

International multicentre project

T-REX Study

International Prospective Observational Cohort Study for
Optimal Bowel Resection Extent and Central Radicality for
Colon Cancer

STUDY PROTOCOL (English version)



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SUMMARY

FULL TITLE OF STUDY	International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radicality for Colon Cancer
STUDY ACRONYM	T-REX Study
PROJECT LEADER	Kenichi Sugihara, MD, PhD (President of the Japanese Society for Cancer of the Colon and Rectum: JSCCR)
CHIEF INVESTIGATORS	Kazuo Hase, MD, PhD (Japan) Philip Quirke (United Kingdom) Werner Hohenberger (Germany) Nam Kyu Kim (Korea)
BACKGROUND <p>In colon cancer, the incidence of metastasis in the pericolic lymph nodes (LNs) located along the bowel and marginal artery is high. The optimal extent of bowel resection is closely associated with how we define 'regional' pericolic LNs, which should be resected because of the risk of metastasis. However, there are no standardised criteria for 'regional' LNs in the pericolic area.</p> <p>In Western countries, the length of bowel resection is thought to depend on the removal of the arterial supply of the colon. Surgeons usually resect the vascular arcade next to the primary feeding artery; consequently, wide bowel resection is routinely employed. On the other hand, bowel resection at 10 cm from a tumour edge ('10 cm from tumour' rule) has long been employed in routine practice in Japan. In addition, the '5 cm from the feeding artery' rule (bowel resection at 5 cm from the primary feeding artery) has newly been adopted as a standard resection margin in the Japanese guidelines. The length of bowel resection in Japan is shorter than that of bowel resection in Erlangen.</p> <p>Currently, we have no robust scientific evidence to support the appropriateness of the extent of bowel resection based on the Western-type wide resection, '10 cm from</p>	

tumour' and '5 cm from feeding artery' rules. In both complete mesocolic excision (CME) with central vascular ligation (CVL) and Japanese D3 dissection, which reported good surgical outcome, radical central lymph node dissection, including removal of LNs located around the superior mesenteric artery and vein or the inferior mesenteric artery and vein (main nodes), is employed. However, whether or not the resection of these main nodes should be included in central radical LN dissection has not been confirmed.

To establish a consensus for the extent of bowel resection and appropriate central LN dissection, international prospective studies focusing on the distribution of metastatic LNs along the bowel and the primary feeding artery are conducted.

AIM

The T-REX study aims to clarify the actual status of metastatic LN distribution in colon cancer and provide reliable evidence regarding the optimal length of bowel resection and the extent of central lymph node dissection in colon cancer surgery.

OUTCOMES

Primary analysis

- Distribution of metastatic LNs

Secondary outcomes

- Prognostic outcomes according to the length of bowel resection and central radicality

STUDY DESIGN

Prospective observational cohort study

INCLUSION CRITERIA

- Histologically proven colon adenocarcinoma
- Pathological stage I, II or III
- Potentially curative surgery
- Informed consent for observational data collection

EXCLUSION CRITERIA

- Tis (mucosal cancer)
- Multiple cancers
- All patients with preoperative adjuvant therapy

SETTING

This study will be coordinated from JSCCR and will internationally recruit collaborating institutions. A total of 4000 patients with stage I, II and III colon cancer are planned to

be included in the T-REX study.	
DATE OF STUDY START	30 May 2013
DATE OF LAST PATIENT ENROLMENT	31 December 2017

■ 1. INTRODUCTION

1.1 Background

Oncological outcomes of colon cancer surgery are greatly influenced by quality of surgery, particularly that of lymph node (LN) resection. In colon cancer, the incidence of metastasis in the pericolic LNs located along the bowel and marginal artery is high. The optimal extent of bowel resection is closely associated with how we define ‘regional’ pericolic LNs, which should be resected because of the risk of metastasis. Currently, there are no standardised criteria for ‘regional’ LNs in the pericolic region. As per the tumour–node–metastasis (TNM) classification, all pericolic LNs are treated as regional LNs, with no sub-classification on the basis of their clinical implications.¹

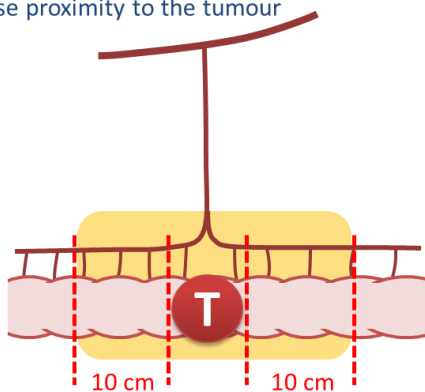
In Western countries, the length of bowel resected is thought to depend on the removal of the arterial supply of the colon.² Surgeons usually resect the vascular arcade next to the primary feeding artery,³ consequently, wide bowel resection is routinely employed.^{3,4} For example, right hemicolectomy, wherein the ileocolic, right colic and right branch of the middle colic arteries and veins are ligated, is typically used to treat lesions of the cecum or ascending colon.⁴

In Japan, bowel resection at 10 cm from a tumour edge (‘10 cm from tumour’ rule) has been employed in routine clinical practice on the assumption that the ‘10 cm from tumour’ rule ensures that no regional pericolic LNs remain.^{5,6} Studies have reported that the length of resected bowel specimens in Japan was approximately half as compared with that of resected specimens from specialist institutions in Western countries such as Germany.³

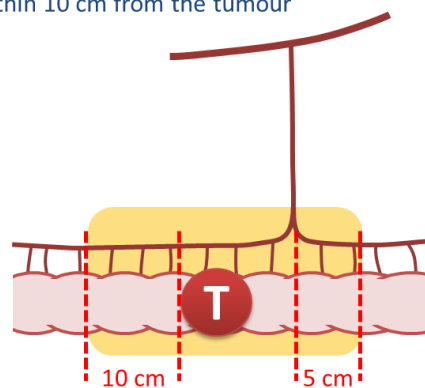
Recently, in Japan, an additional standard to define pericolic regional LNs has been introduced in the Japanese Classification of Colorectal Carcinoma (2nd English edition, 2009) published by the Japanese Society for Cancer of the Colon and Rectum (JSCCR).⁷ The distribution of the feeding artery is classified into 4 patterns (Fig. 1), and the

regional LN area was determined according to the pattern of the feeding artery. More specifically, bowel resection at 5 cm from the primary feeding artery ('5 cm from the feeding artery' rule) was newly employed, with a single exception of a case, wherein the primary feeding artery entry was located just below the primary tumour. When the vascular arcade next to the primary feeding artery enters within 10 cm from the tumour, it is considered to be treated as the primary feeding artery.

