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ORIGINAL ARTICLE

Rarity of Severe Bleeding and Perforation in Endoscopic Ultrasound-Guided Fine Needle Aspiration for Submucosal Tumors

Tsuyoshi Hamada · Hideo Yasunaga · Yousuke Nakai · Hiroyuki Isayama · Hiromasa Horiguchi · Shinya Matsuda · Kiyohide Fushimi · Kazuhiko Koike

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Abstract
Background Endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) is an established procedure for the pathological diagnosis of gastrointestinal submucosal tumors (SMTs). Although bleeding and perforation are potentially severe complications of EUS-FNA, the incidences and severities of these complications have not yet been fully evaluated because of their relative rarity.
Aim The purpose of this study was to evaluate the incidences and mortality of severe bleeding and perforation in patients who underwent EUS-FNA for SMTs.
Methods The records of 1,135 consecutive patients who underwent EUS-FNA for SMTs at 219 hospitals, with low- to high-volume, were reviewed using a Japanese nationwide administrative database.
Results Of the targeted lesions 73.5 % were located in the stomach, 13.4 % in the esophagus, 8.2 % in the duodenum, and 4.9 % at other sites. Five patients (0.44 %) experienced severe bleeding requiring red blood cell transfusion or endoscopic treatment, with none experiencing perforation. Only one patient (0.09 %) died in-hospital within 30 days of EUS-FNA (0.09 %), with death not associated with bleeding or perforation.
Conclusions EUS-FNA is safe in evaluating SMTs, with low risks of bleeding and perforation.

Keywords Bleeding · Endoscopic ultrasound · Fine needle aspiration · Perforation · Submucosal tumor

Introduction

Endoscopic ultrasound (EUS) is an established modality for morphologic evaluation of masses derived from the gastrointestinal tract or surrounding tissues [1], and EUS-guided fine needle aspiration (EUS-FNA) permits the cytological and histological diagnoses of masses derived

T. Hamada · Y. Nakai · H. Isayama (✉) · K. Koike
Department of Gastroenterology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: isayama-tky@umin.ac.jp

T. Hamada
e-mail: hamada-tky@umin.ac.jp

Y. Nakai
e-mail: ynakai-tky@umin.ac.jp

K. Koike
e-mail: kkoike-tky@umin.ac.jp

H. Yasunaga · H. Horiguchi
Department of Health Management and Policy, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
e-mail: yasunagah-tky@umin.ac.jp

H. Horiguchi
e-mail: hiromasa-tky@umin.ac.jp

S. Matsuda
Department of Preventive Medicine and Community Health, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyūshū 807-8555, Japan
e-mail: smatsuda@med.uoeh-u.ac.jp

K. Fushimi
Department of Health Care Informatics, Tokyo Medical and Dental University, 1-5-45 Yushima, Bunkyo-ku, Tokyo 113-8510, Japan
e-mail: kfushimi.hci@tmd.ac.jp

from the gastrointestinal tract and surrounding tissues [2, 3]. Although EUS-FNA has been shown useful in the diagnosis of gastrointestinal submucosal tumors (SMTs) [4–6], it is associated with susceptibility to bleeding and perforation, since it entails echoendoscope insertion and needle penetration through the gastrointestinal mucosa [7, 8].

Although one systematic review reported that no patient experienced severe bleeding or perforation after EUS-FNA for SMTs [8], the pooled sample size was relatively small (263 patients), too few to accurately assess the incidence and severity of these relatively rare complications. Moreover, the studies included in this systematic review were based on the results of EUS-FNA performed by one or a few expert endosonographers in high-volume centers, potentially leading to underestimation of complications. In addition, the complication rates in retrospective and prospective studies differed, implying a publication bias.

We therefore retrospectively examined a Japanese nationwide administrative database, the Diagnosis Procedure Combination (DPC) database, of patients who underwent EUS-FNA for SMTs to evaluate their incidences of severe bleeding and perforation.

Methods

Data Source

The DPC database provides data on admission/discharge abstracts and administrative claims, along with implementation of interventional procedures, of patients throughout Japan [9, 10]. Main diagnoses and complications during hospitalization were recorded using the International Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes, supplemented by Japanese text data. The database also contains detailed demographic and clinical information, including patients' age and sex; length of hospital stay; discharge status including in-hospital death; as well as medications including drugs and interventional/surgical procedures indexed by Japanese original codes.

