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ORIGINAL ARTICLE

Retrospective Cohort Study

Mortality associated with gastrointestinal bleeding in children: A retrospective cohort study

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Abstract

AIM

To determine the clinical characteristics of children with gastrointestinal bleeding (GIB) who died during the course of their admission.

METHODS

We interrogated the Pediatric Hospital Information System database, including International Classification of Diseases, Current Procedural Terminology and Clinical Transaction Classification coding from 47 pediatric tertiary centers extracting the population of patients (1-21 years of age) admitted (inpatient or observation) with acute, upper or indeterminate GIB (1/2007-9/2015). Descriptive statistics, unadjusted univariate and adjusted multivariate analysis of the associations between patient characteristics and treatment course with mortality was performed with mortality as primary and endoscopy a secondary outcome of interest. All analyses were performed using the R statistical package, v.3.2.3.

RESULTS

The population with GIB was 19528; 54.6% were male, overall mortality was 2.07%; (0.37% in patients with the principal diagnosis of GIB). When considering

only the mortalities in which GIB was the principal diagnosis, 48% (12 of 25 principal diagnosis GIB mortalities) died within the first 3 d of admission, whereas 19.8% of secondary diagnosis GIB patients died with 3 d of admission. Patients who died were more likely to have received octreotide (19.8% *c.f.* 4.04%) but tended to have not received proton pump inhibitor therapy in the first 48 h, and far less likely to have undergone endoscopy during their admission (OR = 0.489, $P < 0.0001$). Chronic liver disease associated with a greater likelihood of endoscopy. Mortalities were significantly more likely to have multiple complex chronic conditions.

CONCLUSION

GIB associated mortality in children is highest within 7 d of admission. Multiple comorbidities are a risk factor whereas early endoscopy during the admission is protective.

Key words: Pediatrics; Gastrointestinal hemorrhage; Endoscopy; Proton pump inhibitors; Mortality; Liver disease; Hospital Information Systems; Octreotide

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Core tip: The management of gastrointestinal haemorrhage in children is challenging insofar as the timing and impact of different interventions remains poorly defined. The authors analysed the characteristics and associated interventions associated with mortality as an outcome with gastrointestinial bleeding in children past infancy. Death associated with gastrointestinal haemorrhage was reported in 2% overall albeit less (0.4%) in the cohort with haemorrhage as admitting diagnosis. Patients who died were far less likely to have undergone endoscopy during the admission and more likely to have received octreotide and less likely to have received proton pump inhibitor therapy during the first two days of admission.

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INTRODUCTION

Gastrointestinal bleeding (GIB) is a foremost indication for emergent diagnostic and therapeutic endoscopy requiring prompt, including disease-specific pharmacotherapy[1,2]. Although acute GIB in adults has been exhaustively studied including epidemiology and predictors of adverse outcomes, there is a paucity of the corresponding evidence in children[3,4]. This deficit hinders the evidence based allocation of resources and the implementation of standardized protocols, potentially adversely impacting outcomes in children.

One of the co-authors, has identified the presence of > 3 comorbid conditions, presentation to a teaching hospital, the presence of upper GIB; age under 5 years and health coverage with private insurance as independent risk factors associated with an increased rate of hospital admission with GIB[5]. Hemorrhage occurred in 0.5% of all discharges from inpatient care, was more prevalent in males and older than 11 years. Esophageal and intestinal perforation were identified as at highest risk of associated mortality, together accounting for 17% of all patients with GI haemorrhage and who died[6].

Disease classification in adult GIB cannot be extrapolated to the pediatric population. Risk factors identifiable in adults, foremost amongst which are age, non-steroidal anti-inflammatory drug, selective serotonin reuptake inhibitor, aspirin, antiplatelet and anticoagulant therapy and chronic renal and cardiovascular disease, are clearly not applicable to children[7]. Conversely, the impact of predominantly pediatric and especially neonatal disease processes (*e.g.,* prematurity) on the risk of GIB remain unknown. This limits the applicability of pre- and postendoscopic predictive scoring systems [Rockall, Blatchford (aka Glasgow), Addenbrooke] to identify patients at high risk (need for blood transfusion, surgical intervention, rebleeding and mortality) and those requiring immediate endoscopic intervention as opposed to at low risk who can be safely discharged[8-10]. The Sheffield Scoring system is, to date the only successful attempt at predicting the need for endoscopic hemostatic intervention based on the clinical presentation, hemodynamic parameters and need for blood products[11]. An understanding of the epidemiologic context of GIB in children holds the promise of directing future research toward improving predictive models of disease outcomes including mortality.

The Pediatric Health Information System (PHIS) database is a repository of diagnostic, therapeutic and procedure records from 48 regional pediatric tertiary centers in the United States that has been in existence since 2004, the data is available in de-identified form to health information management administrators and academicians in the respective institutions.

Herein we report on the PHIS recorded demographic and clinical profile of children with upper or indeterminate gastrointestinal bleeding at admission or during their inpatient course and resulting in death.

MATERIALS AND METHODS

Data source

We conducted a retrospective cohort study using data obtained from the PHIS, an administrative database that contains inpatient, emergency department,

ambulatory surgery and observation encounter-level data from 49 not-for-profit, tertiary care pediatric hospitals in the United States. The PHIS hospitals are 49 of the largest and most advanced children's hospitals in America, and constitute the most demanding standards of pediatric service in America. These hospitals are affiliated with the Children's Hospital Association (Overland Park, KS, United States). Data quality and reliability are assured through a joint effort between the Children's Hospital Association and participating hospitals. Portions of the data submission and data quality processes for the PHIS database are managed by Truven Health Analytics (Ann Arbor, MI, United States). For the purposes of external benchmarking, participating hospitals provide discharge/encounter data including demographics, diagnoses, and procedures. Nearly all of these hospitals also submit resource utilization data (*e.g.,* pharmaceuticals, imaging, and laboratory) into PHIS. Data are de-identified at the time of data submission, and data are subjected to a number of reliability and validity checks before being included in the database. For this study, data from 47 hospitals was included. This study was approved by the Institutional Review Board (16050358).

Study patients

Children between the ages of 1 and 21 years at the time of admission were eligible for inclusion if they were diagnosed with an upper gastrointestinal bleed (UGIB) or GIB of indeterminate location and admitted as an inpatient or under observation with Emergency Department charges between January 1, 2007 and September 30, 2015. Study participants with UGIB were identified through International Classification of Diseases, Ninth Revision (ICD-9) discharge diagnosis codes (Supplementary Table 1).

Demographic characteristics included age in years at time of admission, sex, race/ethnicity (non-Hispanic White, non-Hispanic Black, Hispanic, Asian, Other, Unknown), discharge disposition (routine/home, expired and rural *vs* urban zip code of residence. Complex chronic conditions (CCCs) were defined using a previously described ICD-9 coding scheme for 9 types of CCCs (neuromuscular, cardiovascular, respiratory, renal, gastrointestinal, hematologic/immunologic, metabolic, congenital or genetic, and malignancy), as well as organ transplant patients and technology dependent patients[12]. A given patient could have could have more than 1 CCC, and the total number of CCCs for each patient was calculated. Chronic liver disease was also identified by ICD-9 diagnosis codes, and coded as a dichotomous variable. The need for packed red blood cell transfusions was used to control for severity of bleeding [0 = no transfusion, 1 = transfusion(s) received].

Procedures were identified through ICD-9-CM codes (Supplementary Table 2), and pharmaceuticals and imaging procedures were identified through Clinical Transaction Classification System for revenue codes.

Outcome measures

The primary outcome of interest in this study was mortality. Secondary outcomes examined include whether or not the patient underwent endoscopy.

Statistical analysis

Unadjusted, univariate analyses of the associations between patient characteristics and treatment course with mortality were carried out. Continuous variables were summarized using the median and interquartile ranges (IQR) and compared using the Wilcoxon rank-sum test. Categorical variables were summarized using counts and frequency as a percentage, and compared using the χ^2 test of association or Fisher's exact test, where appropriate. Complex chronic conditions were treated categorically as the number of complex chronic conditions present in a single patient. The levels of the category were defined as 0 complex chronic conditions, 1 or 2 complex chronic conditions, and 3 or more complex chronic conditions. These levels were chosen after assessing the median and interquartile range of the distribution of number of CCCs. Receipt of pharmaceuticals on the first or second day of admission was coded as a dichotomous variable, as was the receipt of packed red blood cell transfusions and platelet transfusions. All procedures were coded as 0 (procedure not billed) or 1 (procedure billed). Unadjusted *P*-values were reported for the univariate analysis.

Adjusted analysis of the association between patient characteristics and treatment course with mortality were examined using multivariable generalized linear mixed models to assess the odds of exposure to treatment among mortality cases (binomial family, logit link). A quasi-likelihood method was used to estimate effects (Laplace approximation). All candidate models were adjusted for potential confounding by age in years at admission, race/ethnicity, and sex and by the need for packed red blood cell transfusions as a surrogate of severity of bleed. Chronic liver disease, comorbid complex chronic conditions, and urban *vs* rural zip code of residence at time of admission were tested as covariates. Other covariates included perforation type injury, administration of proton pump inhibitor (PPI), H_2RA, octreotide, and vasopressin pharmaceuticals on the first or second day of admission and endoscopic procedures performed. Interactions between vasopressin and shock, endoscopy and chronic liver disease, and endoscopy and CCCs were also tested to investigate potential effect modification. To account for increased variability due to clustering within hospitals, a random intercept was included using a unique hospital ID. Model selection was carried out using -2 log likelihood tests with the χ^2 approximation. Individual covariates were tested by approximation to the *Z*-value. The Holm procedure was used to account

Table 1 Patient characteristics by principal and secondary diagnosis of gastrointestinal bleeding *n* (%)

	GI bleed		Overall (*n* = 19528)	*P* value
	Principal Dx (*n* = 6733)	Secondary Dx (*n* = 12795)		
Age in years (IQR)	10 (4, 15)	9 (4, 15)	9 (4, 15)	< 0.0001
Gender				< 0.0001
Female	2925 (43.44)	5941 (46.43)	8866 (45.40)	
Male	3808 (56.56)	6854 (53.57)	10762 (55.11)	
Race				< 0.0001
Non-Hispanic White	3608 (53.59)	6596 (51.55)	10204 (52.25)	
Non-Hispanic Black	1180 (17.53)	2257 (17.64)	3437 (17.60)	
Hispanic	1159 (17.21)	2580 (20.16)	3739 (19.15)	
Asian	251 (3.73)	332 (2.59)	583 (2.99)	
Other	412 (6.12)	779 (6.09)	1191 (6.10)	
Unknown	123 (1.83)	251 (1.96)	374 (1.92)	
Urban/rural				0.1247
Urban	5730 (85.10)	10930 (85.42)	16660 (85.31)	
Rural	873 (12.97)	1573 (12.29)	2446 (12.53)	
Unknown	130 (1.93)	292 (2.28)	422 (2.16)	
Complex chronic conditions				< 0.0001
0	3767 (55.95)	5969 (46.65)	9736 (49.86)	
1-2	1771 (26.30)	4328 (33.83)	6099 (31.23)	
⩾ 3	1195 (17.75)	2498 (19.52)	3693 (18.91)	
GIH symptoms				
Hematemesis	2333 (34.65)	4263 (33.32)	6596 (33.78)	0.0635
Melena	1983 (29.45)	6018 (47.03)	8001 (40.97)	< 0.0001
Hypovolemia	52 (0.77)	90 (0.70)	142 (0.73)	0.5956
Pharmaceutical Interventions				
PPI on day 0 or 1	4473 (66.43)	6038 (47.19)	10511 (53.83)	< 0.0001
H_2RA on day 0 or 1	1301 (19.32)	2715 (21.22)	4016 (20.57)	0.0019
Erythromycin on day 0 or 1	197 (2.93)	313 (2.45)	510 (2.61)	0.0511
Vasopressin on day 0 or 1	15 (0.22)	142 (1.11)	157 (0.80)	< 0.0001
Octreotide on day 0 or 1	349 (5.18)	439 (3.43)	788 (4.04)	< 0.0001
Diagnostic Imaging				
Meckel's Scan day 0-2	497 (7.38)	378 (2.95)	875 (4.48)	< 0.0001
Abdomen CT day 0-2	425 (6.31)	1298 (10.14)	1723 (8.82)	< 0.0001
Abdomen MRI day 0-2	44 (0.65)	170 (1.33)	214 (1.10)	< 0.0001
Arteriography day 0-2	75 (1.11)	93 (0.73)	168 (0.86)	0.0070
Surgical interventions				
Laparotomy, exploratory	23 (0.34)	44 (0.34)	67 (0.34)	0.9999
Laparotomy, other	2 (0.03)	19 (0.15)	21 (0.11)	0.0191
Laparoscopy	54 (0.80)	96 (0.75)	150 (0.77)	0.7303
EGD	2304 (34.22)	2317 (18.11)	4621 (23.66)	< 0.0001
Other endoscopy	845 (12.55)	845 (6.6)	1690 (8.65)	< 0.0001
Transcatheter embolization	8 (0.12)	8 (0.06)	16 (0.08)	0.1977
Ligation, esophag. varices	0 (0.0)	5 (0.04)	5 (0.03)	0.1719
Ligation, gastric varices	1 (0.01)	5 (0.04)	6 (0.03)	0.6713
Packed red blood cell transfusions	1265 (18.79)	2337 (18.26)	3602 (18.45)	0.3808
Platelet transfusions	194 (2.88)	799 (6.24)	993 (5.09)	< 0.0010
ICU stay as part of encounter	880 (13.07)	2328 (18.19)	3208 (16.43)	< 0.0001
Chronic liver disease	171 (2.54)	400 (3.13)	571 (2.92)	0.0234
GIH present on admit	4980 (73.96)	8585 (67.10)	11084 (56.76%)	< 0.0001
Shock	144 (2.14)	584 (4.56)	728 (3.73)	< 0.0001
Sepsis	30 (0.45)	666 (5.21)	696 (3.56)	< 0.0001
Hospital lOS (IQR)	2 (1, 4)	3 (2, 7)	3 (1, 6)	< 0.0001
Day of EGD	1 (0, 2)	2 (1, 3)	1 (0, 2)	< 0.0001
Mortality	25 (0.37)	379 (2.96)	404 (2.07)	< 0.0001

IQR: Interquartile ranges; GER: Gastroesophageal reflux; PPI: Proton pump inhibitor; H_2RA: H_2-receptor antagonists; CT: Computed tomography; MRI: Magnetic resonance imaging; GIB: Gastrointestinal bleeding; EGD: Esophagogastroduodenoscopy.

for multiple testing of covariates for each outcome, and the adjusted *P*-values are reported for the significance test of model covariates. An adjusted, two-tailed $P < 0.05$ was considered statistically significant. All analyses were performed using the R statistical package, v.3.2.3.

RESULTS

Descriptive statistics

There were 19528 patients with upper or indeterminate GIB discharged between January 1, 2007 and September 30, 2015 (Table 1). Overall, 54.6% of

patients were male, and the median age was 9 years (IQR 4-15). Nearly half (49.68%) of the patients had no documented CCCs, 30.32% had 1 or 2 CCCs, and 20.01% had 3 or more CCCs. The most common CCC was gastrointestinal conditions (28.22%), followed by technology dependence[12,13] (20.24%) and neurologic and neuromuscular disorders (13.90%). Of the patients included in the analysis, 33.78% experienced hematemesis, 40.97% melena, 12.18% had gastroesophageal reflux (GER), 3.73% experienced shock, 3.56% experienced sepsis, and 18.45% required packed red blood cell transfusion while 5.09% required a platelet transfusion. Most patients resided in an urban area (85.31%), although a small portion of the data was missing (2.16%).

Overall mortality rate was 2.07% with 0.37% mortality among patients with principal diagnosis of GIB and 2.96% among patients with secondary diagnosis of GIB. The median time until death was 19 d (5, 49). For all patients, 21.53% of deaths occurred within the first 3 d of admission, and 31.9% occurred within 7 d of admission. When considering only the mortalities in which GIB was the principal diagnosis, 48% (12 of 25 principal diagnosis GIB mortalities) died within the first 3 d of admission, and 64% expired within 7 d of admission. Among secondary diagnosis patients, 19.8% died with 3 d of admission, and 29.8% died within 7 d of admission. Although the majority of patients were male, females and males had similar mortality rates (50% of mortalities were male). There were apparent racial/ethnic distributional differences, with non-Hispanic Whites being the only group that comprised a smaller proportion of the mortalities than the surviving cases.

Early intervention with pharmaceuticals was more frequent among mortality cases (Table 2). Receipt of PPI on the first or second day of admission occurred in 53.83% of patients, with higher usage among mortalities (68.56% *vs* 53.31%). H_2RA were administered on the first or second day of admission in 20.57% of patients, with higher usage in mortality than non-mortality cases (37.62% *vs* 20.20%). Octreotide was only used in 4.04% of patients; 19.80% of patients who died received octreotide on the first or second day of admission, and 3.70% surviving cases received octreotide. Vasopressin was only given to 0.80% of patients; 24.50% of the mortality cases and 0.30% of surviving cases received vasopressin on the first or second day of admission.

Table 3 displays the top admitting diagnosis codes for mortalities and non-mortalities. Mortalities included several diagnosis codes not related to GI symptoms, including dyspnea and respiratory abnormalities, cardiac arrest, pneumonia, diseases of white blood cells, and respiratory failure. Non-mortalities more frequently carried GI-specific admitting diagnoses.

Multivariable analysis

Factors associated with mortality in all GIB diagnoses: After adjustment for other covariates, race was not significantly associated with mortality in patients with a primary diagnosis of UGIB or unspecified GIB (adjusted $P = 0.999$). Although the majority of patients were male, mortality tended to be higher in females; however, gender was not significantly associated with mortality (adjusted $P = 0.339$). Age was also not significantly associated with mortality (adjusted $P = 0.999$). These covariates were retained in the model for their role as potential confounders. Urban *vs* rural zip code of residence, H_2RA within the first or second day of admission, and the interaction between endoscopy and chronic liver disease were not statistically significant and did not improve fit, thus were removed from the model [$\chi^2(4) = 4.505$, $P = 0.342$]. Furthermore, chronic liver disease, and the interaction between endoscopy and CCCs were not significant and did not significantly improve model fit and were also removed from the final model [$\chi^2(3) = 4.612$, $P = 0.203$]. Although PPI on the first or second day of the encounter was not significant after correcting for multiple testing, the inclusion of this variable significantly improved model fit [$\chi^2(1) = 5.451$, $P = 0.020$].

Those patients who died were far less likely to have undergone an endoscopic procedure (OR = 0.489, 95%CI: 0.356-0.672, $P < 0.0001$), indicating a protective association with endoscopy. Mortalities were also less likely to have a GIB documented as present on admission (OR = 0.464, 95%CI: 0.362-0.596, $P < 0.0001$), and less likely to have had the GIB as the principal diagnosis for the encounter (OR = 0.266 95%CI: 0.165-0.429, $P < 0.0001$). This may suggest that GIB more commonly complicates inpatient stays for patients admitted or being primarily treated for other conditions. PPI administration on the first or second day of admission tended to be protective; however, the effect was not statistically significant after correction for multiple testing (OR = 0.723, 95%CI: 0.552-0.947, $P = 0.074$).

The odds of having 1 or 2 CCCs compared to 0 CCCs were 9.090 times higher for mortalities over non-mortalities (95%CI: 4.907-16.841, $P < 0.0001$), and the odds of having 3 or more CCCs compared to 0 CCCs was 27.338 (95%CI: 14.940-50.027, $P < 0.0001$) times higher for mortalities over non-mortalities. Mortalities have significantly increased odds of having multiple complex chronic conditions. Table 4 differentiates the presence of concomitant CCC in patients with GIB as principal as opposed to secondary diagnosis whereas Table 5 summarizes the distribution of CCCs between mortality and non-mortality patients.

Mortalities had significantly higher odds of perforation as well (OR = 5.505, 95%CI: 1.717-17.650, $P =$

Table 2 Univariate analysis of factors affecting mortality *n* (%)

	Survived (*n* = 19124)	Died (*n* = 404)	Overall (*n* = 19528)	*P* value
Age in years (IQR)	9 (4, 15)	8 (3, 15)	9 (4, 15)	0.2997
Gender				0.0679
Female	8864 (46.35)	202 (50)	9066 (46.43)	
Male	10460 (54.70)	202 (50)	10662 (54.60)	
Race				0.0005
Non-Hispanic White	10036 (52.48)	168 (41.58)	10204 (52.25)	
Non-Hispanic Black	3358 (17.56)	79 (19.55)	3437 (17.60)	
Hispanic	3646 (19.07)	93 (23.02)	3739 (19.15)	
Asian	565 (2.95)	18 (4.46)	583 (2.99)	
Other	1156 (6.04)	35 (8.66)	1191 (6.10)	
Unknown	363 (1.90)	11 (2.72)	374 (1.92)	
Urban/rural				0.2524
Urban	16324 (85.36)	336 (83.17)	16660 (85.31)	
Rural	2385 (12.47)	61 (15.10)	2446 (12.53)	
Unknown	415 (2.17)	7 (1.73)	422 (2.16)	
Complex chronic conditions				< 0.0001
0	9689 (50.66)	12 (2.97)	9701 (49.68)	
1-2	5825 (30.46)	95 (23.51)	5920 (30.32)	
⩾ 3	3610 (18.88)	297 (73.51)	3907 (20.01)	
GIH symptoms				
Hematemesis	6508 (34.03)	88 (21.78)	6596 (33.78)	< 0.0001
Melena	7899 (41.30)	102 (25.25)	8001 (40.97)	< 0.0001
Hypovolemia	131 (0.69)	11 (2.72)	142 (0.73)	0.0002
GER	2329 (12.18)	50 (12.38)	2379 (12.18)	0.9653
Pharmaceutical interventions				
PPI first 24 h	10234 (53.51)	277 (68.56)	10511 (53.83)	< 0.0001
H_2RA first 24 h	3864 (20.20)	152 (37.62)	4016 (20.57)	< 0.0001
Erythromycin first 24 h	480 (2.51)	30 (7.43)	510 (2.61)	< 0.0001
Vasopressin first 24 h	58 (0.30)	99 (24.50)	157 (0.80)	< 0.0001
Octreotide first 24 h	708 (3.70)	80 (19.80)	788 (4.04)	< 0.0001
Surgical interventions				
Laparotomy, exploratory	54 (0.28)	13 (3.22)	67 (0.34)	< 0.0001
Laparotomy, other	16 (0.08)	5 (1.24)	21 (0.11)	< 0.0001
Laparoscopy	144 (0.75)	6 (1.49)	150 (0.77)	0.1347
EGD	4569 (23.89)	52 (12.87)	4621 (23.66)	< 0.0001
Other endoscopy	1638 (8.57)	52 (12.87)	1690 (8.65)	0.0031
Transcatheter embolization	14 (0.07)	2 (0.50)	16 (0.08)	0.0423
Ligation, esophag. varices	4 (0.02%)	1 (0.25%)	5 (0.03)	0.0993
Ligation, gastric varices	6 (0.03)	0 (0.00)	6 (0.03)	0.9999
Diagnostic imaging				
Meckel's Scan day 0-2	873 (4.56)	2 (0.50)	875 (4.48)	0.0001
Abdomen CT day 0-2	1675 (8.76)	48 (11.88)	1723 (8.82)	0.0356
Abdomen MRI day 0-2	212 (1.11)	2 (0.50)	214 (1.10)	0.3340
Arteriography day 0-2	163 (0.85)	5 (1.24)	168 (0.86)	0.4031
Packed red blood cell Transfusion	3361 (17.57)	241 (59.65)	3602 (18.45)	< 0.0001
Platelet transfusion	819 (4.28)	174 (43.07)	993 (5.09)	< 0.0001
ICU stay as part of encounter	2863 (14.97)	345 (85.40)	3208 (16.43)	< 0.0001
Chronic liver disease	536 (2.80)	35 (8.66)	571 (2.92)	< 0.0001
GIB Present on admit	13386 (70.00)	179 (44.31)	11084 (56.76)	< 0.0001
Principal Dx GIB	6708 (35.07)	25 (6.18)	6733 (34.48)	< 0.0001
Sepsis	516 (2.70)	180 (44.55)	696 (3.56)	< 0.0001
Shock	562 (2.94)	166 (41.09)	728 (3.73)	< 0.0001
Hospital LOS (IQR)	3 (1, 6)	19 (5, 49)	3 (1, 6)	< 0.0001
Day of EGD	1 (0, 2)	3 (1, 14)	1 (0, 2)	< 0.0001

IQR: Interquartile ranges; GER: Gastroesophageal reflux; PPI: Proton pump inhibitors; H_2RA: H_2-receptor antagonists; CT: Computed tomography; MRI: Magnetic resonance imaging; GIB: Gastrointestinal bleeding; EGD: Esophagogastroduodenoscopy.

0.021). There was a significant association between mortality and diagnosis of sepsis during the encounter and mortality (OR = 2.583, 95%CI: 1.823-3.659, P < 0.0001). Mortalities had substantially higher odds of shock (OR = 3.585, 95%CI: 2.489-5.163, P < 0.0001), but this effect was modified by vasopressin. Mortalities had 4.834 times the odds of experiencing shock and receiving vasopressin compared to shock alone over non-mortalities (95%CI: 2.729-8.562, P < 0.0001). Vasopressin is primarily used to treat shock in critically ill children[3]. Higher mortality in patients receiving vasopressin and shock does not necessarily represent

Table 3 Top 10 admitting diagnoses for mortalities and non-mortalities

ICD-9 code	ICD-9 code description	*n* (%)
Mortalities		
780.60	Fever	32 (7.92)
786.09	Other dyspnea and respiratory abnormality	23 (5.69)
787.03	Vomiting alone	15 (3.71)
03.89	Unspecified septicemia	14 (3.47)
578.0	Hematemesis	13 (3.22)
427.5	Cardiac arrest	13 (3.22)
578.9	Hemorrhage of GI tract, unspecified	12 (2.97)
486.0	Pneumonia, organism unspecified	11 (2.72)
288.00	Diseases of white blood cells	10 (2.48)
518.81	Acute respiratory failure	10 (2.48)
Non-mortalities		
578.0	Hematemesis	3058 (15.99)
578.1	Blood in Stool	2750 (14.38)
578.9	Hemorrhage of GI tract, unspecified	1289 (6.74)
789.00	Other symptoms involving abdomen and pelvis	755 (3.95)
787.03	Vomiting alone	748 (3.91)
N/A	Not available or Missing	707 (3.70)
780.60	Fever	559 (2.92)
276.51	Dehydration	515 (2.69)
787.91	Diarrhea	500 (2.61)
2859	Anemia	292 (1.53)

GI: Gastrointestinal; ICD-9: International Classification of Diseases, Ninth Revision.

Table 4 Complex chronic conditions by principal and secondary diagnosis of gastrointestinal bleeding *n* (%)

	Principal Dx is GI bleed (*n* = 4521)	Secondary Dx is GI bleed (*n* = 15007)	*P* value
GI flag	1681 (24.39)	3892 (15.39)	< 0.0001
Cardiovascular flag	513 (7.44)	1192 (4.71)	< 0.0001
Hem/immunologic flag	422 (6.12)	1392 (5.5)	< 0.0001
Malignancy	284 (4.12)	1015 (4.01)	< 0.0001
Metabolic flag	258 (3.74)	1015 (4.01)	< 0.0001
Neurologic/neuromusc flag	972 (14.1)	1743 (6.89)	0.1234
Congenital/genetic flag	727 (10.55)	1192 (4.71)	0.0010
Renal/urologic flag	249 (3.61)	811 (3.21)	< 0.0001
Respiratory flag	244 (3.54)	601 (2.38)	0.0005
Technology depend flag	1353 (19.63)	2599 (10.28)	0.7331
Transplant flag	318 (4.61)	578 (2.29)	0.5374

GI: Gastrointestinal.

Table 5 Complex chronic conditions by discharge disposition *n* (%)

	Survived (*n* = 19124)	Died (*n* = 404)	*P* value
Gastrointestinal flag	5351 (27.98)	159 (39.36)	< 0.0001
Cardiovascular flag	1543 (8.07)	162 (40.10)	< 0.0001
Hem/immunologic flag	1662 (8.69)	152 (37.62)	< 0.0001
Malignancy	1164 (6.09)	135 (33.42)	< 0.0001
Metabolic flag	1138 (5.95)	135 (33.42)	< 0.0001
Neurologic/neuromusc flag	2570 (13.44)	145 (35.89)	< 0.0001
Congenital/genetic flag	1838 (9.61)	81 (20.05)	< 0.0001
Renal/urologic flag	927 (4.85)	133 (32.92)	< 0.0001
Respiratory flag	780 (4.08)	65 (16.09)	< 0.0001
Technology depend. flag	3710 (19.40)	242 (59.90)	< 0.0001
Transplant flag	802 (4.19)	94 (23.27)	< 0.0001

a causal chain - it may merely be highlighting the pattern that severe cases of shock were more frequently given vasopressin. The strength of the association is striking and the administration of vasopressin in shock cases did not associate with significantly improved outcomes. The effect of vasopressin on GI bleeds

and shock warrants further investigation in pediatric patients.

Receiving octreotide or vasopressin was significantly associated with having a portal hypertension diagnosis [χ^2 (1) = 3261.5, P < 0.0001], and with having varices with bleeding [χ^2 (1) = 2477.2, P < 0.0001]. Receiving octreotide within the first 24 h was associated with a 2.934 fold increase in odds of death (OR = 2.936, 95%CI: 1.981-4.351, P < 0.0001). This is more likely an indicator of severity of illness and early treatment as more severe patients who would eventually expire received more aggressive treatment.

Factors affecting mortality in GIB as principal, admitting or present on admit: As a sensitivity analysis, we isolated only those patients whose principal diagnosis was a GIB, or the GIB was present on admit or the admitting diagnosis to see if the trends observed associations pertained to a more refined group of GIB patients (n = 15539, 185 mortalities). After applying the model-fitting procedure, the final model yielded results similar to those observed for the full cohort of GIB patients in PHIS, with most of the associations being strengthened (the exception being CCCs), suggesting the secondary GIB may have biased estimates toward the null Age, race, and gender were not statistically significantly associated with mortality when controlling for other covariates (P = 0.999, P = 0.999, P = 0.937, respectively). Again, residing in an urban area, administration of H_2RA on day 0 or 1, chronic liver disease, and the interaction between endoscopy and chronic liver disease were not significant and did not improve model fit [χ^2 (5) = 4.527, P = 0.476]. Perforation-type injury and GIB present on admission were not significant and subsequently removed from the final model [χ^2 (2) = 3.644, P = 0.162].

In this smaller cohort, patients who died were even less likely to have undergone an endoscopic procedure (OR = 0.327, 95%CI: 0.202-0.539, P < 0.0001). Mortalities had marginally lower odds of receipt of a PPI on the first or second day of admission (OR = 0.613, 95%CI: 0.417, 0.902, P = 0.051). Receiving octreotide on the first or second day of admission was associated with an increase in odds of death (OR = 2.219, 95%CI: 1.286-3.831, P = 0.025).

The strength of the association with CCCs was not quite as pronounced in the smaller cohort. The odds of having 1 or 2 CCCs compared to 0 CCCs were 8.710 times higher for mortalities over non-mortalities (95%CI: 3.861-19.651, P < 0.0001), and the odds of having 3 or more CCCs compared to 0 CCCs was 24.098 (95%CI: 10.778-53.884, P < 0.0001) times higher for mortalities over non-mortalities. Mortalities have significantly increased odds of having multiple complex chronic conditions in the smaller cohort, but the associations are less strong.

There was a significant association between mortality and diagnosis of sepsis during the encounter (OR = 2.040, 95%CI: 1.197-3.477, P = 0.044). Mortalities had substantially higher odds of shock (OR = 5.426, 95%CI: 3.212-9.168, P < 0.0001) but this effect was modified by vasopressin, with a stronger association marked in the smaller cohort. Mortalities had 12.090 times the odds of experiencing shock and receiving vasopressin compared to shock alone over non-mortalities (95%CI: 5.327-27.442, P < 0.001).

Factors associating with endoscopy: In a separate model, we examined the association between various patient characteristics and whether or not the patient underwent endoscopy. A total of 5939 patients received endoscopy. Supplementary Table 2 stratifies therapeutic endoscopy type. The vast majority of endoscopic procedures were esophagogastroduodenoscopy. We adjusted the model for those factors relating to mortality and severity (shock, sepsis, packed red blood cell transfusion, GIB diagnosis present on admit, and GIB diagnosis as principal diagnosis). We found that those patients with chronic liver conditions were more likely to undergo endoscopy (OR = 2.378, 95%CI: 1.970-2.869, P < 0.0001), which may explain partially why this factor was not found significant in the mortality model. If endoscopy is protective and patients with chronic liver disease are more likely to undergo endoscopy, it stands to reason that they will then be less likely to die. We also found that living in a rural area was positively associated with endoscopy compared to living in an urban area (OR = 1.196, 95%CI: 1.076-1.329, P = 0.007). Compared to non-Hispanic white patients, Hispanics were 18.5% less likely to have undergone an endoscopic procedure (OR = 0.815, 95%CI: 0.737-0.900, P = 0.001). Age was also significantly associated with endoscopy, with a 6.39% increase in odds for every additional year (OR = 1.064, 95%CI: 1.058-1.070, P < 0.0001). Patients with 1 or 2 CCCs did not have increased odds of endoscopy (P = 0.999), but those with 3 or more had a 24.53% reduction in the odds of endoscopy (OR = 0.755, 95%CI: 0.686-0.830, P < 0.0001). Perforation injuries were also far less likely to undergo endoscopy (OR = 0.169, 95%CI: 0.116-0.247). GIBs as the principal diagnosis were associated with higher odds of endoscopy (OR = 2.626, 95%CI: 2.448-2.817, P < 0.0001). Those who underwent endoscopy were more likely to have experienced shock (OR = 1.752, 95%CI: 1.409-2.179, P < 0.0001), but less likely to have become septic (OR = 0.473, 95%CI: 0.370-0.604, P < 0.0001).

DISCUSSION

This is the first study describing the demographic and clinical characteristics of pediatric patients with GI hemorrhage in tertiary referral pediatric centers. In our cohort more than 75% of patients with GIB presented with hematemesis or blood in the stool. Mortality at, or before 3 d was more likely in patients with GIB as

a primary diagnosis, and in this subgroup mortality was highest in the first 7 d of admission. The mortality in patients with a principal diagnosis of GIB was 0.37% whereas the mortality in patients with GIB as a secondary diagnosis was 2.96% signalling that GIB can be a terminal event in children with other severe disease processes.

We also found that in pediatric patients, race, gender, and age were not significantly associated with mortality. Death was most strongly associated with shock, sepsis, multiple complex chronic conditions and use of vasopressin and octreotide, although these pharmaceutical treatments may represent aggressive treatment of haemorrhage (octreotide) or hemodynamic support (vasopressin) for severely ill patients.

Our observations in children are analogous to published studies in adults showing mortality to be many times higher for upper GIB complicating the inpatient course in the presence of comorbidities[14]. In our cohort, we could not determine whether the increased mortality in patients with multiple chronic comorbidities was related to the GIB event or was intrinsic to the medical frailty of these patients. However, we observed the association to be consistent between both patients with any diagnosis of GIB as well as the more focused group with primary GIB diagnosis. GIB patients with multiple chronic illnesses are at incremental risk, and mortality in patients with primary GIB is significantly associated, albeit less robustly, with multiple complex chronic conditions than children with a secondary diagnosis. More specifically, our observations support the validity of the Sheffield Scoring System which identifies significant pre-existing condition as an independent determinant of the need for therapeutic endoscopy[11].

The observed increased mortality associated with GIB with chronic comorbidities and infection can be explained through several mechanisms. For example, the strong relationship between sepsis and mortality with GIB may relate to the development of disseminated intravascular coagulation that would exacerbate bleeding. Conversely septicemia may be a terminal complication in a child with multi-organ injury from bleeding-hypovolemic shock. Similarly oncologic comorbidities signal a greater degree of overall debility as a function of immunosuppression, impaired fluid and electrolyte balance, poor nutrition, suppressed erythropoiesis and several potential iatrogenic factors impacting homeostatic responses.

We could not, in this analysis, confirm a relationship between GIB related admission mortality and distance travelled to care as defined by rural compared with urban address; a significant relationship was noted when analysis was performed looking at all GIB associated mortality, this was not borne out when the cohort was defined by admitting or principal diagnosis.

Endoscopy was associated with lower mortality, as was the administration of a PPI on the first or second day of admission. Mortality was also lower for patients with GIB that was present on admission or the principal diagnosis, supporting the impression that GIB can be viewed as an ominous complication defining a generally more dismal outcome in children.

We did find that certain patients were more likely to undergo endoscopy. Endoscopy during admission with GIB diagnosis was significantly protective (OR = 0.49); the effect was most pronounced in children with a principal diagnosis of GIB (OR = 0.28). Chronic liver disease patients were much more likely to undergo endoscopy, which may explain why this comorbidity, in turn, was not found to be significantly associated with mortality although it is a known risk factor. Racial and urban *vs* rural differences were also noted. Hispanics were significantly less likely to undergo endoscopy during admission with GIB and mortality with GIB is lowest in non-Hispanic white children.

The sensitivity analysis yielded similar results when we focused on a smaller cohort of patients with principal diagnosis of GIB, admitting diagnosis of GIB, or GIB present on admit. The purpose of examining the smaller cohort was to exclude as much as possible those secondary GIB cases that arose as complication of a non-GIB disease course. We found even stronger association for most of the covariates, suggesting possible masking and bias toward the null by including more complex and severely ill patients whose hospital stay was not chiefly attributed to a GIB.

As a retrospective observational study using primarily administrative billing data, there are several limitations to the study. The use of ICD-9 diagnosis codes has been shown to be sensitive and specific for some conditions and procedures including gastrointestinal hemorrhage[15] but are unknown for all ICD-9 codes. Coding practices may also vary within hospitals, and the reliability of these codes depends on proper documentation. Substantial risk factors or severity factors may be missing from the data.

In summary, we have reported on the mortality associated with admission for acute GI hemorrhage in children. Gastrointestinal hemorrhage can be fatal but more often defines deterioration in a child with other, especially multiple, comorbidities. Intense pharmacologic support associates with mortality underscoring the escalation of therapy with increased clinical compromise. Endoscopy was consistently protective from mortality, and the timing, scope and therapeutic goals of endoscopy in GI hemorrhage are still to be precisely defined and universally applied in children. Emerging scoring systems and prospective implementation of such may go some way to identifying and stratifying the protective effects of endoscopy in children. This study offers new impetus to aggressive, including endoscopic, management.

COMMENTS

Background

The presentation, course and outcome of gastrointestinal haemorrhage in children compared with adults remains poorly characterized; little is known

about factors related mortality associated with gastrointestinal bleeding in children and this impedes an evidence based approach to management in this population.

Research frontiers

Upper gastrointestinal haemorrhage, younger age at presentation and multiple comorbidities are associated with admission, whereas chronic illness, need for transfusion and large haemoglobin drop signal the need for endoscopy during admission. Mortality with gastrointestinal haemorrhage is most frequently associated with esophageal or intestinal perforation.

Innovations and breakthroughs

Gastrointestinal haemorrhage in children resulting in admission is associated with chronic comorbidities, most notably gastrointestinal, liver and cardiovascular disorders. Mortality is greater with more comorbid conditions at admission and more aggressive pharmacologic intervention whereas endoscopy during the admission was protective.

Applications

The prognosis for patients with gastrointestinal haemorrhage complicating the inpatient course especially in children with sepsis or multiple chronic comorbidities and requiring more aggressive hemodynamic support is especially guarded.

Peer-review

This manuscript is a very well designed and conducted retrospective study. There are outstanding information for clinical practice and important clues for prospective trials.

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ORIGINAL ARTICLE

Retrospective Study

Optimizing hepatitis C virus treatment through pharmacist interventions: Identification and management of drug-drug interactions

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Author contributions: Langness JA and Nguyen M contributed equally to this work; Wieland A, Everson GT and Kiser JJ contributed to the original project proposal and identification of key components; Kiser JJ is senior author and oversaw the initial proposal, design, statistical analysis and editing and formatting of manuscript; Langness JA and Nguyen M contributed to data collection, statistical analysis, and manuscript; Wieland A, Everson GT and Kiser JJ edited manuscript; all authors have read and approved final version to be published.

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Informed consent statement: As this was a retrospective review that involved de-identified data and did not affect patient care. Therefore informed consent was not required.

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at jennifer.kiser@ucdenver.edu. All data associated with this study are de-identified and no personal health information is available through the dataset.

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Abstract

AIM

To quantify drug-drug-interactions (DDIs) encountered in patients prescribed hepatitis C virus (HCV) treatment, the interventions made, and the time spent in this process.

METHODS
As standard of care, a clinical pharmacist screened for DDIs in patients prescribed direct acting antiviral (DAA) HCV treatment between November 2013 and July 2015 at the University of Colorado Hepatology Clinic. HCV regimens prescribed included ledipasvir/sofosbuvir (LDV/SOF), paritaprevir/ritonavir/ombitasvir/dasabuvir (OBV/PTV/r + DSV), simeprevir/sofosbuvir (SIM/SOF), and sofosbuvir/ribavirin (SOF/RBV). This retrospective analysis reviewed the work completed by the clinical pharmacist in order to measure the aims identified for the study. The number and type of DDIs identified were summarized with descriptive statistics.

RESULTS
Six hundred and sixty four patients (83.4% Caucasian, 57% male, average 56.7 years old) were identified; 369 for LDV/SOF, 48 for OBV/PTV/r + DSV, 114 for SIM/SOF, and 133 for SOF/RBV. Fifty-one point five per cent of patients were cirrhotic. Overall, 5217 medications were reviewed (7.86 medications per patient) and 781 interactions identified (1.18 interactions per patient). The number of interactions were fewest for SOF/RBV (0.17 interactions per patient) and highest for OBV/PTV/r + DSV (2.48 interactions per patient). LDV/SOF and SIM/SOF had similar number of interactions (1.28 and 1.48 interactions per patient, respectively). Gastric acid modifiers and vitamin/herbal supplements commonly caused interactions with LDV/SOF. Hypertensive agents, analgesics, and psychiatric medications frequently caused interactions with OBV/PTV/r + DSV and SIM/SOF. To manage these interactions, the pharmacists most often recommended discontinuing the medication (28.9%), increasing monitoring for toxicities (24.1%), or separating administration times (18.2%). The pharmacist chart review for each patient usually took approximately 30 min, with additional time for more complex patients.

CONCLUSION
DDIs are common with HCV medications and management can require medication adjustments and increased monitoring. An interdisciplinary team including a clinical pharmacist can optimize patient care.

Key words: Clinical pharmacist; Drug-drug interaction; Hepatitis C virus treatment

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Core tip: Identification and management of potential drug-drug interactions (DDI) is a critical aspect of current hepatitis C virus (HCV) treatment. This retrospective analysis of patients prescribed common HCV treatments identifies DDIs and the interventions made by the clinical pharmacist, as well as the approximate time required to complete these activities. This novel review illustrates that DDIs are common in this population. Identification and management of DDIs is resource intensive and requires medication adjustments and increased monitoring. An interdisciplinary care team including a clinical pharmacist is critical to optimize patient care for new HCV therapies.

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INTRODUCTION

Approximately 4.6 million Americans are estimated to have been exposed to the hepatitis C virus (HCV), and 3.5 million of those have active chronic infection[1]. The "baby boomer" generation (persons born between 1945 and 1965) have the highest incidence of chronic HCV infection *vs* any other age group[2]. Fifteen to twenty percent of people infected with chronic HCV progress to liver cirrhosis within twenty years, which may lead to end-stage liver disease or hepatocellular carcinoma[3]. In the United States, at least 35% of patients on the liver transplant wait list have chronic HCV[4]. HCV-associated mortality is close to 500000 deaths per year world-wide[5]. The previous standard of care, treatment with peginterferon and ribavirin, had significant challenges to treatment including serious adverse events, non-oral administration, and low efficacy rates. Direct-acting antivirals (DAAs) have improved the treatment landscape through increased efficacy, improved safety and tolerability, and all-oral administration. However, drug-drug interactions (DDIs) are a significant challenge and managing the interactions can be complex and time-consuming[6].

Pharmacists are recognized as important members of the health care team. Pharmacists' involvement in anticoagulation services, human immunodeficiency virus (HIV) care, cystic fibrosis, and diabetes has been shown to increase adherence, reduce pill burden and dosing frequency, and decrease medication-related errors[7-19]. The role of pharmacists in improving medical care and managing adverse effects in HCV treatment is well-recognized, but the impact of pharmacy interventions on therapeutic outcomes has not been adequately assessed in patients with HCV[20-24]. Furthermore, there is a lack of evidence for managing real-world DDIs for HCV treatments, especially with oral DAAs.

The University of Colorado Hospital Outpatient Hepatology Clinic has a clinical pharmacist imbedded within the interdisciplinary care team. The hepatologist first assesses a patient with chronic HCV infection, determining the stage of liver fibrosis, diagnosing advanced liver disease or cirrhosis, investigating any

disease complications, ordering all relevant baseline labs, and prescribing HCV treatment. The clinical pharmacist then reviews each patient prescribed HCV treatment to ensure correct dosing and dose adjustments as needed based on hepatic and renal function, to minimize therapeutic duplication, and to identify and manage DDIs. Each HCV medication has specific interactions with cytochrome P450 enzymes as well as transporters; and these medications can act as both victims and perpetrators in a number of DDIs. Potential DDIs are assessed using various resources including co-administration studies, medication package inserts, medication databases, and online tools such as www.hep-druginteractions.org. In situations where co-administration has not been studied, the pharmacology of each medication was reviewed to determine the potential for DDIs. Unfortunately, many herbal supplements lack data on pharmacokinetics and drug-drug interaction potential. If an herbal supplement did not have adequate data to ensure safe coadministration, the recommendation was often made to discontinue during HCV treatment. When managing DDIs, patient-specific factors such as vital signs, laboratory values, and concurrent use of other medications were accounted for. The clinical pharmacist coordinates with the internal medication access team to gain approval of the medication through the patient's prescription insurance plan or patient assistance programs. Once the patient is able to obtain medication, he or she meets with a physician assistant and the clinical pharmacist for a "medication start visit". During this visit, the specifics of treatment are reviewed, including the medication, dosing, administration, duration of treatment, potential side effects, and monitoring schedule. Clinically significant DDIs are reviewed with the patient and managed appropriately. The patient is then assessed through treatment by the physician assistant in conjunction with the clinical pharmacist.

Within the context of the role of the clinical pharmacist on the interdisciplinary team, the purpose of this study was to quantify (1) the type of DDI commonly encountered in patients prescribed HCV treatment in an academic outpatient hepatology clinic; (2) the interventions made; and (3) the time spent in identification and management of DDIs.

MATERIALS AND METHODS

This retrospective review identified all patients with chronic HCV infection who were prescribed HCV treatment at the University of Colorado Outpatient Hepatology Clinic between November 2013 and July 2015. Patients were included regardless of their HCV genotype and stage of liver fibrosis. DAAs prescribed during the time period included ledipasvir/sofosbuvir (LDV/SOF), paritaprevir/ritonavir/ombitasvir/dasabuvir (OBV/PTV/r + DSV), simeprevir/sofosbuvir (SIM/SOF), and sofosbuvir/ribavirin (SOF/RBV). Ribavirin may or may not have been used with the first three regimens. Patients were excluded from the study if they were coinfected with HIV or were post-liver transplant.

Demographic data including age, body mass index (BMI), and self-identified gender, race, and ethnicity were collected using the electronic medical record. HCV genotype and stage of liver fibrosis were recorded. Patients were classified as minimal to moderate fibrosis (Stage 0-2), advanced fibrosis (Stage 3), and cirrhosis (Stage 4) including both compensated and decompensated[25]. Baseline medications for each patient were collected, including prescription medication, over-the-counter medication, and vitamin and herbal supplements. Combination products such as multivitamins, vitamin-mineral supplements, and vitamin-mineral-herbal supplements were classified as one product. The number, type, and recommended management of DDIs were recorded for each patient. Baseline medications that were involved with DDIs were classified into nine categories. These categories include analgesics, hypertension/heart failure agents, anticonvulsants, psychiatric agents, proton pump inhibitors (PPIs)/H_2-receptor antagonists (H_2RA), antacids, steroids, vitamin and herbal supplements, and others. The number and type of interactions were summarized with descriptive statistics, due to the heterogeneous nature of the retrospective study.

Management of interactions was classified as: (1) discontinue medication; (2) increase monitoring; (3) alter administration time; (4) separate administration; (5) decrease dose; and (6) continue. The approximate time required for the identification, assessment, and management for clinical pharmacist review was recorded.

RESULTS

664 patients fit the inclusion and exclusion criteria: 369 with LDV/SOF, 48 with OBV/PTV/r + DSV, 114 with SIM/SOF, and 133 with SOF/RBV. Patients were 57% male and averaged 56.7 years old. 83.4% of patients identified as Caucasian, 6.44% as Black or African American, 1.89% as Asian, 0.30% American Indian or Alaska Native, and 7.97% as other or unavailable. 87% identified as Non-Hispanic and 13% Hispanic. The majority (51.5%) of the patients in the study were cirrhotic. See Table 1 for full demographic information.

Overall, 5217 medications were reviewed (7.86 medications per patient) and 781 interactions identified (1.18 interactions per patient) (Table 2). The average number of medications for each regimen was similar and ranged from 6.50 (OBV/PTV/r + DSV) to 8.79 (SIM/SOF). The average number of DDIs was lowest for SOF/RBV with 0.17, then 1.28 and 1.48 for LDV/SOF and SIM/SOF, respectively. OBV/PTV/r + DSV had the most DDIs per patient with 2.48. When accounting for stage of liver disease, the number of medications

Table 1 Baseline characteristics

Number of patients	664
Age (mean, yr)	56.7%
Gender	
Female	42.8%
Male	57.2%
Race	
Caucasian	83.4%
African American or Black	6.44%
Asian American	1.89%
American Indian or Alaska Native	0.30%
Other and unavailable	7.97%
Ethnicity	
Hispanic	13.6%
Non-Hispanic	86.4%
Number of patients on DAAs	
LDV/SOF	369%
OBV/PTV/r + DSV	48%
SIM/SOF	114%
SOF/RBV	133%
Fibrosis stage	
≤ Stage 2 (minimal to moderate fibrosis)	35.8%
Stage 3 (advanced fibrosis)	10.8%
Stage 4 (cirrhosis)	51.5%
Unknown or unavailable	1.90%

LDV: Ledipasvir; SOF: Sofosbuvir; OBV: Ombitasvir; PTV: Paritaprevir; DSV: Dasabuvir; SIM: Simeprevir; RBV: Ribavirin; DAA: Direct acting antiviral.

per patient trended upward from 6.50 for patients with minimal fibrosis to 8.99 for patients with cirrhosis (Table 3). Despite the greater number of concomitant medications, there was a similar average number of DDIs in those with minimal *vs* more advanced disease. The most common interactions (identified as ≥ 10%) were vitamin and herbal supplements (284/781, 36.4%), PPI/H_2RA agents (117/781, 15.0%), and other products (126/781, 16.1%). Table 4 summarizes the interactions amongst the different drug classes. Figure 1 shows the recommendations made for the management of DDIs.

LDV/SOF

In 369 patients prescribed LDV/SOF, 472 drug-drug interactions were identified. Common interactions (defined as ≥ 10%) with LDV/SOF included antacids (72/472, 15.3%), PPI/H_2RA agents (107/472, 22.7%), and vitamin/herbal supplements (227/472, 48.1%). Ledipasvir, an NS5A inhibitor, is better absorbed in an acidic environment. When omeprazole 20 mg was administered once daily 2 h prior to LDV, area underneath the curve (AUC) decreases to 0.58[26]. Therefore, absorption is decreased with any medications that affect stomach acidity. Overall, interactions with antacids and PPI/H_2RA agents occurred with (118/472, 25.0%) of our patients prescribed LDV/SOF. This interaction can be challenging for multiple reasons. These medications are available without prescription and often patients can forget to report them during medication reconciliation. Each patient prescribed LDV/SOF was explicitly asked if they were taking any prescription or non-prescription medications for heartburn or gastric esophagitis reflux diseas, or any other type of antacids and PPI/H_2RA agents. Another challenging aspect is that PPIs are recommended for patients post banding ligation, a comorbidity common in patients with advanced liver disease. In order to manage the DDIs with PPI/H_2RA agents, 54.2% were on the appropriate dose but were required to alter administration time; 40.2% were required to both decrease dose and alter administration time (40.2%). Supplements such as milk thistle, cod liver, krill oil, garlic cap, turmeric, and saw palmetto were recommended to be put on hold (70.4%) or separated from LDV/SOF (28.3%) administration time. Although there were few interactions with anticonvulsants (5/472, 0.85%), each occurrence was associated with a contraindication with LDV/SOF. For patients taking carbamazepine, oxcarbazepine, phenobarbital, and phenytoin, the recommendation was made to transition to an alternative anticonvulsant prior to initiation of HCV treatment.

OBV/PTV/r + DSV

Analgesics (22/119, 18.5%), vitamins and herbal supplements (21/119, 17.6%), and hypertensive agents (19/119, 16.0%) frequently interact with OBV/PTV/r + DSV. Managing interactions with analgesics such as morphine, oxycodone, tramadol, and hydrocodone, can be complicated due to the variability in dosing, patient response, and opioid tolerance. In order to manage the DDIs with analgesics, the dose was most often reduced and monitoring increased (81.8%). Supplements were recommended to be discontinued during HCV therapy (57.1%), separated by at least four hours (28.6%), or increased monitoring for adverse events (14.3%). Hypertensive agents including furosemide and amlodipine can have a greater affect due to the DDI with OBV/PTV/r + DSV. Depending on the dose of the hypertensive medications and the patient's blood pressure, the medications were continued at the same dose with increased monitoring for hypotension (7/19, 36.8%) or to decrease the dose (12/19, 63.2%) in anticipation for increased plasma concentration levels of the hypertensive agents. Other medication classes that interacted were erectile dysfunction agents (tadalafil), lipid lowering agents (pravastatin, rosuvastatin), allergy symptom medications (cetirizine), and insomnia agents (trazodone). Depending on the medication and indication, often the recommendation was to decrease the dose (23.5%) or discontinue the agent (11.8%).

SIM/SOF

Analgesics (21.3%), hypertensive agents (13.0%), psychiatrics (20.1%), and vitamins and herbal supple-

Table 2 Drug-drug interactions identified from baseline medication list

Regimen	*n* = 664	Total number of meds	Total number of interactions, *n* (%)	Average number of meds per patient	Average number of interactions per patient	Contra-indications
LDV/SOF	369	2996	472 (15.8)	8.12	1.28	7
OBV/PTV/r + DSV	48	312	119 (38.1)	6.50	2.48	4
SIM/SOF	114	1002	169 (16.8)	8.79	1.48	19
SOF/RBV	133	964	21 (2.2)	7.25	0.16	1

LDV: Ledipasvir; SOF: Sofosbuvir; OBV: Ombitasvir; PTV: Paritaprevir; DSV: Dasabuvir; SIM: Simeprevir; RBV: Ribavirin.

Table 3 Drug-drug interactions identified per fibrosis stage

Fibrosis stage	*n* = 664	Total number of medications	Total number of interactions *n* (%)	Average number of medications per patient	Average number of interactions per patient
Minimal fibrosis (Stage 0-2)	232	1508	249 (16.5)	6.50	1.07
Advanced fibrosis (Stage 3)	72	575	91 (15.8)	7.99	1.26
Cirrhosis (Stage 4)	341	3066	425 (13.8)	8.99	1.25

Table 4 Drug classes of medications identified as drug-drug interactions from baseline medication list *n* (%)

Drug class	Affected portion of the cohort *n* = 664
PPI/H2RA agents	117 (17.6)
Antacids	72 (10.8)
Vitamin and herbal supplements	284 (42.7)
Hypertensive agents	53 (8.0)
Analgesics	67 (10.1)
Psychiatric agents	46 (6.9)
Anticonvulsants	4 (0.6)
Steroids	12 (1.8)
Others	126 (19.0)

PPI: Proton pump inhibitor; H2RA: H2-receptor antagonists.

ments (10.65%) frequently interact with SIM/SOF. Even though most of these medications have not been evaluated for DDIs with SIM/SOF, we anticipate the plasma concentration of these medications to increase due to mild inhibition of CYP3A4 and OAT1B1 from simeprevir[27]. As a result, increase monitoring for side effects and decrease dose were frequently recommended for analgesics (76.3%; 21.1%), hypertensive agents (70.0%; 25.0%), and psychiatrics (82.4%; 14.7%). Herbal supplements such as St. John's wort and milk thistle are contraindicated with SIM/SOF. When administered with inducers or inhibitors of CYP3A4 enzyme, the plasma concentration of SIM is expected to change[28,29]. Therefore, both St. John's wort and milk thistle were recommended to be discontinued during the course of HCV therapy (100%). Other medications that had potential interaction with SIM/SOF were lipid lowering agents, anti-nausea medications, bladder dysfunction medications, antibacterial agents, and insomnia medications. Based on the metabolism of these medications, the most common recommendations were to increase monitoring for side effects (56.0%) or to reduce the dose (28.0%) of these medications (Figure 1).