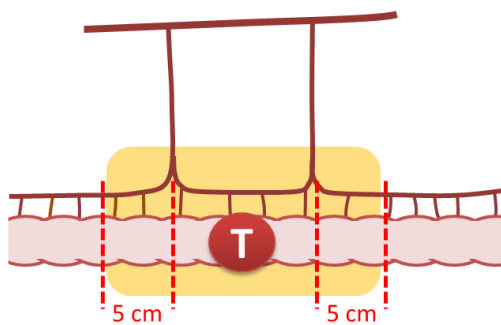
Type I. When there is a feeding artery in close proximity to the tumour



Type II. When there is only one feeding artery within 10 cm from the tumour



Type III. When there are 2 feeding arteries within 10 cm from the tumour



Type IV. When there is no feeding artery within 10 cm from the tumour, the artery closest to the tumor is regarded as its feeding artery

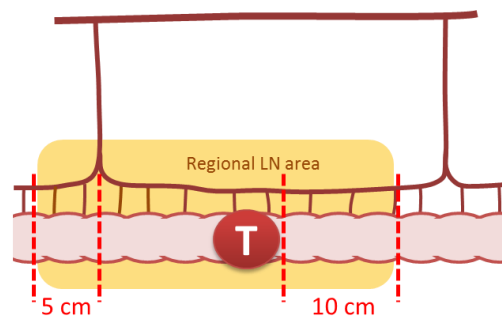


Fig. 1 Pericolic 'regional' lymph nodes in colon cancer [Japanese Classification of Colorectal Carcinoma, 8th edition (2012)]

Currently, we have no robust scientific evidence to support the appropriateness of bowel resection length based on Western-type wide resection, '10 cm from tumour' and '5 cm from feeding artery' rules. We may have to consider that there are differences in body habitus and large bowel structure among populations, which can

effect the length of bowel resection.³ In both complete mesocolic excision (CME) with central vascular ligation (CVL) and Japanese D3 dissection, which reported good surgical outcomes,⁸⁻¹⁰ radical central lymph node dissection, including removal of LNs located around the superior mesenteric artery and vein or the inferior mesenteric artery and vein (main nodes), is employed. However, whether or not the resection of these main nodes should be included in central radical LN dissection has not been confirmed.

To establish a consensus regarding the length of bowel resection and extent of central LN dissection, international prospective studies focusing on the distribution of metastatic LNs and the primary feeding artery are required. Such studies would enable establishment of standardised criteria for the definite area of LNs to be regarded as 'regional' in colon cancer.

1.2 Objectives

The T-REX study aims to clarify the actual status of metastatic LN distribution in colon cancer and provide reliable evidence regarding the optimal length of bowel resection and extent of central LN dissection in colon cancer surgery.

2 STUDY DESIGN

2.1 Overview

The T-REX study is an international, multicentre, prospective, observational, cohort study, which will collect clinical data regarding the metastatic LN distribution status in order to identify the optimal length of bowel resection and central radicality for colon cancer management. All new patients with stages I, II, and III colon cancer who will receive curative surgery in any of the participating centres will be requested to participate in this study.

2.2 Study type

Prospective observational cohort study

2.3 Sample size

To determine an accurate representation of metastatic LN distribution in colon cancer, a large number of patients are needed. One of the important investigations in the T-REX study is sub-population analysis, including analysis of the metastatic LN distribution according to T stage, for which T1, T2, T3, T4a and T4b stages account for 17%, 13%, 56%, 8% and 6% in patients with colon cancer.¹¹ The sample size calculation will depend on the smallest population sub-set, and we aim to include 4000 patients with colon cancer in the T-REX study.

2.4 Recruitment of collaborating investigators

In Japan, the JSCCR multi-institutional study, aiming to identify the optimal resection length for colon cancer, has been initiated in January 2013; this study involves 21 domestic specialist institutions for colorectal cancer treatment and a total of 3000 patients with colon cancer receiving curatively intended surgery between 2013 and 2017 and intends to prospectively evaluate the status of metastatic LN distribution.

We have modified the protocol of the domestic JSCCR study so that the T-REX study can be international in scope. T-REX will recruit collaborating institutions from other countries and continue to add institutions to ensure that the determined sample size is achieved.

2.5 Eligibility

Patients with colon cancer of preoperative stages I, II or III, who will receive potentially curative surgery at participating institutions (see 3.2 Participating institutions) between 30 May 2013 and 31 Dec 2017 are eligible.

Inclusion criteria

- Histologically proven colon adenocarcinoma
- Pathological stage I, II or III
- Potentially curative surgery
- Informed consent for observational data collection

Exclusion criteria

- Tis (mucosal cancer)
- Multiple colon cancers
- All patients with preoperative adjuvant therapy

2.6 Primary and secondary outcomes

Primary outcomes

- Distribution of metastatic LNs

Secondary outcomes

- Prognostic outcomes according to the length of bowel resection and central radicality

2.7 Parameters collected (Appendix 01 and 02)

- Patient characteristics
 - Age
 - Gender

- Basic physical examination
 - Height
 - Weight

- Tumour characteristics
 - Tumour location
 - pT stage
 - Differentiation grade
 - Circumferential margin involvement

- Surgery related
 - Year and month of surgery
 - Surgical method (open surgery/laparoscopic surgery)
 - Intraoperative marking for measurement
 - Resection margin
 - Level of central radicality
 - Plane of surgery based on photographs of resected specimen
 - Operation time and estimated blood loss
 - Morbidity and mortality

- Items associated with feeding artery
 - Pattern of distribution
 - Location

- LN distribution
 - Number of LNs retrieved and involved LNs
 - (a) pericolic LNs (5-cm interval)
 - (b) intermediate LNs
 - (c) main LNs

- Prognostic outcomes
 - Year and month of last follow-up
 - Prognostic outcomes and cause of death
 - Year and month of recurrence
 - Recurrence pattern

2.8 Intraoperative procedure (surgical process)

LN dissection level

The T-REX study does not regulate the LN dissection level.

The location of LNs and level of central radicality will be categorised and recorded as described below.

LN grouping (Fig. 2).

- Pericolic LNs: LNs along the marginal arteries and vasa recta of the colon
- Intermediate LNs:
 - Right-sided colon: LNs along the colic arteries
 - Left-sided colon: 1) LNs along the left colic and sigmoid arteries; 2) LNs along the inferior mesenteric artery between the origin of the left colic artery and the origin of the terminal sigmoid artery
- Main LNs:
 - Right-sided colon: LNs at the origin of each colic artery
 - Left-sided colon: LNs along the inferior mesenteric artery proximal to the origin of the left colic artery

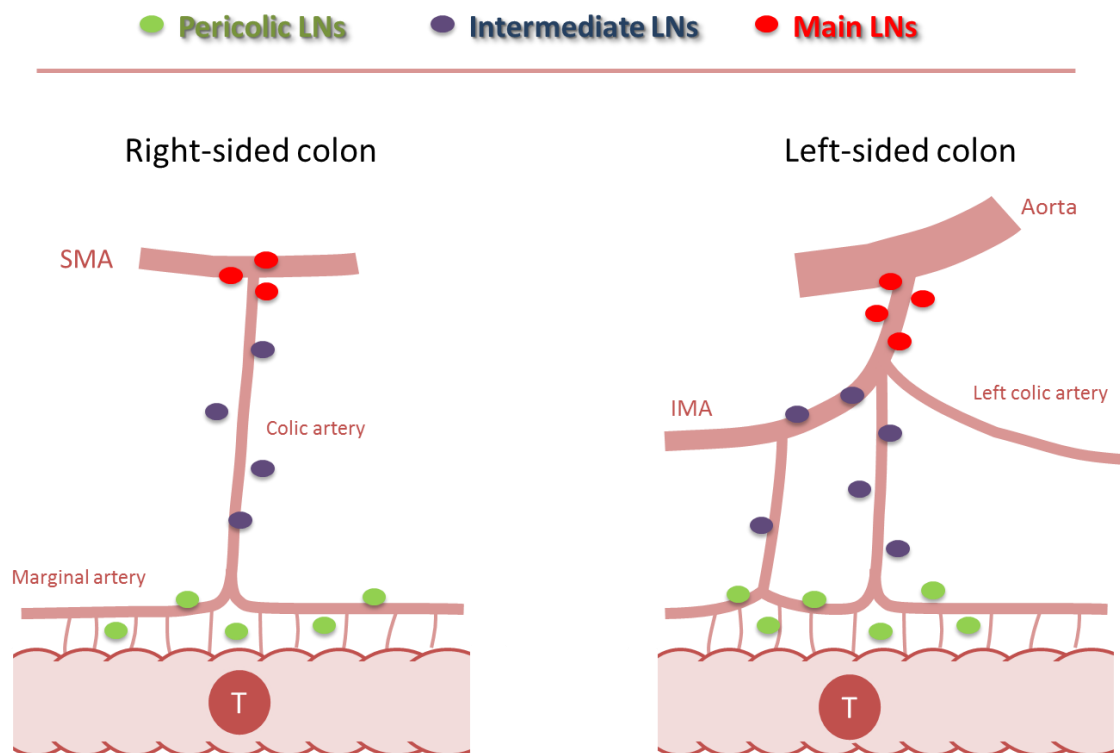
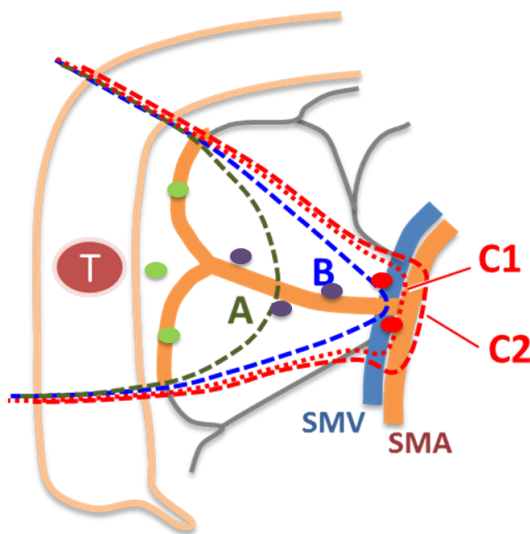


