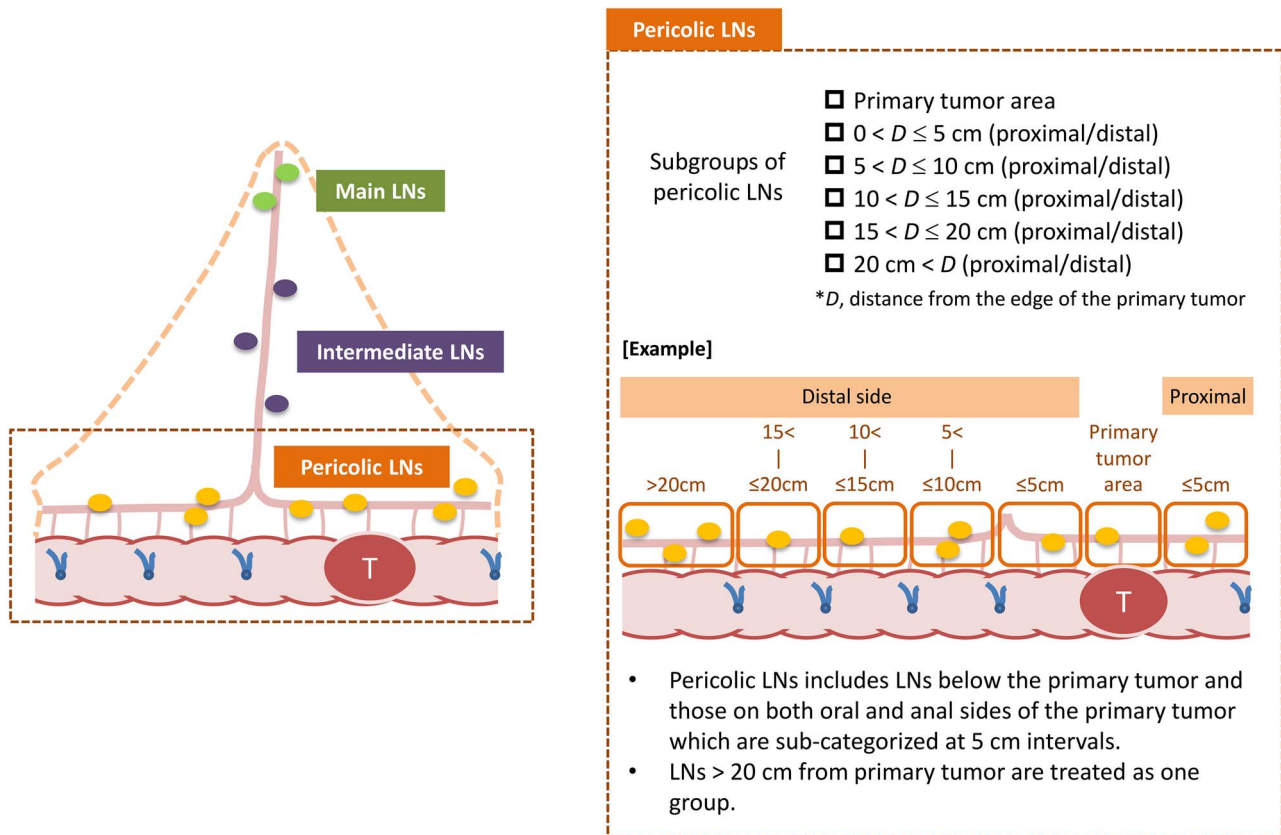# Lymph node (LN) grouping in the harvesting process

Figure 5. Groupings of retrieved lymph nodes in the T-REX study. Retrieved lymph nodes from the resected specimens were classified into pericolic, intermediate and main lymph nodes. The T-REX study provides subgroups of pericolic lymph nodes according to the pericolic segments determined by intraoperative markings at 5 cm intervals.

Evaluation of the anatomical location of feeding arteries (Fig. 3). The anatomical location of the primary feeding artery (a branch of the superior or inferior mesenteric artery located closest to the primary tumor) and the secondary feeding artery (artery arcade next to the primary feeding artery) are evaluated on either fresh surgical specimens or formalin-fixed specimens, depending on the pathological practice adopted in individual institutions. Similar to the location of the feeding arteries, the bowel segment that these feeding arteries flow into is recorded using the abovementioned method of bowel segmentation with intraoperative markings.

