Prognostic factor affecting outcomes in patients with malignant gastrointestinal bleeding treated with a novel endoscopically-delivered hemostatic powder

Rapat Pittayanon

Experimental Surgery, Department of Surgery,

McGill University, Montreal

August 2017

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of Master of Science

Table of Contents

Pages

1. Abstract…….. 3-7
2. Acknowledgements…….. 8
3. Preface and Contributions of authors…….. . 9
4. Introduction……... 10
5. Background and review of relavent literature…….... 10-15
6. Objective and Rationale……15
7. Methods……..16-19
8. Results……19-22
9. Discussion……..23-25
10. Conclusion……..26
11. Summary…….26
12. References…….27-30
13. Figures……31-33
14. Tables……34-48

Prognostic factor affecting outcomes in patients with malignant gastrointestinal bleeding treated with a novel endoscopically-delivered hemostatic powder

Abstract

Background and study aim: The effectiveness of endoscopic hemostatic technique for gastrointestinal (GI) tumor bleeding remains poor. HemosprayTM appears useful in many active GI bleeding etiologies, including tumor bleeding. This study aims to define factors predicting decreased rebleeding and improved six-month survival in affected patients.

Materials and Methods: This is a retrospective study. Ninety-nine patients with active GI bleeding from primary or metastatic tumors to the digestive tract and treated with HemosprayTM were enrolled. Eleven patients were excluded because of incomplete data. Appropriate data on patient characteristics and possible predictive factors of 72-hour, 7, 14 and 30-day re-bleeding rates, as well as six-month survival were assessed.

Results: The majority of patients were male (62/88; 70.5%) with a mean age at 65 ±14 years. Half of patients (43/88) had high ECOG performance status (score 3 or 4). An upper GI cancer was found in nearly 60 percent (50/88), followed by hepatobiliary cancers invading the upper GI tract (17/88; 19%), distant metastases to the upper GI tract (12/88; 14%), and lower GI cancers (9/88;10%). Three-fourths of patients' cancers (64/88) were stage 4, with an overall 55% (48/88) six-month survival. Immediate hemostasis by using HemospayTM was achieved in 97.7% of patients with malignant active GI bleeding. Early (<72 hr) and delayed (7, 14 and 30 days) rebleeding were noted in 13 of 86 (15%) and 11 of 63 (17%) patients, respectively. In univariable

analysis, INR >1.3(38% vs.11%) was significantly associated with early re-bleeding, while an ECOG 3-4 (30% vs. 10%) and not receiving definite hemostatic treatment (39% vs. 9%) were with delayed rebleeding. Comorbidity with another type of cancer vs. no comorbidity (28.6%vs.58.6%), a low ECOG score 0-2 vs. 3-4 (91.1%vs.16.3%), primary upper and lower GI cancer/lymphoma vs. distant metastases to the upper GI tract (62% and 77.8%, respectively vs.25%), disease staging 1-3 vs. 4 (87.5% vs. 42.2%), and receiving definite hemostatic treatment vs. none (82.7% vs. 13.9%) were all significantly predictive of six-month survival. In multivariable analysis, receiving definite hemostastic treatment with any combination of surgery/chemotherapy/ radiotherapy/ embolization was the only significant predictor of delayed rebleeding (p=0.04, OR=0.06, 95%CI 0.01-0.84) and of six-month survival (p=0.002, HR=0.21, 95%CI 0.08-0.57) after adjusting for comorbidity, performance status, type of cancer bleeding and cancer stage.

Conclusions: HemosprayTM is a promising therapy for the initial hemostasis of tumoral GI bleeding as it can stop bleeding acutely in a great majority of cases, and appears to do so for at least the first few days. Definite hemostatic treatment with any combination of modalities is the sole identified independent predictor of delayed rebleeding and six-month survival, regardless of performance status or other patient-dependent variables such as cancer type and staging.

Keywords : Hemospray; GI bleeding; Tumor; predicting factors

Facteurs pronostics influencant le devenir des patients avec une hemorragie digestive maligne ayant ete traites avec une nouvelle poudre hemostatique appliquee par voie ndoscopique

Abstract

Toile de fond et objectifs: L'efficacité des méthodes endoscopiques hémostatiques pour saignements malins demeure limitée. L'Hemospray® apparait utile pour les saignements digestifs de maintes étiologies, y compris les causes malignes. Cette étude a pour objectif de définir les facteurs prédisant une diminution des taux de resaignement et une amélioration de la survie à 6 mois.

Méthodes: Cette étude rétrospective comprend 99 patients présentant une hémorragie digestive active due à une tumeur primaire ou métastatique ayant été traités par Hemospray®. Onze patients furent exclus pour cause de données manquantes. Nous avons évalué les données pertinentes des caractéristiques de patients et facteurs prédisant les resaignements à72 heures, 7, 14, et 30 jours ainsi que les taux de survie à 6 mois.

Résultats: La majorité des patients étaient males (62/88; 70.5%) avec un âge moyen de 65 ±14 ans. La moitié des patients (43/88) présentaient un indice ECOG de performance élevé (scores 3 ou 4). Un cancer du tractus digestif supérieur a été noté chez presque 60 pourcent (50/88) des patients, suivi d'un cancer hepatobiliaire affectant le tractus digestif supérieur (17/88; 19%), des métastases distantes affectant le tractus digestif supérieur (12/88; 14%), et de cancers digestifs des voies basses

(9/88;10%). Trois-quarts des cancers (64/88) étaient de stade 4, avec une survie globale de 55% (48/88) à 6 mois. Une hémostase immédiate fut notée avec l' Hemospray® chez 97.7%. Des resaignements précoces (<72 hres) ou à retardement (7, 14 et 30 jours) furent notés chez 13 de 86 (15%) et 11 de 63 (17%) patients, respectivement. En analyse univariée, l'INR >1.3 (38% vs.11%) était significativement associé à un resaignement précoce alors qu'un score ECOG 3-4 (30% vs. 10%) et l'absence de traitement hémostatique subséquent (39% vs. 9%) l'étaient avec les saignements à retardement. Une comorbidité d'un autre cancer vs. aucune (28.6%vs.58.6%), un score ECOG bas 0-2 vs. 3-4 (91.1% vs.16.3%), une tumeur primaire des tractus digestifs hauts et bas/lymphomes vs. métastases distantes au tractus digestif supérieur (62% and 77.8%, respectivement vs. 25%), stade de cancer 1-3 vs. 4 (87.5% vs. 42.2%), et recevoir un traitement hémostatique définitif vs. aucun (82.7% vs. 13.9%) tous prédirent la survie à 6 mois de façon significative. En analyse multivariée, un traitement hémostatique définitif avec toute combinaison de chirurgie/chimiothérapie/radiothérapie/embolisation était le seul facteur prédictif significatif d'un saignement à retardement (p=0.04, OR=0.06, 95%IC 0.01-0.84) et de survie a 6 mois (p=0.002, HR=0.21, 95%IC 0.08-0.57) après ajustement pour comorbidité, score de performance, type de cancer hémorragique et stade de cancer.

Conclusions: L'HemosprayTM est une thérapie prometteuse pour l'hémostase initiale de tumeurs digestives hémorragiques car ce produit permet de mettre fin au saignement en phase aigüe chez la majorité des patients, et semble accomplir ceci pour les quelques premiers jours. Un traitement hémostatique définitif avec toute combinaison de modalités est le seul facteur prédictif d'un resaignement à retardement

et de survie à 6 mois, indépendamment du stage de performance ou de toute autre caractéristique démographique, y compris le type et le stade du cancer.

Acknowledgements

This research is based on the data from two countries, Canada and Thailand. I would like to pay special thankfulness, warmth and appreciation to the persons below who made my research successful and assisted me at every point to accomplish my goal;

In Montreal, Canada;

My Supervisor, Professor Alan Barkun for his vital support and assistance. His practical and prompt suggestions made it possible to achieve the goal.

Dr.Dan Deckelbaum for providing the great opportunity in Experimental Surgery program.

Mrs. Myrian Martel, whose good advice made me to meet the deadlines.

All nurses and staff members at Endoscopic suites of Montreal General Hospital, whose their services turned my research a success.

