Formula One Study

UK–Japan Joint Study for Risk Factors of Lymph Node Metastasis in Submucosal Invasive (pT1) Colorectal Cancer

STUDY PROTOCOL (English version)

Protocol version	Protocol date
Version 1.0	31 Jan 2016 (84th JSCCR meeting, Kumamoto)
Version 1.1	14 May 2016 (UK–Japan joint meeting, Tokyo)
Version 1.2	30 June 2016 (85th JSCCR meeting, Osaka)
Version 2.0	25 Jan 2018 (88th JSCCR meeting, Tokyo)

1. Table of contents

2. List of abbreviations

CRC	colorectal cancer
F1 study	UK–Japan Joint Study for Risk Factors of Lymph Node Metastasis in Submucosal Invasive (pT1) Colorectal Cancer
IRB	institutional review board
JSCCR	Japanese Society for Cancer of the Colon and Rectum
LNM	lymph node metastasis
MUC	mucinous adenocarcinoma
NPG	nonpolypoid growth
PDC	poorly differentiated cluster
PG	polypoid growth
POR	poorly differentiated adenocarcinoma
SIG	signet-ring cell carcinoma
UK	United Kingdom

3. Time schedule

Milestone	Planned date
Start of making study protocol	01 / 2016
Establishment of study protocol	06 / 2016
Completion of IRB process	12 / 2016
Start of digital slide collection	06 / 2017
End of digital slide collection	01 / 2018
Start of pathological assessment	06 / 2018
End of pathological assessment	12 / 2018
Start of data analysis	01 / 2019
End of data analysis	07 / 2019
Final report of study results	01 / 2020

4. Summary of study

Title	UK–Japan Joint Study for Risk Factors of Lymph Node Metastasis in Submucosal Invasive (pT1) Colorectal Cancer (CRC)
Study acronym	Formula one (F1) study
Study outline	The F1 study is an international, a multicentre, a retrospective, an observational, and a cohort study that will collect clinical data regarding the status of lymph node metastasis (LNM) to identify the most useful risk factors for CRC management after local excision via the endoscopic or surgical approach. This study is also expected to identify any differences in macroscopic or microscopic characteristics in pT1 tumours potentially caused by differences in cancer screening and diagnostic systems between the United Kingdom (UK) and Japan.
Project leaders	Kenichi Sugihara (Japan) Philip Quirke (UK)
Rationale and background	Approximately 10% of patients will have lymph node recurrence after local excision when additional surgical intervention is not performed. Although currently we have global standard criteria for surgery after local excision (i.e. excision margin, tumour grade and lymphovascular invasion), some evidence is emerging from the UK and Japan suggesting that new pathological parameters could benefit patients with pT1 CRC in terms of appropriate selection of treatment after local excision.
Objectives	The F1 study aims to determine the risk factors most useful for management of CRC and their assessment criteria and to identify any differences in the morphological properties of pT1 between the UK and Japan.

Outcomes	**Primary analysis** - Incidence of LNM according to risk factors - Assessment reproducibility of risk factors **Secondary outcomes** - Differences in morphological characteristics of pT1 tumours between the UK and Japan
Study design	Retrospective observational cohort study
Study setting and population	Patients treated for pT1 colorectal cancer in 2008-2013. The image slides of the patients will be pathologically evaluated retrospectively, and the clinical value of new risk factors will be compared between the 2 countries in terms of their relevance to the incidence of LNM.
Study size	The study population will consist of approximately 2000 patients treated in the UK and Japan.
Study start date	January 2016
Study end date	January 2020

5. Rationale and background

The introduction of the bowel cancer screening program[1,2] and recent progress in local excision techniques, including endoscopic[3-6] and trans-anal local resection techniques,[7-9] for malignant polyp have possibly increased the chance for pathologists to encounter locally excised pT1 CRC. One of the current controversies in this field concerns which of the risk factors of LNM should be evaluated in routine practice as the criteria for performing additional laparotomy for lymph node dissection.