Fig. 2 Lymph node grouping in colon cancer

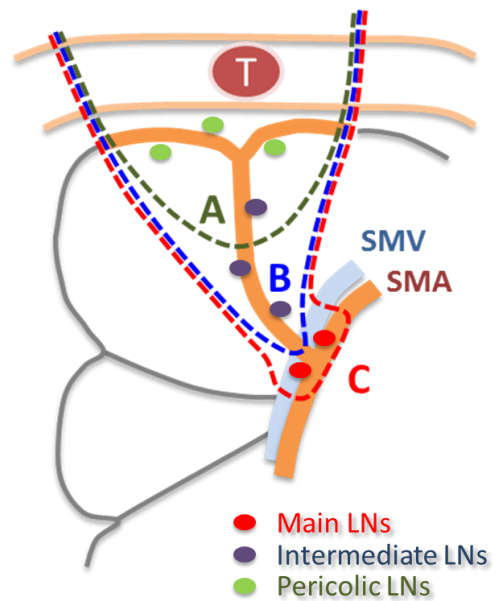
Level of central radicality (Fig. 3)

Central radicality will be categorised into 3 levels (A, B and C) according to the extent of lymphadenectomy for intermediate/main LNs.

Ileocolic/right colic artery (ICA/RCA) area



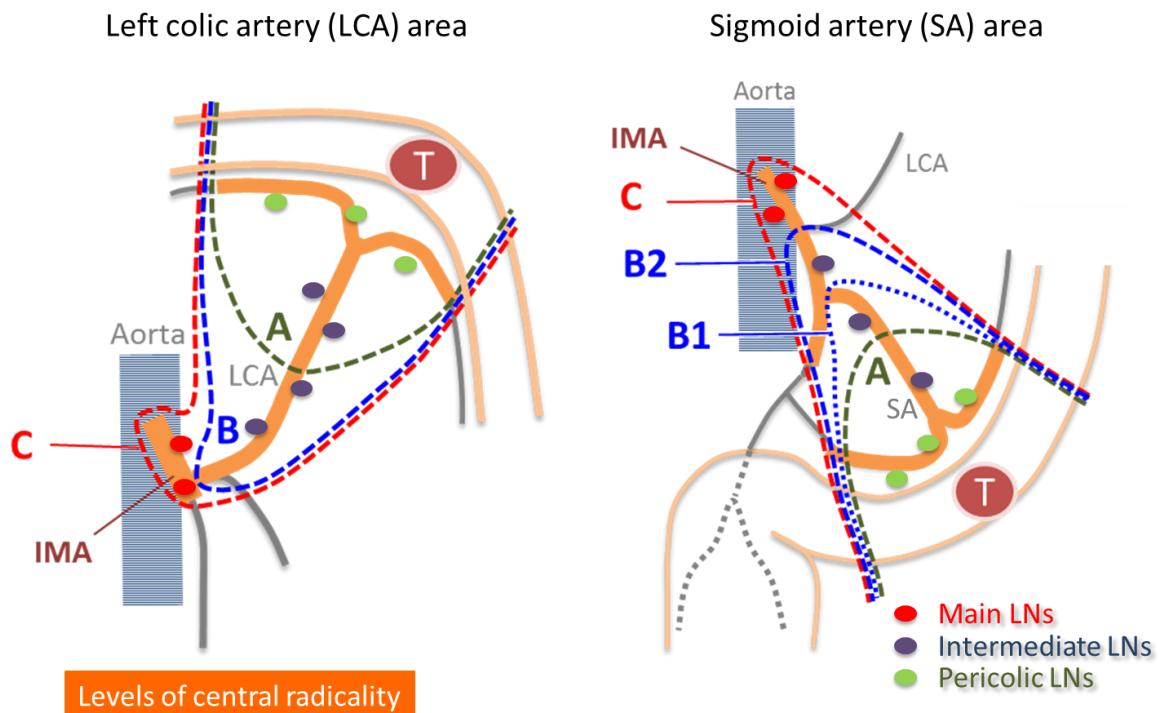
Middle colic artery (MCA) area



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]

Fig. 3(A) Extent of central radicality in colon cancer [right-sided colon]



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

Fig. 3(B) Extent of central radicality in colon cancer [left-sided colon]

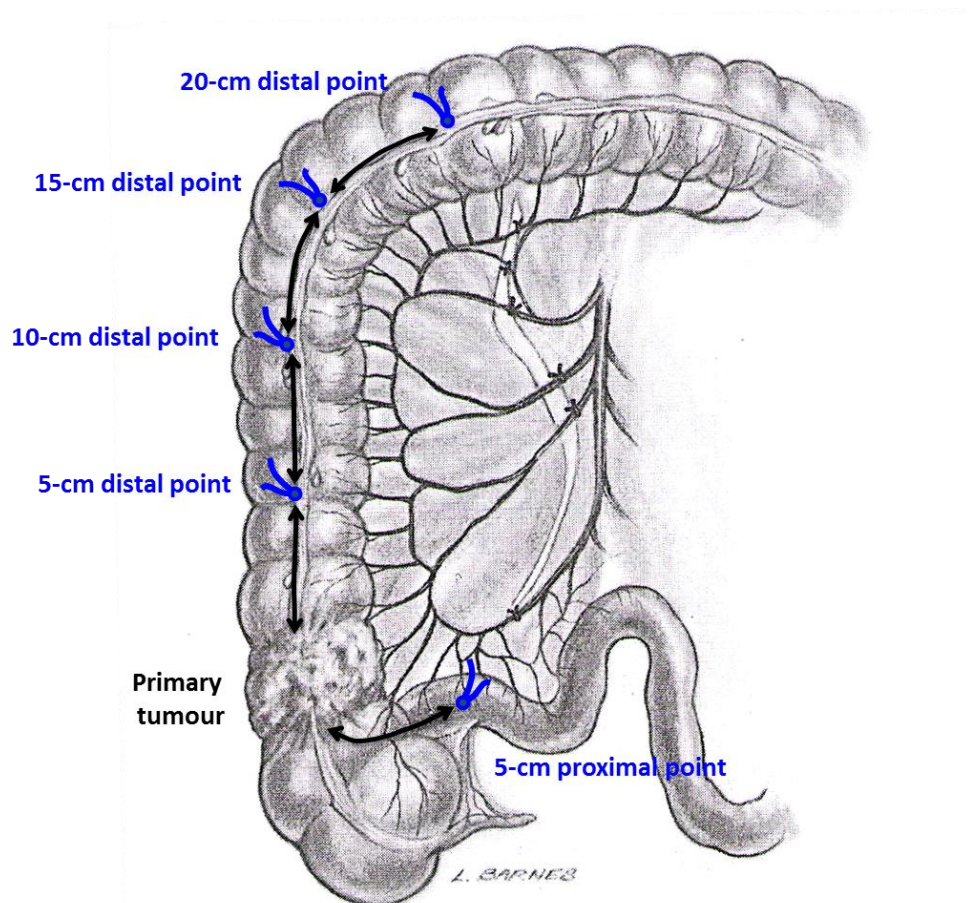
Bowel resection length

The T-REX study does not regulate the bowel resection length.