SOF/RBV

SOF/RBV had the fewest identified DDIs of any regimen. Ribavirin has the fewest direct interactions for any of the HCV medications, and sofosbuvir has relatively few as well. Vitamins and herbal supplements that have not been studied with SOF/RBV represented the largest group of potential DDIs (81.8%). Since DDIs have not been evaluated with supplements such as milk thistle, turmeric, mushroom extract, and horny goat weed, it was recommended to discontinue these while on therapy for treating HCV infection (100%). Due to the DDI between sofosbuvir and carbamazepine, the contraindicated medication was discontinued prior to initiating HCV treatment in one patient.

Time management

The clinical pharmacist was able to record his time spent reviewing medications in 105 consults. These consults included LDV/SOF, OBV/PTV/r + DSV, and SOF/RBV, but did not include SIM/SOF. The time requirement increased with the complexity of the patient and the number of baseline medications and drug-drug interactions identified. Consults for patients prescribed OBV/PTV/r + DSV took the longest for the pharmacist to complete, averaging 30 min per consult. SOF/RBV and LDV/SOF were slightly shorter averaging 20 min per consult. This is consistent in relation to our data that shows more DDIs were identified in patients prescribed OBV/PRV/r + DSV.

DISCUSSION

Drug-drug interactions continue to be a considerable challenge for managing patients with HCV treatment. This study assessed the frequency and pharmacologi-

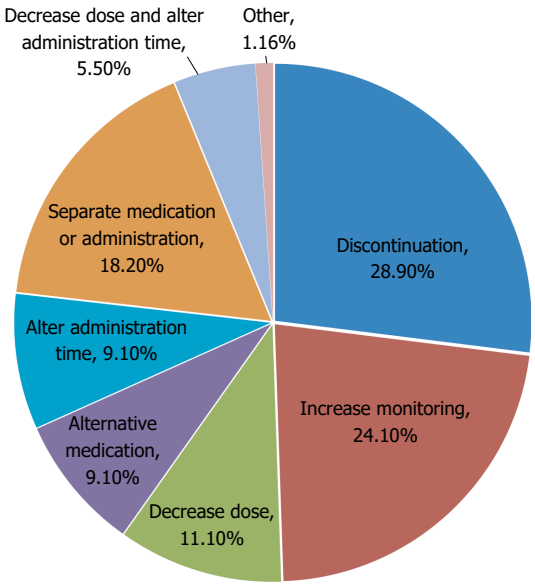

Figure 1 Recommendations for management of drug-drug interactions (*n* = 664). Other recommendations: continue, alternative medication and alter administration, decrease dose and increase monitoring, decrease dose and separate administration, and increase dose.

cal category of identified DDIs in real-world patients with HCV in addition to describing the management of the most common DDIs encountered with the DAAs. Published data on this topic are lacking. In 2010, a US insurance cohort showed the top four medication classes in patients with chronic HCV were analgesics and/or antipyretics, antidepressants, antivirals, and gastrointestinal agents including proton pump inhibitors[29]. Additionally, the study identified the average number of baseline medications as 9.0 and 11.4 in HCV treated and untreated patients, respectively. Höner Zu Siederdissen *et al*[30] published an account of potential drug-drug interactions in a cohort of patients in Hanover, Germany. Our result for the number of medications per patient at baseline study (7.86 medications per patient) was comparable with the US cohort. A significant number of DDIs predicted in our patient cohort were with analgesics (9%), antihypertensives (7%), and psychiatrics (6%). With the exception of psychiatrics and analgesics, this is comparable with both the US and German cohorts.

Use of over-the-counter medications and herbal supplements presents a challenge for assessing and managing DDIs in patients. Herbal products are gaining popularity in the US and there is a perception that herbal medications are safer than conventional medications[31]. These supplements can be recommended by people other than the patient's primary healthcare provider. Other times, patients will forget or not realize to inform the provider about non-prescription medications. In the HALT-C study, 44% of 1145 participants in the study with HCV infection admitted past or current use of herbal supplements[29]. Because the supplements are not prescribed, often they are not documented in the electronic medical records. Additionally, non-prescription medications and herbal supplements are rarely studied for interactions. When data were available or the potential interaction was minimal, the clinical pharmacist usually recommended continuing the product. However, if there were no data to support the safe use of the supplement with HCV treatment, the clinical pharmacist generally recommended it to be discontinued. This was especially true with supplements that had no clear benefit to the patient. Supplements such as multivitamins, fish oil, and probiotics that have shown benefits in certain populations, were most often recommended to separate from the DAAs in order to avoid any potential absorption interaction.

As with most hepatology clinics, the University of Colorado Hospital Hepatology Clinic largely acts as a consult service for liver disease management. As a result, providers through other clinics prescribe most concomitant medications. Adjusting or switching a medication due to DDIs can be relatively straightforward with certain medication classes such as lipid lowering agents and antihypertensive medications. However, management can be complex with other DDIs. All currently available HCV therapies have DDIs with certain anticonvulsants. These anticonvulsants are normally prescribed and managed through a specialty neurology clinic, sometimes outside of the health-system. The clinical pharmacist may not have access to the neurology clinic notes, and *vice versa*. Depending on the disease state being treated and specific patient factors, an alternative anticonvulsant that does not interact may not be appropriate. If an appropriate alternative is found, the switch can involve specific titration schedules and overlap, requiring management and specific monitoring. DDIs involving antipsychotic medication or other mental health medications are also complex. Patient responses are varied and sometimes unpredictable to certain agents, and exacerbation of mental health disease is a significant health concern. In these situations, it may be pertinent to choose a different HCV medication regimen with fewer interactions as opposed to switching the concomitant medications. Prescription insurance companies often have a specific formulary agent, and obtaining approval for an alternative HCV regimen can be challenging and time consuming.

Serious adverse events have been reported due to DDIs. This includes a case of rhabdomyolysis associated with telaprevir and simvastatin, renal failure related to the increased levels of tacrolimus after starting protease inhibitor therapy, new-onset diabetes due to the interactions between LDV/SOF and tenofovir, and severe bradyarrhythmias due to the interaction between amiodarone and sofosbuvir[32-35]. Although relatively rare, these interactions can lead to

very serious patient harm or potentially death. These cases illustrate the importance of having knowledge of possible drug-drug interactions to prevent severe side effects. In our study, there were no documented significant adverse events due to drug-drug interactions. By understanding the pharmacodynamics and pharmacokinetic profiles of the drugs involved with interactions, therapy can be safely and effectively managed in patients with HCV infection.

This study is limited by the retrospective nature of the review. Additionally, it is a single-center study at an academic medical center and regional transplant center, thereby limiting the relatability of the results to smaller clinics with less complexity. Additionally, the region lacks significant diversity and the result may differ with patients of different racial and ethnic backgrounds. Potential selection bias can also limit the results, as the patients were not randomized to each medication regimen but selected based on patient specific characteristics, medication regimen characteristics, provider experience and judgment, and insurance formulary. For patients with cirrhosis, depending on compensation and Child-Pugh Score, he or she may not be eligible to receive certain medication regimens. Due to all of the reasons, only descriptive statistics were used to analyze the results. Additionally, measuring the time requirement for the pharmacists to complete a consult was challenging. Anecdotally, as the pharmacist was more familiar with the medications and common DDIs, the time spent per patient was shortened. Additionally, due to the nature of a consult position, interruptions were common making it hard to capture the true amount of time spent per consult. For these reasons, caution should be warranted when applying these data to other clinics.

In conclusion, DDIs are common in patients prescribed HCV medications and the involvement of a clinical pharmacist can be beneficial to the interdisciplinary hepatology team. Identification and management of DDIs is resource intensive and requires medication adjustments and increased monitoring. Clinical pharmacists can encourage preventive measures on reducing HCV transmission, increase education adherence, assist in initiating HCV treatment, assist in monitoring clinical and adverse effects, and facilitate medication acquisition.

COMMENTS

Background

Identification and management of potential drug-drug interactions (DDIs) is a critical aspect of current hepatitis C virus (HCV) treatment. Direct-acting antivirals (DAAs) have improved the treatment landscape through increased efficacy, improved safety and tolerability, and all-oral administration. However, DDIs are a significant challenge and managing the interactions can be complex and time-consuming.

Innovations and breakthroughs

Drug-drug interactions continue to be a considerable challenge for managing patients with HCV treatment. This study assessed the frequency and pharmacological category of identified DDIs in real-world patients with HCV in addition to describing the management of the most common DDIs encountered with the DAAs.

Applications

This retrospective analysis of patients prescribed common HCV treatments identifies DDIs and the interventions made by the clinical pharmacist, as well as the approximate time required to complete these activities. This novel review illustrates that DDIs are common in this population. Identification and management of DDIs is resource intensive and requires medication adjustments and increased monitoring. An interdisciplinary care team including a clinical pharmacist is critical to optimize patient care for new HCV therapies.

Peer-review

Drug-drug interactions continue to be a considerable challenge for managing patients with HCV treatment. In this study the authors assessed the frequency and pharmacological category of identified drug-drug-interactions in real-world patients with HCV. This study suggests an interdisciplinary approach for managing DDIs. In my opinion, publication will be valuable.

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ORIGINAL ARTICLE

Retrospective Study

Efficacy and safety of limited endoscopic sphincterotomy before self-expandable metal stent insertion for malignant biliary obstruction

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Abstract

AIM

To evaluate the safety and efficacy of limited endoscopic sphincterotomy (ES) before placement of self-expandable metal stent (SEMS).

METHODS

This was a retrospective analysis of 244 consecutive patients with unresectable malignant biliary obstruction, who underwent placement of SEMSs following limited ES from December 2008 to February 2015. The diagnosis of malignant biliary obstruction and assessment of patient eligibility for the study was established by a combination of clinical findings, laboratory investigations, imaging and pathological results. All patients were monitored in the hospital for at least 24 h following endoscopic retrograde cholangio pancreatography (ERCP). The incidence of immediate or early post-ERCP complications such as post-ERCP pancreatitis (PEP) and bleeding related to limited ES were considered as primary outcomes. Also, characteristics and complications according to the cancer type were classified.

RESULTS

Among the 244 patients included, the underlying diagnosis was cholangiocarcinoma in 118 patients,

pancreatic cancer in 79, and non-pancreatic or non-biliary malignancies in the remaining 47 patients. Early post-ERCP complications occurred in 9 patients (3.7%), with PEP in 7 patients (2.9%; mild, 6; moderate, 1) and mild bleeding in 2 patients (0.8%). There was no significant association between the incidence of post-ERCP complications and the type of malignancy (cholangiocarcinoma *vs* pancreatic cancer *vs* others, P = 0.696) or the type of SEMS used (uncovered *vs* covered, P = 1.000). Patients who had more than one SEMS placed at the first instance were at a significantly higher risk of post-ERCP complications (one SEMS *vs* two SEMS, P = 0.031). No other factors were predictive of post-ERCP complications.

CONCLUSION

Limited ES is feasible and safe, and effectively facilitates the placement of SEMS, without any significant risk of PEP or severe bleeding.

Key words: Endoscopic sphincterotomy; Endoscopic retrograde cholangio pancreatography; Complications; Pancreatitis; Bleeding; Cholestasis; Self-expandable metal stent

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Core tip: The role of routine endoscopic sphincterotomy (ES) is still controversial in biliary stenting and there is a lack of systematic study for the extent of ES and its correlation with the incidence of complications. We retrospectively evaluated the safety and efficacy of limited ES before self-expandable metal stent insertion. We have proved in this study that limited ES doesn't increase the risk of post-procedure complications such as post-endoscopic retrograde cholangio pancreatography pancreatitis and bleeding. Also, it is advantageous in facilitating the more complex stenting procedures. Therefore, limited ES can be a safe, feasible, and effective therapeutic strategy in the placement of self-expandable metal stent.

Nam HS, Kang DH, Kim HW, Choi CW, Park SB, Kim SJ, Ryu DG. Efficacy and safety of limited endoscopic sphincterotomy before self-expandable metal stent insertion for malignant biliary obstruction. *World J Gastroenterol* 2017; 23(9): 1627-1636 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1627.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1627

INTRODUCTION

Malignant biliary obstruction is mainly caused by cholangiocarcinoma, pancreatic cancer, gallbladder cancer, and metastatic disease. The prognosis is very poor because the lesions are unresectable at diagnosis in the majority of these patients, with less than 20% of the patients being suitable for surgical resection[1]. Endoscopic retrograde cholangiopancreatography (ERCP) along with biliary stenting is a minimally invasive procedure for palliation of biliary obstruction that provides relief from jaundice and improves the quality of life of patients with unresectable malignant biliary obstruction[2].

Self-expandable metal stents (SEMS), compared to plastic stents, have superior patency and are cost-effective options in selected preoperative patients or in patients whose life expectancy exceeds six months[3-5]. They are, however, reported to be associated with a higher incidence of pancreatitis[6,7]. Previous studies indicate that performing endoscopic sphincterotomy (ES) before stent insertion may lower the incidence of post-ERCP pancreatitis (PEP)[8-10]. ES may also facilitate cannulation of the bile duct during difficult ERCPs, reduce resistance to the passage of stents, improve immediate stent deployment, and increase the luminal diameter of the distal common bile duct (CBD)[9-12]. Many endoscopists routinely perform ES before SEMS placement. However, the role of routine ES before stenting is still controversial and no clear guidelines exist to govern its use. Additionally, ES is also an independent risk factor for complications such as pancreatitis, bleeding, and perforation, with a reported complication rate of approximately 10% and an overall direct or indirect procedure-related mortality of 0.42%, even when performed by experienced endoscopists[2,13-17]. However, an accurate assessment of the incidence of complications based on the extent of ES is difficult to make owing to the lack of such data in previous studies. Herein, we studied the incidence of early post-ERCP complications, such as PEP and bleeding following limited ES accompanying SEMS placement for biliary drainage in patients with malignant biliary obstruction.

MATERIALS AND METHODS

Patients

This was a retrospective analysis of all patients who underwent endoscopic biliary SEMS placement for the first time for malignant biliary obstruction at the Pusan National University Yangsan Hospital during the six-year period from December 2008 to February 2015. Patients that underwent transpapillary SEMS placement after limited ES for a diagnosis of distal or hilar malignant biliary strictures were included in this study. Diagnosis of the disease and assessment of patient eligibility for the procedure was based on a combination of clinical findings, laboratory investigations and radiological studies including computed tomography (CT) scan, magnetic resonance imaging (MRI) and/or endoscopic ultrasound (EUS). In case of without cholangitis, painless jaundice and/or pruritus, sometimes anorexia, weight loss and malaise were main clinical symptoms. The main laboratory parameters recorded were complete blood count (CBC), total bilirubin, liver

function tests including alanine aminotransferase, alkaline phosphatase, γ-glutamyltransferase and tumor markers such as CEA and CA 19-9. CT scan was performed for all patients as an initial test, while MRI was performed in all patients with suspicious malignant biliary strictures. MRI was not performed in uncooperative patients or if contraindicated owing to the presence of intracorporeal metallic device or foreign body. EUS was not routinely performed, and was limited to investigating indeterminate biliary strictures, nonvisible masses, or when tissue acquisition was required for definite diagnosis. Pathology results were reviewed in cases where biopsy was performed during ERCP or EUS. Exclusion criteria were previous ES or stent placement, coagulopathy (international normalized ratio > 1.5), low platelet count (< 50000/mL), current use of anticoagulant or antiplatelet drugs, severe cholangitis with or without septic shock, Billroth II anatomy or Roux-en-Y gastrojejunostomy, and severe heart or pulmonary disease. The study protocol was approved by the ethics committee of the Institutional Review Board of Pusan National University Yangsan Hospital (IRB No. 05-2015-081).

Study protocol

Patient characteristics including age, sex, history of previous procedures and baseline biochemical and hematological values were collected prior to performing ERCP. SEMS placement was performed in all patients by one of two experienced endoscopists (endoscopist A had performed > 10000 ERCPs over 20 years; endoscopist B had performed > 2000 ERCPs over 10 years). All patients received intravenous (IV) broad-spectrum antibiotics. Nafamostat mesilate (20 mg) was administered for all patients for preventing post-ERCP pancreatitis. Nonsteroidal anti-inflammatory drugs were not used routinely. All procedures were performed under conscious sedation by using IV midazolam and pethidine, with the patient in the supine or left lateral decubitus position. Cimetropium bromide 10 mg IV was administered to reduce duodenal peristalsis. All ERCPs were performed by using a standard side-viewing duodenoscope (JF-260 V or TJF-240; Olympus Optical Co., Ltd., Tokyo, Japan). Selective cannulation of the bile duct was achieved by using a pull-type double-lumen sphincterotome (Ultratome XL, Boston Scientific, Natick, Mass) or by a conventional ERCP catheter (Fluoro Tip, Boston Scientific), with or without a hydrophilic guidewire (0.025- or 0.035-inch Jagwire, Boston Scientific). A wire-guided cannulation technique was attempted first, followed by the conventional contrast-assisted cannulation technique if biliary cannulation was not achieved within 10 min. After successful guidewire placement, limited sphincterotomy was performed with blended current. Limited ES was defined as ES limited to one-third the extent of major ES. A metal stent was then inserted over the guidewire under fluoroscopic control. Stent length (4 cm to 12 cm) and the need for unilateral or bilateral stent placement were determined based on the location and length of the biliary stricture. Stent placement ensured that the stent spanned the stricture with either end of the stent extending a minimum of 1 cm beyond the stricture. In the case of distal biliary strictures, the distal end of SEMS was placed across the papilla with 1 cm of the distal end of the stent exposed in the duodenum. In the case of hilar biliary strictures, SEMS was placed above the sphincter of Oddi. All patients were monitored in the hospital for at least 24 h after ERCP to identify early post-ERCP complications. CBC, serum amylase, and lipase levels were routinely evaluated at 4 h and 24 h after the procedure. Endoscopy was performed to evaluate ES-related-bleeding on the day following stent placement. All adverse events were recorded. During the follow up period, ERCP was repeated on suspecting stent complications such as occlusion or migration.

Definitions

According to updated Tokyo guidelines (TG13) for diagnosis and severity grading of acute cholangitis, cholangitis was defined as fever and/or shaking chills, increased inflammatory response (abnormal white blood cell counts, increased serum C-reactive protein levels) and jaundice (total bilirubin ⩾ 2 mg/dL) or abnormal liver function tests (> 1.5 × upper limit of normal value)[18]. Severe cholangitis is defined as the presence of accompanying organ dysfunction caused by biliary sepsis, and requiring intensive care such as respiratory and circulatory support[18]. Limited ES was defined as sphincterotomy less than one-third the extent of major ES[19]. Definitions of individual post-procedure complications were according to the descriptions given by Cotton *et al*[20]. PEP was defined as new-onset or worsening abdominal pain lasting more than 24 h after the procedure, in conjunction with pancreatic enzyme (amylase and/or lipase) elevation that was at least three times the upper limit of the normal, with or without radiographic evidence of acute pancreatitis. The severity of PEP was graded by using the number of hospitalization days: mild, when hospitalization was prolonged by 2 to 3 d, moderate, by 4 to 10 d, and severe, by more than 10 d[20]. Bleeding was defined as the presence of melena or hematemesis, irrespective of the need for blood transfusion or repeat endoscopy. Mild bleeding was defined as hemoglobin drop within 2 g/dL, with no necessity for blood transfusion. The presence of bleeding was identified based on patient's history (melena or hematemesis) and a drop in hemoglobin level following the procedure. Perforation was considered as perforation of retroperitoneum or bowel walls documented by any of the radiographic techniques[21]. Complications were graded according to the grading system described by Cotton *et al*[20]. Early complications or adverse events were defined as any ERCP-related complications occurring within 30 d

Table 1 Patient characteristics and endoscopic retrograde cholangio pancreatography related data *n* (%) (*n* = 244)

Characteristics	Value
Age (yr), mean ± SD (range)	70.8 ± 10.2 (44-95)
Sex	
Male	130 (53.3)
Female	114 (46.7)
Aspirin	3 (1.2)
Total bilirubin (mg/dL), pre-procedure, mean ± SD (range)	7.09 ± 6.45 (0.2-28.9)
Normal	53 (21.7)
Elevated	191 (78.3)
Hyperamylasemia, pre-procedure	14 (5.7)
Cholangitis, pre-procedure	68 (27.9)
Diagnosis	
Cholangiocarcinoma	118 (48.4)
Hilar	75 (63.6)
Distal	43 (36.4)
Pancreatic cancer	79 (32.4)
Head	68 (86.1)
Body/Tail	11 (13.9)
Gallbladder cancer	21 (8.6)
Ampullary cancer	18 (7.4)
Hepatocellular carcinoma	3 (1.2)
Others	5 (2.0)
Pancreatic duct invasion	
Yes	85 (34.8)
No	159 (65.2)
Lymph node metastasis	
Yes	170 (69.7)
No	73 (29.9)
Pancreatic duct injection	
0	187 (76.6)
1-2	24 (9.8)
⩾ 3	33 (13.5)
ERPD	4 (1.6)
Stent success rate	244 (100)
Number of initially inserted SEMS	
1	230 (94.3)
2	14 (5.7)
Stent type	
Uncovered	190 (77.9)
Covered	54 (22.1)
Post-ERCP complication	
Present	9 (3.7)
Absent'	234 (95.9)
Post-ERCP complication type	
Pancreatitis	7 (2.9)
Mild / moderate	6 (2.5)/1 (0.4)
Bleeding, mild	2 (0.8)
Perforation	0 (0)
Post-ERCP hyperamylasemia	30 (12.3)
Stent complication	
None	199 (81.6)
Stent occlusion	44 (18.0)
Stent migration	1 (0.4)
Patency	
No further procedure	199 (81.6)
ERBD restent	1 (0.4)
SEMS restent	32 (13.1)
PTBD	12 (4.9)

SEMS: Self-expandable metal stent; ERPD: *Endoscopic retrograde pancreatic drainage*; ERBD: Endoscopic retrograde biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

of the procedure. Patency interval was defined as the period between the first SEMS deployment and the occurrence of stent complications such as occlusion or migration.

Statistical analysis

The primary outcomes measured were immediate or early complications within 30 d of the procedure. For inter-group differences, Student's *t*-test was performed for continuous variables, and χ^2 test or Fisher's exact test were performed for categorical variables. Results were considered statistically significant at a P value < 0.05. Data were analyzed by using SPSS software version 18.0 (SPSS, Chicago, IL, United States).

RESULTS

A total of 244 patients that underwent limited ES and biliary stenting for malignant biliary obstruction between December 2008 and February 2015 were included in the study. The etiology of malignant biliary obstruction included cholangiocarcinoma (n = 118, 48.4%), pancreatic cancer (n = 79, 32.4%), and others including gallbladder cancer (n = 21, 8.6%), ampullary cancer (n = 18, 7.4%), and hepatocellular carcinoma and metastatic cancer (n = 8, 3.2%). Mean age was 70.8 ± 10.2 (range, 44-95) years and 130 (53.3%) were males and 114 (46.7%) were females. Stents were successfully deployed in all patients.

Early post-ERCP complications occurred in 9 patients (3.7%), including PEP in 7 patients (2.9%; mild, 6; moderate, 1), and mild bleeding in 2 patients (0.8%). All patient with post-ERCP complications responded to conservative management. Stent occlusion and migration developed in 44 patients (18.0%) and 1 patient (0.4%), respectively. Patients with late complications underwent repeat ERCP or percutaneous transhepatic biliary drainage. Patient characteristics and ERCP related data are summarized in Table 1.

On categorizing patients into three groups on the basis of cancer location, PEP developed in 4 patients (3.4%, 4/118) with cholangiocarcinoma, 1 patient (1.3%, 1/79) with pancreatic cancer, and 2 patients (4.3%, 2/47) with non-pancreatic, non-biliary cancers (P = 0.681). There were no significant differences among these three groups as to the incidence of immediate or early complications (P = 0.696) (Table 2). In the cholangiocarcinoma group, the incidence of PEP was 4.0% and 2.3% with hilar and distal cholangiocarcinoma, respectively (P = 0.537). One patient with hilar cholangiocarcinoma had mild bleeding (Table 3). In the pancreatic cancer group, one patient had PEP and another had mild bleeding. Both complications developed in patients with pancreatic head cancer and none were reported in cases of pancreatic body and/or tail cancer (Table 4).

Table 2 Characteristics and complications according to the cancer type *n* (%)

	Cholangiocarcinoma *n* = 118	Pancreatic cancer *n* = 79	non-pancreaticobiliary cancer *n* = 47	*P* value
Age (yr), mean ± SD	73.5 ± 9.4	67.8 ± 10.4	69.3 ± 10.3	0.002
Hyperamylasemia, pre-procedure	6 (5.1)	3 (3.8)	5 (10.6)	0.273
Cholangitis, pre-procedure	28 (23.7)	19 (24.1)	21 (44.7)	0.021
Pancreatic duct invasion				< 0.001
Yes	12 (10.2)	64 (81.0)	9 (19.1)	
No	106 (89.8)	15 (19.0)	38 (80.9)	
Lymph node metastasis				0.345
Yes	77 (65.3)	58 (73.4)	35 (74.5)	
No	41 (34.7)	21 (26.6)	12 (25.5)	
Pancreatic duct injection				0.606
0	92 (78.0)	59 (74.7)	36 (76.6)	
1-2	8 (6.8)	9 (11.4)	7 (14.9)	
⩾ 3	18 (15.3)	11 (13.9)	4 (8.5)	
Number of initially inserted SEMS				0.004
1	106 (89.8)	79 (100.0)	45 (95.7)	
2	12 (10.2)	0 (0.0)	2 (4.3)	
Post-ERCP complication				0.696
Present	5 (4.2)	2 (2.5)	2 (4.3)	
Absent	113 (95.8)	77 (97.5)	45 (95.7)	
Post-ERCP complication type				0.914
Pancreatitis	4 (3.4)	1 (1.3)	2 (4.3)	0.681
Mild/moderate	3 (2.5)/1 (0.8)	1 (1.3)/0 (0)	2 (4.3)/0 (0)	
Bleeding, mild	1 (0.8)	1 (1.3)	0 (0)	
Perforation	0 (0)	0 (0)	0 (0)	
Post-ERCP hyperamylasemia	13 (11.0)	9 (11.4)	8 (17.0)	
Stent complication				0.539
None	90 (76.3)	70 (88.6)	39 (83.0)	
Stent occlusion	27 (22.9)	9 (11.4)	8 (17.0)	
Stent migration	1 (0.8)	0 (0)	0 (0)	
Patency				0.161
No further procedure	90 (76.3)	70 (88.6)	39 (83)	
ERBD restent	1 (0.8)	0 (0)	0 (0)	
SEMS restent	20 (16.9)	9 (11.4)	3 (6.4)	
PTBD	7 (5.9)	0 (0)	5 (10.6)	

SEMS: Self-expandable metal stent; ERBD: Endoscopic retrograde biliary drainage; PTBD: Percutaneous transhepatic biliary drainage.

Table 3 Rates of complications on biliary stenting with limited endoscopic sphincterotomy according to location of cholangiocarcinoma *n* (%)

	Hilar *n* = 75	Distal *n* = 43	*P* value
Post-ERCP complication type			0.717
Pancreatitis	3 (4.0)	1 (2.3)	
Mild/moderate	2 (2.7)/1 (1.3)	1 (2.3)/0 (0)	
Bleeding, mild	1 (1.3)	0 (0.0)	
Perforation	0 (0.0)	0 (0.0)	
Post-ERCP hyperamylasemia	7 (9.3)	5 (11.6)	
Stent complication			0.756
None	57 (76.0)	33 (76.7)	1.000
Stent occlusion	17 (22.7)	10 (23.3)	
Stent migration	1 (1.3)	0 (0.0)	

ERCP: Endoscopic retrograde cholangio pancreatography.

On categorizing patients based on the type of SEMS deployed, 190 patients (78%) had uncovered SEMS while 54 patients (22%) had covered SEMS. Rates of PEP with uncovered and covered SEMS were 2.6% (5/190; mild, 4; moderate, 1) and 3.7% (2/54, both mild), respectively (P = 0.652). Mild bleeding occurred in 2 patients (1.1%) in the uncovered SEMS group alone. No significant differences were found between these two groups as to the incidence of post-ERCP complications (P = 1.000) (Table 5).

On comparing patients with no complications (n = 235) and those with complications (n = 9), the only

Table 4 Rates of complications on biliary stenting with limited endoscopic sphincterotomy according to location of pancreatic cancer *n* (%)

	Head *n* = 68	Body / Tail *n* = 11	*P* value
Post-ERCP complication type			1.000
Pancreatitis	1 (1.5)	0 (0.0)	
Mild/moderate	1 (1.5)	0 (0.0)	
Bleeding, mild	1 (1.5)	0 (0.0)	
Perforation	1 (1.5)	0 (0.0)	
Post-ERCP hyperamylasemia	8 (11.8)	2 (18.2)	0.624
Stent complication			1.000
None	60 (88.2)	10 (90.9)	
Stent occlusion	8 (11.8)	1 (9.1)	
Stent migration	0 (0.0)	0 (0.0)	

ERCP: Endoscopic retrograde cholangio pancreatography.

Table 5 Rates of complications on biliary stenting with limited endoscopic sphincterotomy according to stent type *n* (%)

	Uncovered *n* = 190	Covered *n* = 54	*P* value
Normal	181 (95.3)	49 (90.7)	
Abnormal	9 (4.7)	5 (9.3)	
Post-ERCP complication			1.000
Present	7 (3.7)	2 (3.7)	
Absent'	183 (96.3)	52 (96.3)	
Post-ERCP complication type			0.838
Pancreatitis	5 (2.6)	2 (3.7)	
Mild / moderate	4 (2.1) / 1 (0.5)	2 (3.7) / 0 (0)	
Bleeding, mild	2 (1.1)	0 (0)	
Perforation	0 (0)	0 (0)	
Post-ERCP hyperamylasemia	25 (13.2)	5 (9.3)	0.638
Stent complication			0.758
None	156 (82.1)	43 (79.6)	
Stent occlusion	33 (17.4)	11 (20.4)	
Stent migration	1 (0.5)	0 (0)	
Patency			0.012
No further procedure	156 (82.1)	43 (79.6)	
ERBD restent	1 (0.5)	0 (0)	
SEMS restent	28 (14.7)	4 (7.4)	
PTBD	5 (2.6)	7 (13)	

SEMS: Self-expandable metal stent; ERBD: Endoscopic retrograde biliary drainage; PTBD: Percutaneous transhepatic biliary drainage; ERCP: Endoscopic retrograde cholangio pancreatography.

factor that was significantly different between the two groups was the number of SEMS initially deployed [one SEMS *vs* two SEMS (bilateral), $P = 0.031$] (Table 6). Of the 231 patients with one SEMS, 5 patients developed PEP and 2 patients developed mild bleeding, while of the 13 patients with two SEMS, 2 patients developed PEP.

DISCUSSION

ES is an established technique and is commonly used to facilitate biliary stone removal. In contrast, the role of routine ES prior to stent insertion is still controversial. Many endoscopists prefer to perform ES before stenting to reduce the risk of PEP, achieve better biliary drainage, and facilitate stent placement. However, sphincterotomy carries risks such as bleeding, perforation and pancreatitis[9]. Some studies have reported that the risks of ES might exceed any benefits owing to a high incidence of ES-related complications[15]. Cotton *et al*[20] reported bleeding and pancreatitis as major early complications with ES. Freeman *et al*[15] evaluated early complications following ES and reported their incidence as 9.8% (pancreatitis, 5.4%; bleeding, 2.0%).

Previous studies, however, lack details regarding the extent of ES and its correlation with the incidence of complications. In this study, we performed limited ES before SEMS placement and described the safety of limited ES by evaluating early post-ERCP complications in patients with malignant biliary obstruction. The overall rate of early post-ERCP complications after SEMS placement with limited ES was 3.7%, including a 2.9% incidence of PEP, and 0.8% of mild bleeding. These

Table 6 Characteristics according to complications on biliary stenting with limited endoscopic sphincterotomy *n* (%)

	No complication *n* = 235	Complication *n* = 9	*P* value
Age (yr), mean ± SD (range)	70.61 ± 10.33	75.27 ± 5.55	0.993
Gender			1.000
Male	126 (53.6)	5 (55.5)	
Female	109 (46.6)	4 (44.5)	
Total bilirubin (mg/dL), pre-procedure, mean ± SD	7.00 ± 6.46	8.38 ± 6.54	0.362
Normal	52 (22.2)	1 (11.1)	0.453
Elevated	183 (77.8)	8 (88.9)	
Hyperamylasemia, pre-procedure	13 (5.5)	1 (11.1)	0.485
Cholangitis, pre-procedure	64 (27.2)	4 (44.4)	0.472
Diagnosis			0.748
Cholangiocarcinoma	112 (47.6)	6 (66.7)	
Hilar	71 (30.2)	4 (44.4)	
Distal	41 (17.4)	2 (22.2)	
Pancreatic cancer	77 (32.8)	2 (22.2)	
Head	66 (28.1)	2 (22.2)	
Body/tail	11 (4.7)	0 (0.0)	
Gallbladder cancer	20 (8.5)	1 (11.1)	
Ampullary cancer	18 (7.7)	0 (0.0)	
Hepatocellular carcinoma	3 (1.3)	0 (0.0)	
Others	5 (2.1)	0 (0.0)	
Pancreatic duct invasion			0.324
Yes	80 (34.0)	5 (55.6)	
No	155 (66.0)	4 (44.4)	
Lymph node metastasis			0.176
Yes	166 (70.6)	5 (55.6)	
No	69 (29.4)	4 (44.4)	
Pancreatic duct injection			0.662
0	181 (77.0)	6 (66.7)	
1-2	23 (9.8)	1 (11.1)	
⩾ 3	31 (13.2)	2 (22.2)	
Number of inserted SEMS			0.031
1	224 (95.3)	7 (77.8)	
2	11 (4.7)	2 (22.2)	
Stent type			1.000
Uncovered	183 (77.9)	7 (77.8)	
Covered	52 (22.1)	2 (22.2)	
Stent complication			1.000
Stent occlusion	42 (17.9)	2 (22.2)	
Stent migration	1 (0.4)	0 (0.0)	
Patency			0.512
No further procedure	192 (81.7)	7 (77.8)	
ERBD restent	1 (0.4)	0 (0.0)	
SEMS restent	31 (13.2)	1 (11.1)	
PTBD	11 (4.7)	1 (11.1)	

SEMS: Self-expandable metal stent; ERBD: Endoscopic retrograde biliary drainage; PTBD: Percutaneous transhepatic biliary drainage; ERCP: Endoscopic retrograde cholangio pancreatography.

rates of complications are relatively low compared to the complication rates of approximately 10% and an overall mortality of 0.42% in published data[2,13-17].

Bleeding is a serious complication of ES and its incidence is reported to be between 1 and 10%[12,22-25]. In our study, only 2 patients (0.8%) developed mild bleeding, which could be managed by conservative treatment. No instances of moderate or severe bleeding were reported. Wang *et al*[26], in their analysis of delayed hemorrhage following ES in 1741 patients did not find delayed bleeding in any patient who underwent small ES (*n* = 194). These results might be related to the limited extent of the ES and the compressive effect of the SEMS[27]. On the basis of these studies, limited ES does not seem to be associated with clinically significant bleeding.

A recent meta-analysis by Cui *et al*[28], analyzing biliary stenting for malignant biliary obstruction reported that the incidence of PEP was significantly lower with ES than without ES (3.5% *vs* 8.9%, *P* = 0.04, OR = 0.34, 95%CI: 0.12-0.93) and recommended ES before stent placement as a useful option to reduce the incidence of PEP. Similar low rates (2.2%) were reported by Giorgio *et al*[29] in their randomized control trial involving 10 Fr plastic stent after ES for inoperable malignant common bile duct (CBD) obstruction. In our study, despite the absence of a control group, the low rate of PEP (2.9%) is comparable to the results of the

two above-mentioned studies. Our PEP rates are also low compared to the rates of 9.4% and 6.3%, with metal stent placement following ES for distal biliary strictures, reported by Hayashi *et al*[17] and by Kahaleh *et al*[30], respectively. In our study, the incidence of PEP was 4.0% in hilar cholangiocarcinoma and 2.3% in distal cholangiocarcinoma. Although the outcomes with ES for malignant biliary strictures, especially cholangiocarcinoma, are controversial, several previous studies have demonstrated a lower incidence of PEP in the ES group compared to the non-ES group[8,9,31]. Jeong *et al*[8] investigated the risk of pancreatitis in patients with malignant obstructive jaundice following percutaneous or transpapillary stent placement. They also studied the effect of preliminary ES in the transpapillary stent group. Their results demonstrated a higher rate of pancreatitis in the transpapillary stent group ($P = 0.502$) and the authors concluded that SEMS placement through the intact sphincter of Oddi may increase the risk pancreatitis.

The management of hilar obstruction is more difficult than distal bile duct strictures because of the underlying anatomical and technical complexity. Bilateral stent placements for Bismuth type Ⅱ to Ⅳ hilar cholangiocarcinoma are also very complicated and result in increased endoscopic manipulations[32]. The higher incidence of post-ERCP complications in patients who had two SEMS (bilateral stents) placed could be related to these reasons. In these situations, limited ES before stenting could be an effective strategy for facilitating more complex stenting procedures[33]. Limited ES may allow for easier stent placement and reduce resistance to biliary instrumentation. Additionally, proximal bile duct strictures may contribute to a fulcrum effect resulting in medial displacement of the distal stent and, consequently, stent related compression of the pancreatic duct[9]. Limited ES might prevent the risk of pancreatitis by reducing stent-related pancreatic duct obstruction. In case of distal CBD strictures, ES may allow the stent to achieve a better final diameter, and thus, better drainage.

Our data demonstrated a lower rate of PEP in patients with cholangiocarcinoma compared to previous studies. Limited ES, therefore, could be an effective and useful technique to prevent PEP following stenting for cholangiocarcinoma, especially hilar tumors. The incidence of PEP was lesser in pancreatic cancers than in cholangiocarcinoma in this study (1.3% *vs* 3.4%, $P = 0.681$). Some studies demonstrated that pancreatic cancers with obstruction of the main pancreatic duct had a lower degree of PEP, possibly due to diminished pancreatic exocrine function and suggested that ES may be unnecessary in such cases[12,17,28,32]. Although further confirmation is required, we noted that performing limited ES prior to SEMS placement in patients with unresectable pancreatic cancers did not result in a higher incidence of adverse events compared to published data[17]. Additionally, it is possible that ES may be advantageous in selected cases, depending on pancreatic duct status, stent diameter, stent type (especially fully covered SEMS) or ampulla size, in rendering the procedure easier as biliary strictures secondary to pancreatic cancer tend to be narrow and rigid. ES may also facilitate stent exchange during the follow-up period[32] as demonstrated in our study, where the success rate of SEM restenting, when indicated, was 97%.

Stent migration is a late complications of biliary stenting with ES. Stent migration seems to be associated with stent type as well as ES. Covered SEMS are not fully embedded in bile duct, and therefore, are associated with the potential risk of stent migration. A previous study reported increased frequency of stent migration when ES was performed before placement of covered SEMS[16]. In contrast, other studies did not support this finding[29,34]. In our study, stent migration occurred in only 1 patient (0.4%) and limited ES did not seem to be a significant factor associated with migration, regardless of the stent type.

This retrospective study has a few limitations. First, the possibility of inaccurate data collection cannot be overlooked. For example, procedure-related abdominal pain is difficult to distinguish from the breakthrough pain of malignancy and may have contributed to a bias in measuring the rate of PEP. Second, this study had a single-center design without a control group (non-ES group), which might influence the interpretation of the effect of limited ES. Further prospective multicenter studies with the inclusion of control groups are needed to overcome these limitations.

In conclusion, limited ES is a feasible, safe and effective procedure to facilitate placement of SEMS in patients with malignant biliary obstruction. Limited ES is not significantly associated with complications like severe bleeding or PEP and its use may represent a better strategy to achieve successful stent placement, especially in cases like hilar strictures that require complex procedural techniques.

COMMENTS

Background

Endoscopic biliary stent placement has become the primary management therapy for palliation in patients with malignant biliary obstruction. Endoscopic sphincterotomy (ES) is performed to reduce the risk of post-ERCP pancreatitis (PEP) and facilitate stent placement. Although many endoscopists routinely perform ES before self-expandable metal stent (SEMS) placement, the role of ES is still controversial in biliary stenting. Effects and complications on the degree of ES also need to be investigated. There have been few studies on the complications or effects of limited ES.

Research frontiers

At present, there have been some reports to evaluate the safety and efficacy of ES before placement of SEMS and the existing data is contradictory. Currently, there are no guidelines regarding ES for biliary stenting. There is a lack of detail, regarding the extent of ES, and its correlation with complications.

Innovations and breakthroughs

Limited ES is not significantly associated with complications like severe

bleeding or PEP. It may be useful to achieve successful stent placement. Limited ES is a feasible, safe and effective procedure to facilitate placement of SEMS in patients with malignant biliary obstruction.

Applications

This retrospective study showed that limited ES could be useful to facilitate placement of SEMS, especially in cases, like hilar strictures, requiring complex procedural techniques without major complications. Further large randomized controlled trials are required.

Terminology

ES is a method to provide access to the biliary system for therapy, which means cutting of the sphincter or muscle that lies at the juncture of the intestine with both the bile and pancreatic ducts. Limited ES is defined as sphincterotomy less than one-third the extent of major ES.

Peer-review

This is an interesting manuscript that has not been published extensively. The authors showed in this study that the clinical outcomes in patients who did undergo limited ES before placement of SEMS for malignant biliary obstruction. The results provide new evidence that limited ES could be a feasible strategy for SEMS placement without significant complications.

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ORIGINAL ARTICLE

Retrospective Study

Fibrin sealant for closure of mucosal penetration at the cardia during peroral endoscopic myotomy: A retrospective study at a single center

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Author contributions: Zhang WG analyzed the data and wrote the manuscript; Li HK acquired the data; Linghu EQ designed the research.

Institutional review board statement: The study was carried out under the ethics committee approval from the Chinese PLA General Hospital (Beijing China).

Informed consent statement: Informed consent was waived due to the retrospective nature of this study.

Conflict-of-interest statement: We declare that we have no financial and personal relationships with other people or organizations that can inappropriately influence our work.

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Abstract

AIM

To assess the efficacy and safety of fibrin sealant for closure of mucosal penetration at the cardia during peroral endoscopic myotomy (POEM).

METHODS

Twenty-four patients who underwent POEM and experienced mucosal injury of the cardia during the procedure were retrospectively identified. Of the 24 patients, 21 had mucosal penetration and 3 had only slight mucosal damage without penetration. The 21 patients with mucosal penetration received fibrin sealant for closure at the site of penetration. Penetration-related characteristics, treatment, and recovery were reviewed for all 21 patients to assess the efficacy and safety of fibrin sealant for closure of mucosal penetration at the cardia. Clinical data, including general characteristics, procedure-related parameters, Eckardt scores, lower esophageal sphincter pressures (LESP), and esophagogastroduodenoscopy (EGD) results, were analyzed to determine their influence on treatment success after mucosal penetration during POEM.

RESULTS

All 21 patients had a solitary mucosal penetration in the cardia (12 in esophageal region of the cardia, 9 in the stomach region of the cardia, and 1 in both the esophageal and stomach regions). Twelve had a

hole-like penetration and 9 had a linear penetration. For those with a hole-like penetration, the mean size was 0.14 cm^2 (0.02-0.32 cm^2). For those with a linear penetration, the median size was 0.37 cm (0.10-1.00 cm). Closure of the mucosal penetration using fibrin sealant was performed successfully in all 21 patients (two patients required 5 mL fibrin sealant, and the remaining 19 patients required 2.5 mL). Two patients had a nasogastric tube placed for five days after POEM; the remaining 19 patients were kept fasting for 3 d. All 21 patients were discharged after a median of 5 d (range: 5-7 d) postoperatively. During a median 42 mo (range: 9-62 mo) follow-up, all 21 patients with a mucosal penetration successfully healed without the occurrence of infection, ulcer, or esophagitis. Furthermore, the median LESP decreased from 31.9 mmHg (range: 21.9-67.1 mmHg) preoperatively to 20.3 mmHg (range: 6.0-41.0 mmHg) postoperatively ($P < 0.05$). The median preoperative and postoperative Eckardt scores were 5.0 (range; 4-10) and 1.0 (range: 0-4), respectively ($P < 0.05$). Of the 21 patients with mucosal penetration, symptom remission, which is defined as a postoperative Eckardt score $\leqslant 3$, was achieved in 20 patients (95.2%) indicating that mucosal penetration did not influence the success of POEM treatment if closed successfully using fibrin sealant.

CONCLUSION

Fibrin sealant is safe and effective for closure of mucosal penetration during POEM. Mucosal penetrations do not appear to influence the treatment success of POEM if closed successfully using fibrin sealant. Additional studies regarding the feasibility, efficacy, and safety of fibrin sealant for closure of larger mucosal penetrations is warranted.

Key words: Fibrin sealant; Mucosal penetration; Peroral endoscopic myotomy; Efficacy; Safety

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Core tip: Mucosal penetration is one of the most dangerous adverse events during peroral endoscopic myotomy (POEM). We first reported the feasibility of fibrin sealant for closure of mucosal penetration at the cardia in two cases in 2012. However, there remains a lack of evidence about the treatment response to fibrin sealant for mucosal penetration in a cohort of patients who experienced this complication. Thus, we retrospective identified and analyzed the cases for 21 patients who experienced a mucosal penetration and received fibrin sealant for penetration closure during POEM, providing further support for the efficacy and safety of fibrin sealant for penetration closure. Moreover, instructions regarding the usage of fibrin sealant for penetration closure were provided for endoscopists who might be worried about mucosal penetrations during POEM.

Zhang WG, Linghu EQ, Li HK. Fibrin sealant for closure of mucosal penetration at the cardia during peroral endoscopic myotomy: A retrospective study at a single center. *World J Gastroenterol* 2017; 23(9): 1637-1644 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1637.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1637

INTRODUCTION

Peroral endoscopic myotomy (POEM) is an effective and safe procedure for achalasia, and is becoming one of the first-line therapies to treat achalasia[1-4]. However, some major perioperative adverse events after POEM have been reported; mucosal penetration is one of the most dangerous adverse events[1,2,5,6]. Mucosal penetration has been reported to occur in 4.2%-17.3% of POEM procedures[1,2,5,7]. Different studies have reported on different treatment strategies, including observation without special treatment, sealing of the penetration injury by hemostatic clips, and closing the penetration defect using fibrin sealant[8,9]. Mucosal penetration usually occurs at the cardia, where a myotomy is performed during POEM. We previously reported the usage of fibrin sealant for mucosal penetration at the cardia in two cases in 2012[7]. However, long-term outcomes with a larger population are needed to further assess this treatment strategy. To the best of our knowledge, there is still no evidence regarding the treatment response to fibrin sealant for mucosal penetration during POEM in a larger cohort. The purpose of the present study was to evaluate the efficacy and safety of fibrin sealant for closure of mucosal penetration at the cardia during POEM.

MATERIALS AND METHODS

Patients

Twenty-four patients who underwent POEM and experienced mucosal injury of the cardia during the procedure between November 2010 and February 2016 were identified and collected. Of these, 21 had mucosal penetration and 3 had only minor mucosal damage without penetration. All 21 patients with a penetrating injury received fibrin sealant for closure of the mucosal penetration; these 21 patients were included in the analysis.

Prior to undergoing POEM, all patients had undergone esophagogastroduodenoscopy (EGD), high-resolution manometry (HRM), and had their symptoms evaluated using Eckardt scores to confirm a diagnosis of achalasia.

POEM procedure

Patients were admitted and fasted for 48 h before

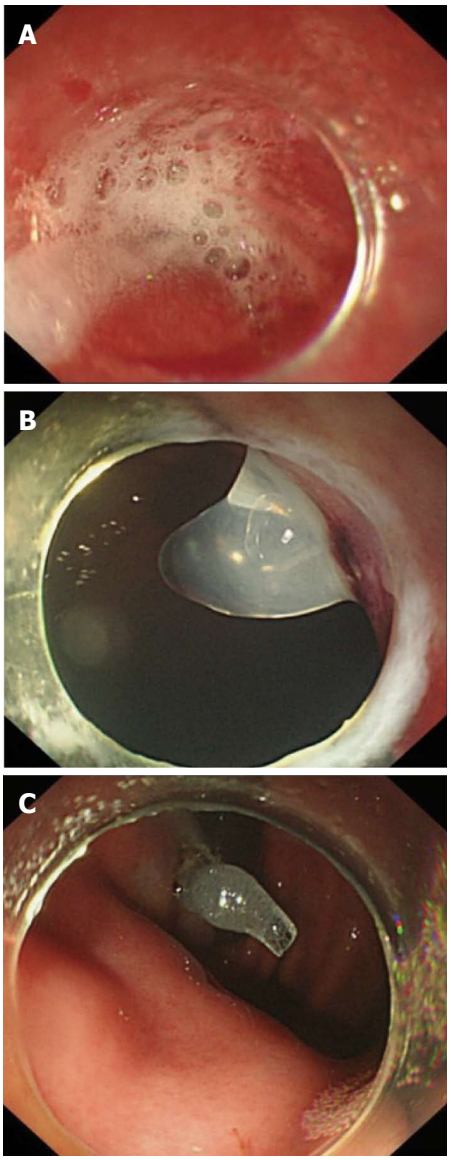

Figure 1 Closure of the mucosal penetration using fibrin sealant. A: Spraying fibrin sealant in the submucosal tunnel; B: Fibrin sealant fully covers the penetration (imaging from esophageal lumen); C: Fibrin sealant fully covers the penetration (imaging from stomach lumen).

POEM. Patients underwent EGD prior to POEM to ensure that there was no residual food in the esophageal lumen. During the procedure, patients were kept in a supine position with the right shoulder elevated, and general anesthesia was administered with continuous monitoring of electrocardiography (ECG), respirations, blood pressure, and oxygen saturation.

An additional cap attached at the top of the gastroscopy was required. With the outside cap diameter (12.0 mm) as reference, the penetration size was estimated. Then, POEM was performed. First, a submucosal injection was performed with methylene blue saline solution (1:10000), and a mucosal incision was made at the right posterior esophageal wall approximately 6-10 cm from the gastroesophageal junction (GEJ). Then, a submucosal tunnel was established, passing over the GEJ to approximately 2-3 cm into the proximal stomach. The myotomy started 2 cm distal to the incision and extended 2-3 cm into the stomach. After complete hemostasis and ensuring that an endoscope could easily pass the cardia, the mucosal incision was sutured with hemostatic clips.

In the present study, four different types of myotomy were performed, including inner circular muscle myotomy, full-thickness myotomy, glasses-style anti-reflux myotomy, and progressive full-thickness myotomy.

Glasses-style anti-reflux myotomy retains about 1 cm of longitudinal muscle at the level of the dentate line after incision of the inner circular muscle, and makes selective incision of the longitudinal muscle right above and below the dentate line. The retained 1 cm of longitudinal muscle is expected to achieve the best result to prevent reflux after POEM.

Closure of mucosal penetration

Once mucosal penetration occurred during the POEM procedure, fibrin sealant was sprayed into the penetrating injury in the submucosal tunnel under direct endoscopic visualization to ensure that the fibrin sealant fully covered the defect (Figure 1). The amount of fibrin sealant consumed was based on the size of the defect. For large penetrations, which were difficult to close only using fibrin sealant, a hemostatic clip was used to make a preliminary clipping that approximated the edges of the defect; then, fibrin sealant was sprayed to fully cover the penetration defect (Figure 2).

Postoperative treatment

X-ray or chest and abdomen computed tomography (CT) was routinely performed postoperatively to evaluate for gas-related complications immediately after POEM. Delayed hemorrhage, pulmonary infection, and other complications were also monitored under EGD after the procedure. Evaluation of tunnel infection or penetration-raised esophagitis also occurs during the postoperative EGD examination, especially if the mucosa was penetrated during the procedure. After fasting for 3 d postoperatively, a liquid diet was followed for 1 d, then a soft diet. A regular diet was resumed 1 mo after POEM. Postoperative medications, including double-dose proton pump inhibitor (PPI) and antibiotics, were prescribed; PPI was required for at least 4 wk.

Follow-up

Patients were scheduled for a follow-up visit at 3 mo, 6 mo, 1 year, and 2 years after POEM. EGD, high-resolution manometry, and 24-h esophageal pH monitoring were required at the follow-up to assess the healing of the mucosal penetration or the entry incision, lower esophageal sphincter pressures, and postoperative esophagitis, respectively. For patients who experienced mucosal penetration during POEM,

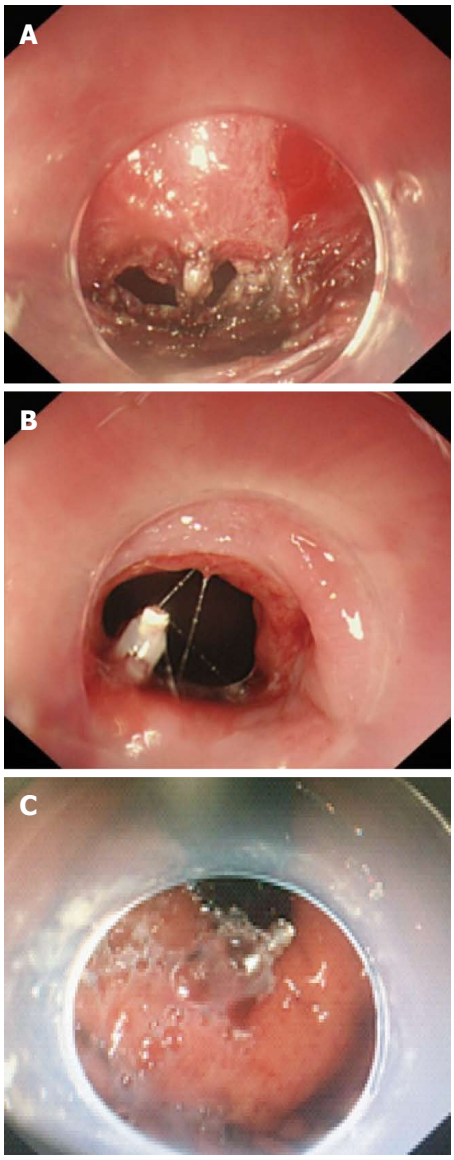

Figure 2 Closure of a 0.8 cm × 0.4 cm mucosal penetration using a hemostatic clip and fibrin sealant. A: The appearance of the 0.8 cm × 0.4 cm mucosal penetration (imaging from the submucosal tunnel); B: A hemostatic clip was used to make a preliminary clipping (imaging from esophageal lumen); C: Fibrin sealant fully covers the preliminary clipped penetration (imaging from stomach lumen).

two additional follow-ups at one week and six weeks postoperatively were added. Postoperative complications and Eckardt scores for each patient were recorded *via* the telephone. Treatment success was defined as Eckardt scores no greater than 3.

Statistical analysis

All statistical analyses were performed using SPSS software version 17.0. Variables are expressed as mean or median. Paired-samples Student's *t*-test or Wilcoxon matched-pairs signed-ranks test was used to estimate the treatment outcomes of POEM. All reported *P*-values are two-tailed; *P*-values of < 0.05 were considered statistically significant.

Table 1 Clinical characteristics and procedure-related parameters for 21 consecutive patients who experienced mucosal penetration during peroral endoscopic myotomy procedure

Patient characteristics	
Sex, female/male (*n*)	12/9
Age (yr), mean (range)	38.0 (15-64)
Symptom duration (mo), median (range)	26.0 (10-360)
Previous treatment (*n*)	
Botox injection	3
Bouginage	1
Chicago classification (*n*)	
Type Ⅰ	2
Type Ⅱ	18
Type Ⅲ	1
Procedure-related parameters	
Procedure time (min.), median (range)	58.9 (20.0-141.0)
Tunnel length (cm), mean (range)	11.7 (7-18)
Myotomy length (cm), mean (range)	5.6 (3-10)
Myotomy type (*n*)	
Inner circular muscle myotomy	10
Full-thickness myotomy	1
Glasses-style anti-reflux myotomy	1
Progressive full-thickness myotomy	9

Table 2 Characteristics of the 21 mucosal penetrations and the treatment outcomes using fibrin sealant

Penetration shape, *n* (%)	
Hole-like penetration	12 (57.1)
Linear penetration	9 (42.9)
Penetration location	
Esophageal part of cardia	12 (61.9)
Stomach part of cardia	8 (38.1)
Both esophageal and stomach parts of cardia	1 (4.8)
Penetration size	
Hole like penetration (cm^2), mean (range)	0.14 (0.02-0.32)
Linear penetration (cm), median (range)	0.37 (0.10-1.00)
Consumed fibrin sealant amount (*n*)	
5.0 mL	3
2.5 mL	18
Postoperative treatment	
Placement of nasogastric tube (*n*)	2
Postoperative stay (d), median (range)	5 (5-7)

RESULTS

Patient characteristics and procedure-related parameters

As shown in Table 1, the study cohort consisted of 9 men and 12 women, aged 15 to 64 years (mean, 38.0 years). Among the 21 patients with mucosal penetration, the median duration of symptoms was 26.0 mo (range, 10-360 mo). Three patients had a previous Botox injection, and one had a previous bouginage. According to the Chicago classification, 2 patients were classified as type Ⅰ, 18 as type Ⅱ, and 1 as type Ⅲ. All 21 patients successfully underwent POEM with a median operative time of 58.9 min (range, 20.0-141.0 min). The mean length of the submucosal tunnel and myotomy was 11.7 cm (range, 7-18 cm) and 5.6 cm

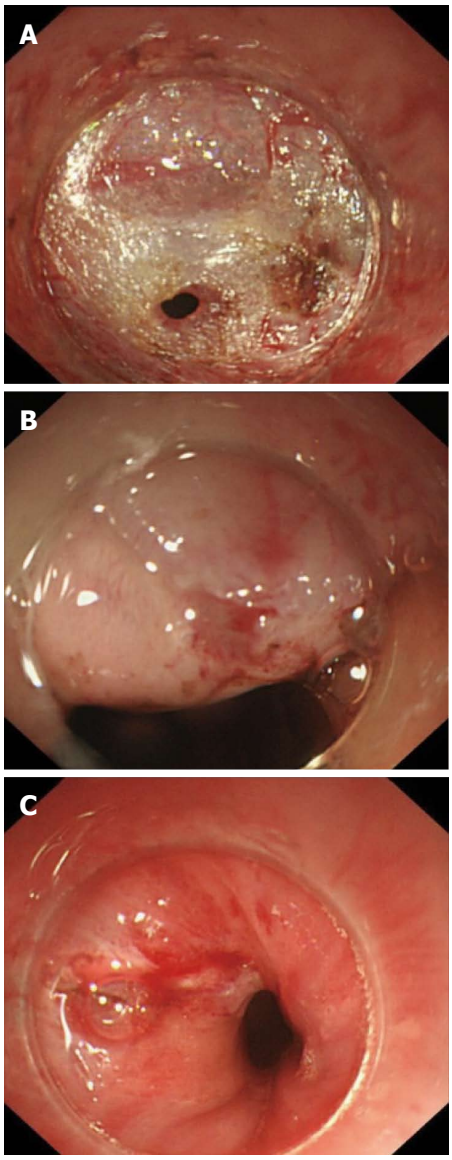

Figure 3 Two kinds of mucosal penetration under esophagogastroduodenoscopy. A: Hole-like penetration (imaging from submucosal tunnel); B: Hole-like penetration (imaging from esophageal lumen); C: Linear penetration (imaging from esophageal lumen).

