Diagnostic Reference Levels for Fluoroscopy-guided Gastrointestinal Procedures in Japan from the REX-GI Study: A Nationwide Multicentre Prospective Observational Study

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Summary

Background Diagnostic reference levels (DRLs) are required to optimize medical exposure. However, data on DRLs for interventional fluoroscopic procedures are lacking, especially in gastroenterology. This study aimed to prospectively collect currently used radiation doses and help establish national DRLs for fluoroscopy-guided gastrointestinal procedures in Japan.

Methods This multicentre, prospective, observational study collected actual radiation dose data from endoscopic retrograde cholangiopancreatography (ERCP), interventional endoscopic ultrasound (EUS), balloon-assisted enteroscopy (BAE), enteral metallic stent placement, and enteral tube placement from May 2019 to December 2020. The

Abbreviations: DRLs, diagnostic reference levels; ERCP, endoscopic retrograde cholangiopancreatography; EUS, endoscopic ultrasound; BAE, balloon-assisted enteroscopy; FT, fluoroscopy time; K<sub>air</sub>, air kerma at the patient entrance reference point; RDR, radiation dose rate

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study outcomes were fluoroscopy time (FT: min), air kerma at the patient entrance reference point (K_a,r: mGy), air kerma area product (P_KA: Gycm²), and radiation dose rate (RDR: mGy/min). Additionally, the basic settings of fluoroscopy equipment and the factors related to each procedure were investigated. This study was registered in the UMIN Clinical Trial Registry (UMIN 000036525).

Findings Overall, 12959 fluoroscopy-guided gastrointestinal procedures were included from 23 hospitals in Japan. For 11162 ERCPs, the median/third quartile values of K_a,r (mGy), P_KA (Gycm²), and FT (min) were 69/145 mGy, 16/32 Gycm², and 11/20 min, respectively. Similarly, these values were 106/219 mGy, 23/41 Gycm² and 17/27 min for 374 interventional EUSs; 53/104 mGy, 16/32 Gycm² and 12/18 min for 599 tube placements; and 35/81 mGy, 16/43 Gycm² and 7/15 min for 301 BAEs, respectively. For the overall radiation dose rate, the median/third quartile values of RDR were 5.9/9.4 (mGy/min). The RDR values at each institution varied widely.

Interpretation This study reports the current radiation doses of fluoroscopy-guided gastrointestinal procedures expressed as DRL quantities. This will serve as a valuable reference for national DRL values.

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Research in context

Evidence before this study
We searched PubMed (accessed January 1, 2021) for English language articles using the terms "radiation," "fluoroscopy," and "diagnostic reference level (DRL)." Additionally, we referred to the publications of ICRP, NCRP, European Commission, and J-RIME as of June 1, 2021. The search found that it is essential to optimize medical exposure by introducing DRLs, but therapeutic fluoroscopy procedures are still challenging, as ICRP 135 states complexity. EUCLID (European Study on Clinical Diagnostic Reference Levels for X-ray Medical Imaging) 2021 suggests the induction of subgroups by difficulty or clinical background for interventional radiology. However, there were only two in the gastrointestinal field, transcatheter arterial chemoembolization and biliary drainage, without subgroups. A 2020 update of the Japan DRLs subcategorized cerebrovascular and cardiovascular procedures. However, there were only two in the gastrointestinal field: upper GI contrast divided into a screen and detailed examination, and endoscopic retrograde cholangiopancreatography (ERCP) divided into therapeutic and diagnostic. Especially in the gastrointestinal field, there are still not enough data to introduce DRLs to interventional procedures.

Added value of this study
We registered over ten thousand fluoroscopy-guided gastrointestinal procedures across 23 hospitals in Japan. These procedures include ERCP, interventional endoscopic ultrasound (EUS), metallic stent placement, tube placement, and balloon-assisted enteroscopy (BAE). We showed the DRL values for these procedures. There have been no comprehensive reports on EUS and BAE. ERCP alone has more than 10,000 cases and is one of the largest cohorts compared to previous reports. The large cohorts enabled the ERCP subcategory by disease site. Proximal malignant biliary obstruction (MBO) was the highest in those subcategories and approximately twice the others (common bile duct stone, distal MBO and pancreatic disease).

Implications of all the available evidence
These results provide the DRL value for fluoroscopy-guided gastrointestinal procedures. The ERCP subcategory may be one solution to the complexity of interventional radiology. These DRL values will significantly contribute to the proper use of medical exposure in the endoscopy unit.