Before resecting the bowel, markings will be performed in the following manner.

Intraoperative markings (Fig. 4)

Before resecting the bowel, the distance from the tumour edge will be measured in the natural state. The bowel wall at 5 cm, 10 cm, 15 cm and 20 cm from the proximal and distal edge of the tumour will be marked with a stitch.



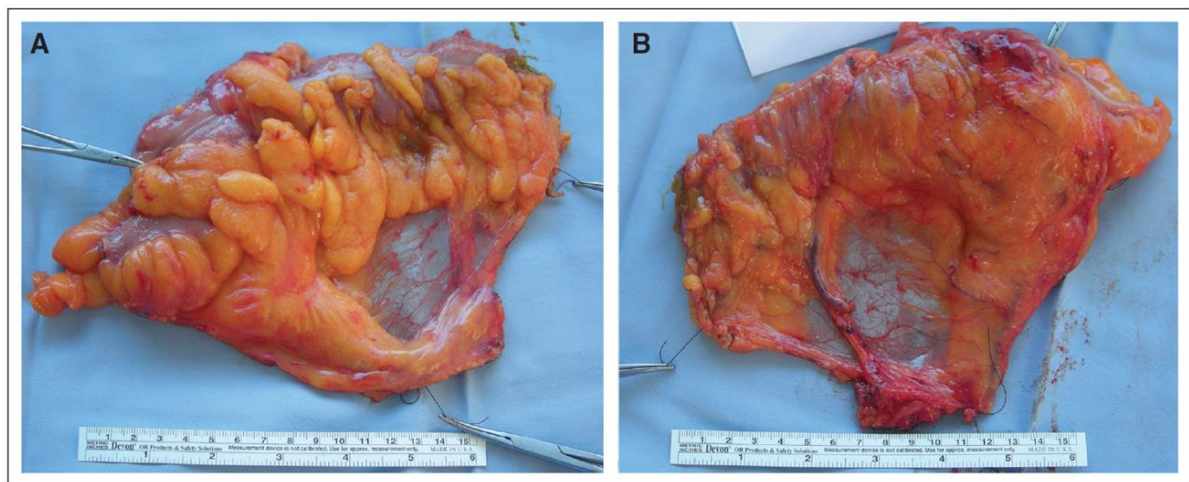
 Marking on the bowel at intervals of 5 cm

Fig. 4 Intraoperative markings [original figure: Corman's colon and rectal surgery (6th edition), Lippincott, Williams & Wilkins]

2.9 Postoperative procedure (pathological process)

Photographs of resected surgical specimens

High-resolution digital color photographs will be taken on fresh specimens immediately after resection, including anterior and posterior views alongside a metric scale for calibration (Fig. 5). The mesentery will be laid out flat without external tension, and the sites of tumour and vascular ties will be made identifiable.^{3,9,14}



(A) Anterior and (B) posterior views of a fresh right-sided hemicolectomy specimen taken alongside a metric scale. The position of the caecal tumor is indicated by forceps, and the two vascular ties are visible. Note the smooth posterior surgical margin and intact peritoneal window.

Fig. 5 Photographs of fresh surgical specimens.: [quoted from ref. 3: NP West, et al. Understanding optimal colonic cancer surgery: comparison of Japanese D3 resection and European complete mesocolic excision with central vascular ligation. *Journal of Clinical Oncology* 2012; 30(15); 1763-1769]

Evaluation of the anatomical location of the feeding arteries (Fig. 6)

Anatomical location of the primary feeding artery (a branch of the superior or inferior mesenteric artery located closest to the primary tumour) and the secondary feeding artery (artery arcade next to the primary feeding artery) will be evaluated on either of fresh surgical specimens or formalin-fixed specimens. The location of feeding arteries will be recorded by evaluating the bowel segment they flow in. Categories of bowel segments according to intraoperative markings are as follows:

- (1) Within the tumour area
- (2) $0 < D \leq 5$ cm (proximal/distal sides)
- (3) $5 < D \leq 10$ cm (proximal/distal sides)
- (4) $10 < D \leq 15$ cm (proximal/distal sides)
- (5) $15 < D \leq 20$ cm (proximal/distal sides)
- (6) 20 cm $< D$ (proximal/distal sides)

D, distance from the edge of the primary tumour

Anatomical grouping of feeding arteries

[Example]

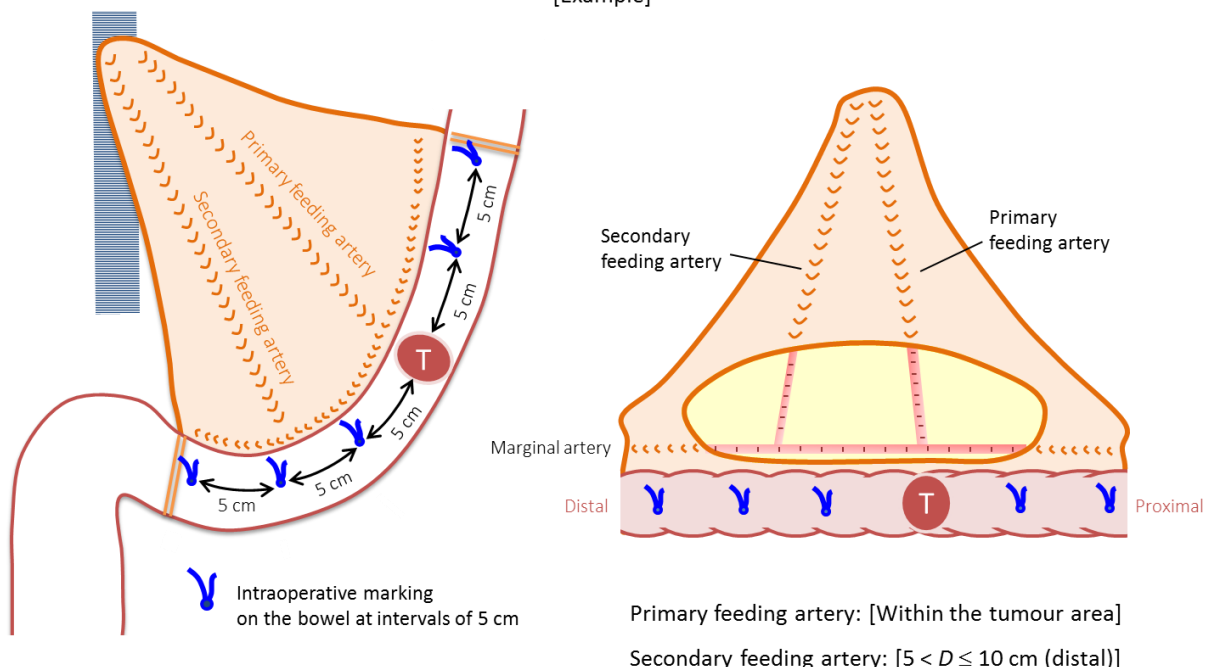


Fig. 6 Anatomical grouping of the feeding arteries

Grouping of the retrieved LNs (Fig. 7)