The initial series of studies to identify histopathological risk factors for LNM in early invasive CRC was conducted in the 1980s, and since then, unfavourable tumour grade,[10-15] vascular invasion[10,12-16] and resection margin[11,17,18] have been regarded as important adverse features. Recent studies have shown that there are other potential parameters useful for determining the requirement of additional laparotomy in patients with pT1 CRC that is locally excised endoscopically or by trans-anal resection. Examples include tumour budding,[19-21] which is listed in the guidelines of the European Society for Medical Oncology guidelines[22] and Japanese Society for Cancer of the Colon and Rectum (JSCCR).[23] Furthermore, poorly differentiated clusters (PDCs) reportedly reflecting the metastatic potential of CRC more accurately than conventional histopathological features, such as tumour grade and vascular invasion or tumour budding,[24-26] could be a potentially useful index of LNM risk in early invasive CRC.[26]

Among the quantitative risk factors for LNM in pT1 CRC, Haggitt's classification was the first to describe the clinical significance, although the value is limited to polypoidal lesions.[27] A sizable body of literature, including Kudo's classification,[28] has examined the association between submucosal invasive depth and LNM by dividing the submucosal layer into thirds; however, this method cannot be applied to pT1 tumours removed endoscopically. In Japan, according to a multi-institutional study to determine the optimal depth of submucosal invasion to be used in routine practice,[29] the 1000-μm rule of submucosal invasion depth is recognised by the JSCCR guidelines as a parameter indicating the necessity of additional laparotomy.[23]

On the other hand, the emerging literature suggests that the greatest density of lymphatic vessels in the submucosal layer is in the superficial third, with a significant decrease in the deepest third.[30] The width of submucosal invasion has been reported to be closely related to the LNM rate.[20,31] These observations might suggest the more important role of measurements of the area or volume of submucosal invasion as guides for treatment by additional laparotomy.[31,32]

The growing pursuit of novel indicators over the last decade has raised expectations of further advancement in the treatment of early invasive CRC. However, most proposed parameters have not been internationally implemented because of the lack of evaluations of the reproducibility of pathological assessments and to validate the clinical value of these new factors in a large international case series. Furthermore, differences among countries in clinical practice, such as the type of the bowel cancer screening program or diagnostic technology and accuracy, could lead to differences in the time to diagnosis of tumours or characteristics of tumours at the time of diagnosis. Although there are few studies addressing this issue in terms of morphometric analysis of pT1 tumour, the results of such studies could have new valuable clinical implications in CRC practice.

6. Objectives

In the present study, we performed histological assessments of pT1 CRC in the UK and Japanese populations. The primary purpose of this study is to determine the value of novel histopathological risk factors, including qualitative parameters (e.g. tumour budding and PDC) and quantitative parameters (e.g. the depth, width and area of submucosal invasion) for their ability to predict LNM and to determine assessment reproducibility. This international study is expected to demonstrate the potential value of new risk factors and identify potential issues, including diagnostic reproducibility, resulting from the use of these factors in routine practice.

The second purpose of this study is to identify possible timing and technique differences in diagnosis using morphometric methods of pT1 CRC in the UK and Japan.

7. Research methods

7.1 Study design

This is a retrospective cohort study in patients treated in the UK and Japan.

7.2 Setting and population

A total of 2000 patient with pT1 CRC who had received curative surgery between 2008 and 2013 are eligible.

