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A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

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Complete List of Authors:	Nishida, Tsutomu ; Toyonaka Municipal Hospital, Department of Gastroenterology Hayashi, Shiro; Toyonaka Municipal Hospital, Department of Gastroenterology; Kento Hayashi Clinic, Department of Gastroenterology and Internal Medicine Takenaka, Mamoru ; Kindai University, Department of Gastroenterology and Hepatology Hosono, Makoto ; Kindai University, Department of Radiology Kogure, Hirofumi; The University of Tokyo, Department of Gastroenterology Hasatani, Kenkei ; Fukui Prefectural Hospital, Department of Gastroenterology Yamaguchi, Shinjiro ; Kansai Rosai Hospital, Department of Gastroenterology and Hepatology Maruyama, Hirotsugu ; Osaka City University, Department of Gastroenterology Doyama, Hisashi ; Ishikawa Prefectural Central Hospital, Department of Gastroenterology Ihara, Hideyuki ; Tonan Hospital, Department of Gastroenterology Yoshio, Toshiyuki ; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Department of Gastroenterology Nagaike, Koji ; Suita Municipal Hospital, Department of Gastroenterology and Hepatology Yamada, Takuya ; Osaka Rosai Hospital, Department of Gastroenterology and Hepatology, Yakushijin, Takayuki ; Osaka General Medical Center, Department of Gastroenterology and Hepatology Takagi, Tadayuki ; Fukushima Medical University School of Medicine, Department of Gastroenterology Tsumura, Hidetaka ; Hyogo Cancer Center, Department of Gastroenterological Oncology, Kurita, Akira ; Kitano Hospital, Department of Gastroenterology and Hepatology, Digestive Disease Center Asai, Satoshi ; Tane General Hospital, Department of Gastroenterology Ito, Yukiko ; Japanese Red Cross Medical Center, Department of Gastroenterology Kuwai, Toshio ; Kure Medical Center, Department of Gastroenterology Hori, Yasuki ; Nagoya City University Graduate School of Medical Sciences Department of Gastroenterology and Metabolism

	Maetani, Iruru ; Toho University Ohashi Medical Center, Division of Gastroenterology and Hepatology, Department of Internal Medicine Ikezawa, Kenji ; Osaka International Cancer Institute, Department of Hepatobiliary and Pancreatic Oncology Iwashita, Takuji ; Gifu University Hospital, First Department of Internal Medicine Matsumoto, Kengo; Toyonaka Municipal Hospital, Department of Gastroenterology Inada, Masami ; Toyonaka Municipal Hospital, Department of Gastroenterology
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A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

Tsutomu Nishida[1)], Shiro Hayashi[1)2)], Mamoru Takenaka[3)], Makoto Hosono[4)], Hirofumi Kogure[5)], Kenkei Hasatani[6)], Shinjiro Yamaguchi[7)], Hirotsugu Maruyama[8)], Hisashi Doyama[9)], Hideyuki Ihara[10)], Toshiyuki Yoshio[11)], Koji Nagaike[12)], Takuya Yamada[13)], Takayuki Yakushijin[14)], Tadayuki Takagi[15)], Hidetaka Tsumura[16)], Akira Kurita[17)], Satoshi Asai[18)], Yukiko Ito[19)], Toshio Kuwai[20)], Yasuki Hori[21)], Iruru Maetani[22)], Kenji Ikezawa[23)], Takuji Iwashita[24)], Kengo Matsumoto[1)], Masami Inada[1)]

1) Department of Gastroenterology, Toyonaka Municipal Hospital, Toyonaka, Osaka, Japan
2) Department of Gastroenterology and Internal Medicine, Kento Hayashi Clinic, Suita, Osaka, Japan
3) Department of Gastroenterology and Hepatology, Kindai University, Faculty of Medicine, Osaka-Sayama, Osaka, Japan
4) Department of Radiology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan
5) Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
6) Department of Gastroenterology, Fukui Prefectural Hospital, Fukui, Fukui, Japan
7) Department of Gastroenterology and Hepatology, Kansai Rosai Hospital,

Amagasaki, Hyogo, Japan

8) Department of Gastroenterology, Osaka City University, Graduate School of Medicine, Osaka, Osaka, Japan

9) Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa, Japan

10) Department of Gastroenterology, Tonan Hospital, Sapporo, Hokkaido, Japan

11) Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Ariake, Tokyo, Japan

12) Department of Gastroenterology and Hepatology, Suita Municipal Hospital, Osaka, Japan

13) Department of Gastroenterology and Hepatology, Osaka-Rosai Hospital, Sakai, Osaka, Japan

14) Department of Gastroenterology and Hepatology, Osaka General Medical Center, Osaka, Osaka, Japan

15) Department of Gastroenterology, Fukushima Medical University School of Medicine, Fukushima, Japan

16) Department of Gastroenterological Oncology, Hyogo Cancer Center, Akashi, Japan

17) Department of Gastroenterology and Hepatology, Digestive Disease Center, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Osaka, Japan

18) Department of Gastroenterology, Tane General Hospital, Osaka, Osaka, Japan

19) Department of Gastroenterology, Japanese Red Cross Medical Center, Tokyo,

Japan

20) Department of Gastroenterology, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan

21) Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

22) Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Ohashi Medical Center, Tokyo, Japan

23) Department of Hepatobiliary and Pancreatic Oncology, Osaka International Cancer Institute, Osaka, Osaka, Japan

24) First Department of Internal Medicine, Gifu University Hospital, Gifu, Japan

Address all correspondence to: Tsutomu Nishida, M.D.

Department of Gastroenterology, Toyonaka Municipal Hospital

4-14-1 Shibahara, Toyonaka, Osaka 560-8565 Japan

Email: tnishida.gastro@gmail.com

Tel: +81-6-6843-0101

Email address: Tsutomu Nishida: tnishida. gastro@gmail.com, Shiro Hayashi: hayashishiro1976@yahoo.co.jp, Mamoru Takenaka: mamoxyo45@gmail.com, Makoto Hosono: hosono@med.kindai.ac.jp, Hirofumi Kogure: kogureh-tky@umin.ac.jp, Kenkei Hasatani: hasatani9@yahoo.co.jp, Shinjiro Yamaguchi: smay-0608@diary.ocn.ne.jp,

Hirotsugu Maruyama: hiromaruyama99@gmail.com, Hisashi Doyama: doyama.134@gmail.com, Hideyuki Ihara: h-ihara@tonan.gr.jp, Toshiyuki Yoshio: toshiyuki.yoshio@jfcr.or.jp, Koji Nagaike: nagaike.koji@gmail.com, Takuya Yamada: yamtak1973@gmail.com, Takayuki Yakushijin: yakushijin@gh.opho.jp, Tadayuki Takagi: daccho@fmu.ac.jp, Hidetaka Tsumura: h.tsumura@hp.pref.hyogo.jp, Akira Kurita: kuritaaki1976@gmail.com, Satoshi Asai: bonyaritetsu1226@hotmail.co.jp, Yukiko Ito: yukikomd1224@gmail.com, Toshio Kuwai: toshiokuwai@gmail.com, Yasuki Hori: yhori@med.nagoya-cu.ac.jp, Iruru Maetani: mtnir50637@med.toho-u.ac.jp, Kenji Ikezawa: ikezawa-ke@mc.pref.osaka.jp, Takuji Iwashita: takuji@w7.dion.ne.jp, Kengo Matsumoto: ken5@gh.med.osaka-u.ac.jp, Masami Inada: inada-intoyo@chp.toyonaka.osaka.jp

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ABSTRACT

INTRODUCTION: Recently, the use of various endoscopic procedures under X-ray fluoroscopic guidance, such as endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS), enteral endoscopy, and stenting, has been rapidly increasing because of the minimally invasive nature of these procedures compared to that of surgical intervention. With the spread of computed tomography and fluoroscopic interventions, including endoscopic procedures under X-ray guidance, high levels of radiation exposure (RE) from medical imaging have led to major concerns throughout society. However, information about RE related to these image-guided procedures is scarce, and their reference levels have not been established. The aim of this study is prospectively to collect the actual RE dose and to help establish diagnostic reference levels (DRLs) in the field of gastroenterology in Japan.

METHODS AND ANALYSIS: This study is a multicenter, prospective observational study that aims to collect the actual RE from treatments and diagnostic procedures, including ERCP, interventional EUS, balloon-assisted enteroscopy, and enteral metallic stent and enteral tube placement. We will measure the total fluoroscopy time (FT, min), the total dose-area product (DAP, $Gycm^2$) and air-kerma (AK, mGy) of those procedures. Because we will be collecting the actual RE data and identifying the affecting factors through a prospective, nationwide design, this study will help to set the DRLs of ERCP, interventional EUS, balloon-assisted enteroscopy, and enteral metallic stent and enteral tube placement.

ETHICS AND DISSEMINATION: This trial (Radiation EXposure from GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials Registry at http://www.umin.ac.jp/ctr/ with number UMIN000036525 (registered 1 May 2019). Approval was obtained from each institutional review board. The requirement for informed consent will be waived via the *opt-out* method of each hospital website.

Article summary

This is a research protocol of a study that aims to collect actual data on radiation exposure (RE) and to identify the factors affecting RE during treatments and diagnostic procedures under different types of fluoroscopic guidance for gastroenterology procedures, including the gastrointestinal, hepatobiliary and pancreatic fields, to serve as a basis for DRLs in Japan.

Strengths and limitations of this study

- A large, multicenter, nationwide dataset of radiation exposure doses for gastrointestinal fluoroscopic procedures, including endoscopic retrograde cholangiopancreatography, interventional endoscopic ultrasonography, balloon-assisted enteroscopy, and enteral metallic stent and enteral tube placement, serves as a basis for the diagnostic reference levels in Japan.
- This study will include data from relatively recently launched fluoroscopic systems. Therefore, these data may not always be valid for old models of fluoroscopic systems.
- This study will be conducted in hospitals where gastroenterologists or endoscopists who are concerned about medical radiation exposure work. Therefore, the collected values of radiation exposure may be lower than those in the real world.

INTRODUCTION

Medical radiation is widely used in both medical imaging and radiation treatment. In medical imaging, fluoroscopy employs radiation to show a continuous X-ray image on a monitor and plays a major role in the daily practices of gastroenterology, digestive endoscopy, and hepatobiliary and pancreatic studies. Radiological medical imaging has both benefits and drawbacks for patients. The latter is split into two types: deterministic risks [1], determined by the threshold dose, as represented by skin injury; and stochastic risks, determined by a linear no-threshold model, such as cancer risk [2]. Therefore, all medical staff involved in medical radiation are required to have correct knowledge of the appropriate use of medical radiation. Historically, medical radiation has rapidly increased since the 1990s with the spread of computed tomography (CT), and radiation-associated cancer risk was recognized in the same period, even with small doses [3 4 5]. In particular, the use of CT has increased approximately 12-fold in the United Kingdom and more than 20-fold in the United States in the last 25 years [6]. The International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and other radiological societies have been trying to manage medical RE according to the “as low as reasonably achievable” (ALARA) principle by establishing diagnostic reference levels (DRLs) to optimize protection from medical radiation. The concept of DRLs was first introduced by ICRP 73 [7] in 1996. Then, the ICRP emphasized the important role of DRLs as a tool for optimizing patient protection [8 9]. Accordingly, the ICRP set specific target levels for various X-ray-related

procedures in 2007 [8]. This movement of setting DRLs has been led by radiation-related societies in each region, although mainly in Western countries. The ICRP 135 recommends that all individuals who are involved in patient procedures with the risk of medical exposure should be familiar with the DRL process as a tool for optimizing protection [10]. DRLs are now widely accepted in not only Western countries but also Japan (Japan DRLs 2015) [11], and DRLs have been the global standard for all procedures that use ionizing radiation. The introduction of DRLs in the UK could achieve a reduction in radiation dose of approximately 50% in typical X-ray examinations over 15 years [12]. However, there is still not enough available data on RE for gastrointestinal fluoroscopic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS), small bowel endoscopy, and enteral stent placement; these techniques are still being developed and have recently been used with increasing frequency [13].

Our gastroenterologists and endoscopists are still unfamiliar with the DRL concept. Among gastrointestinal endoscopy associations, the 2012 European Gastrointestinal Endoscopy Society (ESGE) guidelines for radiation protection states that the entrance skin dose (ESD; approximately equivalent to air-kerma in this study) and kerma-area product (KAP; approximately equivalent to dose-area product (DAP) in this study) during ERCP are 55-347 mGy and 3-115/8-333 Gycm^2, respectively, although information regarding DRLs of ERCP is limited because this statement is based on approximately only 600 cases of ERCP, including 7 reports [14]. No guidelines on RE from the American Society for Gastrointestinal Endoscopy (ASGE) exist, but the ASGE

recommends measuring and documenting fluoroscopy time (FT) and radiation dose in all ERCP procedures as a quality indicator (level of evidence: 2C) [15]. Although no guidelines for exposure have been developed at the Japan Gastroenterological Endoscopy Society (JGES), a description of FT exists in the item about ERCP in the Japan Endoscopy Database (JED) [16], which is scheduled to be implemented as a nationwide endoscopic survey in 2020. Therefore, we aim to collect the actual RE data and identify the affecting factors in the REX-GI study and to establish data based on the DRLs of ERCP, interventional EUS, balloon-assisted enteroscopy, and enteral metallic stent and enteral tube placement.

