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Retrospective Cohort Study

Assessment of the July effect in post-endoscopic retrograde cholangiopancreatography pancreatitis: Nationwide Inpatient Sample

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Abstract**AIM**

To assess incidence of post-endoscopic retrograde cholangiopancreatography (post-ERCP) pancreatitis in the early (July/August/September) vs the late (April/May/June) academic year and evaluate in-hospital mortality, length of stay (LOS), and total hospitalization charge between these time periods.

METHODS

This was a retrospective cohort study using the 2012 Nationwide Inpatient Sample (NIS). Patients with International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM) procedure codes for ERCP were included. Patients were excluded from the study if they had an ICD-9 CM code for a principal diagnosis of acute pancreatitis, if the ERCP was performed before or on the day of admission or if they were admitted to non-teaching hospitals. Post-ERCP pancreatitis was defined as an ICD-9 CM code for a secondary diagnosis of acute pancreatitis in patients who received an ERCP as delineated above. ERCPs performed during the months of July, August and September was compared to those performed in April, May and June in academic hospitals. ERCPs performed at academic hospitals during the early vs late year were compared. Primary outcome was incidence of post-ERCP

pancreatitis. Secondary outcomes included in-hospital mortality, length LOS, and total hospitalization charge. Proportions were compared using Fisher's exact test and continuous variables using student *t*-test. Multivariable regression was performed.

RESULTS

From the 36480032 hospitalizations in 2012 in the United States, 6248 were included in the study (3065 in July/August/September and 3183 in April/May/June) in the 2012 academic year. Compared with patients admitted in July/August/September, patients admitted in April/May/June had no statistical difference in all variables including mean age, percent female, Charleston comorbidity index, race, median income, and hospital characteristics including region, bed size, and location. Incidence of post-ERCP pancreatitis in early *vs* late academic year were not statistically significant (OR = 1.03, 95%CI: 0.71-1.51, *P* = 0.415). Similarly, the adjusted odds ratio of mortality, LOS, and total hospitalization charge in early compared to late academic year were not statistically significant.

CONCLUSION

Incidence of post-ERCP pancreatitis does not differ at academic institutions depending on the time of year. Similarly, mortality, LOS, and total hospital charge do not demonstrate the existence of a temporal effect, suggesting that trainee level of experience does not impact clinical outcomes in patients undergoing ERCP.

Key words: Pancreatitis; Academic training; Endoscopic retrograde cholangiopancreatography; Endoscopy; July effect

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Core tip: The changeover of medical trainees has been shown to negatively impact patient care. At academic institutions, endoscopic retrograde cholangiopancreatography (ERCP) involves advanced endoscopy fellows, and outcomes may vary based on the time of year. We assessed the incidence of post-ERCP pancreatitis in the early *vs* the late academic year and evaluated in-hospital mortality, length of stay (LOS), and total hospitalization charge between these time periods. We found that the incidence of post-ERCP pancreatitis in early *vs* late academic year were not statistically significant. Furthermore, mortality, LOS, and total hospitalization charge in early compared to late academic year were not statistically significant.

Schulman AR, Abougergi MS, Thompson CC. Assessment of the July effect in post-endoscopic retrograde cholangiopancreatography pancreatitis: Nationwide Inpatient Sample. *World J Gastrointest Endosc* 2017; 9(7): 296-303 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v9/i7/296.htm> DOI: <http://dx.doi.org/10.4253/wjge.v9.i7.296>

INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is frequently used for the diagnosis and management of many biliary and pancreatic diseases. Pancreatitis is the most common and serious complication of ERCP, accounting for more than half of all complications following this procedure^[1-3]. The estimated incidence of post-ERCP pancreatitis (PEP) varies substantially and is reported to be between 1% to 15%, with select studies reporting incidences as high as 30% in some populations^[4,5]. While the majority of PEP is mild, up to 20% of reported cases are moderate or severe^[6], and in some instances even fatal^[4]. In a small number of patients, it can lead to prolonged hospitalizations, anatomical complications such as bile duct or duodenal obstruction, pseudoaneurysms, and pseudocysts, as well as a significant financial burden to hospitals^[7].

The changeover of medical trainees at the beginning of the academic year has been shown in a variety of settings to negatively impact the quality of patient care, an observation referred to as the "July effect"^[8-10]. Although results have been substantially variable across studies addressing the July effect, most large and high-quality studies find a relatively small but statistically significant increase in mortality at the start of the academic year across multiple medical conditions^[10-14]. Furthermore, numerous studies have demonstrated decreased efficiency in healthcare delivery during turnover months in teaching hospitals as demonstrated by increased length of hospital stay (LOS) and increased mean total hospitalization charges^[15-19].

At teaching institutions, ERCP involves the participation of advanced endoscopy fellows who are trainees with minimal experience with this procedure, especially at the commencement of the academic year. These fellows are expected to gradually gain mastery and independence in performing ERCP. This learning curve is particularly relevant since several studies have shown that a number of endoscopic technique-related factors predict the occurrence of PEP. For example, papillary trauma induced by multiple attempts at cannulation was reported to be an independent risk factor for development of this complication in a large, prospective, multicenter study^[20]. Furthermore, multiple pancreatic injections and pancreatic duct instrumentation have also been identified as factors that independently increase the risk of PEP^[21].

These findings support the fact that physician technique, expertise, and experience may play a role in the occurrence of PEP. Consequently, outcomes may vary based on the time of year during which the procedure is performed. Specifically, the incidence of PEP may decrease at the end of the academic year when the advanced endoscopy fellows are more seasoned and possess enhanced procedural skills.

Large national databases are ideal resources for

addressing such clinical questions because they contain sufficient data to overcome participation and reporting biases, and the results are readily generalizable. We used the National Inpatient Sample (NIS), the largest publically available all-payer inpatient database in the United States. The primary aim of the current study is to assess incidence of PEP among hospitalized patients in the early (July/August/September) vs the late (April/May/June) academic year. Secondary aims assess in-hospital mortality, length of stay (LOS), and total hospitalization charges between these time periods.

MATERIALS AND METHODS

Data source

This was a retrospective cohort study using the 2012 National Inpatient Sample (NIS) database. This database was created and is maintained by the Agency for Healthcare Research and Quality. It is the largest publically available all-payer inpatient database in the United States. The NIS is designed as a stratified probability sample to be representative of all non-federal acute care inpatient hospitalizations in the United States. Briefly, hospitals are stratified according to ownership/control, bed size, teaching status, urban/rural location, and geographic region. A random 20% sample of all discharges from all participating hospitals within each stratum is then collected and information about patients' demographics, diagnoses, resource utilization including length of hospital stay, procedures and total hospitalization charges are entered into the NIS. Each discharge is then weighted (weight is equal to the total number of discharges from all acute care hospital in the United States divided by the number of discharges included in the 20% sample) to make the NIS nationally representative. In 2012, the NIS included 7296968 discharges from 4378 hospitals in 44 states.

The NIS contains both patient and hospital level information. Up to 25 discharge diagnoses and 15 procedures are collected on each patient using the International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9 CM) coding system. The NIS has been used to provide reliable estimates of the burden of gastrointestinal diseases^[22,23].

Study sample

Patients were included in the study if they had an ICD-9 CM procedure codes for ERCP. Patients were excluded from the study if they had an ICD-9 CM code for a principal diagnosis of acute pancreatitis, if the ERCP was performed before or on the day of admission or if they were admitted to non-teaching hospitals. Post-ERCP pancreatitis was defined as an ICD-9 CM code for a secondary diagnosis of acute pancreatitis in patients who received an ERCP as delineated above. ERCPs performed during the months of July, August and September was compared to those performed in April, May and June in academic hospitals.

Study variables

Admission month, vital status at discharge, length of hospital stay and total hospitalization charges are directly provided in the NIS for each hospitalization. Patient demographics collected are: Age (assessed as a continuous variable), sex, race (Caucasian, African American, Hispanic, Asian or Pacific Islander, native American and other), median income in the patient's zip code (Quartile 1: \$1-\$38999; Quartile 2: \$39000-\$47999; Quartile 3: \$48000-\$63999; quartile 4: \$64000+), primary insurance (Medicare, Medicaid, private insurance and uninsured), comorbidities measured by Charlson comorbidity index (categorized as 0, 1 to 2, or greater than 2), hospital location (rural vs urban), region (North-east, Midwest, West, or South), teaching status, and size (small, medium or large). Patients' demographics were directly provided in the NIS except for Charlson comorbidity index which was calculated for each patient using the Deyo adaptation of the Charlson comorbidity Index for administrative data^[24].

Outcomes

The primary outcome was incidence of post-ERCP pancreatitis. Secondary outcomes were: All cause in-hospital mortality, length of hospital stay (LOS) and total hospitalization charges for patients who developed PEP.

Statistical analysis

Proportions were compared using Fisher's exact test and continuous variables were compared using Student's *t*-test (under the assumption of the Central Limit Theorem). Confounders were adjusted for using multivariable regression models. Linear regression was used for continuous outcomes and logistic regression was used for binary outcomes. Each model was constructed by including all variables that were statistically significantly associated with the outcome on univariate analysis with a cutoff *P*-value of 0.2. In addition, variables that were considered clinically important predictors of the outcome based on prior studies' findings were included in the models irrespective of the *P*-value on univariate analysis. Patients with missing information on any of the variables included in the regression analyses were excluded.