(range, 3-10 cm), respectively.

With regards to myotomy type, 10 patients received an inner circular muscle myotomy, 9 had a progressive full-thickness myotomy, 1 had a full-thickness myotomy, and 1 had a glasses-style anti-reflux myotomy.

Mucosal penetration characteristics and treatment outcomes after fibrin sealant

As shown in Table 2, all 21 patients had a solitary mucosal penetration in the cardia (12 in the esophageal region of cardia, 9 in the stomach region of cardia, and 1 in both the esophageal and stomach regions). Twelve patients had a hole-like penetration, while 9 had a linear penetration (Figure 3). Among those with a hole-like penetration, the mean size was 0.14 cm^2 (range, 0.02-0.32 cm^2). For the linear penetrations,

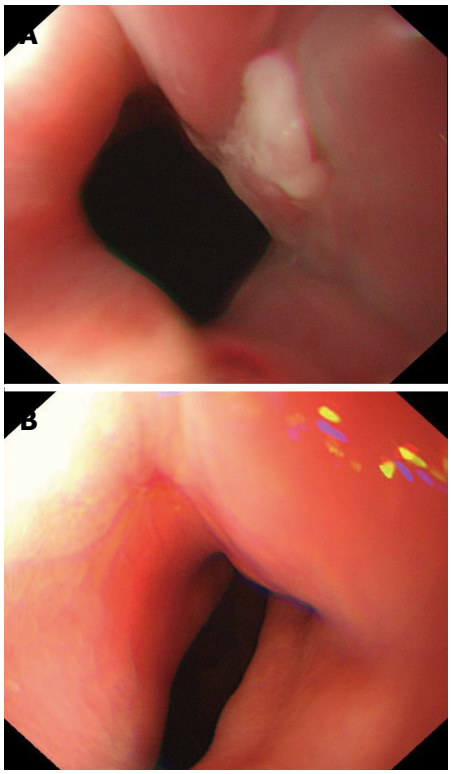

Figure 4 Healing process of the mucosal penetration after being closed using fibrin sealant. A: The appearance of penetration at one week after peroral endoscopic myotomy (POEM) (imaging from esophageal lumen); B: The appearance of penetration at six weeks after POEM (imaging from esophageal lumen).

the median size was 0.37 cm (range, 0.10-1.00 cm). Closure of mucosal penetration using fibrin sealant was performed successfully in all 21 patients. Two cases, one of which was a relatively longer linear penetration (1.0 cm), consumed 5 mL of fibrin sealant. Only 2.5 mL of sealant was required for the remaining 19 cases. One case had a 0.8 cm × 0.4 cm hole-like penetration that was difficult to close using only fibrin sealant; thus, one hemostatic clip was used to make a preliminary closure of the penetration, and fibrin sealant was then sprayed to fully cover the mucosal defect. The first two patients to experience mucosal penetration had a nasogastric tube placed for 5 d after POEM; the remaining 19 patients were kept fasting for 3 d. The mucosal penetrations had an appearance on EGD at one week postoperatively as shown in Figure 4A and an appearance at 6 wk as shown in Figure 4B. All 21 patients were discharged after a median of 5 d (range, 5-7 d) postoperatively. During a median 42 mo (range, 9-62 mo) follow-up, all 21 mucosal penetrations successfully healed without the occurrence of penetration-raised tunnel-infection, ulcer, esophagitis, mediastinal leak, or peritoneal leak. Detailed data of the 21 patients with mucosal penetrations are shown in Table 3.

Treatment outcomes of POEM and complications

Symptom remission, which was defined as postopera-

Table 3 Detailed data of the mucosal penetrations from all 21 patients

Number	Shape	Location	Estimated size (cm/cm^2)	Postoperative treatment	Postoperative stay (d)	Amount of consumed fibrin sealant (mL)	Postoperative complaint
1	Hole like	GOC	0.4 × 0.4	NG tube	7	5	Slight abdominal pain
2	Hole like	GOC	0.4 × 0.5	NG tube	7	2.5	Normal
3	Hole like	GOC	0.3 × 0.2	Fasting	7	2.5	Normal
4	Linear	EOC	0.3	Fasting	7	2.5	Normal
5	Hole like	EOC	0.4 × 0.3	Fasting	7	2.5	Normal
6	Linear	EOC	0.3	Fasting	6	2.5	Normal
7	Linear	EOC	0.1	Fasting	6	2.5	Normal
8	Linear	GOC	0.4	Fasting	6	2.5	Normal
9	Linear	GOC	0.4	Fasting	6	2.5	Normal
10	Hole like	EOC	0.3 × 0.2	Fasting	5	2.5	Normal
11	Linear	EOC	0.2	Fasting	5	2.5	Normal
12	Hole like	EOC	0.2 × 0.2	Fasting	5	2.5	Normal
13	Linear	BOC	1.0	Fasting	5	5	Normal
14	Hole like	EOC	0.8 × 0.4	Fasting	5	2.5 (one hemostatic clip)	Normal
15	Linear	EOC	0.3	Fasting	5	2.5	Normal
16	Hole like	GOC	0.5 × 0.5	Fasting	5	2.5	Normal
17	Hole like	EOC	0.4 × 0.4	Fasting	5	2.5	Normal
18	Hole like	GOC	0.3 × 0.3	Fasting	5	2.5	Normal
19	Hole like	EOC	0.4 × 0.4	Fasting	5	2.5	Normal
20	Linear	GOC	0.3	Fasting	5	2.5	Normal
21	Hole like	EOC	0.1 × 0.2	Fasting	5	2.5	Normal

NG tube: Nasogastric tube; GOC: Gastric part of the cardia; EOC: Esophageal part of the cardia; BOC: Both gastric and esophageal parts of the cardia.

Table 4 Symptom relief, manometry outcomes, and reflux complications of the 21 patients who experienced mucosal penetration during peroral endoscopic myotomy

Follow-up period (mo), median (range)	42.0 (9-62)
Symptom relief	
Eckardt score, median (range)	
Pre-treatment	5.0 (4-10)
Post-treatment	1.0 (0-4)
Pre/post-treatment difference value	4.8 (1-9)
Treatment success (Eckardt score ⩽ 3), *n* (%)	20 (95.2)
Manometry outcomes	
Manometry follow-up rate, *n* (%)	15 (71.4)
LESP (mmHg), median (range)	
Pre-treatment	31.9 (21.9-67.1)
Post-treatment	20.3 (6.0-41.0)
Pre/post-treatment difference value	14.1 (9.6-35.2)
Post-POEM esophagitis on EGD	
LA-A	1
LA-B	2
Overall, *n* (%)	3 (14.3)
Gas-related complications, *n*	
Pneumothorax	1
Pneumoperitoneum	1
Pneumomediastinum	1
Overall	3

POEM: Peroral endoscopic myotomy; EGD: Esophagogastroduodenoscopy; LA-A: Los Angeles classification A; LA-B: Los Angeles classification B; LESP: Lower esophageal sphincter pressure.

tive Eckardt score ⩽ 3, was achieved in 20 patients (95.2%) during a median of 42 mo (range, 9-62 mo) follow-up (Table 4). The median preoperative and postoperative Eckardt score were 5.0 (range, 4-10) and 1.0 (range, 0-4), respectively ($P < 0.05$). A total of 15 patients had HRM both before and after treatment; 6 patients did not undergo post-operative HRM due to procedure-related discomfort or for other personal reasons. The median lower esophageal sphincter (LES) pressure decreased from 31.9 mmHg (range, 21.9-67.1 mmHg) preoperatively to 20.3 mmHg (range, 6.0-41.0 mmHg) postoperatively ($P < 0.05$), indicating a statistically significant decrease after POEM. All the treatment outcomes, mentioned above, indicated that mucosal penetration did not influence the treatment success of POEM if the defect was closed successfully using fibrin sealant.

In terms of complications, 3 patients had post-POEM esophagitis on EGD; 2 were classified as Los Angeles classification B and one as Los Angeles classification A. Moreover, another 3 patients had gas-related complications: 1 experienced pneumothorax, 1 experienced pneumoperitoneum, and 1 experienced pneumomediastinum.

DISCUSSION

Esophageal achalasia is an esophageal motility disorder of unknown cause and is characterized by failure of the LES to relax and impaired peristalsis of the esophageal body[10]. Conventional therapies for achalasia include pharmacological therapy, endoscopic balloon dilation, and Heller-Dor surgery. With recent advances in endoscopic treatment techniques and devices, Inoue *et al*[9] have developed peroral endoscopic myotomy, in which the myotomy is performed through a submucosal tunnel. Excellent long-term outcomes after POEM have been reported[1,2], and POEM is expected to become a first-line therapy for achalasia

requiring surgical intervention. However, some major perioperative adverse events from POEM have also been reported, with mucosal penetration being one of the most dangerous adverse events[1,2,5,6]. Mucosal penetration during POEM occurs at a rate ranging from 4.2%-17.3% depending on the study[1,2,5,7]. Treatment for this complication has varied, with some patients undergoing observation without special treatment, being sealed by multiple clips or an endoscopic suture device (OverStitch™ Endoscopic Suturing System; Apollo Endosurgery Austin, Texas), or being treated with the defect being closed using fibrin sealant[11-15]. Closure using hemostatic clips is not an ideal method. Once target mucosa is clipped, adjacent mucosa has the tendency to spontaneously split, making it hard to completely seal the penetration. Using endoscopic suture with the OverStitch system is usually considered when the mucosal penetration is large and difficult to close using conventional clips.

We first reported the usage of fibrin sealant for closure of mucosal penetration at the cardia in two cases in 2012[7]. The present study further supports the efficacy and safety of fibrin sealant for closure of mucosal penetration, including long-term follow-up in a larger population (21 patients). The biggest risk of mucosal penetration is that the fluids from the stomach or the esophagus could flow into the submucosal tunnel or the mediastinum and cause tunnel-infection, ulceration, esophagitis, mediastinal leak, or peritoneal leak[15,16]. In our study, all 21 mucosal penetrations healed successfully without tunnel-infection, ulceration, esophagitis, mediastinal leak, or peritoneal leak occurring. Of note, all 21 mucosal penetrations in the present study occurred at the cardia; one explanation for this might be that the small operating space and abundant submucosal vessels that demand repeated electrocoagulation during the POEM procedure make the mucosa in this area vulnerable. We presented the healing process of the mucosa after being closed using fibrin sealant (Figure 4). During a median 42 mo (range, 9-62 mo) follow-up, all patients had completely healed.

The required amount of fibrin sealant to adequately cover the mucosal injury was based on the size of the penetration; the endoscopist must ensure that the penetration is fully covered. In this cohort, we utilized 5 mL of fibrin sealant in the first patient with penetration because of lack of experience using this technique. Another patient who had a longer linear penetration (1.0 cm) consumed 5 mL fibrin sealant. The remaining 19 cases only required 2.5 mL. Of note, for penetration injuries that create larger defects, which are difficult to close using only fibrin sealant, it is suggested that one or two hemostatic clips be used to make a preliminary clipping that approximates the edges of the mucosal defect before then using fibrin sealant to fully cover the hole. Nasogastric tubes were placed postoperatively in the first two cases with penetration, again due to lack of experience with patient recovery from this technique. However, the remaining 19 cases did not require a nasogastric tube and had excellent healing results, suggesting that the postoperative placement of a nasogastric tube is not necessary in cases with a relatively small penetration.

The treatment outcomes of POEM for the 21 patients with mucosal penetration were excellent, with a 95.2% treatment success (Eckardt score $\leqslant$ 3), a 14.3% rate of gas-related complications, and a 14.3% rate of post-POEM esophagitis, indicating that mucosal penetration did not influence the treatment success of POEM if closed successfully using fibrin sealant.

Given that the sizes of the mucosal penetrations in this study were all relatively small, it is not clear whether the defects could have been observed and would have closed spontaneously. Therefore, a prospective randomized controlled trial comparing observation without special treatment to treatment with fibrin sealant is warranted. In previous studies evaluating intraoperative mucosal penetration during POEM, the injured mucosa could be closed only by prolonged fasting in those who received inner circular muscle myotomy. In the present study, 10 patients had an inner circular muscle myotomy, 1 had a full-thickness myotomy, 1 had a glasses-style anti-reflux myotomy, and 9 had a progressive full-thickness myotomy. Further research is needed to determine if the injured mucosa was more likely to close spontaneously in those who received inner circular muscle myotomy than in those who received a full-thickness myotomy. Our study is not without limitations. One limitation was that the submucosal defects in our study were all relatively small, so we cannot draw conclusions regarding the feasibility, efficacy, and safety of fibrin sealant in closing large mucosal penetrations. Additionally, with a small sample size of only 21 patients, we were not able to stratify our results to draw conclusions regarding the required amount of fibrin sealant based on the penetration size. Another limitation is that this was a single center study, suggesting that our results may not be representative of findings in other hospitals. However, to the best of our knowledge, this is the largest published study regarding the treatment response to fibrin sealant for mucosal penetration during POEM, incorporating data from 21 patients. The present study also provides instruction regarding the usage of fibrin sealant for penetration closure for endoscopists, which may be especially helpful for those who are unfamiliar with the technique or who might be worried about mucosal penetrations during POEM.

In conclusion, the use of fibrin sealant to close mucosal penetration during POEM is safe and effective. Mucosal penetrations do not appear to influence the treatment success of POEM if closed successfully using fibrin sealant. However, further research regarding the feasibility, efficacy, and safety of fibrin sealant for closing larger mucosal penetrations is warranted.

COMMENTS

Background

Peroral endoscopic myotomy (POEM) has been proved to be an effective and safe procedure for achalasia. However, mucosal penetration has been reported to be one of the most dangerous adverse events during POEM.

Research frontiers

The treatments for the injured mucosa include observation without special treatment, sealed by multiple clips hemostatic clips, endoscopic suture device (OverStitch™ Endoscopic Suturing System; Apollo Endosurgery Austin, Texas) or closed using fibrin sealant. Fibrin sealant seems to be effective and safe for the penetration closure and the authors have reported a case in 2012. However, there is still no evidence regarding the treatment response to fibrin sealant for mucosal penetration during POEM in a larger cohort.

Innovations and breakthroughs

To the best of our knowledge, this is the largest published study regarding the treatment response to fibrin sealant for mucosal penetration during POEM, incorporating data from 21 patients.

Applications

The present study provided an instruction about the usage of fibrin sealant for penetration closure for endoscopists, especially for novices, who might be worried about the mucosal penetrations during POEM.

Terminology

POEM: Peroral endoscopic myotomy, a recently developed endoscopic therapeutic technique, was performed for achalasia. peroral endoscopic myotomy.

Peer-review

This is an interesting, retrospective study from one center, on fibrin sealant for closure of cardia mucosal penetration during POEM.

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ORIGINAL ARTICLE

Clinical Trials Study

Outcomes of gastrointestinal defect closure with an over-the-scope clip system in a multicenter experience: An analysis of a successful suction method

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the Kagawa Medical University Hospital and each institution.

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of the Kagawa Medical University Hospital and each institution.

Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at kobara@med.kagawa-u.ac.jp. Informed consent form participants for data sharing was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM

To demonstrate the clinical outcomes of a multicenter experience and to suggest guidelines for choosing a suction method.

METHODS

This retrospective study at 5 medical centers involved 58 consecutive patients undergoing over-the-scope clips (OTSCs) placement. The overall rates of technical success (TSR), clinical success (CSR), complications, and procedure time were analyzed as major outcomes. Subsequently, 56 patients, excluding two cases that used the Anchor device, were divided into two groups: 14 cases of simple suction (SS-group) and 42 cases using the Twin Grasper (TG-group). Secondary evaluation was performed to clarify the predictors of OTSC success.

RESULTS

The TSR, CSR, complication rate, and median procedure time were 89.7%, 84.5%, 1.8%, and 8 (range 1-36) min, respectively, demonstrating good outcomes. However, significant differences were observed between the two groups in terms of the mean procedure time (5.9 min *vs* 14.1 min). The CSR of the SS- and TG-groups among cases with a maximum defect size $\leqslant$ 10 mm and immediate or acute refractory bleeding was 100%, which suggests that SS is a better method than TG in terms of time efficacy. The CSR in the SS-group (78.6%), despite the technical success of the SS method (TSR, 100%), tended to decrease due to delayed leakage compared to that in the TG-group (TSR, CSR; 88.1%), indicating that TG may be desirable for leaks and fistulae with defects of the entire layer.

CONCLUSION

OTSC system is a safe and effective therapeutic option for gastrointestinal defects. Individualized selection of the suction method based on particular clinical conditions may contribute to the improvement of OTSC success.

Key words: Over-the-scope clip; Leak; Gastrointestinal refractory bleeding; Fistula; Endoscopic closure

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Core tip: The efficacy of over-the-scope clips (OTSCs) for gastrointestinal defects has been widely known. However, few large studies with more than 50 cases have been performed. Additionally, an optimal strategy for selecting a suction method, which is a critical factor of OTSC success, is needed. This study, with a large number of cases and a multicenter design, demonstrated excellent outcomes of OTSC and revealed which type of suction method was appropriate for particular situations according to the following characteristics: defect size, duration since onset, and indication. The individualized choice of the suction method is the most important factor determining OTSC success.

Kobara H, Mori H, Fujihara S, Nishiyama N, Chiyo T, Yamada T, Fujiwara M, Okano K, Suzuki Y, Murota M, Ikeda Y, Oryu M, AboEllail M, Masaki T. Outcomes of gastrointestinal defect closure with an over-the-scope clip system in a multicenter experience: An analysis of a successful suction method. *World J Gastroenterol* 2017; 23(9): 1645-1656 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1645.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1645

INTRODUCTION

Conventional endoscopic therapy-resistant gastrointestina diseases have traditionally required invasive surgery. These diseases mainly consist of GI refractory bleeding and leaks, including perforations, anastomotic leakage, and fistulae, which are encountered during endoscopic evaluation and are related to significant morbidity and mortality[1]. Recently, with the development of endoscopic submucosal dissection (ESD)[2] and natural orifice transluminal endoscopic surgery (NOTES)[3], technological advances in endoscopic devices have allowed for the endoscopic closure of GI defects. Among several full-thickness suturing devices[4,5], the over-the-scope clip (OTSC) (Ovesco Endoscopy GmbH, Tübingen, Germany) has the advantage of rapid and convenient use in rescue therapy. Currently, many case reports[6-10] and preliminary case series[11-14] have reported on the efficacy of OTSCs for the closure of GI defects, eliminating the need for invasive surgery.

However, there are few studies that have used large samples[15], and few randomized controlled trials[16,17] have been performed with OTSCs. Specifically, a strategy for choosing a suction method into the application cap of the OTSC system has not been clearly described. Successful OTSC closure depends on the secure suction of the target lesion into the application cap. The options available for OTSC closure include three suction methods, including simple suction (SS), which is similar to endoscopic variceal band ligation, and two accessory devices (Ovesco Endoscopy GmbH), which are referred to as the Twin Grasper (TG) and the tissue-anchoring device called the Anchor. Functioning as grasping forceps, the TG is applied to easily approximate the grasping edges of a large lesion, whereas the Anchor can better approximate indurated tissue. As both devices are expensive, selection of the appropriate suction method needs to be made according to the characteristics of the target lesion, which include the size of the defect, indications, and the duration since onset. The primary goal

Table 1 Demographics and characteristics of patients, defects, and over-the-scope clips

Characteristics	Details	Total patients (n = 58)
Age, median (range), yr		77 (37-98)
Indications, *n*		
Refractory bleeding		18
	Ulcer (peptic, Behçet's, anastomosis)	12
	Mallory-Weiss tear	1
	Diverticula	2
	Post-endoscopic resection	3
Leaks		28
	Peptic ulcer	3
	Boerhaave	1
	Iatrogenic (ESD)	16
	Iatrogenic (ERCP)	2
	Iatrogenic (surgery)	4
	Iatrogenic (other)	2
Fistula		12
	PEG	6
	Rectum-bladder	1
	Rectum-pelvis	2
	Gastric tube-trachea	1
	Gastric-pseudopancreatic cyst	1
	Colon-gallbladder	1
Location, *n*		
Esophagus		3
Stomach		28
Duodenum		13
Small intestine		2
Colon		12
Maximum defect size (D) mm, *n*		
D ⩽ 10		25
10 < D ⩽ 20		9
20 < D		24
Median (range), mm		15 (3-50)
Duration since onset to OTSC placement, *n*		
Immediate ⩽ 1 d		25
1 < Acute ⩽ 7 d		11
Chronic > 7 d		22
Suction method into the applicator cap		
Simple suction		14
Twin Grasper (TG) assist		42
Anchor assist		2
The number of OTSC deployments, *n*		
0		2[1]
1		39
2		12
3		5

[1]Procedural inability. OTSC: Over-the-scope clip; PEG: Percutaneous endoscopic gastrostomy; ERCP: Endoscopic retrograde cholangiopancreatography; SS: Simple suction; TG: Twin Grasper.

of this study was to demonstrate clinical outcomes of a multicenter experience with OTSCs for the management of GI refractory bleeding, leaks, and fistulae. The secondary goals were to propose a directional strategy for choosing a suction method into the application cap of the OTSC system by comparing the clinical data of SS to that of TG.

MATERIALS AND METHODS

Study design

This retrospective study was conducted at 5 medical centers in the Shikoku area of Japan. Between November 2011 and November 2015, fifty-eight patients who underwent attempted OTSC placement for GI refractory bleeding, leaks, or fistulae were enrolled. The detailed clinical data are summarized in Table 1. Patient characteristics, including age, indications with details, location of the defect, maximum defect size (D, mm), duration from onset to OTSC placement (immediate, ⩽ 1 d, acute, 1-7 d, or chronic, > 7 d), and the numbers of OTSC deployments, were collected. The indication for OTSC application for GI nonvariceal and refractory bleeding was defined as cases in which 2 time trials by conventional interventions failed to achieve complete hemostasis. Perforations, deep defects of the gut with the risk of delayed perforations, and anastomotic leakages were included as leaks. Subsequently, 56 patients, excluding two cases that used the Anchor, were divided into two groups: 14 cases of simple suction (SS-group) *vs* 42 cases using the Twin Grasper (TG-group). All of the data were extracted and compiled into a central database at Kagawa University. Written informed consents related to the use of OTSCs were obtained from all patients. The Clinical Ethics Committee of Kagawa University Hospital and each institution approved this study. This study was registered under UMIN 000017767.

OTSC procedures

The OTSC system is primarily composed of an OTSC mounted onto an application cap and a hand wheel. Users can easily apply the simple mechanism. As previously reported[18], the OTSC procedure involved several steps. First, the endoscope on which the cap with the loaded OTSC was mounted was inserted into the GI tract either orally or anally. Either a gastroscope (GIF-Q260J, ø 9.9 mm or H260Z, ø 10.8 mm Olympus, Tokyo, Japan) or a colonoscope (PCF-Q260AI, ø 11.3 mm, Olympus) with a maximum diameter of 9.9 mm and a working channel with greater than a 2.8 mm diameter was applied. Second, the defect in the GI tract was sucked to an application cap using SS or application aids such as the TG or the Anchor. The choice of the suction method ultimately depended on the discretion of the operator in this study. Finally, the clip was fired by stretching the wire with the hand wheel, and the entire defect of the lesion was completely closed. The OTSC procedures for the SS and TG methods and the Anchor assist are shown as schemas in Figure 1. Additional OTSCs were deployed until the defect was entirely closed. Regarding the types of OTSCs that were used, the gastrostomy closure type for gastric walls and the traumatic (t) type for other organs with thin walls were introduced, depending

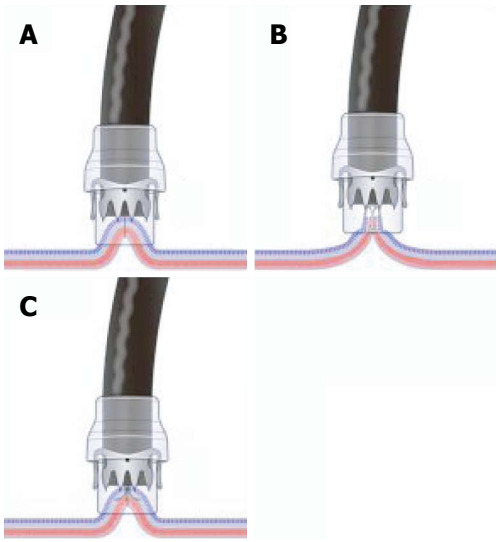

Figure 1 Key factor for the success of over-the-scope clips: schema of three suction methods into the application cap of the target lesion. A: Simple suction, similar to endoscopic variceal band ligation (simple suction method); B: Assist of grasping forceps: Twin Grasper device (Twin Grasper method); C: Assist of tissue anchoring device (Anchor assist).

on the lesion and the assessment of the operator; the atraumatic (a) type was not used in this study. Six expert endoscopists (H.K., H.M., T.Y., N.N., M.M., and M.O.) who had gained experience with the OTSC system procedure in a porcine model during a hands-on seminar session performed the OTSC deployments.

Outcome measures

Major outcomes: The overall rates of technical success (TSR), clinical success (CSR), complications, and procedure time of the 58 patients were examined. Technical success was defined as the complete closure of the entire defect by the successful deployment of OTSCs. Clinical success was defined as the resolution of the troubled situation by the assessment of blood analysis, endoscopic, and/or radiographic imaging (surgery or further endoscopic intervention was not required during at least 1 mo of follow-up after OTSC placement). The procedure time of the suction method was defined as the duration between the attempts at aspiration or the application of the TG or Anchor on the target lesion and complete closure of the defect with OTSC placement, as reviewed by endoscopic images and/or movies. The number of OTSC placements per single defect was calculated when the entire defect of the lesion was completely closed.

Secondary outcomes: A secondary evaluation was performed to clarify the predictors of OTSC success in the SS- and TG-groups. The TSR, CSR, procedure time, and complication rates of both groups were compared.

Subsequently, the TSR and CSR of each parameter and the indications, location of the defect, maximum defect size (≤ 10, 10-20, or > 20 mm), and duration since onset (immediate, acute, or chronic) were compared between the SS- and TG-groups. We supposed that a maximum defect size of 10 mm might be suitable for complete closure in the SS-group, considering the caliber of the application cap (11 or 12 mm in diameter). Previous studies have shown that factors that promote OTSC failure include a large defect size (greater than 20 mm)[14], fibrosis of the target tissue, such as a fistula, and the duration from onset to OTSC placement[15]. Thus, the maximum defect size was defined using the cut-off values of 10 and 20 mm, and the duration from onset was evaluated as one parameter. Simultaneously, the CSRs in both groups in terms of the combined parameters, the defect size, and the duration since the onset of each indication were estimated to better clarify the quality of each method.

Table 2 Results of major outcomes

Outcomes	Total patients (n = 58)
Technical success rate, % (95%CI)	89.7 (81.0-98.4)
Clinical success rate, % (95%CI)	84.5 (74.3-94.7)
Complications, n (%)	1 (1.8) in 56 cases used
The procedure time, median (range), min	8 (1-36) in 52 successful cases

Statistical analysis

Normally distributed data are presented as medians and ranges. The TSRs, CSRs and complication rates in the SS- and TG-groups were compared using two-sided Fisher's exact tests. The mean procedure times of both methods were compared using two-sided Wilcoxon/Kruskal-Wallis tests. The TSRs and CSRs of each parameter were compared using a χ^2 test. $P < 0.05$ was considered statistically significant. All statistical analyses were conducted using JMP version 9.0 (SAS Institute Inc., Cary, NC, United States).

RESULTS

The results for the major outcomes are summarized in Table 2. The TSR and CSR were 89.7% and 84.5%, respectively. The complication rate was 1.8% in the 56 cases analyzed. The median procedure time (range) was 8 (1-36) min in 52 successful cases. Additionally, the TSR and CSR of each parameter are shown in Table 3. While the TSR decreased as defect size and duration since onset increased, the CSR decreased as duration since onset increased.

The results of the comparison between the SS- and TG-groups with respect to the major outcomes are summarized in Table 4. No significant differences were identified between the SS- and TG-groups in terms of TSR [100% (14/14) *vs* 88.1% (37/42), respectively] and CSR [78.6% (11/14) *vs* 88.1% (37/42), respectively], $P > 0.05$). However, the CSR in the SS-group [78.6% (11/14)], despite the technical

Table 3 Results of the technical and clinical success rates for each parameter

Parameters	Total patients (n = 58)	
	Technical success rate	Clinical success rate
Indications		
Refractory bleeding	88.9 (16/18)	83.3 (15/18)
Leak	89.3 (25/28)	85.7 (24/28)
Fistula	91.7 (11/12)	83.3 (10/12)
Location		
Upper GI tract	86.4(38/44)	81.8 (36/44)
Lower GI tract	100 (14/14)	92.9 (13/14)
Maximum defect size (D), mm		
D ⩽ 10	96 (24/25)	84 (21/25)
10 < D ⩽ 20	88.9 (8/9)	88.9 (8/9)
20 < D	83.3 (20/24)	83.3 (20/24)
Duration since onset, % (n)		
Immediate ⩽ 1 d	96 (24/25)	96 (24/25)
1 < Acute ⩽ 7 d	90.9 (10/11)	81.8 (9/11)
Chronic > 7 d	81.8 (18/22)	72.7 (16/22)
Suction method into the applicator cap		
Simple suction (SS)	100 (14/14)	78.6 (11/14)
Twin Grasper (TG)	88.1 (37/42)	88.1 (37/42)
Anchor assist	50 (1/2)	50 (1/2)
The number of OTSC deployments, n		
1	92.3 (36/39)	84.6 (33/39)
2	100 (12/12)	100 (12/12)
3	80 (4/5)	80 (4/5)

success of the procedure (TSR, 100%), tended to decrease compared to that in the TG-group (TSR, CSR; 88.1%). Additionally, no significant differences were identified between the two groups in terms of the rate of complications [0% (0/14) *vs* 2.4% (1/42), $P > 0.05$]. However, significant differences were observed between the two groups regarding the mean procedure time (SS, 5.9 *vs* TG, 14.1 min, $P < 0.05$). A flow diagram of patient enrollment and outcomes is illustrated in Figure 2.

There were no significant differences in the TSRs and CSRs between the two groups for any parameter ($P > 0.05$) (Table 5). The CSR in the TG-group decreased as defect size and duration since onset increased. The CSRs of the combined parameters, defect sizes and duration since onset in each indication are summarized in Table 6. For refractory bleeding, the CSRs for cases of D ⩽ 10 were 85.7% (6/7) in the SS-group and 100% (2/2) in the TG-group. The CSR of the SS- and TG-groups among cases with D ⩽ 10 and immediate or acute refractory bleeding was 100%, which suggested that SS is a better method than TG in terms of time efficacy. However, the CSRs of cases with leaks and fistulae and D ⩽ 10 were 71.4% (5/7) in the SS-group and 100% (7/7) in the TG-group. Delayed leakages occurred in two cases in the SS-group (D ⩽ 10 and acute leakage and D ⩽ 10 and chronic fistula). These data suggest that the SS method sometimes fails to provide an acceptable clinical outcome despite the technical success, even if the defect size is small (D

Table 4 Outcomes of the simple suction and Twin Grasper methods n (%)

Parameters	SS-method (n = 14)	TG-method (n = 42)	P value
Technical success rate	14 (100)	37 (88.1)	0.176[1]
Clinical success rate	11 (78.6)	37 (88.1)	0.378[1]
Procedure time, median (range), min	5 (1-16)	12 (3-36) in 37 successful cases	0.0004[2]
Complications	0 (0)	1 (2.4)	0.587[1]

[1]Fisher's exact test (2-sided), [2]Wilcoxon/Kruskal-Wallis test. SS: Simple suction; TG: Twin Grasper.

⩽ 10). These aspects of the SS method suggest that the TG is desirable for leaks and fistulae with defects of the entire layer.

Case presentation

A representative success of SS in refractory bleeding is shown in Figure 3. In a failure case in the SS-group with D ⩽ 10 and a chronic duration, conventional therapy-resistant ulcer bleeding that in the terminal ileum occurred during steroid treatment for myelodysplastic syndrome. Despite the successful closure of the defect with the SS method, additional surgery was needed because of re-bleeding that might have been caused by angiogenesis from the steroid treatment in specific circumstances (Table 7, case No. 1). The CSR of the TG-group among cases with D > 20 showed the lowest success rate, 33.3% (1/3). In these 2 failure cases of chronic, fibrotic ulcers with D > 20, technical success could not be achieved due to an inability to suck rigid tissues into the cap, even when using the TG (Table 7, case No. 2 and No. 3). Although the use of the Anchor might have been helpful[18], we did not introduce the device because of the risk of perforation by the bear claw of the device. Finally, these bleeds were managed with conventional therapies using hemostatic forceps. At the indication of a leak, the TG method provided good clinical outcomes for defects with D ⩽ 10 and immediate duration during endoscopic retrograde cholangiopancreatography (ERCP); an image of a representative case is shown in Figure 4. On the other hand, there were three clinical failure cases with leaks: one with SS with D ⩽ 10 and an acute duration, one with the TG with 10 < D ⩽ 20 and an immediate duration, and one with the TG with D > 20 and an acute duration. In the first case, an acute anastomotic leakage with D ⩽ 10 after surgery for gastric cancer that was located in the esophageal-gastric junction was successfully closed using SS, but additional surgery was needed because of a delayed leakage (Table 7, case No. 4). In the second case, a large perforation of approximately 20 mm occurred during ERCP, and the TG was used to approximate the defect. The collapse of the intestine because of air leakage made technical success impossible, and this

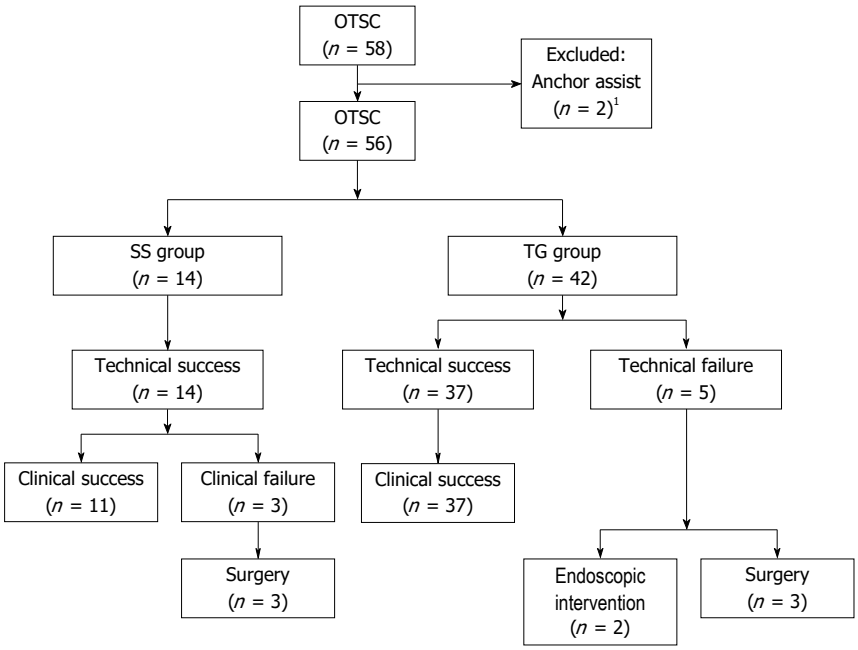

Figure 2 Flow diagram of patient enrollment and outcomes. [1]Clinical outcomes of two cases that used the Anchor: one case with an incomplete closure of an esophageal-gastric anastomotic leakage, and another case with clinical success of gastric fistula after percutaneous endoscopic gastrostomy. SS: Simple suction; TG: Twin Grasper.

Table 5 Results of the technical and clinical success rates of the simple suction- and Twin Grasper-groups for each parameter

Parameters	Technical success rate			Clinical success rate		
	SS (n = 14)	TG (n = 42)	P value[1]	SS (n = 14)	TG (n = 42)	P value[1]
Indication						
Refractory bleeding	100 (7/7)	81.8 (9/11)	0.2315	85.7 (6/7)	81.8 (9/11)	0.8288
Leak	100 (2/2)	92 (23/25)	0.6776	50 (1/2)	92 (23/25)	0.0690
Fistula	100 (5/5)	83.3 (5/6)	0.3384	80 (4/5)	83.3 (5/6)	0.8865
Location						
Upper GI tract	100 (8/8)	85.3 (29/34)	0.8725	75 (6/8)	85.3 (29/34)	0.8725
Lower GI tract	100 (6/6)	100 (8/8)		83.3 (5/6)	100 (8/8)	0.2308
Maximum defect size (D), mm						
D ⩽ 10	100 (14/14)	100 (9/9)		78.6 (11/14)	100 (9/9)	0.1364
10 < D ⩽ 20	-	88.9 (8/9)	-	-	88.9 (8/9)	-
20 < D	-	83.3 (20/24)	-	-	83.3 (20/24)	-
Duration since onset, % (n)						
Immediate ⩽ 1 d	100 (3/3)	95.5 (21/22)	0.6994	100 (3/3)	95.5 (21/22)	0.6994
1 < Acute ⩽ 7 d	100 (3/3)	87.5 (7/8)	0.1247	66.7 (2/3)	87.5 (7/8)	0.1247
Chronic > 7 d	100 (8/8)	75 (9/12)	0.1250	75 (6/8)	75 (9/12)	1.0000

[1]χ^2 test (2-sided). SS: Simple suction; TG: Twin Grasper.

case required surgical repair (Table 7, case No. 5). In the third case, a delayed perforation with a 50-mm defect size occurred after gastric endoscopic submucosal dissection. The defect could not be closed with the TG because of a narrow lumen in the prepylorus and the large defect size. The misplacement of the OTSC on the exposed muscularis propria induced additional tears, which represents the only case of an OTSC complication in this study. Although the use of several hemoclips at the perforation site seemed to be effective, surgery was performed due to the re-appearance of free air in computed tomography (CT) images 3 d after endoscopic therapy (Table 7, case No. 6, shown as the only complication in Figure 5). Among the fistula cases, there were two clinical failures: one with SS with D ⩽ 10 and a chronic duration and one with TG with 10 < D ⩽ 20 and a chronic duration. The first case was an 8-mm gastric fistula that occurred after an interventional endoscopic ultrasound for a pseudopancreatic cyst (Table 7, case No. 7), which is shown in Figure 6. Although the fistula was successfully closed using SS, leakage occurred 2 wk after OTSC placement, which necessitated additional surgery. The other case was a large (22 mm in diameter) gastric tube-tracheal fistula that occurred after radiation for esophageal carcinoma. The fistula could not be treated with the TG and required surgery (Table 7, case No. 8). Details of these 8 clinical failure cases are summarized

Table 6 Comparison of the clinical success rates for the combined parameters in each indication

Indications	Clinical success rate					
	Refractory bleeding (n = 18)		Leak (n = 27)		Fistula (n = 11)	
Combined parameters	SS (n = 7)	TG (n = 11)	SS (n = 2)	TG (n = 25)	SS (n = 5)	TG (n = 6)
D ≤ 10, Immediate	100%	100%	-	100%	-	-
D ≤ 10, Acute	100%	-	50%	100%	-	-
D ≤ 10, Chronic	66.7%	100%	-	-	80%	100%
10 < D ≤ 20, Immediate	-	100%	-	66.7%	-	-
10 < D ≤ 20, Acute	-	100%	-	100%	-	-
10 < D ≤ 20, Chronic	-	100%	-	-	-	100%
D > 20, Immediate	-	100%	-	100%	-	-
D > 20, Acute	-	-	-	75%	-	-
D > 20, Chronic	-	33.3%	-	-	-	50%

SS: Simple suction; TG: Twin Grasper.

Table 7 Details of over-the-scope clips clinical failure cases (n = 8)

Indication	Max. defect size, mm	Cause, comorbidity	Location	Prior therapy	Duration since onset	Technical success	Technical or clinical failure factor	Additional therapy	Clinical outcome
Refractory bleeding	8	Ileal ulcer bleeding due to steroid treatment for myelodysplastic syndrome	Terminal ileum	EI (hemoclips and coagulation)	Chronic	Yes	Suspicion of angiogenesis due to steroid in particular circumstances	Elective surgery	Survival
Refractory bleeding	20	Peptic ulcer, Refractory neurogenic disease	Stomach (body)	EI (coagulation)	Chronic	No	Fibrotic tissue	Retry of EI	Survival
Refractory bleeding	50	Peptic ulcer, Advanced gallbladder carcinoma	Stomach (body)	EI (coagulation)	Chronic	No	Fibrotic tissue	Retry of EI	Survival
Leak	7	Anastomotic leakage after surgery for gastric cancer	Esophageal gastric junction	None	Acute	Yes	Leakage by mucosal suture (suspected)	Elective surgery	Survival
Leak	21	Perforation during ERCP	Duodenal 2nd portion	None	Immediate	No	Inability of platform	Emergency surgery	Survival
Leak	50	Delayed perforation after ESD	Stomach (prepyrolus)	None	Acute	No	Location with narrow lumen	Elective surgery	Survival
Fistula	8	Interventional EUS	Gastric (prepyrolus)-pseudopancreatic cyst	None	Chronic	Yes	Leakage by mucosal suture (suspected)	Elective surgery	Survival
Fistula	22	Radiation for esophageal carcinoma	Gastric tube-trachea	Bronchial embolization	Chronic	No	Fibrotic tissue	Elective surgery	Survival

SS: Simple suction; TG: Twin Grasper; EI: Endoscopic intervention; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound.

in Table 7.

DISCUSSION

A newly developed endoscopic full-thickness suturing device, the OTSC system, has allowed for the endoscopic closure of conventional therapy-resistant GI defects. The efficacy of OTSC has been widely known since its introduction in 2009 in Western countries. However, there have been few studies that used large samples of more than fifty cases and a multicenter design.

Additionally, the type of suction method that should be applied to each target lesion based on the particular lesion characteristics remains unclear. Successful OTSC closure depends on the secure suction of the target lesion into the application cap. This success is closely related to the extent of tissue fibrosis in proportion to the duration from onset to OTSC placement, as previously described[14,15]. Therefore, an optimal strategy for choosing a suction method for the OTSC system is needed. This study is the first to clarify these issues by comparing the clinical data of SS to TG.

SS vs TG

Compared to TG, SS has the advantage of rapid and convenient use with a system that is similar to endoscopic variceal band ligation (mean procedure time; SS 5.9 min *vs* TG 14.1 min, $P < 0.05$). Moreover, another merit of SS is its lower cost if accessory devices are not applied. A maximum defect size of 10 mm per clip can be completely closed with the SS method, considering the caliber of the application cap. If OTSC is not fired due to insufficient suction into the cap during SS method, TG assist can be an alternative choice to close the defect. Although no significant differences in TSR or CSR were observed between the two groups in this study, the CSR of the SS-group (78.6%, 11/14),

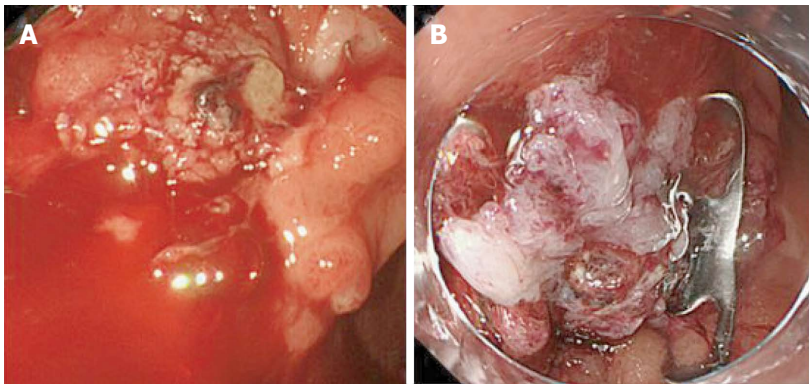

Figure 3 Representative clinical success case in the simple suction-group that exhibited refractory bleeding with a defect size of ⩽ 10 mm and an immediate duration since onset. A: A spurting, bleeding ulcer that was located in a rectal anastomotic site; B: Complete hemostasis *via* over-the-scope clip closure using the simple suction method after the failure of conventional endoscopic intervention.

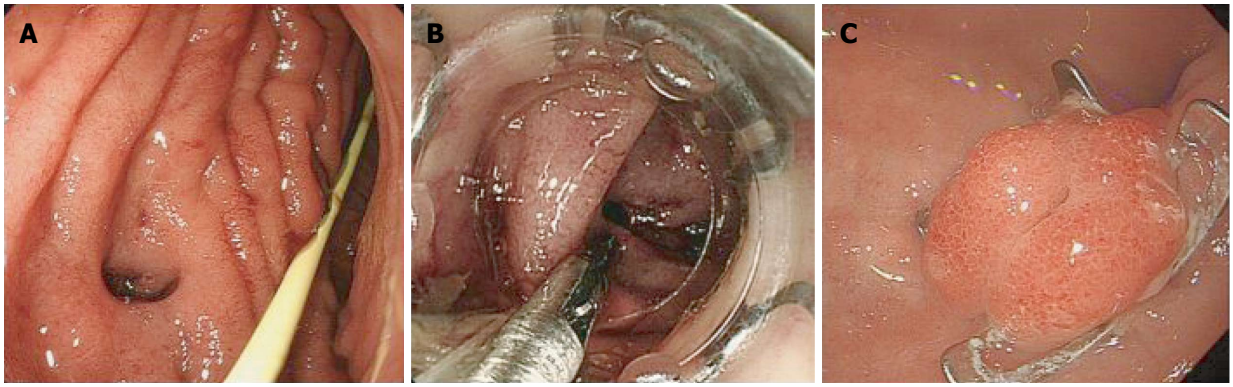

Figure 4 Representative clinical success case in the Twin Grasper-group of a leak with a defect size of ⩽ 10 mm and an immediate duration since onset. A: An iatrogenic perforation site approximately 10 mm in size, located in the 2nd portion of the duodenum during endoscopic retrograde cholangiopancreatography; B: Application of the Twin Grasper device; C: Complete defect closure three months after over-the-scope clip deployment.

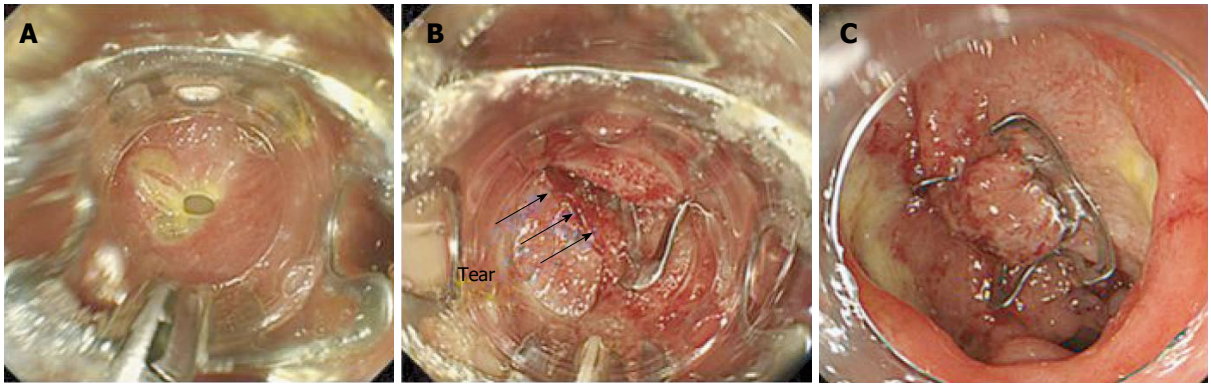

Figure 5 Representative case with an over-the-scope clips complication. A: A delayed perforation with a 50-mm defect size after gastric endoscopic submucosal dissection; B: The misplacement of the over-the-scope clips to the exposed muscularis propria induced additional tears (black arrows); C: The defect could not be closed by the Twin Grasper due to a narrow lumen located in the prepylorus.

despite its technical success (TSR, 100%, 14/14), tended to decrease compared to the TG-group (TSR, CSR; 88.1%, 37/42) due to delayed leakage. This finding indicates that the SS method might result in some clinical failures despite its technical success. Therefore, a secondary evaluation regarding each parameter or combined parameters for each indication was performed to better clarify the quality of each method. The CSR of the SS-group with D ⩽ 10 and immediate or acute refractory bleeding was 100%, which suggested that SS was a better method than TG in terms of time efficacy. However, the CSRs of leaks and fistulae with D ⩽ 10 were 71.4% (5/7) in the SS-group and 100% (7/7) in the TG-group. Delayed

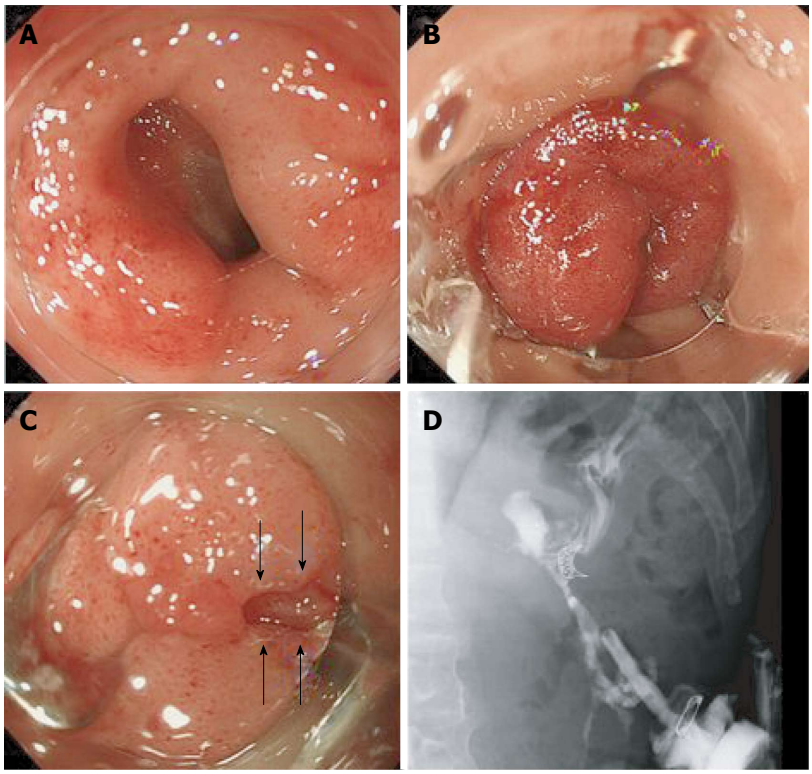

Figure 6 Clinically unsuccessful case in the simple suction-group of a fistula with a defect size of ⩽ 10 mm and a chronic duration. A: An 8-mm gastric fistula after interventional endoscopic ultrasound for a pseudo-pancreatic cyst; B: Complete closure with one over-the-scope clip (OTSC) using the simple suction method; C: A delayed leakage (black arrows) that occurred 2 wk after OTSC placement; D: X-ray contrast photo via a percutaneous drainage tube that revealed the delayed leakage.

leakages occurred in two cases in the SS-group (D ⩽ 10 and acute leakage and D ⩽ 10 and chronic fistula). These interesting data suggest that the SS method might sometimes fail in full-thickness suturing and could result in mucosal suturing for the target tissue, even if the defect size is small. Moreover, OTSC system using TG assist after clinical failure of SS method is not applicable for the same defect, because it is difficult to remove endoscopically the deployed OTSC on the target lesion. In this situation, surgery will be the only suitable therapy as shown in Figure 2. Thus, the use of TG may be desirable for leaks and fistulae with defects of the entire layer.

The TG is commonly used for large defects, but details regarding defect sizes and indications are unknown. The CSR in the TG-group decreased as defect size and duration since onset increased (Table 5). In particular, the success rate in the TG-group was the lowest for defects with D > 20 and those that were chronic, which indicates the limitations of the TG for large defects with fibrosis. If the TG method fails in this condition, a retrial with the Anchor might be valuable. Further comparative studies that include the Anchor are needed to clarify its efficacy and limitations.

Overall clinical success

Currently, there are limited data from large sample sizes[15] and few comparative studies[16,17]. Specifically, clinical studies including more than 50 cases, as in the present study, are rare. Here, we summarized the overall CSR in human studies between 2011 and 2015 that involved a minimum of 2 wk of follow-up, and we included several important parameters (*e.g.,* defect size, use of accessory devices) (Table 8)[19-26]. The mean rate of overall clinical success was 68.4% (range 53-90) (329/481 cases), which includes our results. Our data revealed a high rate of overall clinical success (84.5%). This finding may be why no significant differences in TSR or CSR were observed between the two groups in this study. Additionally, the proportion of fistulae and/or the defect size included in other studies may be associated with the OTSC success rate. According to a large sample of data, a defect type with fibrotic tissue, such as a fistula, is the most important predictor of OTSC failure[15]. Therefore, we evaluated the success rates of three types of indications separately (refractory bleeding, leaks, and fistulae). The mean rates of overall clinical success in refractory bleeding, leaks, and fistulae were 87.8%, (79/90 cases), 83.2% (109/131), and 53.0% (133/251), respectively.

Similar to the overall mean rate of complications (1.66%, 8/481), there was only one case in which the misplacement of the OTSC to exposed muscularis propria induced additional tears in this study (1.8% complication rate). Although OTSCs have been dem-

Table 8 Current clinical outcomes of over-the-scope clips for each indication

Ref.	Year	Country	Patients (*n*)	Overall clinical success rate, (success/ total)					Mean defect size (mm)	Described data of suction method	Complications, *n* (%)
				Refractory bleeding	Leaks and/or perforations	Fistula	Others	Total			
Albert *et al*[20]	2011	Germany	19	57.1 (4/7)	87.5 (7/8)	25 (1/4)	-	63.2	Unknown	Unknown	0
Surace *et al*[21]	2011	France, Monaco	19	-	-	74 (14/19)	-	73.7	Unknown	Unknown	1 (5)
Kirschniak *et al*[22]	2011	Germany	50	92.6 (25/27)	100 (11/11)	37.5 (3/8)	100 (4/4)	86	6	Unknown	0
Baron *et al*[19]	2012	United States	45	100 (7/7)	62.5 (5/8)	67.9 (19/28)	50 (1/2)	71	Unknown	TG: 8 cases AC: 17 cases	2 (4.4)
Manta *et al*[23]	2013	Italy	30	90 (27/30)	-	-	-	90	Unknown	Unknown	0
Haito-Chavez *et al*[15]	2014	International[2]	188	-	Leaks 73.3 (22/30), 2[1] Perforations 90 (36/40), 8[1]	42.9 (39/91), 17[1]	-	60.2	Leaks: 8 Perforations: 7 Fistula: 5	Use of TG and/or AC, 50% (70/140 cases)[3]	0
Law *et al*[24]	2014	United States	47	-	-	53 (25/47)	-	53	Unknown	Unknown	0
Sulz *et al*[25]	2014	Switzerland	21	100 (1/1)	66.7 (4/6)	63.6 (7/11)	100 (3/3)	71.4	8	SS:[4] 100% (10/10) TG:100% (1/1) AC: 87.5% (7/8) TG + AC: 0% (0/1)	0
Mercky *et al*[26]	2015	France, Monaco	30	-	-	53 (16/30)	-	53	7.2	SS: 17 procedures TG: 9 procedures AC: 5 procedures	4 (13.3)
Our study	2016	Japan	58	83.3 (15/18)	85.7 (24/28)	83.3 (10/12)	-	84.5	19.6	CSR SS[4]:78.6% (11/14) TG: 88.1% (37/42) AC: 50% (1/2)	1 (1.8)
Total			507	87.8 (79/90)	83.2 (109/131)	53.0 (133/251)	88.9 (8/9)	68.4 (329/481)			8/481 (1.66)

[1]Excluded number of patients lost to follow-up; [2]United States, Netherlands, Germany, Italy, and Chile; [3]Use of accessory devices was not a predictor of clinical success; [4]Clinical success rate. SS: Simple suction; TG: Twin Grasper; AC: Anchor.

onstrated to be safe, a careful approach is needed to avoid OTSC placement on exposed muscularis propria, which can occur in a defect after endoscopic resection.