LNs retrieved from resected surgical specimens will be categorised as follows:

- Pericolic LNs (D , distance from the edge of the primary tumour)
 - (1) Within the tumour area
 - (2) $0 < D \leq 5$ cm (proximal/distal sides)
 - (3) $5 < D \leq 10$ cm (proximal/distal sides)
 - (4) $10 < D \leq 15$ cm (proximal/distal sides)
 - (5) $15 < D \leq 20$ cm (proximal/distal sides)
 - (6) $20 \text{ cm} < D$ (proximal/distal sides)
- Intermediate LNs
 - (1) LNs around the primary feeding artery
 - (2) LNs around the other feeding arteries
- Main LNs

LN grouping in the harvesting process

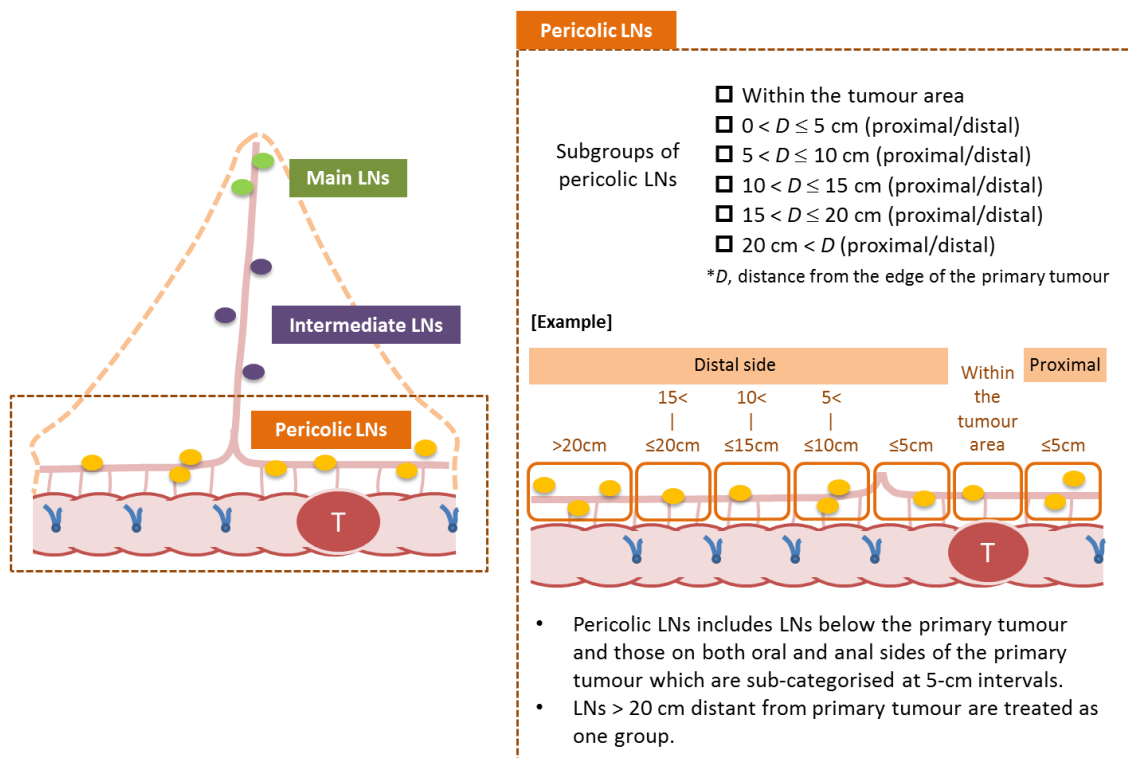


Fig. 7 Grouping of the retrieved lymph nodes

The timing of the LN retrieval process, either before or after formalin fixation, will be recorded.

Specimens retrieved from resected surgical specimens and submitted as LNs will be pathologically examined in routine practice. In the T-REX study, all tumour nodules with no pathological evidence of LN structure will be considered as LN metastases, irrespective of their size or contour morphology.^{12,13}

2.10 Data collection

In each participating institution, the data manager will enter data into a database sheet (Appendix 01 and 02). The patient's name and personal data will remain confidential and will not be disclosed in any way. Patients in this database will be identified by a unique subject number allocated by each participating institution.

After validation, these data will be sent to the central T-REX database or be entered into the electronic data capture (EDC) system managed by the T-REX study administrator. All data collected for the T-REX study will be anonymously stored in a main database and will be available for all research purposes.

Regarding digital color photographs of fresh surgical specimens, they will be submitted to Leeds University where the plane of surgery will be graded from the photographs on the basis of the presence and extent of any identifiable mesocolic defects.^{3,9,14}

2.11 Analysis

Primary analyses will be performed to determine the distribution of metastatic LNs (please refer 2.6: Primary and secondary outcomes). Sub-group analyses for primary outcomes will be based on various important clinicopathological factors, including pT, types of feeding artery, tumour location and populations. Results for these outcomes will be presented as frequencies of metastasis and percentage of accuracy with a measure of precision (95% confidence intervals).

Moreover, the T-REX study will estimate prognostic outcomes according to the bowel resection length and central radicality as a secondary outcome. As another secondary outcome, the T-REX study will focus on plane of surgery. Various statistical methods, including the chi-square test and t-test, will be used to evaluate the differences. For survival times, we will use Kaplan–Meier survival curves and the log-rank test for comparison of curves.

2.12 Publication and dissemination of results

All efforts will be made to ensure that the study protocol and results derived from the T-REX study are published in an established peer-reviewed journal. At least 1 publication of the main study results will be documented. Results will be disseminated to all participating institutions through the JSCCR website (<http://www.jsccr.jp/>) and publications.

3. STUDY ORGANISATION

3.1 Study organisation

Project Leader

Kenichi Sugihara (Tokyo Medical and Dental University, Japan)

Chief Investigators

Kazuo Hase (National Defense Medical College, Japan)

Werner Hohenberger (University Hospital Erlangen, Germany)

Philip Quirke (University of Leeds, UK)

Nam Kyu Kim (Yonsei University, Korea)

Collaborating Investigators

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2. Toshihiko Sato (Yamagata Prefectural Central Hospital)
3. Norio Saito (National Cancer Centre Hospital East)
4. Toshimasa Yatsuoka (Saitama Cancer Center)
5. Yukihide Kanemitsu (National Cancer Centre Central Hospital)
6. Yojiro Hashiguchi (Teikyo University School of Medicine)
7. Kenichi Takahashi (Tokyo Metropolitan Cancer and Infectious Disease Centre Komagome Hospital)
8. Tadahiko Masaki (Kyorin University School of Medicine)
9. Shingo Kameoka (Tokyo Women's Medical University)
10. Hideaki Yano (International Medical Centre of Japan)
11. Itaru Endo (Yokohama-city University)
12. Hideyuki Ike (Saisei-kai Yokohama-shi Nanbu Hospital)
13. Manabu Shiozawa (Kanagawa Cancer Centre Hospital)
14. Yusuke Kinugasa (Shizuoka Cancer Centre Hospital)
15. Koji Komori (Aichi Cancer Centre Hospital)

16. Yasuhiro Inoue (Mie University Graduate School of Medicine)
17. Masayuki Oue (Osaka Medical Centre for Cancer and Cardiovascular Diseases)
18. Yoshito Akagi (Kurume University School of Medicine)
19. Kazutaka Yamada (Takano Hospital)