This study was approved by the institutional review board of The University of Tokyo, which waived the requirement for patient informed consent because of the anonymous nature of the data.

Patient Cohort

EUS-FNA was included in the Japanese health insurance system in April 2010, and the DPC database covered the consecutive patients who underwent EUS-FNA thereafter. We extracted data on all consecutive patients who underwent EUS-FNA (indexed by the Japanese original code) for SMTs and were discharged between 1 July 2010 and 31 October 2011. We identified SMTs as targeted lesions of EUS-FNA by screening for potential lesions using the ICD-10 codes (esophagus, C159, D130, D377; stomach, C169, D131, D371, K319; duodenum, C170, D132, D372, K319; small intestines, C179, D133, D372; colon, C189, D139, D374 and rectum, C19, C20, D375), followed by manual verification of SMTs through the diagnoses recorded by Japanese text data. Hospital type was categorized as academic and non-academic. The number of patients who underwent EUS-FNA for any lesions annually at each hospital was determined, with hospitals categorized into low-, medium- and high-volume tertiles.

Complications

Severe bleeding was identified based on the requirement for red blood cell (RBC) transfusion, endoscopic treatment or vascular embolization for gastrointestinal bleeding with/without the ICD-10 codes for intraperitoneal (K66.1) or gastrointestinal (K92.2) bleeding. Perforation was identified based on ICD-10 codes for perforation of the esophagus (K22.3), stomach (K25.1 and K25.2), duodenum (K26.1 and K26.2), small intestine (K27.1 and 27.3), and colon/rectum (K63.1). Complications diagnosed within three days of EUS-FNA were included, since those occurring after three days may have been due to other conditions requiring the same treatments.

Statistical Analysis

Descriptive statistics were used to document the characteristics of severe bleeding and perforation after EUS-FNA for SMTs. Complication rates were compared between groups using the χ^2 test or Fisher's exact test, as appropriate. All statistical analyses were performed using IBM SPSS Statistical software, version 19 (IBM, Armonk, NY, USA). A P value <0.05 was considered significant.

Results

Patient Characteristics

Among a total of 6,827 patients who underwent EUS-FNA for any lesions, a survey of DPC records identified 1,135 eligible patients who underwent EUS-FNA for SMTs between 1 July 2010 and 31 October 2011 at 219 hospitals, including 77 academic and 142 non-academic hospitals. Patient characteristics relative to targeted lesion locations are summarized in Table 1. Mean ± standard deviation (SD) patient age was 62.8 ± 13.6 years, and 55.3 % of the

Table 1 Patient characteristics relative to SMT locations examined by endoscopic ultrasound-guided fine needle aspiration

Location of SMT	Total	Esophagus	Stomach	Duodenum	Small intestines	Colon	Rectum
Number of patients	1,135	152	834	93	4	6	46
Age (years)	62.8 ± 13.6	59.4 ± 16.0	63.5 ± 13.2	61.5 ± 13.7	64.8 ± 21.7	64.6 ± 12.8	64.9 ± 12.7
Sex							
Males	628 (55.3 %)	100 (65.8 %)	436 (52.3 %)	62 (66.7 %)	2 (50.0 %)	3 (50.0 %)	25 (54.3 %)
Females	507 (44.7 %)	52 (34.2 %)	398 (47.7 %)	31 (33.3 %)	2 (50.0 %)	3 (50.0 %)	21 (45.7 %)
Hospital volume							
Low	511 (45.0 %)	53 (34.9 %)	394 (47.2 %)	33 (35.5 %)	1 (25.0 %)	5 (83.3 %)	25 (54.3 %)
Medium	301 (26.5 %)	47 (30.9 %)	208 (24.9 %)	34 (36.6 %)	2 (50.0 %)	1 (16.7 %)	9 (19.6 %)
High	323 (28.5 %)	52 (34.2 %)	232 (27.8 %)	26 (28.0 %)	1 (25.0 %)	0 (0 %)	12 (26.1 %)
Hospital type							
Academic	520 (45.8 %)	79 (52.0 %)	369 (44.2 %)	54 (58.1 %)	1 (25.0 %)	1 (16.7 %)	16 (34.8 %)
Non-academic	615 (54.2 %)	73 (48.0 %)	465 (55.8 %)	39 (41.9 %)	3 (75.0 %)	5 (83.3 %)	30 (65.2 %)
GIST	169 (14.9 %)	14 (9.2 %)	145 (17.4 %)	6 (6.5 %)	3 (75.0 %)	0 (0 %)	1 (2.2 %)