Introduction
Medical radiation is widely used in both imaging and treatment. Ionizing radiation provides tremendous benefits despite a small risk of adverse health effects. It is never appropriate to implement dose limits when specific doses are justified for effective treatment. However, there are also concerns about side effects, such as carcinogenicity and tissue reactions. To reduce and optimize medical exposure, the International Commission on Radiological Protection (ICRP) and other radiological societies have tried to establish diagnostic reference levels (DRLs) for various x-ray-related procedures, and radiation-related societies in each region, such as the Japan Network for Research and Information on...
Medical Exposure, have also worked on establishing these levels. The DRL values are usually set at the 75th percentile of the distribution of a typical sample dose.3 The ICRP 135 publication recommends that all individuals involved in patient procedures with the risk of medical exposure be familiar with the DRL process as a tool for optimizing protection.4 DRLs are now widely accepted as the global standard for all procedures with ionizing radiation and are established in Japan (Japan DRLs 2015, updated in 2020).5,6

DRLs were introduced for diagnostic radiology examination in the 1980s and came into wide use in the 1990s. The ICRP recommends considering DRLs as much as possible during all procedures using radiation because the cumulative fluoroscopy exposure time is a poor metric of patient radiation dose. The ICRP states that DRLs are most useful for diagnostic imaging examinations, such as chest radiography, with relatively few procedural variables. However, it is challenging to set DRLs in interventional procedures, such as fluoroscopy-guided gastrointestinal procedures, because of the wide distribution of patient doses even for the same procedure at the same facility. They have different objectives and difficulty levels, resulting in a wide distribution of patient doses.4,7 In gastroenterology, fluoroscopy-guided procedures, such as typified endoscopic retrograde cholangiopancreatography (ERCP), have decreased for diagnostic usage but have increased as treatment modalities.8,9,10 DRLs have yet to be fully implemented for fluoroscopy-guided gastrointestinal procedures11, and only a few recommendations and guidelines have been acknowledged.12,13,14,15 The updated Japan DRLs from 2020 added DRLs for ERCP and tube placement, where PKA values of interventional ERCP and tube placement were evaluated in 1082 and 232 procedures, respectively. National surveys and registries for setting national DRL values for fluoroscopy-guided gastrointestinal procedures are required to include medium- and large-sized healthcare hospitals that have sufficient procedures to ensure that a sufficient amount of data for a representative selection of patients can be obtained. Based on this background, we launched the REX-GI (radiation exposure from gastrointestinal fluoroscopic procedures) study that aimed to establish DRLs for the following interventional procedures in gastrointestinal endoscopy units from 23 hospitals from all around Japan: ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement, and enteral tube placement.16

Study design

The REX-GI study was a multicentre, prospective observational cohort study. The study was conducted at 23 hospitals in Japan, including eight university hospitals, four cancer centres, nine general hospitals, and two municipal hospitals (Figure 1, Table 1). During the study period, 12959 fluoroscopy-guided gastrointestinal procedures were included. This study was conducted in accordance with the Declaration of Helsinki, and approval was obtained from each institutional review board. The requirement for informed consent was waived by the opt-out method of each hospital website. The rationale and methodology of the study have been published, and the full protocol is available online.10 The study was registered with the UMIN Clinical Trials Registry (UMIN000036525, May 1, 2019).

Study population

We included consecutive patients receiving standard clinical care who underwent the following treatment and diagnostic procedures under fluoroscopic guidance: (i) ERCP; (ii) interventional EUS; (iii) balloon-assisted enteroscopy; (iv) enteral metallic stent placement; and (v) enteral tube placement. In addition, we subcategorized ERCP, which had a larger number of registered cases than other procedures, into the following four disease sites according to previous reports17,18: 1) common bile duct stones, 2) proximal malignant biliary obstruction, 3) distal malignant biliary obstruction, and 4) pancreatic disease. There were no age restrictions. We examined air kerma at the patient entrance reference point (Kær; mGy), air kerma-area product (PKA; Gy·cm²), fluoroscopy time (FT; min), and radiation dose rate (RDR) (mGy/min) during these procedures between May 2019 and December 2020. RDR was calculated as Kær divided by FT. These data were collected from the fluoroscopy equipment by each institution. The facility representative sent them to the data centre every three months throughout the study period. Patients who did not want to participate in this study via the opt-out method on each hospital website, patients with multiple missing primary outcomes (e.g., Kær and PKA) and duplicate enrolments were judged to be unsuitable for inclusion in this study and were excluded by Hayashi S and Nishida T. Although it is necessary to specify the participating institutions, we have purposely not shown the data for each institution in order to maintain the anonymity of each institution.