In Bangkok, Thailand;

My first mentor in novel endoscopic treatment research, Professor Rungsun Rerknimitr for his motivation and encouragement.

All the faculty, fellows, nurses and staff members of Division of Gastroenterology, Chulalongkorn University and King Chulalongkorn Memorial Hospital the Thai Red Cross, without whom it was impossible to accomplish the end task.

Finally, my family, for the support and truly love. They all kept me going, and this research would not have been possible without them.

Preface and Contributions of authors

All authors have contributed to and agreed on the content of the manuscript. The respective roles of each author are the followings;

1. **Rapat Pittayanon:** Write the proposal, submit the proposal to the Institutional Review Board and/or its delegate sites in Canada, the Chulalongkorn University Institutional Review Board and ClinicalTrials.gov, collect the data, analyze the data, select the articles, write up the manuscript
2. **Alan Barkun:** Facilitate the study, help select the articles, assist revision of the manuscript and final approval.

The content of the manuscript is original and has not been published previously, in any language, in whole or in part, and is not currently under consideration elsewhere.

Prognostic factor affecting outcomes in patients with malignant gastrointestinal bleeding treated with a novel endoscopically-delivered hemostatic powder

INTRODUCTION

GI bleeding arising from malignant tumors is currently increasingly recognized as a result of oncological advances and improved detection methods.(1, 2) Either primary GI or metastatic tumors to the GI tract increase the risk of GI bleeding and control of bleeding using conventional hemostatic endoscopic equipments is poor.(2-5) Moreover, the mortality rate is increased if patients develop rebleeding.(6) This study was therefore designed to evaluate the effectiveness of a novel endoscopic hemostatic technique called “HemosprayTM (generic name: Tc-325)” and possible prognostic factors of early and delayed rebleeding as well as six-month survival.

BACKGROUND

Gastrointestinal (GI) bleeding is the most common cause of hospitalization in the United State.(7)The majority of GI bleeding is from non-cancerous etiology; in contrast, cancerous lesions are an uncommon cause of upper GI bleeding.(2, 8-10) For instance, peptic ulcer and diverticular etiologies represent the most common causes of upper and lower GI bleeding, respectively.(8-10) In 1980, a retrospective review of upper GI bleeding in 55 patients with primary or metastatic GI malignancy revealed that only 20% were related to tumor invasion of the GI lume causing bleeding.(11) Nevertheless, Malignant tumor bleeding in the GI tract is currently increasingly recognized because of

the advancement in oncological detection and treatment(1, 2) Moreover, malignant tumor bleeding exhibits unique physiological features as haemorrhage incurs in part owing to progressive local vessel damage from direct invasion as well as from friable mucosa of the tumor itself,(2, 12) which makes the lesions not suitable for conventional endoscopic treatment. This realization explains the failure of both immediate and long-term hemostatic control using standard conventional endoscopic modalities. (2-4) In addition, the mortality rate of these patients is high after rebleeding. For example, the median survival rate dropsfrom 45% to 15% and 35% if patients experience early (<72hr) and delayed (≥ 72hr) rebleeding, respectively. (6)

Conventional endoscopic hemostatic methods include injection (dilute epinephrine, mixed with sclerosant agent or *N*-butyl-2-cyanoacrylate), thermal (let it be contact such as electrocautery,heater probe, or non-contact methods such as Argon plasma coagulation(APC)) and mechanical (Clipping or Band ligation) devices.(4) (**Table 1**) Although these standard methods can improve treatment outcomes in both upper and lower GI bleeding(9), the data on their respective hemostatic efficacies in treating GI neoplasms is scarce displaying varying success or poor effectiveness in achieving initial hemostasis, let alone high rebleeding rates.(12, 13)

In non-cancerous bleeding, standard conventional endoscopic hemostatic techniques play a major role for bleeding control.(7)Serious rebleeding is high, up to 60%, if patients with peptic ulcer bleeding do not undergo endoscopic treatment.(9, 14) The effectiveness of these conventional endoscopic modalities in upper GI bleeding from ulcer is good in experienceed hands, providing significant reductions in further

bleeding.(7, 15) For non-ulcer, non-cancerous GI bleeding such as Mallory-Weiss tear(MWT), a linear mucosal laceration of the distal esophagus often including the gastroesophageal junction and upper part of the stomach(16) due to vomiting or retching.(17), endoscopic band ligation and hemoclip placement have proven to be highly effective therapies for MWT.(18) In addition, endoscopic hemostasis appears to also be effective in lower GI bleeding from non-cancerous etiologies.(5)

Physiological and mechanical abnormalities that are associated with bleeding tumors include hematological derangements such as thrombocytopenia, local disseminated intravascular coagulation, and neutropenia,(2) as well as the endoscopic manipulation of friable, diffusely bleeding surfaces when attempting hemostasis.(12) For instance, the heat from thermal devices can cause further tumor surface necrosis, resulting in further recurrent tumor bleeding.(12) In addition, malignant tumor bleeding is usually diffuse without a specific bleeding point or obvious visible vessel that the endoscopist can target with standard equipment.(4) (**Figure 1**)

The natural history of malignant GI bleeding is different from that of other causes such as ulcers as well as other non-malignant etiologies. Compared to peptic ulcer bleeding, rates of rebleeding, surgery, and mortality are much higher in patients with malignant bleeding.(1) As a result additional therapeutic modalities are often required, including chemotherapy, radiation, embolization or surgery to control bleeding.(19) Moreover, mortality rates are high(1, 6, 20), which implies that it is a “pre-terminal” stage.

For instance, one study in 1996 revealed the rebleeding rate in patients with malignant upper GI bleeding was no different whether they were treated with heater probe or nothing.(21) Another study subsequently described using APC in 5 patients to control the bleeding from advanced gastric cancer with complete hemostasis achieved in only 60%.(22) A recent 2013 study reported 92% initial hemostasis using various conventional endoscopic techniques in unresectable gastric cancer bleeding; however, in this series, one-fifth of bleeding sources were non-bleeding visible vessels- a finding associated witha good outcome when treated with conventional endoscopic treatment, similar to a peptic ulcer etiology. Nevertheless, the authors concluded that early and delayed rebleeding rates remained high to 44% and 56%, respectively.(6) The effectiveness of mechanical hemostasis techniques was demonstrated in a case report describing the use of hemoclips in non-bleeding visible vessels present on a gastrointestinal stromal tumors (GISTs).(23) Overall, however, there is still a lack of good evidence to support the advantage of mechanical techniques when approaching GI tumor bleeding.

It therefore, appears that malignant tumor bleeding is not easily amenable or responsive to conventional endoscopic therapy.(4, 12) According to available information, the success rate of immediate hemostasis could be as low as 40% while the re-bleeding rate rises to 56% within one month after treatment.(1, 2, 4, 6) Moreover, ninety-five percent of those patients died within three months.(20)

Currently, endoscopy is used only for identifying the bleeding site. On the other hand, other recognized single or multimodality treatment approaches such as surgery,

interventional angiography and embolization, or radiotherapy can provide better immediate hemostatic rates, approximating 50-100% with acceptable re-bleeding rates at 0-36%.(24, 25) Nevertheless, rebleeding rate and mortality rates are high if treatment is performed in an emergency setting, especially with surgery.(26) Therefore, resuscitation and stabilization of these patients are essential before providing the patients with more definitive targeted treatment options.

Methods providing at least temporary arrest of bleeding prior to more definitive hemostasis are thus favoured. A novel hemostatic powder called Hemospray or TC-325 (Cook Medical,Winston-Salem, North Carolina, USA), which contains 20 gram of nano-power per treatment cartridge, is an endoscopic hemostatis powder that was recently commercialized. (**Figure 2**) It is comprised of an inorganic, non-absorbable powder which acts locally at the mucosa. When spraying the powder on to the bleeding site, it creates an adherent stable barrier sheath that allows for at least temporary hemostasis during its residency time which is about 12-24 hours.(27) (**Figure 3**) Neither luminal nor systemic side effects have been reported to date.(13, 27, 28)

Recently, European guidelines recommended using HemosprayTM as rescue treatment of any causesof upper GI bleeding, even in the absence of high-quality evidence.(8) This powder has the potential for providing effective hemostasis in patients with active upper GI bleeding from tumors as it is a non contact method that does not cause tissue injury; however, at this time, rebleeding and mortality rates have been shown to be not different from other treatments, even when matching for age-groups and site of tumor.(12) Consequently, we hypothesize that there exist as yet undefined

prognostic factors such as age, tumor size, type of malignancy, tumor staging, performance of patients related to the outcome of HemosprayTM treatment in tumor bleeding that may assist in opimal patient section for this promising modality.