GI refractory bleeding

The OTSC system offers the strongest impact in regards to GI bleeding compared to other indications, as evidenced by the mean rate of overall clinical success of 87.8%, (79/90 cases), which is similar to the findings in our study (83.3%, 15/18). Therefore, an OTSC is a good device with which to achieve hemostasis in conventional therapy-resistant GI bleeding. However, as our 2 failure cases with D > 20 and chronic fibrotic ulcers revealed, OTSC usage may be limited in particular situations.

Leaks

Perforations, deep defects with the risk of delayed perforations, and anastomotic leakages were included as leaks in this study. As the mean rate of overall clinical success and our CSR were 83.2% (range 62.5-100) (109/131) and 85.7% (24/28), respectively, the OTSC is valuable in avoiding emergency surgery for leaks.

Fistulae

Among all of the indications, the mean rate of overall clinical success for fistula was the lowest (53.0%, range 25-81.8, 133/251 cases). Similarly, recent studies have demonstrated a limited success rate of approximately 50%. Despite the introduction of the OTSC system, fistula closure appears to be a challenge. However, compared to other studies, our study delivered good outcomes with both technical (91.7%, 11/12 cases) and clinical success (83.3%, 10/12 cases). Law *et al*[24] reported that nearly 50% of patients with endoscopic and radiologic evidence of fistula closure at completion of the index procedure went on to require additional interventions in the subsequent days and months due to fistula recurrence. Accordingly, we recommend the use of sufficient suc-

tion into the cap with the aggressive use of accessory devices for the successful long-term closure of fistulae. In the future, the issue of managing refractory fistulae may be overcome by utilizing one or more of the following modalities: the injection of tissue sealants[27], stent placement[28,29], and newly developed endoscopic suturing devices[4,5,30].

Limitations

The main limitation of this study is its retrospective design. Additionally, the selection of the suction method depended on the operator's discretion, so patient inclusion criteria were subjective. Therefore, the Anchor device was applicable only for a small number of cases in our experience.

Strengths of this study

This study has several strengths. Compared to related studies, it is a relatively large, multicenter study. Additionally, this study is the first to investigate which type of suction method is appropriate for particular situations according to the following characteristics: defect size, duration since onset, and indication.

In conclusion, the OTSC system is a safe and effective therapeutic option for the treatment of GI defects. The individualized choice of the suction method in the OTSC system is the most important factor for OTSC success. Thus, OTSCs can serve as reliable and productive devices for GI refractory diseases when the size of the defect, the duration since onset and the indication are considered.

COMMENTS

Background

Although the efficacy of over-the-scope clip (OTSC) for gastrointestinal (GI) defects involving GI refractory bleeding, leakages, and fistulae had been described, there are few data using large samples over fifty cases. Additionally, a successful key of OTSC closure depends on the secure suction into the application cap of the target lesion. There are three suction methods: simple suction (SS) and two accessory devices, referred to as the Twin Grasper (TG) and the tissue anchoring device, the Anchor. However, an optimal strategy for selecting a suction method, which is a critical factor of OTSC success, remains unclear.

Research frontiers

This study demonstrates clinical outcomes of OTSCs using large samples and proposes a directional strategy for choosing a suction method into the application cap of the OTSC system.

Innovations and breakthroughs

Compared to related studies, this is a multicenter study with a large number of cases. Additionally, this study is the first to investigate which type of suction method is appropriate for particular situations according to the following characteristics: defect size, duration since onset, and indication. Although the SS method is indicated for cases with a maximum defect size $\leqslant$ 10 mm and immediate or acute refractory bleeding in terms of time efficacy, SS sometimes fails in full-thickness suturing. Thus, the use of TG may be desirable for leaks and fistulae with defects of the entire layer.

Applications

This study emphasizes that OTSC system is a safe and effective therapeutic option for GI defects. Moreover, individualized selection of the suction method based on particular clinical conditions may contribute to the improvement of OTSC success.

Terminology

OTSC: A newly developed endoscopic full-thickness suturing device applicable for refractory bleeding, perforations, anastomotic leakage, and fistulae. Suction method: a method to suck the target lesion into the application cap, which is a critical factor of OTSC success among OTSC procedures.

Peer-review

The authors reported a multicenter retrospective study analyzing the role of the OTSCs for GI defects based on the suction method. The authors suggested that TG is desirable for leaks and fistulae with defects of the entire layer. However, further prospective studies by comparing suction methods are needed to clarify the type of suction method that should be applied to each target lesion based on the particular lesion characteristics.

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ORIGINAL ARTICLE

Observational Study

Usefulness of a novel slim type FlushKnife-BT over conventional FlushKnife-BT in esophageal endoscopic submucosal dissection

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Institutional review board statement: The study was reviewed and approved by the Ethics Committees of Kobe University Hospital No. 160051 and Kishiwada Tokushukai Hospital No. 28-10.

Informed consent statement: All study participants provided informed written consent prior to study enrollment.

Conflict-of-interest statement: Dr. Toyonaga invented FlushKnife-BT and FlushKnife-BTS in conjunction with Fujifilm and receives royalties from their sales.

Data sharing statement: No additional data are available.

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Abstract

AIM

To investigated the usefulness of a novel slim type ball-tipped FlushKnife (FlushKnife-BTS) over ball-tipped FlushKnife (FlushKnife-BT) in functional experiments and clinical practice.

METHODS

In order to evaluate the functionality of FlushKnife-BTS, water aspiration speed, resistance to knife insertion through the scope, and waterjet flushing speed were compared between FlushKnife-BTS and BT. In clinical practice, esophageal endoscopic submucosal dissection (ESD) performed using FlushKnife-BTS or BT by an experienced endoscopist between October 2015 and January 2016 were retrospectively reviewed. The treatment speed and frequency of removing and reinserting the knife to aspirate fluid and air during ESD sessions were analyzed.

RESULTS

Functional experiments revealed that water aspiration speed by the endoscope equipped with a 2.8-mm working channel with FlushKnife-BTS was 7.7-fold faster than that with conventional FlushKnife-BT. Resistance to knife insertion inside the scope with a 2.8-mm working channel was reduced by 40% with FlushKnife-BTS. The waterjet flushing speed was faster with the use of FlushKnife-BT. In clinical practice, a comparison of 6 and 7 ESD using FlushKnife-BT and BTS, respectively, revealed that the median treatment speed was 25.5 mm^2/min (range 19.6-30.3) in the BT group and 44.2 mm^2/min (range 15.5-55.4) in the BTS group (P = 0.0633). However, the median treatment speed was significantly faster with FlushKnife-BTS when the resection size was larger than 1000 m^2 (n = 4, median 24.2 mm^2/min, range 19.6-27.7 *vs* n = 4, median 47.4 mm^2/min, range 44.2-55.4, P = 0.0209). The frequency of knife replacement was less in the BTS group (median 1.76 times in one hour, range 0-5.45) than in the BT group (7.02 times in one hour, range 4.23-15) (P = 0.0065).

CONCLUSION

Our results indicate that FlushKnife-BTS enhances the performance of ESD, particularly for large lesions, by improving air and fluid aspiration and knife insertion during ESD and reducing the frequency of knife removal and reinsertion.

Key words: Endoscopic submucosal dissection; Novel slim type ball-tipped FlushKnife; ball-tipped FlushKnife; Resistance to knife insertion; Water aspiration speed

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Core tip: Devices utilized in endoscopic submucosal dissection (ESD) play an important role in facilitating the safe and effective procedure. A novel slim type ball-tipped FlushKnife (FlushKnife-BTS) has been developed to enhance the performance of aspiration and insertion of the knife through the scope. We herein investigated the usefulness of FlushKnife-BTS over FlushKnife-BT in functional experiments and clinical practice. FlushKnife-BTS showed a faster water aspiration speed, reduced resistance to knife insertion, a faster treatment speed when the resection size was large, and low frequency of knife replacement. Our results indicate that FlushKnife-BTS supports the efficient performance of ESD, particularly for large lesions.

Ohara Y, Toyonaga T, Hoshi N, Tanaka S, Baba S, Takihara H, Kawara F, Ishida T, Morita Y, Umegaki E, Azuma T. Usefulness of a novel slim type FlushKnife-BT over conventional FlushKnife-BT in esophageal endoscopic submucosal dissection. *World J Gastroenterol* 2017; 23(9): 1657-1665 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1657.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1657

INTRODUCTION

Endoscopic submucosal dissection (ESD) is a standard treatment for early-stage tumors in the digestive tract[1-6]. Many devices have been developed to safely and efficiently facilitate this procedure[7-14]. One of these devices is FlushKnife and the subsequently developed ball-tipped FlushKnife (FlushKnife-BT) (DK2618JN, DK2618JB; Fujifilm Medical Co., Ltd., Tokyo, Japan)[13,14]. Some of the features and functions of these knives are advantageous such as injection, irrigation by waterjets, dissection, hemostasis, and vessel sealing[15]. However, when they are used with endoscopes equipped with a working channel of 2.8 mm, difficulties are associated with aspirating fluid and air in the working space and finely controlling the knife length due to limited space with friction resistance in the channel with a knife with a diameter of 2.7 mm.

Therefore, a novel slim type FlushKnife BT (FlushKnife-BTS, DK2620JBS; Fujifilm) was developed to provide more space in the working channel (Figure 1). FlushKnife-BTS is characterized by its slim sheath (2.2 mm), but same sized sheath tip (2.7 mm, approximately 30 mm long) as the conventional knife, which maintains stable maneuverability.

In an attempt to clarify whether the performance of ESD is better with FlushKnife-BTS than with FlushKnife-BT, we retrospectively investigated the usefulness of FlushKnife-BTS over FlushKnife-BT in functional experiments and clinical practice. In the clinical practice, we included esophageal ESD because esophagus is a narrow tract compared to stomach and colorectum, which procedure is affected easily by air inflation, and was thought to be a good candidate for first investigation into the efficiency of FlushKnife-BTS.

MATERIALS AND METHODS

Functional experiment

Water aspiration speed with the knife inserted in the scope, resistance to knife insertion inside the scope, and waterjet flushing speed were compared between FlushKnife-BTS and FlushKnife-BT. Regarding the speed of water absorption, a total of 200 mL water in a graduated cylinder was aspirated using the 2.8-mm scope and 3.2-mm channel with FlushKnife-BT or FlushKnife-BTS inserted, and the amount of water aspirated in 10 s was measured. The experiment was repeated 9 times. Resistance to the insertion of Flushknife-BT or Flushknife-BTS inside the scope was measured with various endoscopic angles. A measuring instrument named force gage FGP-5 produced by NIDEC-SHIMPO CORPORATION was equipped with the FlushKnife-BTS and FlushKnife-BT, inserted into the endoscope equipped with a working channel of 2.8 mm and the resistance during the insertion was determined. The experiment was repeated 3 times. The waterjet flushing speeds of the knives were measured

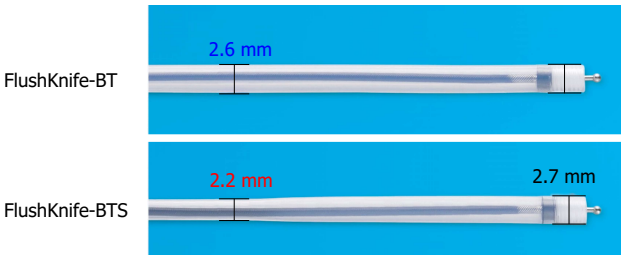

Figure 1 Ball-tipped FlushKnife and a novel slim type ball-tipped FlushKnife. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

at three different water pressure settings 9 times using waterjet equipment (JW-2; Fujifilm, waterjet volume; min/mid/max 80/135/190 mL/min).

Patients

All cases that underwent esophageal ESD performed using FlushKnife-BTS or FlushKnife-BT at Kobe University Hospital and Kishiwada Tokushukai Hospital between October 2015 and January 2016 were retrospectively reviewed. Of these, cases that underwent ESD performed by an experienced endoscopist (T.T.) were analyzed in the study.

Indications for esophageal ESD were defined according to the esophageal ESD guidelines issued by the Japan Esophageal Society[16]: (1) absolute criteria; lesions that do not exceed the mucosal layer (T1a), those remaining within the mucosal epithelium (EP) or the lamina propria mucosae (LPM), and (2) relative criteria; lesions reaching the muscularis mucosae (MM) or slightly infiltrating the submucosa (up to 200 μm, T1b-SM1). ESD was not recommended for a 10%-15% risk of lymph node metastasis with lesions filling the relative criteria; however, it was performed on patients who were too frail to tolerate more invasive surgical approaches due to comorbidities, those who requested a diagnostic endoscopic treatment before surgery, or those who requested ESD with chemoradiation.

All patients underwent an initial screening examination including esophagogastroduodenoscopy with magnified narrow band imaging and computed tomography in order to evaluate submucosal invasion and lymph node metastasis. When submucosal invasion was suspected, endoscopic ultrasonography was performed.

ESD procedure

Patients were mainly sedated using dexmedetomidine hydrochloride, flunitrazepam, and pentazocine. ESD was performed with a single-channel endoscope equipped with a working channel of 2.8 mm (GIF-Q240, H290Z; Olympus Corporation, Tokyo, Japan). ERBE VIO 300 D high performance cautery (Erbe Elektromedizin GmbH, Tubingen, Germany) was utilized in all cases. Carbon dioxide insufflation was routinely used.

The knife was removed and reinserted to aspirate fluid and air when required, to clean the endoscope lens for better visualization, and/or when the thread-traction method was needed[17].

Evaluated points

The patient and lesion characteristics including sex, age, lesion site, circumference of the resected area, major axis diameter of the resected specimen, size of resected area, major axis diameter of the tumor, histology of the tumor and depth of the tumor were investigated.

Furthermore, the procedure time, treatment speed, frequency of knife removal and reinsertion for aspiration, *en bloc* resection rate, and adverse events were assessed and compared between the FlushKnife-BTS (BTS) group and FlushKnife-BT (BT) group.

The procedure time was defined as the time between the first submucosal injection and completion of dissection. The treatment speed was calculated by dividing the area of the resected specimen by the procedure time (cm^2/min). The approximate oval area (cm^2) of the resected specimen was calculated as follows; 3.14 × 0.25 × long axis diameter × short axis diameter.

Adverse events

Perforation and postoperative bleeding were counted as adverse events related to the procedure.

Postoperative bleeding was recorded if one of the following conditions was identified: (1) bleeding that required endoscopic hemostatic treatment; and (2) bleeding with a reduction in total hemoglobin of more than 2 g/dL from the preoperative level. Perforation was diagnosed by endoscopic findings during ESD or by the presence of free air on computed tomography.

Ethics

All patients were informed of the risks and benefits of ESD, and provided written informed consent to undergo the procedure. This study was approved by the Ethics Committees of Kobe University Hospital (No. 160051) and Kishiwada Tokushukai Hospital (No. 28-10).

Statistical analysis

The Mann-Whitney *U* test was used to compare continuous variables, and the χ^2 test or Fisher's exact probability test was used to compare categorical variables. $P < 0.05$ was considered significant. All statistical analyses were performed using JMP version 10 (SAS Institute Inc., Cary, NC, United States).

RESULTS

Results of functional experiments

The results of the functional experiments revealed that water aspiration speed by the endoscope equipped

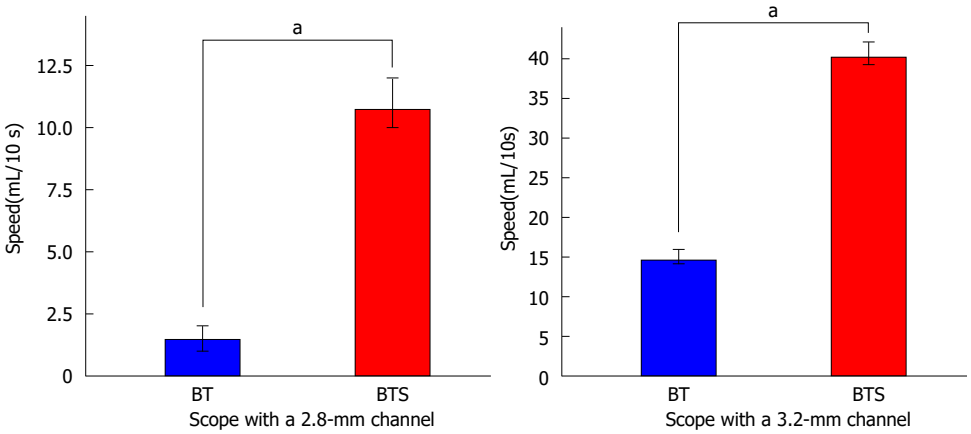

Figure 2 Water aspiration speed. A total of 200 mL water in a graduated cylinder was aspirated by scopes with 2.8-mm and 3.2-mm channels with FlushKnife-BT or FlushKnife-BTS inserted, and the amount of aspirated water in 10 s was measured. The column denotes mean data and the bar shows the range of experiments performed 9 times. Water aspiration speed was markedly faster with FlushKnife-BTS than with FlushKnife-BT. [a]*P* < 0.05, BT *vs* BTS. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

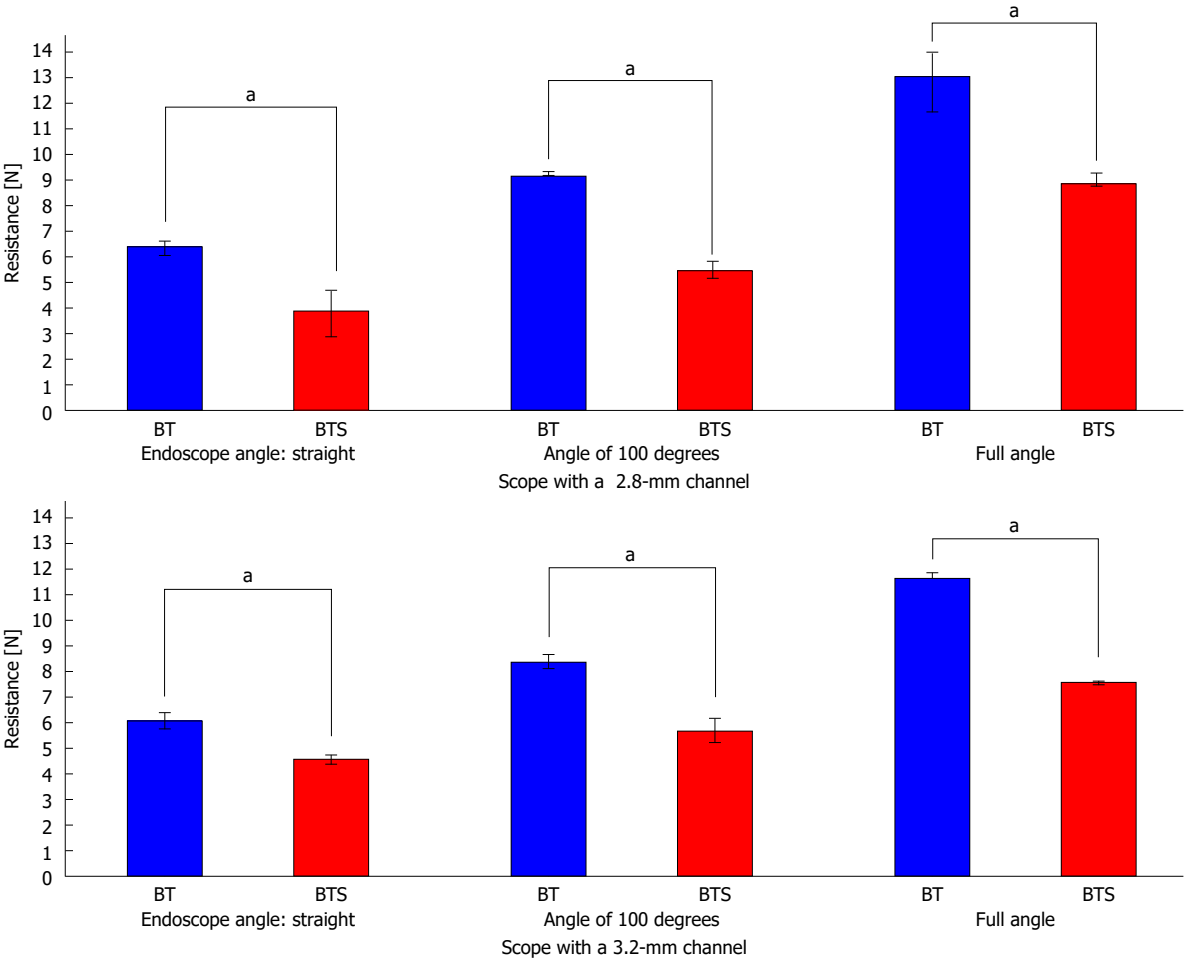

Figure 3 Resistance to knife insertion inside the scope. Resistance to the insertion of Flushknife-BT or Flushknife-BTS inside the scope at various endoscopic angles was measured using a measuring instrument by NIDEC-SHIMPO CORPORATION. The column denotes mean data and the bar shows the range of experiments performed in triplicate. Resistance was lower at all endoscopic angles with Flushknife-BTS than with Flushknife-BT. [a]*P* < 0.05, BT *vs* BTS. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

with a 2.8-mm working channel with FlushKnife-BTS inserted was 7.7-fold faster than that with FlushKnife-BT (Figure 2). Even when using an endoscope with a 3.2-mm working channel, water aspiration speed was 2.7-fold faster with FlushKnife-BTS than with FlushKnife-BT. Resistance to knife insertion through the 2.8-mm working channel in a straight endoscopic position was 40% less using the new slim knife than

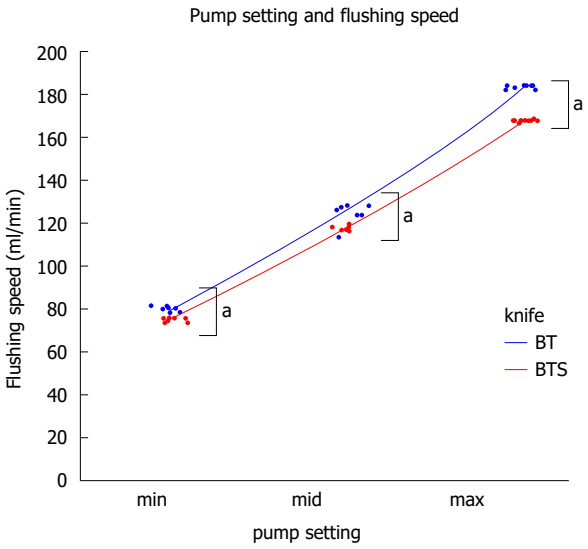

Figure 4 Waterjet flushing speed. Waterjet flushing speed was faster with FlushKnife-BT than with FlushKnife-BTS at all pump settings tested. [a]*P* < 0.05, BT *vs* BTS. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

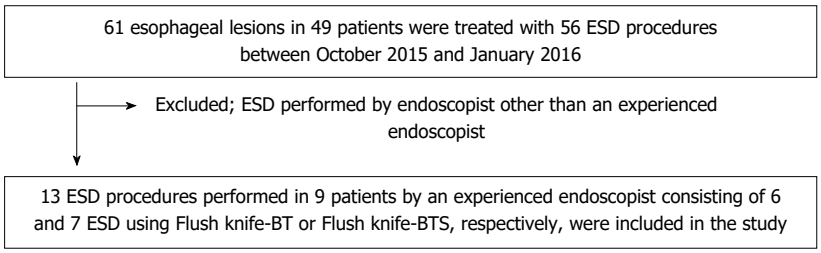

Figure 5 Flow diagram of cases that underwent endoscopic submucosal dissection included in the analysis. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT; ESD: Endoscopic submucosal dissection.

Table 1 Patient and lesion characteristics

	FlushKnife-BT (*n* = 6)	FlushKnife-BTS (*n* = 7)	*P* vaule[1]
Male/Female	3[2]/1[2]	4[2]/1	0.559
Age, median (range), years	73.5 (68-78)	57 (57-74)	0.0235
Lesion site Ut/Mt/Lt	0/4/2	0/6/1	0.559
Circumference of the resected area, median (range)	68% (25-100)	75% (50-92)	0.599
Major axis diameter of the resected specimen, median (range), mm	39.5 (30-55)	40 (31-60)	0.277
Resected area, median (range), mm²	1117 (636-2547)	1193 (511-2418)	0.943
Major axis diameter of the tumor[3], median (range), mm	33 (19-42)	32 (25-50)	0.616
Histology of the tumor HGIN/SCC	0/6	0/7	0.000
Depth of the tumor EP/LPM/MM	0/5/1	1/5/1	0.629

[1]The Mann-Whitney *U* test was used to compare continuous variables, and the chi-squared test or Fisher's exact probability test was used to compare categorical variables; [2]One patient had multiple esophageal lesions treated by endoscopic submucosal dissection; [3]In the case of multiple lesions resected simultaneously, the maximum distance between the edges of each tumor was defined as the major axis diameter of the tumor. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

the conventional knife (Figure 3). Reductions in resistance were detected using both scopes with 2.8-mm and 3.2-mm working channels and at any endoscopic angle. Waterjet flushing speed was lower with FlushKnife-BTS than with FlushKnife-BT at all water pressure settings tested (Figure 4). This difference became larger with increases in water pressure.

Clinical results

During the study period, 61 esophageal lesions in 49 patients were treated with 56 ESD procedures. Of these, 13 ESD procedures performed in 9 patients, consisting of 6 and 7 ESD using FlushKnife-BT and FlushKnife-BTS, respectively, were completed by an experienced endoscopist and these cases were

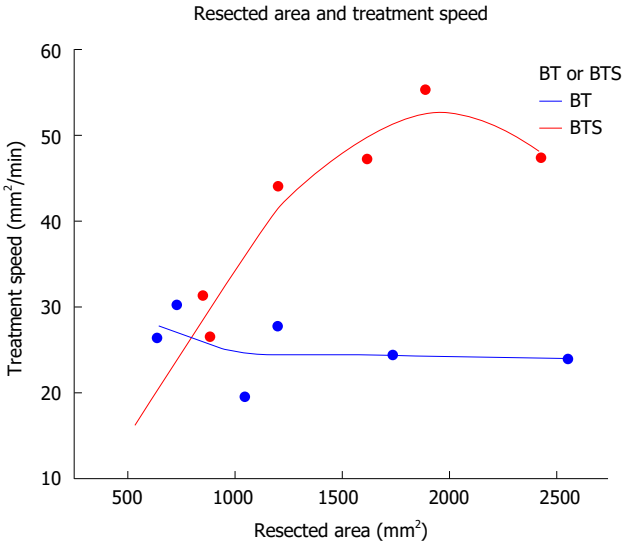

Figure 6 Treatment speed was faster with a novel slim type ball-tipped FlushKnife when the resected size was large, but was similar to that with the conventional knife when the resected size was small. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

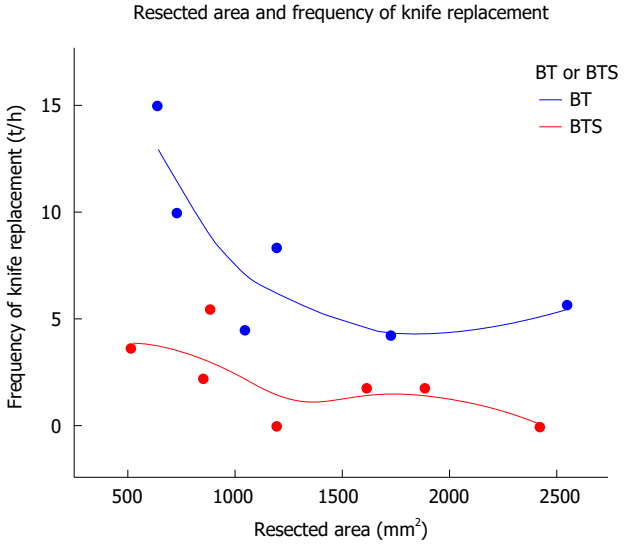

Figure 7 Frequency of knife replacement was reduced with a novel slim type ball-tipped FlushKnife regardless of the resected size, while a slightly reduced frequency was observed as the resected size became larger. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

included in the study (Figure 5).

The characteristics of the patients and lesions are shown in Table 1. There were 3 males and 1 female in the BT group, and 4 males and 1 female in the BTS group. Two patients in the BT group and one patient in the BTS group had multiple lesions that were treated separately. Ages ranged between 68 and 78 years with a median age of 73.5 years in the BT group, and between 57 and 74 years with a median age of 57 years in the BTS group (P = 0.0235). Lesion sites (Ut/Mt/Lt) were 0/4/2 and 0/6/1, respectively (P = 0.559).

The circumference of the resected area ranged between 25% and 100% with a median of 68% in the BT group, and between 50% and 92% with a median of 75% in the BTS group (P = 0.599).

The median major axis diameters of resected specimens were 39.5 mm (range 30-55) and 40 mm (range 31-60) respectively (P = 0.277) in BT and BTS groups, respectively.

The median resected area was 1117 mm^2 (range 636-2547) in the BT group and 1193 mm^2 (range 511-2418) in the BTS group (P = 0.943).

The median major axis diameter of tumors was 33 mm (range 19-42) in the BT group and 32 mm (range 25-50) in the BTS group (P = 0.616). In the case of multiple lesions resected together, the maximum distance between the edges of each tumor was defined as the tumor size.

The histology of tumors revealed SCC in all cases. The depths of tumors (EP/LPM/MM) were 0/5/1 in the BT group and 1/5/1 in the BTS group (P = 0.629). The outcomes of ESD are shown in Table 2. The thread-traction method was performed on 3 out of 6 cases in the BT group and 2 out of 7 cases in the BTS group (P = 0.592). Median procedure times were 48 min (range 24-106) and 33 (range 27-51) min in the BT and BTS groups, respectively (P = 0.389).

The median treatment speed was 25.5 mm^2/min (range 19.6-30.3) in the BT group and 44.2 mm^2/min (range 15.5-55.4) in the BTS group (P = 0.0633). However, it was significantly faster with FlushKnife-BTS when the resection size of ESD was larger than 1000 m^2 (n = 4, median 24.2, range 19.6-27.7 *vs* n = 4, median 47.4 mm^2/min, range 44.2-55.4, P = 0.0209) (Table 3). The relationship between the resected area and treatment speed is shown in Figure 6; the treatment speed was faster with FlushKnife-BTS when the resected size was large, but was similar to that with FlushKnife-BT when it was small.

The number of times the knife was replaced was 5.5 (range 4-10) and 1 (range 0-3) in the BT and BTS groups, respectively (P = 0.0025).

The frequency of knife replacement was lower (median 1.76, range 0-5.45 *vs* median 7.02, range 4.23-15 times in one hour, P = 0.0065) with FlushKnife-BTS than with FlushKnife-BT. Figure 7 shows the relationship between the resected area and frequency of knife replacement, and demonstrates a reduced frequency of knife replacement with FlushKnife-BTS regardless of the resected size and slightly reduced frequency as the resected size became larger. *En bloc* resection rates were 100% and muscle injury was detected in one case in the BT group.

DISCUSSION

ESD is the first-line therapeutic option for superficial gastrointestinal tract tumors[1,6,18-20]. The devices used in ESD are important for performing the procedure safely. A large number of devices have been developed

Table 2 Outcomes of endoscopic submucosal dissection by novel slim type ball-tipped FlushKnife and ball-tipped FlushKnife

	FlushKnife-BT (n = 6)	FlushKnife-BTS (n = 7)	P vaule[1]
Use of the thread-traction method, yes/no	3/3	2/5	0.592
Procedure time, median (range), min	48 (24-106)	33 (27-51)	0.389
Treatment speed, median (range), mm^2/min	25.5 (19.6-30.3)	44.2 (15.5-55.4)	0.0633
Number of times the knife was replaced, median (range), times	5.5 (4-10)	1 (0-3)	0.0025
Frequency of knife replacement, median (range), times/hour	7.02 (4.23-15)	1.76 (0-5.45)	0.0065
En bloc resection rate	6/6 (100%)	7/7 (100%)	0.000
Adverse events, Perforation/muscle injury/postoperative bleeding	0/1/0	0/0/0	0.462

[1]The Mann-Whitney U test was used to compare continuous variables, and the χ^2 test or Fisher's exact probability test was used to compare categorical variables. FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

Table 3 Treatment speed of endoscopic submucosal dissection for a resected size more than 1000 mm^2

	FlushKnife-BT (n = 4)	FlushKnife-BTS (n = 4)	P vaule
Treatment speed, median (range), mm^2/min	24.4 (19.6-27.7)	47.4 (44.2-55.4)	0.0209

FlushKnife-BT: Ball-tipped FlushKnife; FlushKnife-BTS: A novel slim type FlushKnife-BT.

to date[8-10,12,13]. FlushKnife-BT is one of the most frequently used knives and has advantageous functions including injection, irrigation by waterjets, dissection, and vessel sealing[14]. However, when this knife is used with endoscopes equipped with a 2.8-mm channel, difficulties are associated with the aspiration of fluid and mucus in the working space during the procedure and finely controlling the knife length because of its diameter of 2.7 mm. Uncontrolled fluid and mucus pooling and air inflation/deflation may complicate ESD. In order to precisely dissect the appropriate plane between the vessel network in the submucosa and muscle layer[21], subtle endoscope movements in addition to adjustments in knife length are needed. Therefore, smooth aspiration and delicate knife control are essential for performing this procedure safely and efficiently.

In an attempt to overcome these limitations, we developed a novel slim type FlushKnife-BT.

Functional experiments revealed that fluid aspiration speed by the endoscope with a 2.8-mm working channel with FlushKnife-BTS inserted was 7.7-fold faster than that with the conventional knife. Resistance to the insertion of the knife inside the scope with a 2.8-mm working channel was 40% less with the new knife than with the conventional knife.

In clinical practice, though the number of the patients was small, increase was achieved in the treatment speed with FlushKnife-BTS when large resection was required, but remained the same as that with the conventional knife when the resected size was small. The frequency of knife replacement was less with FlushKnife-BTS than with FlushKnife-BT regardless of the resected size.

The faster aspiration of bubbles, air, mucus, and fluid by FlushKnife-BTS contributed to a clear field of view, which may have, in turn, reduced the frequency of knife removal from the working channel.

The reason why treatment speed only improved with FlushKnife-BTS when the resection size was large may be that, in ESD of a small resection size, the effects by a reduced frequency of knife replacement, smooth knife insertion, and fine knife control with FlushKnife-BTS were not clearly reflected due to the short procedure time and fewer knife replacements, but became more evident as the resection size became larger and the procedure time increased. Therefore, FlushKnife-BTS is considered to exhibit its effectiveness when large resection is needed.

Waterjet flushing speed was slower with FlushKnife-BTS in functional experiments. This result was expected due to the difference in the diameters of the two knives. However, this did not markedly affect the clinical practice of ESD in our analysis. Since FlushKnife-BT offers a high-flow flushing function, the speed reductions observed with FlushKnife-BTS do not appear to be of clinical importance. Moreover, the mid pump setting is typically used in clinical practice and may be resolved by turning up the setting to its maximum where necessary.

Although the safety and efficacy of ESD in the esophagus have already been reported[2,6,22], intraoperative perforation, muscle layer damage, and bleeding may occur because of the anatomically thin wall and narrow working space. Moreover, postoperative esophageal stricture is one of the main complications associated with large esophageal ESD[23,24]. Muscle layer damage with entire circumferential esophageal ESD has been linked to refractory post-ESD stenosis[25]. Hence, ESD in the esophagus requires a highly skilled endoscopic technique and careful operation, and the provision of a more comfortable environment for ESD will contribute to reductions in complications. Based on the results presented above, FlushKnife-BTS is considered to contribute to safer esophageal ESD.

Though the present clinical study focused on only esophageal ESD because esophagus is the narrow

tract in which inflated air inside affects the procedure easily, further investigation including ESD in other organs such as stomach and colorectum would be desired in the near future.

The limitations of this study include its retrospective design and small patient population. Furthermore, the procedure was only performed by one endoscopist. Therefore, the generalizability of the results obtained remains unclear and, thus, further studies with more cases undergoing ESD performed by other endoscopists including less experienced operators are warranted. However, our results still support FlushKnife-BTS creating better conditions for and contributing to the efficient performance of ESD.

In conclusion, our results demonstrate that FlushKnife-BTS supports the efficient performance of ESD, particularly for large lesions, by improving air and fluid aspiration and allowing for smooth knife insertion without frequent knife removal and reinsertion during ESD.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) has been widely accepted as a treatment for early-stage tumors in the digestive tract. Devices utilized in ESD play an important role in facilitating the safe and effective performance of this procedure. A novel slim type ball-tipped FlushKnife (FlushKnife-BTS) has been developed to enhance the performance of aspiration and insertion of the knife through the scope.

Research frontiers

This study investigated the usefulness of FlushKnife-BTS over FlushKnife-BT in functional experiments and clinical practice and is the first report comparing the conventional ESD knife and the developed new one.

Innovations and breakthroughs

This study indicated that FlushKnife-BTS enhances the performance of ESD, particularly for large lesions, by improving air and fluid aspiration and knife insertion during ESD and reducing the frequency of knife removal and reinsertion.

Applications

This study suggested that FlushKnife-BTS supports the efficient performance of ESD, particularly for large lesions.

Terminology

FlushKnife-BTS is a novel slim type FlushKnife BT that has been developed to enhance the performance of aspiration and insertion of the knife through the scope.

Peer-review

Theoretically, the new device facilitates use in a standard scope with 2.8 mm of working channel. The paper compares a new and an older device with respect to the ability of insertion and suction in the laboratory as well as the resection speed by the measurement of the mm^2 per minute in esophageal lesions in clinical practice.

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ORIGINAL ARTICLE

Prospective Study

Spectral computed tomography in advanced gastric cancer: Can iodine concentration non-invasively assess angiogenesis?

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Abstract

AIM

To investigate the correlation of iodine concentration (IC) generated by spectral computed tomography (CT) with micro-vessel density (MVD) and vascular endothelial growth factor (VEGF) expression in patients with advanced gastric carcinoma (GC).

METHODS

Thirty-four advanced GC patients underwent abdominal enhanced CT in the gemstone spectral imaging mode. The IC of the primary lesion in the arterial phase (AP) and venous phase (VP) were measured, and were then normalized against that in the aorta to provide the normalized IC (nIC). MVD and VEGF were detected by immunohistochemical assays, using CD34 and VEGF-A antibodies, respectively. Correlations of nIC with MVD, VEGF, and clinical-pathological features were analyzed.

RESULTS

Both nICs correlated linearly with MVD and were higher in the primary lesion site than in the normal control site, but were not correlated with VEGF expression. After stratification by clinical-pathological subtypes, nIC-AP showed a statistically significant correlation with MVD, particularly in the group with tumors at stage T4, without nodular involvement, of a mixed Lauren type, where the tumor was located at the antrum site, and occurred in female individuals. nIC-VP showed a positive correlation with MVD in the group with the tumor at stage T4 and above, had nodular involvement, was poorly differentiated, was located at the pylorus site, of a mixed and diffused Lauren subtype, and occurred in male individuals. nIC-AP and nIC-VP showed significant differences in terms of histological differentiation and Lauren subtype.

CONCLUSION

The IC detected by spectral CT correlated with the MVD. nIC-AP and nIC-VP can reflect angiogenesis in different pathological subgroups of advanced GC.

Key words: Micro-vessel density; Iodine concentration; Spectral computed tomography; Vascular endothelial growth factor; Gastric cancer

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Core tip: We investigated the correlation between iodine concentration (IC) value generated from spectral computed tomography (CT) and angiogenesis in gastric cancer (GC) with clinical-pathological data. Our results showed that normalized IC (nIC) in both the arterial (AP) and venous phases (VP) had a positive linear correlation with micro-vessel density. nIC-AP reflected the angiogenesis in relatively earlier and well-differentiated GC, while nIC-VP reflected this in further advanced and poorly differentiated GC. Spectral CT with quantitative IC value offers a new choice for evaluating the angiogenesis of gastric cancer noninvasively.

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INTRODUCTION

Despite a recent decrease, gastric cancer (GC) remains the most common cancer and is the third leading cause of cancer-related death globally[1]. In China, the incidence and mortality rates of GC remain high, and the vast majority of cases are in the advanced stage[2], which requires more attention.

Angiogenesis is fundamental to the growth, invasion, and metastasis of GC, and greatly influences the response to anti-tumor therapies[3]. To date, the standard method for studying angiogenesis has been histopathological counting of micro-vessel density (MVD), which is specimen- and immunostaining-dependent. This is impractical in advanced patients undergoing anti-angiogenesis or chemotherapy. Compared with MVD counting, using preoperative imaging modalities for the noninvasive assessment of tumor angiogenesis is more acceptable and feasible. A previous study has revealed that MVD, vascular endothelial growth factor (VEGF), and the absolute enhanced value show some positive correlations with conventional contrast-enhanced computed tomography (CT)[4]. Additionally, CT perfusion has shown the potential for evaluating tumor angiogenesis[5,6], but the complicated measurement and high radiation dosage have limited the extensive application of CT in this regard.

The recently developed spectral CT yields material-decomposition (MD) images that can quantitatively map the iodine concentration (IC) of the tissue in enhanced images. This IC value has been proven to show a strong correlation with the actual iodine concentration in the phantom[7]. Recently, preliminary studies have reported the use of the IC value to differentiate benign and malignant lesions, to find embolisms, and to evaluate the efficacy of anticancer therapy[8-11]. Particularly in the evaluation of neoadjuvant chemotherapy of GC, the IC value was proven to be a more robust imaging biomarker than the morphology index[11]. However, it was not clear how this correlated with radiological-pathological features. On the other hand, the IC value has shown a correlation with vascularization in solid tumors, such as pancreatic carcinoma, hepatocarcinoma, and non-small-cell lung cancer[12-14], while there has been no such report for GC, to provide a basis for using image indicators, other than morphology, for assessing chemo-efficacy. Therefore, our purpose was to investigate the correlation between IC value and angiogenesis in GC cases with clinical-pathological data.

MATERIALS AND METHODS

Study population

Adult patients with advanced GC confirmed by endoscopic biopsy, who were scheduled for surgery, were enrolled. This study was approved by the institutional review board, and informed consent was obtained from each participant. All procedures were performed in accordance with the ethical standards of the institution.

Exclusion criteria were: (1) allergies to intravenous contrast media; (2) cardiac or renal insufficiency; (3) history of chemotherapy or radiotherapy; (4) inability to visualize the tumor on CT; (5) early tumor staging (T1) or presence of distant metastasis (M1); and (6)

specimen with poor fixation for immunostaining.

From June 2014 to May 2015, a total of 41 patients prospectively underwent spectral CT examination. Of these, two patients with serious interface artifacts on CT images, one patient with tumor tissue necrosis that influenced MVD counting, one patient with no tumor cells on hematoxylin and eosin (HE) slices, and three patients with failed immunostaining were excluded.

Ultimately, the data of 34 patients were collected and statistically analyzed. Patient records and pathological data, including gender, age, tumor size, tumor location, invasion depth, lymph nodes involvement, Lauren subtypes, and differentiation, were documented.

CT scan methods

After fasting overnight, all patients were administered 10 mg anisodamine (Minsheng Pharmaceutical Group Co., Ltd., Hangzhou, China) intramuscularly to reduce gastrointestinal motility 20 min prior to CT examination, and ingested 800-1000 mL of water to distend the stomach. During scanning, patients were instructed to suspend respiration.

All examinations were performed on a Discovery CT750 HD system (GE Healthcare, Milwaukee, WI, United States), and included bi-phasic enhanced spectral scanning in the arterial and venous phases (AP and VP, respectively). Spectral CT imaging was performed with a 0.5 ms switch of tube voltage between 140 kVp and 80 kVp; a rotation speed of 0.6 s, and a helical pitch of 1.375:1. The scan range was from the diaphragmatic dome to the symphysis pubis. Non-ionic contrast material, iohexol (350 mg I/mL, GE Pharmaceutical, Shanghai of China), at 1.3 mL per kilogram of body weight was used (total volume: 60-110 mL) at a flow rate of 2.5-4.5 mL/s was injected *via* a peripheral vein, using a dual high-pressure syringe. The AP acquisition time was triggered at 9 s after the attenuation of diaphragmatic abdominal aorta reached 100 HU (SmartPrep; GE Healthcare). The VP followed with a 30 s interval. Raw data were reconstructed to 1.25-mm slice images, using decompose projection-based software. An additional 40% adaptive statistical iterative reconstruction algorithm was applied to suppress image noise and decrease the radiation dose required for spectral CT.

Image analysis

All CT images were transferred to a commercially available workstation (Advantage Windows 4.6; GE Medical Systems, Chicago, IL, United States) to generate iodine-based MD images (Figures 1 and 2). Two experienced radiologists (J.G. and P.L., with 25 and 5 years of experience with abdominal CT, respectively), who were blinded to the pathological results, analyzed the images. Three manually drawn regions of interests (ROIs) that encompassed the maximum lesion in the consecutive 1.25-mm layers of bi-phasic axial images were measured. Areas containing prominent artifacts, necrosis, and vessels were carefully avoided (mean square: 871 mm^2; range: 122-1308 mm^2). For the normal site, we chose a distance longer than 5 cm from the lesion edge that was thick enough to place the ROI. Three small circular ROIs with a diameter exceeding 2 mm were measured as ROI-normal. Images were compared to ensure the measurements were as consistent as possible in both phases. The ICs in the AP (IC-AP) and in the VP (IC-VP) were generated simultaneously (unit: 100 μg/mL). At the same time, a round ROI was placed on the abdominal aorta in the same layer as the target, to calculate the normalized IC (nIC = IC_{target}/IC_{aorta})[15], aiming to reduce the individual circulatory variability. All the ICs and nICs obtained from the same patient were averaged and disagreement on measurement was resolved by consensus.

Histopathologic evaluation

A surgeon (K.R) and a radiologist (X.C) performed sampling together to guarantee that the specimen and the ROI were from virtually the same level, by re-examining the axial and multi-planar reconstruction images. The distance to the cardia or pylorus of the sample site and the thickness were compared on both CT images and surgical specimens. Then, the selected samples (tumor and normal wall) were fixed overnight in 10% formalin, and subsequently dehydrated in alcohol and paraffin-embedded. Wax blocks comprising the central part of the adenocarcinoma were sectioned into 4-μm-thick slices. A ready-to-use two-step streptavidin-peroxidase method was applied. The mouse anti-CD34 monoclonal antibody (diluted 1:150) and rabbit anti-VEGF-A polyclonal antibody (diluted 1:200) (Beijing Zhongshan Goldenbridge Company, Beijing, China) were used to stain all pathological tissues. Positive and negative immunohistochemistry controls were prepared as routine. A pathologist (K.C, with 25 years' experience in MVD and VEGF immunostaining), who was blinded to the spectral CT imaging results, performed the counting and evaluation of all slides.

MVD counting was performed using the Weidner method[16]. The area where vascular endothelial cells stained most intensively was first identified at low (× 100) magnification. Then, five fields were randomly selected at × 400 magnification to count the CD34-positive cell clusters and the mean was recorded as the final value (Figures 1 and 2). VEGF (stained brown), located in the cytoplasm, was scored using an established method[17]: scores of the percentage of positive tumor cells and signal intensity were summed. If the score was less than 4, the section was considered negative, whereas a score of 4 or more was considered positive (Figures 1 and 2).

Statistical analysis

All statistical procedures were performed with a software package (SPSS 21.0, Chicago, IL, United States).

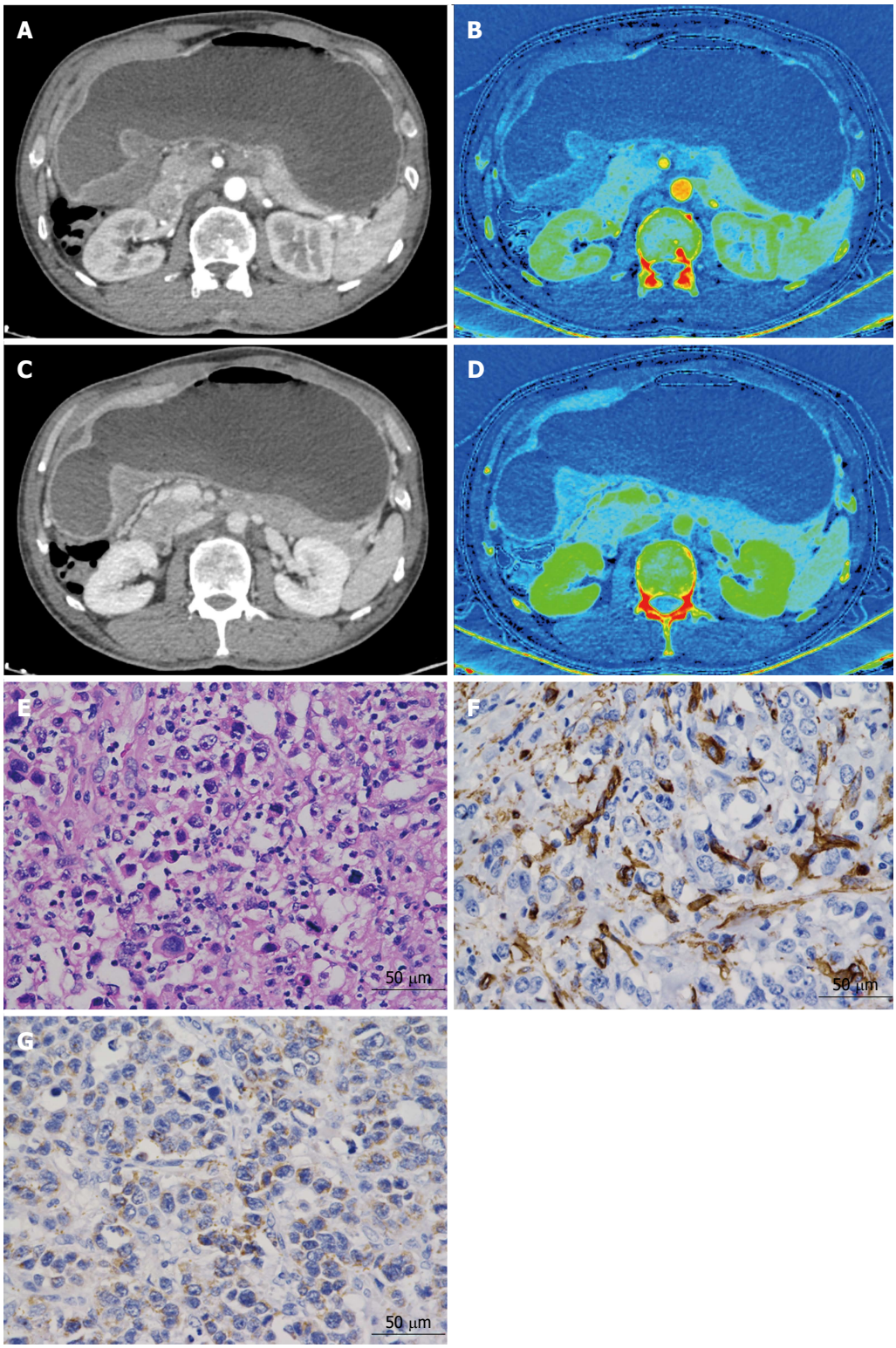

Figure 1 Detection of the iodine concentration value in a 51-year-old man with poorly differentiated adenocarcinoma, with staging Ⅲc (T4aN3M0). A: The monochromatic image shows focal wall thickening in the gastric antrum; B: The iodine-water image with iodine concentration (IC) value 12.83 (100 μg/cm^3), normalized IC (nIC) value 0.11 in the arterial phase. Monochromatic image (C) and iodine-water image (D) with IC value 23.91 (100 μg/cm^3), nIC value 0.53 in the venous phase; E: Hematoxylin and eosin staining of a pathological section obtained from radical surgery shows poorly differentiated, diffused subtype in the Lauren classification (× 400); F: CD34-staining shows endothelial cells stained brown; micro-vessels form clusters or have tiny hollow lumens (micro-vessel density 45/magnification × 400). G: Weak vascular endothelial growth factor staining in the cytoplasm (× 400) with score 2.

A *P*-value of less than 0.05 was considered to indicate a statistically significant difference. Nodal status was classified as positive and negative for lymph node metastasis, and the depth of invasion was classified as positive and negative serosal involvement. A single highly differentiated patient was grouped together

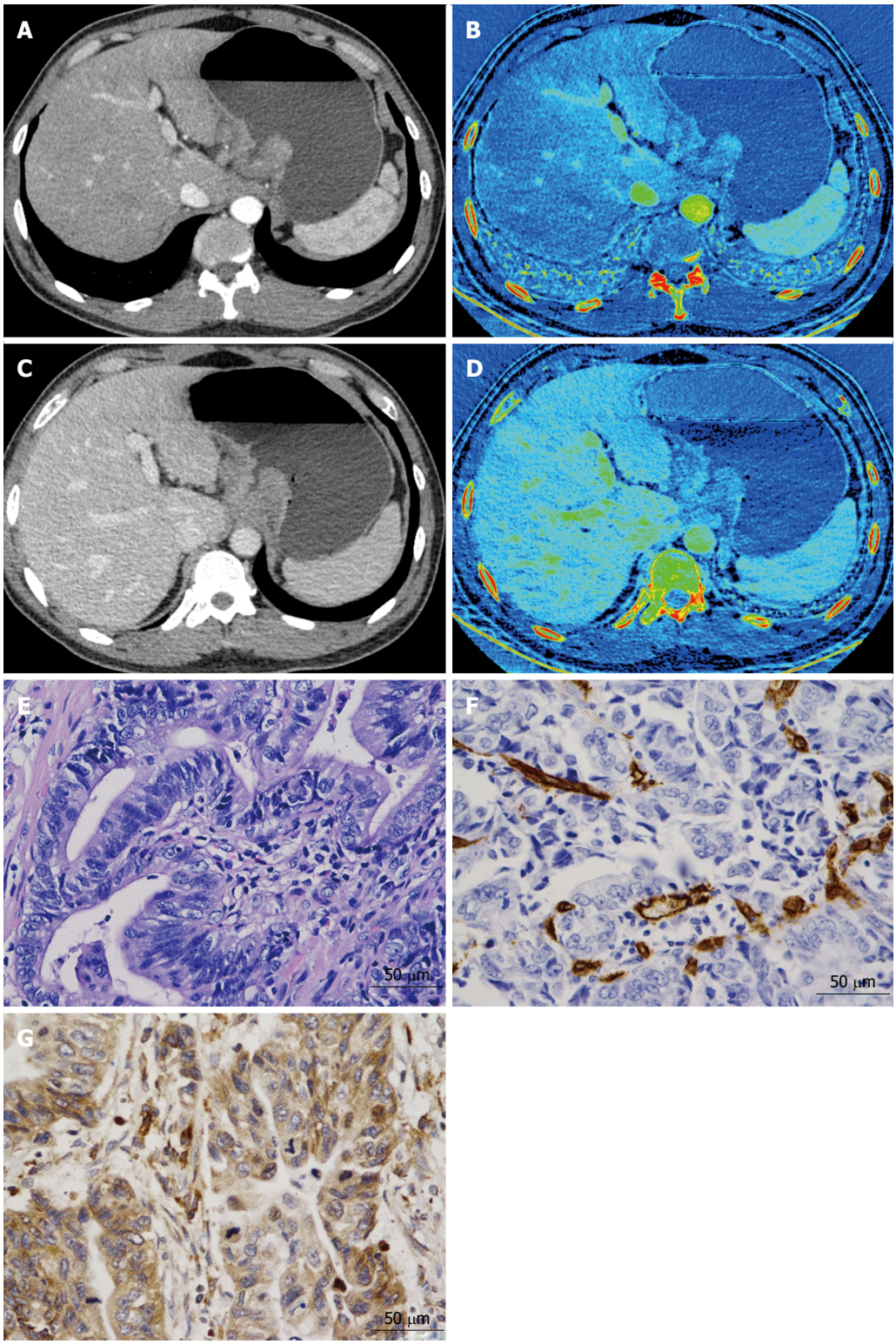

Figure 2 Detection of iodine concentration value in a 50-year-old man with moderate differentiated adenocarcinoma, of staging Ⅲa (T4aN1M0). A: Monochromatic image shows focal wall thickening in the gastric cardia and lesser curvature; B: The iodine-water image with iodine concentration (IC) value 11.78 (100 μg/cm^3), normalized IC (nIC) value 0.09 in the arterial phase; Monochromatic image (C) and (D) iodine-water image with IC value 18.63 (100 μg/cm^3), nIC value 0.34 in the venous phase; E: Hematoxylin and eosin staining shows a moderately differentiated, intestinal Lauren subtype (× 400); F: Immunohistochemical staining shows CD34 positive micro-vessel (micro-vessel density count: 27/magnification × 400); G: Strongly positive vascular endothelial growth factor staining (× 400) with score 5.

with the moderately differentiated patients. Data were subjected to a Kolmogorov-Smirnov normality test and continuous variables were presented as means and standard errors of the mean. When analyzing the correlation of nIC and MVD and VEGF, scatter plots were made first between continuous variables, followed by the Pearson or the Spearman rank-correlation test (Figure 3). Student's *t*-test, correct *t* test, and one-way

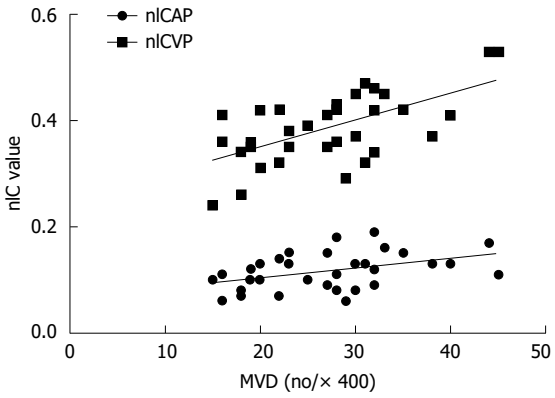

Figure 3 Scatter plots of normalized iodine concentration in arterial phase, normalized iodine concentration in venous phase, and microvessel density counts in tumor lesions (r = 0.423 for normalized iodine concentration in arterial phase, r = 0.606 for normalized iodine concentration in venous phase). VEGF: Vascular endothelial growth factor; nIC: Normalized iodine concentration; nIC-AP: nIC-arterial phase; nIC-VP: nIC-venous phase; MVD: Microvessel density.

analysis of variance (ANOVA)-LSD test were performed to analyze differences in categorical data between groups (serosal involvement, lymph node metastasis, histologic differentiation, Lauren subtype, tumor location, and gender).