All analyses were performed using STATA version 13 (STATACorpLP, College Station, TX, United States). Survey (svy) commands were used to account for the stratified sampling design of the NIS. A two tailed *P*-value of 0.05 was chosen as the threshold for significance for all tests.

The statistical methods of this study were reviewed by Marwan Abougergi from Catalyst Medical Consulting.

RESULTS

Patient characteristics

Figure 1 shows the flow diagram for study inclusion. From the 36480032 hospitalizations in 2012 in the

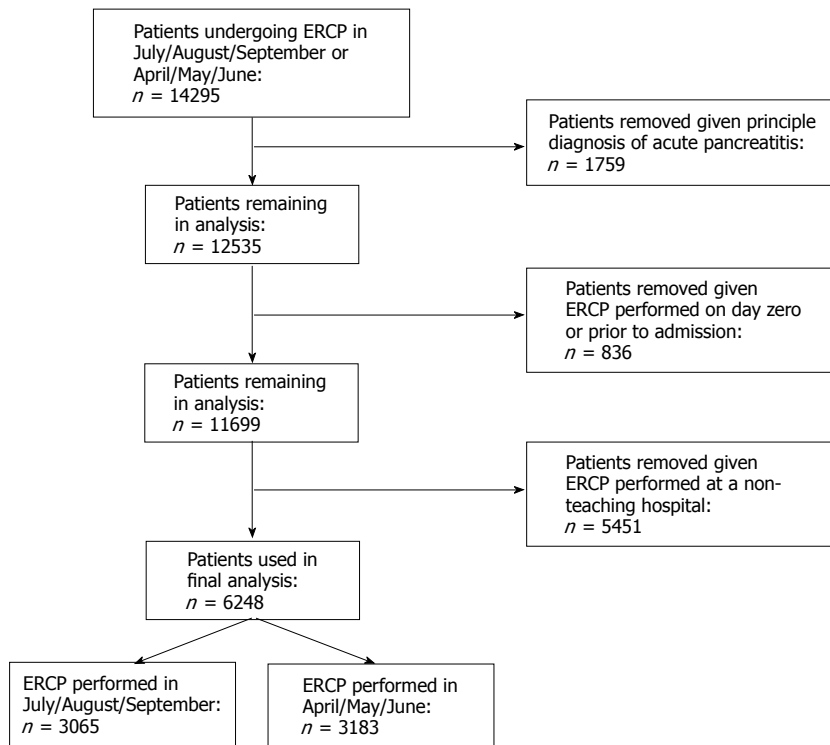


Figure 1 Flow diagram demonstrating selection of patients. ERCP: Endoscopic retrograde cholangio-pancreatography.

United States, 6248 were included in the study (3065 in July/August/September and 3183 in April/May/June) in the 2012 academic year. Patient's characteristics are presented in Table 1. Compared with patients admitted in July/August/September, patients admitted in April/May/June had no statistical difference in all variables including mean age, percent female, Charleston comorbidity index, race, median income, and hospital characteristics including region, bed size, and location.

Incidence of post-ERCP pancreatitis based on time during academic year

The overall post-ERCP pancreatitis incidence was 12.9%. Table 2 shows the post-ERCP pancreatitis incidence based on time of the academic year, as well as the adjusted odds ratio of PEP. Compared with patients admitted in July/August/September, patients admitted in April/May/June had similar odds of developing PEP after adjusting for confounders (adjusted OR = 1.03, 95%CI: 0.71-1.51; $P = 0.41$).

Mortality following post-ERCP pancreatitis based on time during academic year

The overall mortality rate following PEP was 19/801 = 2.37%. Table 3 shows the mortality rate following post-ERCP pancreatitis based on time of the academic year along with the mortality adjusted odds ratio. The adjusted odds of mortality following PEP was similar in April/May/June compared with July/August/September (adjusted OR = 33.2, 95%CI: 0.55-1980.7; $P = 0.09$).

Length of hospital stay following post-ERCP pancreatitis based on time during academic year

Following PEP, the overall LOS was 10.48 d. The mean

adjusted LOS following post-ERCP pancreatitis based on time of the academic year along with the mean additional LOS for patients admitted in July/August/September compared with April/May/June are shown in Table 4. The adjusted mean LOS following PEP was similar in July/August/September compared with April/May/June, with an adjusted mean difference of 2.04 d, 95%CI: -0.76 to 4.84; $P = 0.15$.

Total hospitalization charges for post-ERCP pancreatitis based on time of time academic year

The mean adjusted total hospitalization charges for patients who developed PEP was \$101218. The mean total hospitalization charges among patients who developed PEP in July/August/September and April/May/June are shown in Table 4. The adjusted mean total hospitalization charges were similar in July/August/September compared with April/May/June: \$20990, 95%CI: -563210 to 1434; $P = 0.24$.

DISCUSSION

This large nationwide study found no difference in incidence of post-ERCP pancreatitis following in-hospital ERCP at academic institutions over the course of the academic year. To our knowledge, this study is the first to address the presence, or lack thereof, of a July effect in the incidence and treatment of post-ERCP pancreatitis following in-hospital ERCP. It is also among the few studies that measures the PEP incidence rate after in-hospital ERCP. Our findings suggest that close supervision by attending endoscopists in the academic inpatient setting mitigates potential risks incurred by novice advanced endoscopy fellows, as evidenced by

Table 1 Baseline characteristics of patients included *n* (%)

Variable	July/August/ September	April/May/ June
Total number of ERCPs	3065	3183
Post-ERCP pancreatitis	404 (13.2)	402 (12.6)
Age (mean \pm SD)	58.9 \pm 0.8	59.5 \pm 0.9
Female	1672 (54.6)	1617 (50.8)
Charleston Comorbidity Score		
0	190 (6)	131 (4)
1-2	490 (16)	550 (17)
> 2	2385 (78)	2503 (79)
Race		
Caucasian	1834 (64)	1967 (66)
African American	395 (14)	441 (15)
Hispanic	411 (14)	311 (11)
Asian or Pacific Islander	123 (4)	96 (3)
Native American	15 (1)	23 (1)
Other	98 (3)	130 (4)
Median income (\$) in zip code		
1-38999	836 (28)	865 (28)
39000-47999	636 (22)	688 (22)
48000-63999	726 (24)	845 (27)
64000+	819 (27)	732 (23)
Hospital region		
Northeast	791.8 (26)	819.5 (26)
Midwest	679.2 (22)	918.1 (29)
South	997.6 (33)	925.5 (29)
West	596.9 (19)	520.4 (16)
Hospital bed size		
Small	293.2 (10)	343.3 (10)
Medium	680.2 (22)	728 (23)
Large	2092 (68)	2112 (67)
Hospital location		
Rural	43.2 (1)	20.4 (1)
Urban	3022 (99)	3163 (99)

ERCP: Endoscopic retrograde cholangiopancreatography.

similar PEP adjusted incidence across the academic year.

Whether these results are also true for PEP following outpatient ERCP is still controversial. Several smaller previous studies have sought to determine whether a difference in outcomes exists between ERCP that involves trainees and those that do not, and results have been inconsistent. The study by Freeman *et al* was among the first prospective studies investigating trainee participation in ERCP. Specifically, the authors measured the complications that occurred within 30 d of endoscopic biliary sphincterotomy in consecutive patients treated at 17 institutions over a two year period^[20]. The study failed to show an increased risk of adverse events including pancreatitis due the presence of a trainee. Subsequently, Rabenstein *et al*^[25] sought to analyze the risk factors associated with complications of endoscopic sphincterotomy in a series of 436 consecutive patients. While several independent risk factors for the development of PEP were identified, trainee involvement did not significantly affect the outcome. However, more recently, Cheng *et al*^[26] found that trainee involvement did increase the risk of PEP, and was attributed to a variety of procedural-related factors

Table 2 Incidence and incidence rates of patients who develop post-endoscopic retrograde cholangiopancreatography pancreatitis in the early vs late academic year

		Incidence <i>n</i> (%)	Adjusted OR (95%CI)	<i>P</i> value
July/August/ September	ERCPs performed	3065	1.03 (0.71-1.51)	0.415
	Post-ERCP	404 (13.2)		
	Pancreatitis rates			
April/May/ June	ERCPs performed	3183		
	Post-ERCP	402 (12.6)		
	Pancreatitis rates			

ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Mortality rate in patients who develop post-endoscopic retrograde cholangiopancreatography pancreatitis in the early academic year compared to the late academic year

	Mortality <i>n</i> /total	%	Adjusted OR (95%CI)	<i>P</i> value
July/August/September	5/404	1.24	33.2 (0.55-1980.7)	0.092
April/May/June	14/402	3.48		

Table 4 Length of stay and total hospitalization charges in patients who develop post-endoscopic retrograde cholangiopancreatography pancreatitis in the early academic year compared to the late academic year

	Length of stay		Total charges	
	Mean (95%CI) (d)	<i>P</i> value	Mean (95%CI) (\$)	<i>P</i> value
July/August/ September	10.6 (8.5-12.7)	0.91	101904 (78785-125023)	0.938
April/May/ June	10.4 (8.2-12.6)		100519 (70214-130824)	

including traumatic cannulation, prolonging a difficult cannulation, and delivering excess electrosurgical current during sphincterotomy.