OBJECTIVE AND RATIONALE

Primary objective: This study aims to identify prognostic factors of favorable outcomes in patients presenting with upper GI bleeding from tumors, who have received endoscopic application of HemosprayTM for hemostatic control. The outcomes that will be assessed include immediate hemostasis, no rebleeding at 72 hours as well as 7, 14 and 30 days following presentation.

Secondary objective: To indicate the associated factor of six-month survival in patients presenting with upper GI bleeding from tumors and treated with HemosprayTM.

Rationale and justification of the choice of outcomes: Immediate hemostasis is the benchmark by which efficacy attributable to different hemostatic methods is measured. Seventy-two hours is the usual window of time at which hemostasis is assessed following initial endoscopic treatment with or without subsequent additional therapy such as radiation, based on experience in ulcer bleeding. Moreover, 7, 14 and 30-day rebleeding rates are also standard times for measurement of hemostatic outcomes in patients with upper GI bleeding. A six-month survival rate allows the determination of any survival benefit in this patient population with a limited life expectancy.

METHODS

Study population, inclusion & exclusion criteria and methodology

We conducted a multi-centre retrospective study where cases were defined as patients who unequivocally bled as a result of a malignant etiology which could be either a primary GI tumor or metastases to the upper or lower GI tract with no other source of bleeding identified on endoscopy. Cases were treated at the McGill University Health Centre in Montreal, Canada (MUHC; Royal Victoria Hospital - RVH and Montreal General Hospital - MGH sites) and King Chulalongkorn Memorial Hospital (KCMH), Chulalongkorn University, Bangkok, Thailand. Eligible cases were selected using standardized search protocols: formal computer searches were performed to identify all patients seen in the emergency room and/or hospitalized for malignant gastrointestinal haemorrhage from 2011 to 2016. The only exclusion criterion was age < 18 years.

All possible factors associated with the outcome of immediate hemostasis, as well as early (72 hour) and delayed (7,14 and 30 days) rebleeding, and mortality were collected including gender, age, co-morbid illnesses, performance status (Eastern Cooperative Oncology Group; ECOG score), history of antiplatelet/anticoagulant/ NSAIDs, Blatchford score (severity score of upper GI bleeding which is assessed before endoscopy), type of malignancy and its stage, size of tumor, amount of blood transfusion, the presence of coagulopathy (platelet < 100,000 or INR > 1.3), bleeding stigmata on endoscopic findings, number of re-treatments with HemosprayTM, number of subsequent additional therapies required for hemostatic purposes including surgery, adjuvant embolization, chemotherapy and radiotherapy (definite hemostatic treatments)

as well as when these were performed, and length of hospital stay (LOS). These variables were obtained through manual chart review and abstracted by one author (RP).

Immediate hemostasis is defined as no further bleeding at least one minute after applying adequate amount of HemosprayTM powder. Rebleeding from the GI tract was suspected if one or more of the following criteria are fulfilled(29);

1. Hematemesis or bloody NG > 6 h after endoscopy (upper)
2. Melena after normalization of stool color
3. Hematochezia after normalization of stool color or melena
4. Development of tachycardia (HR ≥ 110) or hypotension(SBP ≤ 90) after ≥ 1 h of vital sign stability without other cause
5. Hemoglobin drop of ≥ 20 gm / L after two consecutive stable hemoglobin values (defined as within 5 gm / L of each other) ≥ 3 h apart
6. Tachycardia or hypotension that does not resolve within 8 h after index endoscopy despite appropriate resuscitation (in the absence of an alternative explanation), associated with persistent melena or hematochezia
7. Persistently dropping hemoglobin of > 30 gm / L in 24 h associated with persistent melena or hematochezia

Repeat upper or lower GI endoscopy was performed in all cases to confirm the site of haemorrhage was from the malignant site in the upper or lower digestive tract, as

documented on initial endoscopy. The 72-hour and 7, 14 and 30 day-rebleeding rate as well as 6-month survival rate were assessed as outcomes of treatment.

Sample size

Patient volumes with bleeding tumors from the GI tract receiving HemosprayTM have averaged 10-15 cases per year at MUHC sites and 5-10 cases per year in KCMH, Thailand over the past 3 years. From initial estimation, approximately 80 cases could thus be recruited. Indeed, assuming a 40% rebleed rate, this would allow adequate statistical powering to identify up to 4 independent predictors.

Statistical analysis

Baseline descriptive data were analyzed and reported as means and standard deviations for continuous variables, and percentage and frequency for categorical variables. For univariable analysis, continuous variables were compared using the Student's t test, and categorical variables with the chi-square (x^2) test. Multivariable analysis models were created to predict immediate hemostasis, early and delayed rebleeding, and mortality. These were conducted using either a logistic regression model (failure of immediate hemostasis), or Cox regression models and log rank testing to determine the hazard ratios (HR) attributable to the different factors related to 72-hour, 7, 14 and 30-day rebleeding and also 6-month survival rates. SPSS version 23.0 (SPSS (Thailand) Co., Ltd., Bangkok, Thailand) for Windows systems was used with differences considered significant at the 0.05 level.

Confidentiality

This is a chart review method with no direct linking of data to participants. All collected information was anonymized, and data was maintained in a locked personal computer with secured code provided by the first author.

Ethical consideration

This study was conducted according to ethical principles stated in the Declaration of Helsinki (2013). Every precaution was taken to protect the privacy of research subjects and the confidentiality of their personal information.

This study was submitted to the Institutional Review Board and/or its delegate sites in Canada. The Institutional Review Board of Chulalongkorn University, Thailand, had already approved this study for patients in that Institution. In addition, this study was registered and approved by ClinicalTrials.gov (NCT03066700).

RESULTS

There were nighty-nine patients with active tumor bleeding during the study period. Of those, eleven patients were excluded because of incomplete data. Subsequently, there were eighty-eight patients eligible for analysis.

The majority of patients were male (62/88; 70.5%) with mean age at 65 ±14 years. Of those, sixty percent (53/88) were from MUHC, Canada. One-third (29/88; 33%) had no co-morbid illness. Half of patients (43/88; 48.9%) had a performance status (ECOG score) 3 or 4. The history of current antiplatelet/anticoagulant use was

noted in one-fifth of patients (22/88; 25%). The mean Blatchford score was 8.7±3.7 (range from 0 to 18). An upper GI cancer site was noted in the majority, nearly 60 percent (50/88), including 42/88 adenocarcinomas (47.7%), 4/88 squamous cell carcinomas (4.5%), 2/88 gastrointestinal stromal tumors (GISTs) (2.3%) and 2/88 lymphomas (2.3%). Most were in stage 4 (64/88; 72.7%). Less than 30 percent of patient (23/88; 26.1%) presented with low platelets (<100,000/10^9/L) or a prolonged INR (>1.3). The majority of patients (52/88; 59.1%) received subsequent definite therapies for bleeding control within one month after treatment with HemosprayTM (mean±SD and median times of 27.9±33.4 and17 days, respectively). Nearly half (31/64; 48.4%) of patients in stage 4 received one of definitive hemostatic treatments, for instance embolization alone in 7/64(10.9%), embolization plus chemotherapy in 1/64(1.6%), chemotherapy alone in 8/64(12.5%), radiation alone in 7/64(10.9%) and combination treatment with chemotherapy and radiation in 7/64(10.9%). The length of hospital stay was usually under two weeks. One patient (1.1%) needed cardiopulmonary resuscitation (CPR) in the endoscopic suite while using HemosprayTM. (**Table 2**)

