

## Diagnosis and treatment of postoperative bleeding in patients after gastrectomy: a retrospective case series study

Yongshi Shen<sup>1#</sup>, Min Xiao<sup>1#</sup>, Jinsen Weng<sup>1#</sup>, Liuxin Yang<sup>2</sup>, Ye Feng<sup>1</sup>, Yong Ye<sup>1</sup>, Peng Zheng<sup>1</sup>

<sup>1</sup>Department of Intensive Care Unit, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China; <sup>2</sup>Department of Thoracic Surgical Oncology, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, Fuzhou, China *Contributions:* (I) Conception and design: Y Ye, P Zheng; (II) Administrative support: None; (III) Provision of study materials or patients: L Yang, Y Feng; (IV) Collection and assembly of data: L Yang, Y Shen; (V) Data analysis and interpretation: M Xiao, J Weng; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

"These authors contributed equally to this work.

*Correspondence to:* Peng Zheng; Yong Ye. Department of Intensive Care Unit, Clinical Oncology School of Fujian Medical University, Fujian Cancer Hospital, 420 Fuma Road, Jin'an District, Fuzhou 350014, China. Email: fjzlzp@163.com; 331006931@qq.com.

**Background:** There are significant differences in terms of the pathophysiology and clinical manifestations between intra- and extra-luminal bleeding, and it is also difficult to determine the reasonable management of the bleeding. This study is to analyze the clinical characteristics of postoperative bleeding in gastric cancer, and to explore the management of postoperative intra-intestinal and extra-intestinal bleeding.

**Methods:** We collected the clinical data of 2,978 patients with gastric cancer from the Department of Surgery, Fujian Cancer Hospital, from May 2014 to September 2019. A total gastrectomy or a distal or proximal subtotal gastrectomy with regional lymph node dissection (D1+ or D2) was included. The clinic data and management of both early (postoperative days  $\leq 6$  d) and delayed (postoperative days  $\geq 7$  d) postoperative hemorrhage were explored. This retrospective study is to compare the clinical characteristics and treatment of intra-intestinal and extra-intestinal hemorrhage.

**Results:** The incidence of postoperative bleeding in gastric cancer was 2.85% (n=85), and the bleeding-related mortality was 4.7% (4/85). There were 67 men and 18 women, and four patients died, with a bleeding-related mortality rate of 4.7%. There were 46 cases of intra-intestinal hemorrhage and 39 cases of extra-intestinal hemorrhage. The reoperation rate in the extraneous bleeding group was higher than that in the intra-intestinal bleeding group (66.67% *vs.* 19.57%, P<0.001), and the incidence of delayed bleeding in the extra-intestinal bleeding group was higher than that in the intra-intestinal bleeding group was higher than that in the intra-intestinal bleeding group (46.15% *vs.* 8.70%, P<0.001). In the delayed phase, 11 patients underwent reoperation to stop the bleeding, and three patients died due to bleeding-related complications. Hemostasis was successfully achieved in four patients by transcatheter arterial embolization (TAE). In the reoperation group, 72.73% (8/11) suffered hemodynamic instability and 63.64% (7/11) had an abdominal infection, while in the TAE group, 25% (1/4) had hemodynamic instability and 50% (2/4) had an abdominal infection.

**Conclusions:** A greater number of gastric cancer patients with intra-intestinal hemorrhage are treated conservatively, while more patients with extra-intestinal hemorrhage are treated by reoperation. External bleeding is more likely to occur in the delayed period of bleeding. TAE is a safe and effective means of hemostasis if the hemodynamics is stable.

**Keywords:** Postoperative bleeding; transcatheter arterial embolization (TAE); gastric cancer (GC); radical gastrectomy; re-laparotomy

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### Introduction

Owing to the advances in surgical techniques and perioperative patient care in recent decades, the incidence of postoperative bleeding following gastrectomy has been decreasing. The incidence of post-gastrectomy bleeding is reported to be 0.6-4% and has a high mortality (1-7). Hemorrhagic complications after gastric cancer (GC) surgery are infrequent and can be managed with conservative treatment, endoscopic intervention, radiologic intervention and re-laparotomy; however, they can be lifethreatening in some patients. Post-gastrectomy bleeding can be classified as either an early or delayed type based on its timing. Early postoperative hemorrhage (EPH) is defined as hemorrhage occurring within 6 days postoperatively, while delayed postoperative hemorrhage (DPH) often occurs after 7 days. Moreover, post-gastrectomy bleeding can also be divided into intra-intestinal and extra-intestinal bleeding according to the location of the bleeding. There are significant differences in terms of the pathophysiology and clinical manifestations between intra- and extra-luminal bleeding, and it is also difficult to determine the reasonable management of the bleeding. However, there have been few studies that deal with postgastrectomy bleeding.