Data analysis

For continuous variables, we report the medians and interquartile ranges (IQRs). Categorical variables are expressed as the numbers in each category or as frequencies. DRLs were set at the 75% percentile of the distribution of each sample dose. Essentially, DRLs are not optimum doses, but they help identify potentially unusual practices and serve as a tool for optimization of practices. Therefore, we did not use the statistical tests for comparison between institutions in this study that aimed to establish national DRLs. All statistical analyses
were performed using JMP software (ver. 15.2.0, SAS Institute, Inc., Cary, NC, USA).

Results

Patient and hospital characteristics
The median age of the patients was 72 years (IQR: 64-80), and 8,033 patients were male (62.0%). The hospitals consisted of 8 university hospitals, four cancer centres, nine general hospitals, and two municipal hospitals. Regarding the fluoroscopy equipment in the institutions, 15 (65%) were the overtube type. The median year of fluoroscopy equipment introduction in each hospital was 2016 (2006-2019). The median irradiated field and frame per second were 441 cm² (IQR: 441-900) and 12.5 (IQR: 7.5-15), respectively. Fluoroscopy was performed inside the same room in fourteen hospitals (61%) (Tables 1 and 2). The procedures included ERCP (n=11,162, 86.1%), interventional EUS (n=374, 2.9%), metallic stent (n=523, 4.4%), tube placement (n=599, 4.6%) and BAE (n=301, 2.3%) (Table 3).

Ka,R, PKA and FT of each procedure
The air kerma at the patient entrance reference point (Ka,R; mGy), air kerma-area product (PKA; Gycm²), and fluoroscopy time (FT; min) for each procedure were accumulated. For ERCP, the median/third quartile values of Ka,R (mGy), PKA (Gycm²), and FT (min) were 69/145 mGy, 16/32 Gycm² and 11/20 min, respectively. Similarly, these values were 106/219 mGy, 23/41 Gycm² and 17/27 min for interventional EUS; 53/104 mGy, 16/32 Gycm² and 10/15 min for metallic stents; 56/104 mGy, 28/47 Gycm² and 12/18 min for tube placement; and 35/81 mGy, 16/43 Gycm² and 7/15 min for BAE, respectively (Supplementary Figure 1). Based on the disease sites where ERCP was used, the values from common bile duct stones, proximal malignant biliary obstruction, distal malignant biliary obstruction and pancreatic disease were 62/126 mGy, 15/30 Gycm², and 10/18 min; 118/223 mGy, 27/48 Gycm², and 18/31 min; 59/121 mGy, 14/29 Gycm² and 10/18 min; and 74/148 mGy, 15/30 Gycm² and 11/20 min, respectively (Table 3).

RDR between hospitals
RDR was calculated as Ka,R per FT for each procedure. Overall, the median/third quartile values of RDR were 5.9/9.4 (mGy/min). Similarly, the RDR values were 5/6, 4.9/6.9, 6.9/9.1, 3.5/5.2, 4.8/7.1, 7.1/12.2, 4.9/6.4, 8.9/11.1, 14.3/20.2, 15.7/21.1, 6.3/8, 5.6/7.6, 6.1/10.3, 5.3/6.7, 11.6/15, 6.1/8.5, 32/32, 13.9/19.5, 4.4/5.5, 9.2/14.4, 8.7/14.4, 8.7/10.1 and 5.9/9.4 for each hospital, and each hospital’s name was alphabetized and anonymized (Supplementary Figure 2).

Discussion
This was a nationwide, prospective study to establish DRLs in the gastrointestinal field worldwide, and this

Figure 1. Map of participating hospitals. The REX-GI (radiation exposure from gastrointestinal fluoroscopic procedures) study aimed to establish DRLs for the following interventional procedures in gastrointestinal endoscopy units at 23 hospitals from all around Japan: ERCP, interventional EUS, balloon-assisted enteroscopy, enteral metallic stent placement, and enteral tube placement.
study included 23 hospitals from all around Japan and encompassed 12,959 gastrointestinal fluoroscopic procedures. Although some DRLs in the gastrointestinal field have been reported to date, the number of patients was either not described or too few patients were enrolled (Supplementary Table). This study had a larger sample size than previous studies that established DRLs in gastroenterology because this study prospectively registered more than 10,000 ERCPs, whereas the total number of ERCPs was approximately 1,300 in the Japan DRLs 2020. In addition, we registered several fluoroscopy-guided gastrointestinal procedures in addition to ERCP. For ERCP, this study showed a relatively low Ka,r and PKA compared to the Japan DRL value (Ka,r: 104-154 mGy, FT: 18-28.3 min), which may be because this study included endoscopist-centred data, including the placement methods that were assisted by endoscopy.