In terms of endoscopic findings, almost all of the patients (83/88; 94.3%) presented with Forrest Ib (blood oozing) and were treated with one session of HemosprayTM monotherapy (77/88; 87.5%). In other words, HemosprayTM used as a rescue treatment after failure other hemostasis techniques was applied in a minority of cases (11/88; 12.5%), and this modality provided immediate hemostasis in the great majority of patients.(**Table 3**)

The immediate hemostasis was achieved in almost all of the patients with malignant GI bleeding and treated with HemosprayTM (86/88; 97.7%). Rebleeding rates

at 72 hours, 7, 14 and 30 days were 13/86(15%), 5/71(7%), 5/64(7.8%) and 1/53 (1.9%), respectively. The mean rebleeding time was around one week. More than half of patients (48/88; 54.5%) were alive at 6-months. **(Table 4)**

There were 63 patients available for rebleeding assessment because 25 patients (28.4%) died before the time that we started to assess rebleeding at 72 hours, 7, 14 and 30 days. Two of those died before 72 hours. Mostly, causes of death in these patients were not from GI bleeding. Overall, 24/88 patients (27.3%) rebled within 30 days after receiving HemosprayTM and none were from lower GI cancer/lymphoma. Half of those (13/24; 54.2%) rebled within the first 72 hours (early rebleeding) and all were due to either a primary upper GI cancer or local invasion from a hepatobiliary cancer into the upper GI tract. (**Table 5**)

Despite no evidence of rebleeding during the observation period, additional definite hemostatic treatments including surgery, chemotherapy or radiotherapy performed in 41/62 patients (66.1%). Therefore, 33.9% of patients without rebleeding (21/62) in the first 30 days after getting HemosprayTM treatment did not receive any other hemostatic treatment. (**Table 6**)

In univariable analysis, the International normalized ratio (INR) value > 1.3 was a significant predicting factor of the development of early rebleeding (p=0.02, OR=5.08, 95%CI 1.33-19.33) while performance status (ECOG score) ≥ 3 and not receiving subsequent definite hemostatic treatment were significantly associated with delayed rebleeding. (p=0.049, OR=3.94, 95%CI 1.01-15.38 and p=0.009, OR=0.15, 95%CI 0.04-0.62, respectively). (**Table 7**) In term of 6-month survival, we identified 6 significant

factors, including comorbidity with other cancer, low ECOG at 0-2, primary upper or lower GI cancer/lymphoma, cancer staging 1-3 and receiving definite hemostastic treatment. (**Table 8**) No differences were noted in outcomes between patients from both participating sites (data available upon request). (**Figure 4)**

In multivariable analysis, only receiving definite hemostastic treatment was a significant predictor of delayed rebleeding (p=0.04, OR=0.06, 95%CI 0.01-0.84) and six-month survival (p=0.002, HR=0.21, 95%CI 0.08-0.57) after adjusting for comorbidity, performance status, type of cancer bleeding and its stage. (**Table 9)** The patients who received any combination of definitive hemostatic treatment modalities including surgery, chemotherapy, radiotherapy and embolization, had a significant better survival than the patients who did not receive, regardless of either stage 1-3 or stage 4. **(Figure 5**)

DISCUSSION

To our knowledge, this is the largest study assessing the efficacy of HemosprayTM in active GI bleeding from tumors. This study revealed a near-perfect immediate hemostasis rate of 97.7%, supported other preliminary data(12, 13, 30) that HemosprayTM is a promising endoscopic technique for immediate hemostasis in GI bleeding from tumors in term of either monotherapy or rescue treatment after failure standard hemostatic techniques. Regarding the previous retrospective studies published in 2013, conventional endoscopic hemostastic methods provided immediate hemostasis rates varying from 31% to 93% in active upper GI bleeding from tumors.(1,

6, 31) Therefore, HemosprayTM seems to be more effective in providing initial hemostasis in upper GI tumor bleeding, compared to conventional methods.

However, rebleeding occurred in 13 from 34 (38%) patients who did not get the definite hemostasis treatment within 30 days. This rate is comparable to the rebleeding rate described when using conventional hemostatic techniques (40-50%).(1, 6) It implies that the long-term effect of current available endoscopic modalities is not different and still remains unsatisfactory. In contrast, the usefulness of HemosprayTM in lower GI bleeding from malignancy in term of immediate hemostasis, early and delayed rebleeding was recognized in this study. Indeed, in all eight cases of lower GI adenocarcinomas and one case of lower GI lymphoma immediate bleeding control was achieved, and no rebleeding occurred while scheduling patients for surgery or chemotherapy within the subsequent 30 days. Causes for the differences in rebleeding rates between upper and lower GI tract are unclear may partly be due to the presence of acid in the upper GI tract, which is one of the important mechanisms of rebleeding in upper but not in lower GI tract. From previous studies, the second-look at 24 hour after index HemosprayTM treatment showed no HemosprayTM covering of tumor,(27, 32) thus rebleeding in the upper GI tract can subsequently be affected by acid exposure after disappearance of the powder (even if most of the patients were also put on intravenous proton pump inhibition). In contrast, rebleeding in the lower GI tract principally results from tumor necrosis itself, and gradually developed as an occult blood loss. Avoiding traumatizing the friable tumor surface by using HemosprayTM may be sufficient for preventing overt rebleeding in the lower GI tract. However, additional data from larger sample sizes of patients with lower GI bleeding from tumor are needed.

Although 73% of patients in this study were diagnosed as end-stage cancers, the six-month survival rate of these patients was high at 45.5%. Most of the cancers were adenocarcinomas which, from the previous studies, result in median survivals for stage 4 tumor bleeding of approximately 1-3 months.(6, 21, 33, 34) The high survival rate may results from the greater chance of subsequent definite hemostatic treatment observed in this study (59%). Indeed, any prolonged effect attributable to HemosprayTM is unlikely based on the know methods of action of this compound. But HemosprayTM, by providing more immediate hemostasis, may have provided better bridging to definitive methods of hemostasis. Indeed, even if in end-stage of a malignancy, patient survival could be extended if they remained fit enough for subsequent radiation or chemotherapy.

Coagulopathy (INR value >1.3) was identified as a significant predictor of early rebleeding in univariable analysis. The presence of a coagulopathy is known to cause GI bleeding even in low-risk lesions, explaining the recent guideline by the European Endoscopy Society, recommending keeping INR value <2.5 before performing endoscopy, regardless of the therapy to be performed.(8) However, this factor did not affect delayed rebleeding. Indeed, prognostic factors for delayed rebleeding were a high ECOG score of 3-4 and not undergoing definite hemostatic treatment. Patients with poor performance status are usually in advanced stage of cancer as well as with aggressive tumor behaviour. Consequently, they potentially develop rebleeding easier, compared to patients with good performance status.

Receiving definite hemostatic treatment was the only predictive factor related to non-delayed rebleeding and six-month survival. This study emphasizes the important

realization that HemosprayTM provides only a temporary hemostatic effect to control active GI bleeding from tumors, while other definitive treatments such as chemotherapy, radiotherapy or surgery need to subsequently be considered.(12, 35)

Limitations of this study include its retrospective design. However, malignant tumor bleeding of the GI tract accounts for only 5% of patients hospitalized with overt GI bleeding.(1, 21) Thus, it is difficult to conduct adequately powered randomized control trials among in this patient population. An example of missing data include the amount of blood transfusions administered that ideally should be retrieved and analysed as a surrogated outcome but, unfortunately, this information could not be found in 40% of patients. Despite of this limitation, this study was able to demonstrate at least one independent predicting factor of primary and secondary outcome (delayed rebleeding and six-month survival, respectively), without a need to assess surrogate outcomes. Additionally, this study gathered information from two tertiary care hospitals in North America and Asia, thus there was the possibility that the results may not be generalized to other regions where standard of care may be different. Nevertheless, the value of this study is still evident as its results can be used as guidance for physicians handling patients with GI bleeding from malignancy.

CONCLUSIONS

HemosprayTM is effective at temporarily arresting GI bleeding from tumors. Even in end-stage GI cancers, HemosprayTM results in lower delayed rebleeding rates, allowing for patients to subsequently receive definite hemostatic treatment with improved 6-month survival.