This study aims to identify proper therapeutic management for PH by analyzing the clinical presentation, diagnostic measures and means of treatment. We present

#### **Highlight box**

#### Key findings

• Postoperative hemorrhage for gastric cancer is an infrequent complication. The clinical situation is more complicated and the reoperation rate is higher in extra-intestinal hemorrhage. TAE is a safe and effective method if the hemodynamics are stable in delayed exsanguination.

#### What is known and what is new?

- Re-operation is currently recognized as a method for early-onset extra-intestinal bleeding. As for delayed extra-intestinal bleeding, the choice of re-operation or TAE is still controversial.
- Extra-intestinal hemorrhage is more likely to occur in delayed bleeding, and it is usually complex bleeding. Most cases are associated with an anastomotic fistula. TAE is a safe and effective means of hemostasis if the hemodynamics is stable.

#### What is the implication, and what should change now?

• The clinical situation is more complicated and the re-operation rate is higher in patients with extra-intestinal hemorrhage. TAE is a safe and effective method if the hemodynamics is stable.

the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/ article/view/10.21037/jgo-22-1203/rc).

#### **Methods**

#### Patients selection

This study was a retrospective analysis performed in a single high-volume GC center. The patients' characteristics and medical therapy data between May 2014 and September 2019 were abstracted from medical records of the Department of Surgery of Fujian Cancer Hospital, Fuzhou, China. Patients who were diagnosed with postoperative bleeding at the discharge diagnosis and met the definition of postoperative bleeding were included. A total gastrectomy or a distal or proximal subtotal gastrectomy with regional lymph node dissection (D1+ or D2) was performed according to the 4<sup>th</sup> edition Japanese Stomach Cancer Treatment Guidelines. Gastrointestinal surgeons with sufficient experience in gastrectomy and D2 lymphadenectomy performed or supervised all of the operations. The tumor stages of GC were classified according to the 8<sup>th</sup> edition Tumor Node Metastasis (TNM) classification of the Union for International Cancer Control (UICC). Mortality was calculated based on the patient's survival status at the time of discharge. Patients who underwent exploratory laparotomy, bypass surgery, invasion of the adjacent organs, distant metastasis, or gastric stump carcinoma, and those with incomplete or missing medical records were not included in this study. All participants gave informed consent before taking part. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Fujian Cancer Hospital (No. K2022-209-01).

#### Variables and definitions

Postoperative hemorrhage was defined as bleeding with a hemoglobin level decrease of more than 20 g/L within 24 hours. The diagnostic procedures of PH were considered as follows: clinical manifestation, blood routine, blood pressure measurement, bedside ultrasonography, abdominocentesis, or angiography and so on. Based on its origin, the bleeding was classified as either intra-intestinal bleeding and extra-intestinal bleeding. intra-intestinal bleeding was diagnosed according to its symptoms, such as melena, hematemesis, or hematochezia, with a drop

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Characteristics	Total (n, %)	Intra-Intestinal, n	Extra-Intestinal, n	P value
Sex				
Male	67 (78.8)	35	32	0.052
Female	18 (21.2)	11	7	
Age (years), mean ± SD	59.09±10.7	58.07±11.67	60.31±9.50	0.340
Previous abdominal operation	16 (18.8)	10	6	0.327
Neoadjuvant chemotherapy	20 (23.5)	10	10	0.673
Surgical approach method				
Open	39 (45.9)	20	19	0.629
Laparoscopic	46 (54.1)	26	20	
Primary operation				
STG	27 (31.8)	17	10	0.264
TG	58 (68.2)	29	29	
Extent of lymphadenectomy				
D1	9 (10.6)	1	8	0.019
D2	38 (44.7)	21	17	
D2+	38 (44.7)	24	14	
Combined resection	5 (5.9)	2	3	0.516
TNM stage				
I	19 (22.4)	10	9	0.205
II	23 (27.1)	15	8	
III	37 (43.5)	20	17	
IV	6 (7.1)	1	5	