Grouping of the retrieved lymph nodes (Fig. 5). The timing of the lymph node retrieval process (i.e. either before or after formalin fixation) is recorded. Specimens retrieved as lymph nodes are examined by routine pathological practice. In this study, tumor nodules with no pathological evidence of lymph node structure are considered as lymph node metastases, irrespective of their size and contour morphology.

Lymph nodes retrieved from resected surgical specimens are categorized as follows: pericolic lymph nodes (tumor area; $0 < D \leq 5$ cm; $5 < D \leq 10$ cm; $10 < D \leq 15$ cm; $15 < D \leq 20$ cm; and 20 cm $< D$), intermediate lymph nodes (lymph nodes around the primary feeding artery and lymph nodes around the other feeding arteries) and main lymph nodes.

Analysis

All data, except prognostic data, will be fixed for analyses at the end of June 2020. Primary analyses will be performed to elucidate the distribution of metastatic lymph nodes. We will analyze not only lymph node status in the resected specimen but also the status of lymph node recurrence for the purpose of elucidating the actual distribution of metastatic lymph node. Sub-group analyses for primary outcomes will be based on various essential clinicopathological factors, including pT, types of feeding artery, tumor location and populations. The results of these outcomes will be presented as the frequency of metastasis and the percentage of accuracy with a measure of precision (95% confidence intervals).

The T-REX study will also estimate prognostic outcomes according to the bowel resection length and central radicality as a secondary outcome. As another secondary outcome, this study will focus on the morphometric data of resected specimens, as well as on the plane of surgery evaluated by the quality of surgical specimens. Various statistical methods, including the chi-squared test and t-test, will be used to evaluate the differences. To analyze the survival durations, the Kaplan–Meier survival curves and the log-rank test will be used.

Discussion

The oncological outcomes of colon cancer surgery are greatly influenced by the quality of surgery, particularly with lymph node

Table 1. Collaborating institutions in the T-REX study

Japan (from north to south)
1. Keiyukai Sapporo Hospital
2. Yamagata Prefectural Central Hospital
3. Tochigi Cancer Center
4. National Defense Medical College
5. Saitama Cancer Center
6. National Cancer Center Hospital East
7. Teikyo University Chiba Medical Center
8. National Cancer Center Central Hospital
9. Tokyo Medical and Dental University
10. Teikyo University School of Medicine
11. Tokyo Metropolitan Cancer and Infectious Diseases Center Komagome Hospital
12. Kyorin University School of Medicine
13. Tokyo Women's Medical University
14. Kanagawa Cancer Center Hospital
15. Yokohama City University
16. Yokohama City University Medical Center
17. Saiseikai Yokohamashi Nanbu Hospital
18. Niigata Cancer Center
19. Shizuoka Cancer Center Hospital
20. Aichi Cancer Center Hospital
21. Fujita Health University
22. Mie University Graduate School of Medicine
23. Shiga University of Medical Science
24. Osaka International Cancer Institute
25. Wakayama Medical University
26. Kurume University School of Medicine
27. Takano Hospital

South Korea
1. Yonsei University
2. Asan Medical Center

Germany
1. University Hospital Erlangen

Russia
1. First Moscow State Medical University

Lithuania
1. Klaipeda University Hospital
2. National Cancer Institute

Taiwan
1. National Taiwan University Hospital
2. China Medical University Hospital

UK
1. Leeds University[a]

[a]Protocol development and evaluation of the photographs of resected surgical specimens.

dissection. The pericolic lymph nodes located along the bowel and marginal artery are the most common site of metastasis in colon cancer (8). Currently, there are no standardized criteria for *regional* lymph nodes in the pericolic region, which should be resected in routine practice because of the possibility of harboring metastasis. For example, the tumor–node–metastasis classification regards all pericolic lymph nodes as regional lymph nodes, with no sub-classification based on their clinical implications. The T-REX study is expected to identify the anatomical distribution of metastatic pericolic lymph nodes, particularly in terms of their association with the location of the primary tumor and feeding arteries, which determines regional pericolic lymph nodes.