SUMMARY

Receiving definitive hemostatic treatment including surgery, chemotherapy, radiotherapy or embolization, is the only independent prognostic factor affecting delayed rebleeding rate and six-month survival in patients with malignant GI bleeding treated with a novel endoscopically-delivered hemostatic powder (HemosprayTM) that allows effective bridging to then. The study results can be used as guidance for physicians managing patients with malignant GI bleeding, and also future research in this therapeutic area.

REFERENCES

1. Sheibani S, Kim JJ, Chen B, et al. Natural history of acute upper GI bleeding due to tumours: short-term success and long-term recurrence with or without endoscopic therapy. Aliment Pharmacol Ther 2013;38:144-50.
2. Heller SJ, Tokar JL, Nguyen MT, et al. Management of bleeding GI tumors. Gastrointest Endosc 2010;72:817-24.
3. Lightdale CJ, Kurtz RC, Sherlock P, et al. Aggressive endoscopy in critically ill patients with upper gastrointestinal bleeding and cancer. Gastrointest Endosc 1974;20:152-3.
4. Asge Technology C, Conway JD, Adler DG, et al. Endoscopic hemostatic devices. Gastrointest Endosc 2009;69:987-96.
5. Strate LL, Gralnek IM. ACG Clinical Guideline: Management of Patients With Acute Lower Gastrointestinal Bleeding. Am J Gastroenterol 2016;111:755.
6. Kim YI, Choi IJ, Cho SJ, et al. Outcome of endoscopic therapy for cancer bleeding in patients with unresectable gastric cancer. J Gastroenterol Hepatol 2013;28:1489-95.
7. Laine L. Upper Gastrointestinal Bleeding Due to a Peptic Ulcer. N Engl J Med 2016;375:1198.
8. Gralnek IM, Dumonceau JM, Kuipers EJ, et al. Diagnosis and management of nonvariceal upper gastrointestinal hemorrhage: European Society of Gastrointestinal Endoscopy (ESGE) Guideline. Endoscopy 2015;47:a1-46.
9. Laine L, Jensen DM. Management of patients with ulcer bleeding. Am J Gastroenterol 2012;107:345-60; quiz 61.

10. Committee ASoP, Pasha SF, Shergill A, et al. The role of endoscopy in the patient with lower GI bleeding. Gastrointest Endosc 2014;79:875-85.
11. Padmanabhan A, Douglass HO, Jr., Nava HR. Role of endoscopy in upper gastrointestinal bleeding in patients with malignancy. Endoscopy 1980;12:101-4.
12. Pittayanon R, Prueksapanich P, Rerknimitr R. The efficacy of Hemospray in patients with upper gastrointestinal bleeding from tumor. Endosc Int Open 2016;4:E933-6.
13. Chen YI, Barkun AN, Soulellis C, et al. Use of the endoscopically applied hemostatic powder TC-325 in cancer-related upper GI hemorrhage: preliminary experience (with video). Gastrointest Endosc 2012;75:1278-81.
14. Laine L, Peterson WL. Bleeding peptic ulcer. N Engl J Med 1994;331:717-27.
15. Laine L, McQuaid KR. Endoscopic therapy for bleeding ulcers: an evidence-based approach based on meta-analyses of randomized controlled trials. Clin Gastroenterol Hepatol 2009;7:33-47; quiz 1-2.
16. Okada M, Ishimura N, Shimura S, et al. Circumferential distribution and location of Mallory-Weiss tears: recent trends. Endosc Int Open 2015;3:E418-24.
17. Cherednikov EF, Kunin AA, Cherednikov EE, et al. The role of etiopathogenetic aspects in prediction and prevention of discontinuous-hemorrhagic (Mallory-Weiss) syndrome. EPMA J 2016;7:7.
18. Higuchi N, Akahoshi K, Sumida Y, et al. Endoscopic band ligation therapy for upper gastrointestinal bleeding related to Mallory-Weiss syndrome. Surg Endosc 2006;20:1431-4.

19. Yarris JP, Warden CR. Gastrointestinal bleeding in the cancer patient. Emerg Med Clin North Am 2009;27:363-79.

20. Roberts SE, Button LA, Williams JG. Prognosis following upper gastrointestinal bleeding. PLoS One 2012;7:e49507.

21. Savides TJ, Jensen DM, Cohen J, et al. Severe upper gastrointestinal tumor bleeding: endoscopic findings, treatment, and outcome. Endoscopy 1996;28:244-8.

22. Akhtar K, Byrne JP, Bancewicz J, et al. Argon beam plasma coagulation in the management of cancers of the esophagus and stomach. Surg Endosc 2000;14:1127-30.

23. Cheng AW, Chiu PW, Chan PC, et al. Endoscopic hemostasis for bleeding gastric stromal tumors by application of hemoclip. J Laparoendosc Adv Surg Tech A 2004;14:169-71.

24. Kondoh C, Shitara K, Nomura M, et al. Efficacy of palliative radiotherapy for gastric bleeding in patients with unresectable advanced gastric cancer: a retrospective cohort study. BMC Palliat Care 2015;14:37.

25. Lee HJ, Shin JH, Yoon HK, et al. Transcatheter arterial embolization in gastric cancer patients with acute bleeding. Eur Radiol 2009;19:960-5.

26. Clarke MG, Bunting D, Smart NJ, et al. The surgical management of acute upper gastrointestinal bleeding: a 12-year experience. Int J Surg 2010;8:377-80.

27. Sung JJ, Luo D, Wu JC, et al. Early clinical experience of the safety and effectiveness of Hemospray in achieving hemostasis in patients with acute peptic ulcer bleeding. Endoscopy 2011;43:291-5.

28. Haddara S, Jacques J, Lecleire S, et al. A novel hemostatic powder for upper gastrointestinal bleeding: a multicenter study (the "GRAPHE" registry). Endoscopy 2016;48:1084-95.

29. Laine L, Spiegel B, Rostom A, et al. Methodology for randomized trials of patients with nonvariceal upper gastrointestinal bleeding: recommendations from an international consensus conference. Am J Gastroenterol 2010;105:540-50.

30. Arena M, Masci E, Eusebi LH, et al. Hemospray for treatment of acute bleeding due to upper gastrointestinal tumours. Dig Liver Dis 2017;49:514-7.

31. Koh KH, Kim K, Kwon DH, et al. The successful endoscopic hemostasis factors in bleeding from advanced gastric cancer. Gastric Cancer 2013;16:397-403.

32. Barkun AN, Moosavi S, Martel M. Topical hemostatic agents: a systematic review with particular emphasis on endoscopic application in GI bleeding. Gastrointest Endosc 2013;77:692-700.

33. Allum WH, Brearley S, Wheatley KE, et al. Acute haemorrhage from gastric malignancy. Br J Surg 1990;77:19-20.

34. Loftus EV, Alexander GL, Ahlquist DA, et al. Endoscopic treatment of major bleeding from advanced gastroduodenal malignant lesions. Mayo Clin Proc 1994;69:736-40.

35. Chen YI, Barkun A, Nolan S. Hemostatic powder TC-325 in the management of upper and lower gastrointestinal bleeding: a two-year experience at a single institution. Endoscopy 2015;47:167-71.