Our data suggest that the overall efficiency of the hospital, similar to mortality rate, does not seem to exhibit a temporal effect. LOS and total hospital charge were not significantly increased at the beginning of the academic year, suggesting no effect on adeptness during turnover months at teaching hospitals. It is important to note that, since the number of patients who died following PEP was very low, the lack of difference in mortality at the beginning and the end of the academic year could be either due to a beta error or a true lack of difference. Case-control studies or cohort studies combining patients from the NIS over several years could help distinguish between these two possibilities. However, combining patients over several years has its own limitations, including the inherent necessity to adopt the assumption that time is not a

significant confounder in the relationship between PEP and mortality.

Several previous studies have examined length of hospital stay and hospitalization charge for a broad range of admission diagnosis as a marker for the July effect, and conflicting conclusions have been reached. In one multicenter retrospective study, LOS in the intensive care unit was examined and, after adjusting for illness severity, no differences in LOS were found between early and late academic year^[15]. Similarly, a single center study analyzing hospital LOS and ancillary charges in over 2700 patients admitted for any condition over a two year period found no evidence of a temporal effect^[27]. In contrast, a study in a single institution over seven years demonstrated a significant and steady decline in both total hospital charge and LOS for a variety of diagnoses over the academic year^[16]. For each additional month of house staff experience, total charges declined by approximately 0.94% in total charges, or about 11% during a one-year period. Furthermore, for each additional month of house staff experience, there was a 0.036-d decline in length of hospital stay, leading to a 0.43-d reduction during a one-year period.

Inexperienced fellow involvement in ERCP procedures has clear implications for patient outcomes, with the potential to lead to increased complications and higher medical expenditures. Our results, however, do not suggest that this is the case. We have demonstrated the lack of existence of a July effect. Novice fellow participation in these procedures at the beginning of the academic year does not seem to be associated with worse patient outcomes or increased charges compared to late academic year, when trainees have substantially more procedural experience. To clarify, these results do not suggest that novice endoscopists can safely perform ERCP in an unsupervised setting. However, the results of this study show that our current training method allows for the safe development of ERCP skills in a clinical setting, with close supervision from expert endoscopists.

Our study has several strengths. NIS is one of the largest medical databases in the United States, which allows for the analysis of health care practice patterns at the national level. Selection and participation biases, as well as regional variations in healthcare delivery and medical practice which commonly limit smaller studies, are minimized given that the sample is taken from a broad range of patient demographics and hospital characteristics from almost every state. Furthermore, the generalizability of the results to different hospitals and regions of the United States is tremendously enhanced for the same reason.

There are also several limitations of our study. First, some academic institutions may not have gastroenterology and/or advanced endoscopy fellowships, possibly diluting any effect that may be attributable to the involvement of a trainee. However, since caring for patients with PEP is a multi-disciplinary approach,

this fact should not have had a major impact on our outcomes, with the possible exception being PEP incidence. Second, there is no ICD-9 CM code specific for PEP pancreatitis. The definition we adopted (secondary diagnosis of pancreatitis for admissions during which ERCP was performed) could potentially include patients who had ERCP because of acute pancreatitis. However, we minimized this possibility by excluding patients who had a principal diagnosis of acute pancreatitis and limiting the inclusion to patients who had ERCP on day 1 of admission. Third, the severity of PEP is difficult to ascertain using ICD-9 codes, which lead us to restrict treatment outcomes to mortality only. Fourth, despite controlling for confounders and hospital characteristics, residual confounding is an inherent limitations to all retrospective studies where randomization is impossible. Fifth, while these results are compelling given the number of patients included in this database, we are unable to assess whether differences in technique affected PEP rates in this study. The NIS database does not allow the ability to control for factors that may affect the incidence of PEP but do not have a discrete ICD-9 code including inadvertent cannulation of the pancreatic duct, time until successful cannulation, use of sphincterotomy, degree of supervision by attending physician, and so on. Additionally, the database does not reveal the number of ERCPs performed for biliary vs pancreatic indications. Finally, coding errors have been shown to exist in the NIS data^[28]. However, such errors are theoretically randomly distributed among patients who had PEP early vs late in the academic year and therefore should not be a source of bias.

In conclusion, the safety of ERCP at academic institutions is consistent over the course of the year, with no difference in incidence or mortality following post-ERCP pancreatitis. Similarly, outcomes of healthcare delivery in the treatment of PEP are also steady across the academic year, as evidenced by similar LOS and total hospital charges. Our results suggest that trainee level of experience does not impact clinical outcomes in patients undergoing ERCP. As we train the next generation of endoscopic proceduralists, efforts to continue graduated responsibility, while maintaining optimal patient outcomes, will remain a top priority in the field of therapeutic endoscopy.

COMMENTS

Background

Endoscopic retrograde cholangiopancreatography (ERCP) is frequently used for the diagnosis and management of many biliary and pancreatic diseases. Pancreatitis is the most common and serious complication of ERCP. At teaching institutions, ERCP involves the participation of advanced endoscopy fellows who are trainees with minimal experience with this procedure, especially at the commencement of the academic year. As the changeover of medical trainees at the beginning of the academic year has been shown in a variety of settings to negatively impact the quality of patient care, an observation referred to as the July effect, they sought to determine whether a July effect existed with ERCP.

Research frontiers

The authors sought to determine whether a "July effect" existed with ERCP in

academic hospitals.

Innovations and breakthroughs

This large nationwide study found no difference in incidence of post-ERCP pancreatitis following in-hospital ERCP at academic institutions over the course of the academic year. To the knowledge, this study is the first to address the presence, or lack thereof, of a July effect in the incidence and treatment of post-ERCP pancreatitis following in-hospital ERCP.

Applications

These findings suggest that close supervision by attending endoscopists in the academic inpatient setting mitigates potential risks incurred by novice advanced endoscopy fellows, as evidenced by similar PEP adjusted incidence across the academic year. These results do not suggest that novice endoscopists can safely perform ERCP in an unsupervised setting. However, the results of this study show that the current training method allows for the safe development of ERCP skills in a clinical setting, with close supervision from expert endoscopists.

Terminology

ERCP is frequently used for the diagnosis and management of many biliary and pancreatic diseases. Pancreatitis is the most common and serious complication of ERCP, accounting for more than half of all complications following this procedure. This is referred to as post-ERCP pancreatitis (PEP).

Peer-review

This is a valuable paper, objectively reflects the incidence of PEP, and reveals no relationship with the beginner.