(1) Approximately 1000 cases treated within the Yorkshire region identified via the Northern and Yorkshire Cancer Registry and Information Service Registry

(2) Approximately 1000 cases treated at participating JSCCR institutions

Inclusion criteria

- Histologically proven colorectal adenocarcinoma
- Pathological pT1
- Patients with potentially curative surgery with lymphadenectomy and patients treated only with local excision

Exclusion criteria

- Preoperative adjuvant therapy
- Piecemeal resection
- Synchronous CRC (except for carcinoma in situ)

7.3 Primary and secondary outcomes

Primary outcomes

- Incidence of LNM and recurrence
- Interobserver agreement of the judgment

Secondary outcome

- Comparison of morphological characteristics between the UK and Japanese populations

7.4 Parameters collected

- Patient characteristics
  - Age
  - Gender
  - Tumour location (cecum/ascending colon/transverse colon/descending colon/sigmoid colon/rectum)

- Treatment related
  - Year and month of surgery
  - Treatment types (laparotomy only/endoscopic excision followed by laparotomy /transanal local resection followed by laparotomy/endoscopic excision only/ transanal local resection only)

- Endoscopic classification of tumour [see, APPENDIX 01.3.1]

- Conventional pathological characteristics of tumour
  - Pathological classification of growth type of tumour [see, APPENDIX 01.3.2]
  - Number of lymph node involved
  - pM stage
  - Tumour grade (predominant)
  - Lymphatic invasion [see, APPENDIX 01.4.1]
  - Venous invasion [see, APPENDIX 01.4.2]
  - Number of lymph node examined

- New pathological characteristics of tumour
  - Tumour budding [see, APPENDIX 01.5.1]
  - Poorly differentiated clusters [see, APPENDIX 01.5.2]
  - Tumour grade (invasive front) [see, APPENDIX 01.5.3]
  - Depth of submucosal invasion (JSCCR method) [see, APPENDIX 01.5.4]

- Morphometric factors [see, APPENDIX 01.5.5]
  - Maximum width of lesion
  - Maximum width of carcinoma
  - Maximum vertical depth of carcinoma from luminal surface
  - Maximum vertical depth of carcinoma from muscularis mucosae (if muscularis mucosae to be assessed is present)
  - Maximum depth of invasion within neck of polypoid/semipedunculated lesions

- Resection margin
- Distance from the deepest point of the invading carcinoma up to the muscularis propria (if muscularis propria is present)
- Total area of lesion
- Total area of carcinoma (intramucosal and submucosal)
- Total area of submucosal invasion by carcinoma

- Information of recurrence
- Prognosis

7.5 Preparation of digital slides to evaluate pathological parameters

New pathological risk parameters and pathological growth type of tumour will be evaluated using digital (virtual) slides that include no information that can identify individuals. More specifically, high-resolution whole slide images will be acquired from haematoxylin and eosin slides that have been prepared in routine practice.

The digitized slides will be uploaded to a study website (www.virtualpathology.leeds.ac.uk) for online viewing through a digital microscope interface.

7.6 Data analysis

Primary analyses will be performed to determine the value of novel histopathological risk factors for the prediction of LNM and to determine assessment reproducibility in pT1 CRC. The weighing of the presence of an individual risk factor on LNM will be calculated using various statistical methods for comparisons, including the chi-square test and logistic analysis, and eventually, after multivariate analysis, an optimal combination of risk factors will be determined. In addition, inter-observer agreement on the assessment of for each pathological risk factor will be evaluated using kappa coefficient statistics.
Moreover, the F1 study will identify possible morphological differences in pT1 CRC between the UK and Japan as a secondary outcome. Various statistical methods, including the chi-square test and t-test, will be used to determine if there are any differences in pT1 CRC, particularly in tumour shape and morphometric factors, between the UK and Japanese population.

7.7 Publication and dissemination of results

All efforts will be made to ensure that the study protocol and results derived from the F1 study are published in an established peer-reviewed journal. Results will be disseminated to all participating institutions through the JSCCR website (http://www.jsccr.jp/) and publications.