Age is shown as mean and standard deviation. Other variables are shown as the number (%). Hospital volume was defined as the number of EUS-FNAs for any lesions performed annually at each hospital and categorized as low- (≤42 patients), medium- (43–86 patients) and high- (≥87 patients) volume

GIST gastrointestinal stromal tumor, *SMT* submucosal tumor

patients were male. Most SMTs were located in the stomach (73.5 %). Assessment of hospital volume, defined as the number of EUS-FNAs performed annually for any lesions, showed that 34.2, 33.0 and 32.7 % of the patients underwent this procedure at hospitals performing ≤42 (low-volume), 43–86 (medium-volume) and ≥87 (high-volume) EUS-FNAs annually for any lesions. Most GISTs were located in the stomach (85.8 %). Three patients (0.3 %) underwent EUS-FNA without stopping treatment with antithrombotic agents, including one patient each being treated with low-dose aspirin, clopidogrel and warfarin.

Severe Bleeding and Perforation

Only one patient (0.09 %) experienced severe bleeding requiring RBC transfusion within 3 days after EUS-FNA. This patient, who underwent EUS-FNA for a duodenal GIST, received transfused RBCs on day 2 after EUS-FNA. Four other patients (0.35 %) underwent endoscopic treatment for gastrointestinal bleeding within 3 days, but did not require RBC transfusions. Of these four patients, one underwent endoscopic treatment on the day of EUS-FNA, two on day 2, and one on day 3. No patient underwent vascular embolization.

Overall, severe bleeding requiring RBC transfusion or endoscopic treatment occurred in five patients (0.44 %). There were no procedures performed between EUS-FNA and RBC transfusion/endoscopic treatment, which was confirmed via manual verification of data on these patients. The characteristics of these five patients are summarized in Table 2. None of these had chronic renal failure and liver cirrhosis as risk factors for gastrointestinal bleeding. Four patients underwent EUS-FNA for gastric SMTs and one for a duodenal SMT, accounting for 0.5 and 1.1 %, respectively, of those who underwent EUS-FNA for these indications. The rates of severe bleeding did not differ significantly between SMT locations ($P = 0.618$). Severe bleeding was observed in three patients (0.59 %) in low-volume hospitals, one (0.33 %) in a medium-volume hospital and one (0.31 %) in high-volume hospitals ($P = 0.796$). Severe bleeding rates also did not differ significantly in patients who underwent EUS-FNA at academic and non-academic hospitals (0.58 vs. 0.33 %, $P = 0.665$).

No gastrointestinal tract perforation, as indicated by ICD-10 codes, was observed in any patient. In-hospital death within 30 days of EUS-FNA occurred in one patient (0.09 %), whose direct cause of death was unavailable because of the nature of the DPC database, but this death was not associated with severe bleeding. Severe bleeding occurred in one patient with gastric GIST (0.69 %) and one with duodenal GIST (16.7 %). The rates of severe bleeding in patients with and without GIST did not differ significantly (1.2 vs. 0.31 %, $P = 0.189$).

EUS-FNA was performed without cessation of antithrombotic agents in three patients, one each with an SMT in the stomach, duodenum and rectum. None of these patients experienced severe bleeding.