REFERENCES

- 1 **Abdel Aziz AM**, Lehman GA. Pancreatitis after endoscopic retrograde cholangio-pancreatography. *World J Gastroenterol* 2007; **13**: 2655-2668 [PMID: 17569133 DOI: 10.3748/wjg.v13.i19.2655]
- 2 **Freeman ML**, DiSario JA, Nelson DB, Fennerty MB, Lee JG, Bjorkman DJ, Overby CS, Aas J, Ryan ME, Bochna GS, Shaw MJ, Snady HW, Erickson RV, Moore JP, Roel JP. Risk factors for post-ERCP pancreatitis: a prospective, multicenter study. *Gastrointest Endosc* 2001; **54**: 425-434 [PMID: 11577302 DOI: 10.1067/mge.2001.117550]
- 3 **Christensen M**, Matzen P, Schulze S, Rosenberg J. Complications of ERCP: a prospective study. *Gastrointest Endosc* 2004; **60**: 721-731 [PMID: 15557948 DOI: 10.1016/S0016-5107(04)02169-8]
- 4 **Dumonceau JM**, Riphaus A, Aparicio JR, Beilenhoff U, Knappe JT, Ortmann M, Paspatis G, Ponsioen CY, Racz I, Schreiber F, Vilmann P, Wehrmann T, Wientjes C, Walder B. European Society of Gastrointestinal Endoscopy, European Society of Gastroenterology and Endoscopy Nurses and Associates, and the European Society of Anaesthesiology Guideline: Non-anaesthesiologist administration of propofol for GI endoscopy. *Eur J Anaesthesiol* 2010; **27**: 1016-1030 [PMID: 21068575 DOI: 10.1097/EJA.0b013e32834136bf]
- 5 **Freeman ML**, Guda NM. Prevention of post-ERCP pancreatitis: a comprehensive review. *Gastrointest Endosc* 2004; **59**: 845-864 [PMID: 15173799 DOI: 10.1016/S0016-5107(04)00353-0]
- 6 **Cotton PB**, Lehman G, Vennes J, Geenen JE, Russell RC, Meyers WC, Liguory C, Nickl N. Endoscopic sphincterotomy complications and their management: an attempt at consensus. *Gastrointest Endosc* 1991; **37**: 383-393 [PMID: 2070995 DOI: 10.1016/S0016-5107(91)70740-2]
- 7 **Hauser G**, Milosevic M, Stimac D, Zerem E, Jovanović P, Blazevic I. Preventing post-endoscopic retrograde cholangiopancreatography pancreatitis: what can be done? *World J Gastroenterol* 2015; **21**: 1069-1080 [PMID: 25632179 DOI: 10.3748/wjg.v21.i4.1069]
- 8 **Haller G**, Myles PS, Taffé P, Perneger TV, Wu CL. Rate of undesirable events at beginning of academic year: retrospective cohort study. *BMJ* 2009; **339**: b3974 [PMID: 19826176 DOI: 10.1136/bmj.b3974]
- 9 **Barzansky B**, Etzel SI. Medical schools in the United States, 2007-2008. *JAMA* 2008; **300**: 1221-1227 [PMID: 18780853 DOI: 10.1001/jama.300.10.1221]
- 10 **Young JQ**, Ranji SR, Wachter RM, Lee CM, Niehaus B, Auerbach AD. "July effect": impact of the academic year-end changeover on patient outcomes: a systematic review. *Ann Intern Med* 2011; **155**: 309-315 [PMID: 21747093 DOI: 10.7326/0003-4819-155-5-201109060-00354]
- 11 **Anderson KL**, Koval KJ, Spratt KF. Hip fracture outcome: is there a "July effect"? *Am J Orthop* (Belle Mead NJ) 2009; **38**: 606-611 [PMID: 20145785]
- 12 **Shuhaiber JH**, Goldsmith K, Nashef SA. Impact of cardiothoracic resident turnover on mortality after cardiac surgery: a dynamic human factor. *Ann Thorac Surg* 2008; **86**: 123-130; discussion 130-131 [PMID: 18573410 DOI: 10.1016/j.athoracsur.2008.03.041]
- 13 **Jen MH**, Bottle A, Majeed A, Bell D, Aylin P. Early in-hospital mortality following trainee doctors' first day at work. *PLoS One* 2009; **4**: e7103 [PMID: 19774078 DOI: 10.1371/journal.pone.0007103]
- 14 **Phillips DP**, Barker GE. A July spike in fatal medication errors: a possible effect of new medical residents. *J Gen Intern Med* 2010; **25**: 774-779 [PMID: 20512532 DOI: 10.1007/s11606-010-1356-3]
- 15 **Barry WA**, Rosenthal GE. Is there a July phenomenon? The effect of July admission on intensive care mortality and length of stay in teaching hospitals. *J Gen Intern Med* 2003; **18**: 639-645 [PMID: 12911646 DOI: 10.1046/j.1525-1497.2003.20605.x]
- 16 **Rich EC**, Gifford G, Luxenberg M, Dowd B. The relationship of house staff experience to the cost and quality of inpatient care. *JAMA* 1990; **263**: 953-957 [PMID: 2299762 DOI: 10.1001/jama.1990.03440070041029]
- 17 **Bakaen FG**, Huh J, LeMaire SA, Coselli JS, Sangsriy S, Atluri PV, Chu D. The July effect: impact of the beginning of the academic cycle on cardiac surgical outcomes in a cohort of 70,616 patients. *Ann Thorac Surg* 2009; **88**: 70-75 [PMID: 19559195 DOI: 10.1016/j.athoracsur.2009.04.022]
- 18 **Dhaliwal AS**, Chu D, Deswal A, Bozkurt B, Coselli JS, LeMaire SA, Huh J, Bakaen FG. The July effect and cardiac surgery: the effect of the beginning of the academic cycle on outcomes. *Am J Surg* 2008; **196**: 720-725 [PMID: 18789415 DOI: 10.1016/j.amjsurg.2008.07.005]
- 19 **Rich EC**, Hillson SD, Dowd B, Morris N. Specialty differences in the 'July Phenomenon' for Twin Cities teaching hospitals. *Med Care* 1993; **31**: 73-83 [PMID: 8417272 DOI: 10.1097/00005650-199301000-00006]
- 20 **Freeman ML**, Nelson DB, Sherman S, Haber GB, Herman ME, Dorsher PJ, Moore JP, Fennerty MB, Ryan ME, Shaw MJ, Lande JD, Pheley AM. Complications of endoscopic biliary sphincterotomy. *N Engl J Med* 1996; **335**: 909-918 [PMID: 8782497 DOI: 10.1056/NEJM199609263351301]
- 21 **Ding X**, Zhang F, Wang Y. Risk factors for post-ERCP pancreatitis: A systematic review and meta-analysis. *Surgeon* 2015; **13**: 218-229 [PMID: 25547802 DOI: 10.1016/j.surge.2014.11.005]
- 22 **Go JT**, Vaughan-Sarrazin M, Auerbach A, Schnipper J, Wetterneck TB, Gonzalez D, Meltzer D, Kaboli PJ. Do hospitalists affect clinical outcomes and efficiency for patients with acute upper gastrointestinal hemorrhage (UGIH)? *J Hosp Med* 2010; **5**: 133-139 [PMID: 20235292 DOI: 10.1002/jhm.612]
- 23 **Wolf AT**, Wasan SK, Saltzman JR. Impact of anticoagulation on rebleeding following endoscopic therapy for nonvariceal upper gastrointestinal hemorrhage. *Am J Gastroenterol* 2007; **102**: 290-296 [PMID: 17100959 DOI: 10.1111/j.1572-0241.2006.00969.x]
- 24 **Deyo RA**, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol* 1992; **45**: 613-619 [PMID: 1607900 DOI: 10.1016/0895-4356(92)90133-8]
- 25 **Rabenstein T**, Schneider HT, Bulling D, Nicklas M, Katalinic A, Hahn EG, Martus P, Ell C. Analysis of the risk factors associated with endoscopic sphincterotomy techniques: preliminary results of a prospective study, with emphasis on the reduced risk of acute pancreatitis with low-dose anticoagulation treatment. *Endoscopy* 2000; **32**: 10-19 [PMID: 10691266 DOI: 10.1055/s-2000-138]
- 26 **Cheng CL**, Sherman S, Watkins JL, Barnett J, Freeman M, Geenen J, Ryan M, Parker H, Frakes JT, Fogel EL, Silverman WB,

- Dua KS, Aliperti G, Yakshe P, Uzer M, Jones W, Goff J, Lazzell-Pannell L, Rashdan A, Temkit M, Lehman GA. Risk factors for post-ERCP pancreatitis: a prospective multicenter study. *Am J Gastroenterol* 2006; **101**: 139-147 [PMID: 16405547 DOI: 10.1111/j.1572-0241.2006.00380.x]
- 27 **Buchwald D**, Komaroff AL, Cook EF, Epstein AM. Indirect costs for medical education. Is there a July phenomenon? *Arch Intern Med* 1989; **149**: 765-768 [PMID: 2495778 DOI: 10.1001/archinte.1989.00390040007001]
- 28 **Berthelsen CL**. Evaluation of coding data quality of the HCUP National Inpatient Sample. *Top Health Inf Manage* 2000; **21**: 10-23 [PMID: 11143275]

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Retrospective Cohort Study

**Efficacy of a newly developed dilator for endoscopic
ultrasound-guided biliary drainage**

Yoshihide Kanno, Kei Ito, Shinsuke Koshita, Takahisa Ogawa, Kaori Masu, Yoshiharu Masaki, Yutaka Noda

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Author contributions: Kanno Y designed research and wrote the manuscript; Kanno Y, Ito K, Masu K and Masaki Y performed the research; Kanno Y, Koshita S, Ogawa T and Noda Y analyzed the data.

Institutional review board statement: Institutional review board approved this study.

Informed consent statement: All study participants or their legal guardian provided informed written consent about personal and medical data collection prior to study enrolment.

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Data sharing statement: The original anonymous dataset is available on request from the corresponding author at yoshi-hk@openhp.or.jp.

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Abstract**AIM**

To evaluate the efficacy of a newly developed dilator for endoscopic ultrasound (EUS)-guided drainage (ES Dilator).

METHODS

Fourteen consecutive patients who had undergone EUS-guided choledochoduodenostomy (EUS-CDS) with the ES Dilator were identified from a prospectively maintained database and enrolled in the study group. Fourteen other patients who had undergone EUS-CDS without the dilator just prior to its introduction were analyzed as the control group. A historical cohort study was carried out comparing the two groups. The main outcome measurement was the procedure time. The technical success rate and early AE rate were also compared between the two groups.

RESULTS

There were no significant differences in age, sex and etiology of biliary obstruction. The utilization rate of a plastic stent was higher in the control group (36% vs 0%). The technical success rate was 100% in both groups. The mean procedure time was significantly shorter in the study group than in the control group (27 ± 7 min vs 44 ± 26 min, $P = 0.026$). Additionally, there were no patients who required more than 40 min for the procedure in the study group. Early adverse events occurred in 29% (4/14) of the control group whereas none in the study group. The adverse events in all 4 patients was bile peritonitis, including pan-peritonitis in one patient. All patients

recovered with conservative treatment by medication.

CONCLUSION

The newly developed dilator was found to be useful for shortening procedure time and would prevent adverse events related to bile leakage in EUS-CDS.