Figures

Figure 1 Diffuse bleeding from malignant GI lesion without specify bleeding point

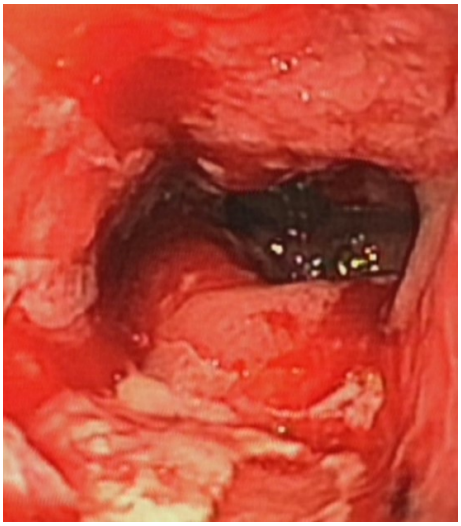
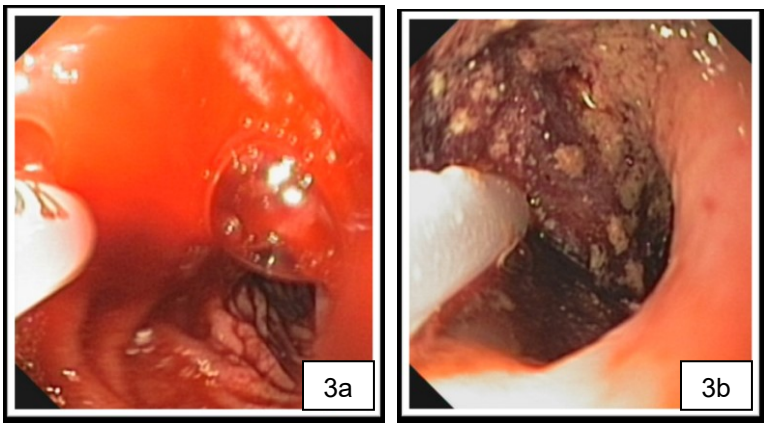


Figure 2 HemosprayTM(Tc-325)

Figure 3 HemosprayTM(Tc-325) at tumor bleeding at duodenum



3a) Before 3b) After spraying HemosprayTM

Figure 4 Survival graph in patients from MUHC, Canada and KCMH, Thailand

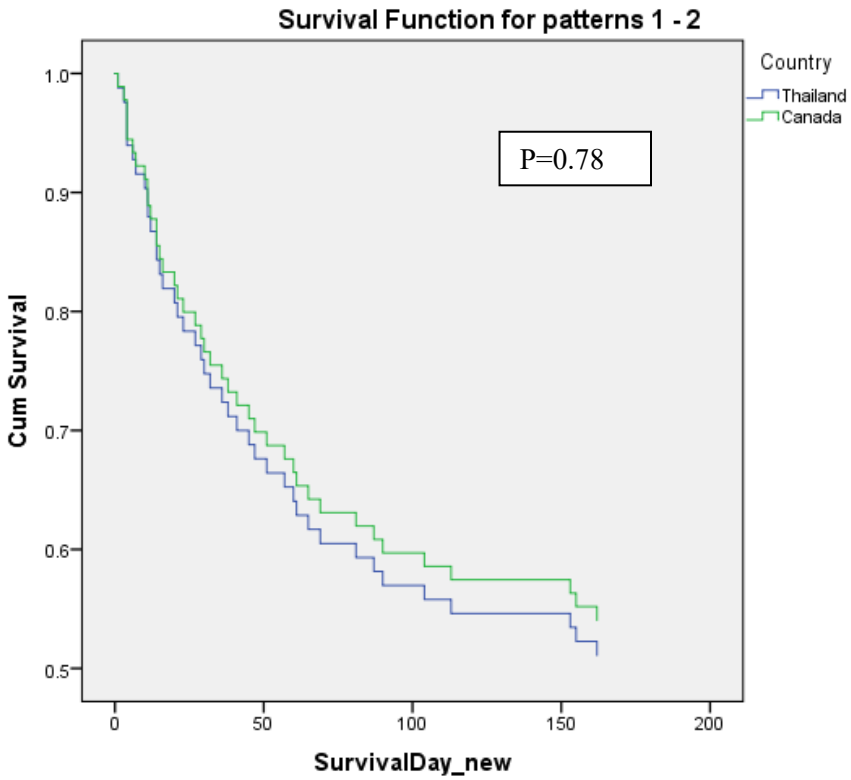
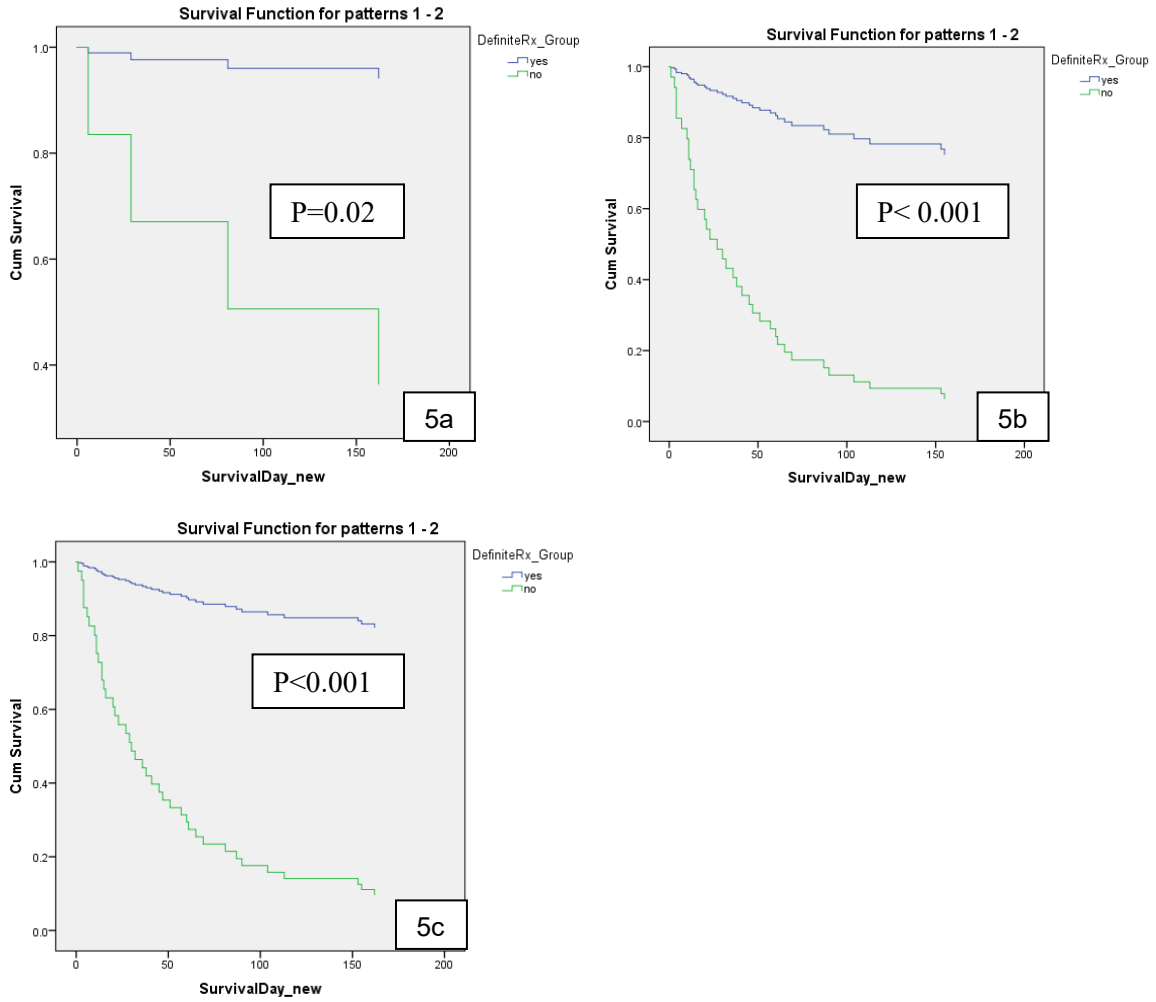


Figure 5 Survival graph in patients receiving definite hemostatic treatment vs. not receive