Discussion

This nationwide study of 1,135 patients who underwent EUS-FNA for SMTs showed that severe bleeding and

Table 2 Description of patients who experienced severe bleeding after endoscopic ultrasound-guided fine needle aspiration for SMTs

No.	<40	40–60	>60	Sex	Location of SMT	GIST	Hospital volume	Hospital type	RBC transfusion	Endoscopic procedure
1	✔			Male	Stomach		Medium	Academic		✔
2		✔		Female	Stomach		Low	Academic		✔
3			✔	Female	Stomach	✔	Low	Academic		✔
4			✔	Female	Stomach		High	Non-academic		✔
5			✔	Female	Duodenum	✔	Low	Non-academic	✔	

Hospital volume was defined as the number of EUS-FNAs for any lesions performed annually at each hospital and categorized as low- (≤42 patients), medium- (43–86 patients) and high- (≥87 patients) volume

SMT submucosal tumor, *GIST* gastrointestinal stromal tumor, *RBC* red blood cell

perforation after the procedure were rare, occurring in 0.44 and 0 % of patients, respectively. Moreover, only one patient (0.09 %) died in-hospital within 30 days of EUS-FNA, with mortality not associated with bleeding or perforation.

Severe bleeding and perforation are rare but potentially life-threatening complications of EUS-FNA for SMTs, but were not previously evaluated in large-scale studies [7, 8]. The DPC database covers approximately 7 million inpatients from more than 1,000 hospitals between 1 July 2010 and 30 June 2011 [9, 10]. Thus, the results presented here can provide robust estimates of the rates of these complications, especially since EUS-FNA has been performed on an inpatient basis in the vast majority of Japanese hospitals, and thus the DPC database covered most patients who underwent EUS-FNA in Japan. The attending physicians at the DPC hospitals were obliged to record the abovementioned items at the time of each patient's discharge. Moreover, even if the overall complication rates of EUS-FNA are higher in low- than in high-volume hospitals, we found that the rates of bleeding and perforation were low enough, indicating that this procedure is generally safe and associated with low bleeding and perforation rates. Moreover, to our knowledge, this study is the first to evaluate complications of EUS-FNA based on the locations of SMTs, finding that the rates of severe bleeding and perforation did not differ by SMT location.

GISTs are hyper-vascular masses, which often appear endoscopically as SMTs [11, 12]. Although EUS-FNA has been reported useful for the diagnosis of GIST [13, 14], the vascularity of these tumors may increase the risk of bleeding after needle penetration. We found that only 2 of 169 patients (1.2 %) with GIST experienced severe bleeding, a rate not significantly higher than that in patients with non-GIST lesions (0.31 %).

The necessity to stop treatment with antithrombotic agents prior to EUS-FNA is unclear, especially since the number of patients taking antithrombotic agents has increased. Despite the enhanced risk of bleeding associated with the cessation of antithrombotic agents [15, 16], there has been no consensus on how to manage these agents [17, 18]. In this study, three patients underwent EUS-FNA without first stopping antithrombotic agents, with none experiencing severe bleeding. However, the small sample size prevented a definitive conclusion. In addition, since the DPC database is an inpatient database, it was impossible to identify those patients who took antithrombotic agents regularly and discontinued these medications prior to admission for preparation of EUS-FNA. A prospective randomized controlled trial is needed to determine whether treatment with antithrombotic agents should be stopped prior to EUS-FNA for SMTs.

This study had several limitations. The values of hemoglobin before and after EUF-FNA were unavailable in the DPC database, and we could not evaluate clinically non-significant bleeding requiring neither RBC transfusion nor endoscopic treatment. Some important clinical data were unavailable from the DPC database, e.g. the size of needles, the number of passes, the size of SMTs and the experience of the endosonographers. Lack of data in the DPC database inhibited the evaluation of complications other than severe bleeding and perforation, such as abdominal pain, fever and infection. The detailed results of the pathological examinations were unavailable from the DPC database, and GIST was diagnosed based on the description by attending physicians, not pathologically. RBC transfusion and endoscopic treatment may have been performed for reasons other than bleeding associated with EUS-FNA, leading to an overestimation of the incidence of severe bleeding after EUS-FNA. Despite these limitations, the strength of the present study was a large sample size from a large number of low- to high-volume hospitals consecutively collected via a nationwide database.

In conclusion, severe bleeding and perforation requiring RBC transfusion and additional interventions were rare complications of EUS-FNA for SMTs. EUS-FNA is a safe diagnostic procedure for patients with SMTs.

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Conflict of interest None.

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