In Western countries, the bowel resection length is generally thought to depend on the area of the arterial supply to the colon (9). In addition, the vascular arcade next to the primary feeding

Table 2. Clinical and pathological data collected from the T-REX study

Clinical and pathological data
Patient characteristics
  – Age and sex
  – Height and body weight
  – Tumor location
Surgery-related factors
  – Year and month of surgery
  – Operation type (open/laparoscopic)
  – Intraoperative marking method (under direct vision/laparoscopic)
  – Length of the bowel resected (proximal/distal to the tumor)
  – Level of central radicality (Fig. 2)
  – Operation time and blood loss
  – Morbidity (Clavien–Dindo grade) and 30-day mortality
Feeding artery information
  – Name of first and second feeding arteries
  – Location of first and second feeding arteries (distal/proximal/within the tumor area)
  – Distance from the primary tumor (cm) (Fig. 3)
  – Pattern of feeding artery distribution (Fig. 4)
Pathological information
  – Timing of lymph node retrieval (before fixation/after fixation)
  – pT stage
  – Tumor grade
  – Residual tumor (R0/R1)
  – Circumferential resection margin
  – Number of lymph nodes retrieved and involved
    (a) Pericolic lymph nodes according to the 5 cm interval (Fig. 5)
    (b) Intermediate lymph nodes (around first feeding artery/around other feeding arteries)
    (c) Main lymph nodes

Postoperative treatment
  – Adjuvant chemotherapy
Prognostic outcomes
  – Year and month of final follow-up
  – Prognostic outcomes and cause of death
  – Year and month of recurrence
  – Recurrence site
    (remnant mesenteric lymph nodes/anastomosis/liver/lung/peritoneum/non-mesenteric
    lymph nodes/other)
Other
    Photographs of resected specimen (Fig. 6)

artery is routinely resected (2). Consequently, wide bowel resection is conventionally applied in routine practice (2, 3). In Japan, in contrast, bowel resection 10 cm from the tumor edge (the 10 cm rule) has long been used in routine clinical practice on the assumption that the 10 cm rule ensures that no regional pericolic lymph nodes remain (10, 11).

Recently, in Japan, the definition of pericolic regional lymph nodes was revised in the Japanese Classification of Colorectal Carcinoma (second English edition, 2009) published by the JSCCR (4). In this definition, the distribution of the feeding artery is classified into four patterns (Fig. 4), and in addition to an anatomical landmark of 10 cm from the primary tumor, another landmark (5 cm from the feeding artery) was adopted to define regional lymph nodes depending on feeding artery distribution (the feeding artery-oriented rule) (4).

Currently, we have no robust scientific evidence to support the appropriateness of the extent of bowel resection based on the Western-type wide resection, the 10 cm rule or the feeding artery-oriented rule. With both CME with central vascular ligation and Japanese D3 dissection, which have reported good surgical outcomes (1, 6, 12), radical central lymph node dissection, including removal of the main nodes (lymph nodes located around the superior mesenteric artery/vein or the inferior mesenteric artery/vein), is applied. However, the questions of whether the resection of main nodes should be included in central lymph node dissection and who should receive this kind of extended operation, if it should be included, have not been solved.