RESULTS

A total of 34 advanced GC patients (23 males, 11 females; mean age: 56 ± 3.7 years; age range: 30-73 years) were included (Table 1). Tumor size ranged from 1.5 cm to 13.0 cm (median: 4.0 cm). Fourteen tumors located in the gastric cardia-fundus, nine in the gastricum, and 11 in antrum. All patients were treated surgically by radical gastrectomy and D2 lymph node dissection. Based on pathologic results, the adenocarcinoma was well differentiated in one patient, moderately differentiated in 16 patients, and poorly differentiated in 17 patients. According to the 7th American Joint Committee on staging classification (AJCC), five patients were classified as T2, two as T3, twenty-two as T4a and five as T4b; eleven as N0, eight as N1, seven as N2, and eight as N3. No patient had distant metastasis. The Lauren classification was as follows: 15 were intestinal type, seven were mixed type, and 12 were diffuse type. Additionally, the immunostaining analysis revealed that 25 patients (73.53%) stained positive for VEGF with a score of 4 (n = 11), 5 (n = 9), or 6 (n = 5). The mean MVD count for these 34 tumors was 26.94 ± 1.35.

In general, the bi-phasic nIC values and the MVD counts were positively correlated (P = 0.013, P < 0.001, respectively). VEGF did not correlate with either nIC value or with MVD, as shown in Table 2. When stratified by different clinical features, the correlation coefficient value increased. nIC-AP positively correlated with MVD in patients with tumor stage less than T4 (r = 0.851, P = 0.015), tumor of N0 stage (r = 0.620, P = 0.042), with a tumor located in the pylorus region (r = 0.616, P = 0.044), and who were female (r = 0.696, P = 0.017). On the other hand, nIC-VP correlated with MVD in the more advanced group of patients, with tumors above T4 stage (r = 0.656, P < 0.001), with nodular involvement (r = 0.644, P = 0.001), that were poorly differentiated (r = 0.799, P < 0.001), were of mixed and diffused Lauren subtypes (r = 0.827, P = 0.022; r = 0.765, P = 0.004, respectively), and male gender (r = 0.606, P = 0.002), as shown in Table 3.

The nIC values in the primary GC and normal gastric wall were 0.116 ± 0.033 and 0.101 ± 0.023 in arterial phase (P = 0.033), 0.386 ± 0.061, and 0.286 ± 0.066 in the venous phase (P < 0.001) (Figure 4A). For the VEGF-positive and -negative group, neither nIC-AP nor nIC-VP showed statistically significant differences (Figure 4B).

When stratified by clinical subgroups, both nIC-AP and nIC-VP were higher in patients with serosal involvement, lymph node metastasis, poor differentiation, and diffused Lauren type than in those with depth invasion under T4, nodal status N0, high and moderate differentiation, intestinal and mixed Lauren type, but these differences did not reach statistical significance.

Table 1 Clinical characteristics of the patients (n = 34)

Sex	Male	23	67.65%
	Female	11	32.35%
Age	30 -73 yr (56 ± 3.7 yr)		
Size	1.5 -13.0 cm (median 4.0 cm)		
Tumor location	Cardia/Fundus	14	41.18%
	Gastricum	9	26.47%
	Antrum	11	32.35%
Nodal status	N0	11	32.35%
	N1	8	23.53%
	N2	7	20.59%
	N3	8	23.53%
Depth of invasion	pT2	5	14.71%
	pT3	2	5.89%
	pT4a	22	64.71%
	pT4b	5	14.71%
Lauren subtype	Intestinal type	15	44.12%
	Mixed type	7	20.59%
	Diffuse type	12	35.29%
Histological grading	Highly differentiated	1	2.38%
	Moderately differentiated	16	47.06%
	Poorly differentiated	17	50.00%

Table 2 Correlation of nIC values, microvessel density and vascular endothelial growth factor expression

Varieties	MVD		VEGF	
	r	P value	r	P value
nIC-AP	0.423	0.013[a]	0.170	0.358
nIC-VP	0.606	0.000[a]	0.311	0.073
MVD	1.000		0.210	0.233

[a]P < 0.05. nIC-AP: Normalized iodine concentration in arterial phase; nIC-VP: Normalized iodine concentration in venous phase; MVD: Microvessel density; VEGF: Vascular endothelial growth factor.

Table 3 Correlations between bi-phase normalized iodine concentration and microvessel density in different clinical-pathological subgroups

Varieties	*n*	nIC-AP *vs* MVD		nIC-VP *vs* MVD	
		r	*P* value	*r*	*P* value
Depth of invasion					
< T4	7	0.851	0.015[a]	0.600	0.154
T4	27	0.370	0.057	0.656	0.000[a]
Nodal status					
N0	11	0.620	0.042[a]	0.600	0.051
N1-3	23	0.330	0.124	0.644	0.001[a]
Histologic differentiation					
Highly and Moderately differentiated	17	0.250	0.334	0.190	0.466
Poorly differentiated	17	0.427	0.087	0.799	0.000[a]
Lauren subtype					
Intestinal type	15	0.222	0.427	0.101	0.719
Mixed type	7	0.741	0.057[a]	0.827	0.022[a]
Diffuse type	12	0.145	0.653	0.765	0.004[a]
Tumor location					
Cardia/Fundus	14	0.311	0.279	0.760	0.796
Gastricum	9	0.385	0.307	0.507	0.163
Antrum	11	0.616	0.044[a]	0.891	0.000[a]
Sex					
Male	23	0.385	0.070	0.606	0.002[a]
Female	11	0.696	0.017[a]	0.605	0.049

[a]$P < 0.05$. nIC-AP: Normalized iodine concentration in arterial phase; nIC-VP: Normalized iodine concentration in venous phase; MVD: Microvessel density.

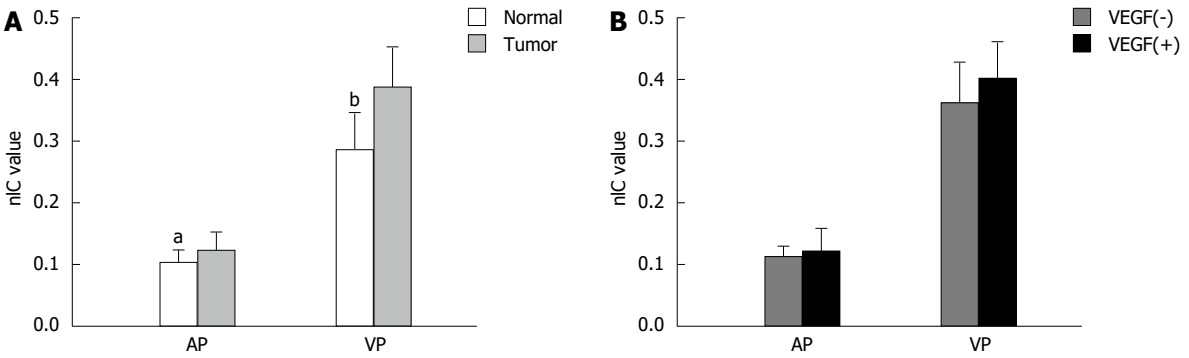

Figure 4 Comparison of normalized iodine concentration in arterial phase; and normalized iodine concentration in venous phase between the normal gastric wall and tumor site (A); comparison of normalized iodine concentration in arterial phase and normalized iodine concentration in venous phase between the vascular endothelial growth factor-positive and -negative group (B). [a]$P < 0.05$, [b]$P < 0.001$. VEGF: Vascular endothelial growth factor; nIC: Normalized iodine concentration; AP: Arterial phase; VP: Venous phase.

nIC-AP and nIC-VP showed statistically significant differences between differentiation categories ($P = 0.003$, $P = 0.001$, respectively) and between Lauren subtypes ($P = 0.016$, $P = 0.006$, respectively). The LSD test revealed that nIC-AP and nIC-VP were significantly different between intestinal and diffuse Lauren subtypes ($P = 0.005$, $P = 0.004$, respectively). nIC-VP was also significantly different between intestinal and mixed Lauren subtypes ($P = 0.013$), as shown in Table 4.

DISCUSSION

There were four major findings from this study. First, the bi-phasic nICs showed a significantly linear positive relationship with MVD in primary GC. The nIC-AP and nIC-VP correlated with MVD in different subgroups; the former correlated significantly with MVD in the relative earlier stage of advanced GC, while the latter correlated with MVD in the more advanced stage. Second, no significant correlation was found between nICs and VEGF. Third, nIC values in the normal gastric wall were observed to be significant lower than that in the tumor. Fourth, nICs were observed to differ between histological grades and Lauren subtypes of advanced GC; the greater the malignancy, the higher the nICs. Taken together, these observations demonstrate that quantification of iodine in spectral CT imaging have the potential to reflect angiogenesis of advanced GC.

Iodine, a commonly used CT contrast material, is generally known to produce higher attenuation at low tube voltage settings[18]. Based on this effect, spectral CT using high and low voltage switching settings could

Table 4 Difference of bi-phase normalized iodine concentration between different clinical-pathological subgroups

Varieties	*n*	nIC-AP		nIC-VP	
		mean ± SD	*P* value	mean ± SD	*P* value
Depth of invasion					
< T4	7	0.101 ± 0.042	0.195	0.363 ± 0.079	0.302
> T4	27	0.120 ± 0.031		0.392 ± 0.063	
Nodal status					
N0	11	0.112 ± 0.033	0.321	0.385 ± 0.085	0.923
N1-3	23	0.125 ± 0.035		0.387 ± 0.057	
Histologic differentiation					
Highly and moderately differentiated	17	0.100 ± 0.028	0.003[a]	0.352 ± 0.048	0.001[a]
Poorly differentiated	17	0.132 ± 0.031		0.421 ± 0.065	
Lauren subtype					
Intestinal type	15	0.099 ± 0.029	0.016[a]	0.347 ± 0.048	0.006[a]
Mixed type	7	0.120 ± 0.032		0.417 ± 0.061	0.013[1,a]
Diffuse type	12	0.135 ± 0.030	0.005[2,a]	0.417 ± 0.067	0.00[2,a]
Tumor location					
Cardia/Fundus	14	0.109 ± 0.033	0.445	0.385 ± 0.046	0.874
Gastricum	9	0.128 ± 0.024		0.387 ± 0.064	
Antrum	11	0.116 ± 0.040		0.387 ± 0.091	
Sex					
Male	23	0.113 ± 0.033	0.377	0.390 ± 0.069	0.633
Female	11	0.124 ± 0.035		0.378 ± 0.062	

[1]One-way ANOVA-LSD, mixed type *vs* intestinal type; [2]Diffuse type *vs* intestinal type. [a]$P < 0.05$. nIC-AP: Normalized iodine concentration in arterial phase; nIC-VP: Normalized iodine concentration in venous phase; MVD: Microvessel density; SD: Standard deviation.

differentiate materials of the same density[19] and the IC value could be extracted[20]. With water-iodine based material decomposition images, Lv *et al*[9] concluded that the IC in images of hepatic lesions acquired in a quantitative parameter was highly precise. Thieme *et al*[21] found a very good correlation between vessel occlusion depicted at CTA and IC defects in the dual-energy image, indicating that iodine distribution in the parenchyma is closely related to pulmonary perfusion. Therefore, the IC may be considered as an indirect marker of perfusion and tumor vascularity.

Tumor angiogenesis is defined as the formation of new blood vessels from pre-existing vessels[22]. MVD and identification of VEGF in tissues are commonly used biomarkers of angiogenesis[23]. In previous studies, the relationships between dynamic contrast-enhanced perfusion CT parameters and immunohistological markers of angiogenesis have been studied in different tumors, including colorectal cancer[24], advanced GC[6,25], lung cancer[26], *etc.* However, the studies produced discrepant results on whether the use of blood flow or permeability surface area product were efficacious.

Our results proved a positive linear relationship between IC and MVD in primary GC. The nIC values were significantly elevated in the tumor as compared to the normal gastric wall. Similar results were acquired by Pang *et al*[27], who considered the nIC value of the infarcted myocardium to be an important indicator of MVD in the 1-min and 3-min CT images. Additionally, the study by Hu *et al*[12] indicated that the nIC values of three-phase scans had a positive correlation with MVD for detecting the therapeutic response in a pancreatic carcinoma xenograft nude mouse model. Taken together, spectral CT imaging can be used to evaluate angiogenesis in disease.

On the other hand, nIC had a low correlation with VEGF expression, and no significant differences were found in the comparison between IC parameters and VEGF group. VEGF, one of the most prominent biomarkers of angiogenesis studied to date, has been shown to correlate well with CT perfusion in peripheral pulmonary nodules[28]. Moreover, the study of Zhou *et al*[13] in a rabbit VX2 liver model suggested that nIC and contrast-enhanced ultrasound parameters positively correlated with VEGF and FGF2 expression, while several reports failed to show such a correlation, for example, the GC study performed by Yao *et al*[6] and the colorectal cancer research by Goh *et al*[24]. The relationship between VEGF expression and imaging of tumor vascularity is complex. Further investigations of IC and VEGF in a large population with different clinical-pathology are needed.

At the same time, nIC in arterial phase and venous phase displayed different character when stratified. The nIC-AP showed correlations with MVD in relative earlier and differentiated advanced GC, while nIC-VP correlated with MVD in more advanced stage and poorly differentiated advanced GC.

In terms of the acquisition time of our routine abdominal CT scanning, the AP was performed at about 25-30 s after contrast media injection, when the mucosa at the lesion presented as a focal enhanced line. nIC-AP can reflect the blood supply and functional capillary density. In the VP of GC, the markedly increased interstitial fibrous tissue reduced the flow-out speed of the contrast media[29]; thus, more dysfunctional neo-vessels should be considered. Therefore, the nIC-VP may represent the distribution of iodine in

interstitial spaces. Under such conditions, the bi-phasic nIC demonstrated the vascular character of GC, and nIC-VP may be better correlated with MVD in advanced GC.

Furthermore, both nICs were different between histological differentiations and Lauren subgroups. The nIC-VP was more effective than nIC-AP in displaying the difference between Lauren subtypes. In general, the nIC value was higher in poorly differentiated and diffused types than that in highly or moderately differentiated and intestinal types. A previous study[30] has found that the degree of tumor angiogenesis was closely related to the pathological grade, that is, the poorer the differentiation of the tumor, the higher the MVD values. Another study[31] demonstrated a correlation between MVD and tumor histological type according to the Lauren classification. Accordingly, it is likely that the nIC value can be used to evaluate histology by mapping the neovascularization of advanced GC. The finding in the present study was also supported by the results of Pan *et al*[15] and Wang *et al*[32] in GC research.

The nICs increased in patients with serosal involvement and lymphatic metastasis, but the differences from patients without serosal involvement and lymphatic metastasis did not reach significant difference, for reasons that are not immediately clear, as these clinical-pathological features should reflect the functional status of the vasculature. Both nIC-AP and nIC-VP correlated with MVD of GC located in the antrum and occurring in different genders. However, nICs were not very effective in differentiating between these groups.

There are several potential limitations in our study. First, the tumor vasculature is spatially heterogeneous. Although we selected specimens carefully under the guide of two major specialists, the excision level was barely achieved. It may be questioned whether the part of the histopathological part selected and matched to the imaging measurement represented the angiogenesis of the whole tumor. Second, the sample numbers were limited, especially when subdivided by clinical classification. A larger prospective investigation is needed to confirm the present findings. Third, given the limitations of CT resolution, flat and light ulcerous lesions without enhancement would have been missed in the images, which inducing selection bias.

In conclusion, the bi-phasic nIC values had a positive linear correlation with MVD. nIC-AP reflected the angiogenesis in relatively earlier and well-differentiated advanced GC, while nIC-VP reflected this in further advanced and poorly differentiated GC. Spectral CT with quantitative IC value offers a new choice to evaluate the angiogenesis of gastric cancer noninvasively.

COMMENTS

Background

Angiogenesis is fundamental to the growth, invasion, and metastasis of gastric cancer (GC). To date, the standard method for studying angiogenesis has been histopathological counting of micro-vessel density (MVD). This is impractical for patients who undergoing anti-angiogenesis or chemotherapy. The current trial was designed to evaluate if the iodine concentration (IC) generated by spectral computed tomography could non-invasively judge the features of tumoral MVD and vascular endothelial growth factor with clinical data.

Research frontiers

Iodine-water material-decomposition (MD) images can quantitatively map the IC of the tissue in enhanced scanning. In this study, there is suggestion that IC value has the potential to reflect angiogenesis of advanced GC.

Innovations and breakthroughs

The authors measured the normalized IC value in spectral computed tomography (CT) with manually drawn regions of interests to avoid the selection bias. Data stratified by clinical subgroups further revealed the connection between imaging index and patho-index. They finally proved that the normalized IC value in different scanning phase could reflect angiogenesis in different pathological subgroups of advanced GC.

Applications

Radiological-pathological correlation in angiogenesis, although with not much high coefficient, will offer a new choice to clinical decision in judging the status of GC, especially for neoadjuvant chemotherapy or radiochemotherapy patients.

Terminology

IC: Iodine is a commonly used contrast material in performing enhanced CT scanning. The iodine concentration here refers an imaging data, representing iodine distribution of the organ with spectral CT modality, not the real iodine concentration of contrast material itself.

Peer-review

The study on the spectral computed tomography in advanced gastric cancer is quite interesting with novelties.

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EVIDENCE-BASED MEDICINE

Inflammatory bowel disease: An evaluation of health information on the internet

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Abstract

AIM

To evaluate the quality and accuracy of websites written to the public on inflammatory bowel disease (IBD) (Crohn's disease and ulcerative colitis) and assess their readability level.

METHODS

Google™, Bing™, and Yahoo™ search engines were searched independently by three researchers in December 2014. Only English-language websites were selected on the basis of predetermined inclusion and exclusion criteria. Researchers independently evaluated the quality of each website by using the DISCERN and the HONcode instruments. The readability levels were calculated using two formulas; the Flesch-Kincaid Grade Level Index, and the Coleman-Liau Readability Index. The agreement between the evaluators was calculated using Cohen kappa coefficient.

RESULTS

Eighty-four websites were finally identified. Scores varied from a minimum DISCERN score of 18 to a maximum of 68 [mean ± SD, 42.2 ± 10.7; median = 41.5, interquartile range, interquartile range (IQR) = 15.8] and a minimum score of HONcode of 0.14 and a maximum of 0.95 (mean ± SD, 0.16 ± 0.19; median = 0.45, IQR = 0.29). Most of these websites were reviewed in 2014 and 2015 (n = 51). The creators of these websites were: universities and research centers (n = 25, 30%), foundations and associations (n = 15, 18%), commercial and pharmaceutical companies (n =

25, 30%), charities and volunteer work (*n* = 9, 10%), and non-university educational bodies (*n* = 10, 12%). The Flesch-Kincaid Grade Level readability score (mean ± SD) was 11.9 ± 2.4 and the Coleman-Liau Readability Index score was 12.6 ± 1.5. Significant correlation was found between the two readability scores (R^2 = 0.509, *P* = 0.001). The overall agreement between evaluators measured by Cohen kappa coefficient was in the range of 0.804-0.876; rated as "Good".

CONCLUSION

The DISCERN and the HONcode scores of websites varied and the readability levels of most websites were above the public readability level. The study highlights the areas that need further improvement and development in patient education online materials about IBD.

Key words: Inflammatory bowel disease; The internet; Patients' information; Evidence; Patients' education; Online resources

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Core tip: This is a comprehensive study analyzing the quality and accuracy of content and the readability level of websites in the English language on inflammatory bowel disease dedicated to the public. Two standardized instruments were used in assessing quality and accuracy and two methods were used in calculating readability level. The study showed variability in scores and the readability levels of most websites were above that for the public. Based on evidence, the study highlights the need for improving online patient education.

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INTRODUCTION

Inflammatory bowel disease (IBD) refers to two chronic inflammatory disorders, Crohn's disease and ulcerative colitis. Both are life long, relapsing disorders of unknown etiology; possibly the result of interaction between genetic and environmental factors[1]. The diagnosis of these disorders is based on clinical features, endoscopy, and histological changes[2]. Crohn's disease may affect any part of the gastrointestinal tract but most commonly affects the distal ileum and proximal colon. The disease is characterized by inflammatory changes involving all the layers of the affected regions. In contrast, ulcerative colitis is characterized by continuous ulceration starting in the rectum and limited to the colonic mucosa[3]. IBD occurs worldwide with the highest incidence in developed countries mainly North America, United Kingdom and northern Europe. The incidence of ulcerative colitis in North America is approximately 19.5 per 100000 person years and 243 per 100000 person years in Europe while the incidence of Crohn's disease in North America is approximately 20.2 per 100000 person years and 12.7 per 100000 person years in Europe[4]. The aims of treatment are to induce remission in active disease and to maintain remission/prevent relapse. Therapeutic modalities include lifestyle modification, nutritional support, and medications. Surgery is reserved for the treatment of complications or when the medical therapy is ineffective. In addition to other complications, patients with IBD are at a higher risk of developing colorectal cancer. Therefore, patients have to undergo to regular checkup for early detection of the development of colon cancer[5].

With this information in mind, patients with IBD, as it is the case with other chronic diseases, usually seek information about the nature of the disease, its causes, investigations needed to diagnose the disease and therapeutic options. The advances in treatment modalities and options, and the increasing desire for patients to participate in decision-making about treatment choices necessitate the need for resources to support these decisions. Nowadays, patients have increasingly used the Internet as a source of health information because of its global accessibility, speed, and cost effectiveness[6]. Approximately 80% of the Internet users look for medical or health-related information through the Internet[7]. The topics most searched were information about specific disease or medical condition, treatment options, diet and nutrition, exercise and fitness and medications[7]. The increasing use of the Internet embraces a variety of aspects of topics searched, which gives the person an opportunity to investigate their questions from several resources. However, with the abundance of such information there is concern about the quality, accuracy, and readability level of the information available on the Internet about health care[8].

Therefore, the aims of this study were: to evaluate the quality, and accuracy of web-based information about IBD using two instruments, the DISCERN and the HONcode, as well as calculate the readability level by using two formulas, the Flesch-Kincaid Grade Level Index, and the Coleman-Liau Readability Index. The rationales for the study were to assess the educational usefulness of web-based information on IBD particularly their quality, accuracy and areas of deficiencies that need improvement. Also to assess whether these resources are easily read and understood by the public. Therefore our research questions are: (1) for the websites targeting the public and patients with IBD, what is the accuracy and the quality of these information resources? and (2) does the readability level of these online resources match with the recommended level for the public?

MATERIALS AND METHODS

Search design

In this study we assessed websites written for patients and the public on IBD by searching three search engines (Google™, Bing™ and Yahoo™), the selection of these three search engines was based on current statistical information that showed that these engines are the most searched by the public for health information[9]. The quality and accuracy of information provided on websites were assessed using two instruments: the DISCERN (www.discern.org.uk) and HONcode (www.hon.ch/HONcode/) instrument. Details about these instruments and the justification for selecting them are discussed later. The readability of the websites was assessed using two methods: the Flesch-Kincaid Grade Readability Level and the Coleman-Liau Readability Index. After piloting the work and ensuring satisfactory use of these instruments by researchers, the work was carried out to assess the quality of websites. The Institutional Review Board, College of Medicine King Saud University, has approved the project and the approval number: F06/2014.

Searching the internet

Using the following key words: "inflammatory bowel disease", "Crohn's disease", "ulcerative colitis", "inflammatory bowel disease patient information", "Crohn's disease patient information", and "ulcerative colitis patient information", three search engines (Google™, Bing™ and Yahoo™) were searched. Researchers independently from 1 to 20 December 2014 conducted the search. Information for each website was recorded; these included: website title, website URL, name of creator, year of publication on the Internet, last date updated, and the objectives of the website. This information about each website was collected using the following online meter: http://whois.domaintools.com/. The data collected were evaluated on the bases of the inclusion and the exclusion criteria.

Inclusion and exclusion criteria

The inclusion criteria included: (1) websites covering public education about Crohn's disease, ulcerative colitis or IBD; and (2) websites focusing on patient education and in the English language. The excision criteria comprised: (1) websites addressing doctors or health professionals; (2) lectures, and advertisement on IBD; (3) websites in languages other than English; and (4) presentations at conferences.

Assessing accuracy and quality of information

Two instruments were used in assessing the quality and accuracy of information provided, namely the DISCERN instrument and the HONcode instrument. These two instruments have been widely used in the literature in assessing information on the Internet particularly health related issues and patients' education online resources[8,10-12]. More details about these two instruments can be summarized as follows:

DISCERN instrument: This instrument is a standardized set of criteria for judging the quality of health information and is written for the public to assess treatment options[8,10-12]. The DISCERN instrument was created by the University of Oxford, and the project was funded by the British Library and the National Health Service (NHS) Research & Development Programme[13] The instrument consists of 15 questions plus an overall quality rating question. The questions can be grouped under the three key topics as follows: Questions 1 to 8 addressing reliability, Questions 9 to 15 addressing specific detail about the information provided and treatment choices, and Q16 covering the overall quality rating[14]. The instrument has been used to assess healthcare-related websites and online resources. For example, the quality of patients' information on surgical treatment of haemorrhoids[12], and colorectal cancer information[11].

HONcode instrument: The Health on the Net (HON) Foundation, a non-profit, and non-government organization created this instrument in 1995. The instrument focuses on key questions on the provision of health information available on the Net, and provides a code of conduct addressing eight principles: (1) authoritative (indicates the qualifications of the authors); (2) complementarity (Information should support, not replace, the doctor-patient relationship); (3) privacy (Respect the privacy and confidentiality of personal data submitted to the site by the visitor); (4) attribution [cite the source(s) of published information, date medical and health pages]; (5) justifiability (site must back up claims relating to benefits and performance); (6) transparency (Accessible presentation, accurate email contact); (7) financial disclosure (Identify funding sources); and (8) advertising policy (Clearly distinguish advertising from editorial content)[15-17]. To earn HONcode certification, a website must conform to the eight principles of the HONcode of Conduct. An HONcode expert then assesses the candidate website using precise guidelines for each principle. Recently, the HON Foundation has developed an automated system to assist in detecting a website's HONcode conformity. Therefore, the automated assistance in conducting HONcode reviews can expedite the current time-consuming tasks of HONcode certification and ongoing surveillance. A recent study showed that there is concordance between automated and expert manual compliance detection for the criteria[18]. In this research we have used the electronic system available at: http://www.readabilityformulas.com/free-readability-formula-tests.php.

The HONcode has been widely used in the literature in assessing health-related websites[19]. The two instruments, the DISCERN and HONcode, do not exactly cover the same issues/topics, although there are some

overlaps. Therefore, using these two instruments with these differences in mind could provide a better evaluation of the websites.

Piloting the study

The aims of piloting the study were: (1) to introduce the two instruments to the researchers and orient them on how to use each instrument in assessing the websites; and (2) identify difficulties facing the researchers on applying the two instruments and the sources of disagreements among them. Such exercise prior to the implementation of the two instruments was vital for ensuring optimal use of the instruments and maximizing the degree of agreement among evaluators when they apply these two instruments in the actual research. The piloting part was conducted as follows: (1) approximately 10 websites other than those identified for the research study were evaluated independently by three researchers using the two instruments; (2) the results of their evaluation were discussed with the aim to identify sources for difficulties/disagreements; (3) the identified differences were resolved after discussing them reaching to a solution; and (4) the same process was repeated on another 10 websites until the agreement between the researchers reached to an optimal level[20].

Conduction of the study

Along with the same approach described under piloting the study, the researchers evaluated the websites identified by applying the two instruments on each website and giving a score. The process was conducted by each researcher independently first by applying the DISCERN instrument then the HONcode instrument. The results of the assessment were placed on an Excel sheet for each researcher. The degree of agreement was measured using Cohen kappa coefficient[21].

Calculating website readability

The aims of calculating readability level of websites was to assess if they were written at the readability level of the general public and patients; should not exceed the 6th grade readability level[22,23]. Two methods were used to calculate readability: The Flesch-Kincaid Grade Level Index[24], and the Coleman-Liau Readability Index[25,26]. It was decided to use these two methods rather than one method so that we can compare the readability scores and examine if there were an agreement between the two methods, and hence strengthening the outcomes of our readability assessment and our conclusions. The two methods can be summarized as follows:

Flesch-Kincaid grade level index: This test helps in indicating how difficult a reading passage in the English language to understand. The test was developed by Rudolf Flesch and finalized by J Peter Kincaid for use by the United States Navy, hence the name of the test[24]. The test is based on the word length and the sentence length and is based on the following formula:

0.39 × [(total words)/(total sentences)] + 11.8 × [(total syllables)/(total words)] - 15.59

This method has been widely used in assessing the readability of websites and educational material[27].

Coleman-Liau readability index: This test differs from the above method in relying on characters instead of syllables per word. It enables the users however to grade the readability level. It has been widely used in assessing the readability of educational material[27].

We used a free online calculator (www.readability-formulas.com) to calculate the readability level using the two readability methods. As per instructions provided by the website, the top, middle and bottom 150-200 words of each website were placed in the calculator and then the text readability was checked by calculating the number of sentences, words, syllables, and characters in the sample. A sufficient sample size of four to five full sentences; approximately 200-500 words in total were used. The scores recorded for each website were placed on an Excel sheet and reviewed by two other researchers before conducting final analysis for the means and standard deviations.

Grouping the websites under five categories

Assessment of the identified websites revealed variability in their creators. These can be grouped into 5 categories: (1) university, affiliated hospitals, and research centres; (2) foundations and associations; (3) commercial and pharmaceutical companies; (4) charities and volunteer works; and (5) non-university educational bodies such as colleges, academies, and councils. The grouping of websites under these five categories was carried out by researchers independently and was reviewed in a meeting for any disagreements.

Statistical analysis

The collected data were placed on an Excel Sheet (Microsoft Excel for Mac 2011, Microsoft Corporation, Redmond, WA, United States). All analysis was conducted by using SPSS software (SPSS Statistics version 22 for Mac, IBM Corporation, Armonk, NY, United States). For the data collected from measuring website accuracy, and the readability scores, the means, standard deviations, the median and interquartile range (IQR) were calculated. Pearson correlation studies and *P*-values for significance were calculated to examine if there were correlations between the scores obtained from the two readability methods[28]. A *P*-value of < 0.05 was considered significant. The agreement between the evaluators measured by the degree of inter-rater agreement using Cohen kappa coefficient was also carried out using SPSS software. This has been interpreted as "Poor", if the results in the range:

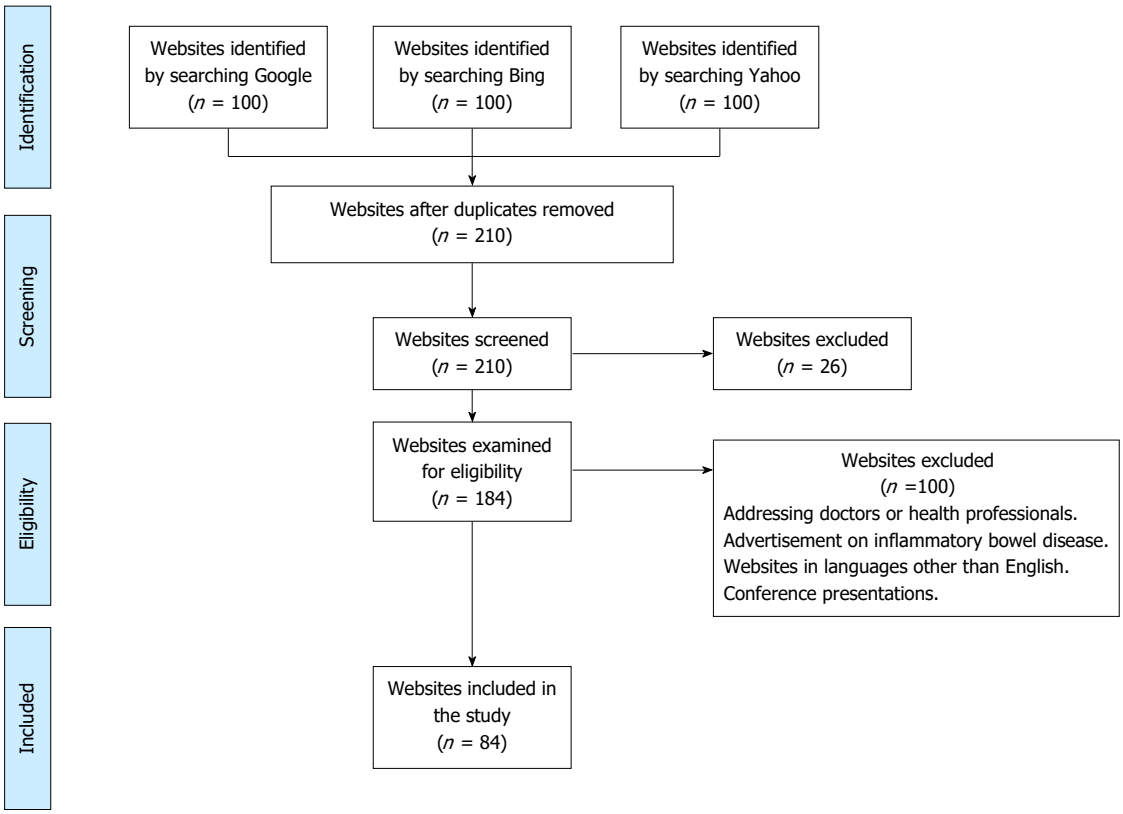

Figure 1 PRISMA flowchart showing the websites on inflammatory bowel disease searched on the Internet and those finally included in the study.

0.21-0.40; "Fair" 0.41-0.60; "Moderate" 0.61-0.80; "Good" 0.81-1.00.

RESULTS

General information about websites

The search of the three databases, Google™, Bing™ and Yahoo™, resulted in the identification of 300 websites. After the duplicates were removed we ended with 210 websites. On applying the inclusion and exclusion criteria, 84 websites were finally identified and included in the study (Figure 1).

Table 1 summarizes the general information about the 84 websites, including: website title, URL, author/ownership, year created, last updated, number of pages, number of tables, images and illustrations. The oldest two websites were created by the University of North Carolina (UNC), School of Medicine, North Carolina, United States and the Department of Surgery, University of California, California, United States, while the most recent was published in 2013 and created by New Health Guide, United States.

For other websites, four websites were published in 1987-1994, 44 were published in 1995-2002, and 29 were published in the years 2003-2011. Only four websites were difficult to identify the exact year of their publication. Websites were updated regularly, 51 websites were updated in 2015 and 2014, while 33 websites were updated earlier, including one website was updated in 2006.

Of the 84 websites, 60 websites comprised 1-5 pages, 16 websites had 6-10 pages, 8 had more than 11 pages. The website titled Crohn's disease by the University of Maryland medical center had the highest number of pages, 20 pages. The number of tables varied from zero to 6. Out of the 84 websites only 24 websites used tables to explain their content. The total number of tables in these websites was 55. The number of images varied from zero to 27. Out of the 84 websites only 42 websites had images to explain the content. The total number of images in these websites was 141. Again the number of illustrations varied from zero to 10. Out of the 84 websites, only 28 had illustrations to explain the content. The total number of illustrations was 53.

DISCERN and the HONcode scores of websites

In order to calculate the accuracy of the websites, we used two instruments, the DISCERN and the HONcode instruments. Table 2 summarizes the scores calculated from applying the DISCERN and the HONcode scores expressed as mean ± SD for each website. The DISCERN scores varied from a minimum of 18 to a maximum of 68 (mean ± SD, 42.2 ± 10.7; median = 41.5, IQR = 15.8). The lowest DISCERN score was scored by the website, Crohn's Disease Diagnosis, New health guide, while the highest DISCERN score was scored by the website, Crohn's Disease, the National Institute of Diabetes and Digestive and Kidney Diseases. The HONcode trust worthy scores

Table 1 Summarizes general information about websites on inflammatory bowel disease included in the study

No.	Website title, Organisation	URL	Authority/ownership, state, country	Year created	Last updated	Number of pages	Number of tables	Number of images	Number of illustrations
1	Inflammatory Bowel Disease (IBD), Mayo Clinic	http://www.mayoclinic.org/diseases-conditions/inflammatory-bowel-disease/basics/definition/con-20034908	Mayo Foundation for Medical Education and Research, Arizona, United States	1997	04 Feb 2014	11	0	0	0
2	Inflammatory Bowel Disease Health Center, WebMd	http://www.webmd.com/ibd-crohns-disease/	WebMD, Inc., Georgia, United States.	1998	06 Sep 2013	2	0	3	0
3	Inflammatory Bowel Disease (IBD), Center for Disease Control and Prevention (CDC)	http://www.cdc.gov/ibd/	Centers for Disease Control and Prevention (CDC), Georgia, United States.	1999	04 Sep 2014	3	0	1	1
4	Inflammatory Bowel Disease, NHS Choices	http://www.nhs.uk/conditions/inflammatory-bowel-disease/pages/introduction.aspx	NHS England, Wakefield, United Kingdom.	1996	29 Apr 2013	2	0	0	0
5	What are Crohn's and Colitis? Crohn's and Colitis Foundation	http://www.ccfa.org/what-are-crohns-and-colitis/	Crohns and Colitis Foundation of America, New York, United States.	1996	14 Apr 2014	1	0	1	0
6	Inflammatory Bowel Disease, KidsHealth	http://kidshealth.org/parent/medical/digestive/ibd.html	Kids Health Organisaion, The Nemours Foundation, Orlando, United States.	1995	27 Jan 2015	4	0	1	0
7	Inflammatory Bowel Disease (IBD). FamilyDoctor	http://familydoctor.org/familydoctor/en/diseases-conditions/inflammatory-bowel-disease.html	American Academy of Family Physicians, New Jersey, United States.	1998	22 Jan 2015	7	0	0	0
8	Inflammatory Bowel Disease, Healthline	http://www.healthline.com/health/inflammatory-bowel-disease#Overview1	Healthline, California, United States.	2004	29 Nov 2011	6	0	0	0
9	Crohn's and Colitis, Australia	https://www.crohnsandcolitis.com.au/about-crohns-colitis/inflammatory-bowel-disease/	Crohn's and Colitis Australia, Victoria, Australia.	2009	24 Jul 2014	3	0	1	0
10	Crohn's and Colitis UK	http://www.crohnsandcolitis.org.uk/information-and-support/information-about-ibd/what-is-IBD	Crohn's and Colitis UK, United Kingdom.	2010	13 Nov 2014	2	0	1	0
11	Inflammatory Bowel Disease (IBD) (Intestinal Problems of IBD), MedicineNet	http://www.medicinenet.com/inflammatory_bowel_disease_intestinal_problems/article.htm	Medicine.Net.com, WebMed Network, New York, United States.	1995	6 Sep 2013	12	0	27	0
12	Inflammatory Bowel Disease Center, Cedars-Sinai	http://www.cedars-sinai.edu/Patients/Programs-and-Services/Inflammatory-Bowel-Disease-Center/	Cedars-Sinai Medical Center, California, United States.	1992	5 Jul 2013	2	0	0	0
13	Inflammatory Bowel Diseases Symptoms and Treatment: Livescience	http://www.livescience.com/39880-inflammatory-bowel-disease.html	Tanya Lewis, LiveScience Contributor, New York, United States.	2001	10 Apr 2014	11	0	1	0
14	Inflammatory Bowel Diseases Program, Penn Medicine.org	http://www.pennmedicine.org/gastroenterology/patient-care/gi-diseases/inflammatory-bowel-disease-ibd/	Penn Medicine, Pennsylvania, United Stats.	2003	6 Nov 2014	4	0	0	0
15	Inflammatory Bowel Diseases Support Groups, IBDsupport.org	http://www.ibdsupport.org/	IBD support.org, Utah, United States.	2011	30 May 2014	2	0	0	0
16	Inflammatory Bowel Disease (IBD), ABC Health and wellbeing	http://www.abc.net.au/health/library/stories/2012/02/22/3435688.htm	Australian Broadcasting Corporation, NSW, Australia.	2001	3 Dec 2014	4	0	1	0

17	Inflammatory Bowel Disease (IBD), GIKids	http://www.gikids.org/content/7/en/IBD	GIKids and The NASPGHAN Foundation, Pennsylvania, United States.	2009	11 Jun 2013	2	0	1	0
18	Inflammatory Bowel Disease, Vitamin D Council	https://www.vitamindcouncil.org/health-conditions/inflammatory-bowel-disease/	The Vitamin D Council, California, United States.	2007	17 Jun 2011	6	0	0	0
19	Inflammatory Bowel Disease Symptoms and Diagnosis, Seattle children's	http://www.seattlechildrens.org/medical-conditions/digestive-gastrointestinal-conditions/ibd-symptoms/	Children's Hospital and Regional Med. Ctr, Washington, United States.	1993	23 Apr 2014	2	0	0	0
20	Crohn's Disease, Patient.co.uk	http://www.patient.co.uk/health/crohns-disease-leaflet	Patient, Patient information Publications, Leeds, United Kingdom.	1997	05 Mar 2013	8	0	0	1
21	Patient Information Crohn Disease (Beyond and the Basics), Uptodate	http://www.uptodate.com/contents/crohn-disease-beyond-the-basics	UpToDate, Wolters Kluwer Health, Illinois, United States.	1998	29 Jul 2014	5	0	0	0
22	Crohn's Disease, Centre for digestive diseases	http://www.cdd.com.au/pages/disease_info/crohns_disease.html	The Centre for Digestive Diseases, NSW, Australia.		08 Jul 2013	4	0	0	0
23	Crohn's Disease, Patients: British Society for Gastroenterology	http://www.bsg.org.uk/patients/general/crohn-s-disease.html	British Society of Gastroenterology, London, United Kingdom.	1996	05 Aug 2014	6	0	0	0
24	Crohn's Disease, Bupa	http://www.bupa.co.uk/health-information/directory/c/crohns-disease	The British United Provident Association Ltd, London, United Kingdom	1996	16 Jun 2014	6	0	0	1
25	Crohn's Disease, University of Maryland Medical Center	http://umm.edu/health/medical/reports/articles/crohns-disease	University of Maryland Medical Center, Maryland, United States	1996	19 Sep 2013	20	0	0	0
26	Crohn's Disease, Symptoms, Diagnosis, Treatment, Southern Cross	https://www.southerncross.co.nz/AboutTheGroup/HealthResources/MedicalLibrary/tabid/178/vw/1/ItemID/523/Crohns-disease-symptoms-diagnosis-treatment.aspx	Southern Cross Healthcare Group; Auckland, New Zealand.	1998	01 Feb 2015	5	0	0	0
27	Crohn's Disease, American family physician	http://www.aafp.org/afp/2011/1215/p1379.html	American Academy of Family Physicians, Kansas, United States	1995	02 Jul 2014	2	0	0	0
28	What is Crohn's Disease? What Causes Crohn's Disease? MNT	http://www.medicalnewstoday.com/articles/151620.php	Christian Nordquist, MNT, Sussex, United Kingdom.	2003	02 Jan 2014	7	0	0	0
29	Crohn's Disease, Netdoctor	http://www.netdoctor.co.uk/diseases/facts/crohnsdisease.htm	NetDoctor.co. Ltd, London, United Kingdom.	1998	24 Aug 2014	7	0	1	0
30	Crohn's Disease, UCSF medical center	http://www.ucsfhealth.org/conditions/crohns_disease/	University of California San Francisco Medical Center, California, United States.	2000	04 Jan 2012	2	0	0	0
31	Crohn's Disease Symptoms and Treatment, US.news Wellness	http://health.usnews.com/health-news/health-wellness/articles/2013/08/03/crohns-disease-symptoms-and-treatment	Guido Zanni, US News, New York, United States,	1995	22 Jan 2015	3	0	0	0
32	What are the treatments for Crohn's disease? Beth Israel Deaconess Medical Center	http://www.bidmc.org/Centers-and-Departments/Departments/Digestive-Disease-Center/Inflammatory-Bowel-Disease-Program/Crohns-Disease/What-are-the-treatments-for-Crohns-disease.aspx	Beth Israel Deaconess Medical Center, Massachusetts, United States.	2002	16 Mar 2006	15	0	4	1

33	Diagnosing Crohn's, Crohn's and Me.	http://www.crohnsandme.com/crohns-information/crohns-disease-diagnosis.aspx	UCB Multinational Biopharmaceutical Company, Brussels, Belgium	2005	29 Apr 2014	9	1	1	1
34	Understanding Crohn's Disease, Crohn's and Colitis.	http://www.crohnsandcolitisinfo.com/Crohns/What-is-Crohns-Disease	Crohn's and Colitis, Illinois, United States	2011	02 Oct 2014	8	0	1	1
35	Learning About Crohn's Disease, National Human Genome Research Institute	http://www.genome.gov/25521854	National Human Genome Research Institute, Massachusetts, United States		27 Sep 2011	2	0	0	0
36	Crohn's Disease, UPMC Life Changing Medicine	http://www.upmc.com/services/digestive-disorders-center/services/ibd/conditions/pages/crohns-disease.aspx	UPMC Digestive Disorders Center, UPMC Presbyterian, Pennsylvania, United States	1999	04 Mar 2014	3	0	0	0
37	Crohn's Disease, Cincinnati Children's	http://www.cincinnatichildrens.org/health/c/crohns/	Cincinnati Children's Hospital Medical Center, Ohio, United States	1998	15 may 2012	4	0	1	0
38	Crohn's Disease, Cleveland clinic	http://my.clevelandclinic.org/health/diseases_conditions/hic_Inflammatory_Bowel_Disease_IBD_QandA/hic_Crohns_Disease	The Cleveland Clinic Foundation, Ohio, United States	1998	02 Jan 2015	2	0	0	0
39	Treatment of Crohn's Disease, UNC Multidisciplinary Center for IBD Research and Treatment	http://www.med.unc.edu/gi/specialties/ibd/about-ibd/treatment-of-ibd-1/treatment-of-crohns-disease	UNC, School of Medicine, North Carolina, United States	1986	07 Mar 2013	9	0	9	10
40	Crohn's Disease, Emedicine health	http://www.emedicinehealth.com/crohn_disease/article_em.htm	EMedicine.com Inc, WebMD Network, Georgia, United States	2003	06 Sep 2013	10	0	0	1
41	Understanding Crohn's Disease and Ulcerative Colitis. Australian Gastroenterology Institute.	http://www.nevdgp.org.au/info/gastro/crohns.htm	Australian Gastroenterology Institute, Digestive Health Foundation, New South Wales, Australia		02 Jun 2014	3	0	0	0
42	Crohn's Disease, Health Centers	http://www.drweil.com/drw/u/ART00339/Crohns-Disease.html	Weil's Foundation, Arizona, United States	1999	16 Jan 2012	3	0	1	0
43	Crohn's Disease-An Overview, the Royal Children's Hospital Melbourne	http://www.rch.org.au/kidsinfo/fact_sheets/Crohns_Disease_an_overview/	The Royal Children's Hospital Melbourne, Victoria, Australia		19 Jun 2014	3	0	0	0
44	Fighting Inflammatory Bowel Disease Together, the Irish Society for Colitis and Crohn's Disease	http://www.iscc.ie/page.php?id=18&title=What%20is%20IBD	The Irish Society for Colitis and Crohn's Disease, Dublin, United Kingdom	2000	05 Jan 2014	4	0	10	1
45	Crohn's Disease Diagnosis, New health guide	http://www.newhealthguide.org/Crohn%27s-Disease-Diagnosis.html	New Health Guide, United States	2013	10 Feb 15.	3	0	1	0
46	Crohn's Disease, HealthDay.	http://consumer.healthday.com/encyclopedia/digestive-health-14/digestion-health-news-200/crohn-s-disease-644392.html	HealthDay, New York, United States	2002	15 Apr 2014	4	0	0	0
47	Ulcerative Colitis, Wikipedia	http://en.wikipedia.org/wiki/Ulcerative_colitis	Wikimedia Foundation, Inc, California, United States	2001	08 May 2012	14	6	6	1
48	Living with UC, Do You Know Your Treatment Options?	http://www.livingwithuc.ca/	Janssen Inc., Canada	2010,	May 2014	8	4	0	2

49	What Is Ulcerative Colitis? Everyday Health	http://www.everydayhealth.com/conditions/ulcerative-colitis	Everyday Health Media, LLC, New York, United States	2004	10 Feb 2014	14	0	0	0
50	What Is Ulcerative Colitis? News Medical	http://www.news-medical.net/health/What-is-Ulcerative-Colitis.aspx	The AZO Network, New South Wales, Australia	2004	26 Feb 2015	2	0	0	0
51	Crohn's Disease and Ulcerative Colitis, Better Health Channel	http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Crohn%27s_disease_and_ulcerative_colitis	Crohn's and Colitis, The State Government of Victoria, Victoria, Australia	2007	28 Sep 2014	4	0	0	0
52	Ulcerative Colitis, Jackson Siegelbaum Gastroenterology	http://gicare.com/diseases/ulcerative-colitis/	Jackson Gastroenterology Ltd, Central Pennsylvania, Pennsylvania, United States	1997	07 April 2014	3	0	0	3
53	Ulcerative Colitis, Crohn's and Colitis Canada	http://www.crohnsandcolitis.ca/site/c.dtJRL9NUJmL4H/b.9012449/k.C223/Ulcerative_Colitis.htm	Crohn's and Colitis, Canada	2008	19 Dec 2013	12	0	0	1
54	Ulcerative Colitis, Healthgrades	http://www.healthgrades.com/conditions/ulcerative-colitis	HealthGrades, Inc, Colorado, United States	1999	08 May 2014	4	0	0	0
55	Information for Those with Ulcerative Colitis, Colitis UK	http://www.ulcerativecolitis.org.uk/	Colitis UK, Buckinghamshire, United Kingdom	2005	20 Oct 2013	10	0	0	0
56	Colitis and Chronic Ulcerative Colitis, Virginia Mason	https://www.virginiamason.org/ColitisandChronicUlcerativeColitis	Virginia Mason Medical Center, Washington, United States	1998	07 May 2008	3	0	0	0
57	Ulcerative Colitis, GastroNet	http://www.gastro.net.au/diseases/ulcerativecolitis.html	GastroNet Australia Pty Ltd, Canberra, Australia	2009	12 May 2014	5	2	4	5
58	Ulcerative Colitis, Ulcerative Colitis Net.	http://www.ulcerativecolitis.net/	Serovera, Florida, United States	2000	28 Feb 2014	9	3	1	0
59	Inflammatory Bowel Disease, Lab Tests Online	http://labtestsonline.org/understanding/conditions/inflammatory-bowel	American Association for Clinical Chemistry (AACC), Washington, DC, United States	2001	08 Nov 2010	3	3	0	2
60	Inflammatory Bowel Disease Fact Sheet, Womenshealth.gov	http://www.womenshealth.gov/publications/our-publications/fact-sheet/inflammatory-bowel-disease.html	Womenshealth.gov, the US Department of Health and Human Services	1995	29 Nov 2014	3	0	0	3
61	Inflammatory Bowel Disease (IBD), Innerbody	http://www.innerbody.com/diseases-conditions/ibd	InnerBody, California, United States	1996	02 Oct 2012	5	2	3	4
62	Inflammatory Bowel Disease (IBD), Rightdiagnosis	http://www.rightdiagnosis.com/i/inflammatory_bowel_disease/intro.htm	Rightdiagnosis. com, United States	2005	11 Jul 2013	2	1	5	0
63	Inflammatory Bowel Disease, Lifescript.com	http://www.lifescript.com/health/centers/digestive/related_conditions/inflammatory_bowel_disease.aspx	LifeScript, California, United States	1999	05 May 2014	1	5	2	1
64	Inflammatory Bowel Disease (IBD), MUSC Health	http://www.ddc.musc.edu/public/symptomsDiseases/diseases/smallBowel/IBD.html	Digestive Disease Center, The Medical University of South Carolina, South Carolina, United States	1990	21 May 2013	1	1	1	0
65	Inflammatory Bowel Disease (IBD): Ulcerative Colitis, Crohn's Disease, New York-Presbyterian Digestive Diseases.	http://nyp.org/services/digestive/ibd.html	NewYork-Presbyterian Hospital, New York, United States	1998	24 Aug 2007	1	2	0	0

66	Inflammatory Bowel Disease, Human Diseases and Conditions Forum.	http://www.humanillnesses.com/original/Her-Kid/Inflammatory-Bowel-Disease.html	Human Diseases and Conditions Forum, United States	2006	16 Oct 2013	2	3	1	0
67	Facts About Crohn's Disease, US. Food and Drug Administration	http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107358.htm	US Food and Drug Administration, The US Department of Health and Human Services, Maryland, United States	1997	14 Oct 2014	1	3	2	1
68	Crohn's Disease Symptoms and warning Signs, SymptomFind	http://www.symptomfind.com/diseases-conditions/crohns-disease-symptoms-warning-signs/	Symptom.Find.Com. United States	2008	21 Jun 2014	3	2	1	2
69	Crohn's Disease-At a Glance, SixPartsWater.Org	http://www.sixpartswater.org/knowledge-centre/crohns-disease/glance	SixPartsWater.Org, United Kingdom	2007	02 Oct 2012	2	1	3	0
70	Ulcerative Colitis, eMedTV	http://colitis.emedtv.com/ulcerative-colitis/ulcerative-colitis.html	eMedTV, Washington, United States	2005	07 May 2014	3	0	5	2
71	Crohn's Disease, Department of Surgery, University of California.	http://colorectal.surgery.ucsf.edu/conditions--procedures/crohns-disease.aspx	Department of Surgery, University of California, California, United States	1986	10 Oct 2013	1	1	4	1
72	Crohn's Disease, the National Institute of Diabetes and Digestive and Kidney Diseases	http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/crohns-disease/Pages/facts.aspx	The National Institutes of Diabetes and Digestive and Kidney Diseases, NIDDK, Maryland, United States	2002	20 Jul 2014	1	1	2	0
73	Crohn's Disease, Patient Education Center	http://www.patienteducationcenter.org/articles/crohns-disease/	Patient Education Center, Harvard Medical School, Harvard Medical Publications, Massachusetts, United States	2003	20 Jun 2014	2	0	3	0
74	Crohn's Disease Information, alot health	http://health.alot.com/conditions/crohns-disease-information--163	Alot Health.Com, Arkansas, United States	1994	15 Aug 2014	3	1	1	1
75	Crohn's Disease, Diagnose-me.Com	http://www.diagnose-me.com/symptoms-of/crohns-disease.html	Diagnose-me.Com, Hawaii, United States	2002	21 Jan 2014	1	3	4	1
76	Crohns Disease Information: Is Colon Cleansing the Answer, Colon Cleanse Information	http://www.colon-cleanse-information.com/crohns-disease-information.html	Colon-Cleanse-Information.Com, MKR Concepts, Oregon, United States	2007	11 Nov 2014	3	0	5	0
77	Crohn's Disease or Regional Enteritis, MD India.	http://www.medindia.net/patients/patientinfo/Crohns-Disease.htm	Medindia4u.com Pvt. Ltd, Chennai, India	2000	21 Nov 2014	5	0	1	0
78	Crohn's Disease Information, Digestive Disorders	http://www.articleinsider.com/health-and-fitness/digestive-disorders/crohns-disease-information	Digestive Disorders, United States	2003	03 Sep 2014	2	1	2	1
79	Inflammatory Bowel Disease, Patient Center, American College of Gastroenterology	http://patients.gi.org/topics/inflammatory-bowel-disease/	Patient Center, American College of Gastroenterology, Maryland, United States	1996	16 May 2013	4	3	1	2
80	Crohn's Disease: Symptoms, Diagnosis and Treatment, Disabled World. Com	http://www.disabled-world.com/health/digestive/crohns-disease/	Disabled World. Com, New York, United States	2004	29 Oct 2012	1	3	4	1
81	Crohn's Disease, Nutritionist Resource	http://www.nutritionist-resource.org.uk/articles/crohns-disease.html	Nutritionist Resource, Surrey, United Kingdom	2010	9 Feb 15	3	1	3	0

82	Crohn's Disease: Symptoms, Diagnosis and Treatment, verywell.com	http://seniorhealth.about.com/cs/digestivetract/a/crohns_2.htm	Verywell.com part of about.com, Inc., United States	1999	10 Feb 14	6	0	4	0
83	Ulcerative Colitis, Halyard Surgical.	http://www.ulcerative-colitis.org/	Halyard Surgical, New South Wales, Australia	2003	7 Nov 14	2	0	6	1
84	Ulcerative Colitis Overview, Health Communities.com	http://www.healthcommunities.com/colitis/ulcerative-colitis-overview.shtml	Healthcommunities.com, New York, United States	1998	10 May 13	3	2	0	0

IBD: Inflammatory bowel disease; NHS: National Health Service; UNC: University of North Carolina.