Project Administrator

Hideki Ueno (National Defense Medical College, Japan)

3.2 Participating institutions

Japan

1. Keiyukai Sapporo Hospital
2. Yamagata Prefectural Central Hospital
3. National Cancer Centre Hospital East
4. Saitama Cancer Centre
5. National Defense Medical College
6. National Cancer Centre Central Hospital
7. Tokyo Medical and Dental University
8. Teikyo University School of Medicine
9. Tokyo Metropolitan Cancer and Infectious Disease Centre Komagome Hospital
10. Kyorin University School of Medicine
11. Tokyo Women's Medical University
12. International Medical Centre of Japan
13. Yokohama-city University
14. Saisei-kai Yokohama-shi Nanbu Hospital
15. Kanagawa Cancer Centre Hospital
16. Shizuoka Cancer Centre Hospital
17. Aichi Cancer Centre Hospital
18. Mie University Graduate School of Medicine
19. Osaka Medical Centre for Cancer and Cardiovascular Diseases
20. Kurume University School of Medicine

21. Takano Hospital

United Kingdom

University of Leeds

Germany

University Hospital Erlangen

Korea

Yonsei University

3.3 Protocol development

The Protocol Committee comprises following investigators who will be responsible for developing and approving the final protocol.

PROJECT LEADER	Kenichi Sugihara (President of JSCCR) - Tokyo Medical and Dental University, Japan
CHIEF INVESTIGATOR	Kazuo Hase - National Defense Medical College, Japan Philip Quirke - University of Leeds Werner Hohenberger - University Hospital Erlangen Nam Kyu Kim - Yonsei University
PROJECT ADMINISTRATOR	Hideki Ueno - National Defense Medical College, Japan

3.4 Financial support

- JSCCR
- Ministry of Health, Labour and Welfare (Japan) [Japan Initiated Global Clinical Trials System Development Project] (Translational Research Informatics Center)

4. ETHICAL CONSIDERATIONS

4.1 Regulation statement

This study will be conducted in accordance with the Declaration of Helsinki (<http://www.wma.net/en/30publications/10policies/b3/index.html>), as amended on 22 October 2008 by the 59th World Medical Association General Assembly in Seoul. The final study protocol, including the final version of Subject Information and Consent Forms, must be approved in writing by the Ethics Committee of JSCCR and the Investigational Review Board (IRB) of each institution.

4.2 Patient enrolment

All patients diagnosed with colon cancer in any of the participating institutions who meet the inclusion criteria will be requested to participate in the T-REX study. The investigator will ensure that the patient is provided full and adequate oral and written information regarding the nature, purpose and benefits of the study. Patients will be notified that they are free to choose to participate or not, and their decision will not affect further treatment by their treating physician.

Patients will be included in the T-REX study only after written informed consent is obtained.

4.3 Informed consent

Informed consent for longitudinal observational clinical data collection is mandatory for participation in the T-REX study. All patients for this study will be given a consent form that describes this study and provides sufficient information for the patients to make an informed decision regarding their participation in this study. Samples of the English version of the Patient Information Leaflet and Informed Consent form are enclosed ([Appendix 03](#)). The consent form will be submitted along with the study protocol for review and approval by IRB.

The T-REX study will not require further time and efforts of all patients. This observational cohort study does not involve clinical interventions or treatments.

Patients can quit the T-REX study at any time and for any reason, without further consequences.

4.4 Benefit and risk assessment

Despite on-going progress in the treatment of colon cancer, it is currently unclear how surgeons determine the resection margin of the bowel during surgery. To optimise treatment for individual patients, detailed information regarding the distribution of involved LNs is necessary to be clarified on the basis of large-scale data. Further, the exact impact of the resected length of the bowel on survival and recurrence is largely unknown. Therefore, evidence-based recommendations are required to promote/incorporate optimal surgical techniques for colon cancer.

By participating in the T-REX study, patients will enable investigators to gather evidence regarding the optimal bowel length which should be resected for colon cancer. This will lead to better and more personalised treatment for future colon cancer patients.

4.5 Compensation and incentives

Because the T-REX study is an observational study which does not involve extra clinical investigation or treatment, adverse events as a result of participating in the T-REX study are not expected. Patients of this cohort will not receive any compensation or incentives.

4 ABBREVIATIONS USED

T-REX	International Prospective Observational Cohort Study for Optimal Bowel Resection Extent and Central Radiality for Colon Cancer
JSCCR	Japanese Society for Cancer of the Colon and Rectum
LN	Lymph node
TNM	Tumour–node–metastasis
SMA	Superior mesenteric artery
IMA	Inferior mesenteric artery
ICA	Ileocolic artery
RCA	Right colic artery
MCA	Middle colic artery
MCA(rt)	Middle colic artery (right branch)
MCA(lt)	Middle colic artery (left branch)
LCA	Left colic artery
SA	Sigmoid artery
IRB	Investigational Review Board
CRF	Case report form
EDC	electronic data capture



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6 APPENDICES

Appendix 01: CRF (A)-Clinical and pathological data (No. 1, No. 2)

Appendix 02: CRF (B)-Prognostic data

Appendix 03: Patient information leaflet and informed consent

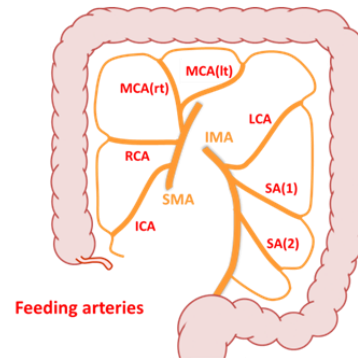
Appendix 01: CRF (A)-Clinical and pathological data (No. 1)

CRF (A)-Clinical and Pathological Data (No.1)		
Institution :	ID number :	Name of investigator :

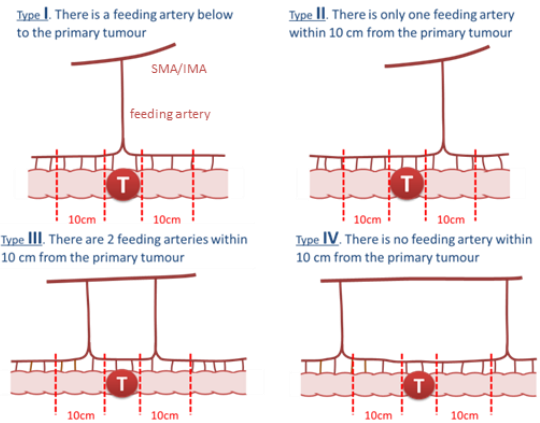
■ Basic data (1)