METHODS AND ANALYSIS

Aims

The primary aim of this nationwide, prospective study is to collect actual data on RE and identify the factors affecting RE during treatments and diagnostic procedures under different types of fluoroscopic guidance for gastroenterology procedures, including the gastrointestinal, hepatobiliary and pancreatic fields, to serve as a basis for DRLs in Japan.

Design

This is a multicenter, prospective observational cohort study of consecutive patients who underwent the following 5 treatments and diagnostic procedures under fluoroscopic guidance in the field of gastroenterology: 1) ERCP, 2) interventional EUS, 3) balloon-assisted enteroscopy, 4) enteral metallic stent placement; and 5) enteral tube placement. We examined the procedure time (min), total FT (min), AK (mGy), DAP ($Gycm^2$), total number of roentgenography, and radiation dose rate (RDR) (mGy/min) during the procedures. The participating clinicians will manage patients according to usual clinical practice, and the patients will undergo the above 5 procedures. For analysis, all data, including the related variables and outcome data (Tables 1 and 2), will be collected for all patients. The study (Radiation EXposure from GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials Registry at http://www.umin.ac.jp/ctr/ with number UMIN000036525 (registered 1 May 2019).

Setting

The study was conducted at 7 university hospitals, 4 cancer centers, 9 general hospitals and 2 municipal hospitals in Japan. The participating hospitals are Toyonaka Municipal Hospital, Kindai University, the University of Tokyo, Fukui Prefectural Hospital, Kansai Rosai Hospital, Osaka City University, Ishikawa Prefectural Central Hospital, Tonan Hospital, Japanese Foundation for Cancer Research, Suita Municipal Hospital, Osaka Rosai Hospital, Osaka General Medical Center, Fukushima Medical University School of Medicine, Hyogo Cancer Center, Kitano Hospital, Tane General Hospital, Japanese Red Cross Medical Center, Kure Medical Center and Chugoku Cancer Center, Nagoya City University Hospital, Toho University Ohashi Medical Center, Osaka International Cancer Institute, and Gifu University Hospital (Figure 1). The central sites of the study are located at the Toyonaka Municipal Hospital and Kindai University.

Study population

We will include all patients following usual clinical care who underwent the following treatments and diagnostic procedures under fluoroscopic guidance: 1) ERCP; 2) interventional EUS; 3) balloon-assisted enteroscopy; 4) enteral metallic stent placement; and 5) enteral tube placement. There is no age restriction. We will exclude patients who do not want to participate in this study via the *opt-out* method of each

hospital website and patients who the attending physicians judge inadequate for this study.

Primary outcomes

The primary outcomes will be the total FT (min), RDR (mGy/min), dose-area parameters (AK (mGy) and DAP ($Gycm^2$)) and total number of imaging studies that the patients who meet the individual inclusion and exclusion criteria will undergo (Table 1).

Secondary outcomes

The secondary outcome will be the RE-related factors that affect the radiation dose in each procedure. The details are shown in Table 2.

Setting the sample size

According to the preliminary questionnaire survey (data not shown), the numbers of examinations per year in the 8 centers that plan to participate in March 2019 are 4000 ERCP procedures, 125 EUS procedures, 320 small intestine endoscopy procedures, 44 esophageal stent placements, 150 gastroduodenal stent placements, 75 colorectal stent placements, 180 transanal ileus tube placements, and 75 ileus tube placements. To set the DRL and to reduce intraprocedural variability in each hospital, we believe that initially enrolling a high number of facilities and patients is desirable; therefore, we did not set an upper limit for the goals.

Data analysis plan

Continuous variables will be expressed as medians with interquartile ranges. The categorical variables will be expressed as numbers in each category or as frequencies. Simple linear regression analysis will be performed to identify the relationships between procedure time, FT and RD. A multiple linear regression analysis will be performed to identify the factors related to RD. A P value of 0.05 will be considered statistically significant. All statistical analyses will be performed with JMP software (SAS Institute, Inc., Cary, NC, USA).

Patient and public involvement and patient recruitment

Clinical factors related to ERCP and interventional EUS have been retrospectively collected at two sites (Toyonaka Municipal Hospital and Kindai University) [17-20] . We used those published data to develop plans for the design or implementation of the study and to determine the research question or the outcome measures. No patients were requested to advise us on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants, but we will consider disseminating the results of the research to the relevant patient community.

Data collection

The clinical factors have been modified to comply with local patient flow and administrative requirements and have been assessed and approved by the study steering committee. Case report forms will be de-identified after all data points have

been completed and all data queries have been addressed. Data collection will be scheduled to be performed at 3-month intervals to prevent data loss. Data analysis will take place at the central study site (Kindai University). This study does not require data monitoring due to its nature as an observational study without interventions. Data will be retained for either a minimum of 5 years after the end of the study or for 10 years after publication, whichever is later.

Time plan

May 2019 - December 2020: Patient recruitment.

2021: Data analysis and writing and submission of the main manuscript for publication.

Ethics and dissemination

This observational study will be conducted in accordance with the Declaration of Helsinki, and approval has been obtained from each institutional review board. The requirement for informed consent will be waived via the *opt-out* method of each hospital website.

Author contributions

Nishida T, Hayashi S (Toyonaka Municipal Hospital), and Takenaka M (Kindai University) designed this study. Hosono M (Kindai University) critically reviewed the protocol. Nishida T, Hayashi S (Toyonaka Municipal Hospital), Takenaka M (Kindai

University), Kogure H (The University of Tokyo), Hasatani K (Fukui Prefectural Hospital), Yamaguchi S (Kansai Rosai Hospital), Maruyama H (Osaka City University), Doyama H (Ishikawa Prefectural Central Hospita), Ihara H, (Tonan Hospital) Yoshio T (Cancer Institute Hospital, Japanese Foundation for Cancer Research), Nagaike K (Suita Municipal Hospital), Yamada T (Osaka-Rosai Hospital), Yakushijin T (Osaka General Medical Center), Takagi T (Fukushima Medical University School of Medicine), Tsumura H (Hyogo Cancer Center), Kurita A (Kitano Hospital), Asai S (Tane General Hospital), Ito Y (Japanese Red Cross Medical Center), Kuwai T (National Hospital Organization, Kure Medical Center and Chugoku Cancer Center), Hori Y (Nagoya City University Graduate School of Medical Sciences), Maetani I (Toho University Ohashi Medical Center), Ikezawa K (Osaka International Cancer Institute), Iwashita T (Gifu University Hospital), Matsumoto K, and Inada M (Toyonaka Municipal Hospital) participated this study and will recruit the patients. All authors accepted the final version of the protocol (ver. 1.1: 2019-Mar-14, ver.1.5: 2019-July-15).

Acknowledgements and collaborators

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Publication and data sharing

After completion of the study, a main manuscript will be prepared to present the results and will be submitted to a clinical journal for peer review. This study will ensure that the public has access to the published data. A file containing the clean dataset used for

final analysis to determine the main data of the study, and an explanation of variables will be made publicly accessible in an anonymized format.

Consent for publication

The principal investigators will form a publication committee, which will include key members of this study, and the committee will grant authorship according to individual input. Investigators who do not qualify for authorship will be acknowledged by name in the final manuscript.

Conflicts of interest statement.

None of the authors have any competing interests arising from this research.

Discussion

Currently, the establishment of DRLs is an international requirement for protection from medical radiation. Generally, for diagnostic radiology, national and regional DRLs are usually set at the 75% percentile of the distribution of a typical sample dose [21]. All physicians or medical staff who are involved in radiological imaging or procedures under fluoroscopic guidance should be familiar with the DRL process as a tool for optimizing protection. In addition, separate DRLs must be established for each country and/or region because the equipment and procedure protocols can vary among different regions [21]. However, the amount of RE depends on procedure complexity, patient anatomy, lesion characteristics, disease severity [10] and type of fluoroscopic devices [18]; thus, setting the upper limit of radiation use by applying uniform standards is difficult. Generally, DRLs are not dose limits and do not help distinguish between good and poor medical practices [21]. Therefore, a high demand exists for a large amount of real-world evidence. The 2015 Japan DRLs state that the methods for establishing DRLs not only includes setting radiation dose levels but also includes determining the dose quantities and units used to set the DRLs, thus standardizing the methodology for dose measurements, data collection and identification of the applications of DRLs [11]. Unfortunately, most gastroenterologists are unfamiliar with not only DRLs but also radiation protection because information on RE from gastrointestinal medical treatment is currently very scarce, and few RE standards, including DRLs, have been established worldwide. Given this background, the REX-GI study is planned as an observational, nationwide study in Japan. Our results will help to promote radiation optimization and

patient radiation protection in gastroenterology studies, such as digestive endoscopy, and hepatobiliary and pancreatic procedures.

Table 1. Primary outcomes

Factors	Variables
Patients	▪ Procedure type ▪ Age ▪ Sex
Fluoroscopic system	▪ Fluoroscopic device (company, device model, manufacturing year) ▪ Basic use setting: frame per second (FPS), radiation field (cm^2)
Radiation exposure	▪ Total fluoroscopy time (FT) (min) ▪ Air-Kerma (AK) (mGy) ▪ Dose-area product (DAP) ($Gycm^2$) ▪ Total number of roentgenography procedures ▪ Radiation dose rate (RDR) (mGy/min)

Table 2. Secondary outcomes

Procedures	Radiation exposure-related factors
ERCP	(A) Surgically altered gastrointestinal anatomy Billroth I reconstruction, Billroth II reconstruction, Roux-en-Y reconstruction, pancreaticoduodenectomy (B) Type of endoscope (C) Naïve papilla (D) Indications for ERCP (including suspicion) are classified into the following five categories: 1) Choledocholithiasis (maximum diameter, number of stones, presence of cholangitis, tube exchange for the above diseases, treatment for choledocholithiasis with or without balloon catheter, basket catheter, crusher, etc.) 2) Distant malignant bile duct stricture (papillary tumor, distal cholangiocarcinoma, pancreatic cancer, etc.) 3) Proximal malignant bile duct stricture (Hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, gallbladder cancer, etc.) 4) Pancreatic duct examination (pancreas cancer, intraductal papillary mucinous neoplasm, etc.) 5) Other diseases apart from those listed above (benign bile duct stricture, pancreatobiliary junction abnormality, etc.) (E) Total procedure time (min) * 1) Cannulation time

	2) Treatment time (F) Experience of the high-volume endoscopist (HVE) or low-volume endoscopist: (LVE) † (G) Facility scale: The number of ERCP procedures per year (H) Whether the fluoroscopic operator is inside or outside in the fluoroscopy room (I) Various treatments (endoscopic sphincterotomy, stone treatment, bile duct/pancreatic stent, cytology, biopsy, naïve papilla, cannulation method, contrast agent, intubation time, first-use catheter, large balloon, crusher, drainage area or method, stent type used, cholangioscopy) (J) Sedation: Medication and the depth of the anesthesia ‡
Interventional EUS	(A) Indication for interventional EUS (EUS-guided hepaticogastrostomy (HGS), choledochoduodenostomy (CDS), cyst drainage (CD), antegrade treatment (AG), rendezvous technique (RV), pancreatic duct drainage (PD) (B) Total procedure time‡ 1) Endoscope insertion time 2) Treatment time (C) Facility scale: The number of EUS interventions per year, the number of EUS-guided fine-needle aspiration (FNA) procedures per year (D) Double stenting (presence or absence of duodenal stenosis) (E) Device (F) Scope position (G) Sedation: Medication and the depth of anesthesia
Balloon-assisted	(A) Disease indicating balloon-assisted enteroscopy

enteroscopy	1) Hemostatic or bleeding confirmation 2) Crohn's disease 3) Small intestine tumor examination 4) Others (B) Insertion site: perioral or transanal (C) Insertion length (cm) (D) Total procedure time (min)
Enteral metallic stent placement	(A) Stent location 1) Esophagus (Upper/Mid-Low/Trans) 2) Gastro-duodenum (Above pylorus/Trans pylorus /Below pylorus) 3) Colon stent (Right/Left/Rectum) (B) Total procedure time (min) § 1) Endoscope insertion time 2) Treatment time
Enteral ileus tube placement	(A) Disease indicating ileus tube (B) Intranasal ileus tube insertion for ileal obstruction or transanal ileus tube insertion for malignant colonic obstruction 1) Tube insertion length for peroral ileus tube placement (cm) 2) The occlusion site for the transanal tube (Right/Left/Rectum) (D) Total procedure time (min) §

ERCP: endoscopic retrograde cholangiopancreatography

* Cannulation time is defined as the time from endoscope insertion until successful biliary cannulation, and treatment time was defined as the time from successful biliary cannulation until the scope was removed from the patient. The total procedure time was defined as the time from endoscope insertion until the scope was removed from the patient (cannulation time +treatment time).