8. Study organisation

8.1 Members of study

Project Leaders

Kenichi Sugihara	Tokyo Medical and Dental University, Tokyo
Philip Quirke	Section of Pathology & Tumour Biology, University of Leeds

Collaborative Investigators

Yoich Ajioka	Division of Molecular and Diagnostic Pathology, Graduate School of Medical and Dental Science, Niigata University
Takahiro Fujimori	Department of Pathology, Shinko Hospital
Hiroaki Ikematsu	Department of Gastrointestinal Oncology & Endoscopy, National Cancer Center Hospital East
Megumi Ishiguro	Department of Translational Oncology, Tokyo Medical and Dental University
Yukihide Kanemitsu	Division of Colorectal Surgery, National Cancer Center Hospital
Hiroshi Kawachi	Department of Pathology, Cancer Institute Hospital
Hirotoshi Kobayashi	Department of Surgery, Tokyo Metropolitan Hiroo Hospital
Motohiro Kojima	Pathology Division, Research Center for Innovative Oncology, National Cancer Center Hospital East
Takahiro Nakamura	Department of Mathematics, National Defense Medical College
Hiroaki Nozawa	Department of Surgical Oncology, Graduate School of Medicine, The University of Tokyo
Shiro Oka	Department of Endoscopy, Hiroshima University Hospital
Shoichi Saito	Department of Lower GI Medicine, Cancer Institute Hospital
Yutaka Saito	Endoscopy Division, National Cancer Center Hospital
Shigeki Sekine	Molecular Pathology Division, National Cancer Center Research Institute
Hideyuki Shimazaki	Department of Laboratory Medicine, National Defense Medical College

Tamotsu Sugai	Division of Pathology, Iwate Medical University
Manabu Takamatsu	Department of Pathology, Cancer Institute Hospital
Shinji Tanaka	Department of Endoscopy, Hiroshima University Hospital
Masashi Ueno	Colorectal Surgery Department, Cancer Institute Hospital
Nicholas West	Leeds Institute of Cancer & Pathology
Masayoshi Yamada	Endoscopy Division, National Cancer Center Hospital
Hiroo Yamano	Division of Gastroenterology, Akita Red Cross hospital

Study administrator

Hideki Ueno	Department of Surgery, National Defense Medical College
Yoshiki Kajiwara	Department of Surgery, National Defense Medical College

8.2 Participating institutions

Japan

1. Akita Red Cross hospital
2. Cancer Institute Hospital
3. Hiroshima University Hospital
4. Iwate Medical University
5. National Cancer Centre Central Hospital
6. National Cancer Centre Hospital, East
7. Niigata University
8. Shinko Hospital
9. The University of Tokyo
10. Tokyo Medical and Dental University
11. Tokyo Metropolitan Hiroo Hospital
12. National Defense Medical College

United Kingdom

1. University of Leeds

8.3 Protocol development

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

Kenichi Sugihara	Tokyo Medical and Dental University
Philip Quirke	University of Leeds
Hideki Ueno	National Defense Medical College

8.4 Financial support

- JSCCR

9. Ethical considerations

9.1 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 in October 2013 by the 64th World Medical Association General Assembly in Brazil.
The final study protocol must be approved in writing by the Ethics Committee of JSCCR and the institutional review board (IRB).

9.2 Data management

At the first of the study, the study administrator will anonymously collect basic data, including information on patient characteristics, treatment-related information and conventional pathological characteristics of tumours. Data concerning new pathological characteristics of tumours and morphometric factors also will be collected by the study administrator after each pathological investigator finishes their pathological assessment of the digital images, which will include no information that can identify individual patients. These data will be integrated and used for analyses.

A correspondence table linking personal information (e.g. name and birthday) and the database submitted to the study administrator will be under the strict control of a person appointed for personal information management in each institution. The study administrator will not have any personal information.

9.3 Information disclosure

Informed consent for data collection is not mandatory for participation in the F1 study; however, the research content must be disclosed via the homepages of JSCCR and each institution. The document in the homepage provides sufficient information for the patients to make an informed decision regarding their participation in this study. Patients can quit the F1 study at any time and for any reason without further consequences by expressing their

will to their hospital doctor or study administrator.