Key words: Endoscopic ultrasound; Dilation; Adverse event; ES Dilator; Cautery

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Core tip: The newly developed dilator (ES Dilator®) was useful for shortening procedure time and would prevent adverse events related to bile leakage in endoscopic ultrasound-guided choledochoduodenostomy.

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INTRODUCTION

Endoscopic ultrasound (EUS)-guided biliary drainage (EUS-BD) is a challenging palliative treatment for biliary obstruction in patients who have unsuccessfully undergone transpapillary stenting^[1]. Despite its difficulty, the technical success rate of this procedure is over 90% according to reports from high volume centers, which seems sufficiently high and acceptable^[2-4]. When EUS-BD has been successfully accomplished, biliary decompression is achieved in most patients^[2,5,6]. Moreover, the patency of the deployed stent is expected to be reasonably long^[2,5,6].

EUS-BD can cause some adverse events (AEs) induced by bile leakage. Although bile always leaks in varying degrees in EUS-BD, a lesser amount of bile leakage may result in fewer AEs, including peritonitis and biloma formation.

Bile leakage occurs between puncture of the bile duct and stent deployment at the puncture tract, and thus shortening of the procedure time between puncture and stenting would contribute to less bile leakage. One of the most important factors resulting in longer procedure time is the difficulty of dilation of the puncture tract. When the dilation is unimpededly achieved, EUS-BD would be smoothly performed in many cases.

Recently, a new dilator for smooth dilation of the puncture tract has been developed. In this study, the efficacy of this dilator in EUS-guided choledochoduodenostomy (EUS-CDS) was evaluated.

MATERIALS AND METHODS

Patients

Fourteen consecutive patients who had undergone EUS-CDS utilizing the new dilator for malignant biliary obstruction at Sendai City Medical Center (Sendai, Japan) between November 2012 and January 2016 were identified from a prospectively maintained database and enrolled in the study group. Fourteen other consecutive patients who had undergone EUS-CDS without the dilator just prior to its introduction between February 2010 and October 2012 were analyzed as a control group. This retrospective study was conducted after approval by the Sendai City Medical Center Institutional Review Board. The ID issued by UMIN was 000020772.

Dilator

The newly developed dilator, ES Dilator® (Zeon Medical Co., Tokyo, Japan), 7 French (Fr) in diameter, is characterized by high pushability and a lesser difference in diameters of the inner lumen and the guidewire (Figure 1). It has two types of internal diameter tailored to accommodate 0.025-inch and 0.035-inch guidewires. The ES Dilator was utilized in all patients after its use was commenced in November 2012. It is commercially available in Japan.

Procedures

With a linear echoendoscope (UC240P or UCT260, Olympus Medical Systems Co., Tokyo, Japan), the extrahepatic bile duct was punctured from the duodenum by a 19-gauge needle for endosonography-guided fine needle aspiration (EUS-FNA) (EchoTip, Cook Co. Bloomington, Indiana; or Expect, Boston Scientific, Natick, Massachusetts). After contrast medium had been injected into the bile duct, a guidewire was advanced to the hilar side. After the puncture tract was dilated along the guidewire, a stent was finally placed at the puncture site (Figure 2).

Prior to the availability of the ES Dilator in November 2012, dilation was performed with a 5- to 7-French tapered catheter, including a Soehendra dilator (Boston Scientific), and a 4-mm balloon dilator. After November 2012, insertion of the ES Dilator was initially attempted in all patients in the study group. When dilation was not achieved with these catheters, a cautery dilator was utilized.

Procedures were performed by one of 6 expert endoscopists who had experience performing 10 or more EUS-guided drainage procedures as an operator or assistant. All of them had also experienced more than 1000 endoscopic retrograde cholangiopancreatography (ERCP) procedures and 1000 EUS examinations as an operator.

Study design

A historical cohort study was carried out, the population

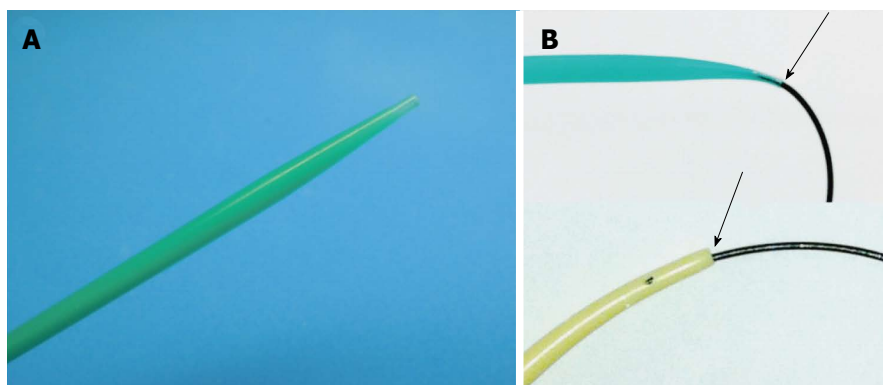


Figure 1 Newly developed dilator, ES Dilator® (Zeon Medical Co., Tokyo, Japan), characterized by high pushability and lesser difference in diameters of the inner lumen and the guidewire. A: Tip of the ES Dilator; B: The ES Dilator has a lesser difference between the diameter of the inner lumen and that of the guidewire (upper figure), compared with traditional tapered catheters for ERCP (lower figure). ES Dilator: Endoscopic ultrasound-guided drainage; ERCP: Endoscopic retrograde cholangiopancreatography.

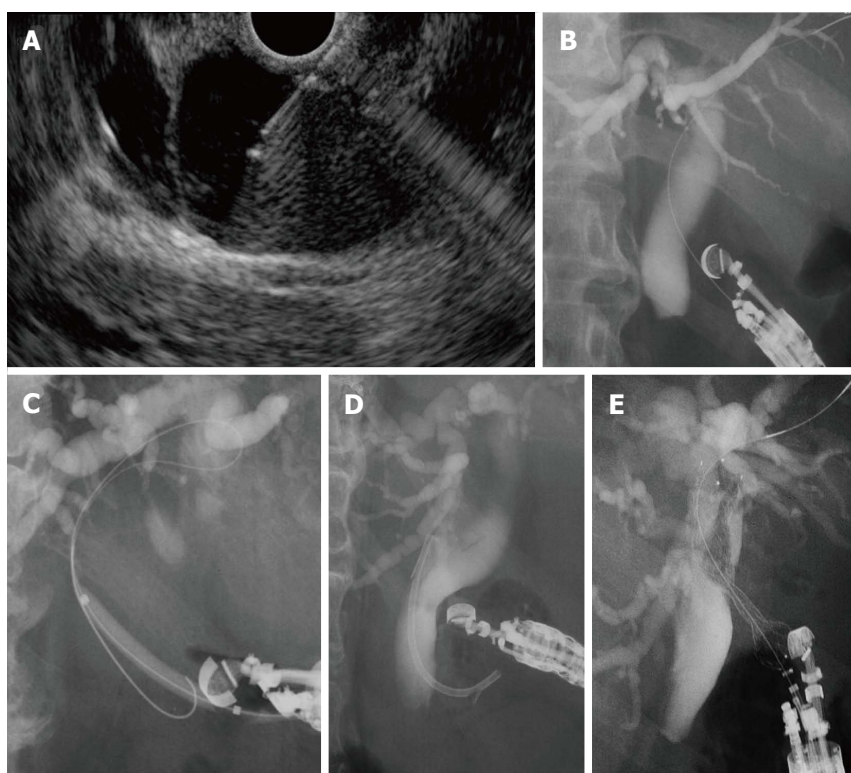


Figure 2 Technique of endoscopic ultrasound-guided choledochoduodenostomy. A: The extrahepatic bile duct is punctured by a 19-gauge needle under EUS guidance; B: After contrast medium is injected, a guidewire is inserted; C: The puncture tract is dilated with a tapered catheter, a balloon dilator, and/or ES Dilator; D and E: A plastic stent (D) or a metal stent is deployed at the puncture site (E). EUS: Endoscopic ultrasound.

being divided into a control group consisting of 14 patients who received the intervention without use of the ES Dilator and a study group of 14 patients in whom the dilator was used.

Procedure time was defined as the main outcome measure. The technical success rate and early AE rate were also compared between the two groups.

Early AEs investigated included bile peritonitis, biloma formation, hemorrhage requiring endoscopic/radiological/surgical intervention or blood transfusion, stent dislocation within 7 d, and procedure-related death. Bile peritonitis was defined as a state with abdominal tenderness accompanied by peritoneal symptoms which

appeared within 24 h after the intervention.

Statistical analysis

Student's *t*-test was used for continuous data comparison. Fisher's exact probability test and χ^2 test were used for comparison of categorical data. A *P*-value of < 0.05 was considered to be significant. For analyses, SPSS software (ver.11, SPSS, Chicago, IL, United States) was used.