‡ Depth of anesthesia is divided into 3 levels based on the Richmond Agitation-Sedation Scale (RASS), Ramsay Scale, and Sedation-Agitation Scale (SAS): good, poor, and very bad. The good level is defined as RASS score: -5 ~ -1, SAS score: 1 ~ 3, and Ramsay score: 3 ~ 6 equivalent, without additional unplanned doses. The poor level is defined as RASS score: 0 ~ + 1, SAS score: 4 ~ 5, and Ramsay score: 1 ~ 2, without physical restraint but with unplanned doses. The very bad level is defined as requiring physical restraint with a manpower considered dangerous, RASS score: +2 to +4, and SAS score: 6 to 7 regardless of Ramsay score.

† HVE: Endoscopists with more than 200 ERCP results and who have been involved in ERCP for over 10 years. LVE: Non-HVE endoscopists who perform ERCP.

‡ Endoscope insertion time is defined as the time from endoscope insertion until the initial EUS-guided needle puncture, and treatment time was defined as the time from initial EUS-guided needle puncture until the scope was removed from the patient. The total procedure time was defined as the time from endoscope insertion until the scope was removed from the patient (endoscope insertion time +treatment time).

‡Endoscope insertion time is defined as the time from endoscope insertion until initial guidewire exploration, and treatment time was defined as the time from initial guidewire exploration until the scope was removed from the patient. The total procedure time was defined as the time from endoscope insertion until the scope was removed from the patient (endoscope insertion time +treatment time).

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Figure legends

Figure 1. The participating hospitals in this study.

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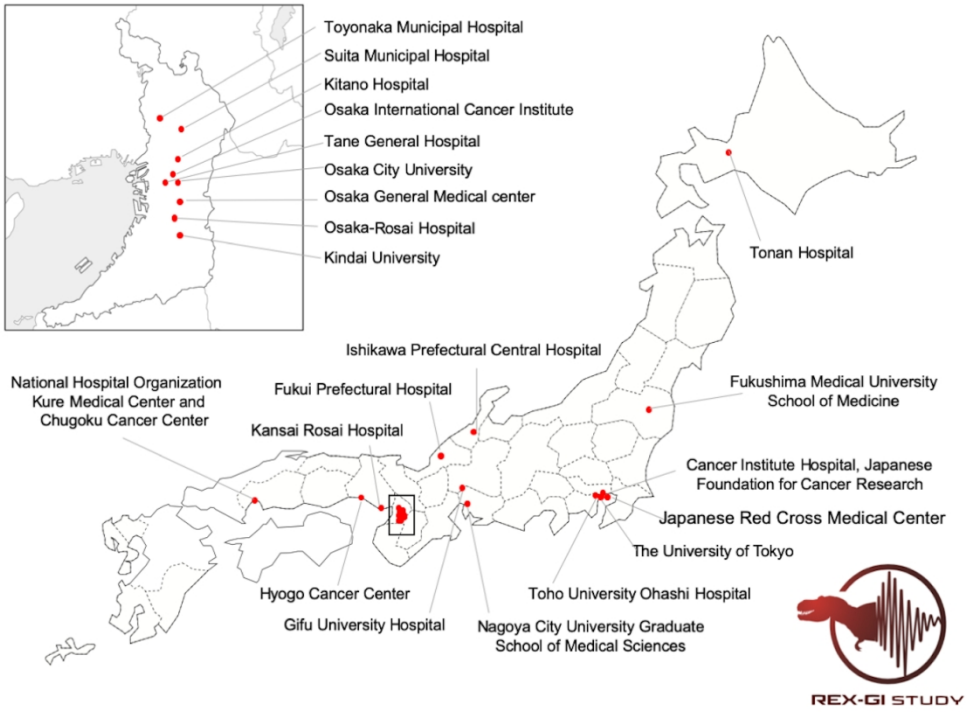

Figure 1. The participating hospitals in this study.

119x90mm (300 x 300 DPI)

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Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6, 11
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6, 11
Protocol version	#3	Date and version identifier	16
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N.A.
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N.A.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12, 14
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	9-10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N.A.
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N.A.
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N.A.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N.A.
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	N.A.

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N.A.
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N.A.
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N.A.
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N.A.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N.A.
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N.A.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N.A.
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N.A.
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N.A.
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17, 18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N.A.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N.A.
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N.A.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N.A.

BMJ Open

A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

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Complete List of Authors:	Nishida, Tsutomu ; Toyonaka Municipal Hospital, Department of Gastroenterology Hayashi, Shiro; Toyonaka Municipal Hospital, Department of Gastroenterology; Kento Hayashi Clinic, Department of Gastroenterology and Internal Medicine Takenaka, Mamoru ; Kindai University, Department of Gastroenterology and Hepatology Hosono, Makoto ; Kindai University, Department of Radiology Kogure, Hirofumi; The University of Tokyo, Department of Gastroenterology Hasatani, Kenkei ; Fukui Prefectural Hospital, Department of Gastroenterology Yamaguchi, Shinjiro ; Kansai Rosai Hospital, Department of Gastroenterology and Hepatology Maruyama, Hirotsugu ; Osaka City University, Department of Gastroenterology Doyama, Hisashi ; Ishikawa Prefectural Central Hospital, Department of Gastroenterology Ihara, Hideyuki ; Tonan Hospital, Department of Gastroenterology Yoshio, Toshiyuki ; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Department of Gastroenterology Nagaike, Koji ; Suita Municipal Hospital, Department of Gastroenterology and Hepatology Yamada, Takuya ; Osaka Rosai Hospital, Department of Gastroenterology and Hepatology, Yakushijin, Takayuki ; Osaka General Medical Center, Department of Gastroenterology and Hepatology Takagi, Tadayuki ; Fukushima Medical University School of Medicine, Department of Gastroenterology Tsumura, Hidetaka ; Hyogo Cancer Center, Department of Gastroenterological Oncology, Kurita, Akira ; Kitano Hospital, Department of Gastroenterology and Hepatology, Digestive Disease Center Asai, Satoshi ; Tane General Hospital, Department of Gastroenterology Ito, Yukiko ; Japanese Red Cross Medical Center, Department of Gastroenterology Kuwai, Toshio ; Kure Medical Center, Department of Gastroenterology Hori, Yasuki ; Nagoya City University Graduate School of Medical Sciences Department of Gastroenterology and Metabolism

	Maetani, Iruru ; Toho University Ohashi Medical Center, Division of Gastroenterology and Hepatology, Department of Internal Medicine Ikezawa, Kenji ; Osaka International Cancer Institute, Department of Hepatobiliary and Pancreatic Oncology Iwashita, Takuji ; Gifu University Hospital, First Department of Internal Medicine Matsumoto, Kengo; Toyonaka Municipal Hospital, Department of Gastroenterology Inada, Masami ; Toyonaka Municipal Hospital, Department of Gastroenterology
Primary Subject Heading:	Gastroenterology and hepatology
Secondary Subject Heading:	Radiology and imaging, Public health, Research methods
Keywords:	Radiation Exposure, Diagnostic Reference Levels, ERCP, Gastrointestinal Fluoroscopic Procedure, Endoscopy < GASTROENTEROLOGY

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A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

Tsutomu Nishida[1)], Shiro Hayashi[1)2)], Mamoru Takenaka[3)], Makoto Hosono[4)], Hirofumi Kogure[5)], Kenkei Hasatani[6)], Shinjiro Yamaguchi[7)], Hirotsugu Maruyama[8)], Hisashi Doyama[9)], Hideyuki Ihara[10)], Toshiyuki Yoshio[11)], Koji Nagaike[12)], Takuya Yamada[13)], Takayuki Yakushijin[14)], Tadayuki Takagi[15)], Hidetaka Tsumura[16)], Akira Kurita[17)], Satoshi Asai[18)], Yukiko Ito[19)], Toshio Kuwai[20)], Yasuki Hori[21)], Iruru Maetani[22)], Kenji Ikezawa[23)], Takuji Iwashita[24)], Kengo Matsumoto[1)], Masami Inada[1)]

1) Department of Gastroenterology, Toyonaka Municipal Hospital, Toyonaka, Osaka, Japan
2) Department of Gastroenterology and Internal Medicine, Kento Hayashi Clinic, Suita, Osaka, Japan
3) Department of Gastroenterology and Hepatology, Kindai University, Faculty of Medicine, Osaka-Sayama, Osaka, Japan
4) Department of Radiology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan
5) Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
6) Department of Gastroenterology, Fukui Prefectural Hospital, Fukui, Fukui, Japan
7) Department of Gastroenterology and Hepatology, Kansai Rosai Hospital,

Amagasaki, Hyogo, Japan

8) Department of Gastroenterology, Osaka City University, Graduate School of Medicine, Osaka, Osaka, Japan

9) Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa, Japan

10) Department of Gastroenterology, Tonan Hospital, Sapporo, Hokkaido, Japan

11) Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Ariake, Tokyo, Japan

12) Department of Gastroenterology and Hepatology, Suita Municipal Hospital, Osaka, Japan

13) Department of Gastroenterology and Hepatology, Osaka-Rosai Hospital, Sakai, Osaka, Japan

14) Department of Gastroenterology and Hepatology, Osaka General Medical Center, Osaka, Osaka, Japan

15) Department of Gastroenterology, Fukushima Medical University School of Medicine, Fukushima, Japan

16) Department of Gastroenterological Oncology, Hyogo Cancer Center, Akashi, Japan

17) Department of Gastroenterology and Hepatology, Digestive Disease Center, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Osaka, Japan

18) Department of Gastroenterology, Tane General Hospital, Osaka, Osaka, Japan

19) Department of Gastroenterology, Japanese Red Cross Medical Center, Tokyo,

Japan

20) Department of Gastroenterology, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan

21) Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

22) Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Ohashi Medical Center, Tokyo, Japan

23) Department of Hepatobiliary and Pancreatic Oncology, Osaka International Cancer Institute, Osaka, Osaka, Japan

24) First Department of Internal Medicine, Gifu University Hospital, Gifu, Japan

Address all correspondence to: Tsutomu Nishida, M.D.

Department of Gastroenterology, Toyonaka Municipal Hospital

4-14-1 Shibahara, Toyonaka, Osaka 560-8565 Japan

Email: tnishida.gastro@gmail.com

Tel: +81-6-6843-0101

Email addresses: Tsutomu Nishida: tnishida.gastro@gmail.com, Shiro Hayashi: hayashishiro1976@yahoo.co.jp, Mamoru Takenaka: mamoxyo45@gmail.com, Makoto Hosono: hosono@med.kindai.ac.jp, Hirofumi Kogure: kogureh-tky@umin.ac.jp, Kenkei Hasatani: hasatani9@yahoo.co.jp, Shinjiro Yamaguchi: smay-0608@diary.ocn.ne.jp,

Hirotsugu Maruyama: hiromaruyama99@gmail.com, Hisashi Doyama: doyama.134@gmail.com, Hideyuki Ihara: h-ihara@tonan.gr.jp, Toshiyuki Yoshio: toshiyuki.yoshio@jfcr.or.jp, Koji Nagaike: nagaike.koji@gmail.com, Takuya Yamada: yamtak1973@gmail.com, Takayuki Yakushijin: yakushijin@gh.opho.jp, Tadayuki Takagi: daccho@fmu.ac.jp, Hidetaka Tsumura: h.tsumura@hp.pref.hyogo.jp, Akira Kurita: kuritaaki1976@gmail.com, Satoshi Asai: bonyaritetsu1226@hotmail.co.jp, Yukiko Ito: yukikomd1224@gmail.com, Toshio Kuwai: toshiokuwai@gmail.com, Yasuki Hori: yhori@med.nagoya-cu.ac.jp, Iruru Maetani: mtnir50637@med.toho-u.ac.jp, Kenji Ikezawa: ikezawa-ke@mc.pref.osaka.jp, Takuji Iwashita: takuji@w7.dion.ne.jp, Kengo Matsumoto: ken5@gh.med.osaka-u.ac.jp, Masami Inada: inada-intoyo@chp.toyonaka.osaka.jp

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Keywords: Radiation Exposure, Diagnostic Reference Levels, ERCP, Gastrointestinal Fluoroscopic Procedure, Endoscopy.

ABSTRACT

INTRODUCTION: Recently, the use of various endoscopic procedures under X-ray fluoroscopic guidance, such as endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS), enteral endoscopy, and stenting, has been rapidly increasing because of the minimally invasive nature of these procedures compared to that of surgical intervention. With the spread of computed tomography and fluoroscopic interventions, including endoscopic procedures under X-ray guidance, high levels of radiation exposure (RE) from medical imaging have led to major concerns throughout society. However, information about RE related to these image-guided procedures in gastrointestinal endoscopy is scarce, and the RE reference levels have not been established. The aim of this study is to prospectively collect the actual RE dose and to help establish diagnostic reference levels (DRLs) in the field of gastroenterology in Japan.