| Number of Hospital Beds | Company | Device model | Apparatus type | Year of introduction | Location |
|-------------------------|---------|--------------|----------------|---------------------|----------|
| Toyonaka Municipal Hospital | Hitachi | Exavista | Overtube | 2016 | Endoscopy |
| Kindai University | Hitachi | Curevista | Overtube | 2017 | Endoscopy |
| The University of Tokyo | Hitachi | Curevista | Overtube | 2009 | Radiology |
| | Hitachi | Exavista | Overtube | 2013 | |
| | Canon Toshiba | Ultimax-I | Undertube | 2016 | |
| Fukui Prefectural Hospital | Hitachi | Versiflex | Overtube | 2008 | Endoscopy |
| Kansai Rosai Hospital | Canon Toshiba | Zexira | Overtube | 2011 | Radiology |
| | Canon Toshiba | Ultimax-I | Undertube | 2017 | |
| Osaka City University | Hitachi | Curevista | Overtube | 2011 | Endoscopy |
| | Hitachi | Versiflex | Overtube | 2017 | Endoscopy |
| Ishikawa Prefectural Central Hospital | Hitachi | Curevista | Overtube | 2013 | Radiology |
| Toho University Ohashi Medical Center | Canon Toshiba | ZEXIRA | Overtube | 2016 | Endoscopy |
| | Hitachi | Versiflex | Overtube | 2018 | Endoscopy |
| | Osaka Rosai Hospital | Hitachi | Curevista | Overtube | 2018 | Radiology |
| Osaka General Medical Center | Hitachi | Curevista, Versiflex | Overtube | 2018 | Endoscopy |
| Fukushima Medical University | Hitachi | Zexira FPD1717 | Overtube | 2012 | Radiology |
| School of Medicine | Canon Toshiba | | | | |
| Hyogo Cancer Center | Hitachi | Curevista | Overtube | 2019 | Endoscopy |
| Kitano Hospital | Hitachi | Versiflex | Overtube | 2017 | Endoscopy |
| | Hitachi | Curevista | Overtube | | |
| Tane General Hospital | Hitachi | Exavista | Overtube | 2011 | Radiology |
| Japanese Red Cross Medical Center | Hitachi | Curevista | Overtube | 2016 | Radiology |
| | Hitachi | Exavista | Overtube | 2010 | Endoscopy |
| Kure Medical Center and Chugoku Cancer Center | Hitachi | Exavista | Overtube | 2010 | Endoscopy |
| Nagoya City University Hospital | Canon Toshiba | Ultimax-I | Undertube | 2018 | Endoscopy |
| Toho University Ohashi Medical Center | Canon Toshiba | Ultimax-I | Undertube | 2018 | Radiology |
| Osaka International Cancer Institute | Canon Toshiba | Ultimax-I | Undertube | 2017 | Endoscopy |
| Gifu University Hospital | Shimadzu | C-Vision Safire | Undertube | 2004 | Radiology |
| Juntendo University Hospital | Hitachi | Curevista | Overtube | 2019 | Endoscopy |

Table 1: Fluoroscopic systems and units under fluoroscopic guidance.
We found that the DRL values differed between institutions. Interinstitutional studies depend greatly on the population of procedure types and difficulty levels, and the abovementioned procedure-related factors greatly influence FT. However, RDR, \(K_{a,r}\) per FT, can compare the rough difference in settings between institutions without being affected by FT. In addition, DRL values using multiple quantities may help identify the cause when radiation use has not been optimized and may simplify the investigation. The 3rd quartile value of RDR ranged widely from 3.3 to 32 mGy/min, and the 3rd quartile value of RDR in all hospitals was 9.4 mGy/min. Since RDR is a number per minute and is not dependent on the duration of the procedure, this wide dispersion is mainly due to the output and the settings of the fluoroscopy equipment. Regarding the fluoroscopy equipment in this study, the median year of the unit was 2016, and the date of the equipment ranged from 2006 to 2019. Given that the registration period started in May 2019, these were relatively new devices. This may be because the primary outcome was \(K_{a,r}\), FT, and hospitals that had relatively older equipment (due to the lack of fluoroscopic parameters) were excluded. Updated fluoroscopy equipment reduces radiation exposure; thus, the participating hospitals in these studies had high awareness of radiation exposure, which could have caused a bias. The results in this study may therefore be relatively more generalizable than those of the whole cohort in Japan.