Table 1 Baseline of postoperative hemorrhage after radical gastrectomy

SD, standard deviation; STG, subtotal gastrectomy; TG, total gastrectomy; TNM, tumor node metastasis.

in hemoglobin levels ( $\geq 2 \mod/dL$  in 24 h), or based on endoscopic findings. Extra-intestinal bleeding was diagnosed by a bloody abdominal drain or abdominal distension, with radiological findings and a drop in hemoglobin. Also, based on the occurrence of bleeding on the day after the operation, it can be divided into early [postoperative days (POD)  $\leq 6$  d] and delayed (POD  $\geq 7$  d) bleeding.

## Statistical analysis

The Statistical Package for Social Science (SPSS) version 26.0 for Windows (IBM, Chicago, IL, USA) was used for all statistical analyses. Most of the analyses are descriptive. The results were expressed as percentages or as the mean ±

standard deviation (SD). Univariate analysis was performed using the chi-square test or Fisher's exact test to determine the associations between the variables and bleeding complications. All tests were two sided, with a priori significance level set at P<0.05.

## **Results**

## Basic characteristics of patients

A total of 2,978 patients underwent radical gastrectomy, and 85 patients (2.85%) suffered postoperative bleeding. The clinical characteristics of these 85 patients are summarized in *Table 1*. There were 67 men and 18 women, and four patients died, with a bleeding-related mortality rate of 4.7%.

## Journal of Gastrointestinal Oncology, Vol 14, No 1 February 2023

Table 2 Demographics	clinical characteristics	and outcome	between intra-intestinal	and e	extra_intestinal	orouns
Table 2 Demographics,	cinincal citaracteristics.	, and outcome	Detween mua-miesunai	anu	extra-intestinal	groups

Variables	Intra-intestinal (n=46)	Extra-intestinal (n=39)	P value
Onset time (days), n (%)			
EPH (POD ≤6)	42 (91.30)	21 (53.85)	<0.001
DPH (POD ≥7)	4 (8.70)	18 (46.15)	
Hb drop (mg/dL), mean $\pm$ SD	46.5±18.8	46.0±19.4	0.831
Bleeding site, n (%)			
Anastomosis	46 (100.00)	3 (7.69)	
Artery	0	32 (82.05)	
Unknown	0	4 (10.26)	
Abdominal infection, n (%)			0.001
Yes	6 (13.04)	19 (48.72)	
No	40 (86.96)	20 (51.28)	
Anastomotic fistula, n (%)			
Yes	2 (4.35)	12 (30.77)	0.002
No	44 (95.65)	27 (69.23)	
Confirmative diagnostic tools, n (%)			
Clinical symptoms	36 (78.26)	14 (35.90)	
Endoscopy	3 (6.52)	0	
Angiography	0	4 (10.26)	
СТ	4 (8.70)	15 (38.46)	
Ultrasonography	3 (6.52)	6 (15.38)	
Therapeutic approach, n (%)			
Conservative	34 (73.91)	9 (23.08)	
Endoscopic intervention	3 (6.52)	0	
Radiologic intervention	0	4 (10.26)	
Laparotomy	9 (19.57)	26 (66.67)	<0.001
Bleeding-related mortality	1 (2.17)	3 (7.69)	0.329

EPH, early postoperative hemorrhage; DPH, delayed postoperative hemorrhage; POD, postoperative day; Hb, haemoglobin; SD, standard deviation; CT, computerized tomography.

## Clinical characteristics of intra-intestinal and extraintestinal hemorrhages

*Table 2* summarizes the clinical manifestations and characteristics of intra-intestinal and extra-intestinal hemorrhages. There were 46 cases of intra-intestinal hemorrhage and 39 cases of extra-intestinal hemorrhage. All cases of intra-intestinal bleeding were anastomotic

bleeding, and 32 cases (32/39) of extra-intestinal bleeding were arterial bleeding. The incidence of intraperitoneal infection and anastomotic leakage in the intra-intestinal bleeding group was higher than that in the extra-intestinal bleeding group (48.72% vs. 13.04%, P=0.001; 30.77% vs. 4.35%, P=0.002). Also, 78.26% (36/46) of intra-intestinal hemorrhage cases were diagnosed by clinical symptoms; 8.70% (4/46) were diagnosed by computerized tomography



**Figure 1** Comparison of the number of patients with intraintestinal and extra-intestinal bleeding between the EPH and DPH groups. EPH, early postoperative hemorrhage; DPH, delayed postoperative hemorrhage.