METHODS AND ANALYSIS: This study is a multicenter, prospective observational study that is being conducted to collect the actual RE from treatments and diagnostic procedures, including ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement. We will measure the total fluoroscopy time (FT, min), the total dose-area product (DAP, $Gycm^2$) and air-kerma (AK, mGy) of those procedures. Because we are collecting the actual RE data and identifying the influential factors through a prospective, nationwide design, this study will provided guidance regarding the DRLs of ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement.

ETHICS AND DISSEMINATION: This trial (Radiation EXposure from GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials Registry at http://www.umin.ac.jp/ctr/ under number UMIN000036525 (registered 1 May 2019). Approval was obtained from the Institutional Review Board of Toyonaka Municipal Hospital (2019-02-04). The need for informed consent will be waived via the *opt-out* method of each hospital website.

Strengths and limitations of this study

- The large, multicenter, nationwide dataset of radiation exposure doses for gastrointestinal fluoroscopic procedures in gastrointestinal endoscopy gathered in this study will serve as a basis for the development of diagnostic reference levels in Japan.
- Gastrointestinal fluoroscopic procedures have been rapidly increasing in number and complexity, but there are still not enough available local and national DRLs in gastrointestinal endoscopy units.
- These data may not be valid for old models of fluoroscopic systems because this study will include data from fluoroscopic systems with available radiation data.

INTRODUCTION

Medical radiation is widely used in both medical imaging and radiation treatment. In medical imaging, fluoroscopy employs radiation to show a continuous X-ray image on a monitor and plays a major role in the daily practices of gastroenterology, digestive endoscopy, and hepatobiliary and pancreatic studies. Radiological medical imaging has both benefits and drawbacks for patients. The latter is split into two types: deterministic risks [1], determined by the threshold dose, as represented by skin injury, and stochastic risks, determined by a linear no-threshold model, such as the cancer risk [2]. There have been some reports on radiation-induced skin injury in cardiology and interventional radiology (IVR) [3], but reports from gastrointestinal endoscopy units are rare. However, all medical staff in gastrointestinal endoscopy units need to have correct knowledge of the appropriate use of medical radiation. Historically, the use of medical radiation has rapidly increased since the 1990s with the spread of computed tomography (CT), and the radiation-associated cancer risk was recognized in the same period, even when the doses of radiation were small [4 5 6]. In particular, the use of CT has increased approximately 12-fold in the United Kingdom and more than 20-fold in the United States in the last 25 years [7].

The International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and other radiological societies have been attempting to manage medical radiation exposure (RE) according to the “as low as reasonably achievable” (ALARA) principle by establishing diagnostic reference levels

(DRLs) to optimize protection from medical radiation. The concept of DRLs was first introduced by the ICRP 73 [8] in 1996. Then, the ICRP emphasized the important role of DRLs as a tool for optimizing patient protection [9 10]. Accordingly, the ICRP set specific target levels for various X-ray-related procedures in 2007 [9]. This movement of setting DRLs has been led by radiation-related societies in each region, although the movement has mainly been driven by Western countries. The ICRP 135 recommends that all individuals who are involved in patient procedures with the risk of medical exposure should be familiar with the DRL process as a tool for optimizing protection [11]. DRLs are now widely accepted in not only Western countries but also Japan (Japan DRLs 2015) [12], and DRLs have become the global standard for all procedures that use ionizing radiation. Legislation has made it mandatory to establish and record DRLs in Europe, but that is not the case worldwide. The introduction of DRLs in the UK achieved a reduction of approximately 50% in the radiation dose in typical X-ray examinations over 15 years [13]. However, there is still not enough available data on RE for gastrointestinal fluoroscopic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS), small bowel endoscopy, and enteral stent placement; these techniques are still being developed and have recently been used with increasing frequency [14-16].

Our gastroenterologists and endoscopists are still unfamiliar with the DRL concept. Among the guidelines developed by gastrointestinal endoscopy associations, the 2012 European Gastrointestinal Endoscopy Society (ESGE) guidelines for radiation

protection state that the entrance skin dose (ESD; approximately equivalent to air-kerma in this study) and kerma-area product (KAP; approximately equivalent to the dose-area product (DAP) in this study) during diagnostic and therapeutic ERCP are 55-347 mGy and 3-115/8-333 Gycm^2, respectively, although information regarding the DRLs of ERCP is limited because this statement is based on only approximately 600 cases of ERCP in 7 reports [14]. No guidelines on RE from the American Society for Gastrointestinal Endoscopy (ASGE) exist, but the ASGE recommends measuring and documenting fluoroscopy time (FT) and radiation dose in all ERCP procedures as a quality indicator (level of evidence: 2C) [17]. Although no guidelines for exposure have been developed by the Japan Gastroenterological Endoscopy Society (JGES), a description of FT exists in the item regarding ERCP in the Japan Endoscopy Database (JED) [18], which is scheduled to be implemented as a nationwide endoscopic survey in 2020.

Recently, various endoscopic procedures performed under fluoroscopic guidance are rapidly increasing in popularity in gastrointestinal endoscopy units, where the aim is not only diagnosis but also therapeutic intervention. The ICRP recommends that DRLs should be used to manage patient doses during both diagnostic and interventional procedures. There is difficulty in applying the DRL concept to interventional procedures because the RE level depends on the complexity of the procedure and the individual clinical circumstances [10 19 20]. There have been attempts to establish DRLs for IVR

procedures, where grouping by disease site may help minimize the wide distribution of RE [21 22].

The Japanese DRLs were established on a basis of a survey and released in 2015; these guidelines defined the DRL value for fluoroscopically guided interventional procedures as a fluoroscopic radiation dose rate (interventional reference point dose rate) of 20 mGy/min [12]. However, it did not include information for specific procedures in the field of gastroenterology [12]. Therefore, we aim to prospectively collect actual RE data and identify the influential factors, such as disease site, in this REX-GI study and to establish DRLs for the following interventional procedures in gastrointestinal endoscopy units: ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement.

METHODS AND ANALYSIS

Aims

The primary aim of this nationwide, prospective study is to collect actual data on RE and identify the factors affecting RE during treatments and diagnostic procedures under different types of fluoroscopic guidance for gastroenterology procedures, including the gastrointestinal, hepatobiliary and pancreatic fields, to serve as a basis for the establishment of DRLs in Japan.

Design

This is a multicenter, prospective observational cohort study of consecutive patients undergoing the following 5 treatments and diagnostic procedures under fluoroscopic guidance in the field of gastroenterology: 1) ERCP, 2) interventional EUS, 3) balloon-assisted enteroscopy, 4) enteral metallic stent placement; and 5) enteral tube placement. We will examine the procedure time (min), total FT (min), AK (mGy), DAP ($Gycm^2$), total number of roentgenography procedures, and radiation dose rate (RDR) (mGy/min) during the procedures. The participating clinicians will manage patients according to the usual clinical practice, and the patients will undergo the above 5 procedures. For the analysis, all data, including the related variables and outcome data (Tables 1 and 2), will be collected for all patients. The study (Radiation EXposure from GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials Registry at http://www.umin.ac.jp/ctr/ under the number UMIN000036525 (registered 1 May 2019).

Setting

The study will be conducted at 7 university hospitals, 4 cancer centers, 9 general hospitals and 2 municipal hospitals in Japan. The participating hospitals are Toyonaka Municipal Hospital, Kindai University, the University of Tokyo, Fukui Prefectural Hospital, Kansai Rosai Hospital, Osaka City University, Ishikawa Prefectural Central Hospital, Tonan Hospital, Japanese Foundation for Cancer Research, Suita Municipal Hospital, Osaka Rosai Hospital, Osaka General Medical Center, Fukushima Medical University School of Medicine, Hyogo Cancer Center, Kitano Hospital, Tane General Hospital, Japanese Red Cross Medical Center, Kure Medical Center and Chugoku Cancer Center, Nagoya City University Hospital, Toho University Ohashi Medical Center, Osaka International Cancer Institute, and Gifu University Hospital (Figure 1). Table 1 shows the fluoroscopic systems and units performing procedures under fluoroscopic guidance in each institution. The central sites of the study are located at the Toyonaka Municipal Hospital and Kindai University. The participating physicians are gastroenterologists or endoscopists, including all experts and trainees working at all involved hospitals. The quality of the fluoroscopic devices will be regularly monitored according to the procedures in each institution.

Study population

We will include all patients receiving usual clinical care who undergo the following treatments and diagnostic procedures under fluoroscopic guidance: 1) ERCP; 2)

interventional EUS; 3) balloon-assisted enteroscopy; 4) enteral metallic stent placement; and 5) enteral tube placement. There is no age restriction. We will exclude patients who do not want to participate in this study via the *opt-out* method on each hospital website and patients who the attending physicians judge to be unsuitable for inclusion in this study.

Primary outcomes

The primary outcomes will be the total FT (min), RDR (mGy/min), dose-area parameters (AK (mGy) and DAP ($Gycm^2$) and the total number of imaging studies that the patients who meet the individual inclusion and exclusion criteria will undergo (Table 2).

Secondary outcome

The secondary outcome will be the RE-related factors that affect the radiation dose in each procedure. The details are shown in Table 3.

Setting the sample size

According to the preliminary questionnaire survey (data not shown), the numbers of examinations per year in the 8 centers that plan to participate in March 2019 are as follows: 4000 ERCP procedures, 125 EUS procedures, 320 small intestine endoscopy procedures, 44 esophageal stent placements, 150 gastroduodenal stent placements, 75 colorectal stent placements, 180 transanal ileus tube placements, and 75 ileus tube

placements. The ICRP 135 recommends using data from 20-30 facilities to set national DRLs, and a survey for a particular examination in a facility should usually involve the collection of data from at least 20 patients [11].

To set the DRLs and to reduce intraprocedural variability in each hospital, we set the minimum sample size to at least 400 patients for each procedure. We believe that initially enrolling a high number of facilities and patients is desirable; therefore, we did not set an upper limit for the goals.

Data analysis plan

After obtaining the data, we will perform normality tests. Continuous variables will be expressed as medians with interquartile ranges or means with standard deviations. The categorical variables will be expressed as numbers in each category or as frequencies. To explore surrogate markers of RD, simple linear regression analysis will be performed to identify the relationships between procedure time, FT and RD. A multiple linear regression analysis will be performed to identify the factors related to RD. A P value of 0.05 will be considered statistically significant. All statistical analyses will be performed with JMP software (SAS Institute, Inc., Cary, NC, USA).

Patient and public involvement

Clinical factors related to ERCP and interventional EUS have been retrospectively collected at two sites (Toyonaka Municipal Hospital and Kindai University) [21 23-25] . We used those published data to develop plans for the design or implementation of the

study and to determine the research question or the outcome measures. No patients were asked to advise us on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants, but we will consider disseminating the results of the research to the relevant patient community.

Data collection

The clinical factors have been modified to comply with local patient flow and administrative requirements and have been assessed and approved by the study steering committee. We are collecting the password-protected case report forms by e-mail from each institution; these will be de-identified after all data have been collected, and all data queries have been addressed. A unique study identification number will identify each participant and the associated clinical data. Data collection will be performed at 3-month intervals to prevent data loss. Data analysis will take place at the central study site (Kindai University). This study does not require data monitoring due to its nature as an observational study without interventions. Data will be retained for either a minimum of 5 years after the end of the study or for 10 years after publication, whichever is later.

Patient recruitment and time plan

Patient recruitment will be carried out at the participating hospitals from May 2019 - December 2020.

2021: Data analysis and writing and submission of the main manuscript for publication.

Ethics and dissemination

This observational study will be conducted in accordance with the principles of the Declaration of Helsinki, and approval has been obtained from the Institutional Review Board of Toyonaka Municipal Hospital (2019-02-04) and the institutional review board of each participating facility. The need for informed consent will be waived via the *opt-out* method on each hospital website. The results of this study will be presented at gastroenterology-, endoscopy-, or radiology-related congresses and will be published in a peer-reviewed journal.

Author contributions

Nishida T, Hayashi S (Toyonaka Municipal Hospital), and Takenaka M (Kindai University) designed this study. Hosono M (Kindai University) critically reviewed the protocol. Nishida T, Hayashi S (Toyonaka Municipal Hospital), Takenaka M (Kindai University), Kogure H (The University of Tokyo), Hasatani K (Fukui Prefectural Hospital), Yamaguchi S (Kansai Rosai Hospital), Maruyama H (Osaka City University), Doyama H (Ishikawa Prefectural Central Hospita), Ihara H, (Tonan Hospital) Yoshio T (Cancer Institute Hospital, Japanese Foundation for Cancer Research), Nagaike K (Suita Municipal Hospital), Yamada T (Osaka-Rosai Hospital), Yakushijin T (Osaka

General Medical Center), Takagi T (Fukushima Medical University School of Medicine), Tsumura H (Hyogo Cancer Center), Kurita A (Kitano Hospital), Asai S (Tane General Hospital), Ito Y (Japanese Red Cross Medical Center), Kuwai T (National Hospital Organization, Kure Medical Center and Chugoku Cancer Center), Hori Y (Nagoya City University Graduate School of Medical Sciences), Maetani I (Toho University Ohashi Medical Center), Ikezawa K (Osaka International Cancer Institute), Iwashita T (Gifu University Hospital), Matsumoto K, and Inada M (Toyonaka Municipal Hospital) participated this study and will recruit the patients. All authors accepted the final version of the protocol (ver. 1.1: 2019-Mar-14, ver.1.5: 2019-July-15).