5a) Stage 1-3 of cancer, 5b) Stage 4 of cancer, 5c) All stages of cancer

Tables

Table 1 Conventional modalities for endoscopic hemostasis

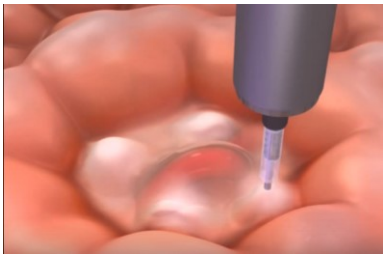
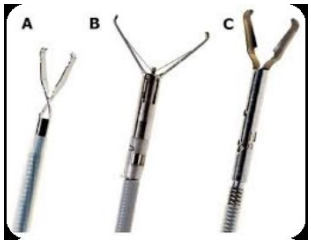
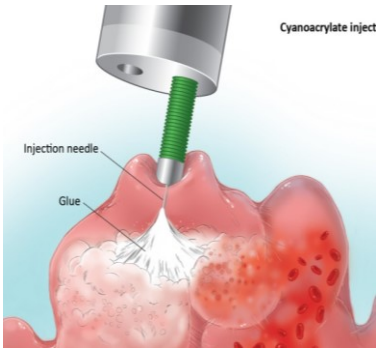
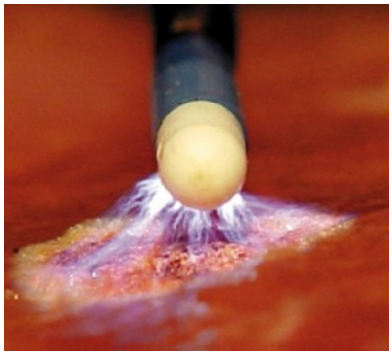
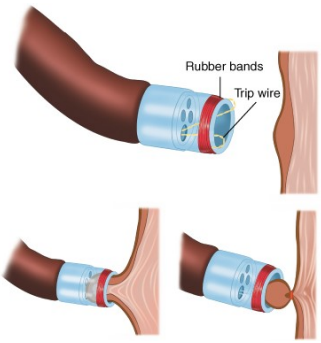
Injection	Thermal	Mechanical
Dilute epinephrine Sclerosing agents: ethanol 	Electrocautery: mono or bipolar Heater probe 	Clips 
N-butyl-2-cyanoacrylate 	Argon plasma coagulation 	Band ligation 

Table 2 Patient and disease characteristics

Patient and disease characteristics	**Canada(%) N=53**	**Thailand(%) N=35**	**Total (%) N=88**
Gender, male	38(71.7%)	24 (68%)	62(70.5)
Age (mean± SD), years	68.4±12.8	60.2±14	65.1 ±14
Comorbidity			
- Cardiovascular disease	9(17)	4(11.4)	13(14.8)
- Diabetes	7(13.2)	1(2.9)	8(9.1)
- Cirrhosis	0	5(14.3)	5(5.7)
- Other malignancy	14(26.4)	6(17.1)	21(23.8)
- More than two comorbidities	2(3.8)	2(5.7)	4(4.5)
- Others(CKD, Alzheimer's)	4(7.5)	5(14.3)	9(10.2)
- No comorbidity	17(32.1)	12(34.3)	29(33)
Performance status			
- ECOG Score 0	6(11.3)	0	6(6.8)
- ECOG Score 1	12(22.6)	7(20)	19(21.6)
- ECOG score 2	11(20.8)	9(25.7)	20(22.7)
- ECOG score 3	15(28.3)	10(28.6)	25(28.4)
- ECOG score 4	9(17)	9(25.7)	18(20.5)
Current antiplatelet/Anticoagulant	18(34)	4 (11.4)	22(25)
Blatchford score (mean±SD),(min,max)	7.4±3.2 (0,15)	10.7±3.4 (3,18)	8.7±3.7 (0,18)

Table 2 Patient and disease characteristics (Cont.)

Patient and disease characteristics	**Canada(%) N=53**	**Thailand(%) N=35**	**Total (%) N=88**
Type of cancer			
- Upper GI cancer/lymphoma	34(64.2)	16(45.7)	50(56.8)
- Lower GI cancer/lymphoma	7(13.2)	2(5.7)	9(10.2)
- Hepatobiliary cancer invade upper GI	4(7.5)	13(37.1)	17(19.3)
- Distant metastasis to upper GI	8(15.1)	4(11.4)	12(13.6)
Staging of cancer			
- Stage 1	6(11.3)	2(5.7)	8(9.1)
- Stage 2	4(7.5)	1(2.9)	5(5.7)
- Stage 3	6(11.3)	5(14.3)	11(12.5)
- Stage 4	37(69.8)	27(77.1)	64(72.7)
Tumor size (mean± SD), (min, max), centimeters	6.1±3.7, (0.9,15)	5.3±3.2, (1,15)	5.8 ±3.5, (0.9,15)
Presence of bleeding tendency			
- Platelet <100x10^9/L	1(1.9)	8(22.9)	9(10.2)
- INR >1.3	1(1.9)	13(37.1)	14(15.9)

Table 2 Patient and disease characteristics (Cont.)

Patient and disease characteristics	**Canada (%) N=53**	**Thailand (%) N=35**	**Total (%) N=88**
Definite treatment for hemostasis (>1 in each patient)	31(58.5)	21(60)	52(59.1)
- Surgery	17(32.1)	6(17.1)	23(26.1)
- Embolization	1(1.9)	8(22.9)	9(10.2)
- Chemotherapy	20(37.7)	5(14.3)	25(28.4)
- Radiotherapy	10(18.9)	5(14.3)	15(17.0)
-Number of session (mean±SD), (min,max)	3.6±3.4 (1,10)	19.5±8.4 (10,28)	9.4±9.6 (1,28)
-Dose on average(mean±SD), (min,max),Gy	15.3±9.5 (8,30)	44±23.0 (20,70)	25.7±20.6 (8,70)
Time to intervention (mean±SD), median,(min,max), days	26.7±33.5, 19,(1,182)	27.3±34.1, 16,(1,114)	27.9±33.4, 17,(1,182)
Unexpected adverse event	1(1.9)	0	1 (1.1)
Length of hospital stay (mean±SD), (min,max), days	9.2±11.1 (0,65)	20±20.5 (1,78)	13.5±16.3 (0,78)

* CKD; chronic kidney disease, ECOG; Eastern Cooperative Oncology Group, INR; International normalized ratio

Table 3 Endoscopic findings and procedure-related characteristics

Procedure-related characteristics	**Canada (%) N=53**	**Thailand (%) N=35**	**Total (%) N=88**
Endoscopic findings			
- Adherent clot	4(7.5)	0	4(4.5)
- Blood oozing	49(92.5)	34(97.1)	83(94.3)
- Blood spurting	0	1(2.9)	1(1.1)
Monotherapy with HemosrpayTM	43(81.1)	34(97.1)	77(87.5)
HemosprayTM as a rescue treatment	10(18.9)	1(2.9)	11 (12.5%)
Amount of HemosprayTM (mean±SD), (min,max), grams	15.4±5.8 (4,35)	8.7±2.3 (5,15)	12.7±5.7 (4,35)
Repeated HemosprayTM due to rebleeding within 30 days	5(9.4)	7(20)	12 (13.6)
- Before72-hour	2	5	7
- Within 7-day	2	1	3
- Within 30-day	1	1	2

Table 4 Outcomes in patient treated with HemosprayTM

Outcomes	**Canada (%) N=53**	**Thailand (%) N=35**	**Total (%) N=88**
Immediate hemostasis	53(100)	33(94.3)	86(97.7)
72-hour rebleeding rate (N total=86)	2/52(3.8)	11/34(31.4)	13 (15.1)
7-day rebleeding rate (N total=71)	3/48(6.3)	2/23(5.7)	5 (7.0)
14-day rebleeding rate (N total=64)	3/44(6.8)	2/20(5.7)	5 (7.8)
30-day rebleeding rate (N total=53)	1/35(2.6)	0/18	1 (1.9)
Day of rebleeding (mean±SD), day	8.6±5.4	4.5±5.3	6.0±5.6
Six-month survival	29(54.7)	19(54.3)	48(54.5)

Table 5 Early and delayed rebleeding rates regarding to type of cancer

Type of cancer (N=84)	**Early rebleeding (<72 hr) (%)**	**Delayed rebleeding (≥72 hr) (%)**	**No rebleeding in 30 day (%)**	**Died before assessment (%)**
Upper GI cancer/lymphoma (N=50)	8 (16)	7 (14)	22 (44)	13 (26)
Lower GI cancer/lymphoma (N=9)	0	0	7(77.8)	2 (22.2)
Hepatobiliary cancer invade upper GI tract (N=17)	5 (29.4)	2 (11.8)	3 (17.6)	7 (41.2)
Distant metastasis to upper GI tract (N=12)	0	2(16.7)	7 (58.3)	3 (25)
Total	13 (14.8)	11 (12.5)	39 (44.3)	25(28.4)