Table 3 Treatment and outcomes in delayed extra-intestinalbleeding between the TAE and surgery groups

urgery (n=11)	TAE (n=4)
8 (72.73)	1 (25.00)
7 (63.64)	2 (50.00)
7 (63.64)	2 (50.00)
3 (27.27)	0
	urgery (n=11) 8 (72.73) 7 (63.64) 7 (63.64) 3 (27.27)

TAE, transcatheter arterial embolization.



**Figure 2** Comparison of the treatment between intra-intestinal and extra-intestinal hemorrhages. PH, postoperative hemorrhage; TAE, transcatheter arterial embolization.

(CT), and 6.52% (3/46) were diagnosed by B-ultrasound. As for extra-intestinal hemorrhage, 35.90% (14/39) of cases were diagnosed by clinical manifestations, 38.46% (15/39) were diagnosed by CT, and 10.26% (4/39) were diagnosed by angiography, 15.38% (6/39) were diagnosed by B-ultrasound.

## Occurrence time of intra-intestinal and extra-intestinal bleeding

*Figure 1* summarizes the differences in the timing of intraintestinal and extra-intestinal bleeding. The incidence of delayed bleeding in the external bleeding group was higher than that in the internal bleeding group (46.15% *vs.* 8.70%, P<0.001). The bleeding time of intra-intestinal hemorrhage was 3 days, while that of external bleeding was 6 days.

# Comparison of the delayed bleeding reoperation and transcatheter arterial embolization (TAE) groups

*Table 3* summarizes the clinical characteristics of the delayed bleeding reoperation and TAE groups. A total of 11 patients underwent reoperation to stop the bleeding. In the reoperation group, eight patients had hemodynamic instability, eight had an abdominal infection, and three patients died of bleeding-related complications. Moreover, a total of four patients underwent TAE hemostasis, all of whom were hemodynamically stable, and two of them had an abdominal infection, both of which were successfully hemostatic.

## Differences in the treatment methods between intraintestinal and extra-intestinal bemorrhages

Figure 2 summarizes the treatment of intra-intestinal and extra-intestinal bleeding. Patients with external bleeding were more likely to undergo reoperation for hemostasis than those with internal bleeding (66.67% vs. 19.57%, P<0.001). Thirty-four patients (34/46) with intra-intestinal hemorrhage were treated conservatively, and one patient died of multiple organ failure. Furthermore, eight patients (8/46) with intra-intestinal hemorrhage underwent endoscopy first, of which three patients were successfully hemostatic under endoscopy, and five patients were successfully hemostatic due to the inability of endoscopy to explore the bleeding site. Additionally, four patients with intra-intestinal hemorrhage were directly treated with exploratory laparotomy for hemostasis, and the hemostasis was successful. Among the patients with extra-intestinal bleeding, 26 (26/39) patients chose re-laparotomy as the first choice for hemostasis, and three patients died due to bleeding-related complications. Nine patients (9/39) were treated conservatively, and four patients (4/39) underwent interventional embolization and achieved successful hemostasis.