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Publication and data sharing

After completion of the study, a main manuscript will be prepared to present the results and will be submitted to a clinical journal for peer review. This study will ensure that the public has access to the published data. A file containing the clean dataset used for the final analysis to determine the main data of the study and an explanation of the variables will be made publicly accessible in an anonymized format.

Consent for publication

The principal investigators will form a publication committee, which will include key members of this study, and the committee will grant authorship according to individual input. Investigators who do not qualify for authorship will be acknowledged by name in the final manuscript.

Conflicts of interest statement

None of the authors have any competing interests related to this research.

Discussion

Currently, the establishment of DRLs is an international requirement for protection from medical radiation. For diagnostic radiology, national and regional DRLs are usually set at the 75% percentile of the distribution of a typical sample dose [26]. All physicians or medical staff who are involved in radiological imaging or procedures under fluoroscopic guidance should be familiar with the DRL process as a tool for optimizing protection. In addition, separate DRLs must be established for each country and/or region because the equipment and procedure protocols can vary among different regions [26]. However, the amount of RE depends on the procedure complexity, patient anatomy, lesion characteristics, disease severity [11] and type of fluoroscopic devices [21]; thus, setting the upper limit of radiation use by applying uniform standards is difficult. Generally, DRLs are not dose limits and do not help distinguish between good and poor medical practices [26]. Therefore, a high demand exists for a large amount of real-world evidence. The 2015 Japan DRLs state that the methods for establishing DRLs not only include setting radiation dose levels but also includes determining the dose quantities and units used to set the DRLs, thus standardizing the methodology for dose measurements, data collection and identification of the applications of DRLs [12].

Unfortunately, most gastroenterologists are unfamiliar with not only DRLs but also radiation protection because information on RE from gastrointestinal medical treatment is currently very scarce, and few RE standards, including DRLs, have been established worldwide. Given this background, the REX-GI study is planned as an observational, nationwide study in Japan. Our results will help to promote radiation optimization and

patient radiation protection in gastroenterology studies, such as digestive endoscopy, and hepatobiliary and pancreatic procedures.

Table 1. Fluoroscopic system and units performing procedures under fluoroscopic guidance

	Number of Hospital Beds	Fluoroscopy Device				Fluoroscopy Unit
		Company	Device model	Apparatus type	Year of introduction	Location
Toyonaka Municipal Hospital	613	Hitachi	Exavista	Over-tube	2016	Endoscopy
Kindai University	929	Hitachi	Curevista	Over-tube	2017	Endoscopy
The University of Tokyo	1216	Hitachi Canon Toshiba Canon Toshiba	Curevista Exavista Ultimax-I	Over-tube Over-tube Under-tube	2009 2013 2016	Radiology
Fukui Prefectural Hospital	880	Hitachi	Versiflex	Over-tube	2008	Endoscopy
Kansai Rosai Hospital	642	Canon Toshiba Canon Toshiba	Zexira Ultimax-I	Over-tube Under-tube	2011 2017	Radiology
Osaka City University	891	Hitachi Hitachi	Curevista Versiflex vista	Over-tube Under-tube	2011 2015	Endoscopy Endoscopy
Ishikawa Prefectural Central Hospital	639	Canon Toshiba	Drex-zx80	Over-tube	2016	Endoscopy
Tonan Hospital	283	Hitachi Canon Toshiba	Curevista ZEXIRA	Over-tube Over-tube	2013 2016	Radiology

Japanese Foundation for Cancer Research	686	Canon Toshiba	Ultimax-i	Under-tube	2016	Radiology
Suita Municipal Hospital	431	Hitachi	Versiflex	Under-tube	2018	Endoscopy
Osaka Rosai Hospital	678	Hitachi	Exavista	Under-tube	2018	Radiology
Osaka General Medical Center	768	Hitachi Hitachi	Curevista, Versiflex	Over-tube	2018	Endoscopy
Fukushima Medical University School of Medicine	778	Canon Toshiba Canon Toshiba	Zexira FPD1717	Over-tube	2012	Radiology
Hyogo Cancer Center	400	Hitachi	Curevista	Over-tube	2019	Endoscopy
Kitano Hospital	699	Hitachi Hitachi	Versiflex Curevista	Under-tube Over-tube	2017	Endoscopy
Tane General Hospital	304	Hitachi	Exavista	Over-tube	2011	Radiology
Japanese Red Cross Medical Center	708	Hitachi	Curevista	Over-tube	2016	Radiology
Kure Medical Center and Chugoku Cancer Center	700	Hitachi	Exavista	Over-tube	2010	Endoscopy
Nagoya City University Hospital	800	Canon Toshiba	Ultimax-I	Under-tube	2018	Endoscopy
Toho University Ohashi Medical Center	319	Canon Toshiba	Ultimax-I	Under-tube	2018	Radiology

Osaka International Cancer Institute	500	Canon Toshiba	Ultimax-I	Under-tube	2017	Endoscopy
Gifu University Hospital	606	Shimadzu	C-Vision Safire	Under-tube	2004	Radiology

Table 2. Primary outcomes

Factors	Variables
Patients	▪ Procedure type ▪ Age ▪ Sex
Fluoroscopic system	▪ Fluoroscopic device (company, device model, manufacturing year) ▪ Basic use setting: frame per second (FPS), radiation field (cm^2)*
Radiation exposure	▪ Total fluoroscopy time (FT) (min) ▪ Air-Kerma (AK) (mGy) ▪ Dose-area product (DAP) ($Gycm^2$) ▪ Total number of roentgenography procedures ▪ Radiation dose rate (RDR) (mGy/min)

*When the setting changes during the procedure, we will record the basic setting.

Table 3. Secondary outcomes

Procedures	Radiation exposure-related factors
ERCP	(A) Surgically altered gastrointestinal anatomy Billroth I reconstruction, Billroth II reconstruction, Roux-en-Y reconstruction, pancreaticoduodenectomy (B) Type of endoscope (C) Naïve papilla (D) Indications for ERCP (including suspicion) are classified into the following five categories: 1) Choledocholithiasis (maximum diameter, number of stones, presence of cholangitis, tube exchange for the above diseases, treatment for choledocholithiasis with or without balloon catheter, basket catheter, crusher, etc.) 2) Distant malignant bile duct stricture (papillary tumor, distal cholangiocarcinoma, pancreatic cancer, etc.) 3) Proximal malignant bile duct stricture (Hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, gallbladder cancer, etc.) 4) Pancreatic duct examination (pancreas cancer, intraductal papillary mucinous neoplasm, etc.) 5) Other diseases apart from those listed above (benign bile duct stricture, pancreatobiliary junction abnormality, etc.) (E) Total procedure time (min) *

	1) Cannulation time 2) Treatment time (F) Experience of the high-volume endoscopist (HVE) or low-volume endoscopist: (LVE) † (G) Facility scale: The number of ERCP procedures per year (H) Whether the fluoroscopic operator is inside or outside in the fluoroscopy room (I) Various treatments (endoscopic sphincterotomy, stone treatment, bile duct/pancreatic stent, cytology, biopsy, naïve papilla, cannulation method, contrast agent, intubation time, first-use catheter, large balloon, crusher, drainage area or method, stent type used, cholangioscopy) (J) Sedation: Medication and the depth of the anesthesia ‡
Interventional EUS	(A) Indication for interventional EUS (EUS-guided hepaticogastrostomy (HGS), choledochoduodenostomy (CDS), cyst drainage (CD), antegrade treatment (AG), rendezvous technique (RV), pancreatic duct drainage (PD) (B) Total procedure time‡ 1) Endoscope insertion time 2) Treatment time (C) Facility scale: The number of EUS interventions per year, the number of EUS-guided fine-needle aspiration (FNA) procedures per year (D) Double stenting (presence or absence of duodenal stenosis) (E) Device (F) Scope position (G) Sedation: Medication and the depth of anesthesia

Balloon-assisted enteroscopy	(A) Disease indicating balloon-assisted enteroscopy 1) Hemostatic or bleeding confirmation 2) Crohn's disease 3) Small intestine tumor examination 4) Others (B) Insertion site: perioral or transanal (C) Insertion length (cm) (D) Total procedure time (min)
Enteral metallic stent placement	(A) Stent location 1) Esophagus (Upper/Mid-Low/Trans) 2) Gastro-duodenum (Above pylorus/Trans pylorus /Below pylorus) 3) Colon stent (Right/Left/Rectum) (B) Total procedure time (min) § 1) Endoscope insertion time 2) Treatment time
Enteral ileus tube placement	(A) Disease indicating ileus tube (B) Intranasal ileus tube insertion for ileal obstruction or transanal ileus tube insertion for malignant colonic obstruction 1) Tube insertion length for peroral ileus tube placement (cm) 2) The occlusion site for the transanal tube (Right/Left/Rectum) (D) Total procedure time (min) §

ERCP: endoscopic retrograde cholangiopancreatography

* Cannulation time is defined as the time from endoscope insertion until successful biliary cannulation, and treatment time is defined as the time from successful biliary cannulation until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is removed from the patient (cannulation time +treatment time).

‡ Depth of anesthesia is divided into 3 levels based on the Richmond Agitation-Sedation Scale (RASS), Ramsay Scale, and Sedation-Agitation Scale (SAS): good, poor, and very bad. The good level is defined as RASS score: -5 ~ -1, SAS score: 1 ~ 3, and Ramsay score: 3 ~ 6 equivalent, without additional unplanned doses. The poor level is defined as RASS score: 0 ~ + 1, SAS score: 4 ~ 5, and Ramsay score: 1 ~ 2, without physical restraint but with unplanned doses. The very bad level is defined as requiring physical restraint with a force considered dangerous, RASS score: +2 to +4, and SAS score: 6 to 7 regardless of Ramsay score.

† HVE: Endoscopists with more than 200 ERCP results and who have been involved in ERCP for over 10 years. LVE: Non-HVE endoscopists who perform ERCP.

‡ Endoscope insertion time is defined as the time from endoscope insertion until the initial EUS-guided needle puncture, and treatment time is defined as the time from initial EUS-guided needle puncture until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time +treatment time).

‡Endoscope insertion time is defined as the time from endoscope insertion until initial guidewire exploration, and treatment time is defined as the time from initial guidewire exploration until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time +treatment time).

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Figure legends

Figure 1. The participating hospitals in this study.

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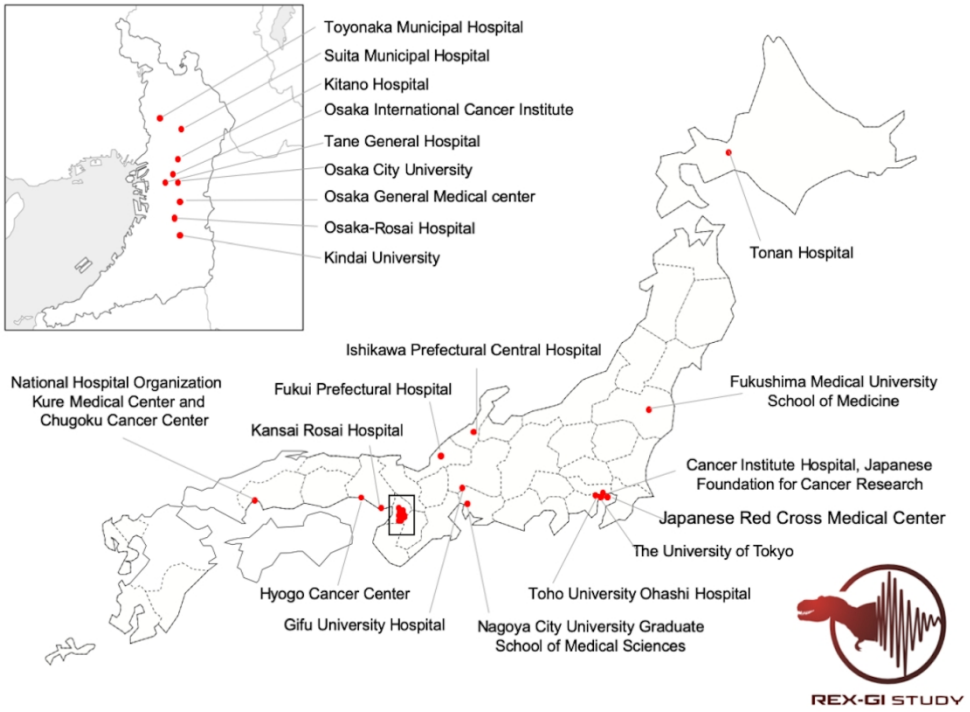

Figure 1. The participating hospitals in this study.