RESULTS

The patient characteristics of the two groups are shown

Table 1 Patient characteristics and deployed stents

	Study group (<i>n</i> = 14)	Control group (<i>n</i> = 14)	<i>P</i> value
Age (yr), mean ± SD	74.6 ± 16.1	73.5 ± 9.3	0.82
Sex (male:female)	9:5	8:6	1.00
Etiology			0.28
Pancreatic cancer	8	12	
Biliary cancer	3	1	
Duodenal cancer	2	0	
Metastatic lymph nodes	1	1	
Deployed stent			0.041
Plastic stent	0	5	
Metal stent	14	9	

Table 2 Procedure time

	Study group (<i>n</i> = 14)	Control group (<i>n</i> = 14)	<i>P</i> value
Procedure time (min), mean ± SD	44 ± 26	27 ± 7	0.026
≤ 20	3	1	
20–40	11	8	
40–60	0	2	
> 60	0	3	

in Table 1. There were no significant differences in age, sex and etiology of biliary obstruction. The utilization rate of a plastic stent was higher in the control group. Plastic stents used in the control group were 7-Fr Flexima (Boston Scientific, Natick, Mass, United States). Metal stents, 10-mm covered Zeostents (a delivery system 8 Fr in diameter, Zeon Medical Co.) were used in all 9 patients of the control group and in 9 patients of the study group; 10-mm X-SuiteNIR stents (a delivery system approximately 7.5 Fr in diameter, Olympus Medical Systems Co.) were used in 3 patients of the study group; and 10-mm partially covered Niti-S stents (a delivery system approximately 8.5 Fr in diameter, TaeWoong Medical Co., Wolgot-myeon, South Korea) were used in 2 patients of the study group.

The technical success rate was 100% in both groups.

The procedure time was significantly shorter in the study group than in the control group (27 ± 7 min vs 44 ± 26 min, *P* = 0.026, Table 2). Additionally, there were no patients who required more than 40 min for the procedure in the study group.

Because neither a 5-French tapered catheter nor a balloon catheter could pass through the puncture tract, a cautery catheter was used in only one patient (7%) in the control group. In the study group, the ES Dilator passed through the puncture site on the first attempt and a cautery dilator was not used in any of the patients.

The mean procedure time in the patients who received metal stent placement in the control group was 38 ± 23 min. In comparison with the study group, it was also found to be shorter although the difference was not statistically significant (*P* = 0.18).

Early AEs occurred in 29% (4/14) in the control

Table 3 Procedure-related complications

	Study group (<i>n</i> = 14)	Control group (<i>n</i> = 14)	<i>P</i> value
Overall	0	4 (29%)	NA
Localized peritonitis	0	3	
Pan-peritonitis	0	1	
Hemorrhage	0	0	
Death	0	0	

NA: Not applicable.

group whereas no AEs occurred in the study group (Table 3). The AE in all 4 patients was bile peritonitis, including pan-peritonitis in one patient. All patients recovered with conservative treatment by medication. The procedure time in the 4 patients who developed peritonitis was 39, 45, 67, and 95 min. Among these 4 patients, a metal stent was deployed in 2 and a plastic stent in 2. The patients whose intervention required a longer procedure time (95 min) with a metal stent had severe pan-peritonitis although it did not progress to death.

DISCUSSION

Many reports on EUS-guided drainage have been published at an accelerated pace in the past decade^[1–4,7], and this procedure has rapidly superseded percutaneous biliary drainage as an alternative technique after failed ERCP^[4,8]. Some studies have reported that EUS-BD has a similar level of efficacy and results in fewer adverse events in comparison with percutaneous drainage^[9,10]. EUS-BD seems to be the palliative intervention of choice after failed ERCP in cases with malignant distal biliary obstruction^[9,10].

Due to a lack of dedicated devices for EUS-guided drainage, various devices developed for other endoscopic interventions, including EUS-FNA and ERCP, have been applied. Dilation of the puncture tract in EUS-CDS has been performed with tapered catheters and balloon catheters developed for the purpose of aspiration of bile or pancreatic juice, dilation of a biliary stricture, or endoscopic papillary balloon dilation in ERCP. However, they are inadequate for advancement into the narrow tract made by a fine needle because of their deficiency of stiffness and the difference of diameter between the inner lumen of the device and the guidewire. The ES Dilator seems to have resolved these problems.

Cautery devices would also be better in dilation of the puncture tract. It remains unknown whether physical dilation or electric dilation is more appropriate because there have been no studies comparing them. Cautery devices have not been initially used at our institution because an unexpected huge hole might be formed by electric ablation^[9]. However, such a device has been used initially in some institutions with a high success rate and low AE rate^[3,10]. Although there is a retrospective study reporting that electric dilation by a needle knife was the risk factor for postprocedural AEs, it is doubtful that mere needle-knife utilization was

actually related to AEs because it was used only when insertion of a 6-Fr tapered catheter failed^[2].

Whereas the ES Dilator shortens procedure time in EUS-CDS, such shortening would be uncertain in EUS-guided hepaticogastrostomy (EUS-HGS). EUS-HGS is considered to include other various factors relevant to longer procedure time, *i.e.*, difficulty in puncture of an appropriate hepatic duct, difficulty in guidewire insertion into the hilar side, and an inexpedient increase of the distance between the liver and the gastric wall which move apart from each other when a metal stent is advanced. Moreover, dilation of the puncture tract is often easier because of less mobility of the intrahepatic bile duct in EUS-HGS, whereas the extrahepatic bile duct can move and separate from the gastrointestinal wall in EUS-CDS. In addition, although the liver parenchyma always intervenes in the puncture tract and prevents bile leakage in EUS-HGS as in the case of percutaneous transhepatic gallbladder/biliary drainage, there is little intervening tissue in EUS-CDS, resulting in the likelihood of bile leakage. Thus, prevention of bile leakage is considered to be more essentially important in EUS-CDS than in EUS-HGS. Therefore, especially in EUS-CDS, the ES Dilator is considered to have a favorable effect, and thus this study was limited to EUS-CDS.

The ES Dilator, unfortunately, has an extremely low visibility of the fluoroscopic image. Although it did not seem to affect the procedural success rate and the adverse events rate, it would need to be improved.

The type of deployed stent can affect the procedural outcomes. Although covered metal stents are more difficult to advance through the narrow tract than plastic stents, the procedure time was significantly shorter in the study group in which all the patients underwent intervention with a covered metal stent. Additional dilation after dilation with the 7-Fr ES Dilator was unnecessary in all patients of the study group, indicating that the most important factor related to successful EUS-CDS is dilation just up to 7-Fr, not up to the diameter of the stent which is to be inserted. On the other hand, covered metal stents could limit bile leakage after stent deployment. It is also worth noting that the 2 patients among 4 who had peritonitis in the control group received intervention with a metal stent. Metal stents are not always advantageous in preventing bile peritonitis.

This study has some limitations, namely, it was a retrospective investigation with a small population. Additionally, the proficiency level of the endoscopist may have been associated with the shorter procedure time. Despite these limitations, the present data appear to be of value because this study was carried out at a referral center which had experienced more than 30 cases of successful EUS-guided drainage before the study period. It seems to be less valuable to prospectively carry out large population studies for evaluation of a mere dilator in a field which has been rapidly evolving regardless of the low number of such patients.

In conclusion, the newly developed ES Dilator which was dedicated to EUS-BD was found to be useful for shortening procedure time and may prevent AEs relevant to bile leakage in EUS-CDS.

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Dr. Naotaka Fujita, the former vice director of our center, made an enormous contribution to the development of the new dilator introduced in the present study. I would like to express my deepest gratitude to him.

COMMENTS

Background

Endoscopic ultrasound (EUS)-guided biliary drainage is now an alternative option when transpapillary drainage has failed. Due to the lack of dedicated devices for use in such cases, dilation of the punctured tract is often difficult, resulting in longer procedure time and adverse events.

Research frontiers

Many new devices have been developing for EUS-guided drainage.

Innovations and breakthroughs

The newly developed dilator characterized by high pushability and a lesser difference in diameter tailored to accommodate 0.025-inch and 0.035-inch guidewires has become available.

Applications

The dilator was found to be useful.

Peer-review

The authors reported a novel dilator for the use of EUS-guided choledochoduodenostomy (EUS-CDS). In this paper the authors retrospectively compare the incidence of complications in patients who palliatively underwent EUS-CDS with/without ES Dilator.