#### Discussion

In this study, we found that the incidence of postoperative bleeding in GC patients was 2.85%, intra-intestinal hemorrhage occurred mostly in the early postoperative period, and the success rate of conservative treatment was high. In total, 34 cases (34/46) of early intra-intestinal hemorrhage were treated conservatively, and one patient died. Intravenous bleeding was typically caused by the failure of blood vessels at the broken end of the digestive tract to close or reopen effectively, resulting in blood flowing into the digestive tract, which is clinically manifested as hematemesis or nasogastric tube drainage of fresh blood. Despite the obvious decrease in hemoglobin, the hemodynamics of patients are generally stable, and thus, the success rate of conservative treatment is high (8). In addition, with intravenous bleeding, the pressure in the intestinal cavity increases rapidly, which can also play a role in local compression and hemostasis. Conservative treatments, such as intravenous supplementation of clotting factors, hemostatic drugs, infusion of blood products, and close observation, are usually successful in stopping bleeding. If the amount of bleeding is large and the hemodynamic is unstable, it is necessary to actively stop the bleeding through endoscopy or surgery (9). Previous studies have reported the effectiveness of hemostasis under endoscopy using a hemostatic clip, heater coagulation hemostasis, epinephrine, and other means (4,10). However, endoscopy for early intra-intestinal bleeding usually involves the risk of anastomotic complications, and accurately determining the bleeding site under endoscopy may not be feasible. In this study, eight cases of early intra-intestinal hemorrhage underwent endoscopic examination, among which three cases were successfully hemostasis. Also, a large number of blood clots in the intestinal cavities were visible under endoscopy in five patients; however, observing the bleeding site was not possible in these cases, so they chose to perform abdominal exploration again for hemostasis, and all of them successfully achieved hemostasis.

Extra-intestinal bleeding after radical gastrectomy represents the most severe hemorrhage, manifesting as abdominal arterial bleeding or external anastomotic bleeding (or both). Compared with intra-intestinal bleeding, early extra-luminal bleeding is usually characterized by more significant bleeding, more unstable hemodynamics, a higher probability of reoperation, and higher mortality. Most of the extra-luminal bleeding is arterial, and thus, it is difficult to stop the bleeding by conservative treatment. Furthermore, the abdominal cavity space is larger, making it difficult to limit the hematoma. Persistent bleeding from the abdomen is ultimately managed with surgery or TAE.

In this study, 32 patients (32/39) with extra-intestinal blood were cases of arterial bleeding. In addition, for patients with delayed hemorrhage, the proportion of extraintestinal blood was very high, with 18 cases (18/22) of delayed hemorrhage being extra-intestinal bleeding. The possible reasons for this are as follows: (I) during radical gastrectomy, to perform a thorough lymph node dissection, the surgeon usually performs "vascular skeletonization", which may damage the vascular outer membrane of the artery and cause postoperative arterial bleeding; (II) in cases where there is a postoperative digestive tract fistula, the leakage of intestinal fluid, pancreatic fluid, and/or bile corrodes the artery wall and causes bleeding; and (III) abdominal infection can also cause damage to the artery wall, and may also damage the anastomosis and form an anastomotic fistula, further damaging the artery membrane and causing bleeding. The most common incidence time of anastomotic fistula is about 1 week postoperatively, and it also takes some time for bleeding caused by digestive fluid or abdominal infection to corrode the artery, which may be a possible reason why bleeding in the delayed period is usually extra-intestinal bleeding. When extra-intestinal bleeding occurs, clinicians prefer to stop bleeding with reoperation or TAE, as compared to intravenous bleeding. In this study, 26 cases (26/39) of extra-intestinal bleeding were stopped by re-operation, and three patients died.

Early-onset extra-intestinal bleeding is caused by technical failure (11). Re-operation is currently recognized as a method for exact hemostasis. In the present study, early and late extra-intestinal bleeding occurred in 25 cases and reoperation was performed in 15 cases. In these cases, the vital signs deteriorated rapidly and there was obvious intraabdominal bleeding, which usually required emergency relaparotomy to control the success of the bleeding. Only one patient was successfully treated by TAE because of a ruptured pseudoaneurysm on the 6<sup>th</sup> day postoperatively.