119x90mm (300 x 300 DPI)

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6, 11
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6, 11
Protocol version	#3	Date and version identifier	16
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N.A.
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N.A.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12, 14
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	9-10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N.A.
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N.A.
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N.A.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N.A.
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	N.A.

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N.A.
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N.A.
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N.A.
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N.A.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N.A.
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N.A.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N.A.
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N.A.
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N.A.
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17, 18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N.A.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N.A.
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N.A.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N.A.

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A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

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Complete List of Authors:	Nishida, Tsutomu ; Toyonaka Municipal Hospital, Department of Gastroenterology Hayashi, Shiro; Toyonaka Municipal Hospital, Department of Gastroenterology; Kento Hayashi Clinic, Department of Gastroenterology and Internal Medicine Takenaka, Mamoru ; Kindai University, Department of Gastroenterology and Hepatology Hosono, Makoto ; Kindai University, Department of Radiology Kogure, Hirofumi; The University of Tokyo, Department of Gastroenterology Hasatani, Kenkei ; Fukui Prefectural Hospital, Department of Gastroenterology Yamaguchi, Shinjiro ; Kansai Rosai Hospital, Department of Gastroenterology and Hepatology Maruyama, Hirotsugu ; Osaka City University, Department of Gastroenterology Doyama, Hisashi ; Ishikawa Prefectural Central Hospital, Department of Gastroenterology Ihara, Hideyuki ; Tonan Hospital, Department of Gastroenterology Yoshio, Toshiyuki ; Cancer Institute Hospital, Japanese Foundation for Cancer Research, Department of Gastroenterology Nagaike, Koji ; Suita Municipal Hospital, Department of Gastroenterology and Hepatology Yamada, Takuya ; Osaka Rosai Hospital, Department of Gastroenterology and Hepatology, Yakushijin, Takayuki ; Osaka General Medical Center, Department of Gastroenterology and Hepatology Takagi, Tadayuki ; Fukushima Medical University School of Medicine, Department of Gastroenterology Tsumura, Hidetaka ; Hyogo Cancer Center, Department of Gastroenterological Oncology, Kurita, Akira ; Kitano Hospital, Department of Gastroenterology and Hepatology, Digestive Disease Center Asai, Satoshi ; Tane General Hospital, Department of Gastroenterology Ito, Yukiko ; Japanese Red Cross Medical Center, Department of Gastroenterology Kuwai, Toshio ; Kure Medical Center, Department of Gastroenterology Hori, Yasuki ; Nagoya City University Graduate School of Medical Sciences Department of Gastroenterology and Metabolism

	Maetani, Iruru ; Toho University Ohashi Medical Center, Division of Gastroenterology and Hepatology, Department of Internal Medicine Ikezawa, Kenji ; Osaka International Cancer Institute, Department of Hepatobiliary and Pancreatic Oncology Iwashita, Takuji ; Gifu University Hospital, First Department of Internal Medicine Matsumoto, Kengo; Toyonaka Municipal Hospital, Department of Gastroenterology Inada, Masami ; Toyonaka Municipal Hospital, Department of Gastroenterology
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A Multicenter Prospective Observational Study Protocol for Radiation Exposure from Gastrointestinal Fluoroscopic Procedures (REX-GI study)

Tsutomu Nishida[1)], Shiro Hayashi[1)2)], Mamoru Takenaka[3)], Makoto Hosono[4)], Hirofumi Kogure[5)], Kenkei Hasatani[6)], Shinjiro Yamaguchi[7)], Hirotsugu Maruyama[8)], Hisashi Doyama[9)], Hideyuki Ihara[10)], Toshiyuki Yoshio[11)], Koji Nagaike[12)], Takuya Yamada[13)], Takayuki Yakushijin[14)], Tadayuki Takagi[15)], Hidetaka Tsumura[16)], Akira Kurita[17)], Satoshi Asai[18)], Yukiko Ito[19)], Toshio Kuwai[20)], Yasuki Hori[21)], Iruru Maetani[22)], Kenji Ikezawa[23)], Takuji Iwashita[24)], Kengo Matsumoto[1)], Masami Inada[1)]

1) Department of Gastroenterology, Toyonaka Municipal Hospital, Toyonaka, Osaka, Japan
2) Department of Gastroenterology and Internal Medicine, Kento Hayashi Clinic, Suita, Osaka, Japan
3) Department of Gastroenterology and Hepatology, Kindai University, Faculty of Medicine, Osaka-Sayama, Osaka, Japan
4) Department of Radiology, Kindai University Faculty of Medicine, Osaka-Sayama, Osaka, Japan
5) Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, Tokyo, Japan
6) Department of Gastroenterology, Fukui Prefectural Hospital, Fukui, Fukui, Japan
7) Department of Gastroenterology and Hepatology, Kansai Rosai Hospital,

Amagasaki, Hyogo, Japan

8) Department of Gastroenterology, Osaka City University, Graduate School of Medicine, Osaka, Osaka, Japan

9) Department of Gastroenterology, Ishikawa Prefectural Central Hospital, Kanazawa, Ishikawa, Japan

10) Department of Gastroenterology, Tonan Hospital, Sapporo, Hokkaido, Japan

11) Department of Gastroenterology, Cancer Institute Hospital, Japanese Foundation for Cancer Research, Ariake, Tokyo, Japan

12) Department of Gastroenterology and Hepatology, Suita Municipal Hospital, Osaka, Japan

13) Department of Gastroenterology and Hepatology, Osaka-Rosai Hospital, Sakai, Osaka, Japan

14) Department of Gastroenterology and Hepatology, Osaka General Medical Center, Osaka, Osaka, Japan

15) Department of Gastroenterology, Fukushima Medical University School of Medicine, Fukushima, Japan

16) Department of Gastroenterological Oncology, Hyogo Cancer Center, Akashi, Japan

17) Department of Gastroenterology and Hepatology, Digestive Disease Center, Kitano Hospital, Tazuke Kofukai Medical Research Institute, Osaka, Osaka, Japan

18) Department of Gastroenterology, Tane General Hospital, Osaka, Osaka, Japan

19) Department of Gastroenterology, Japanese Red Cross Medical Center, Tokyo,

Japan

20) Department of Gastroenterology, National Hospital Organization, Kure Medical Center and Chugoku Cancer Center, Kure, Japan

21) Department of Gastroenterology and Metabolism, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

22) Division of Gastroenterology and Hepatology, Department of Internal Medicine, Toho University Ohashi Medical Center, Tokyo, Japan

23) Department of Hepatobiliary and Pancreatic Oncology, Osaka International Cancer Institute, Osaka, Osaka, Japan

24) First Department of Internal Medicine, Gifu University Hospital, Gifu, Japan

Address all correspondence to: Tsutomu Nishida, M.D.

Department of Gastroenterology, Toyonaka Municipal Hospital

4-14-1 Shibahara, Toyonaka, Osaka 560-8565 Japan

Email: tnishida.gastro@gmail.com

Tel: +81-6-6843-0101

Email addresses: Tsutomu Nishida: tnishida.gastro@gmail.com, Shiro Hayashi: hayashishiro1976@yahoo.co.jp, Mamoru Takenaka: mamoxyo45@gmail.com, Makoto Hosono: hosono@med.kindai.ac.jp, Hirofumi Kogure: kogureh-tky@umin.ac.jp, Kenkei Hasatani: hasatani9@yahoo.co.jp, Shinjiro Yamaguchi: smay-0608@diary.ocn.ne.jp,

Hirotsugu Maruyama: hiromaruyama99@gmail.com, Hisashi Doyama: doyama.134@gmail.com, Hideyuki Ihara: h-ihara@tonan.gr.jp, Toshiyuki Yoshio: toshiyuki.yoshio@jfcr.or.jp, Koji Nagaike: nagaike.koji@gmail.com, Takuya Yamada: yamtak1973@gmail.com, Takayuki Yakushijin: yakushijin@gh.opho.jp, Tadayuki Takagi: daccho@fmu.ac.jp, Hidetaka Tsumura: h.tsumura@hp.pref.hyogo.jp, Akira Kurita: kuritaaki1976@gmail.com, Satoshi Asai: bonyaritetsu1226@hotmail.co.jp, Yukiko Ito: yukikomd1224@gmail.com, Toshio Kuwai: toshiokuwai@gmail.com, Yasuki Hori: yhori@med.nagoya-cu.ac.jp, Iruru Maetani: mtnir50637@med.toho-u.ac.jp, Kenji Ikezawa: ikezawa-ke@mc.pref.osaka.jp, Takuji Iwashita: takuji@w7.dion.ne.jp, Kengo Matsumoto: ken5@gh.med.osaka-u.ac.jp, Masami Inada: inada-intoyo@chp.toyonaka.osaka.jp

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ABSTRACT

INTRODUCTION: Recently, the use of various endoscopic procedures under X-ray fluoroscopic guidance, such as endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS), enteral endoscopy, and stenting, has been rapidly increasing because of the minimally invasive nature of these procedures compared to that of surgical intervention. With the spread of computed tomography and fluoroscopic interventions, including endoscopic procedures under X-ray guidance, high levels of radiation exposure (RE) from medical imaging have led to major concerns throughout society. However, information about RE related to these image-guided procedures in gastrointestinal endoscopy is scarce, and the RE reference levels have not been established. The aim of this study is to prospectively collect the actual RE dose and to help establish diagnostic reference levels (DRLs) in the field of gastroenterology in Japan.

METHODS AND ANALYSIS: This study is a multicenter, prospective observational study that is being conducted to collect the actual RE from treatments and diagnostic procedures, including ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement. We will measure the total fluoroscopy time (FT, min), the total dose-area product (DAP, $Gycm^2$) and air-kerma (AK, mGy) of those procedures. Because we are collecting the actual RE data and identifying the influential factors through a prospective, nationwide design, this study will provided guidance regarding the DRLs of ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement.

ETHICS AND DISSEMINATION: This trial (Radiation EXposure from GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials Registry at http://www.umin.ac.jp/ctr/ under number UMIN000036525 (registered 1 May 2019). Approval was obtained from the Institutional Review Board of Toyonaka Municipal Hospital (2019-02-04). The need for informed consent will be waived via the *opt-out* method of each hospital website.

Strengths and limitations of this study

- The large, multicenter, nationwide dataset of radiation exposure doses for gastrointestinal fluoroscopic procedures in gastrointestinal endoscopy gathered in this study will serve as a basis for the development of diagnostic reference levels in Japan.
- Gastrointestinal fluoroscopic procedures have been rapidly increasing in number and complexity, but there are still not enough available local and national DRLs in gastrointestinal endoscopy units.
- These data may not be valid for old models of fluoroscopic systems because this study will include data from fluoroscopic systems with available radiation data.

INTRODUCTION

Medical radiation is widely used in both medical imaging and radiation treatment. In medical imaging, fluoroscopy employs radiation to show a continuous X-ray image on a monitor and plays a major role in the daily practices of gastroenterology, digestive endoscopy, and hepatobiliary and pancreatic studies. Radiological medical imaging has both benefits and drawbacks for patients. The latter is split into two types: deterministic risks [1], determined by the threshold dose, as represented by skin injury, and stochastic risks, determined by a linear no-threshold model, such as the cancer risk [2]. There have been some reports on radiation-induced skin injury in cardiology and interventional radiology (IVR) [3], but reports from gastrointestinal endoscopy units are rare. However, all medical staff in gastrointestinal endoscopy units need to have correct knowledge of the appropriate use of medical radiation. Historically, the use of medical radiation has rapidly increased since the 1990s with the spread of computed tomography (CT), and the radiation-associated cancer risk was recognized in the same period, even when the doses of radiation were small [4 5 6]. In particular, the use of CT has increased approximately 12-fold in the United Kingdom and more than 20-fold in the United States in the last 25 years [7].

The International Atomic Energy Agency (IAEA), the International Commission on Radiological Protection (ICRP), the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), and other radiological societies have been attempting to manage medical radiation exposure (RE) according to the “as low as reasonably achievable” (ALARA) principle by establishing diagnostic reference levels

(DRLs) to optimize protection from medical radiation. The concept of DRLs was first introduced by the ICRP 73 [8] in 1996. Then, the ICRP emphasized the important role of DRLs as a tool for optimizing patient protection [9 10]. Accordingly, the ICRP set specific target levels for various X-ray-related procedures in 2007 [9]. This movement of setting DRLs has been led by radiation-related societies in each region, although the movement has mainly been driven by Western countries. The ICRP 135 recommends that all individuals who are involved in patient procedures with the risk of medical exposure should be familiar with the DRL process as a tool for optimizing protection [11]. DRLs are now widely accepted in not only Western countries but also Japan (Japan DRLs 2015) [12], and DRLs have become the global standard for all procedures that use ionizing radiation. Legislation has made it mandatory to establish and record DRLs in Europe, but that is not the case worldwide. The introduction of DRLs in the UK achieved a reduction of approximately 50% in the radiation dose in typical X-ray examinations over 15 years [13]. However, there is still not enough available data on RE for gastrointestinal fluoroscopic procedures, such as endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasonography (EUS), small bowel endoscopy, and enteral stent placement; these techniques are still being developed and have recently been used with increasing frequency [14 15].