Table 2 Summarizes websites included in the study on inflammatory bowel disease included in the study: The accuracy scores (calculated using the DISCERN score and the HONcode score) and the readability scores

No.	Website title, Organisation	URL	Accuracy scores		Readability scores	
			The DISCERN Score (mean ± SD)	The HONcode score (Out of 100)*	The Flesch-Kincaid Grade Level Index	The Coleman-Liau Readability Index
1	Inflammatory Bowel Disease (IBD), Mayo Clinic	http://www.mayoclinic.org/diseases-conditions/inflammatory-bowel-disease/basics/definition/con-20034908	65.0 ± 1.0	0.86*	13.1 ± 0.0	15.0 ± 0.0
2	Inflammatory Bowel Disease Health Center, WebMd	http://www.webmd.com/ibd-crohns-disease/	41.3 ± 1.1	0.70*	10.5 ± 3.2	13.3 ± 2.5
3	Inflammatory Bowel Disease (IBD), Center for Disease Control and Prevention (CDC)	http://www.cdc.gov/ibd/	28.7 ± 0.6	0.90	10.9 ± 2.7	13.3 ± 0.6
4	Inflammatory Bowel Disease, NHS Choices	http://www.nhs.uk/conditions/inflammatory-bowel-disease/pages/introduction.aspx	53.7 ± 0.6	0.63	12.2 ± 1.6	12.3 ± 1.5
5	What are Crohn's and Colitis? Crohn's and Colitis Foundation	http://www.ccfa.org/what-are-crohns-and-colitis/	50.3 ± 0.6	0.81	16.2 ± 9.3	13.7 ± 0.6
6	Inflammatory Bowel Disease, KidsHealth	http://kidshealth.org/parent/medical/digestive/ibd.html	50.7 ± 0.6	0.45	12.0 ± 0.7	11.7 ± 0.6
7	Inflammatory Bowel Disease (IBD). FamilyDoctor	http://familydoctor.org/familydoctor/en/diseases-conditions/inflammatory-bowel-disease.html	45.0 ± 1.0	0.63*	9.6 ± 1.4	10.7 ± 0.6
8	Inflammatory Bowel Disease, Healthline	http://www.healthline.com/health/inflammatory-bowel-disease#Overview1	41.0 ± 1.0	0.59*	8.7 ± 0.6	11.7 ± 0.6
9	Crohn's and Colitis, Australia	https://www.crohnsandcolitis.com.au/about-crohns-colitis/inflammatory-bowel-disease/	41.7 ± 0.6	0.34	13.6 ± 3.2	13.0 ± 1.0
10	Crohn's and Colitis UK	http://www.crohnsandcolitis.org.uk/information-and-support/information-about-ibd/what-is-IBD	60.7 ± 0.6	0.45	10.4 ± 1.6	10.3 ± 3.1
11	Inflammatory Bowel Disease (IBD) (Intestinal Problems of IBD), MedicineNet	http://www.medicinenet.com/inflammatory_bowel_disease_intestinal_problems/article.htm	57.3 ± 1.5	0.75*	13.3 ± 1.5	14.3 ± 1.5
12	Inflammatory Bowel Disease Center, Cedars-Sinai	http://www.cedars-sinai.edu/Patients/Programs-and-Services/Inflammatory-Bowel-Disease-Center/	25.7 ± 1.1	0.27	13.1 ± 2.9	14.0 ± 3.6
13	Inflammatory Bowel Diseases Symptoms and Treatment: Livescience	http://www.livescience.com/39880-inflammatory-bowel-disease.html	39.3 ± 0.6	0.27	11.1 ± 1.4	11.3 ± 1.5
14	Inflammatory Bowel Diseases Program, Penn Medicine.org	http://www.pennmedicine.org/gastroenterology/patient-care/gi-diseases/inflammatory-bowel-disease-ibd/	38.0 ± 0.0	0.54	15.1 ± 2.6	13.0 ± 2.0

15	Inflammatory Bowel Diseases Support Groups, IBDsupport.org	http://www.ibdsupport.org/	52.0 ± 1.7	0.61*	12.8 ± 3.7	13.0 ± 3.6
16	Inflammatory Bowel Disease (IBD), ABC Health and wellbeing	http://www.abc.net.au/health/library/stories/2012/02/22/3435688.htm	34.0 ± 0.0	0.45	11.1 ± 0.3	11.3 ± 0.6
17	Inflammatory Bowel Disease (IBD), GIKids	http://www.gikids.org/content/7/en/IBD	31.0 ± 0.0	0.52	12.5 ± 0.3	12.7 ± 0.6
18	Inflammatory Bowel Disease, Vitamin D Council	https://www.vitamindcouncil.org/health-conditions/inflammatory-bowel-disease/	31.3 ± 1.1	0.43	11.0 ± 10.4	10.7 ± 1.5
19	Inflammatory Bowel Disease Symptoms and Diagnosis, Seattle children's	http://www.seattlechildrens.org/medical-conditions/digestive-gastrointestinal-conditions/ibd-symptoms/	37.3 ± 0.6	0.43	8.9 ± 1.0	11.0 ± 1.0
20	Crohn's Disease, Patient.co.uk	http://www.patient.co.uk/health/crohns-disease-leaflet	55.7 ± 1.5	0.59*	8.5 ± 2.0	10.0 ± 1.7
21	Patient Information Crohn's Disease (Beyond and the Basics), Uptodate	http://www.uptodate.com/contents/crohn-disease-beyond-the-basics	36.7 ± 1.1	0.70	11.2 ± 1.9	12.3 ± 0.6
22	Crohn's Disease, Centre for digestive diseases	http://www.cdd.com.au/pages/disease_info/crohns_disease.html	34.7 ± 0.6	0.52	12.0 ± 0.6	14.3 ± 1.1
23	Crohn's Disease, Patients: British Society for Gastroenterology	http://www.bsg.org.uk/patients/general/crohn-s-disease.html	49.7 ± 0.6	0.56	11.3 ± 1.7	10.7 ± 1.1
24	Crohn's Disease, Bupa	http://www.bupa.co.uk/health-information/directory/c/crohns-disease	52.0 ± 0.0	0.77*	8.2 ± 0.5	9.0 ± 1.7
25	Crohn's Disease, University of Maryland Medical Center	http://umm.edu/health/medical/reports/articles/crohns-disease	64.7 ± 1.5	0.81	15.3 ± 4.8	15.0 ± 1.0
26	Crohn's Disease, Symptoms, Diagnosis, Treatment, Southern Cross	https://www.southerncross.co.nz/AboutTheGroup/HealthResources/MedicalLibrary/tabid/178/vw/1/ItemID/523/Crohns-disease-symptoms-diagnosis-treatment.aspx	42.7 ± 0.6	0.40	13.8 ± 0.3	13.7 ± 0.6
27	Crohn's Disease, American family physician	http://www.aafp.org/afp/2011/1215/p1379.html	42.3 ± 1.1	0.18	9.0 ± 2.9	12.3 ± 4.2
28	What is Crohn's Disease? What Causes Crohn's Disease? MNT	http://www.medicalnewstoday.com/articles/151620.php	45.7 ± 1.5	0.50*	11.2 ± 2.1	10.7 ± 1.5
29	Crohn's Disease, Netdoctor	http://www.netdoctor.co.uk/diseases/facts/crohnsdisease.htm	43.0 ± 0.0	0.59	10.0 ± 1.6	12.3 ± 1.5
30	Crohn's Disease, UCSF medical center	http://www.ucsfhealth.org/conditions/crohns_disease/	41.0 ± 1.0	0.40	11.4 ± 0.5	11.3 ± 0.6
31	Crohn's Disease Symptoms and Treatment, US.news Wellness	http://health.usnews.com/health-news/health-wellness/articles/2013/08/03/crohns-disease-symptoms-and-treatment	48.3 ± 0.6	0.50	6.7 ± 0.8	12.3 ± 2.5
32	What are the treatments for Crohn's disease? Beth Israel Deaconess Medical Center	http://www.bidmc.org/Centers-and-Departments/Departments/Digestive-Disease-Center/Inflammatory-Bowel-Disease-Program/Crohns-Disease/What-are-the-treatments-for-Crohns-disease.aspx	41.7 ± 1.5	0.59	14.3 ± 2.2	14.3 ± 1.1
33	Diagnosing Crohn's, Crohn's and Me.	http://www.crohnsandme.com/crohns-information/crohns-disease-diagnosis.aspx	43.3 ± 1.1	0.27	13.6 ± 1.1	12.7 ± 2.5
34	Understanding Crohn's Disease, Crohn' and Colitis.	http://www.crohnsandcolitisinfo.com/Crohns/What-is-Crohns-Disease	41.7 ± 0.6	0.45	12.4 ± 2.0	12.0 ± 2.6
35	Learning About Crohn's Disease, National Human Genome Research Institute	http://www.genome.gov/25521854	29.0 ± 0.0	0.40	10.8 ± 0.5	12.3 ± 1.5

36	Crohn's Disease, UPMC Life Changing Medicine	http://www.upmc.com/services/digestive-disorders-center/services/ibd/conditions/pages/crohns-disease.aspx	44.3 ± 0.6	0.27	20.3 ± 9.5	15.0 ± 2.0
37	Crohn's Disease, Cincinnati Children's	http://www.cincinnatichildrens.org/health/c/crohns/	44.7 ± 0.6	0.40	9.3 ± 1.1	10.7 ± 0.6
38	Crohn's Disease, Cleveland clinic	http://my.clevelandclinic.org/health/diseases_conditions/hic_Inflammatory_Bowel_Disease_IBD_QandA/hic_Crohns_Disease	26.3 ± 1.1	0.50*	12.9 ± 1.2	12.3 ± 2.3
39	Treatment of Crohn's Disease, UNC Multidisciplinary Center for IBD Research and Treatment	http://www.med.unc.edu/gi/specialties/ibd/about-ibd/treatment-of-ibd-1/treatment-of-crohns-disease	42.3 ± 0.6	0.45	12.3 ± 0.5	13.3 ± 0.6
40	Crohn's Disease, Emedicine health	http://www.emedicinehealth.com/crohn_disease/article_em.htm	59.3 ± 1.2	0.86*	13.0 ± 1.2	13.0 ± 1.7
41	Understanding Crohn's Disease and Ulcerative Colitis. Australian Gastroenterology Institute.	http://www.nevdgp.org.au/info/gastro/crohns.htm	42.3 ± 1.1	0.27	10.4 ± 0.7	11.3 ± 0.6
42	Crohn's Disease, Health Centers	http://www.drweil.com/drw/u/ART00339/Crohns-Disease.html	37.0 ± 0.0	0.50	11.9 ± 1.1	12.7 ± 1.5
43	Crohn's Disease- An Overview, the Royal Children's Hospital Melbourne	http://www.rch.org.au/kidsinfo/fact_sheets/Crohns_Disease_an_overview/	33.7 ± 1.1	0.50	7.7 ± 2.0	11.3 ± 1.5
44	Fighting Inflammatory Bowel Disease Together, the Irish Society for Colitis and Crohn's Disease	http://www.iscc.ie/page.php?id=18&title=What%20is%20IBD	37.7 ± 0.6	0.40	11.6 ± 1.4	10.7 ± 0.6
45	Crohn's Disease Diagnosis, New health guide	http://www.newhealthguide.org/Crohn%27s-Disease-Diagnosis.html	18.3 ± 0.6	0.65	13.5 ± 0.7	13.7 ± 1.1
46	Crohn's Disease, HealthDay.	http://consumer.healthday.com/encyclopedia/digestive-health-14/digestion-health-news-200/crohn-s-disease-644392.html	61.0 ± 1.0	0.86*	10.9 ± 1.4	12.0 ± 0.0
47	Ulcerative Colitis, Wikipedia	http://en.wikipedia.org/wiki/Ulcerative_colitis	54.0 ± 0.0	0.63	15.2 ± 2.1	14.0 ± 2.6
48	Living with UC, Do You Know Your Treatment Options?	http://www.livingwithuc.ca/	44.3 ± 1.1	0.68	12.2 ± 1.6	11.3 ± 2.3
49	What Is Ulcerative Colitis? Everyday Health	http://www.everydayhealth.com/conditions/ulcerative-colitis	40.0 ± 0.0	0.54*	14.1 ± 0.7	13.0 ± 1.0
50	What Is Ulcerative Colitis? News Medical	http://www.news-medical.net/health/What-is-Ulcerative-Colitis.aspx	46.0 ± 1.0	0.59	11.9 ± 0.2	13.0 ± 1.0
51	Crohn's Disease and Ulcerative Colitis, Better Health Channel	http://www.betterhealth.vic.gov.au/bhcv2/bhcarticles.nsf/pages/Crohn%27s_disease_and_ulcerative_colitis	34.3 ± 1.1	0.31	9.8 ± 2.4	11.3 ± 1.5
52	Ulcerative Colitis, Jackson Siegelbaum Gastroenterology	http://gicare.com/diseases/ulcerative-colitis/	52.3 ± 0.6	0.36	10.6 ± 1.4	11.7 ± 2.1
53	Ulcerative Colitis, Crohn's and Colitis Canada	http://www.crohnsandcolitis.ca/site/c.dtJRL9NUJmL4H/b.9012449/k.C223/Ulcerative_Colitis.htm	19.7 ± 0.6	0.31	9.2 ± 1.8	10.0 ± 1.0
54	Ulcerative Colitis, Healthgrades	http://www.healthgrades.com/conditions/ulcerative-colitis	52.7 ± 1.1	0.68	14.5 ± 3.5	14.0 ± 1.0
55	Information for Those with Ulcerative Colitis, Colitis UK	http://www.ulcerativecolitis.org.uk/	49.0 ± 1.7	0.45	14.5 ± 2.0	11.7 ± 1.1

56	Colitis and Chronic Ulcerative Colitis, Virginia Mason	https://www.virginiamason.org/ColitisandChronicUlcerativeColitis	40.7 ± 0.6	0.31	16.7 ± 3.9	15.0 ± 2.0
57	Ulcerative Colitis, GastroNet	http://www.gastro.net.au/diseases/ulcerativecolitis.html	26.7 ± 0.6	0.60	13.1 ± 1.1	13.3 ± 2.3
58	Ulcerative Colitis, Ulcerative Colitis Net.	http://www.ulcerativecolitis.net/	41.3 ± 0.6	0.30	11.4 ± 3.3	12.0 ± 2.0
59	Inflammatory Bowel Disease, Lab Tests Online	http://labtestsonline.org/understanding/conditions/inflammatory-bowel	38.3 ± 0.6	0.32*	13.0 ± 0.7	12.0 ± 1.0
60	Inflammatory Bowel Disease Fact Sheet, Womenshealth.gov	http://www.womenshealth.gov/publications/our-publications/fact-sheet/inflammatory-bowel-disease.html	55.7 ± 1.5	0.40	8.8 ± 0.7	10.0 ± 1.0
61	Inflammatory Bowel Disease (IBD), Innerbody	http://www.innerbody.com/diseases-conditions/ibd	39.0 ± 1.0	0.25	17.2 ± 5.7	16.7 ± 1.5
62	Inflammatory Bowel Disease (IBD), Rightdiagnosis	http://www.rightdiagnosis.com/i/inflammatory_bowel_disease/intro.htm	38.0 ± 1.0	0.33	15.9 ± 4.1	15.7 ± 2.1
63	Inflammatory Bowel Disease, Lifescript.com	http://www.lifescript.com/health/centers/digestive/related_conditions/inflammatory_bowel_disease.aspx	32.0 ± 1.0	0.50	15.1 ± 2.8	12.7 ± 1.5
64	Inflammatory Bowel Disease (IBD), MUSC Health	http://www.ddc.musc.edu/public/symptomsDiseases/diseases/smallBowel/IBD.html	22.7 ± 1.1	0.27	14.2 ± 2.2	15.7 ± 2.9
65	Inflammatory Bowel Disease (IBD): Ulcerative Colitis, Crohn's Disease, New York-Presbyterian Digestive Diseases	http://nyp.org/services/digestive/ibd.html	32.3 ± 0.6	0.27	13.2 ± 0.5	12.7 ± 0.6
66	Inflammatory Bowel Disease, Human Diseases and Conditions Forum.	http://www.humanillnesses.com/original/Her-Kid/Inflammatory-Bowel-Disease.html	35.3 ± 1.5	0.14	10.7 ± 0.9	13.3 ± 2.3
67	Facts About Crohn's Disease, US. Food and Drug Administration	http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm107358.htm	34.7 ± 2.1	0.36	10.6 ± 2.6	13.7 ± 2.1
68	Crohn's Disease Symptoms and warning Signs, SymptomFind	http://www.symptomfind.com/diseases-conditions/crohns-disease-symptoms-warning-signs/	26.0 ± 1.0	0.26*	10.0 ± 1.9	13.7 ± 2.3
69	Crohn's Disease-At a Glance, SixPartsWater. Org	http://www.sixpartswater.org/knowledge-centre/crohns-disease/glance	39.7 ± 0.6	0.15	18.3 ± 3.4	12.7 ± 0.6
70	Ulcerative Colitis, eMedTV	http://colitis.emedtv.com/ulcerative-colitis/ulcerative-colitis.html	55.3 ± 0.6	0.32*	12.1 ± 0.8	11.0 ± 2.0
71	Crohn's Disease, Department of Surgery, University of California.	http://colorectal.surgery.ucsf.edu/conditions--procedures/ulcerative-colitis.aspx	51.0 ± 1.0	0.73	12.4 ± 0.8	12.3 ± 2.5
72	Crohn's Disease, the National Institute of Diabetes and Digestive and Kidney Diseases	http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/crohns-disease/Pages/facts.aspx	68.3 ± 1.2	0.95	13.6 ± 3.9	13.7 ± 5.5
73	Crohn's Disease, Patient Education Center	http://www.patienteducationcenter.org/articles/crohns-disease/	38.0 ± 1.0	0.30	8.9 ± 0.8	12.3 ± 1.5
74	Crohn's Disease Information, alot health	http://health.alot.com/conditions/crohns-disease-information--163	32.3 ± 0.6	0.22	10.4 ± 1.5	12.0 ± 2.6
75	Crohn's Disease, Diagnose-me.Com	http://www.diagnose-me.com/symptoms-of/crohns-disease.html	32.0 ± 1.0	0.28	12.5 ± 1.6	14.3 ± 1.1

76	Crohns Disease Information: Is Colon Cleansing the Answer, Colon Cleanse Information	http://www.colon-cleanse-information.com/crohns-disease-information.html	35.7 ± 2.5	0.36	13.2 ± 0.5	14.7 ± 1.5
77	Crohn's Disease or Regional Enteritis, MD India.	http://www.medindia.net/patients/patientinfo/Crohns-Disease.htm	46.3 ± 1.1	0.54	11.8 ± 1.3	14.0 ± 2.6
78	Crohn's Disease Information, Digestive Disorders	http://www.articleinsider.com/health-and-fitness/digestive-disorders/crohns-disease-information	33.3 ± 0.6	0.60	10.2 ± 0.6	12.3 ± 0.6
79	Inflammatory Bowel Disease, Patient Center, American College of Gastroenterology	http://patients.gi.org/topics/inflammatory-bowel-disease/	58.3 ± 1.2	0.80	12.7 ± 1.3	13.0 ± 1.0
80	Crohn's Disease: Symptoms, Diagnosis and Treatment, Disabled World.Com	http://www.disabled-world.com/health/digestive/crohns-disease/	26.3 ± 2.3	0.19	8.6 ± 0.6	12.00 ± 1.73
81	Crohn's Disease, Nutritionist Resource	http://www.nutritionist-resource.org.uk/articles/crohns-disease.html	39.3 ± 0.6	0.57	10.2 ± 2.6	11.3 ± 1.1
82	Crohn's Disease: Symptoms, Diagnosis and Treatment, verywell.com	http://seniorhealth.about.com/cs/digestivetract/a/crohns_2.htm	44.3 ± 1.5	0.37	12.6 ± 0.7	11.0 ± 1.0
83	Ulcerative Colitis, Halyard Surgical.	http://www.ulcerative-colitis.org/	51.7 ± 1.5	0.25	12.1 ± 0.6	12.7 ± 2.5
84	Ulcerative Colitis Overview, Health Communities.com	http://www.healthcommunities.com/colitis/ulcerative-colitis-overview.shtml	52.7 ± 1.5	0.23*	12.6 ± 1.2	12.7 ± 1.1

*Websites that received HONCode certificates. IBD: Inflammatory bowel disease; NHS: National Health Service; UNC: University of North Carolina.

also varied from a minimum of 0.14 to a maximum of 0.95 (mean ± SD, 0.16 ± 0.19; median = 0.45, IQR = 0.29). The lowest HONcode score was scored by the website, Crohn's Disease, American family physician, while the maximum score was scored by the website, Crohn's Disease, the National Institute of Diabetes and Digestive and Kidney Diseases. Along with the HONcode trust worthy scores, HONcode certificate was indicated for websites that have received such certificates, Table 2.

The top ten websites on IBD as per the DISCREN scores were in the following order: The Crohn's Disease, the National Institute of Diabetes and Digestive and Kidney Diseases (scored 68), Inflammatory Bowel Disease, MayoClinic (Scored 65), Crohn's Disease, University of Maryland Medical Center (scored 64), Crohn's Disease, HealthDay (scored 61), Crohn's Disease and Colitis UK (scored 60), Crohn's Disease, eMedicine health (scored 59), Inflammatory Bowel Disease, Patient Center, American College of Gastroenterology (scored 58), Inflammatory Bowel Disease, MedicineNet (scored 57), Inflammatory Bowel Disease, Fact Sheet, Womenshealth.gov (scored 55), Ulcerative Colitis, eMedTV (scored 55). The top ten websites as per the HONcode tool were in the following order: Crohn's Disease, the National Institute of Diabetes and Digestive and Kidney Diseases (scored 0.95), Inflammatory Bowel Disease, Center for Disease Control and Prevention (scored 0.90), Inflammatory Bowel Disease, MayoClinic (scored 0.86), Crohn's Disease, eMedicine health (scored 0.86), Crohn's Disease, HealthDay (scored 0.86), What are Crohn's & Colitis? Crohn's & Colitis Foundation (scored 0.81), Crohn's Disease, University of Maryland Medical Center (scored 0.81), Inflammatory Bowel Disease, Patient Center, American College of Gastroenterology (scored 0.80), Crohn's Disease, Bupa (scored 0.77), and Inflammatory Bowel Disease, MedicineNet (scored 0.75). It is interesting to note that the website, Crohn's Disease, the National Institute of Diabetes and Digestive and Kidney Diseases was ranked number one as per the two instruments. Seven websites in total were among the top ten websites as per both the DISCERN and the HONcode scores. Nine out of the ten websites were created in United State.

Grouping the websites under five categories

Table 3 summarizes the grouping of the 84 websites under five categories on the basis of the website creators. Universities and research centers created 25 (%), professional foundations and associations created 15 (%), commercial and pharmaceutical companies created 25 (%), charities and volunteers contributed to 9 (%), non-university educational bodies such as colleges, academies, councils, WebMed contributed to 10 (%). Further analysis revealed that there was no

Table 3 Grouping the websites on inflammatory bowel disease included in the study under five categories

Category	Number	DISCERN score		HONcode score	
		mean ± SD[6]	95%CI for means	mean ± SD[7]	95%CI for means
Universities and Research Centers[1]	25	41.3 ± 11.3	36.6-45.9	0.46 ± 0.20	0.37-0.54
Foundations and Associations[2]	15	44.5 ± 10.5	38.6-50.2	0.53 ± 0.16	0.44-0.62
Commercial and Pharmaceutical Companies[3]	25	40.4 ± 10.1	36.3-44.6	0.44 ± 0.18	0.36-0.52
Charities and Volunteer work[4]	9	40.2 ± 11.9	31.0-49.4	0.39 ± 0.17	0.26-0.52
Non-university Educational Bodies[5]	10	46.7 ± 9.7	39.7-53-6	0.63 ± 0.20	0.48-0.76
Total	84	42.1 ± 10.7	39.8-44.5	0.48 ± 0.19	0.44-0.52

[1]This category includes university-affiliated centers, state hospitals, national or state research centers; [2]This category includes gastroenterological societies, foundations, and associations- most were on inflammatory bowel disease, Crohn's disease or ulcerative colitis; [3]This category includes industrial bodies, commercial and pharmaceutical companies aiming at serving the community and patients with inflammatory bowel disease; [4]This category includes charities and websites created by individuals, or groups; [5]This category includes all other non-university educational bodies including colleges, academies, councils, WebMed, *etc.*; [6]The DISCERN scores were not significantly different between the groups as per ANOVA (combined, $P = 0.472$) or (linear term, $P = 0.475$); [7]The HONcode scores were significantly different between the groups as per ANOVA (combined, $P = 0.041$). The linear term, $P = 0.228$.

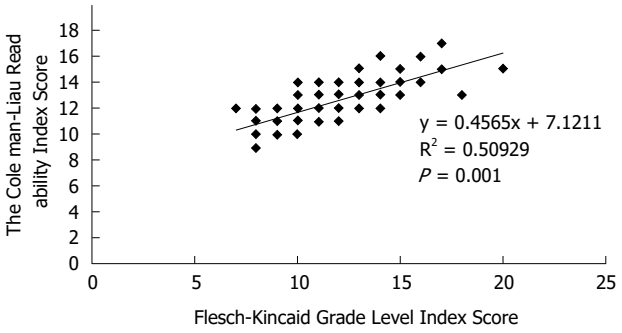

Figure 2 Correlation between the scores of the two readability methods: Coleman-Liau Readability Index and Flesch-Kincaid Grade Level Index.

significant differences in the DISCERN scores between the groups ($P = 0.472$) but the HONcode scores were different ($P = 0.041$). Examples of content deficiencies or scientific content inaccuracies and suggestions for improvement are shown on Table 4.

Readability level of websites

Table 2 summarizes the readability scores calculated by using two methods, the Flesch-Kincaid Grade Level Index and Coleman-Liau Readability Index. The minimum score for the Flesch-Kincaid Grade Level Index was 6.7 for the website Crohn's Disease Symptoms and Treatment, United States news Wellness, while the maximum score was 20.3 for the website Crohn's Disease, UPMC Life Changing Medicine. Out of the 84 websites, 28 received a mean of 6.7 to 10.9, forty-six received a mean of 11.0 to 14.5, and ten websites received a mean of 15.7 to 20.3. The overall mean score for the 84 websites was 11.9 ± 2.4.

For the Coleman-Liau Readability Index the minimum score was 9.0 for the website Crohn's Disease, Bupa, while the maximum score was 16 for the website Inflammatory Bowel Disease, Fact Sheet, Womenshealth. Out of the 84 websites, eleven received a mean score of 9.0 to 10.9, thirty-nine received a score of 11.0 to 12.7, and thirty-four received a score of 13.0 to 16.0. The overall mean score for the 84 websites was 12.6 ± 1.5.

Significant correlation was found between the Flesch-Kincaid Grade Level index scores and the Coleman-Liau Index scores ($R^2 = 0.509$, $P < 0.001$) (Figure 2).

The agreement between the evaluators

Table 5 summarizes the inter-rater agreement between evaluators for the DISCERN instrument items. The overall Cohen kappa scores were in the range of 0.804-0.876.

DISCUSSION

Several studies pointed to continuous progress from paper to electronic and online-based patient education[29,30]. The aims of the study were to evaluate the quality and accuracy of information available on IBD websites and calculate the readability level using two methods. To maximize the yield of the search, we searched three search engines commonly used by the public seeking information related to healthcare. The study showed that the 84 websites identified were created by universities, affiliated hospitals and research centers, professional foundations and associations, commercial and pharmaceutical companies created, charities and volunteers, as well as non-university educational bodies (such as colleges, academies, councils, and WebMed). The involvement of universities, affiliated hospitals, and research centers is directed at health information exchange as well as public and patient education with the aim to improve the quality of care, engage the patient in the decision-making processes and the journey of treatment as well as enhance patient's awareness about the nature of their illness. Such educational approaches while having multiple impacts on the patients' healthcare; it can also help in reducing the costs of treatment[31]. The current move from paper-based to online health care education may be related to the progressive increases in the use of the Internet by the public and patients[32]. Furthermore, Morgan *et al*[33] showed that patients with genetic and chronic diseases have great interest

Table 4 Examples of assessment of the content of some websites on inflammatory bowel disease

Website Number	Title	Areas of deficiencies	Suggestions for improvement
45	Crohn's Disease Diagnosis, New health guide	Symptoms of Crohn's disease are briefly mentioned. Some details are needed to explain the common presenting symptoms. No mention of differential diagnosis. No mention of investigations needed to confirm the diagnosis. Nothing is mentioned about treatment of Crohn's disease.	Symptoms may include abdominal pain, typically in the right lower quadrant, diarrhoea, some blood may be present in stools, fatigue. In more severe disease fever, and weight loss may be present. Some patients may have nausea, and abdominal distention together with abdominal pain. It is worth to mention that Crohn's disease is a lifelong illness (chronic disease). People who have Crohn's will experience periods of flare-ups, when their symptoms are active, and other times when their symptoms go into remission. Up to 30% of patients may have changes in the area around the anus including anal fistulas (internal tracts connecting the anal lumen with the skin around the anus), abscess, skin tags, and anal fissures. About 10%-20% of patients also have joint pains, lower back pain, skin rash known as erythema nodosum, and eye changes. (images showing some of these changes will enhance this part).
53	Ulcerative Colitis, Crohn's and Colitis Canada	Symptoms are briefly stated. No mention of differential diagnosis, investigations and no discussion of medical and surgical treatment.	A section discussing investigations should be added. In addition to detailed medical history, the treating doctor will initiate the evaluation by testing for infectious conditions that can cause inflammation of the colon, screen for endocrine-metabolic disorders such as excessive activity of the thyroid gland. Therefore biochemical tests and stool tests are needed. Endoscopic evaluation (colonoscopy) should be carried out in patients who have symptoms suggestive of inflammatory bowel disease and no evidence for an infection to explain symptoms. Small bowel images, computed tomography (CT) enterography may also be needed. Nutritional changes, medical and surgical treatment should be briefly discussed.
64	Inflammatory Bowel Disease (IBD), MUSC Health	Symptoms of inflammatory bowel disease are not clearly written. One would wonder, are "bowel sores" and "intestinal bleeding" symptoms? Differential diagnosis is not mentioned. The approach for diagnosing inflammatory bowel disease is not mentioned and the treatment of IBD is not explained.	As discussed earlier.
68	Crohn's Disease Symptoms and Warning Signs, SymptomsFind	Although symptoms of Crohn's disease are mentioned briefly, they are not explained. Mild, moderate and severe inflammatory bowel disease are stated but not explained. This should be explained in a simple language. Complications are mentioned but there was no mention how the disease is diagnosed, and what investigations are needed. Nothing is mentioned about nutritional changes, medical and surgical treatment of inflammatory bowel disease.	Patients are described to have mild ulcerative colitis when they have: -Fewer than four bowel motions (stools) per day. -No bleeding or small amounts of bleeding in their stools. -Normal erythrocyte sedimentation rate (ESR) -No fever, no anaemia and no increases in their heart rate, Patients are described to have moderate ulcerative colitis when they have: -More than four stools per day. -Mild elevation in ESR. Patients are described to have severe ulcerative colitis when they have: -More than six stools a day (loose stools). -Fever, rapid heartbeat, and anaemia. -Elevated ESR. The website may also mention changes that necessitate hospital admission and medical attention. Websites may provide key questions that patients may use when they review their treating doctors. Examples of these questions: •I wonder what's causing these symptoms? •What type of tests do I need? Do these tests require any special preparation? •What treatments are available, and which do you recommend? •Are there any medications that I should avoid? •Do I need to follow any dietary restrictions? •Are there any risks if I become pregnant? The MayoClinic website has listed a number of useful questions that patients can use.

12	Inflammatory Bowel Disease Center, cedars-Sinai.	Under symptoms of Crohn's disease, it is written, "The most common signs are pain in the stomach area (usually on the right side) and diarrhea", it is not clear what is meant by pain in the stomach area on the right side? Complications are provided but no signs are stated. No mention of differential diagnosis, no mention of investigations and possible findings. Nutritional changes, medical and surgical treatment are not explained.	The authors should differentiate between symptoms and signs. Scientific errors are noted in the website and common presenting symptoms should be stated. It may be useful to explain the symptoms under two main headings: symptoms in children, and symptoms in adults. Investigations needed to diagnose the disease should be discussed. Patients are usually interested to know more detail about these investigations. Information provided should answer questions such as -Name of the test -Why the test is need? -What is the test about? -Nature of the investigation (invasive *vs* non-invasive) -Are there special preparations needed prior to the test? -Any possible complications related to the investigation? -What can the results of the test tell the patient and the treating doctor? It is also important to state that IBD is an ongoing condition (chronic disease), so some of the tests may need to be repeated from time to time, or extra tests may be needed. These investigations may include: (1) Blood tests including full blood count, inflammatory markers tests including erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), liver function tests, urea and electrolytes, and other biochemical tests, (2) stool tests including stool microscopy, stool culture and sensitivity, fecal markers such as fecal calprotectin, fecal lactoferrin, (3) Endoscopy including colonoscopy, sigmoidoscopy, proctoscopy, with biopsies for histological studies (4) radiological studies such as barium studies, CT scans, MRI scans and PET scans.

Table 5 Summarizes the inter-rater agreement between evaluators calculated using Cohen kappa coefficient scores

DISCERN items	Mean score (95%CI of the difference)			Reviewer variability (κ range)
	Evaluator 1	Evaluator 2	Evaluator3	
1. Are the aims clear?	1.7 (1.5-2.0)	1.7 (1.5-2.0)	1.8 (1.5-2.0)	0.885-0.953
2. Does it achieve its aims?	1.4 (0.9-1.8)	1.5 (1.0-1.9)	1.5 (1.0-1.9)	0.790-0.904
3. Is it relevant?	3.8 (3.6-4.0)	3.8 (3.6-4.0)	3.8 (3.6-4.0)	0.792-0.887
4. Is it clear what sources of information were used to compile the publication (other than the author or producer)?	2.5 (2.2-2.9)	2.5 (2.2-2.8)	2.5 (2.2-2.8)	0.879-0.880
5. Is it clear when the information used or reported in the publication was produced?	2.7 (2.4-3.1)	2.7 (2.3-3.0)	2.7 (2.3-3.0)	0.793-0.875
6. Is it balanced and unbiased?	3.7 (3.5-4.0)	3.8 (3.6-4.0)	3.7 (3.5-3.9)	0.796-0.890
7. Does it provide details of additional sources of support and information?	2.2 (1.9-2.5)	2.2 (1.9-2.5)	2.2 (1.9-2.5)	0.792-0.827
8. Does it refer to areas of uncertainty?	3.2 (3.0-3.4)	3.1 (3.0-3.3)	3.2 (3.0-3.3)	0.764-0.832
9. Does it describe how each treatment works?	3.1 (2.8-3.4)	3.1 (2.8-3.4)	3.1 (2.8-3.4)	0.859-0.874
10. Does it describe the benefits of each treatment?	2.4 (2.2-2.7)	2.4 (2.2-2.7)	2.5 (2.2-2.8)	0.782-0.841
11. Does it describe the risks of each treatment?	2.3 (2.0-2.6)	2.3 (2.0-2.6)	2.3 (2.0-2.7)	0.772-0.902
12. Does it describe what would happen if no treatment is used?	1.5 (1.3-1.7)	1.5 (1.3-1.7)	1.5 (1.3-1.8)	0.870-0.923
13. Does it describe how the treatment choices affect overall quality of life?	2.0 (1.8-2.2)	2.0 (1.8-2.2)	2.1 (1.9-2.3)	0.859-0.906
14. Is it clear that there may be more than one possible treatment choice?	3.6 (3.4-3.9)	3.6 (3.4-3.9)	3.6 (3.4-3.8)	0.773-0.849
15. Does it provide support for shared decision-making?	2.7 (2.4-2.9)	2.8 (2.6-3.0)	2.8 (2.5-3.0)	0.767-0.854
16. Based on the answers to all of the above questions, rate the overall quality of the publication as a source of information about treatment choices?	2.9 (2.7-3.2)	3.0 (2.7-3.2)	2.9 (2.6-3.2)	0.900-0.959

in participating in clinical studies and a desire to understand information discussed during reviewing their healthcare provider. These patients may have more questions after they leave the doctor's clinic and usually tend to search the Internet for answers[33]. Compared to paper-based health education, the Internet appears to provide a wider range of answers and options. However, the quality of information provided and the readability level remain as areas of concern[8,34].

As per this study, the DISCERN and the HONcode scores varied. However, no significant differences in the DISCERN scores were found between the groups but when the groups were compared on the basis of the HONcode scores, the difference was significant. A weak correlation was found between the DISCERN scores and the HONcode scores (R^2 = 0.217). The results are consistent with the variability of the DISCERN scores of websites in each group and the fact that the two instruments are not measuring the same characteristics[25]. Interestingly, seven out of the top 10 websites on IBD scored higher on both the DISCERN and the HONcode scales. Looking into the readability levels of these seven websites, the readability using the Flesch-Kincaid Grade level was in the range 11 to 15, while for the Coleman-Liau Readability Index the range was 12 to 15. This indicates that even the top 7 websites had a readability level not adjusted to the public level.

Out of the 84 websites, only 17 displayed the HONcode certificate. A recent study found that only three websites out of 78 showed HONcode certificates[35]. Although the number of websites granted a HONcode certificate is small yet there is no correlation between the calculated HONcode scores and having a certificate on the website. Absence of the HONcode certificate from a website doesn't necessarily indicate poor quality of the website. This is because the process of issuing the HONcode is based on a voluntary application for the certificate. Therefore, it is possible that the owners/authority responsible for these websites did not apply for the HONcode certificate.

The readability scores were calculated by using two methods, the Flesch-Kincaid Grade Level Index and Coleman-Liau Readability Index. The moderate correlation between the Flesch-Kincaid Grade Level index scores and the Coleman-Liau Index scores is consistent with other work[20] and indicates that the results from the two calculations are consistent. The findings show that the majority of the studies had a readability level equivalent to year 11 and 12. However, the national reading grade level average has been estimated to be about the 6th-grade[36] and the general agreement is that the reading level for patient information materials should not exceed this level and be no less than what a 4th-grade is capable of reading[37]. With these findings in mind, there is a need for editing the content of most websites identified and adjusting the reading levels to meet the recommended reading levels for the public.

This study has a number of strengths; first, we searched three different search engines commonly used by the public seeking health-related information with the aim to maximize the yield of the search. Second, we used two instruments the DISCERN and the HONcode to measure the accuracy of contents. Both instruments have been widely used in assessing online health information material. Third, three evaluators independently conducted the evaluation and the inter-rater agreement among the assessors was within the accepted limits. Finally, the readability was measured by using two different methods. However, this study is not without limitations; the study is just a representation of websites identified at the time of the search. Only websites in the English language were included, and there is the possibility that there are other websites in other languages that match with our inclusion criteria and were not included. A multinational study may be needed to identify any differences if any and resolve gaps in this area. Therefore, despite all efforts and the plans considered, we may have missed some websites.

The results of this study may be of value to general practitioners, physicians, gastroenterologists, nurses, and allied health professionals, the public and medical students interested in online education material on IBD. The top 10 websites with the highest DISCERN and the HONcode scores identified from this study provide examples of educationally useful websites that can be recommended by treating physicians to their patients. However, their readability level was above the recommended level for the public and they may be suitable for educated patients only.

Future directions

This study highlights a number of future directions in research in the area of Internet-based patient education particularly patients with IBD. These can be summarized as follows: First, planning for creating online educational material for the public and patients with IBD necessitates more care for innovation, content accuracy and readability level to match the recommended needs of the public. Second, more work is needed to enhance the use of images, illustrations, and videos in improving the educational usefulness of websites on IBD and engage the patients and the public using such online resources. The use of these educational tools should aim at explaining difficult concepts, and enhancing understanding of the message given. As shown from this study the use of these educational tools was deficient in most websites. Third, future research should aim at assessing the impact of using Internet education and health literacy in patients with IBD and whether such resources have made impacts on number of hospital admissions, costs associated with poor health literacy, effective health education techniques, and how poor health literacy influences management outcome in these patients.

In conclusion, health literacy about IBD and the use of Internet as a medium for education appears to be increasing. Universities, research centers, commercial and pharmaceutical companies, professional foundations and associations were the major contributors to online resources written for the public and patients. Several deficiencies in the content were observed and most websites failed to meet the recommendations set by the National Institute of Health and American Medical Association that patients resources should be written about the 6th-grade level. Effective use of

diagrams, illustrations, videos, and tables to explain difficult concepts should be encouraged. Revising the websites and resolving the gap between the readability of written health information and the literacy skills of the public will improve the purpose of these websites and make them a useful healthcare resource to patients with IBD.

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COMMENTS

Background

Patients with inflammatory bowel disease (IBD), as it is the case with other chronic diseases, seek information about the nature of their disease. The increasing use of the Internet embraces the significance of online resources educating patients and the public.

Research frontiers

With the abundance of information there is concern about the quality, accuracy and readability level of information available on the web, thus it might be useful to assess the quality of these resources, identify specific deficiencies and examine whether these websites meet the recommendations of national bodies.

Innovations and breakthrough

The goal of this paper is to use comprehensive analysis to assess the quality of websites, accuracy of content and readability levels of websites on IBD dedicated to patients and the public.

Applications

The study highlights a number of future directions in the area of Internet-based patient education particularly patients with IBD and raises the need for improving such resources particularly in relation to specific areas identified in the study.

Terminology

Scientific accuracy and quality of content were evaluated using two standardised instruments widely used in research. The readability level was calculated on the bases of word length, sentence length and syllables.

Peer-review

This paper is an interesting evaluation of quality, accuracy, and readability of websites dedicated to the public. It is a novelty and represents a beginning point for judging and improving websites dedicated to IBD.

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SYSTEMATIC REVIEWS

Diabetes mellitus, insulin resistance and hepatitis C virus infection: A contemporary review

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Abstract

AIM

To summarise the literature data on hepatitis C virus (HCV)-infected patients concerning the prevalence of glucose abnormalities and associated risk.

METHODS

We conducted a PubMed search and selected all studies found with the key words "HCV" or "hepatitis C virus" and "diabetes" or "insulin resistance". We included only comparative studies written in English or in French, published from January 2000 to April 2015. We collected the literature data on HCV-infected patients concerning the prevalence of glucose abnormalities [diabetes mellitus (DM) and insulin resistance (IR)] and associated risk [*i.e.*, severe liver fibrosis, response to antivirals, and the occurrence of hepatocellular carcinoma (HCC)].

RESULTS

HCV infection is significantly associated with DM/IR compared with healthy volunteers and patients with hepatitis B virus infection. Glucose abnormalities were associated with advanced liver fibrosis, lack of sustained virologic response to interferon alfa-based treatment and with a higher risk of HCC development. As new antiviral therapies may offer a cure for HCV infection, such data should be taken into account, from a therapeutic and preventive point of view, for liver and non-liver consequences of HCV disease. The efficacy of antidiabetic treatment in improving the response to

antiviral treatment and in decreasing the risk of HCC has been reported by some studies but not by others. Thus, the effects of glucose abnormalities correction in reducing liver events need further studies.

CONCLUSION

Glucose abnormalities are strongly associated with HCV infection and show a negative impact on the main liver related outcomes.

Key words: Hepatitis C virus; Diabetes mellitus; Insulin resistance; Liver fibrosis; Treatment

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Core tip: Hepatitis C virus (HCV) infection is associated with increased rates of glucose abnormalities, including diabetes mellitus and insulin resistance. The presence of glucose abnormalities in HCV infected patients, including diabetes mellitus and insulin resistance, is associated with negative liver-related outcomes (*i.e.*, severe liver fibrosis, decreased response to antivirals, and increased occurrence of hepatocellular carcinoma).

Desbois AC, Cacoub P. Diabetes mellitus, insulin resistance and hepatitis C virus infection: A contemporary review. *World J Gastroenterol* 2017; 23(9): 1697-1711 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1697.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1697

INTRODUCTION

Hepatitis C virus (HCV) infection is a major health problem. The World Health Organization (WHO) estimates that at least 150-170 million people, approximately 3% of the world's population, are chronically infected. These patients are known to be at risk of liver related complications, *i.e.*, cirrhosis and hepatocellular carcinoma (HCC), with an estimated liver-related mortality of 350000 people/year. The total risks of morbidity and mortality are underestimated, because they do not take into account extrahepatic consequences of HCV infection. Numerous extrahepatic manifestations have been reported, suggesting that HCV is more a systemic disease than just a liver disorder. In large prospective cohort studies, up to two-thirds of patients with HCV infection experienced extra-hepatic manifestations[1]. The majority of available data concern HCV-related autoimmune and/or lymphoproliferative disorders, from benign mixed cryoglobulinemia to frank lymphomas, which is consistent with HCV lymphotropism[2]. More recently, other HCV-associated disorders have been reported including cardiovascular, renal, central nervous system and metabolic diseases[3]. Among the latter, some studies assessed the risk of diabetes mellitus (DM) or insulin resistance (IR) while others evaluated the impact of DM/IR on the main liver-related HCV infection outcomes (*i.e.,* liver fibrosis, cirrhosis, HCC). However, the results appear to be conflicting, with great heterogeneity between studies.

In the present study, based on a literature data review, we aimed to analyse: (1) the risk of glucose abnormalities (GA) in HCV-infected patients; and (2) the impact of GA on the main liver-related HCV outcomes, *i.e.,* liver fibrosis, response to interferon alfa-based treatment, and HCC.

MATERIALS AND METHODS

We conducted a PubMed search and selected all studies found with the key words "HCV" or "hepatitis C virus" and "diabetes" or "insulin resistance". We included only comparative studies written in English or in French, published from January 2000 to April 2015. We selected surveys that had evaluated the risk of Type 2 DM or IR in HCV-infected patients compared with healthy controls or with patients with hepatitis B virus (HBV) infection. The definition of DM was usually based on a fasting plasma glucose > 1.26 g/L, or a history of diabetes mellitus, or use of oral antidiabetic agents or insulin. The definition of IR was based on the Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) according to the formula: HOMA-IR = fasting glucose (mmol/L) × fasting insulin (mIU/L)/22.5. We also included studies that assessed the association between the presence of glucose abnormalities (DM or IR) and the main HCV infection outcomes (*i.e.,* liver fibrosis, cirrhosis, response to antiviral treatment, HCC). Conversely, studies that evaluated the impact of antiviral treatment on glucose abnormalities were included. We excluded studies with patients infected with the HBV or human immunodeficiency virus, and those for whom the entire manuscript was not available.

RESULTS

Is HCV infection associated with an increased prevalence of glucose abnormalities?

We included two types of studies: (1) those that assessed the HCV prevalence in diabetic patients compared with non-diabetics; and (2) studies that assessed the prevalence of DM and/or IR in HCV-infected patients compared with controls (healthy volunteers or HBV carriers) (Table 1).

Six studies evaluated HCV prevalence rates in diabetic patients compared with non-diabetic healthy volunteers. The number of participants ranged from 180 to 13000. Four out of the six studies showed a significant increased prevalence of HCV infection markers [HCV antibodies (n = 3), HCV RNA (n = 1)] in DM patients, with an odds ratio (OR) between 2.87 and 3.03[4-7]. Of note, only one study used multivariate

Table 1 Glucose abnormalities and hepatitis C virus infection

Ref.	Year	Country	Study design	Patients	Patients number	Controls	Controls number	Testing for HCV Ab or RNA	Endpoint	Statistical methods	Association	Statistics
HCV infection markers in patients with type 2 diabetes mellitus												
Sangiorgio *et al*[4]	2000	Italy	Retrospective	DM	1514	HV	1300	Ab	HCV	Univariate	Yes	$P < 0.0001$
Chen *et al*[5]	2006	Taiwan	Cross sectional	DM	820	HV	905	Ab	HCV	Univariate adjusted	Yes	OR = 2.87 [1.51, 5.46]; $P < 0.001$
Huang *et al*[6]	2007	Taiwan	Cross sectional	DM	1237	HV	8595	RNA	HCV	Univariate	Yes	6.9% *vs* 4.5%; $P < 0.001$
Jadoon *et al*[7]	2010	Pakistan	ND	DM	3000	HV	10000	Ab	HCV	Univariate	Yes	OR = 3.03 [2.64, 3.48]; $P = 0.001$
Balogun *et al*[53]	2006	Nigeria	case-control	DM	90	HV[2]	90	Ab	HCV	Univariate	No	NS
Costa *et al*[54]	2008	Brazil	Case-control	DM	206	HV	206	RNA	HCV	Multivariate	No	NS
Glucose abnormalities in HCV infected patients *vs* different control groups												
Vs healthy volunteers												
Knobler *et al*[17]	2000	Israel	Case-control	HCV	45	HV[2]	88	RNA	DM	Univariate	Yes	33% *vs* 5.6%; $P < 0.001$
Mehta *et al*[8]	2000	United States	Cross sectional	HCV	230	HV	9611	Ab	DM	Multivariate	Yes	OR = 3.77 [1.8, 7.87]
Marzouk *et al*[18]	2007	Egypt	Cross sectional	HCV	190	HV	575	RNA	DM	Multivariate	Yes	HR = 3.05 [1.19, 7.81]
Shaheen *et al*[19]	2007	United States	ND	HCV	239	HV	10144	ND	IR	Univariate adjusted	Yes	OR = 1.68; $P = 0.02$
Huang *et al*[6]	2007	Taiwan	Cross sectional	HCV	478	HV[2]	7927	RNA	DM	Multivariate	Yes	OR = 1.53 [1.18, 1.98]; $P < 0.001$
Huang *et al*[21]	2008	Taiwan	ND	HCV	683	HV[2]	515	RNA	DM/IGT[1]	Univariate	Yes	OR = 3.51 [2.7, 4.56]; $P < 0.001$
Park *et al*[20]	2008	South Korea	Prospective	HCV[1]	62	HV[2]	172	RNA	IR	Univariate	Yes	22.5% *vs* 5.2%; $P < 0.001$
Mohamed *et al*[22]	2009	Egypt	Cross sectional	HCV[1]	38	HV[2]	12	RNA	IR	Univariate	Yes	HOMA-IR = 3.98 (normal ALT) and 2.69 (a normal ALT) *vs* 1.92; $P < 0.001$
Duseja *et al*[23]	2009	India	ND	HCV[1]	85	HV[2]	25	RNA	IR	Univariate	Yes	62% *vs* 16%; $P = 0.0002$
Lonardo *et al*[24]	2009	Italy	ND	HCV[1]	97	HV	182	RNA	IR	Univariate	Yes	$P < 0.001$
Huang *et al*[25]	2009	Taiwan	ND	HCV[1]	93	HV	144	Ab	IR	Univariate	Yes	HOMA-IR 2.2 *vs* 1.6; $P = 0.02$
Mostafa *et al*[26]	2010	Egypt	ND	HCV	329	HV	173/795	RNA	DM	Univariate adjusted	Yes	OR = 1.35 [1.06, 1.73]; $P = 0.02$
Miyajima *et al*[27]	2013	Japan	Cross sectional	HCV	40	HV	1780/88	RNA	IR	Univariate	Yes	HOMA-IR 3.0 *vs* 1.3; $P < 0.001$
Younossi *et al*[28]	2013	United States	Retrospective	HCV	177	HV	19568	RNA	DM and IR	Multivariate	Yes	OR for DM 2.3 [1.18, 4.54] OR for IR 2.06 [1.19, 3.57]
Pothineni *et al*[29]	2014	United States	Retrospective	HCV	1434	HV[2]	14799	RNA	DM	Univariate	Yes	11.2% *vs* 5.1%; $P < 0.01$
Dai *et al*[30]	2013	Taiwan	Retrospective	HCV	160	HV[2]	480	RNA	DM	Multivariate	Yes	OR = 1.208 [1.009, 2.799]; $P = 0.004$
Mehta *et al*[10]	2003	United States	Case-control	HCV	12	HV[2]	1072	RNA	DM	Univariate	No	NS
Stepanova *et al*[11]	2012	United States	Nationwide survey	HCV	791	HV	38715	RNA	DM and IR	Multivariate	No	NS
Montenegro *et al*[9]	2013	Italy	Prospective	HCV	616	HV	1856	Ab	DM	Univariate adjusted	No	NS
Ruhl *et al*[55]	2014	United States	Cross sectional	HCV	277	HV	14571	RNA	DM	Univariate adjusted	No	NS
Vs hepatitis B virus infection												
Knobler *et al*[17]	2000	Israel	Case-control	HCV	45	HBV	90	RNA	DM	Univariate	Yes	33% *vs* 12%; $P = 0.004$
Ryu *et al*[31]	2001	South Korea	Prospective	HCV, F4	68	HBV	157	Ab	DM	Univariate	Yes	24% *vs* 10.4%; $P = 0.001$
Wang *et al*[32]	2007	Taiwan	Longitudinal	HCV	926	HBV	544	Ab	DM	Multivariate	Yes	HR = 1.7
Huang *et al*[6]	2007	Taiwan	Cross sectional	HCV	478	HBV	1363	RNA	DM	Univariate	Yes	18% *vs* 11.4%; $P < 0.001$
Moucari *et al*[33]	2008	France	Retrospective	HCV	500	HBV[2]	100	RNA	HOMA-IR	Univariate	Yes	35% *vs* 5%; $P < 0.001$
White *et al*[12]	2008	United States	Meta-analysis	HCV	34 studies	HBV/HV	-	Ab/RNA	DM	Meta-analysis	Yes	Adjusted OR for HV 1.68 and for HBV 1.80
Rouabhia *et al*[34]	2010	Algeria	Prospective cross sectional	HCV[1]	290	HBV	126	RNA	DM	Multivariate	Yes	OR = 4.73 [1.7, 13.2]; $P = 0.0029$

Petta *et al*[56]	2011	Italy	Retrospective	HCV	170	HBV[2]	170	RNA	HOMA-IR and DM	Univariate	Yes	42.2% *vs* 25.9%, $P = 0.002$ and 8.8% *vs* 3.6%, $P = 0.04$
Imazeki *et al*[57]	2008	Japan	Retrospective	HCV	544	HBV	286	RNA	DM and IR	Multivariate	No	NS
Tanaka *et al*[58]	2008	Japan	Case-control	HCV[1]	30	HBV[2]	30	RNA	IR	Multivariate	No	NS
Mavrogiannaki *et al*[59]	2008	Greece	prospective case control	HCV	108	HBV	81	RNA	glucose intolerance	Univariate adjusted	No	NS
Persico *et al*[60]	2009	Italy	Retrospective	HCV	726	HBV	126	Ab	DM	Univariate adjusted	No	NS

[1]HCV infection not treated; [2]Matched for confounding factors (age and/or gender and/or BMI and/or ALT…). HCV: Hepatitis C virus infection; Ab: Antibody; HV: Healthy volunteers; G1: Genotype 1; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; DM: Diabetes mellitus; FPG: Fasting Plasma glucose; IGT: Impaired glucose tolerance [after oral glucose tolerance test (OGTT)]; CLD: Chronic liver disease; NAFLD: Non-alcoholic fatty liver disease; NS: Not significant; ND: Not determined.

logic regression analysis, while another adjusted the risk for age, gender, body mass index (BMI) and alanine aminotransferase (ALT) levels. One study showed an increased HCV antibody prevalence rate in DM patients with abnormal ALT levels.

Thirty-two studies evaluated DM and/or IR prevalence rates in HCV patients compared with either healthy volunteers ($n = 20$) or HBV patients ($n = 12$). The size of cohorts ranged from 50 to 39506 subjects. All but four studies assessed DM/IR prevalence in HCV-RNA positive patients. In 10 out of 20 studies that compared HCV patients with healthy volunteers, multivariate or univariate analyses with adjustment for age, gender, BMI, socio-economic status and ethnicity were performed. Thirteen studies evaluated DM prevalence ($n = 11$) or occurrence ($n = 2$), while others ($n = 9$) assessed IR in HCV infected patients. Overall, 16 out of 20 studies found a significant association between the presence of glucose abnormalities (DM/IR) and HCV infection, including 7 out of 10 studies with multivariate or adjusted analyses (OR between 1.2 and 3.77). One study reported a higher risk of DM only in patients older than 40 years[8]. Four studies reported "negative" results. Three out these four studies showed a higher risk of DM only in specific populations (*i.e.*, HCV patients with increased ALT levels[9], HCV patients older than 55 years with a BMI > 25 kg/m^2[10], and a cohort studied between 1988 and 1994, but not in the more recent cohort)[11].

When compared with HBV infected patients, 7 out of 11 studies found a significant association of HCV with DM. In one meta-analysis[12], a positive HCV viremia was associated with an increased risk of DM compared with controls (adjusted OR = 1.68) and with HBV patients (adjusted OR = 1.80).

Are diabetes mellitus or insulin resistance associated with liver fibrosis severity in HCV infected patients?

Thirty studies investigated whether DM/IR was associated with liver fibrosis severity in HCV patients (Table 2). Studies were performed in Asia (Taiwan $n = 3$, Japan $n = 3$, other $n = 1$), Europe ($n = 13$), the United States and Australia ($n = 5$), Saudi Arabia ($n = 1$), Turkey ($n = 1$) and Egypt ($n = 3$). The mean size of the cohorts was 451 patients (min-max range 10 to 3068). The authors searched for an association between liver fibrosis severity and DM ($n = 9$), IR ($n = 19$) or impaired fasting plasma glucose ($n = 2$). All but two studies performed multivariate analyses. Twenty-six out of thirty studies reported a significant association of glucose abnormalities with liver fibrosis severity (OR from 1.28 to 13.72). Three of the four "negative" studies were done on small cohorts. There were some differences related to HCV genotypes, but no systematic relationship was found.