Table 6 Definite hemostatic treatment and rebleeding within 30 days

	Rebleeding in 30 days	**No rebleeding in 30 days**
Undergoing definite hemostasis	11 (45.8)*	41 (66.1)
No definite hemostasis	13 (54.2)	21 (33.9)
Total	24	62

*Undergoing definite hemostatic treatment due to rebleeding

Table 7 Univariable analysis of associated factors in patients with early and delayed rebleeding after HemosprayTM treatment

Outcomes / Predicting factors	Early rebleeding (N=13)		Delayed rebleeding (N=11)	
	N (%)	p-value, OR[95%CI]	N (%)	p-value, OR[95%CI]
Male	9(15)	0.96, 0.97[0.27,3.49]	7(15.6)	0.53, 1.55[0.39,6.12]
Age (mean± SD), years	64.85 ± 11.01	0.91, 1.00[0.96,1.04]	61 ± 10.82	0.24, 1.03[0.98,1.08]
Comorbidity				
-None	4(14.8)	Reference	6(31.6)	Reference
-without cancer	7(18.4)	0.70, 1.29[0.34,4.97]	3(10)	0.07, 4.15[0.89,19.29]
-with other cancer	2(9.5)	0.59, 0.61[0.10,3.67]	2(14.3)	0.26, 2.77[0.47,16.46]
ECOG				
-score 0-2	5(11.1)	0.28, 0.52[0.15,1.73]	4 (10)	**0.049, 3.94[1.01,15.38]**
-score 3-4	8(19.5)		7(30.4)	
Antiplatelet/Anticoagulant				
-Current use	3(13.6)	0.82, 0.85[0.21,3.43]	2(11.1)	0.21, 2.00[0.39,10.33]
- No	10(15.6)		9(20)	

Table 7 Univariable analysis of associated factors in patients with early and delayed rebleeding after HemosprayTM treatment (cont.)

Outcomes / Predicting factors	Early rebleeding (N=13)		Delayed rebleeding (N=11)	
	N (%)	p-value, OR[95%CI]	N (%)	p-value, OR[95%CI]
Blatchford score ≥ 6	2(12.5)	0.75, 1.31[0.26,6.56]	9 (17.6)	0.94. 0.93[0.17,5.01]
Type of cancer				
-Distant metastasis to upper GI	0	Reference	2 (22.2)	Reference
-Upper GI cancer	8(16.7)	1.00, N/A	7(18.9)	0.82, 1.22[0.21,7.22]
-Lower GI cancer	0	1.00, N/A	0	1.00,N/A
-Hepatobiliary cancer invade upper GI	5(29.4)	1.00, N/A	2 (20)	0.91, 1.14[0.13,10.39]
Cancer stage				
-stage 1-3	5(20.8)	0.36,	1(5.3)	0.13,
-stage 4	8(12.9)	1.78[0.52,6.10]	19(22.7)	5.29[0.63,44.71]
Tumor size mean± SD), centimeters	4.62± 3.52	0.21, 0.87[0.71,1.08]	7.01± 4.28	0.24, 0.90[0.75,1.01]

Table 7 Univariable analysis of associated factors in patients with early and delayed rebleeding after HemosprayTM treatment (cont.)

Outcomes / Predicting factors	Early rebleeding (N=13)		Delayed rebleeding (N=11)	
	N (%)	p-value, OR[95%CI]	N (%)	p-value, OR[95%CI]
Platelet < $100x10^9$/L	2(22.2)	0.53,	0	1.00,
Platelet ≥ $100x10^9$/L	11 (14.3)	1.71[0.31,9.35]	11(100)	N/A
INR >1.3	5(38.5)	**0.02,**	0	1.00,
INR ≤1.3	8 (11)	**5.08[1.33,19.33]**	11(100)	N/A
Combination techniques vs. HemosprayTM monotherapy	2(13.3)	0.83, 0.84[0.17,4.25]	0	1.00, N/A
Amount of HemosprayTM <10 grams	6(26.1)	0.09 2.82,[0.84,9.55]	1 (6.7)	0.23, 3.68[0.43,31.47]
Receiving definite hemostatic treatment				
-Yes	7(13.5)	0.60,	4 (8.9)	**0.009,**
-No	6(17.6)	0.73[0.22,2.38]	7(38.9)	**0.15[0.04,0.62]**

*INR; International normalized ratio, ECOG; Eastern Cooperative Oncology Group

Table 8 Univariable analysis of associated factors in patients with six-month survival after HemosprayTM treatment

Outcomes / **Predicting factors**	**Six-month survival (N=48)**	
	N (%)	**p-value, OR [95%CI]**
Male	35 (56.5)	0.58 1.30[0.52,3.25]
Age (mean± SD), years	66.63±13.29	0.28 1.02[0.99,1.05]
Comorbidity		
- None	17(58.6)	Reference
-without cancer	25(65.8)	0.55 1.37[0.50,3.68]
-with other cancer	6(28.6)	**0.04,** **0.28[0.09,0.94]**
ECOG		
-score 0-2	42(91.1)	**<0.001,**
-score 3-4	7(16.3)	**54.71 [14.26,194.88]**
Antiplatelet/Anticoagulant		
-Current use	15(68.2)	0.14,
-No	33(50)	0.47[0.17,1.29]

Table 8 Univariable analysis of associated factors in patients with six-month survival after HemosprayTM treatment (cont.)

Outcomes / **Predicting factors**	**Six-month survival (N=48)**	
	N (%)	**p-value, OR [95%CI]**
Blatchford score ≥ 6	11(68.8)	0.21, 0.48[0.15,1.52]
Type of cancer		
-Distant metastasis to upper GI	3(25)	Reference
-Upper GI cancer	31(62)	**0.03, 4.90[1.18,20.37]**
-Lower GI cancer	7(77.8)	**0.02, 10.50[1.36,81.05]**
-Hepatobiliary cancer invade upper GI	7(41.2)	0.37, 2.10[0.41,10.61]
Cancer stage		
-Stage 1-3	21(87.5)	**<0.001,**
-Stage 4	27(42.2)	**9.59[2.60,35.46]**
Tumor size (mean± SD), centimeters	5.78 ± 3.43	0.98 1.00[0.89,1.13]

Table 8 Univariable analysis of associated factors in patients with six-month survival after HemosprayTM treatment (cont.)

Outcomes / **Predicting factors**	**Six-month survival (N=48)**	
	N (%)	**p-value, OR [95%CI]**
Platelet < $100x10^9$/L	6(66.7)	0.45,
Platelet ≥ $100x10^9$/L	42(53.2)	1.76[0.41,7.55]
INR >1.3	6(42.9)	0.34,
INR ≤1.3	42(58.6)	0.57[0.18,1.81]
Combination techniques vs.	8(53.3)	0.92,
HemosprayTM monotherapy		1.06[0.35,3.23]
Amount of HemosprayTM <10	14(60.9)	0.48,
grams		0.71[0.27,1.86]
Receiving definite hemostatic Rx		
-Yes	43(82.7)	**<0.001,**
-No	5(13.9)	**29.62[9.04,97.06]**

*INR; International normalized ratio, ECOG; Eastern Cooperative Oncology Group

Table 9 Multivariable analysis by Cox-regression analysis of possible predictors of delayed rebleeding and six-month survival

Predicting factors	Delayed rebleeding		Six-month survival	
	p-value	OR [95%CI]	p-value	HR [95%CI]
≥ 2 cancers	0.42	2.04 [0.36,11.57]	0.35	1.43 [0.68,3.01]
ECOG 0-2	0.51	2.30 [0.19,28.62]	0.13	0.37[0.10,1.32]
Upper GI cancer	-	-	0.56	0.82[0.42,1.60]
Lower GI cancer	-	-	0.06	0.22[0.04,1.11]
Cancer stage 1-3	1.00	N/A	0.20	0.45[0.13,1.54]
Receiving definite hemostatic Rx	**0.04**	**0.06 [0.01,0.84]**	**0.002**	**0.21[0.08,0.57]**

* ECOG; Eastern Cooperative Oncology Group