Our gastroenterologists and endoscopists are still unfamiliar with the DRL concept. Among the guidelines developed by gastrointestinal endoscopy associations, the 2012 European Gastrointestinal Endoscopy Society (ESGE) guidelines for radiation

protection state that the entrance skin dose (ESD; approximately equivalent to air-kerma in this study) and kerma-area product (KAP; approximately equivalent to the dose-area product (DAP) in this study) during diagnostic and therapeutic ERCP are 55-347 mGy and 3-115/8-333 Gycm^2, respectively, although information regarding the DRLs of ERCP is limited because this statement is based on only approximately 600 cases of ERCP in 7 reports [14]. No guidelines on RE from the American Society for Gastrointestinal Endoscopy (ASGE) exist, but the ASGE recommends measuring and documenting fluoroscopy time (FT) and radiation dose in all ERCP procedures as a quality indicator (level of evidence: 2C) [16]. Although no guidelines for exposure have been developed by the Japan Gastroenterological Endoscopy Society (JGES), a description of FT exists in the item regarding ERCP in the Japan Endoscopy Database (JED) [17], which is scheduled to be implemented as a nationwide endoscopic survey in 2020.

Recently, various endoscopic procedures performed under fluoroscopic guidance are rapidly increasing in popularity in gastrointestinal endoscopy units, where the aim is not only diagnosis but also therapeutic intervention. The ICRP recommends that DRLs should be used to manage patient doses during both diagnostic and interventional procedures. There is difficulty in applying the DRL concept to interventional procedures because the RE level depends on the complexity of the procedure and the individual clinical circumstances [10 18 19]. There have been attempts to establish DRLs for IVR

procedures, where grouping by disease site may help minimize the wide distribution of RE [20 21].

The Japanese DRLs were established on a basis of a survey and released in 2015; these guidelines defined the DRL value for fluoroscopically guided interventional procedures as a fluoroscopic radiation dose rate (interventional reference point dose rate) of 20 mGy/min [12]. However, it did not include information for specific procedures in the field of gastroenterology [12]. Therefore, we aim to prospectively collect actual RE data and identify the influential factors, such as disease site, in this REX-GI study and to establish DRLs for the following interventional procedures in gastrointestinal endoscopy units: ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement and enteral tube placement.

METHODS AND ANALYSIS

Aims

The primary aim of this nationwide, prospective study is to collect actual data on RE and identify the factors affecting RE during treatments and diagnostic procedures under different types of fluoroscopic guidance for gastroenterology procedures, including the gastrointestinal, hepatobiliary and pancreatic fields, to serve as a basis for the establishment of DRLs in Japan.

Design

This is a multicenter, prospective observational cohort study of consecutive patients undergoing the following 5 treatments and diagnostic procedures under fluoroscopic guidance in the field of gastroenterology: 1) ERCP, 2) interventional EUS, 3) balloon-assisted enteroscopy, 4) enteral metallic stent placement; and 5) enteral tube placement. We will examine the procedure time (min), total FT (min), AK (mGy), DAP ($Gycm^2$), total number of roentgenography procedures, and radiation dose rate (RDR) (mGy/min) during the procedures. The participating clinicians will manage patients according to the usual clinical practice, and the patients will undergo the above 5 procedures. For the analysis, all data, including the related variables and outcome data (Tables 1 and 2), will be collected for all patients. The study (Radiation EXposure from GastroIntestinal fluoroscopic procedures: REX-GI study) was registered with the UMIN Clinical Trials Registry at http://www.umin.ac.jp/ctr/ under the number UMIN000036525 (registered 1 May 2019).

Setting

The study will be conducted at 7 university hospitals, 4 cancer centers, 9 general hospitals and 2 municipal hospitals in Japan. The participating hospitals are Toyonaka Municipal Hospital, Kindai University, the University of Tokyo, Fukui Prefectural Hospital, Kansai Rosai Hospital, Osaka City University, Ishikawa Prefectural Central Hospital, Tonan Hospital, Japanese Foundation for Cancer Research, Suita Municipal Hospital, Osaka Rosai Hospital, Osaka General Medical Center, Fukushima Medical University School of Medicine, Hyogo Cancer Center, Kitano Hospital, Tane General Hospital, Japanese Red Cross Medical Center, Kure Medical Center and Chugoku Cancer Center, Nagoya City University Hospital, Toho University Ohashi Medical Center, Osaka International Cancer Institute, and Gifu University Hospital (Figure 1). Table 1 shows the fluoroscopic systems and units performing procedures under fluoroscopic guidance in each institution. The central sites of the study are located at the Toyonaka Municipal Hospital and Kindai University. The participating physicians are gastroenterologists or endoscopists, including all experts and trainees working at all involved hospitals. The quality of the fluoroscopic devices will be regularly monitored according to the procedures in each institution.

Study population

We will include all patients receiving usual clinical care who undergo the following treatments and diagnostic procedures under fluoroscopic guidance: 1) ERCP; 2)

interventional EUS; 3) balloon-assisted enteroscopy; 4) enteral metallic stent placement; and 5) enteral tube placement. There is no age restriction. We will exclude patients who do not want to participate in this study via the *opt-out* method on each hospital website and patients who the attending physicians judge to be unsuitable for inclusion in this study.

Primary outcomes

The primary outcomes will be the total FT (min), RDR (mGy/min), dose-area parameters (AK (mGy) and DAP ($Gycm^2$) and the total number of imaging studies that the patients who meet the individual inclusion and exclusion criteria will undergo (Table 2).

Secondary outcome

The secondary outcome will be the RE-related factors that affect the radiation dose in each procedure. The details are shown in Table 3.

Setting the sample size

According to the preliminary questionnaire survey (data not shown), the numbers of examinations per year in the 8 centers that plan to participate in March 2019 are as follows: 4000 ERCP procedures, 125 EUS procedures, 320 small intestine endoscopy procedures, 44 esophageal stent placements, 150 gastroduodenal stent placements, 75 colorectal stent placements, 180 transanal ileus tube placements, and 75 ileus tube

placements. The ICRP 135 recommends using data from 20-30 facilities to set national DRLs, and a survey for a particular examination in a facility should usually involve the collection of data from at least 20 patients [11].

To set the DRLs and to reduce intraprocedural variability in each hospital, we set the minimum sample size to at least 400 patients for each procedure. We believe that initially enrolling a high number of facilities and patients is desirable; therefore, we did not set an upper limit for the goals.

Data analysis plan

After obtaining the data, we will perform normality tests. Continuous variables will be expressed as medians with interquartile ranges or means with standard deviations. The categorical variables will be expressed as numbers in each category or as frequencies. To explore surrogate markers of RD, simple linear regression analysis will be performed to identify the relationships between procedure time, FT and RD. A multiple linear regression analysis will be performed to identify the factors related to RD. A P value of 0.05 will be considered statistically significant. All statistical analyses will be performed with JMP software (SAS Institute, Inc., Cary, NC, USA).

Patient and public involvement

Clinical factors related to ERCP and interventional EUS have been retrospectively collected at two sites (Toyonaka Municipal Hospital and Kindai University) [20 22-24] . We used those published data to develop plans for the design or implementation of the

study and to determine the research question or the outcome measures. No patients were asked to advise us on the interpretation or writing up of results. There are no plans to disseminate the results of the research to study participants, but we will consider disseminating the results of the research to the relevant patient community.

Data collection

The clinical factors have been modified to comply with local patient flow and administrative requirements and have been assessed and approved by the study steering committee. We are collecting the password-protected case report forms by e-mail from each institution; these will be de-identified after all data have been collected, and all data queries have been addressed. A unique study identification number will identify each participant and the associated clinical data. Data collection will be performed at 3-month intervals to prevent data loss. Data analysis will take place at the central study site (Kindai University). This study does not require data monitoring due to its nature as an observational study without interventions. Data will be retained for either a minimum of 5 years after the end of the study or for 10 years after publication, whichever is later.

Patient recruitment and schedule

Patient recruitment will be carried out at the participating hospitals from May 2019 - December 2020.

2021: Data analysis and writing and submission of the main manuscript for publication.

Ethics and dissemination

This observational study will be conducted in accordance with the principles of the Declaration of Helsinki, and approval has been obtained from the Institutional Review Board of Toyonaka Municipal Hospital (2019-02-04) and the institutional review board of each participating facility. The need for informed consent will be waived via the *opt-out* method on each hospital website. The results of this study will be presented at gastroenterology-, endoscopy-, or radiology-related congresses and will be published in a peer-reviewed journal.

Discussion

Currently, the establishment of DRLs is an international requirement for protection from medical radiation. For diagnostic radiology, national and regional DRLs are usually set at the 75% percentile of the distribution of a typical sample dose [25]. All physicians or medical staff who are involved in radiological imaging or procedures under fluoroscopic guidance should be familiar with the DRL process as a tool for optimizing protection. In addition, separate DRLs must be established for each country and/or region because the equipment and procedure protocols can vary among different regions [25]. However, the amount of RE depends on the procedure complexity, patient anatomy, lesion characteristics, disease severity [11] and type of fluoroscopic devices [20]; thus, setting the upper limit of radiation use by applying uniform standards is difficult. Generally, DRLs

are not dose limits and do not help distinguish between good and poor medical practices [25]. Therefore, a high demand exists for a large amount of real-world evidence. The 2015 Japan DRLs state that the methods for establishing DRLs not only include setting radiation dose levels but also includes determining the dose quantities and units used to set the DRLs, thus standardizing the methodology for dose measurements, data collection and identification of the applications of DRLs [12].

Unfortunately, most gastroenterologists are unfamiliar with not only DRLs but also radiation protection because information on RE from gastrointestinal medical treatment is currently very scarce, and few RE standards, including DRLs, have been established worldwide. Given this background, the REX-GI study is planned as an observational, nationwide study in Japan. Our results will help to promote radiation optimization and patient radiation protection in gastroenterology studies, such as digestive endoscopy, and hepatobiliary and pancreatic procedures.

Author contributions

Nishida T, Hayashi S (Toyonaka Municipal Hospital), and Takenaka M (Kindai University) designed this study. Hosono M (Kindai University) critically reviewed the protocol. Nishida T, Hayashi S (Toyonaka Municipal Hospital), Takenaka M (Kindai University), Kogure H (The University of Tokyo), Hasatani K (Fukui Prefectural Hospital), Yamaguchi S (Kansai Rosai Hospital), Maruyama H (Osaka City University),

Doyama H (Ishikawa Prefectural Central Hospita), Ihara H, (Tonan Hospital) Yoshio T (Cancer Institute Hospital, Japanese Foundation for Cancer Research), Nagaike K (Suita Municipal Hospital), Yamada T (Osaka-Rosai Hospital), Yakushijin T (Osaka General Medical Center), Takagi T (Fukushima Medical University School of Medicine), Tsumura H (Hyogo Cancer Center), Kurita A (Kitano Hospital), Asai S (Tane General Hospital), Ito Y (Japanese Red Cross Medical Center), Kuwai T (National Hospital Organization, Kure Medical Center and Chugoku Cancer Center), Hori Y (Nagoya City University Graduate School of Medical Sciences), Maetani I (Toho University Ohashi Medical Center), Ikezawa K (Osaka International Cancer Institute), Iwashita T (Gifu University Hospital), Matsumoto K, and Inada M (Toyonaka Municipal Hospital) participated this study and will recruit the patients. All authors accepted the final version of the protocol (ver. 1.1: 2019-Mar-14, ver.1.5: 2019-July-15).

Acknowledgements and collaborators

We thank all the collaborators who are cooperating in this first nationwide study of the Radiation Exposure from Gastrointestinal Fluoroscopic Procedures in Japan (REX-GI). The collaborators involved in the REX-GI study are as follows: Mitsuhiro Fujishiro (Nagoya University Graduate School of Medicine), Masashi Yamamoto, Dai Nakamatsu, Kaori Mukai, Kei Takahashi, Aya Sugimoto, Naoto Osugi, Yu Higaki, Ryo Tomita, Tatsuya Sakamoto, Emi Meren, Kazuki Aochi, Shinji Kuriki, Li-sa Chang, and Koji Fukui (Toyonaka Municipal Hospital), Yousuke Nakai (The University of Tokyo),

Takahiro Suda (Kansai Rosai Hospital), Kazuhiro Matsunaga (Ishikawa Prefectural Central Hospital), Tetsuya Sumiyoshi (Tonan Hospital), Takashi Sasaki, Atsuko Tamashiro, Hiroyuki Hatamori (Cancer Institute Hospital, Japanese Foundation for Cancer Research), Takumi Kanagawa, Yuichi Yoshida, Masafumi Naito (Suita Municipal Hospital), Shuji Ishii (Osaka General Medical Center), Takuto Hikichi (Fukushima Medical University School of Medicine), Naoki Fujimoto (Tane General Hospital), Ikuya Miki (Hyogo Cancer Center), Yuzuru Tamaru (National Hospital Organization Kure Medical Center and Chugoku Cancer Center), Hiromi Kataoka, Kazuki Hayashi (Nagoya City University Graduate School of Medical Sciences), and Hiroaki Shigoka (Toho University Ohashi Medical Center).