It is well recognized that among populations, there are great differences in physical characteristics, including body size and body habitus. We should consider the possible differences in the anatomical structures in the bowel, including the anatomical distribution of feeding arteries to the colon, which can affect the distribution of metastatic lymph nodes and the optimal anatomical area for lymphadenectomy (2). The T-REX study is expected to elucidate whether
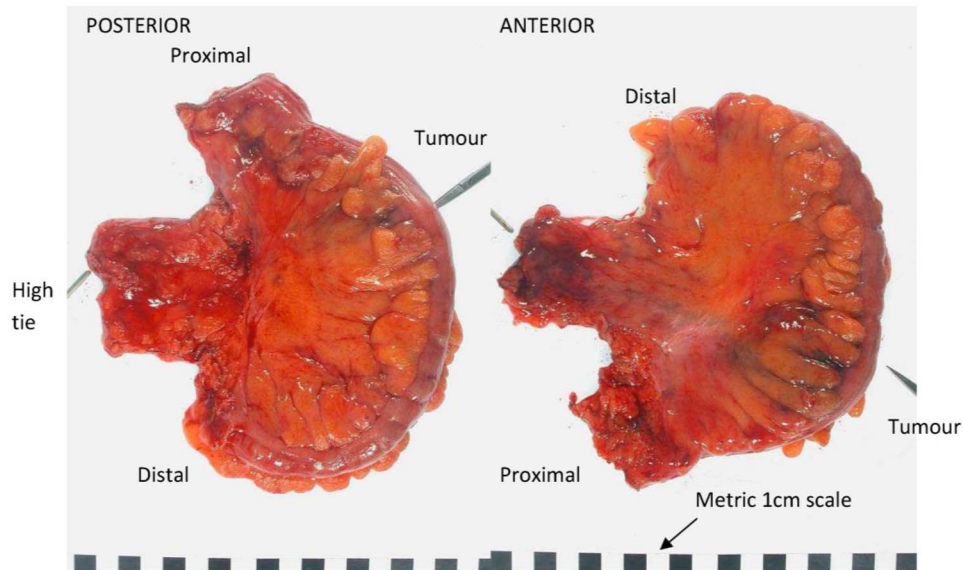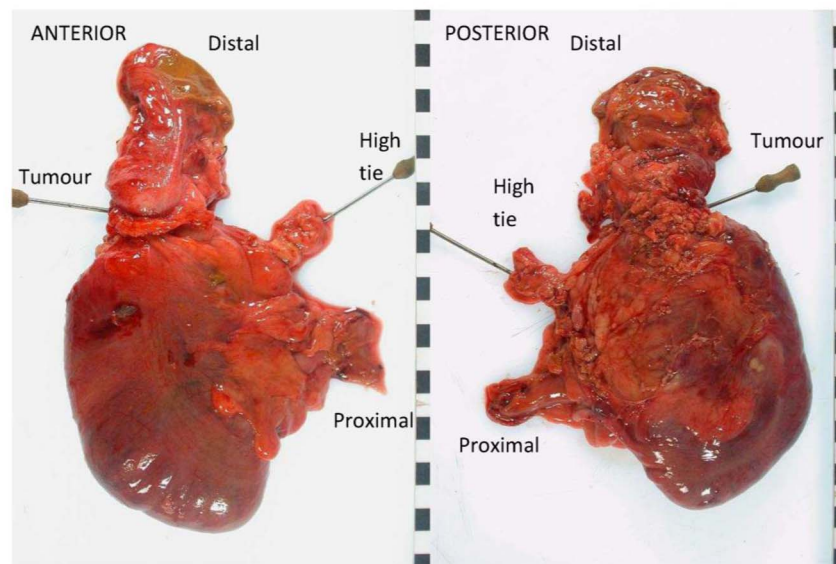
Example of a left-sided resection

Example of a right-sided resection

Figure 6. Photography protocol for of colon cancer specimens. General principles. (1) Photographs should be taken with a high-resolution digital camera; (2) the camera should be mounted on a fixed stand to minimize movement artifacts; (3) images should not contain any direct patient identifiers but should be identified by the unique study number and preferably a second indirect identifier; (4) all images must include a metric scale to allow calibration when using image analysis software and (5) a white background is ideal, although any plain color is acceptable. Whole-specimen photographs: (1) ideally, the whole specimen should be photographed before it is opened; (2) the mesentery should be laid out flat but not under tension; (3) the site of the tumor and the site of the vascular ties must be clearly visible on the photographs; (4) the whole specimen should be visible in the image; (5) photographs should be taken from both the front and the back of the specimen; (6) ideally, the distal and proximal aspects should be labeled (mainly for left-sided and wedge excisions where orientation may be difficult); (7) photographs should be taken directly above the specimen to reduce distortion artifact and (8) additional close-up pictures if any mesocolic defects or perforations exist.

an international standard for regional lymph nodes is possible in colon cancer.

In conclusion, the T-REX study aims to clarify the metastatic lymph node distribution in colon cancer. This study would enable establishment of standardized criteria for the definite area of regional lymph nodes in colon cancer, thereby providing reliable evidence about the optimal length of bowel resection and the extent of central lymphadenectomy in colon cancer surgery.

Acknowledgement

Abbreviations

CME, complete mesocolic excision; *D*, distance from the edge of the primary tumor; JSCCR, Japanese Society for Cancer of the Colon and Rectum; T-REX, International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer

Conflict of interest

The authors declare no conflict of interests.

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Appendix

Co-authors other than those listed in the title page

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