In the present study, many fluoroscopic devices were the overtube type (15/23, 65%), which is a characteristic of the gastrointestinal field in Japan. This is also an issue with regard to managing radiation exposure of staff to upper body scatter and exposure to the eyes of patients.

| Procedure                  | N   | \(K_{a,r}\) (mGy) 1st quartile | Median, 3rd quartile | \(P_{K_A}\) (Gycm\(^2\)) 1st quartile | Median, 3rd quartile | FT (min) 1st quartile | Median, 3rd quartile | No. of images per exam Median |
|----------------------------|-----|--------------------------------|----------------------|--------------------------------------|----------------------|----------------------|----------------------|-----------------------------|
| ERCP                      | 11162 | 35, 69, 145                  | 8, 16, 32           | 6, 11, 20                           | 9                    |
| Common bile duct stone    | 3932 | 32, 62, 126                  | 8, 15, 30           | 6, 10, 18                           | 9                    |
| Proximal malignant biliary obstruction | 1617 | 57, 118, 223                | 14, 27, 48           | 10, 18, 31                          | 10                   |
| Distal malignant biliary obstruction | 2489 | 31, 59, 121              | 7, 14, 29            | 6, 10, 18                           | 8                    |
| Pancreatic disease        | 1163 | 37, 74, 148                  | 8, 15, 30           | 6, 11, 20                           | 10                   |
| Interventional EUS        | 374 | 53, 106, 219                  | 12, 23, 41          | 11, 17, 27                          | 12                   |
| Metallic stent            | 523 | 29, 53, 104                  | 8, 16, 32           | 6, 10, 15                           | 9                    |
| Tube placement            | 599 | 30, 56, 104                  | 14, 28, 47          | 8, 12, 18                           | 4                    |
| BAE                       | 301 | 16, 35, 81                   | 7, 16, 43           | 3, 7, 15                            | 6                    |

Table 3: First quartile, median and third quartile values of \(K_{a,r}\), \(P_{K_A}\), and FT for each procedure.

\(K_{a,r}\): Air kerma at the patient entrance reference point.
\(P_{K_A}\): Air kerma-area product.
FT: Fluoroscopy time.
ERCP: Endoscopic retrograde cholangiopancreatography.
EUS: Endoscopic ultrasonography.
BAE: Balloon-assisted enteroscopy.

We found that the DRL values differed between institutions. Interinstitutional studies depend greatly on the population of procedure types and difficulty levels, and the abovementioned procedure-related factors greatly influence FT. However, RDR, \(K_{a,r}\) per FT, can compare the rough difference in settings between institutions without being affected by FT. In addition, DRL values using multiple quantities may help identify the cause when radiation use has not been optimized and may simplify the investigation. The 3rd quartile value of RDR ranged widely from 3.3 to 32 mGy/min, and the 3rd quartile value of RDR in all hospitals was 9.4 mGy/min. Since RDR is a number per minute and is not dependent on the duration of the procedure, this wide dispersion is mainly due to the output and the settings of the fluoroscopy equipment. Regarding the fluoroscopy equipment in this study, the median year of the unit was 2016, and the date of the equipment ranged from 2006 to 2019. Given that the registration period started in May 2019, these were relatively new devices. This may be because the primary outcome was \(K_{a,r}\), FT, and hospitals that had relatively older equipment (due to the lack of fluoroscopic parameters) were excluded. Updated fluoroscopy equipment reduces radiation exposure; thus, the participating hospitals in these studies had high awareness of radiation exposure, which could have caused a bias. The results in this study may therefore be relatively more generalizable than those of the whole cohort in Japan.