Do diabetes mellitus and insulin resistance have an impact on the virological response to HCV treatment?

Twenty-six studies and three meta-analyses investigated whether GA had an impact on the response to interferon alfa-based antiviral treatment (Table 3). The studies originated from Europe ($n = 11$), Asia ($n = 4$), Egypt ($n = 4$), the United States ($n = 5$), Australia ($n = 1$) and Saudi Arabia ($n = 1$). They included a mean of 503 patients (50 to 5944). Nineteen out of twenty-eight studies showed a significant negative effect of GA in response to interferon alfa-based therapy [*i.e.,* lower sustained viral response (SVR) rates], including 15 multivariate analyses and 3 meta-analyses. Of note, studies that did not find an impact of GA on SVR rates had some limitations, including small size of cohorts (60-600 patients), only G1 or G4 patients (3 out of 10 studies), and only Italian patients (4 out of 10). Two of them evaluated patients treated with peginterferon/ribavirin and telaprevir. The three meta-analyses found a significant association between IR and the absence of SVR, regardless of the genotype (OR for G1 = 2.2, G2 = 3, G3 = 4.45 and G4 = 6.7, respectively).

Table 2 Glucose abnormalities and severe liver fibrosis in hepatitis C virus-infected patients

Ref.	Year	Country	Number of HCV patients	Patient profile	Glucose abnormality	Statistical method	Association with severe fibrosis[1]	Genotypes	Statistics
Konrad *et al*[42]	2000	Germany	10	Non DM	FPG	Multivariate	Yes	All	$P = 0.01$
Sud *et al*[61]	2004	Australia	170	-	HOMA-IR	Multivariate	Yes	All	OR = 1.47 [1.14, 1.89]; $P = 0.003$
Muzzi *et al*[62]	2005	Switzerland	221	Non DM	HOMA-IR	Multivariate	Yes	All (except G3)	OR = 1.57 [1.04, 2.39]
D'souza *et al*[63]	2005	United Kingdom	59	-	HOMA-IR	Multivariate	Yes	All	$P = 0.001$
Taura *et al*[64]	2006	Japan	83	-	HOMA-IR	Multivariate	Yes	All	OR = 7.32 [1.59, 33.73]; $P = 0.01$
Leandro *et al*[65]	2006	Italy	3068	-	DM	Multivariate	Yes	G1	OR = 4.52 [1.07, 19.1]; $P = 0.011$
Bugianesi *et al*[66]	2006	Italy	132	G3 with steatosis	HOMA-IR	Multivariate	Yes	G3	OR = 2.98 [1.13, 7.89]; $P = 0.028$
Kita *et al*[67]	2007	Japan	68	Post tranfusion hepatitis	DM	Multivariate	Yes	All	OR = 8.4 [2.23, 31.54]; $P = 0.002$
Petta *et al*[68]	2008	Italy	201	G1	DM	Multivariate	Yes	G1	OR = 2.69 [1.46, 4.95]; $P < 0.001$
Moucari *et al*[33]	2008	France	500	-	HOMA-IR	Multivariate	Yes	All	OR = 1.8 [1.16, 2.81]; $P = 0.009$
Cua *et al*[69]	2008	Australia	346	G1, G3, untreated	IR	Multivariate	Yes	G3	OR = 3.15 [1.56, 6.35]; $P = 0.001$
Hsu *et al*[70]	2009	Taiwan	528	G1, G2	FPG	Multivariate	Yes	G1	OR = 13.72 [2.15, 87.7]; $P < 0.05$
Moucari *et al*[71]	2009	France	226	G4	HOMA-IR	Multivariate	Yes	G4	OR = 3.86 [1.859, 8.034]; $P < 0.001$
Persico *et al*[60]	2009	Italy	726	-	DM	Multivariate	Yes	All	$P < 0.05$
Hung *et al*[14]	2011	Taiwan	1470	-	DM	Univariate	Yes	All	$P < 0.001$
Patel *et al*[72]	2011	Asia	263	G2, G3	HOMA-IR	Multivariate	Yes	G2 and G3	OR = 8.42 [2.1, 34.3]; $P = 0.003$
Mohamed *et al*[73]	2011	Egypt	50	G4	HOMA-IR	Multivariate	Yes	G4	OR = 3.73; $P = 0.001$
Miyaaki *et al*[74]	2011	Japan	171	-	DM	Multivariate	Yes	All	OR = 8.739 [2.85, 26.85]; $P = 0.0002$
Conjeevaram *et al*[75]	2011	United States	341	G1	HOMA-IR	Multivariate	Yes	G1	OR = 1.28 [1.07, 1.51]; $P = 0.005$
Petta *et al*[56]	2011	Italy	170	G1	HOMA-IR	Multivariate	Yes	G1	OR = 2.64 [1.11, 6.28]; $P = 0.02$
Khattab *et al*[76]	2012	Egypt	107	G4	HOMA-IR	Multivariate	Yes	G4	OR = 1.87 [1.09, 8.29]; $P = 0.04$
Ziada *et al*[77]	2012	Egypt	140	Non DM	HOMA-IR	Multivariate	Yes	All	OR = 1.92 [0.97, 3.4]; $P = 0.049$
Thompson *et al*[13]	2012	United States	1038	Non DM	HOMA-IR	Multivariate	Yes	All	OR = 1.6 [1.1, 2.33]; $P = 0.02$
Alfaleh *et al*[78]	2013	Saudi Arabia	157	-	DM	Multivariate	Yes	All (except G4)	OR = 0.37 [0.148, 0.927]; $P = 0.034$
Dokmeci *et al*[79]	2014	Turkey	104	-	HOMA-IR	Multivariate	Yes	All	OR = 3.36 [1.32, 31.25]; $P = 0.021$
Huang *et al*[80]	2015	Taiwan	1077	-	DM	Multivariate	Yes	All	OR = 1.81 [1.14, 2.65]; $P = 0.002$
Fartoux *et al*[81]	2005	France	141	Non DM	HOMA-IR	Univariate	No	No	NS
Elgouhari *et al*[82]	2008	United States	183	-	DM	Multivariate	No	No	NS
Petta *et al*[83]	2009	Italy	156	Non DM	HOMA-IR	Multivariate	No	No	NS
Rueger *et al*[84]	2014	Switzerland	1461	-	DM	Multivariate	No	No	NS

[1]Severe liver fibrosis: F3 or F4 in Metavir scoring system. HCV: Hepatitis C virus infection; G1: Genotype 1; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; DM: Diabetes mellitus; FPG: Fasting plasma glucose; NS: Not significant.

What is the impact of interferon alfa-based treatment on glucose abnormalities?

Twenty studies assessed the impact of interferon-based antiviral treatment on DM/IR, either as an improvement of GA after treatment or as the occurrence of GA after antiviral treatment (Table 4).

Improvement of GA after antiviral treatment was analysed in fifteen surveys that included 13 to 1038 HCV treated patients. Most of these studies performed univariate analyses. A significant decreased prevalence of GA was noted in 12 out of 15 studies. Eleven of these 12 studies reported a significant change of IR

Table 3 Impact of glucose abnormalities on virological response after interferon alpha based treatment

Ref.	Year	Country	Patients number	Patient profile	Association	Statistical method	Impact on virological response	Genotypes	Statistics
D'souza *et al*[63]	2005	United Kingdom	59		HOMA-IR	Multivariate	Yes	All	OR of SVR: 0.44 [0.22, 0.88]; $P = 0.02$
Tarantino *et al*[85]	2005	Italy	80		GMI	Univariate	Yes	All	40% *vs* 7.5%; $P = 0.0009$
Romero-Gomez *et al*[86]	2005	Spain	159		HOMA-IR	Multivariate	Yes	All	OR of SVR 0.55 [0.33, 0.93]; $P = 0.012$
Jian Wu *et al*[87]	2006	China	98		HOMA-IR	Multivariate	Yes	All	OR of SVR: 0.17; $P = 0.015$
Backus *et al*[88]	2007	United States	5944	G1, G2, G3	DM	Multivariates	Yes	All and G1	OR = 0.76 [0.64, 0.71]; $P = 0.002$
Conjeevaram *et al*[89]	2007	United States	401	G1	HOMA-IR	Multivariates	Yes	G1	OR = 0.87 [0.77, 0.99]; $P = 0.028$
Elgouhari *et al*[82]	2008	United States	183		DM	Multivariate	Yes	All	OR of SVR 0.22 [0.07, 0.55]; $P = 0.003$
Poustchi *et al*[90]	2008	Australia	82	G2, G3 non DM	HOMA-IR	Multivariate	Yes	G2, G3	OR of SVR 0.16 [0.03, 0.77]; $P = 0.02$
Romero-Gomez *et al*[91]	2008	Spain	1059		FPG	Multivariate	Yes	All	OR of SVR 0.56 [0.34, 0.93]; $P < 0.02$
Moucari *et al*[71]	2009	France	226	G4	HOMA-IR	Multivariate	Yes	-	OR of SVR: 0.19 [0.07, 0.51]; $P = 0.001$
Dai *et al*[92]	2009	Taiwan	330	G1, G2	HOMA-IR	Multivariate	Yes	G1, G2	OR of SVR 0.872 [0.79, 097]; $P = 0.01$
Hung *et al*[115]	2010	Taiwan	1470		DM	Multivariate	Yes	All	OR of SVR 0.69 [0.5, 0.96]; $P = 0.029$
Khattab *et al*[93]	2010	Egypt	131	Non DM, G4	HOMA-IR	Multivariate	Yes	G4	OR of SVR 0.07 [0.01, 0.43]; $P = 0.004$
Deltenre *et al*[94]	2011	France	2732	G1-6	IR	Meta-analysis	Yes	All	-
Eslam *et al*[95]	2011		2129	G1-6	IR	Meta-analysis	Yes	All	OR of SVR 0.35 [0.24, 0.51]; $P = 0.0004$
Del Campo *et al*[96]	2012	Spain	240	Non DM	HOMA-IR	Multivariate	Yes	G1, G4	OR of SVR 0.44 [0.17, 0.97]; $P = 0.04$
Ziada *et al*[77]	2012	Egypt	140	Non DM	HOMA-IR	Multivariate	Yes	All	OR of SVR 0.41 [0.18, 0.9]; $P = 0.003$
Laurito *et al*[97]	2013	Brazil	2238	G1-6	IR	Meta-analysis	Yes	All	OR of SVR 0.41 [0.3, 0.56]; $P = 0.022$
Abd El-Wahab *et al*[98]	2014	Egypt	392	Non DM	HOMA-IR	Multivariate	Yes	All	OR of virological response: 0.19 [0.1, 0.38]; $P = 0.0001$
Grasso *et al*[99]	2009	Italy	90	Non DM, G1	HOMA-IR	Multivariate	No	G1	NS
Fattovich *et al*[100]	2010	Italy	412		HOMA-IR	Multivariate	No	No	NS
Khattab *et al*[76]	2012	Egypt	107	G4	HOMA-IR	Multivariate	No	G4	NS
Brandman *et al*[101]	2012	United States	23	Non DM	IGT, FGP, SSGP	Univariate	No	No	NS
Aghemo *et al*[102]	2012	Italy	339		HOMA-IR	Univariate	No	No	NS
Fattovich *et al*[100]	2012	Italy	124	Non DM	HOMA-IR	Multivariate	No	No	NS
Serfaty *et al*[103]	2012	France	161[1]	G4	HOMA-IR	Multivariate	No	G4	NS
Alfaleh *et al*[78]	2013	Saudi Arabia	157		DM	Multivariate	No	No	NS
Younossi *et al*[104]	2013	United States	578[1]	G1	HOMA-IR	Univariate adjusted	No	G1	NS
Jung *et al*[105]	2014	Soutk Korea	60		HOMA-IR	Univariate	No	No	NS

[1]Treated with peginterferon/ribavirin telaprevir. HCV: Hepatitis virus infection; G1: Genotype 1; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; IGT: Impaired glucose tolerance; DM: Diabetes mellitus; FPG: Fasting plasma glucose; SSGP: Steady-state plasma glucose; GMI: Glucose metabolism impairment; NS: Not significant; ND: Not determined.

only in patients who achieved a SVR. One survey found a significant change of IR after antiviral treatment only in genotype 1 patients[13].

Five studies evaluated the risk of GA occurrence according to antiviral treatment response. They included 202 to 2842 HCV treated patients, and all performed multivariate analyses. Four out of five studies showed a significant association between GA occurrence and the absence of SVR.

Do glucose abnormalities increase the risk of HCC in HCV infected patients?

Sixteen studies assessed the association between HCC and DM/IR in HCV infected patients (Table 5). These studies included from 120 to 5186 HCV patients, both treated and non-treated. Most of them (10/16)

Table 4 Glucose abnormalities after interferon alpha based treatment

Ref.	Year	Country	Number of HCV patients	Patient profile	Glucose metabolism parameter	Statistical method	Significant association or difference	Genotypes	Statistics
Improvement of glucose abnormalities after HCV treatment									
Konrad *et al*[42]	2000	United States	13		FPG and FI	Univariate	Yes	All	$P < 0.05$ and $P < 0.01$
Romero-Gomez *et al*[86]	2005	Spain	50		HOMA-IR	Univariate	Yes	All	In SVR; $P < 0.05$
Kawaguchi *et al*[106]	2007	Japan	89		HOMA-IR	Univariate	Yes	All	In SVR; $P < 0.01$
Chehadeh *et al*[107]	2009	Kuwait	181	G4	FPG	Univariate	Yes	G4	In SVR; $P < 0.001$
Kim *et al*[108]	2009	Korea	28	G1, G2	HOMA-IR	Multivariate	Yes	G1, G2	In SVR, OR of decreased IR 50 [3.74, 668.35]; $P = 0.003$
Conjeevaram *et al*[75]	2011	United States	341	G1	HOMA-IR	Univariate	Yes	G1	In SVR; $P < 0.001$
Khattab *et al*[76]	2012	Egypt	107	G4, non cirrhotic	HOMA-IR	Univariate	Yes	G4	In SVR ; $P = 0.001$
Thompson *et al*[13]	2012	United States	1038		HOMA-IR	Multivariate[1]	Yes	All	In G1 SVR; $P = 0.007$
Serfaty *et al*[103]	2012	France	161	G1, non cirrhotic	HOMA-IR	Univariate	Yes	G1	In SVR ; $P < 0.05$
Ziada *et al*[77]	2012	Egypt	140	Non DM, non cirrhotic	HOMA-IR	Univariate	Yes	All	$P = 0.009$
Chan *et al*[109]	2013	Australia	86	Non DM	HOMA-IR	Univariate	Yes	All	In SVR; $P = 0.04$
Jung *et al*[105]	2014	South Korea	60		HOMA-IR	Univariate	Yes	All	In SVR; $P = 0.036$
Mello *et al*[110]	2006	Brazil	30	G1, G3	HOMA-IR	Univariate	No	All	NS
Kawaguchi *et al*[111]	2009	Japan	72	Non DM, non cirrhotic	HOMA-IR, SI and ISI	Univariate[1]	No	No	HOMA-IR: NS In SVR, SI $P = 0.002$ and ISI $P = 0.009$
Brandman *et al*[101]	2012	United States	23	Non cirrhotic	SSGP	Univariate	No	No	NS
Occurrence of glucose abnormalities after HCV treatment									
Simó *et al*[112]	2006	Spain	234	Non DM	DM or IGT	Multivariate[1]	Yes	All	In SVR, OR = 0.48 [0.24, 0.48]; $P = 0.04$
Romero-Gomez *et al*[91]	2008	Spain	1059		DM or IGT	Multivariate[1]	Yes	All	In SVR, OR = 0.44 [0.2, 0.97]; $P = 0.04$
Arase *et al*[113]	2009	Japan	2842		DM	Multivariate[1]	Yes	All	In SVR, HR = 0.36 [0.24; 0.56]
Aghemo *et al*[102]	2012	Italy	339	Non DM	HOMA-IR	Multivariate[1]	Yes	All	In SVR, OR = 0.36 [0.18, 0.72]; $P = 0.004$
Giordanino *et al*[114]	2008	Italy	202	Non DM	DM or IGT	Multivariate[1]	No	No	NS

[1]Association with SVR. HCV: Hepatitis C virus infection; G1: Genotype 1; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; DM: Diabetes mellitus; FPG: Fasting plasma glucose; FI: Fasting insulin; IGT: Impaired glucose tolerance; ISI: Insulin sensitivity index; SI: Serum insulin; SSGP: Steady-state plasma glucose; NS: Not significant.

included Asian patients, and all but one performed multivariate analyses.

Five studies looked for the presence of DM/IR in HCV infected patients with HCC compared with HCV patients without HCC. Four out of five studies found a significant association between DM/IR and HCC (as compared with non-HCC) (OR from 2.0 to 11.6).

Nine out of eleven other studies found a significant association between the presence of DM/IR and the development of HCC in the follow-up of HCV infected patients (HR from 1.10 to 6.9). One study found a higher risk of HCC in diabetic patients only with SVR and without cirrhosis[14], while 2 others reported an increased risk of HCC only in diabetic patients with advanced fibrosis[15,16].

DISCUSSION

Many studies have evaluated the association between HCV chronic infection, insulin-resistance and diabetes mellitus. The abnormalities of carbohydrate metabolism, including hyperinsulinemia and IR, known to be *per se* related to chronic hepatic diseases, were the rationale for speculation on this relationship. Insulin-resistance is an often undetected condition, commonly coexisting with obesity and metabolic syndrome, and possibly progressing to type 2 diabetes. HCV-related type 2 diabetes mellitus may arise from a complex interaction between IR, steatosis and inflammatory processes. Epidemiologic studies supporting the association between type 2 diabetes and HCV infection were

Table 5 Glucose abnormalities and hepatocellular carcinoma in hepatitis C virus-infected patients

Ref.	Year	Country	Patient number	Patient profile	Association	Statistical method	Association DM and HCC	Statistics
Diabetes mellitus/insulin resistance in HCV-related HCC								
K-Kutala *et al*[15]	2014	France	162	HCC, not treated for HCV	DM and HCC	Multivariate	Yes[3]	HR = 3.13 [1.17, 8.38]; *P* = 0.022[3]
Hung *et al*[115]	2010	Taiwan	188	59 HCC; 129 non-HCC	DM and HCC	Multivariate	Yes	OR = 11.6 [2.500, 53.800]; *P* = 0.002
Hung *et al*[115]	2010	Taiwan	188	59 HCC; 129 non-HCC	HOMA-IR and HCC	Multivariate	Yes	OR = 2.0 [1.35, 3]; *P* = 0.001
Khattab *et al*[116]	2012	Egypt	294	147 HCC; 147 non-HCC	HOMA-IR and HCC	Multivariate	Yes	OR = 2.5 [1.7, 3.69]; *P* = 0.001
Mohamed *et al*[73]	2011	Egypt	100	50 HCC; 50 non-HCC; 20 non HCV	HOMA-IR and HCC	Univariate	No	NS
Diabetes mellitus/insulin resistance and development of HCC in HCV-infected patients								
Chen *et al*[117]	2008	Taiwan	1095	-	DM and HCC	Multivariate	Yes	OR = 3.52 [1.29, 9.24]
Veldt *et al*[16]	2008	Europe	541		DM and HCC	Multivariate	Yes[3]	OR = 3.28 [1.35, 7.97]; *P* = 0.009[3]
Konishi *et al*[118]	2009	Japan	197	Non DM, treated for HCV	DM[1] and HCC	Multivariate	Yes	HR = 4.63 [1.677, 12.766]; *P* = 0.003
Hung *et al*[14]	2010	Taiwan	1470	Treated for HCV	DM and HCC	Multivariate	Yes[2]	HR = 4.32 [1.23, 15.25]; *P* = 0.023[2]
Nkontchou *et al*[119]	2010	France	248	Cirrhotics	HOMA-IR and HCC	Multivariate	Yes	HR = 1.10 [1.01, 1.21]; *P* = 0.026
Takahashi *et al*[120]	2011	Japan	203	Non DM, treated for HCV	DM[1] and HCC	Multivariate	Yes	HR = 6.9 [1.7, 28.4]; *P* < 0.05
Arase *et al*[121]	2013	Japan	4302	Non treated for HCV	DM and HCC	Multivariate	Yes	HR = 1.73 [1.3, 2.3]; *P* < 0.001
Elkrief *et al*[45]	2014	France	348	Cirrhotics	DM	Multivariate	Yes	HR = 1.938 [1.129 , 3.328]; *P* = 0.016
Toyoda *et al*[122]	2015	Japan	522	Patients with SVR	DM and HCC	Multivariate	Yes	HR = 2.08 [1.0170, 4.0133]; *P* = 0.045
Lai *et al*[123]	2006	Taiwan	2141	-	DM and HCC	Multivariate	No	NS
Chen *et al*[124]	2013	Taiwan	5186	-	DM and HCC	Multivariate	No	NS

[1]Association of abnormal post-challenge hyperglycaemia and HCC; [2]Only in SVR patients without cirrhosis; [3]Only in advanced liver fibrosis. HCV: Hepatitis virus infection; HCC: Hepatocellular carcinoma; SVR: Sustained virological response; HOMA-IR: Homeostasis Model Assessment of Insulin Resistance; IR: Insulin resistance; DM: Diabetes mellitus; NS: Not significant.

first published in the early 1990s. More recently, larger epidemiologic studies gave more in-depth analyses of the relationship between HCV chronic infection and glucose abnormalities and were included in the present analysis.

HCV infection is associated with increased rates of glucose abnormalities, including diabetes mellitus and insulin resistance

In the present analysis, most studies found a significant association between HCV infection (whether active HCV RNA positive, or not *i.e.,* HCV Ab positive) and diabetes mellitus or insulin resistance. This tight association was confirmed in both directions by the increased rates of HCV infection markers in DM/IR patients and the high rates of glucose abnormalities in HCV infected patients. The consistency of this association was supported by the confirmation of such results compared with different control groups, such as healthy volunteers or HBV carriers[6,8,12,17-34]. The variability of HOMA-IR cut-offs used (between 1.8 and 2.5 generally) may explain the heterogeneous results reported in the literature. Confounding factors might have also led to significant bias. Indeed, some studies comparing HCV patients with healthy volunteers did not perform multivariate analysis or adjust for confounding factors. However, seven out of ten multivariate analyses found a significant increased risk of DM/IR in HCV patients (OR = 1.2-3.7), after adjusting for confounding variables such as age, gender, BMI, ethnicity and education level.

How are we able to explain the increased risk of DM in HCV infected patients? Some authors have suggested that diabetic patients might have been infected by HCV due to injections or nosocomial transmission. The association of HCV infection with IR and the widespread use of universal precautions nowadays in hospitals to avoid virus transmission probably dis-

qualify this hypothesis. There are a variety of other possible mechanisms of increased risk of DM/IR in HCV patients. As shown in this study, glucose abnormalities in HCV patients are associated with liver fibrosis severity. Severe liver fibrosis and cirrhosis are well-known conditions that are able to induce glucose metabolism impairment. However, studies with other liver diseases, including cirrhosis, still showed an excess of risk in HCV patients compared with HBV patients[6,12,17,31-34]. The ability of HCV, particularly genotype 3 viruses, to induce liver steatosis on its own, which might in turn increase the risk of DM/IR, has also been suggested in previous studies[35,36]. Other underlying mechanisms may involve HCV *per se*. Experimental data suggest the role of inflammation. Increased HOMA-IR has been correlated with soluble Tumor Necrosis Factor Receptor1 (sTNFR1) and sTNFR2 levels[37]. Increased abnormal HOMA-IR was not associated with elevated serum levels of TNFα, IL6 and adiponectin in another study[38]. Other studies have also suggested an impairment of glucose uptake in HCV-infected patients. Glucose uptake and the surface expression of Glucose Transporters (GLUT1 and 2) were suppressed in cells infected by HCV compared with controls[39]. Interferon alfa restored glucose uptake, GLUT2 surface expression, mRNA expression and GLUT2 promoter activities. HCV has also been shown to impair glucose uptake and to promote IR by increasing suppressor of cytokine signalling 3 (SOC3), which inhibits insulin phosphorylation of AKT and phosphoinositide 3-kinase (PI3K)[40]. HCV may be involved in the regulation of phosphorylation of insulin receptor substrate 1 (ISR-1), implicated in the insulin pathway[41]. In HCV core transgenic mice, the viral protein was able to induce increasing TNFα levels in the liver, which in turn promoted the induction of IR. The high levels of TNFα inhibited the ISR-1, causing IR and its possible progression to diabetes. A decreased expression of ISR-1 and ISR-2 mediated by ubiquitination was observed and was inversely proportional to the liver fibrosis stage.

Interferon alfa use might lead to glucose metabolism impairment and is a potential bias. However, increased DM/IR rates have been also reported in HCV patients not taking interferon alfa[20,22-25,34]. Many studies found a decreased rate of glucose abnormalities in HCV patients who showed a SVR after interferon alfa-based therapy, and even in non virological responders in one study[42]. This strongly suggests a direct/indirect role of HCV on glucose metabolism impairment. As eradication of HCV seems to be effective in decreasing the occurrence rate of DM/IR, it will very be interesting to analyse the impact of new direct antiviral agents (DAAs) for preventing DM/IR and eventually cardiovascular disorders. Indeed, in a recent study, IFN-free antiviral regimen resulted in rapid changes in serum lipid profiles and intrahepatic expression of lipid-related genes in G1 patients[43].

Presence of glucose abnormalities in HCV infected patients, including diabetes mellitus and insulin resistance, is associated with negative liver-related outcomes

Severe liver fibrosis, the absence of SVR after interferon alfa-based treatment, and the development of HCC are the main negative outcomes of chronic HCV infection. Interestingly, the presence of DM or IR in HCV patients showed a pejorative impact on each of these end points. Most studies found an independent association of glucose abnormalities with advanced liver fibrosis, absence of SVR after antiviral treatment and HCC occurrence. Only few studies did not confirm such associations. This might be explained by the small size cohort of such studies, the heterogeneity of criteria for DM or HOMA-IR and the very high prevalence of other metabolic risk factors (such as elevated BMI) which may underestimates the impact of DM/IR. Our data is consistent with recent studies that demonstrated that DM increases cumulative incidence of decompensated cirrhosis[44]. In another recent survey, diabetes was independently associated with transplantation-free survival, development of ascites, renal dysfunction, bacterial infections, and HCC during the follow-up[45].

Experimental data suggest that increased insulin levels after hyperglycaemia leads to interferon signalling impairment. Insulin may inhibit the ability of interferon alfa to block HCV replication due to the activation of PI3K by insulin, thus leading to inhibition of STAT-1, which is involved in the interferon alfa pathway[40].

The impact of glucose abnormalities on virological response needs to be further evaluated with new DAA, interferon-free combinations. To date, there is very few data on the impact of GA on virological response to new DAA. Preliminary results suggest that the presence of diabetes does not appear to be predictive of treatment failure in G1 patients[46,47]. Further studies are needed to confirm these data and to evaluate the impact of DM on SVR in patients without poor prognostic factors.

Should glucose abnormalities be corrected to increase SVR rates?

A prospective study, including 155 HCV genotype 1 patients with IR, showed no difference in SVR rates after peginterferon alfa and ribavirin were given, regardless of whether or not patients had received pioglitazone, an antidiabetic drug[48]. Of note, most glycemic control indexes improved significantly in the pioglitazone group except for HbA1c. Another study found higher SVR rates in G4 patients treated with pioglitazone[49]. Pioglitazone may alter NK cell functions and thus impair clearance of infected hepatocytes[48]. A retrospective cohort from Taiwan (19349 diabetic patients, 1.7% HCV positive) showed that patients taking metformin and thiazolidinediones had the lowest risk of HCC (HR 0.49 and 0.56, respectively)

after adjusting for age, gender and comorbidities[50]. Consistently, in a prospective cohort of 100 HCV patients with ongoing cirrhosis, metformin treatment was independently associated with a decrease of HCC occurrence and liver-related death or transplantation[51]. In a two-year prospective follow-up of 85 patients with HCV-related HCC, HCC recurrence-free survival was increased in diabetics taking pioglitazone *vs* non-treated diabetics (44.2% *vs* 36.5%, respectively, $P = 0.37$)[52]. A significant decrease in HCC recurrence was observed in the pioglitazone group for patients with a BMI > 24.

We acknowledge some limitations of this study. Although we tried to include all published studies, we may have missed others in non-English literature or data only presented at meetings. Some studies were done with a limited number of patients. For some studies included in the present analysis, it is possible that there are some remaining bias and residual confounding factors. Despite multivariate analyses, the association between glucose abnormalities improvement and improved outcome may have been influenced by unmeasured confounding factors. Such final confirmation should arise from controlled clinical trials with long-term follow-up.

In conclusion, HCV chronic infection is associated with an increased risk of DM or IR, by a likely direct effect on glucose metabolism. In such patients, DM and IR are associated with a pejorative liver-related prognosis, as shown by increased rates of severe liver fibrosis, HCC occurrence, and decreased SVR rates after interferon-based therapy. This tight relationship between DM/IR and HCV infection needs to be further analysed with new DAAs, interferon-free combinations, with special attention to improvement in glucose abnormalities and long-term follow-up.

COMMENTS

Background

During hepatitis C virus (HCV) infection, extra-hepatic disorders are very frequent and polymorphous. Studies that have evaluated the link between glucose metabolism impairment and HCV reported heterogeneous data.

Research frontiers

Further studies are needed to evaluate the impact of glucose abnormalities in patients treated with interferon-free antiviral therapies. The effects of correction of glucose abnormalities in reducing liver event rates also need to be further studied.

Innovations and breakthroughs

This systematic review allows clarifying the close relationship between glucose abnormalities, HCV infection and poor liver outcomes. HCV infection is associated with increased rates of glucose abnormalities, including diabetes mellitus and insulin resistance. The presence of glucose abnormalities in HCV infected patients, including diabetes mellitus and insulin resistance, is associated with negative liver-related outcomes (*i.e.*, severe liver fibrosis, decreased response to antivirals, and increased occurrence of hepatocellular carcinoma).

Applications

These data strongly encourage clinicians to systematically screen HCV-infected patients for the presence of glucose abnormalities. Considering the impact of glucose abnormalities on liver-related outcomes in HCV infected patients, antiviral treatment should also be considered in HCV-infected patients with metabolic syndrome.

Peer-review

This review talks about the relationship between HCV infection and glucose abnormalities. There are already lots of articles about the topic. This review summarizes those articles published from January 2000 to April 2015 in PubMed and gives us a conclusion about the topic.

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SYSTEMATIC REVIEWS

Presacral venous bleeding during mobilization in rectal cancer

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Abstract

AIM

To analyze the anatomy of sacral venous plexus flow, the causes of injuries and the methods for controlling presacral hemorrhage during surgery for rectal cancer.

METHODS

A review of the databases MEDLINE® and Embase™ was conducted, and relevant scientific articles published between January 1960 and June 2016 were examined. The anatomy of the sacrum and its venous plexus, as well as the factors that influence bleeding, the causes of this complication, and its surgical management were defined.

RESULTS

This is a review of 58 published articles on presacral venous plexus injury during the mobilization of the rectum and on techniques used to treat presacral venous bleeding. Due to the lack of cases published in the literature, there is no consensus on which is the best technique to use if there is presacral bleeding during mobilization in surgery for rectal cancer. This review may provide a tool to help surgeons make decisions regarding how to resolve this serious complication.

CONCLUSION

A series of alternative treatments are described; however, a conventional systematic review in which optimal treatment is identified could not be performed because few cases were analyzed in most publications.

Key words: Presacral hemorrhaging; Rectal surgery; Sacral venous plexus; Pelvic surgery; Sacral anatomy

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Core tip: This is a review of 58 published articles on presacral venous plexus injury during the mobilization

of the rectum and on techniques used to treat presacral venous bleeding. We believe that this work is potentially relevant to helping surgeons understand the physiopathology of this complication and making them aware of possible surgical strategies for its treatment.

Casal Núñez JE, Vigorita V, Ruano Poblador A, Gay Fernández AM, Toscano Novella MA, Cáceres Alvarado N, Pérez Dominguez L. Presacral venous bleeding during mobilization in rectal cancer. *World J Gastroenterol* 2017; 23(9): 1712-1719 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1712.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1712

INTRODUCTION

Presacral venous plexus injury during the mobilization of the rectum is one of the most frequent intraoperative complications during rectal cancer surgery[1]. With an incidence that ranges from 0.25% to 8.6%[2,3], it can cause rapid hemodynamic instability in the patient and can even be lethal[4]. The presacral venous plexus cannot be visualized by the surgeon, and injury to the presacral fascia or avulsion of the rectosacral fascia from its insertion into the sacral periosteum can injure the presacral and basivertebral veins, causing bleeding that is difficult to manage with conventional hemostatic maneuvers. Accordingly, a series of techniques that offer alternatives to traditional hemostatic methods for the treatment of presacral venous bleeding have been described. This review aimed to analyze the anatomy of the sacral venous plexus (SVP), the factors influencing the incidence of presacral venous plexus injury, and the flow of bleeding in an effort to classify the available treatment techniques and make surgeons aware of possible strategies for the management of this complication.

MATERIALS AND METHODS

The databases MEDLINE®, PubMed®, and Embase™ were searched for manuscripts published between January 1960 and June 2016 using the following keywords: presacral bleeding, presacral hemorrhage, pelvic surgery, rectal surgery, presacral venous plexus, presacral anatomy, and pelvic packing. The reference lists from the articles were reviewed to identify additional pertinent articles. This review includes 58 articles on the anatomical vascular data of the SVP, the essential factors that influence the flow of bleeding after venous injury, the causes and types of injury, the incidence of presacral bleeding, and treatments applied to control this bleeding in rectal cancer surgery. Due to the limited number of cases reported in most publications and the variety of procedures used to control this complication, conventional systematic review and meta-analysis could not be performed.

RESULTS

Anatomical considerations

The vascular anatomy of the SVP is complex and includes a wide and intricate network of veins primarily formed by the anastomosis between the medial and lateral sacral veins. The medial sacral vein usually drains into the left common iliac vein, whereas the lateral veins drain into the internal iliac vein. The SVP receives contributions from the lumbar veins of the posterior abdominal wall and the basivertebral veins that pass through the sacral foramen. Morphological studies of human sacral bones show that 100% of the specimens feature foramina that communicate with the anterior sacral face and the cancellous bone of the vertebral bodies. Between 16% and 22% of these foramina are 2 to 5 mm in diameter, are located on the anterior face of S4-S5, and are penetrated by the basivertebral veins originating in the cancellous bone, which measures between 0.7 mm and 1.5 mm in this region[4,5] (Figure 1). The small basivertebral veins, which are very thin, allow the bidirectional passage of blood because they lack valves; these veins flow in long, tortuous channels through the spongy tissue of the vertebral bodies. The lateral sacral veins, the medial sacral vein, and the basivertebral veins constitute a wide network of anastomoses that form the venous plexus on the anterior sacral surface[4,6] (Figure 2). The medial sacral vein can be located to the left or the right of the midline and is duplicated in 80% of cases[7]. The vascular anastomoses between the medial sacral vein and the lateral veins are often less than 3 cm from the sacral promontory; specifically, this distance is 2 cm in 90% of cases, and the anastomosis is located at the level of the 3rd and 4th sacral foramen in 70% of cases[6,7]. The retrosacral fascia, also called Waldeyer's fascia, has been described as a sheet of connective tissue that extends from the periosteum of the sacrum to the posterior wall of the rectum approximately 3-4 cm above the anorectal junction. Anatomical and radiological studies have revealed that although its insertion into the sacrum can occur between the 1st coccygeal vertebra and S2, it is located at the level of S3 and S4 in 84%-94% of cases[8-11], just where the foramen that give rise to the basivertebral veins are thickest.

Hydrodynamic studies

The essential factors that influence the flow of blood from an injured vein are the size of the vein and the intravenous pressure at the broken point of the vein. Hydrostatic pressure in the SVP depends on the following: the pressure of the inferior vena cava, the distance from S4-S5 to the coronal axis of the inferior vena cava traced from the renal veins to the iliac bifurcation, and the elevated pressure on the inferior vena cava due to the lithotomy position. Experimental studies and the application of general hydrodynamic principles suggest that the hydrostatic pressure in the

Figure 1 Sacrum specimen. Multiple sacral basivertebral vein foramin, between 2-4 mm, are seen on S4-S5.

sacral plexus in the lithotomy position is approximately twice the venous pressure of the inferior vena cava in the supine decubitus position, and injury to a vein with diameter between 0.5 mm and 4 mm can cause blood flow of 32 mL/min to 1994 mL/min[4,5].

Causes types of injury

Although the height of the tumor in the rectum, the infiltration of the presacral fascia by the tumor, the use of adjuvant radiotherapy, prior rectal surgery, and poor visualization of the surgical field have been described as risk factors that influence the incidence of presacral bleeding during rectal resection, the most common cause is the anatomical relationship of the anorectal fascia. The fascia and its surrounding tissues, including the presacral veins, can be lacerated by the surgeon due to inadequate dissection of the posterior wall of the rectum in the sacral concavity. This maneuver can be caused instrumentally and, more frequently, by blunt dissection by the fingers of the surgeon. The average distance between the ventral surface of the sacrum and the mesorectum is 12 mm or 13 mm as measured by magnetic resonance (MR) and computed tomography (CT), respectively[12]. Laceration of the presacral fascia due to dissection of the sacrum very close to the surface and lifting of this fascia with or without the periosteum are other common causes of presacral bleeding[3,4,13-15].

Wang *et al*[4] describe 3 types of venous injury and direct implications for their handling: injury to the presacral veins (type Ⅰ), injury to the presacral veins and/or basivertebral veins of diameter < 2 mm (type Ⅱ), and injury to the presacral veins and/or basivertebral veins of diameter > 2 mm (type Ⅲ).

Surgical management

In addition to the application of temporary direct pressure on the bleeding area as the first maneuver, various methods have been employed to treat this complication. Ligature of the internal iliac artery is not effective and can cause gluteal and vesical necrosis[16], and ligation of the internal iliac vein makes venous drainage of its tributaries difficult, increases pressure on the sacral plexus, and exacerbates bleeding[4,16-18]. Similarly, Celentano *et al*[19] we propose a classification of techniques (Table 1) and an algorithm for the management of sacral venous bleeding (Figure 3).

Table 1 Classification of techniques for the control of presacral bleeding

Pelvic plugging	
	Traditional with compresses
	Sengstaken-Blakemore tube
	Linton balloon
	Compartmental hemostatic balloon
	IV Saline Bag
	Breast implant
	Plugging with rectus abdominis muscle
	Plugging with Bonewax®
	Plugging with bone cement
	Bakri balloon
Metal implants	
	Simple pins
	Helical titanium pins + Surgicel®
	Staples + cancellous bone + Surgicel®
	Ligaclips®
Topical hemostatic agents	
	Cyanoacrylate
	Cyanoacrylate + Surgicel®
	Ankaferd Blood Stopper®
	Floseal® + Surgicel®
Direct suture	
	Infrarenal aorta clamp + PVS suture
	Suture-circular ligature
Direct/indirect electrocoagulation	
	Spray electrocautery
	Bipolar coagulation
	Argon coagulation
	Electrocoagulation on a piece of epiploic appendix/muscle fragment

Pelvic plugging

Traditional plugging with compresses has been demonstrated to be effective[20], and surgeons should be familiar with this procedure because it may be the only successful mechanism to control potentially fatal bleeding[21]. After abdominoperineal resection, plugging can be performed through the abdomen following closure of the perineum or entirely *via* the perineum. In this case, explantation will require one or more additional laparotomies, and if the perineal route is used, re-bleeding after the explantation will complicate hemostatic maneuvers. The risk of re-bleeding, the increase in infection, the predisposition to dehiscence if the plug is placed adjacent to an anastomosis, and longer hospital admission are the main disadvantages of this procedure[2,14,20,22-24].

Alternatives to classic plugging that attempt to avoid re-intervention have been described, such as the use of an expandable pelvic prosthesis[25] or the use of the Sengstaken-Blakemore probe[26]. Holman

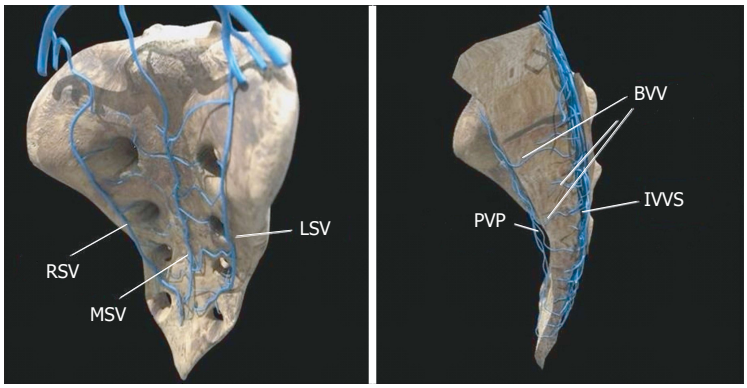

Figure 2 Diagram showing the sacral venous system. RSV: Right sacral vein; LSV: Left sacral vein; MSV: Middle sacral vein; PVP: Presacral venous plexus; IVVS: Internal vertebral venous system; BVV: Basivertebral vein.

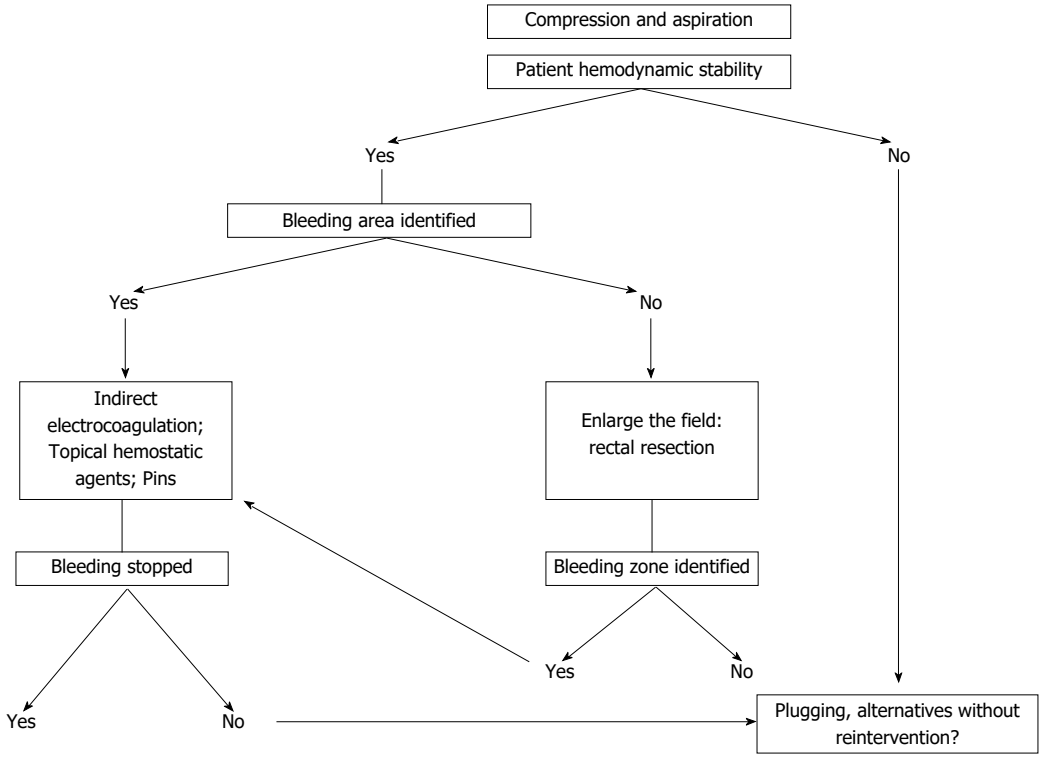

Figure 3 Presacral venous hemorrhaging: treatment algorithm.

et al[27] developed a model hemostatic balloon using MR images of the pelvis. After testing in cadavers, the balloons were used to treat 9 patients with presacral venous bleeding and produced good results in 89% of patients. Ng *et al*[28] describe an alternative to classic plugging after abdominoperineal resection using an empty IV bag filled with 850 mL of saline inserted through the perineum. The advantages of this technique include its adaptability to the sacral concavity and the ease of modifying the hemostatic pressure by infusing or withdrawing fluid through the infusion port. Moreover, the bag can be withdrawn through the perineal wound without requiring additional surgery. After failed attempts at hemostasis with classic plugging and metal implants, some authors[29] successfully used plugging, applying traction with a breast implant that was inflated with 520 mL of saline solution placed in the presacral space and maintaining pressure on the SVP using the traction of the implant, which was connected to a 1-L bag of saline suspended at the end of the bed. Remzi *et al*[30] recommend plugging with a free graft of the rectus abdominis muscle measuring 4 cm × 2 cm × 1 cm sutured to the presacral tissue over the area of bleeding. The absence of necrosis and lack of abscesses with this technique are attributed to the hypervascularization of the presacral area and the revascularization of the graft. Civelek *et al*[31] applied bone wax (Bonewax®) directly to the presacral fascia and the periosteum and simultaneously used pelvic plugging. After the failure of classic pelvic plugging and

metal implants, Becker *et al*[32] recommend plugging the bleeding area directly with bone cement (polymethyl methacrylate). Moreover, the Bakri balloon, created specifically to be introduced into the uterine cavity to control bleeding[33], has been successfully used in 2 patients for the treatment of presacral bleeding after colorectal surgery[34].

Metal implants

Wang *et al*[4] first used pins in 1985 to control presacral bleeding. Since then, their implementation has been the subject of multiple communications, most of which reported good results[35-40]. However, pin placement can be technically difficult[22,37], especially in narrow pelvises[41], when the contour of the sacrum is not sufficiently smooth and regular or when osteoporotic disease is present in the bone[29,42]. Failure of the technique[14,32,41,43], development of a presacral hematoma, chronic pelvic pain, release, migration, and perianal extrusion of the implant[42], and the need for equipment that is not always routinely available in surgery[14,24] are complications and inconveniences associated with the implementation of this procedure. Its ineffectiveness for diffuse bleeding[44] has led to the development of other alternatives. Some authors[13,45] use the ProTack™ device to fix hemostatic sponges (Surgicel®) to the sacrum using helical titanium tacks. Wang *et al*[43] used saw-tooth staples of different sizes that fit into the gap between the staple and the sacrum, along with a spongy bone graft and a plate of Surgicel®. Jivapaisarnpong[46] reported the cessation of bleeding using vascular clips (Ligaclips®) in 3 patients in whom several other techniques, such as electrocauterization, coagulation with argon, indirect coagulation, and pelvic plugging, had failed.

Topical hemostatic agents

Topical hemostatic agents have been widely used, especially in cases of diffuse bleeding or when other methods have failed. For example, cyanoacrylate is a monomer that is purified by removing toxic products during its synthesis. Its contact with anionic substances such as blood causes it to polymerize into long chains that form a solid layer, resulting in hemostasis[47].

Losanoff *et al*[48] achieved hemostasis in 3 patients by evenly applying cyanoacrylate glue to the surface of a gelatin sponge measuring 3 cm × 2 cm; the sponge was then compressed for several minutes to ensure adequate contact with the presacral fascia and polymerization of the adhesive. Chen *et al*[49] used a combination of oxidized cellulose and cyanoacrylate. Specifically, they placed 2 to 5 pieces of 2 cm × 2 cm oxidized cellulose in a Kelly clamp and applied pressure to the injury for a few minutes. They then evenly applied 1 ml of cyanoacrylate to the cellulose surface and to the tissue surrounding the pieces of oxidized cellulose. Zhang *et al*[50] reported the control of bleeding in 5 patients by the application of pressure to the bleeding area with absorbable hemostatic gauze for 20-30 min. This gauze was similar to collagen and was created from cellulose that had been chemically treated and combined with alpha-cyanoacrylate as an adhesive. Karaman *et al*[51] achieved excellent results with the use of topical Ankaferd Blood Stopper® (ABS). ABS exhibits antihemorrhagic properties and is an extract of 5 medicinal plants that exert antithrombotic, antiplatelet, antioxidant, antiatherosclerotic, and antitumoral activities. Germanos *et al*[14] suggest that after several techniques have been tried and failed, presacral bleeding should be treated with direct hemostatic agents. Specifically, they used a gel formed by combining gelatin and thrombin (Floseal®) granules and an absorbable hemostatic agent, Surgicel®, prepared by the controlled oxidation of regenerated cellulose.

Direct suture

Some authors[14] report that clotting and direct suture are ineffective and should be avoided because they can exacerbate bleeding and cause significant blood loss[14]. Alternatively, Papalambros *et al*[52] report the potential benefits of temporarily clamping the infrarenal aorta, which hypothetically decreases blood flow in the vena cava and its tributaries and should reduce the hydrostatic pressure in the sacral plexus and bleeding. This approach would allow the identification of the point of bleeding and its suture. This procedure could be effective for treatment of type Ⅰ injuries described by Wang *et al*[4], which are easiest to treat and can be addressed with less bloody methods. However, in the opinion of other authors[23], this approach would be difficult to apply successfully to injuries of the basivertebral veins after retraction in the sacral periosteum. Ligature and circular suturing were described by Jiang *et al*[53] in 2013 as a method to control presacral venous bleeding. Once the bleeding points have been identified, the venous plexus is ligated and circularly sutured with 4/0 silk. The suture includes the presacral fascia, the presacral veins, and the deep connective tissue. Bleeding that continues after the first suture suggests that the blood originates from the communicating veins or the basivertebral veins, which necessitates a second or even a third suture. However, if bleeding originates from veins retracted in the bone, Jiang *et al*[53] recommend the implementation of a combination of techniques as more efficient than the use of a single method for the control of bleeding in this situation.

Direct or indirect electrocoagulation

Filippakis *et al*[54] controlled bleeding in 4 patients using electrocauterization in the spraying position at the bleeding points of the presacral fascia. Furthermore, Li *et al*[55] proposed direct bipolar coagulation as a simple and effective method for the management of presacral venous bleeding after demonstrating the

cessation of this type of bleeding in 7 patients. Kandeel *et al*[56] and Saurabh *et al*[57] reported 1 and 2 patients, respectively, in whom bleeding was controlled using argon coagulation.

Indirect monopolar electrocoagulation has been successfully used on a portion of an epiploic appendix by maintaining pressure on the bleeding area with a dissection clip[2,3]. Moreover, indirect electrocoagulation through a fragment of the anterior rectus abdominis muscle was described by Xu *et al*[58] and applied with success in 11 patients. The technique involves resecting a fragment of the anterior rectus abdominis muscle approximately 2 cm × 2 cm, placing it in a long dissection clip, applying pressure to the area of bleeding, and applying a monopolar current to induce clotting. Muscle is a soft tissue that contains approximately 75% water and is easily moldable to the bone surface. Water is an excellent conductor of energy due to the solutes dissolved in it. Thus, the implementation of electrocoagulation in muscle results in surgical smoke when the muscle is heated, and the cellular fluid is vaporized by the thermal action of the energy source. The temperature of the muscle gradually increases and reaches the boiling point after 90-120 s of application of monopolar current at maximum power. This temperature is the optimal coagulation point and ensures that the muscle adheres to the bone surface[23,58]. This method has been validated and used by other authors[22-24] with satisfactory results, in some cases after the failure of other alternatives. Specifically, it is a rapid, easily executed, and effective method that is usually free of intra- or post-operative complications and that can be used at several bleeding points. Furthermore, if the muscle does not adhere to the bone, the technique does not fail.

CONCLUSION

Sacral foramina that connect the internal venous plexus with the presacral venous plexus *via* the basivertebral veins are found at the levels of all vertebral bodies, and foramina of greater caliber are located at the level of S4-S5. Therefore, injury at that level presumably causes bleeding with greater flow that is difficult to control. The treatment algorithm we propose is based on the analysis of more than 50 articles presented in this review. This information can help the surgeon understand the physiopathology of and treatment strategies for presacral venous bleeding.

In our opinion and based on our experience with the occurrence of presacral bleeding during rectal surgery, indirect coagulation through the interposition of a fragment of the anterior rectus abdominis muscle is a very effective method when it is possible to identify the site of bleeding[23]. Other methods that have also proven effective are the use of topical hemostatic agents and the use of pins.

COMMENTS

Background

Presacral venous bleeding is a rare but potentially lethal complication of surgery for rectal cancer. Incorrect mobilization of the rectum that injures the presacral fascia or de-insertion of the anorectal fascia can cause bleeding in the sacral venous plexus. This bleeding can be very difficult to control at the level of the last sacral vertebrae due to injury to the large basivertebral veins.

Research frontiers

The present study aims to help surgeons understand the vascular anatomy of the presacral plexus, the pathophysiology of presacral bleeding, the factors influencing the flow of venous injury, the causes and types of damage, the incidence of presacral bleeding and the surgical strategies for treatment.

Innovations and breakthroughs

Due to the lack of cases published in the literature, there is no consensus on which is the best technique to use if there is presacral bleeding during mobilization in surgery for rectal cancer. This review may provide a tool to help surgeons make decisions regarding how to resolve this serious complication.

Applications

This review aims to provide a set of resources to resolve presacral bleeding.

Peer-review

This review will be helping surgeons understand the physiopathology of presacral bleeding and the surgical strategies for its treatment. It is really helpful.

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CASE REPORT

Gastrointestinal stromal tumor of the stomach with axillary lymph node metastasis: A case report

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Author contributions: Kubo N and Takeuchi N participated in the surgery of this case; Takeuchi N treated the patient after surgery; Kubo N drafted the manuscript and all authors read and approved the final manuscript.

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Abstract

Gastrointestinal stromal tumors (GISTs) are the most common type of gastrointestinal mesenchymal tumors, although metastasis to the perigastric lymph nodes is relatively rare, compared with liver or peritoneal metastasis. In this report, we describe a case of stomach GIST with a solitary simultaneous metastasis in the left axillary lymph node. A 68-year-old man was diagnosed with a large upper-stomach GIST, and computed tomography and positron emission tomography revealed masses in the left axilla and right mediastinum. We did not detect evidence of metastases to the liver, or other sites including the perigastric lymph nodes, although findings from the surgically resected axillary lymph nodes were compatible with GIST metastasis. Treatment using imatinib markedly reduced the gastric and mediastinal lesions, and this response persisted for 3 years. The patient subsequently experienced rapid growth of the gastric lesion without mediastinal or axilla recurrence, which required palliative surgery. Despite continuing medical treatment (sunitinib and regorafenib), the patient died of liver metastases 23 mo after the surgery. Based on our findings, it appears that the axillary lymph nodes can be a potential metastatic site for GIST metastasis.

Key words: Gastrointestinal stromal tumor; Axillary; Lymph node; Metastasis; Imatinib

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Core tip: Gastrointestinal stromal tumors (GISTs) are the most common type of gastrointestinal mesenchymal tumors, although metastasis to the perigastric lymph nodes is relatively rare, compared to liver or peritoneal metastasis. In this report, we describe a case of stomach GIST with a solitary simultaneous metastasis in the left axillary lymph node. Based on our findings,

it appears the axillary lymph nodes can be a potential metastatic site of GIST metastasis.

Kubo N, Takeuchi N. Gastrointestinal stromal tumor of the stomach with axillary lymph node metastasis: A case report. *World J Gastroenterol* 2017; 23(9): 1720-1724 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1720.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1720

INTRODUCTION

Gastrointestinal stromal tumors (GISTs) are the most common type of gastrointestinal mesenchymal tumor, although GIST only accounts for approximately 1% of gastric malignancies[1]. GISTs frequently metastasize to the liver or peritoneum, although lymph node metastasis is very rare[2], even to the perigastric area. Therefore, we report the first documented case of stomach GIST with simultaneous axillary lymph node metastasis.

CASE REPORT

A 68-year-old man was admitted to our hospital after complaining of anorexia and obvious weight loss. Gastroscopy revealed a large tumor with ulceration in the upper stomach body (Figure 1), and histological evaluation confirmed a diagnosis of a GIST (positive for c-kit and CD34). The mitotic index was 5/50 in high-power field and the MIB-1 labeling index was 10%. Computed tomography (CT) and positron emission tomography revealed a primary gastric tumor (diameter: 5 cm), a right mediastinal tumor (diameter: 2 cm), and a left axilla mass (diameter: 1 cm) (Figure 2). Based on these findings, we performed a complete gross excision of the left axilla mass. The specimen was 1.4 cm in diameter, and there was no extranodal extension, it exhibited monotonous spindle cells (Figure 3A-D) and was diagnosed as a metastasis of the GIST, because it exhibited positive immunohistochemical staining for c-kit (Figure 3E) and DOG1 (Figure 3F), the mitotic index was 15/50 in high-power field and the MIB-1 labeling index was 10%. Based on these findings, we started treatment using oral imatinib (400 mg/d), and in the next year, after starting imatinib, we followed up the patient every 3 mo by using CT and every 6 mo by using PET. The 6-mo follow-up revealed rapid response of the primary lesion and complete remission in the mediastinal lymph nodes. However, after 3 years of imatinib treatment, the primary gastric tumor exhibited rapid growth that resulted in obstructive symptoms and continuous bleeding, although we did not detect recurrence in the mediastinal and axillary lymph nodes. We performed total gastrectomy as palliative surgery, and all 13 resected perigastric lymph nodes were negative for metastasis; the mitotic index

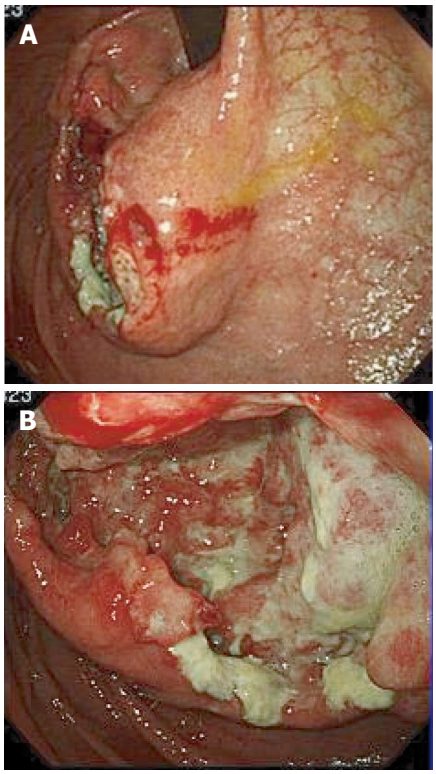

Figure 1 Gastroscopy revealed a large tumor with ulceration in the upper body of the stomach.

was 20/50 in high-power field and the MIB-1 labeling index was 30%. The patient subsequently recovered, and we started postoperative adjuvant treatment using imatinib. However, liver metastases appeared after 13 mo of treatment using imatinib, which we attempted to treat using regorafenib because gene sequence analysis of the tumor showed a KIT exon 11 mutation. The liver metastasis increased 2 mo later, and we started treatment with sunitinib. However, the patient developed renal dysfunction, and died of the liver metastasis 23 mo after the surgery with gastretomy.