Samples of the English version of the document are presented in Appendix 02. The consent form will be submitted along with the study protocol for review and approval by IRB.

9.4 Benefit and risk assessment

The F1 study will not require further time and efforts of the patients and will not involve clinical interventions or treatments.

Because this is a retrospective study, there are no physical potential risks and benefits to patients included in this study. All risks associated with loss of privacy will be prevented by using an anonymising system and pathological observation on digital slides devoid of patient identity information.

By participating in the F1 study, patients will enable investigators to gather evidence regarding the optimal surgical indication after the local excision of pT1 CRC. This will lead to a better and more personalised treatment for future patients with CRC.

9.5 Compensation and incentives

Because the F1 study is a retrospective study that does not involve extra clinical investigation or treatment, adverse events as a result of participating in the study are not expected. Patients of this cohort will not receive any compensation or incentives.

10. References

1. Taylor EF, Morris EJA, Thomas JD, et al. Major improvement in the stage profile of tumours diagnosed in the NHS Bowel Cancer Screening Programme. *Gut* 2010;**59:**A31.
2. Lee TJW, Rutter MD, Blanks RG, et al. Colonoscopy quality measures: experience from the NHS Bowel Screening Programme. *Gut* 2012;**61:**1050-1057.
3. Saito Y, Yamada M, So E, et al. Colorectal endoscopic submusal dissection: technical advantages compared to endoscopic mucosal resection and minimally invasive surgery. *Dig Endosc* 2014;**26:**52-61.
4. Oka S, Tanaka S, Saito Y, et al. Local recurrence after endoscopic resection for large colorectal neoplasia: a multicenter prospective study in Japan. *Am J Gastroenterol* 2015;**110:**697-707.
5. Bhatt A, Abe S, Kumaravel A, Vargo J, Saito Y. Indications and techniques for endoscopic submucosal dissection. *Am J Gastroenterol* 2015;**110:**784-791.
6. Asayama N, Oka S, Tanaka S, Hayashi N, Arihiro K, Chayama K. Endoscopic submucosal dissection as total excisional biopsy for clinical T1 colorectal carcinoma. *Digestion* 2015;**91:**64-69.
7. Atallah S, Albert M, Larach S. Transanal minimally invasive surgery: a giant leap forward. *Surg Endosc* 2010;**24:**2200-2205.
8. Barendse RM, Doornebosch PG, Bemelman WA, Fockens P, Dekker E, de Graaf EJ. Transanal employment of single access ports is feasible for rectal surgery. *Ann Surg* 2012;**256:**1030-1033.
9. Garcia-Flórez LJ, Otero-Díez JL. Local excision by transanla endoscopic surgery. *World J Gastroenterol* 2015;**21:**9286-9296.
10. Cooper H. Surgical pathology of endoscopically removed malignant polyps of the colon and rectum. *Am J Surg Pathol* 1983;**7:**613-623.
11. Morson B, Whiteway J, Jones E, Macrae F, Williams C. Histopathology and prognosis of malignant colorectal polyps treated by endoscopic polypectomy. *Gut* 1984;**25:**437-444.
12. Colacchio T, Forde K, Scantlebury V. Endoscopic polypectomy: Inadequate treatment for invasive colorectal carcinoma. *Ann Surg* 1981;**194:**704-707.
13. Sugihara K, Muto T, Morioka Y. Management of patients with invasive carcinoma removed by colonoscopic polypectomy. *Dis Colon Rectum* 1989;**32:**829-834.
14. Cranley J, Petras R, Carey W, Paradis K, Sivak M. When is endoscopic polypectomy adequate therapy for colonic polyps containing invasive carcinoma? *Gastroenterology* 1986;**91:**419-427.
15. Coverlizza S, Risio M, Ferrari A, Fenoglio-Preiser C, Rossini F. Colorectal adenomas

containing invasive carcinoma: pathologic assessment of lymph node metastatic potential. *Cancer* 1989;**64:**1937-1947.