Funding statement

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Publication and data sharing

After completion of the study, a main manuscript will be prepared to present the results and will be submitted to a clinical journal for peer review. This study will ensure that the public has access to the published data. A file containing the clean dataset used for the final analysis to determine the main data of the study and an explanation of the variables will be made publicly accessible in an anonymized format.

Consent for publication

The principal investigators will form a publication committee, which will include key members of this study, and the committee will grant authorship according to individual input. Investigators who do not qualify for authorship will be acknowledged by name in the final manuscript.

Conflicts of interest statement

None of the authors have any competing interests related to this research.

Table 1. Fluoroscopic system and units performing procedures under fluoroscopic guidance

	Number of Hospital Beds	Fluoroscopy Device				Fluoroscopy Unit
		Company	Device model	Apparatus type	Year of introduction	Location
Toyonaka Municipal Hospital	613	Hitachi	Exavista	Over-tube	2016	Endoscopy
Kindai University	929	Hitachi	Curevista	Over-tube	2017	Endoscopy
The University of Tokyo	1216	Hitachi Canon Toshiba Canon Toshiba	Curevista Exavista Ultimax-I	Over-tube Over-tube Under-tube	2009 2013 2016	Radiology
Fukui Prefectural Hospital	880	Hitachi	Versiflex	Over-tube	2008	Endoscopy
Kansai Rosai Hospital	642	Canon Toshiba Canon Toshiba	Zexira Ultimax-I	Over-tube Under-tube	2011 2017	Radiology
Osaka City University	891	Hitachi Hitachi	Curevista Versiflex Vista	Over-tube Under-tube	2011 2015	Endoscopy Endoscopy
Ishikawa Prefectural Central Hospital	639	Canon Toshiba	Drex-zx80	Over-tube	2016	Endoscopy
Tonan Hospital	283	Hitachi Canon Toshiba	Curevista ZEXIRA	Over-tube Over-tube	2013 2016	Radiology

Japanese Foundation for Cancer Research	686	Canon Toshiba	Ultimax-i	Under-tube	2016	Radiology
Suita Municipal Hospital	431	Hitachi	Versiflex	Under-tube	2018	Endoscopy
Osaka Rosai Hospital	678	Hitachi	Exavista	Under-tube	2018	Radiology
Osaka General Medical Center	768	Hitachi Hitachi	Curevista, Versiflex	Over-tube	2018	Endoscopy
Fukushima Medical University School of Medicine	778	Canon Toshiba Canon Toshiba	Zexira FPD1717	Over-tube	2012	Radiology
Hyogo Cancer Center	400	Hitachi	Curevista	Over-tube	2019	Endoscopy
Kitano Hospital	699	Hitachi Hitachi	Versiflex Curevista	Under-tube Over-tube	2017	Endoscopy
Tane General Hospital	304	Hitachi	Exavista	Over-tube	2011	Radiology
Japanese Red Cross Medical Center	708	Hitachi	Curevista	Over-tube	2016	Radiology
Kure Medical Center and Chugoku Cancer Center	700	Hitachi	Exavista	Over-tube	2010	Endoscopy
Nagoya City University Hospital	800	Canon Toshiba	Ultimax-I	Under-tube	2018	Endoscopy
Toho University Ohashi Medical Center	319	Canon Toshiba	Ultimax-I	Under-tube	2018	Radiology

Osaka International Cancer Institute	500	Canon Toshiba	Ultimax-I	Under-tube	2017	Endoscopy
Gifu University Hospital	606	Shimadzu	C-Vision Safire	Under-tube	2004	Radiology

Table 2. Primary outcomes

Factors	Variables
Patients*	▪ Procedure type ▪ Age ▪ Sex
Fluoroscopic system	▪ Fluoroscopic device (company, device model, manufacturing year) ▪ Basic use setting: frame per second (FPS), radiation field (cm^2)‡
Radiation exposure	▪ Total fluoroscopy time (FT) (min) ▪ Air-Kerma (AK) (mGy) ▪ Dose-area product (DAP) ($Gycm^2$) ▪ Total number of roentgenography procedures ▪ Radiation dose rate (RDR) (mGy/min)

* We will not collect patient weight or height because we will have selected patients of standard size for the Japanese population, whose weight will range from 50 to 70 kg.

‡ When the setting changes during the procedure, we will record the basic setting.

Table 3. Secondary outcomes

Procedures	Radiation exposure-related factors
ERCP	(A) Surgically altered gastrointestinal anatomy Billroth I reconstruction, Billroth II reconstruction, Roux-en-Y reconstruction, pancreaticoduodenectomy (B) Type of endoscope (C) Naïve papilla (D) Indications for ERCP (including suspicion) are classified into the following five categories: 1) Choledocholithiasis (maximum diameter, number of stones, presence of cholangitis, tube exchange for the above diseases, treatment for choledocholithiasis with or without balloon catheter, basket catheter, crusher, etc.) 2) Distant malignant bile duct stricture (papillary tumor, distal cholangiocarcinoma, pancreatic cancer, etc.) 3) Proximal malignant bile duct stricture (Hilar cholangiocarcinoma, intrahepatic cholangiocarcinoma, gallbladder cancer, etc.) 4) Pancreatic duct examination (pancreas cancer, intraductal papillary mucinous neoplasm, etc.) 5) Other diseases apart from those listed above (benign bile duct stricture, pancreatobiliary junction abnormality, etc.) (E) Total procedure time (min) *

	1) Cannulation time 2) Treatment time (F) Experience of the high-volume endoscopist (HVE) or low-volume endoscopist: (LVE) † (G) Facility scale: The number of ERCP procedures per year (H) Whether the fluoroscopic operator is inside or outside in the fluoroscopy room (I) Various treatments (endoscopic sphincterotomy, stone treatment, bile duct/pancreatic stent, cytology, biopsy, naïve papilla, cannulation method, contrast agent, intubation time, first-use catheter, large balloon, crusher, drainage area or method, stent type used, cholangioscopy) (J) Sedation: Medication and the depth of the anesthesia ‡
Interventional EUS	(A) Indication for interventional EUS (EUS-guided hepaticogastrostomy (HGS), choledochoduodenostomy (CDS), cyst drainage (CD), antegrade treatment (AG), rendezvous technique (RV), pancreatic duct drainage (PD) (B) Total procedure time‡ 1) Endoscope insertion time 2) Treatment time (C) Facility scale: The number of EUS interventions per year, the number of EUS-guided fine-needle aspiration (FNA) procedures per year (D) Double stenting (presence or absence of duodenal stenosis) (E) Device (F) Scope position (G) Sedation: Medication and the depth of anesthesia

Balloon-assisted enteroscopy	(A) Disease indicating balloon-assisted enteroscopy 1) Hemostatic or bleeding confirmation 2) Crohn's disease 3) Small intestine tumor examination 4) Others (B) Insertion site: perioral or transanal (C) Insertion length (cm) (D) Total procedure time (min)
Enteral metallic stent placement	(A) Stent location 1) Esophagus (Upper/Mid-Low/Trans) 2) Gastro-duodenum (Above pylorus/Trans pylorus /Below pylorus) 3) Colon stent (Right/Left/Rectum) (B) Total procedure time (min) § 1) Endoscope insertion time 2) Treatment time
Enteral ileus tube placement	(A) Disease indicating ileus tube (B) Intranasal ileus tube insertion for ileal obstruction or transanal ileus tube insertion for malignant colonic obstruction 1) Tube insertion length for peroral ileus tube placement (cm) 2) The occlusion site for the transanal tube (Right/Left/Rectum) (D) Total procedure time (min) §

ERCP: endoscopic retrograde cholangiopancreatography

* Cannulation time is defined as the time from endoscope insertion until successful biliary cannulation, and treatment time is defined as the time from successful biliary cannulation until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is removed from the patient (cannulation time +treatment time).

‡ Depth of anesthesia is divided into 3 levels based on the Richmond Agitation-Sedation Scale (RASS), Ramsay Scale, and Sedation-Agitation Scale (SAS): good, poor, and very bad. The good level is defined as RASS score: -5 ~ -1, SAS score: 1 ~ 3, and Ramsay score: 3 ~ 6 equivalent, without additional unplanned doses. The poor level is defined as RASS score: 0 ~ + 1, SAS score: 4 ~ 5, and Ramsay score: 1 ~ 2, without physical restraint but with unplanned doses. The very bad level is defined as requiring physical restraint with a force considered dangerous, RASS score: +2 to +4, and SAS score: 6 to 7 regardless of Ramsay score.

† HVE: Endoscopists with more than 200 ERCP results and who have been involved in ERCP for over 10 years. LVE: Non-HVE endoscopists who perform ERCP.

‡ Endoscope insertion time is defined as the time from endoscope insertion until the initial EUS-guided needle puncture, and treatment time is defined as the time from initial EUS-guided needle puncture until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time +treatment time).

‡Endoscope insertion time is defined as the time from endoscope insertion until initial guidewire exploration, and treatment time is defined as the time from initial guidewire exploration until the scope is removed from the patient. The total procedure time is defined as the time from endoscope insertion until the scope is removed from the patient (endoscope insertion time +treatment time).

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Figure legends

Figure 1. The participating hospitals in this study.

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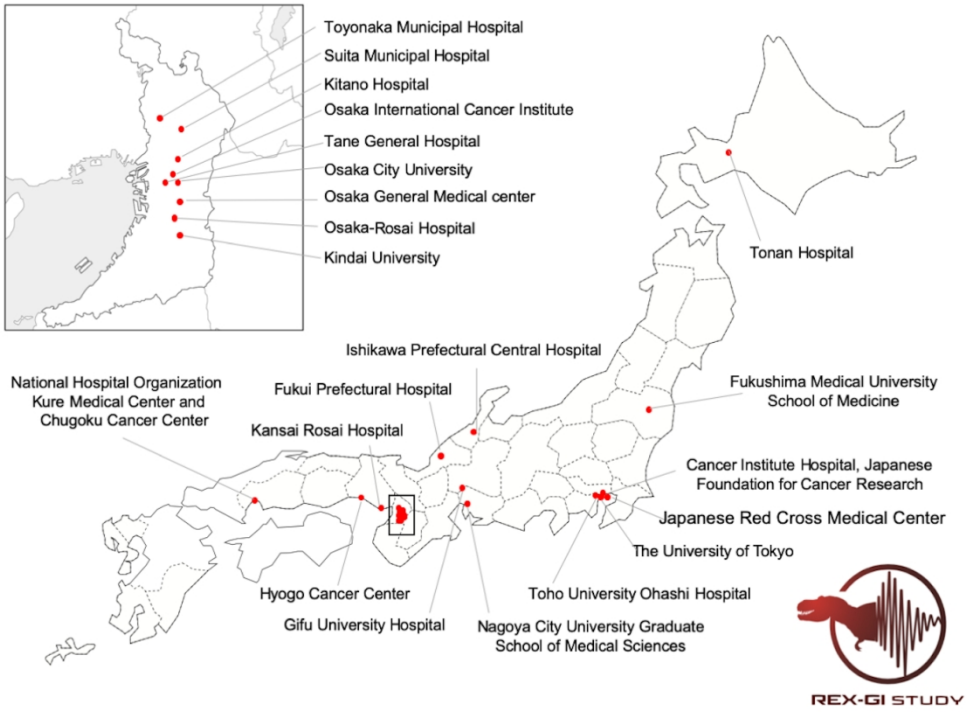

Figure 1. The participating hospitals in this study.

119x90mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet registered, name of intended registry	6, 11
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	6, 11
Protocol version	#3	Date and version identifier	16
Funding	#4	Sources and types of financial, material, and other support	17
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	15

Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	N.A.
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	N.A.
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	12, 14
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	8-10
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	9
Objectives	#7	Specific objectives or hypotheses	9-10
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	11
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	12

Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	12
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	N.A.
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	N.A.
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	N.A.
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N.A.
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	13
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	15
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	13
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	14
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	N.A.

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	N.A.
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	N.A.
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	N.A.
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N.A.
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	14
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	15
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	15
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	14

Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	N.A.
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	15
Methods: Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	15
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	15
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	N.A.
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	N.A.
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	15
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	N.A.
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	15

Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	N.A.
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	14
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	17, 18
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	17
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	N.A.
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	14
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	18
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	N.A.
Appendices			
Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N.A.
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N.A.