REFERENCES

- 1 **Horaguchi J**, Fujita N, Noda Y, Kobayashi G, Ito K, Obana T, Takasawa O, Koshita S, Kanno Y. Endosonography-guided biliary drainage in cases with difficult transpapillary endoscopic biliary drainage. *Dig Endosc* 2009; **21**: 239-244 [PMID: 19961522 DOI: 10.1111/j.1443-1661.2009.00899.x]
- 2 **Park DH**, Jang JW, Lee SS, Seo DW, Lee SK, Kim MH. EUS-guided biliary drainage with transluminal stenting after failed ERCP: predictors of adverse events and long-term results. *Gastrointest Endosc* 2011; **74**: 1276-1284 [PMID: 21963067 DOI: 10.1016/j.gie.2011.07.054]
- 3 **Hara K**, Yamao K, Niwa Y, Sawaki A, Mizuno N, Hijioka S, Tajika M, Kawai H, Kondo S, Kobayashi Y, Matumoto K, Bhatia V, Shimizu Y, Ito A, Hirooka Y, Goto H. Prospective clinical study of EUS-guided choledochoduodenostomy for malignant lower biliary tract obstruction. *Am J Gastroenterol* 2011; **106**: 1239-1245 [PMID: 21448148 DOI: 10.1038/ajg.2011.84]
- 4 **Dhir V**, Itoi T, Khashab MA, Park DH, Yuen Bun Teoh A, Attam R, Messallam A, Varadarajulu S, Maydeo A. Multicenter comparative evaluation of endoscopic placement of expandable metal stents for malignant distal common bile duct obstruction by ERCP or EUS-guided approach. *Gastrointest Endosc* 2015; **81**: 913-923 [PMID: 25484326 DOI: 10.1016/j.gie.2014.09.054]
- 5 **Yamao K**, Bhatia V, Mizuno N, Sawaki A, Ishikawa H, Tajika M, Hoki N, Shimizu Y, Ashida R, Fukami N. EUS-guided choledochoduodenostomy for palliative biliary drainage in patients with malignant biliary obstruction: results of long-term follow-up. *Endoscopy* 2008; **40**:

- 340-342 [PMID: 18389451 DOI: 10.1055/s-2007-995485]
- 6 **Horaguchi J**, Fujita N, Noda Y, Kobayashi G, Ito K, Koshita S, Kanno Y, Ogawa T, Masu K, Hashimoto S, Ishii S. Metallic stent deployment in endosonography-guided biliary drainage: long-term follow-up results in patients with bilio-enteric anastomosis. *Dig Endosc* 2012; **24**: 457-461 [PMID: 23078440 DOI: 10.1111/j.1443-1661.2012.01316.x]
- 7 **Giovannini M**, Moutardier V, Pesenti C, Bories E, Lelong B, Delperro JR. Endoscopic ultrasound-guided bilioduodenal anastomosis: a new technique for biliary drainage. *Endoscopy* 2001; **33**: 898-900 [PMID: 11571690 DOI: 10.1055/s-2001-17324]
- 8 **Artifon EL**, Aparicio D, Paione JB, Lo SK, Bordini A, Rabello C, Otoch JP, Gupta K. Biliary drainage in patients with unresectable, malignant obstruction where ERCP fails: endoscopic ultrasonography-guided choledochoduodenostomy versus percutaneous drainage. *J Clin Gastroenterol* 2012; **46**: 768-774 [PMID: 22810111 DOI: 10.1097/MCG.0b013e31825f264e]
- 9 **Itoi T**, Itokawa F, Sofuni A, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Moriyasu F. Endoscopic ultrasound-guided choledochoduodenostomy in patients with failed endoscopic retrograde cholangiopancreatography. *World J Gastroenterol* 2008; **14**: 6078-6082 [PMID: 18932289 DOI: 10.3748/wjg.14.6078]
- 10 **Hara K**, Yamao K, Hijioka S, Mizuno N, Imaoka H, Tajika M, Kondo S, Tanaka T, Haba S, Takeshi O, Nagashio Y, Obayashi T, Shinagawa A, Bhatia V, Shimizu Y, Goto H, Niwa Y. Prospective clinical study of endoscopic ultrasound-guided choledochoduodenostomy with direct metallic stent placement using a forward-viewing echoendoscope. *Endoscopy* 2013; **45**: 392-396 [PMID: 23338620 DOI: 10.1055/s-0032-1326076]

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Retrospective Study

Use of shape-from-shading to characterize mucosal topography in celiac disease videocapsule images

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Abstract**AIM**

To use a computerized shape-from-shading technique to characterize the topography of the small intestinal mucosa.

METHODS

Videoclips comprised of 100-200 images each were obtained from the distal duodenum in 8 celiac and 8 control patients. Images with high texture were selected from each videoclip and projected from two to three dimensions by using grayscale pixel brightness as the Z-axis spatial variable. The resulting images for celiac patients were then ordered using the Marsh score to estimate the degree of villous atrophy, and compared with control data.

RESULTS

Topographic changes in celiac patient three-dimensional constructs were often more variable as compared to controls. The mean absolute derivative in elevation was 2.34 ± 0.35 brightness units for celiacs vs 1.95 ± 0.28 for controls ($P = 0.014$). The standard deviation of the derivative in elevation was 4.87 ± 0.35 brightness units for celiacs vs 4.47 ± 0.36 for controls ($P = 0.023$). Celiac patients with Marsh III C villous atrophy tended to have the largest topographic changes. Plotted in two dimensions, celiac data could be separated from controls with 80% sensitivity and specificity.

CONCLUSION

Use of shape-from-shading to construct three-dimensional projections approximating the actual spatial geometry of the small intestinal substrate is useful to observe features not readily apparent in two-dimensional videocapsule images. This method represents a potentially helpful

adjunct to detect areas of pathology during videocapsule analysis.

Key words: Celiac disease; Duodenum; Shape-from-shading; Small intestine; Videocapsule

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Core tip: Videocapsule images can assist in determining the presence and status of celiac disease; however, pathology is not always apparent by visual inspection. A computerized shape-from-shading technique was used to characterize the topography of the small intestinal mucosa. It was hypothesized that the automated measure would be helpful to distinguish celiac from control images and to gauge the degree of villous atrophy in the celiac patient data.

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INTRODUCTION

Celiac disease is prevalent throughout the world and affects approximately 1% of the population^[1]. Patients with celiac disease are reactive to the protein gluten, which is present in wheat, rye, and barley grains^[2]. Currently, the only treatment is a lifelong gluten-free diet^[3]. It is a disease with often occult symptoms that differ from one individual to the next^[4]. Diagnosis of celiac disease is difficult owing to the fact that symptoms are highly varied from one individual to another, both in their type and severity. In some patients with celiac disease, no symptoms may be evident^[5]. Diagnosis is made by a positive antibody test, which is followed by biopsy of the abnormal appearing mucosa and confirmation of atrophy by light microscopy^[6]. Utilizing light microscopy, the small intestinal mucosa is evaluated for presence and degree of villous atrophy and an increase in intraepithelial lymphocytes. Mucosal alterations in celiac disease are assigned a Marsh score, which varies from 1 (normal villous architecture but increased intraepithelial lymphocytes) to IIIA-C (severe degrees of villous atrophy accompanied by crypt hyperplasia and increased intraepithelial lymphocytes)^[7].

Recent advances in imaging technology have enabled visualization of the small intestinal mucosa *via* a videocapsule to assess areas of villous atrophy^[8]. This is convenient to use and is minimally invasive. Images are obtained at a rate of 2 per second or more. A light source within the capsule illuminates the mucosal surface. The videocapsule is swallowed, sends information by radio control, and then passes harmlessly through the

gastrointestinal system^[9]. Analysis of two-dimensional videocapsule endoscopy images by quantitative means can assist in determining areas of pathology in these patients.

A difficulty with the use of videocapsule technology, is that areas of pathology are not always clearly identifiable on review of the images^[10]. The two-dimensional images provide a very limited perspective of the actual three-dimensional structure of the substrate when viewed retrospectively by the data analyst. The endoscopist who is performing the procedure, views these same images *via* an endoscopic system, and is similarly at a disadvantage for understanding the three-dimensional mucosal architecture. Hence, it can be difficult for both endoscopist and data analyst to determine the precise regions and boundaries of any abnormality that is present in the images. This renders the detection of regions of patchy villous atrophy, which are important to biopsy for confirmation that there is pathology, and therefore for diagnosis of the disease and to monitor treatment, difficult at best.

For improved analysis, it would be useful to provide additional information regarding the mucosal substrate throughout the small intestine^[11,12]. If it were possible to estimate the three-dimensional architecture of this substrate, and render it visually, it could be useful for improved detection of the presence and severity of villous atrophy, to detect any changes in architecture that occur after onset of a gluten-free diet, as well as to understand the mechanisms by which the structure of the small intestinal mucosa is altered during untreated vs treated celiac disease. In prior quantitative studies, a method was introduced to estimate three-dimensional structure from two-dimensional endoscopic images^[13,14]. This technique uses the principle of shape-from-shading. In the shape-from-shading process, as a first approximation, image brightness is linearly related to image depth. Thus a third spatial axis, the Z-axis, is obtained so that a map of the three-dimensional structure of the substrate can be constructed. In this study, the visual manifestations of three-dimensional image projection are shown for celiac patients with various levels of villous atrophy, vs controls. Special attention is paid to the types of structures that are evident in the projections, and their variation from one patient to the next, which can be helpful to detect the presence and severity of villous atrophy during the diagnosis of celiac disease, and to evaluate treatment efficacy. The purpose of the study is to show that visualization of the three-dimensional architecture can be useful to detect pathology in the small intestinal mucosa when the presence of patchy villous atrophy is suspected.

MATERIALS AND METHODS

A retrospective data series from 8 celiac patients and 8 controls were used for analysis. All patients were evaluated at the Columbia University Medical Center,

New York, NY using both standard and videocapsule endoscopy. Suspected celiac patients were diagnosed by the presence of villous atrophy in standard endoscopy images and improvement on follow-up endoscopy after onset of the gluten free diet. The indication for endoscopy in control patients included obscure bleeding, suspected Crohn's disease, and diarrhea. The study exclusion criteria were patients less than 18 years of age, pregnancy, history of intestinal obstruction, presence of a pacemaker, and chronic use of non-steroidal anti-inflammatory drugs. Only studies in which the videocapsule reached the cecum were included for analysis. All included patients, except one celiac patient with hemophilia, first underwent a standard endoscopic procedure with biopsy to determine the presence and severity of any villous atrophy in the proximal duodenum. The patients then underwent videocapsule endoscopy.