In the present study, many fluoroscopic devices were the overtube type (15/23, 65%), which is a characteristic of the gastrointestinal field in Japan. This is also an issue with regard to managing radiation exposure of staff to upper body scatter and exposure to the eyes of patients.
Many hospitals operate fluoroscopy equipment inside the room (14/23, 61%); this means that more than 61% of endoscopists use fluoroscopic equipment, with not as many radiologists using the equipment. Sethi et al. reported a questionnaire survey in which it was found that most endoscopists (56.6%) had not received training on how to operate a fluoroscopy system despite the majority of endoscopists (61.6%) using fluoroscopy during ERCP. According to our previous report in Japan, only 71% of endoscopists had received a basic lecture on radiation exposure, despite 91% of them using fluoroscopy. Many of the endoscopy units in Japan are handled over tubes, which greatly affects lens exposure. Many administrators are endoscopists who have to understand the basic principles of radiation safety and need to minimize the risk of radiation exposure to both the patients and staff.

We found that the DRL quantities were different for each gastrointestinal procedure. Interventional EUS had the highest $K_{EA}$ (219 mGy at 75% value), followed by ERCP (145 mGy), metallic stents (104 mGy), tube placement (104 mGy), and BAE (81 mGy). Similarly, tube placement had the highest $P_{K_A}$ (47 Gycm$^{-1}$), followed by BAE (43 Gycm$^{-1}$), EUS (41 Gycm$^{-1}$), ERCP (32 Gycm$^{-1}$), and metallic stents (32 Gycm$^{-1}$). These discrepancies in the $K_{EA}$ and $P_{K_A}$ rankings may suggest the use of a larger irradiation field in BAE and tube placement. In terms of ERCP subcategories by disease site, proximal malignant biliary obstruction (PMBO) was higher than the other diseases in all $K_{EA}$, $P_{K_A}$, and FT (Table 3). This was similar to our previous single-centre report.

One of the reasons for the difficulty in setting DRLs for IR is the wide distribution, and one way to overcome this problem is to subcategorize the procedures. In the Japan DRLs 2020, there was a twofold difference between chronic total occlusion (CTO) and non-CTOs in percutaneous coronary intervention (PCI), which was listed as a separate category. This study shows that ERCP might be better categorized into PMBO and non-PMBO instead of into treatment and diagnostic usages.

Medical exposure was estimated to account for approximately 48% of the effective dose to the U.S. population in 2006, compared to the 15% in the early 1980s, according to the National Council on Radiation Protection and Measurements (NCRP) report no. 160. However, the NCRP recently reported a 0.8-fold decrease in the total effective dose of medical exposure over the decade from 2006 to 2016. The breakdown shows that there was almost no change in the effective dose of CT, and there was a 0.6-fold decrease in the interventional fluoroscopic procedures. The aforementioned decrease is attributed to the fact that many diagnostic fluoroscopy procedures have been replaced by CT and MRI, but the introduction of DRL also occurred around the same time, which may explain the decrease in the dose per procedure. In the UK, the introduction of DRLs could achieve a reduction of approximately 50% in the radiation dose during typical x-ray examinations over 15 years. With the Japan DRLs, the RDR values for IR decreased from 20 to 17 mGy/min from 2015 to 2020. In this study, the 3rd quartile value for RDR for all hospitals combined was 9.4 mGy/min, and only 4 of the 23 hospitals had RDRs that were above 17 mGy/min. Understanding and managing radiation exposure in fluoroscopy-guided gastrointestinal procedures will lead to appropriate use, similar to other radiologic procedures.

Conclusion
The REX-GI study provides a significant amount of data regarding the actual radiation exposure of fluoroscopy-guided gastrointestinal procedures: ERCP, interventional EUS, enteral metallic stent placement, enteral tube placement, and BAE. These data will contribute to establishing DRLs for fluoroscopy-guided gastrointestinal procedures and IR as a whole.

Author contributions
Nishida T, Hayashi S, and Takenaka M conceptualized and designed this study. Hosono M critically reviewed and supervised the protocol. Hayashi S wrote the original draft. Nishida T handled funding acquisition as well as review and editing. Hayashi S, Nishida T and Takenaka M performed the data curation and formal analysis. Hayashi S, Nishida T, Takenaka M, Kogure H, Hasatani K, Yamaguchi S, Maruyama H, Matsunaga K, Ihara H, Yoshio T, Nagaie K, Yamada T, Yakashijin T, Takagi T, Tsumura H, Kurita A, Asai S, Ito Y, Kuwai T, Hori Y, Maetani I, Ikezawa K, Ishii S, Nishida T, and Takenaka M participated in this study and recruited the patients.

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

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Data sharing
The data that support the findings of this study are available on request from the corresponding author Nishida T.

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Supplementary materials
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