Items	Categories
Operation time	Year [20_____] Month []
Operation type	<input type="checkbox"/> Open surgery <input type="checkbox"/> Laparoscopic surgery
Intraoperative marking	<input type="checkbox"/> Under direct vision <input type="checkbox"/> Laparoscopic
Age	[]-year old
Gender	<input type="checkbox"/> Male <input type="checkbox"/> Female
Height	[] cm
Body weight	[] kg
Tumour location (1)	<input type="checkbox"/> C <input type="checkbox"/> A <input type="checkbox"/> T <input type="checkbox"/> D <input type="checkbox"/> S
Tumour location (2)	<input type="checkbox"/> Hepatic flex. <input type="checkbox"/> Splenic flex. <input type="checkbox"/> others
Length of the bowel resected	Proximal* [] cm Distal [] cm *including the length of the ileum resected (if resected)
Timing of LN retrieval	<input type="checkbox"/> Before fixation <input type="checkbox"/> After fixation
1 st feeding artery	<input type="checkbox"/> ICA <input type="checkbox"/> RCA <input type="checkbox"/> MCA(rt) <input type="checkbox"/> MCA(lt) <input type="checkbox"/> LCA <input type="checkbox"/> SA(1) <input type="checkbox"/> SA(2) *see, schema 1
2 nd feeding artery	<input type="checkbox"/> NOT included in the resected specimen <input type="checkbox"/> ICA <input type="checkbox"/> RCA <input type="checkbox"/> MCA(rt) <input type="checkbox"/> MCA(lt) <input type="checkbox"/> LCA <input type="checkbox"/> SA(1) <input type="checkbox"/> SA(2)
Feeding artery distribution	<input type="checkbox"/> Type I <input type="checkbox"/> Type II <input type="checkbox"/> Type III <input type="checkbox"/> Type IV *see, schema 2
Central radicality	*see, schema 3
• ICA area	<input type="checkbox"/> no dissection <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C1 <input type="checkbox"/> C2
• RCA area	<input type="checkbox"/> no dissection <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C1 <input type="checkbox"/> C2
• MCA area	<input type="checkbox"/> no dissection <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C
• LCA area	<input type="checkbox"/> no dissection <input type="checkbox"/> A <input type="checkbox"/> B <input type="checkbox"/> C
• SA area	<input type="checkbox"/> no dissection <input type="checkbox"/> A <input type="checkbox"/> B1 <input type="checkbox"/> B2 <input type="checkbox"/> C

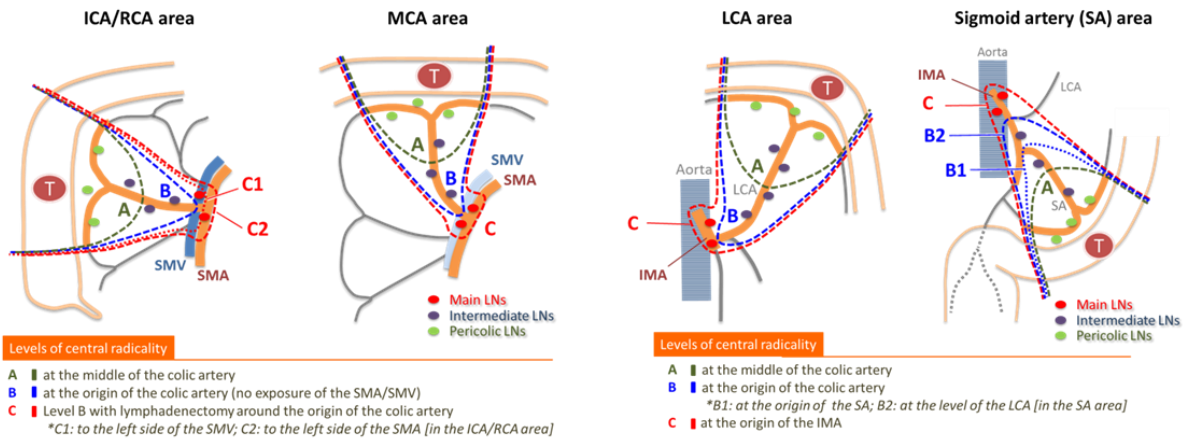
Schema 1. Feeding arteries



Schema 2. Patterns of feeding artery distribution



Schema 3. Extent of central radicality



Appendix 01: CRF (A)-Clinical and pathological data (No. 2)

CRF (A)-Clinical and Pathological Data (No.2)

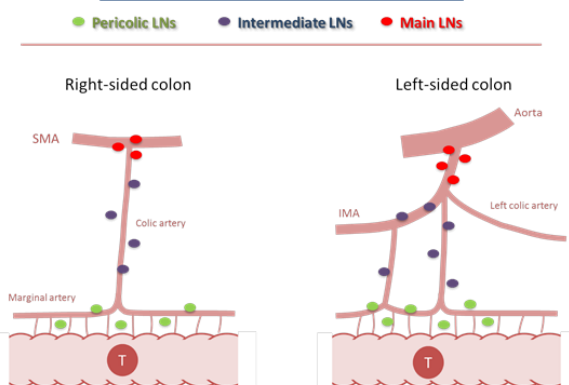
■ Basic data (2)

Items	Categories
Operation time	[] min
Blood loss	[] ml
Morbidity	Clavien Dindo grade *see, Table 1
• Overall	<input type="checkbox"/> None <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> IIIa <input type="checkbox"/> IIIb <input type="checkbox"/> IVa <input type="checkbox"/> IVb <input type="checkbox"/> V
• Cardiovascular	<input type="checkbox"/> None <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> IIIa <input type="checkbox"/> IIIb <input type="checkbox"/> IVa <input type="checkbox"/> IVb <input type="checkbox"/> V
• Respiratory	<input type="checkbox"/> None <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> IIIa <input type="checkbox"/> IIIb <input type="checkbox"/> IVa <input type="checkbox"/> IVb <input type="checkbox"/> V
• Anastomotic Leakage	<input type="checkbox"/> None <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> IIIa <input type="checkbox"/> IIIb <input type="checkbox"/> IVa <input type="checkbox"/> IVb <input type="checkbox"/> V
• Ileus	<input type="checkbox"/> None <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> IIIa <input type="checkbox"/> IIIb <input type="checkbox"/> IVa <input type="checkbox"/> IVb <input type="checkbox"/> V
• Surgical site infection	<input type="checkbox"/> None <input type="checkbox"/> I <input type="checkbox"/> II <input type="checkbox"/> IIIa <input type="checkbox"/> IIIb <input type="checkbox"/> IVa <input type="checkbox"/> IVb <input type="checkbox"/> V
30-day mortality	<input type="checkbox"/> None <input type="checkbox"/> Yes (death)
pT	<input type="checkbox"/> pT1 <input type="checkbox"/> pT2 <input type="checkbox"/> pT3 <input type="checkbox"/> pT4a <input type="checkbox"/> pT4b
Tumour grade	<input type="checkbox"/> G1 <input type="checkbox"/> G2 <input type="checkbox"/> G3 <input type="checkbox"/> G4
Residual tumour	<input type="checkbox"/> R0 <input type="checkbox"/> R1 <input type="checkbox"/> R2
Circumferential resection margin	Histological assessment: [] μm

Table 1. Clavien Dindo grade

Grade I	Any deviation from the normal postoperative course without the need for pharmacological treatment or surgical, endoscopic, and radiological interventions Allowed therapeutic regimens are: drugs as antiemetics, antipyretics, analgetics, diuretics, electrolytes, and physiotherapy. This grade also includes wound infections opened at the bedside
Grade II	Requiring pharmacological treatment with drugs other than such allowed for grade I complications Blood transfusions and total parenteral nutrition are also included
Grade III	Requiring surgical, endoscopic or radiological intervention IIIa: intervention not under general anesthesia IIIb: intervention under general anesthesia
Grade IV	Life-threatening complication requiring IC/ICU management IVa: single organ dysfunction (including dialysis) IVb: multiorgan dysfunction
Grade V	Death of a patient

Schema 4. Lymph node grouping



■ Location of feeding arteries and distribution of **PERICOLIC** LNs

Location of feeding artery and distribution of pericolic LNs											
	Distal side of the primary tumour					Within the tumour area	Proximal side of the primary tumour				
	20cm<	15< 20cm	10< ≤15cm	5< ≤10cm	≤5cm		≤5cm	5< ≤10cm	10< ≤15cm	15< ≤20cm	20cm<
Entry point of the 1 st feeding artery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Entry point of the 2 nd feeding artery	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Number of pericolic LN retrieved	[]	[]	[]	[]	[]	[]	[]	[]	[]	[]	[]
Number of pericolic LNs involved	[]	[]	[]	[]	[]	[]	[]	[]	[]	[]	[]