Arterial erosion, and potential arterial wall injury during lymph node dissection are the two main reasons for the delayed extra-intestinal bleeding (11,12). The erosion of arterial vessels resulting from intra-abdominal contamination of enteric, pancreatic, and/or bile juice from a leaking anastomosis can cause DPH and lead to pseudoaneurysm, which, in turn, can rupture and lead to delayed extra-intestinal bleeding (13). As for delayed extra-intestinal bleeding, the choice of re-operation or TAE is still controversial. Encouraging results have been reported after TAE, which is an effective, stand-alone treatment modality for achieving hemostasis in patients with pseudoaneurysms, with a reported success rate of between 79% and 83% (5,14). TAE has certain advantages for bleeding caused by pseudoaneurysms. The key to the success of TAE treatment is to locate the responsible vessel and embolize it quickly and effectively. Since there is a wide range of communicating branches in the celiac artery system, embolization should be carried out not only at the proximal end but also at the distal end if necessary. Even after effective embolization, some patients will bleed again and require interventional embolization. Yang et al. compared the safety and efficacy of TAE and re-laparotomy in the treatment of delayed bleeding. The re-bleeding rate in the TAE group was higher than that in the re-operation group (36.48% vs. 25.0%) (15). Not all delayed extraintestinal bleeding is caused by a ruptured pseudoaneurysm. Park et al. showed that TAE has no obvious advantage over re-operation for extra-intestinal bleeding caused by non-aneurysms (3). TAE has certain risks for patients with splenic artery bleeding after subtotal gastrectomy. Perfusion of the remnant stomach through the short gastric artery is very important. Complete embolization of the spleen trunk will significantly affect the blood supply of the remnant stomach and spleen. In the study of Han et al., there were two cases of remnant stomach or spleen infarction caused by splenic artery embolization, resulting in death (5).

On the other hand, delayed extra-intestinal bleeding is usually complex bleeding, and most cases are associated with an anastomotic fistula. Pancreatic studies have also confirmed that 100% of patients with complex postoperative bleeding have a pancreatic fistula (11). According to previous reports, 42% of GC patients with delayed postoperative bleeding had a pre-abdominal infection, and 62% were confirmed to have anastomotic or pancreatic leakage (3). This is consistent with the results of our study, in which eight cases (8/13) of delayed extra-intestinal bleeding were confirmed to have an anastomotic fistula or abdominal infection before bleeding. Even if interventional embolization is successful, the abdominal infection cannot be resolved. Re-operation can stop the bleeding, remove the abdominal abscess, and close the fistula, thereby reducing the inflammatory stimulation and digestive juice corrosion of blood vessels, which prevents the occurrence of recurrent bleeding. The difficulty of re-operation lies in abdominal adhesion, which cannot correctly locate the bleeding point, and thus, care must be taken in the second operation to

avoid damage to abdominal organs, and retention of the jejunostomy tube can be considered for postoperative nutritional support.

Finally, patients who suffer delayed extra-intestinal bleeding are usually sent to the intensive care unit (ICU) for further monitoring and treatment. In our hospital, the location of the radiology department is not in the same building as the surgical operating rooms; therefore, if interventional embolization is to be performed, it takes a long time to transport patients to the radiology department. Also, the radiology department does not possess complete resuscitation and intubation equipment. If the intervention fails, it may be too late to send the patient back to the operating room for a second operation. Therefore, surgeons are usually reluctant to send a patient with hemodynamic instability to the radiology department.

In this study, hemodynamic instability was observed in 72.73% (8/11) of patients in the re-operation group for delayed hemorrhage and 25% (1/4) of patients in the TAE group. Patients with delayed extra-intestinal hemorrhage are more often treated with re-operation, and therefore, patients with delayed extra-intestinal bleeding included in this study were more likely to undergo surgery. Ideally, if there is interventional radiation equipment in the surgical operating room as well as the full support of an anesthesiologist, interventional embolization can be used as a first-line treatment. In this situation, if this intervention fails, the next operation can be carried out immediately, and if the condition of interventional embolization is not sufficient, timely open hemostasis is an effective means to save the patient's life.

In this study, TAE intervention was performed in fewer cases, and statistical analysis could not be performed between the re-operation and TAE groups. The choice of intervention approach for postoperative bleeding in GC requires more large-scale studies. In this study, no statistical analysis was performed on the coagulation function of patients, because a large number of patients would have been transfused with plasma after surgery, which would affect the coagulation function indicators. Therefore, further studies are needed to confirm whether abnormal coagulation function is a risk factor for postoperative bleeding.

## Conclusions

Bleeding after GC surgery is an infrequent complication that requires effective management. Compared with

## Journal of Gastrointestinal Oncology, Vol 14, No 1 February 2023

intra-intestinal hemorrhage, the clinical situation is more complicated and the re-operation rate is higher in patients with extra-intestinal hemorrhage. TAE is a safe and effective method if the hemodynamics is stable.

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### Footnote

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*Ethical Statement:* The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All participants gave informed consent before taking part. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethics Committee of Fujian Cancer Hospital (No. K2022-209-01).

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## 118

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