DISCUSSION

GIST is the most common type of gastrointestinal mesenchymal tumor, and commonly exhibits mutations in the c-kit proto-oncogene[3]. GIST frequently metastasizes to the liver or peritoneum, although nodal metastasis is very rare[2]. Among 200 reported patients with digestive tract GIST, 94 patients exhibited metastasis, which included 61 liver metastases (65%), 20 peritoneal metastases (21%), and only 6 lymph node metastases (6%)[4]. To the best of our knowledge, there is only one documented case of distant lymph node metastasis from a stomach GIST, and that case involved inguinal lymph node metastasis[5]. Although a few cases of peripheral lymph nodes metastasis from GIST have been reported[6], the present case is the first documented case of a GIST presenting with solitary axillary lymph node metastasis.

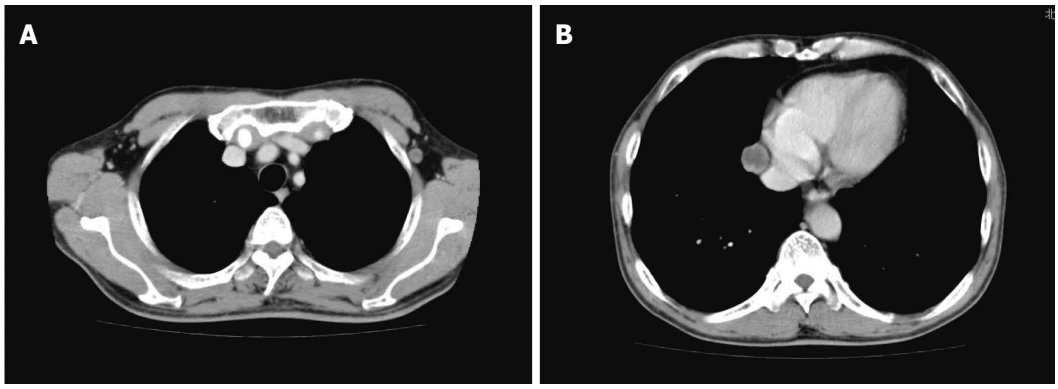

Figure 2 Computed tomography reveals a tumor in the left axilla (A, diameter: 1 cm) and a tumor in the right mediastinum (B, diameter: 2 cm).

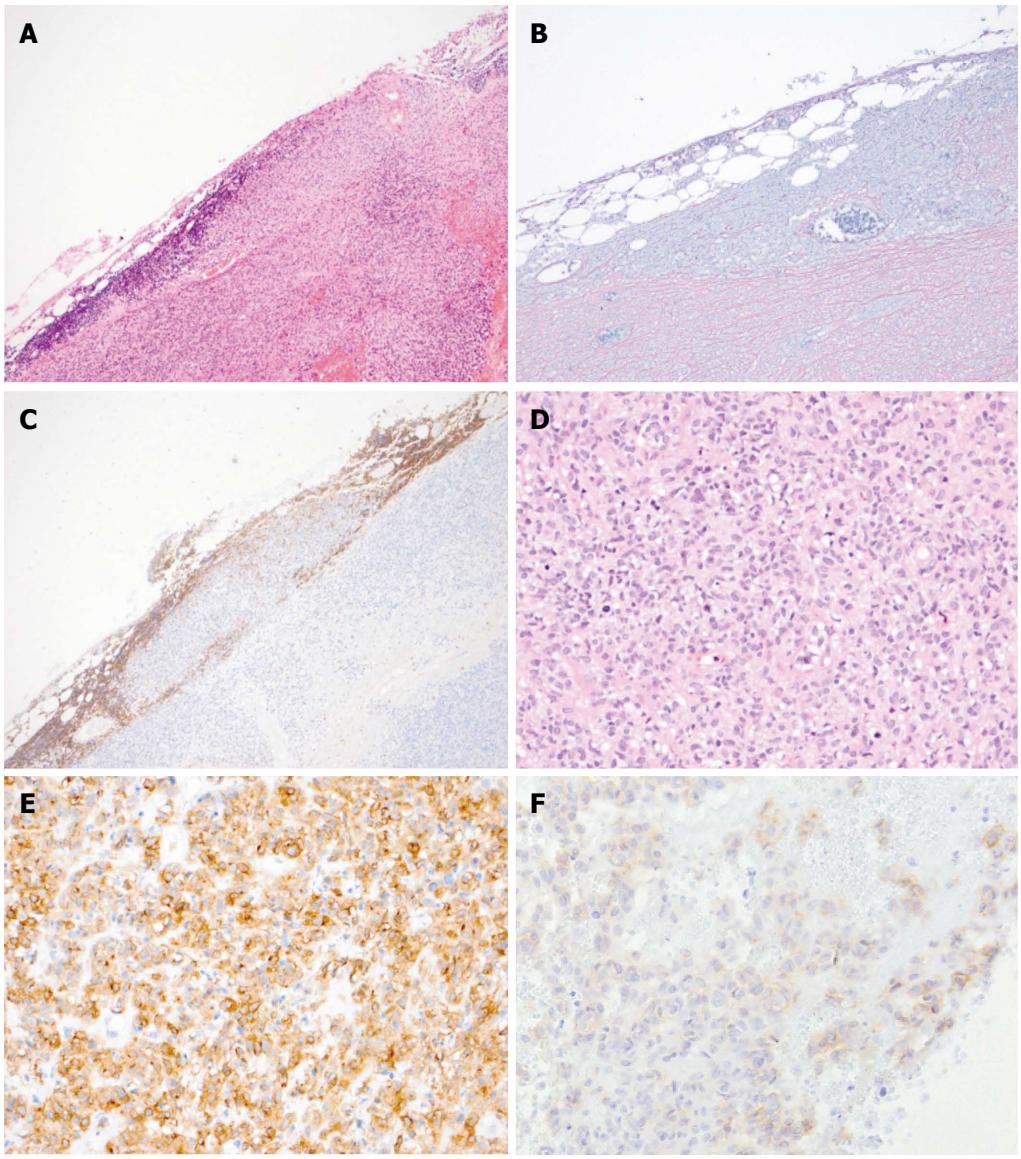

Figure 3 Pathological findings of the biopsied left axilla lymph node. Analysis of the tumor revealed tunicate formation and the survival of lymphoid tissue [hematoxylin and eosin staining(A), silver impregnation (B), and Leukocyte common antigen (C) (magnification × 40)]. The tumor exhibited monotonous spindle cells (D, hematoxylin and eosin staining), and the cells were positive for c-kit (E) and DOG1 (F, magnification × 100).

The three major routes of metastasis to the axillary lymph nodes are clearly documented in lung cancer[7,8]. The first route involves newly developed lymphatic channels that arise from the pleural lesions of adhesive lung tumors. The second route involves retrograde spread in the presence of supraclavicular

lymph node metastasis. The third route involves systemic axial lymph node metastasis. In this context, systemic metastases could be caused by the primary tumor invading nearby blood vessels and the subsequent dissemination of tumor cells into the venous system through the thoracic duct[9,10]. In the present case, the tumor was likely caused by systemic metastasis, as the recurrence was only detected in the right mediastinum, without lung or supraclavicular lymph node metastases.

Tumor size, location, mitotic rate, and C-KIT and PDGFRA genotype are the major determinants of the malignant potential of the tumor, and have significant impact on prognosis[11]. In the TNM (tumor-node-metastasis) system for GISTs, the presences of lymph node metastasis is classified as stage Ⅳ, which generally portends a poor prognosis, but cases with long-term survival have also been reported[5,12]. Valadao reported that lymph node metastasis is not related to poor prognosis; however, the study included a small number of patients[13]. Furthermore, it is unclear whether there is a difference of prognosis according to the site of lymph node metastasis, because reports of distant lymph node metastasis are very rare.

The appropriate therapy for GIST with distant metastasis remains controversial. Surgery is recommended if curative resection is possible, although imatinib therapy is occasionally selected in cases that have complications or may require expansive surgery. In the present case, we performed complete gross excision of the left axilla mass, and imaging revealed that only right mediastinum metastasis remained. However, we selected imatinib therapy, based on the tumor's stage and the patient's surgical stress. Six months of imatinib therapy markedly reduced the gastric lesion and the mediastinal lesion completely disappeared. In this context, resection of residual disease after imatinib pre-treatment is feasible in patients with metastatic GIST, even those with advanced hepatic and peritoneal metastasis[14], and surgery after achieving the best clinical response may be associated with a survival benefit (*vs* historical patients who were treated using imatinib alone)[15]. Therefore, we assumed that the distant metastasis had been controlled by imatinib and that curative resection was possible. However, the patient refused to undergo gastrectomy and elected to continue receiving imatinib. Unfortunately, the primary lesion exhibited rapid regrowth after 3 years of imatinib treatment without reappearance of the mediastinal lesion or other distinct metastases, which led to obstructive symptoms and continuous bleeding. At this point, we performed palliative total gastrectomy and provided ongoing medical treatment (sunitinib and regorafenib), although the patient ultimately died of liver metastases at 23 mo after the surgery. Nevertheless, the patient did not exhibit signs of distant lymph node metastasis.

In conclusion, the axillary lymph nodes can be a site of GIST metastasis, and imatinib chemotherapy may be useful for controlling distant lymph node metastasis from GIST. Although we performed a resection for the original lesion because the distant metastasis had been controlled by imatinib, the appropriate therapy for GIST with distant metastasis remains controversial. Further studies are needed to clarify the duration of chemotherapy and an appropriate surgical intervention that will be effective for treating distant lymph node metastasis.

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COMMENTS

Case characteristics

A 68-year-old man was admitted to our hospital after complaining of anorexia obvious weight loss.

Clinical diagnosis

The patient was diagnosed with malignancies in the stomach.

Differential diagnosis

Gastric cancer.

Imaging diagnosis

Gastroscopy revealed a large tumor with ulceration in the upper stomach body. Computed tomography and positron emission tomography revealed a primary gastric tumor and a left axilla mass.

Pathological diagnosis

Gastrointestinal stromal tumor of the stomach with axillary lymph node metastasis.

Treatment

Surgical resection and chemotherapy (imatinib, regorafenib and sunitinib).

Related reports

There is only one documented case of distant lymph node metastasis from a stomach gastrointestinal stromal tumor (GIST), and that case involved inguinal lymph node metastasis.

Term explanation

The axillary lymph nodes can be a site of GIST metastasis.

Experiences and lessons

Imatinib chemotherapy may be useful for controlling distant lymph node metastasis from GIST.

Peer-review

This is the interesting case report. The authors described lymph node metastasis of GIST is very rare; therefore, the appropriate therapy for GIST with lymph node metastasis remains controversial.

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CASE REPORT

Synchronous coexistence of liver metastases from cecal leiomyosarcoma and rectal adenocarcinoma: A case report

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Author contributions: Aoki H, Arata T, Utsumi M and Kunitomo T performed operations; Mushiake Y, Yasuhara I, Taniguchi F and Katsuda K collected and analyzed the data; Yamasaki R performed the histological examination; Tanakaya K and Takeuchi H supervised the research; Aoki H wrote this paper.

Institutional review board statement: This study was reviewed and approved by the Ethics Committees of Iwakuni Clinical Center.

Informed consent statement: The patient involved in this study gave his informed consent authorizing use and disclosure of his protected health information while he was alive.

Conflict-of-interest statement: We declare that we have no conflicts of interest.

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Abstract

Multiple liver tumors represent a challenging condition for abdominal surgeons both in the selection of technique and the rarity of diagnosis. There are no case reports on co-existence of liver metastases from both intestinal leiomyosarcoma and adenocarcinoma. The patient described in this report successfully underwent resection of both primary lesions and liver metastases in combination with chemotherapy. As for the leiomyosarcoma, the primary cecal lesion was revealed more than three years after the patient's first visit. Peritoneal, lymph-node, and lung recurrences were observed afterward, and thus surgeries on those regions were performed. Pathologically, the peritoneal and lung recurrences comprised leiomyosarcoma and the lymph-node recurrence was diagnosed as adenocarcinoma. Despite newly discovered multiple lung recurrences and regional lymph-node metastases, the patient lived a normal life for 73 mo after the initial operation based on multidisciplinary therapy. He ultimately died of liver failure due to invasive lymph-node recurrence from the rectal adenocarcinoma, in addition to multiple lung recurrences from the leiomyosarcoma. Hepatic recurrence did not occur in this patient's case, which appears to be one reason for his long-term survival.

Key words: Leiomyosarcoma; Chemotherapy; Multiple liver tumors; Liver metastasis; Adenocarcinoma

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Core tip: There have been no case reports on co-existence of liver metastases from intestinal leiomyosarcoma and adenocarcinoma. This patient underwent resection of primary lesions and liver metastases in combination with chemotherapy. As for leiomyosarcoma, liver metastasis was discovered three years prior to discovery of the primary lesion. Peritoneal, lymph-node, and lung recurrences were discovered afterward, and therefore surgeries on those regions were performed. Despite newly discovered multiple lung recurrences and regional lymph-node metastases, the patient lived a normal life for 73 mo after the initial operation. He ultimately died of liver failure due to invasive lymph-node recurrence from the rectal adenocarcinoma.

Aoki H, Arata T, Utsumi M, Mushiake Y, Kunitomo T, Yasuhara I, Taniguchi F, Katsuda K, Tanakaya K, Takeuchi H, Yamasaki R. Synchronous coexistence of liver metastases from cecal leiomyosarcoma and rectal adenocarcinoma: A case report. *World J Gastroenterol* 2017; 23(9): 1725-1734 Available from: URL: http://www.wjgnet.com/1007-9327/full/v23/i9/1725.htm DOI: http://dx.doi.org/10.3748/wjg.v23.i9.1725

INTRODUCTION

Since the appearance of gastrointestinal stromal tumor as a distinctly defined entity, the diagnosis of intestinal leiomyosarcoma has not been common. Among the different types of this sarcoma, cecal leiomyosarcoma is extremely rare[1]. Hepatic leiomyosarcoma is also rare, particularly as a primary cancer[2]. Abdominal surgeons often confront multiple liver tumors, making treatment of such cases challenging. This is particularly the case if the diagnoses of hepatic tumors differ from each other. Until now, there had been no case reports regarding co-existence of liver metastases from a combination of intestinal leiomyosarcoma and adenocarcinoma. We hereby report on a patient who underwent successful treatment involving resection of both primary lesions and liver metastases along with chemotherapy. Peritoneal, lymph-node, and lung recurrences were observed afterward, and thus surgeries on those regions were also performed. Multiple lung recurrences and regional lymph-node metastases were newly discovered, but the patient could live a normal life for 73 mo after the initial surgery based on multidisciplinary therapy, which we will discuss in detail in this report.

CASE REPORT

A 61-year-old male visited our hospital with occult blood in stool and multiple liver tumors at an annual medical examination in October 2009. His past medical history involved only hypertension starting at the age of 57. At the examination, he underwent a colonoscopy examination, whereupon type 2 adenocarcinoma was discovered in the rectum. In addition, an abdominal computed tomography (CT) scan and gadoxetic acid enhanced magnetic resonance imaging revealed liver tumors in Segment 3, Segment 4, and Segment 8 (Figures 1 and 2). Anterior rectal resection with regional lymph-node dissection was carried out in December 2009. A pathological examination revealed extra serosal invasion by a moderately differentiated adenocarcinoma and metastases in eight of 14 resected lymph nodes.

Because genetic analysis confirmed wild-type *KRAS*, the patient received chemotherapy with modified FOLFOX6 plus bevacizumab after the rectal resection. Following four courses of FOLFOX, the S3 liver tumor disappeared and the S8 tumor decreased in size, but the S4 tumor was found to be enlarged. The patient then underwent seven courses of FOLFIRI plus bevacizumab followed by one course of irrinotecan plus cetuximab; as a result, the S4 and S8 tumors decreased in size (Figure 3). Positron emission tomography-CT after the chemotherapy series showed no significant uptake of fluorodeoxyglucose in the liver. The patient subsequently underwent a central bi-segmentectomy and a partial S3 resection in September 2010 (the second operation).

A pathological examination revealed fibrosis and calcification in the S3 and S8 tumors, with a few degenerated residual adenocarcinoma cells, which was compatible with rectal adenocarcinoma metastasis. In contrast, the S4 tumor consisted of irregular fascicles of spindle-shaped cells with eosinophilic cytoplasm and nuclear atypia. An immunohistochemical examination demonstrated that the S4 tumor cells were positive for α-smooth muscle actin and desmin, while negative for CD34, S-100, c-kit, and cytokeratin AE1/3 (Figure 4). Based on these findings, the S4 tumor was designated as leiomyosarcoma. The tumor grade was high according to the classification by Hajdu *et al*[3].

Histologically, chemotherapy had no apparent effect on this tumor. The patient underwent six courses of FOLFIRI plus bevacizumab as adjuvant chemotherapy after hepatic resection. Twenty-two months later (in July 2012), an abdominal CT scan was performed as part of an annual medical examination. A cecal tumor and lymph-node swelling around the common hepatic artery were discovered. Moreover, accumulation at both sites was discovered in a positron emission tomography (PET)-CT scan (Figure 5). The tumor had not been identified in a colonoscopy. Three months later, a type 2 tumor was discovered and a biopsy via colonoscopy revealed leiomyosarcoma. Ileocecal resection with lymph-node dissection and lymph-node sampling around the common hepatic artery were carried out in November 2012 (the third operation).

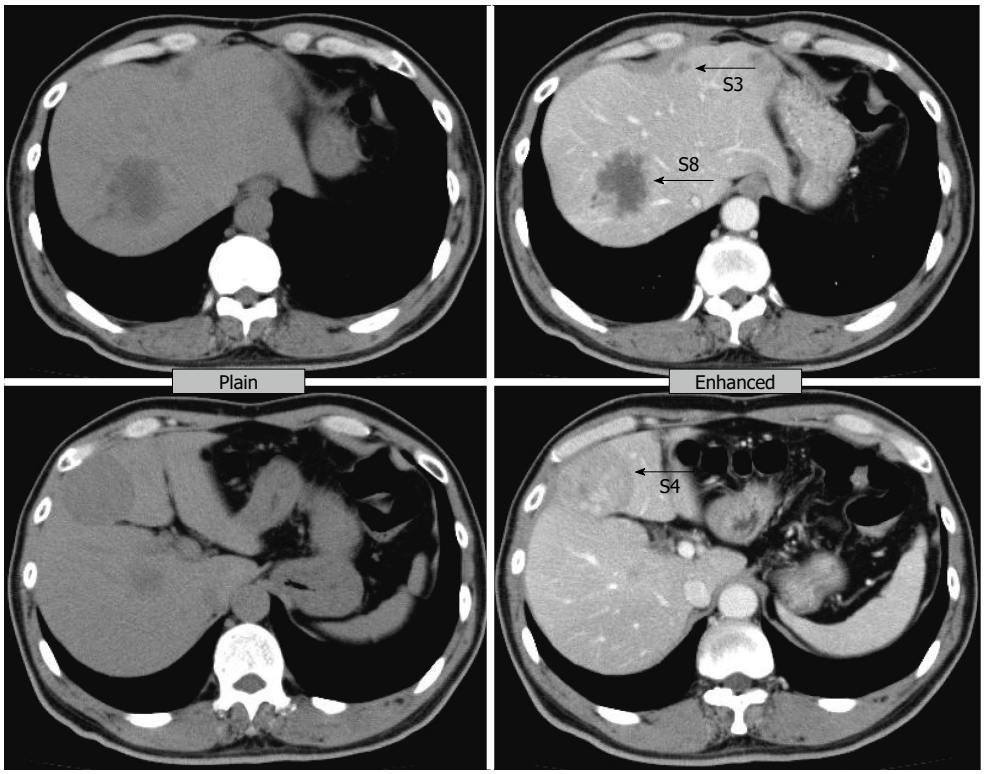

Figure 1 Computed tomography before treatment. An abdominal computed tomography scan revealed liver tumors in Segment 3, Segment 4, and Segment 8. The tumor in Segment 8 is hypodense with peripheral enhancement. The tumor in Segment 4 is a well-defined isodense tumor with homogeneous enhancement.

A pathological examination revealed cecal leiomyosarcoma with regional lymph-node metastases and metastasis from rectal adenocarcinoma in the lymph node around the common hepatic artery. Retrospectively, accumulation had been observed in the cecum in a PET-CT scan in September 2010, and a submucosal tumor had been suspected in a colonoscopy in July 2011. It is likely that rectal adenocarcinoma and cecal leiomyosarcoma existed synchronously from the beginning, and that both tumors had metastasized to the liver synchronously. The patient was then treated with nine courses of XELOX plus bevacizumab.

In a follow-up CT scan in June 2013, a tumor just below the peritoneum was discovered. Because this accumulation was identified in a PET-CT scan and no other accumulation was observed, extirpation of the tumor was carried out (the fourth operation). Pathological diagnosis was leiomyosarcoma of the omentum, compatible with recurrence (Figure 6). The patient was treated with XELOX plus bevacizumab following the surgery. Three months later, in a chest CT scan, two coin lesions were discovered in the left lung. There was no indication of accumulation at both lesions in a PET-CT scan, but lung metastases were strongly suspected. In October 2013 (46 mo after the first operation), partial resections of the left upper lobe and left lower lobe were performed (the fifth operation). Pathological diagnosis was metastatic leiomyosarcoma of the lung (Figure 7).

The patient was subsequently treated with XELOX plus bevacizumab again following surgery (the fifth and final operation). The hepatic hilum lymph node was found to be enlarged in July 2014, and multiple lung metastases were newly discovered in November 2014. Chemotherapy was changed to treatment consisting of CPT-11 plus cetuximab, due to neuropathy experienced by the patient. This clinical time course is demonstrated in Figure 8.

Although lymph-node and multiple lung metastases were present, the patient survived for more than six years after the initial operation. Since the left hepatic duct was constricted by lymph-node metastasis, a plastic stent was inserted in October 2015. The patient received chemotherapy with doxorubicin afterward as an outpatient but was hospitalized with cholangitis due to lymph-node metastatic recurrence in January 2016. The patient died from liver failure due to lymph-node invasion from rectal adenocarcinoma in March 2016 (76 mo after the initial operation). The extended treatment proved worthwhile, given that the patient could live a normal life for 73 mo after the initial operation with help from the multidisciplinary therapy we employed.

DISCUSSION

Hepatic resection for liver metastases from colorectal cancer or neuroendocrine tumor, in combination with chemotherapy, has been established as a safe and

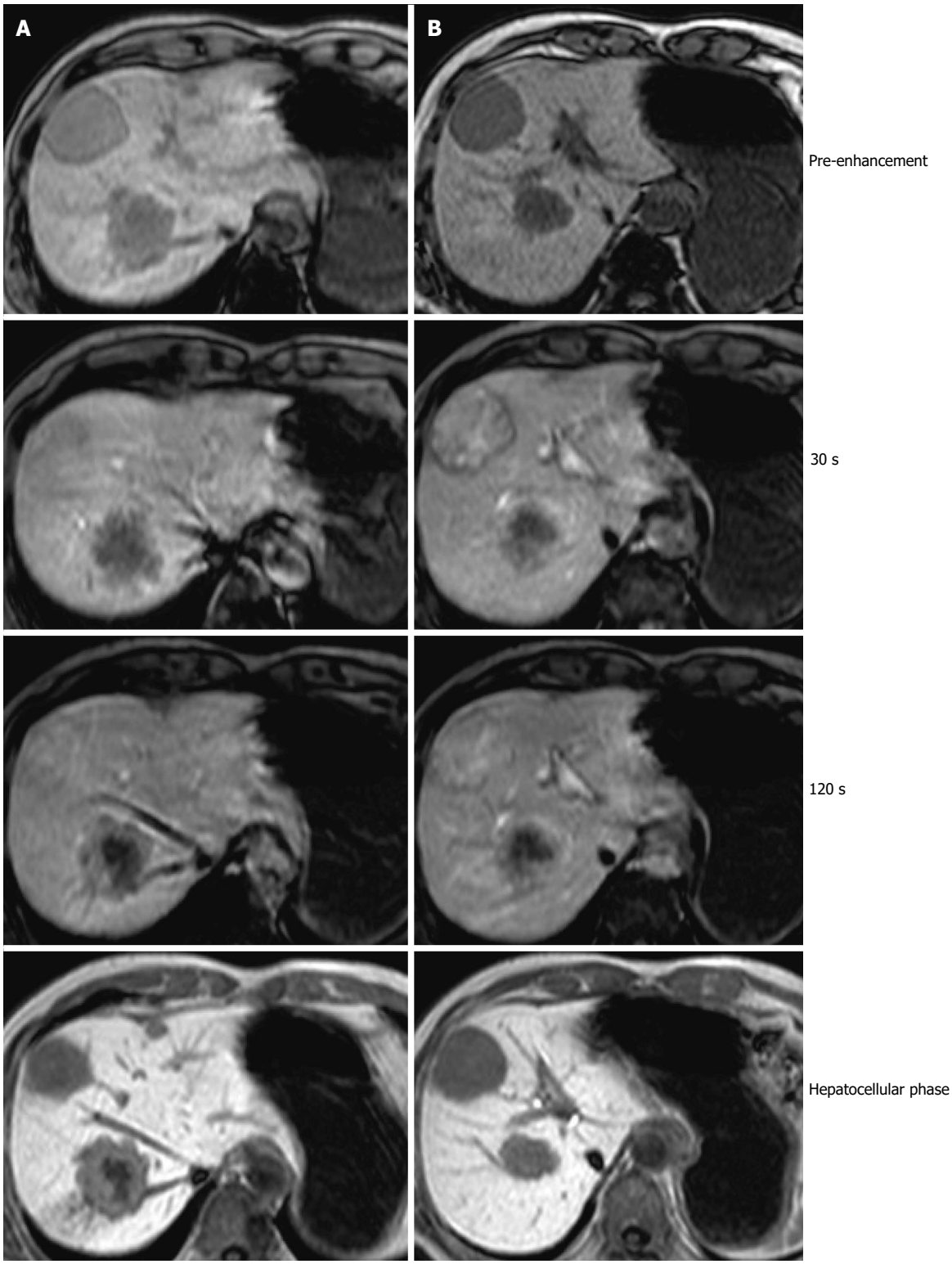

Figure 2 Ethoxibenzyl-magnetic resonance imaging before treatment. The tumors in Segments 3 and 8 showed gradual peripheral enhancement, while the tumor in Segment 4 showed heterogeneous enhancement and washout characteristics. A: S3 and S8 gradual peripheral enhancement; B: S4 heterogeneous enhancement.

standard treatment. The issue in question, however, is how to determine effective treatment for non-colorectal non-neuroendocrine liver metastases (NCNNLM). Hepatic metastasectomy had been thought ineffective for such cases. According to Gladdy's report of 353 patients with primary resectable leiomyosarcoma[4], recurrence occurred in 51% of abdominal and retroperitoneal leiomyosarcoma cases, including 29% of lung, 23% of liver, and 15% of other cases (brain and lymph nodes). Predictive factors for disease-free survival in patients with leiomyosarcoma were size and tumor grade. In addition, DeMatteo *et al*[5] reported

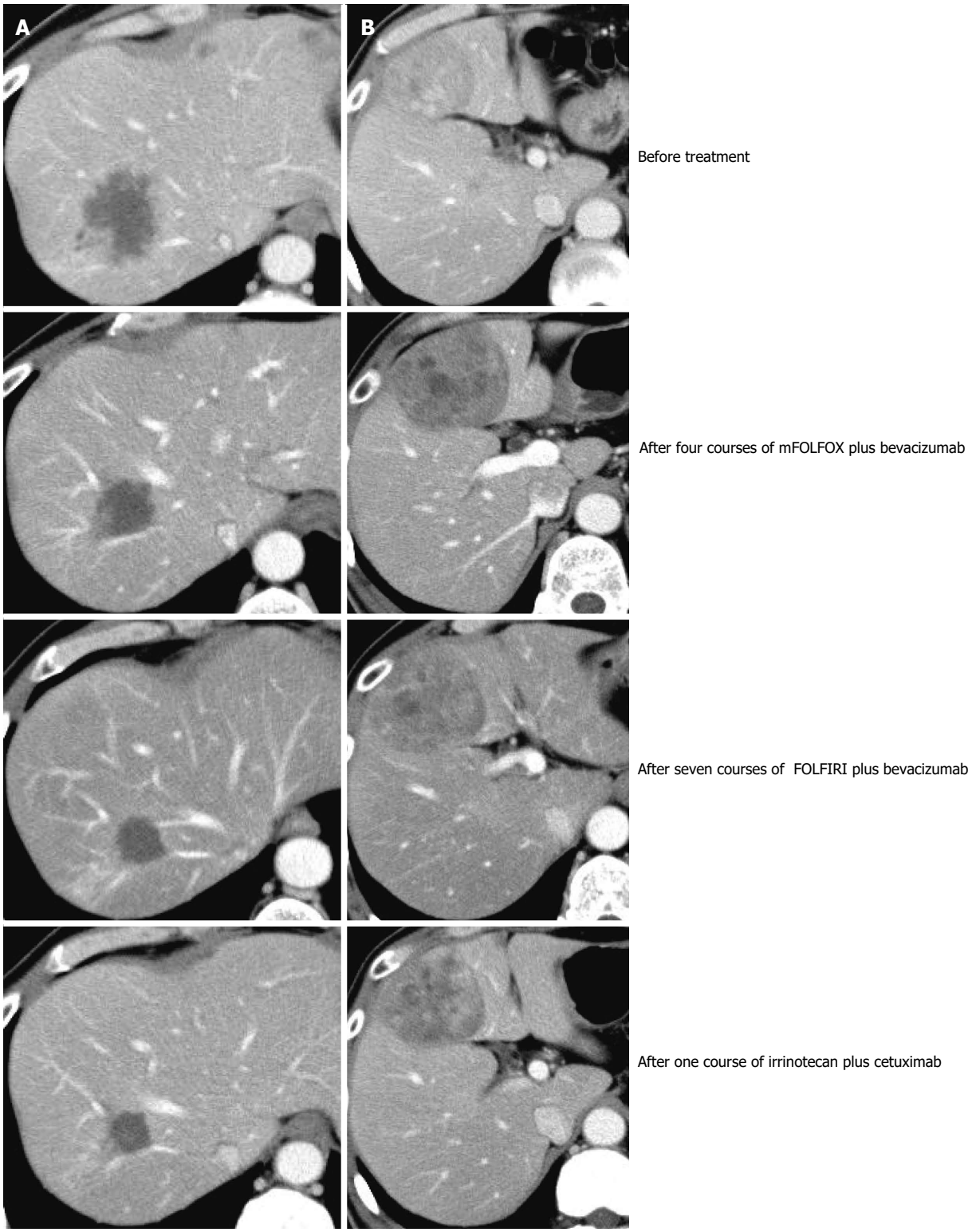

Figure 3 Changes in computed tomography images during treatment. The tumors in Segments 3 and 8 showed a gradual decrease in size, while the tumor in Segment 4 exhibited a one-time increase and then a decrease in size. A: S8 gradually decreased in size/S3 disappeared; B: S4 once increased then decreased in size.

that the rate of recurrence reached as high as 84% even after complete hepatic resection for sarcoma metastasis, although this definition of sarcoma includes gastrointestinal stromal tumors.

Ng *et al*[6] reviewed 191 cases of gastrointestinal leiomyosarcomas, of which colorectal leiomyosarcoma numbered 22 cases (12%). Without hepatectomy, the median survival time for patients with liver metastases from leiomyosarcoma was no more than 14 mo. Before the 21st century, metastases from leiomyosarcomas

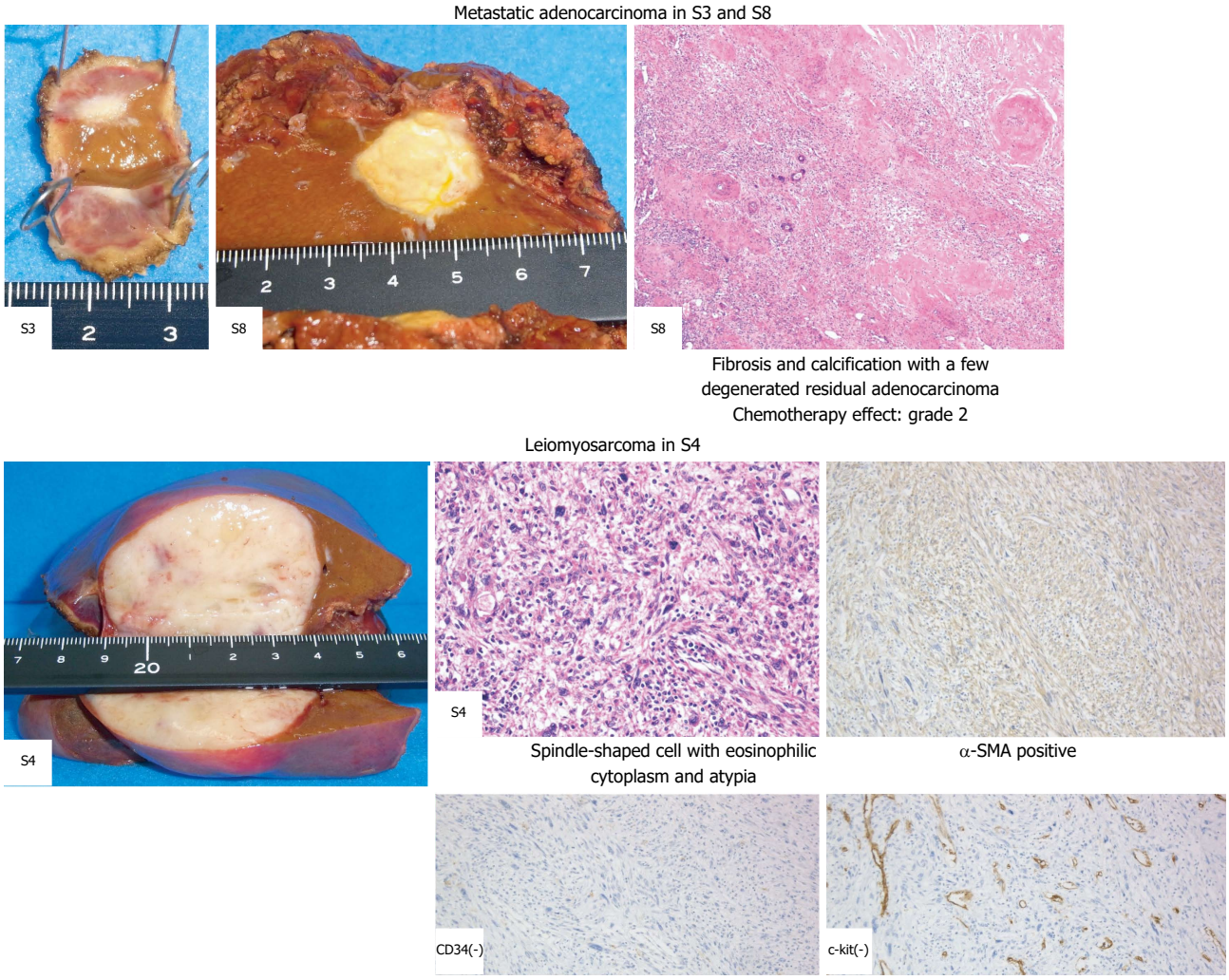

Figure 4 Pathological diagnoses of live lesions. The tumors in Segments 3 and 8 revealed fibrosis and calcification, with a few degenerated residual adenocarcinomas, while the tumor in Segment 4 consisted of irregular fascicles of spindle-shaped cells and was positive for SMA and negative for CD34 and c-kit. SMA: Smooth muscle actin.

were thought to not be sensitive to chemotherapy[7].

Lang *et al*[8] reported on 26 cases of hepatic metastases from leiomyosarcomas. Only one of these 26 cases (3.8%) originated from the colon. The median survival and five-year survival rate after R0 resection were 32 months and 20%, respectively. The presence of extrahepatic tumor growth should be regarded as a contraindication for liver resection only if an R0 resection does not appear possible. Marudanayagam *et al*[9] also emphasized the importance of R0 resection for hepatic metastasectomy of soft tissue sarcomas. Among soft tissue sarcomas, leiomyosarcoma was associated with poor prognosis.

Groeschl *et al*[10] reported on 420 patients who underwent hepatectomy for NCNNLM. The five-year survival rate in recent years was 32% after hepatectomy for liver metastases from sarcomas. Although the rate of recurrence after hepatectomy is as high as 66.5%, NCNNLM can be resected with reasonable survival outcomes when that surgery is appropriately selected as a treatment option. Prognostic factors for NCNNLM are tumor size (greater than 5 cm), lymphovascular invasion, and time-interval to liver metastasis of less than two years. Hepatic recurrence did not occur in the case we present here, which was one of the reasons for the patient's long-term survival.

We reported this patient's case as a primary hepatic leiomyosarcoma with liver metastasis of rectal cancer[2], before our finding of cecal leiomyosarcoma. The cecal leiomyosarcoma was discovered almost three years after the patient's first visit. From a pathological perspective, it was difficult to distinguish the site of primary lesion. Mourra *et al*[11] published a multi-institutional study on metastatic tumors in the colon and rectum. In that paper, only 35 of 10365 patients with colorectal malignancies (0.338%) were identified as having true metastases to the colon and rectum. Of those 35 metastatic colorectal tumors, leiomyosarcoma was identified in only two cases, with both tumors originating from soft tissue. This indicates only a small probability of the primary hepatic leiomyosarcoma metastasizing to the cecum.

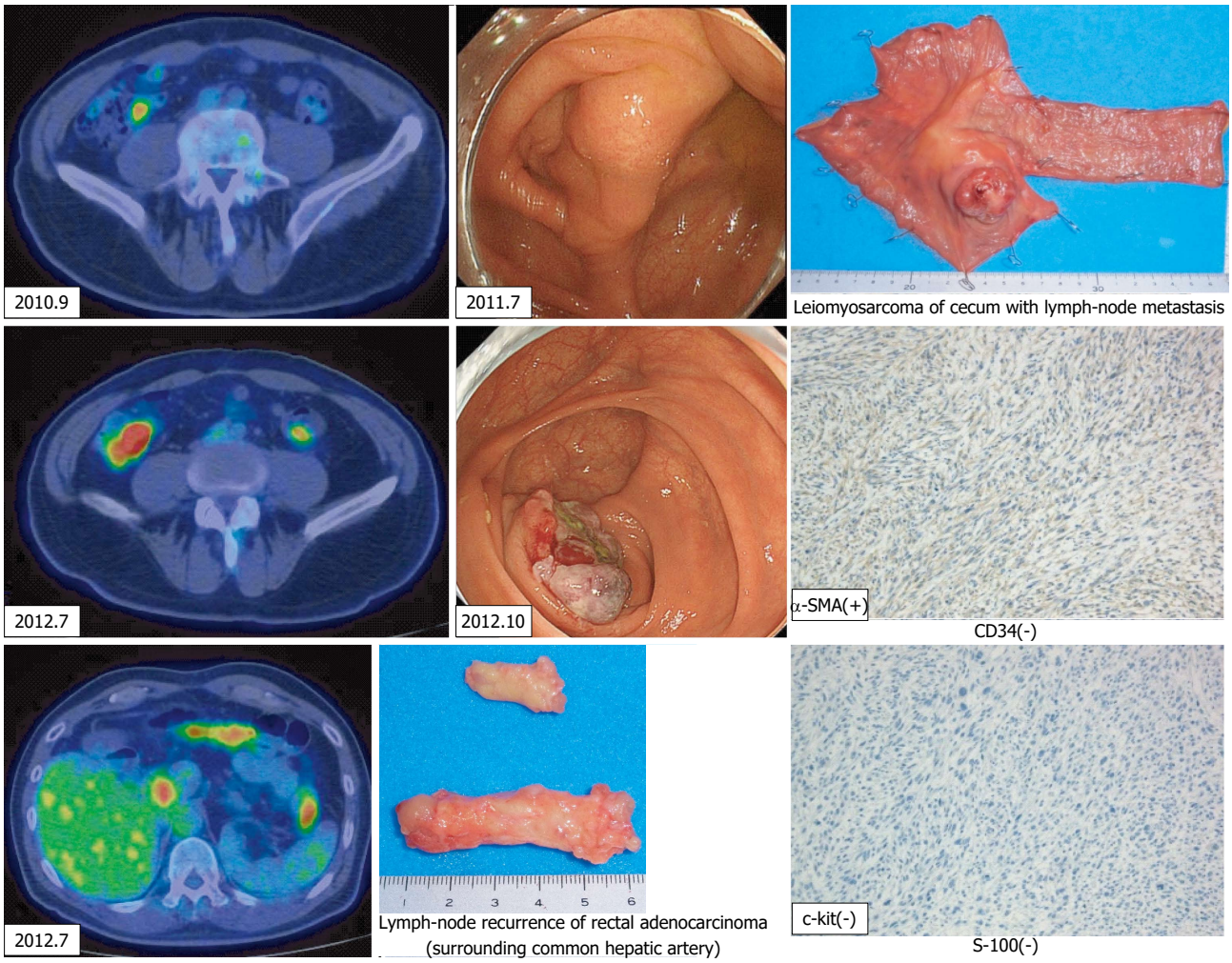

Figure 5 Cecal leiomyosarcoma and lymph-node recurrence. A cecal tumor and lymph-node swelling around the common hepatic artery were discovered in a positron emission tomography-computed tomography (PET-CT) scan. Retrospectively, accumulation had been observed in the cecum in a PET-CT scan in September 2010, and a submucosal tumor was suspected based on a colonoscopy taken in July 2011. SMA: Smooth muscle actin.

In contrast, hepatic metastasis is reported to occur in 20%-66.5% of patients with visceral or retroperitoneal sarcomas[9,10]. Moreover, all 35 patients had a history of metastatic disease in extragastrointestinal sites, with a mean disease-free interval of 10.6 years for sarcomas. We feel that these clinical characteristics were not compatible with our case, and for that reason we concluded that the cecum was the primary lesion site in the patient case we present here. We were aware that primary hepatic leiomyosarcoma is rare, and this patient's case has taught that its diagnosis should be made carefully only after long-term observation. However, rare are cases in which cecal leiomyosarcoma and rectal adenocarcinoma coexisted and metastasized to the liver. Hamai *et al*[12] reported a case of gastric adenocarcinoma with multiple liver tumors. After 14 mo of chemotherapy, the patient underwent total gastrectomy with partial liver resection, upon which the liver tumors were diagnosed pathologically as leiomyosarcomas. During adjuvant chemotherapy two years and five months after the first visit, a new hepatic tumor appeared and a tumor in the colon was discovered. The patient underwent partial colectomy and partial liver resection. The colon tumor and liver tumors were all immunohistochemically diagnosed as leiomyosarcomas. Seven months later, a third liver resection was carried out for the newly discovered liver tumors. Multiple liver and lung metastases eventually developed, and the patient died four years and 10 mo after the first visit. When a liver tumor is diagnosed as leiomyosarcoma, therefore, careful follow-up is needed to identify the primary site.

Leiomyosarcoma was for some time considered to be a relatively chemo-resistant sarcoma subtype. Recent data have demonstrated a reasonable response rate exhibited by some histological subtypes exposed to specific histology-tailored treatments with doxorubicin-containing chemotherapy[13]. Since without chemotherapy median survival is generally up to 12 mo[14], chemotherapy appears to be necessary for leiomyosarcoma treatment. However, the type of adjuvant therapy appropriate for leiomyosarcoma is an issue

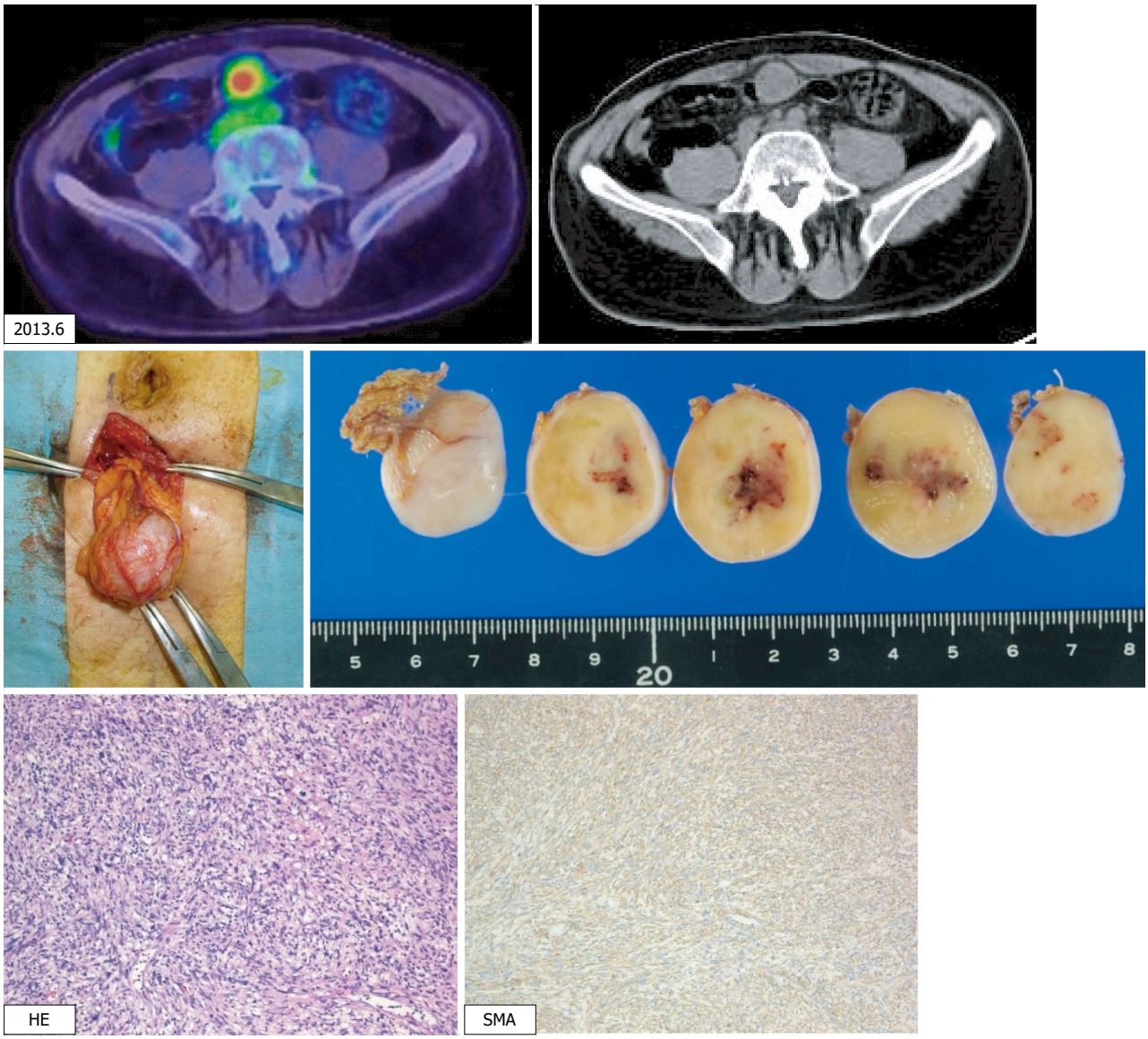

Figure 6 Peritoneal recurrences. A tumor just below the peritoneum was discovered. As the accumulation was recognized in a positron emission tomography-computed tomography scan and no other accumulation was observed, extirpation of the tumor was carried out. Pathological diagnosis was leiomyosarcoma of the omentum, compatible with recurrence. SMA: Smooth muscle actin.

requiring debate. Pazopanib was recently reported to be a feasible option for patients who had been heavily pretreated for metastatic sarcoma[15]. In that report, patients with leiomyosarcomas comprised the majority of long-term responders and survivors.

Both leiomyosarcoma and adenocarcinoma recurred after resection of primary lesions and hepatic metastases, making determination of a chemotherapy regimen for the patient in this report difficult. As we are familiar with adenocarcinomas and the distant lymph-node recurrence was adenocarcinoma pathologically, we chose a regimen mainly designed for colorectal adenocarcinoma. After peritoneal and lung tumors were diagnosed as leiomyosarcoma recurrence, we selected the treatment doxorubicin. At the patient's final hospitalization, lymph-node metastases to the hepatic hilum caused liver failure, which proved to be fatal, and chest X-rays showed numerous nodules in the lung field, which had caused a persistent cough in the patient. The former problem derived from adenocarcinoma and the latter from leiomyosarcoma. By that time, chemotherapy was no longer a treatment option.

The patient survived more than six years after initial diagnosis, even though he had both stage Ⅳ rectal cancer and cecal leiomyosarcoma with liver metastasis. As for long-term survival, Gladdy *et al*[4] reported on late disease-specific mortality in primary leiomyosarcoma. In that report, 6% of extremity and 9% of abdominal or retroperitoneal patients developed distant recurrence more than five years after the primary tumor diagnosis. The authors emphasized the need for long-term follow up.

The prognosis for patients with leiomyosarcoma might be prolonged in the future as chemotherapy

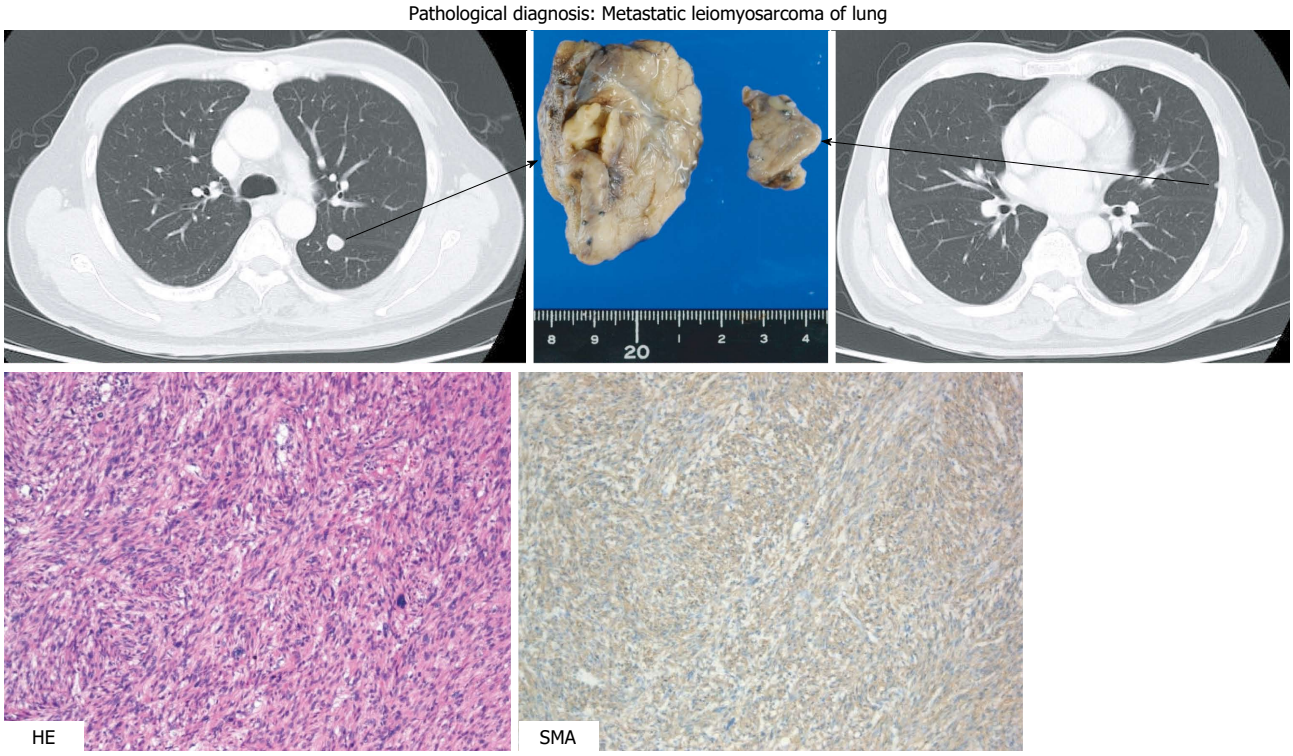

Figure 7 Lung recurrences. In a chest CT scan, two coin lesions were discovered in the left lung. As lung metastases were strongly suspected, partial resections of the left upper lobe and left lower lobe were performed. Pathological diagnosis was metastatic leiomyosarcoma of the lung.

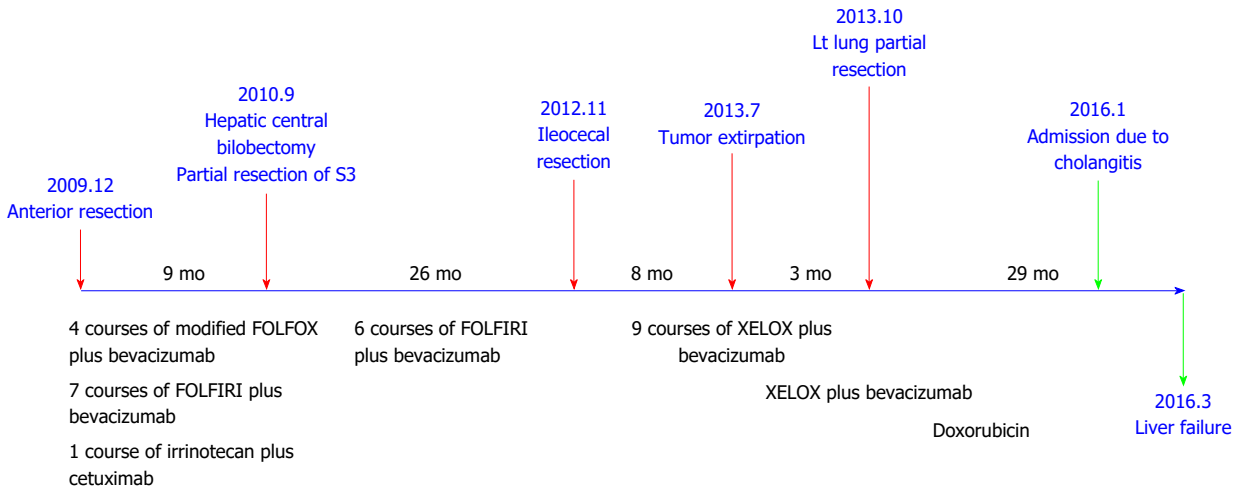

Figure 8 Clinical courses.

continues to advance. Long-term follow-up is important and should be considered.

This patient case was extremely rare for the points mentioned below: (1) cecal leiomyosarcoma and rectal adenocarcinoma coexisted; (2) both metastasized to the liver and were resected successfully; (3) primary colon leiomyosarcoma was diagnosed two years after resection of the hepatic metastatic lesion; and (4) long-term survival was attained based on multidisciplinary therapy.

COMMENTS

Case characteristics

A 61-year-old male patient with occult blood in stool and multiple liver tumors discovered at an annual medical examination.

Clinical diagnosis

Rectal adenocarcinoma with multiple liver metastases.

Differential diagnosis

The authors did not at first recognize a differential diagnosis.

Laboratory diagnosis
All lab measurements were within normal ranges except for slightly elevated serum carcino-embryonic antigen.

Imaging diagnosis
An abdominal computed tomography scan and gadoxetic acid enhanced magnetic resonance imaging revealed liver tumors in Segment 3, Segment 4, and Segment 8.

Pathological diagnosis
The patient had synchronous liver metastases from both cecal leiomyosarcoma and rectal adenocarcinoma.

Treatment
The patient successfully underwent resection of both primary lesions and liver metastases in combination with chemotherapy.

Related reports
There have been no case reports on co-existence of liver metastases from both cecal leiomyosarcoma and rectal adenocarcinoma. Only one report was published regarding a gastric adenocarcinoma with multiple liver tumors, which were diagnosed pathologically as leiomyosarcoma after gastrectomy and hepatectomy. Fifteen months later, a tumor in the colon was discovered, after which a partial colectomy was carried out. The colon tumor was immunohistochemically diagnosed as leiomyosarcoma.

Experiences and lessons
Treatment for multiple liver tumors is challenging, particularly if the diagnoses of hepatic tumors differ from each other.

Peer-review
The main issue regarding diagnosis is whether the hepatic leiomyosarcoma is a primary lesion or a metastasis from the cecum. From a pathological perspective, it is difficult to distinguish which of the sites is a primary lesion. The authors therefore went about trying to make a clinical determination.

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