■ Distribution of the **INTERMEDIATE** and **MAIN** LNs [*see, schema 4](#)

	Intermediate LNs (Around the 1 st feeding artery)	Intermediate LNs (Around the 2 nd and other feeding arteries)	Main LNs
Number of LN retrieved	[]	[]	[]
Number of LN involved	[]	[]	[]

Appendix 02: CRF (B)-Prognostic data

CRF (B)-Prognostic Data		
Institution :	Institutional ID number :	Name of investigator :

Prognostic information

Items	Category
Year/Month of last follow-up	Year [] Month []
Prognostic outcome	<input type="checkbox"/> Alive <input type="checkbox"/> Disease-specific death <input type="checkbox"/> Death caused by other disease/reason
Recurrence	<input type="checkbox"/> (-) <input type="checkbox"/> Recurrence(+)
Year/Month of recurrence	Year [] Month []
Pattern of recurrence (overall)	
<input type="checkbox"/> Recurrence at remnant mesenteric LNs	<input type="checkbox"/> (-) <input type="checkbox"/> Recurrence(+)
<input type="checkbox"/> Anastomotic recurrence	<input type="checkbox"/> (-) <input type="checkbox"/> Recurrence(+)
<input type="checkbox"/> Distant metastasis	<input type="checkbox"/> (-) <input type="checkbox"/> Liver <input type="checkbox"/> Lung <input type="checkbox"/> Peritoneum <input type="checkbox"/> Non-mesenteric LNs <input type="checkbox"/> Others

PATIENT INFORMATION LEAFLET and INFORMED CONSENT

Title of the study:

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

INTRODUCTION

You are being invited to participate in a clinical research study which is a clinician-initiated project.

Before deciding to participate in the study, it is important for you to understand the purpose of this research and what will happen to you. This information sheet will provide information regarding this study and your rights as a research subject so that you can decide if you wish to participate. Please read this information carefully and approach the investigator for clarification if anything is unclear or if you would like more information.

What is the purpose of the study?

The purpose of this study is to determine the optimal resection length of the bowel and the extent of lymph node dissection for colon cancer. In this international multi-centre study, the metastatic lymph node distribution will be assessed and recorded in routine practice. The T-REX study is a prospective observational study; therefore, you will receive standard treatment which will include undergoing appropriate surgery. The T-REX study will not require further time and effort of any subject.

Do I have to participate in the study?

Participation in this study is entirely voluntary. It is up to you to decide whether to participate or not. If you do not wish to participate in this study or if you wish to withdraw from the study at any time, you may do so without having to provide a reason, and you will not lose any benefits to which you would otherwise be entitled. If you withdraw from the study, data collected up to the point of withdrawal will be

analysed for the purpose of the study.

If you decide to participate, you will be provided this information sheet to keep and be asked to provide your signature indicating your consent.

Who is eligible to participate in the study?

Patients with colon cancer diagnosed as preoperative stage I, II or III are eligible to participate in the T-REX study. A total of approximately 4000 patients will participate in this study.

What will happen to me if I participate?

The T-REX study is an observational study which does not involve any extra clinical investigation or treatment. You will be provided standard treatments for colon cancer, including preoperative examinations, surgery, postoperative surveillance as well as a preoperative/postoperative adjuvant chemotherapy regimen.

Your study doctor or data manager at your hospital will enter the following data into a database sheet: patient characteristics (age, gender, height and weight), tumour characteristics (e.g. tumour's location and stage), surgical procedures (e.g. the length of the bowel resected and the level of lymph node dissection), status of morbidity, operative and pathological findings (e.g. location of the feeding artery of the tumour and the distribution of lymph nodes) and prognostic outcomes. Subjects' name and personal data will remain confidential and will not be disclosed in any way.

These data will be anonymously sent to the administrator of the T-REX study located at the Department of Surgery, National Defense Medical College, Japan. Subjects in this database will be identified by subject number allocated by each participating institution. All data collected for the T-REX study will be anonymously stored in a main database and used only for research purposes.

What do I have to do?

If you decide to participate, you must sign the consent form. Because the T-REX study is a prospective observational study, further time and effort on your part will not be required.

What risks or discomforts may occur if I participate?

Because the T-REX study is an observational study which does not involve extra clinical

investigation or treatment, adverse events as a result of participating in this study are not expected.

What are possible benefits of participating?

You may not receive any direct benefit from participating in the T-REX study. However, the information we obtain from this study will extend our existing knowledge and help to determine the optimal surgical procedure for future patients with colon cancer.

Will there be any cost to me if I participate?

There will be no cost to you for participating in this study. You will not receive any compensation or incentives.

Can I withdraw or be withdrawn from the study?

Participating in the study is voluntary. If you decide to participate, you are free to withdraw at any time. If you decide to withdraw, you should immediately inform your study doctor. Your study doctor will not be upset, you will not be penalised in any way, and your future care will not be affected. Should you withdraw from the study, the study data collected before your withdrawal may still be processed along with other data collected as part of the study.

Will my participation in this study be confidential?

Records that identify you will be kept confidential and will not be made publicly available.

The information collected during the study will be stored in a computer maintained by the T-REX study administrator, but your name will not be stored. Only your study doctor or data manager at your hospital will know that the information is related to you. Clinical and pathological data will be sent to the study administrator for analysis, but your name will not be included on any data that is sent to the administrator.

Results of the study may be published in the medical literature and/or presented at a scientific conference, but your identity will not be revealed.

Who is organising and funding the study?

This study is being organised by doctors who are interested in treatment of colon cancer in countries including Japan, Germany, the UK, and Korea. Professor Kenichi

Sugihara, the President of the Japanese Society for Cancer of the Colon and Rectum (JSCCR) is the project leader. The T-REX study is a clinician-initiated project, and the JSCCR and the Ministry of Health, Labour and Welfare (Japan) [Japan Initiated Global Clinical Trials System Development Project] are funding the study.

Who has reviewed the study?

This study has been approved by the JSCCR Ethics Committee and the Investigational Review Board of each institution.

This study complies with the Declaration of Helsinki (version 2000).

Contacts for further information

If during the course of this study, you have questions regarding the nature of the research or your rights, you should contact one of the following:

Dr. _____

Affiliation

TEL

FAX

Professor Kenichi Sugihara

Project Leader

Department of Surgery, Tokyo Medical and Dental University

1-5-45, Yushima, Bunkyo-ku, Tokyo, 113-8519 (JAPAN)

TEL: +81-(0)3-5803-5261

FAX: +81-(0)3-5803-0139

Dr Hideki Ueno

Project Administrator

Department of Surgery, National Defense Medical College

3-2, Namiki, Tokorozawa, Saitama, 359-8513 (JAPAN)

TEL: +81-(0)4-2995-1637

FAX: +81-(0)4-2996-5205

INFORMED CONSENT FORM

Title of the study:

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

Patient ID: _____

Patient name: _____

By signing and dating this document,

- I confirm that I have had time to carefully read and understand the content of the study described on the patient information sheet provided for this study.
- I confirm that I have had the opportunity to discuss the study, ask questions and am satisfied with answers and explanations that I have been provided.
- I understand that my participation is voluntary, I am free to withdraw at any time without having to provide any reason and my medical care or legal rights will not be affected.
- I understand that sections of my medical notes may be reviewed at by responsible individuals involved in the study. I give permission for these individuals to have access to these records.
- I confirm that I have received a signed and dated copy of the Patient Information Sheet and the Informed Consent Form.
- I agree to participate in the T-REX Study.

Name of patient

Signature

Date

Name of person obtaining consent

Signature

Date

WITHDRAWAL FORM

Title of the study:

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

I withdraw my consent for participating in the T-REX study.

Name of patient

Signature

Date