16. Muller S, Chesner I, Egan M, et al. Significance of venous and lymphatic invasion in malignant polyps of the colon and rectum. *Gut* 1989;**30:**1385-1391.
17. Cooper H, Deppisch L, Gourley W, et al. Endoscopically removed malignant colorectal polyps: clinicopathologic correlations. *Gastroenterology* 1995;**108:**1657-1665.
18. Volk E, Goldblum J, Petras R, Carey W, Fazio V. Management and outcome of patients with invasive carcinoma arising in colorectal polyps. *Gastroenterology* 1995;**109:**1801-1807.
19. Hase K, Shatney C, Mochizuki H, et al. Long-term results of curative resection of "minimally invasive" colorectal cancer. *Dis Colon Rectum* 1995;**38:**19-26.
20. Ueno H, Mochizuki H, Hashiguchi Y, et al. Risk factors for an adverse outcome in early invasive colorectal carcinoma. *Gastroenterol* 2004;**127:**385-394.
21. Kawachi H, Eishi Y, Ueno H, et al. A three-tier classification system based on the depth of submucosal invasion and budding/sprouting can improve the treatment strategy for T1 colorectal cancer: a retrospective multicenter study. *Mod Pathol* 2015;**28:**872-879.
22. Schmoll H, Cutsem E-s-V, Stein A, et al. ESMO consensus guidelines for management of patients with colon and rectal cancer. a personalized approach to clinical decision making. *Ann Oncol* 2012;**23:**2479-2516.
23. Watanabe T, Itabashi M, Shimada Y, et al. Japanese Society for Cancer of the Colon and Rectum (JSCCR) guidelines 2010 for the treatment of colorectal cancer. *Int J Clin Oncol* 2009;**17:**1-29.
24. Ueno H, Shimazaki H, Shinto E, et al. New criteria for histologic grading of colorectal cancer. *Am J Surg Pathol* 2012;**36:**193-201.
25. Barresi V, Bonetti L, Branca G, Gregorio C, Leon Md, Tuccari G. Colorectal carcinoma grading by quantifying poorly differentiated cell clusters is more reproducible and provides more rebust prognostic information than conventional grading. *Virchows Arch* 2012;**461:**621-628.
26. Ueno H, Hase K, Hashiguchi Y, et al. Site-specific tumor grading system in colorectal cancer: multicenter pathological review of the value of quantifying poorly differentiated clusters. *Am J Surg Pathol* 2014;**38:**197-204.
27. Haggitt R, Glotzbach R, Soffer E, Wruble L. Prognostic factors in colorectal carcinomas arising in adenomas: implications for lesions removed by endoscopic polypectomy. *Gastroenterology* 1985;**89:**328-336.
28. Kudo S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. *Endoscopy* 1993;**25:**455-461.

29. Kitajima K, Fujimori T, Fujii S, et al. Correlations between lymph node metastasis and depth of submucosal invasion in submucosal invasive colorectal carcinoma: a Japanese collaboration study. *J Gastroenterol* 2004;**39:**534-543.
30. Smith KJE, Jones PF, Burke DA, Treanor D, Finan PJ, Quirke P. Lymphatic vessel distribution in the mucosa and submucosa and potential implications for T1 colorectal tumors. *Dis Colon Rectum* 2011;**54:**35-40.
31. Toh E-W, Brown P, Morris E, Botterill I, Quirke P. Area of submucosal invasion and thdth of invasion predicts lymph node metastasis in pT1 colorectal cancers. *Dis Colon Rectum* 2015;**58:**393-400.
32. Brown PJ, Toh E-W, Smith KJE, et al. New insights into the lymphovascular microanatomy of the colon and the risk of metastases in pT1 colorectal cancer using quantitative methods and 3 dimensional digital reconstruction. *Histopathol* 2015;**67:**167-175.