Videocapsule endoscopy images were acquired using the PillCam SB2 videocapsule (Given Imaging, Yoqneam, Israel). The device included a recorder unit and its container, battery pack, antenna, harness for the recorder unit, and a battery charger. The capsule dimensions were 26 mm × 11 mm, and the frame rate for acquisition was two digital images per second (2/s). After a 12 h overnight fast, all subjects swallowed the PillCam SB2 videocapsule with 200 cc water and 80 mg of simethicone. Subjects were permitted to drink water at 2 h following ingestion of the capsule, and to eat a small meal after 4 h. The data recorder was affixed to a belt worn by the patient, and received radio image signals transmitted by the videocapsule *via* an array sensor as it passed through the gastrointestinal tract. The videocapsule endoscopy images were recorded over an eight hours period. At the end of eight hours, the images were offloaded to a PC-type computer workstation. The videos were subsequently interpreted using Rapid5 software (Given Imaging, Yoqneam, Israel) by gastroenterologists, each with experience in reading many videocapsule endoscopies.

Videoclips of length 100-200 images (50-100 s at 2/s frame rate) were obtained from the distal duodenum in each patient and were deidentified prior to analysis. The use of patient data and the analysis protocols were approved by the Institutional Review Board of Columbia University Medical Center. The quantitative biopsy results obtained during standard endoscopy were used as a reference as to the presence and severity of villous atrophy.

An algorithm was developed to convert the two-dimensional endoscopic images from color to grayscale, and then to project to three dimensions using the shape-from-shading technique. The algorithm used in this study can be described as follows^[13,14]: (1) at each pixel (*x*, *y*) location, extract the grayscale brightness level; (2) write brightness level *b*, which ranges from 0-255 (black to white), to file along with (*x*, *y*) location; (3) the format of the stored information is trivariate (*x*, *y*, *b*); (4) all (*x*, *y*, *b*) information for all image pixels (*x*, *y*),

with the dimensions of the image being 576 × 576, are written to file; (5) display the file in map3d, a program which enables viewing of three-dimensional data objects from any perspective^[15]; (6) separately, store the trivariate information along with the brightness value, *i.e.*, as (*x*, *y*, *b*, *b*) where the fourth variable is used as a false color for enhanced display; and (7) organize the original two-dimensional endoscopic image, the three-dimensional projection, and the false-color three-dimensional image according to Marsh score pathology for the celiac patients, vs the control patients.

Once the data were displayed, special attention was given to the presence of certain three-dimensional structures that had been quantitatively modeled by syntactic means in prior work^[13]. Specifically, the characteristics of mucosal protrusions present in the mucosa were assessed, highlighting differences in celiac patients with villous atrophy (Marsh IIIA, IIIB, or IIIC score) and celiac patients with little or no evident villous atrophy (Marsh II score) vs control patients lacking villous atrophy. The Marsh score was determined by the pathologist, who evaluated biopsy specimens for the presence of villous atrophy under light microscopy.

From the three-dimensional constructs, topographic variation was calculated using a computerized method. The first derivative of the elevation level of each image pixel, done row-by-row in an automated raster scan fashion, was determined. The mean absolute value of this derivative was used as one measure of topographic variation. The standard deviation of the absolute derivative was used as a second measure of topographic alteration. The mean and standard deviation of these parameters were calculated for celiac vs control image data, and the statistical significance of the difference was determined using the two-tailed *t*-test (SigmaPlot ver. 13, 2016, Systat Software Inc., San Jose, California). The parameter values were plotted, with celiac data labeled according to the Marsh score. The best linear discriminant function to separate celiac vs control data was determined, and the sensitivity and specificity for detecting pathology in celiacs, vs the lack of pathology in control patient images, were calculated.

RESULTS

The patient data used in the study are depicted in Tables 1 and 2. Information regarding the age, gender and Marsh score of small intestinal biopsies of celiac patients is shown in Table 1. Six of eight patients (75%) were female. The average age of all celiac patients was 45.8 ± 14.8. The Marsh score of patient 1, who had hemophilia, could not be determined precisely as a biopsy could not be obtained, but significant pathology was apparent from visual inspection of the endoscopic images. This patient was estimated to have Marsh III C pathology. Analysis of biopsy results revealed there were two additional patients with Marsh score pathology of III C, one with II B, two with III A, and two with a Marsh score of II. The control patient data is shown in

Table 1 Patient data - celiac

Number	Age	Gender	Marsh score
1	19	M	NA
2	44	M	III C
3	44	F	III C
4	40	F	III B
5	63	F	III A
6	38	F	III A
7	53	F	II
8	65	F	II

Patient 1 had hemophilia and had no biopsy, but was suspected to have a Marsh III C level of villous atrophy. NA: Not applicable, *i.e.*, no biopsy was performed; M: Male; F: Female.

Table 2. There were four male and four female control patients, with an average age of 48.1 ± 25.3 , similar to the average age of the celiac patients. Three of the control patients received the videocapsule because of abdominal pain presumed to be due to peptic duodenitis, two for suspected Crohn's disease, and one each for inflammation of the esophagus due to reflux, severe esophagitis, and obscure bleeding. None of the control patients had any evidence of villous atrophy on biopsy.

Examples of image processing results are shown in Figures 1 and 2 for celiac patient images (Patients 1 and 2), each from a region of the distal duodenum with high apparent texture and pathology. The data from two patients is shown in each image. In Figure 1 are shown images from a patient with Marsh III C pathology score, and from the patient with hemophilia, who has similar apparent severe pathology and likely Marsh III C score. The two-dimensional endoscopic image is to the left for each patient data. There are similar appearances in rough texture, and the images are thought to have been acquired from regions with villous atrophy. Some scalloping of the mucosal folds is apparent in the celiac patient with Marsh III C score at lower left in the image, for example at the fold noted by the asterisk. The three-dimensional projection using shape-from-shading is provided at center. Large protrusions are evident throughout each three-dimensional construction. For perspective, the same location noted by an asterisk in the left panel is shown in the center panel for patient 2.

Depicted in the right-hand panel are smoothed three-dimensional projections with false color used to show depth. Again for perspective, the location of the scalloped area with asterisk is shown. The highest area in the false color three-dimensional image at right corresponds to the brightest area in the two-dimensional endoscopic image at left (triangular shaped ridge at upper center). Mucosal folds in the two-dimensional endoscopic images of both patients are readily identifiable as three-dimensional structures in the projection panels at center and right. The large fold at top in the two-dimensional endoscopic image of patient 1 is evident as a large mass of three-

Table 2 Patient data-control

Number	Age	Gender	Marsh score
1	31	F	Suspected Crohn's disease
2	36	M	Severe esophagitis
3	36	F	Peptic duodenitis
4	86	F	Obscure bleeding
5	26	F	Peptic duodenitis
6	87	M	Peptic duodenitis
7	55	M	Esophageal inflammation due to reflux
8	28	M	Suspected Crohn's disease

NA: Not applicable, *i.e.*, no biopsy was performed; M: Male; F: Female.

dimensional tissue structure in the projection image in the center and right-hand panels. Also evident in the three-dimensional images are some artifacts at the edges, which are due to the white lettering in the original endoscopic image prior to framing. These are left in the images to show orientation.

In Figure 2, data from celiac patients 3 and 4 are shown, with Marsh scores III C and III B, respectively. The distal duodenum of patient 3 has folds with marked scalloping, which are the curved structures at the edge of each mucosal fold (top panels). These folds are evident as very large and prominent three-dimensional structures in the projection images in the center and right panels. The bright horizontally-oriented ridge at center in the patient 3 endoscopic image at left is converted to a very prominent three-dimensional ridge in the center and right-hand panels. In the patient 4 data (Marsh III B score) there is marked folding, with many large protrusions on each fold (center panel), similar to the visual appearance of patient 3 data (center panel).

Examples of control patient data are shown in Figures 3 and 4. For the control patients, protrusion features appear in the three-dimensional projection images in the center panels. However, the protrusions appear to be diminished and less connected to meandering ripples, as compared with the celiac patients with Marsh III scores whose data are shown in Figures 1 and 2. The three-dimensional protrusion structures are sometimes markedly diminished or even completely absent over some areas of the projections for the control patient data (Figures 3 and 4).

Summary data for all patients are shown in Figure 5. On the abscissa is noted the standard deviation from the mean of the first derivative, while the ordinate axis gives the mean absolute first derivative. Celiac points (black) are labeled according to Marsh score. The patient data can be mostly separated based on the linear discriminant function (straight black line). Thus the sensitivity and specificity for classification are both 80%. The control patient data are mostly clustered together and the celiac patient data are mostly clustered together. Celiac patient data with Marsh III C scores as labeled, are all clustered toward the top right in the graph, *i.e.*, they possess larger topographic variation

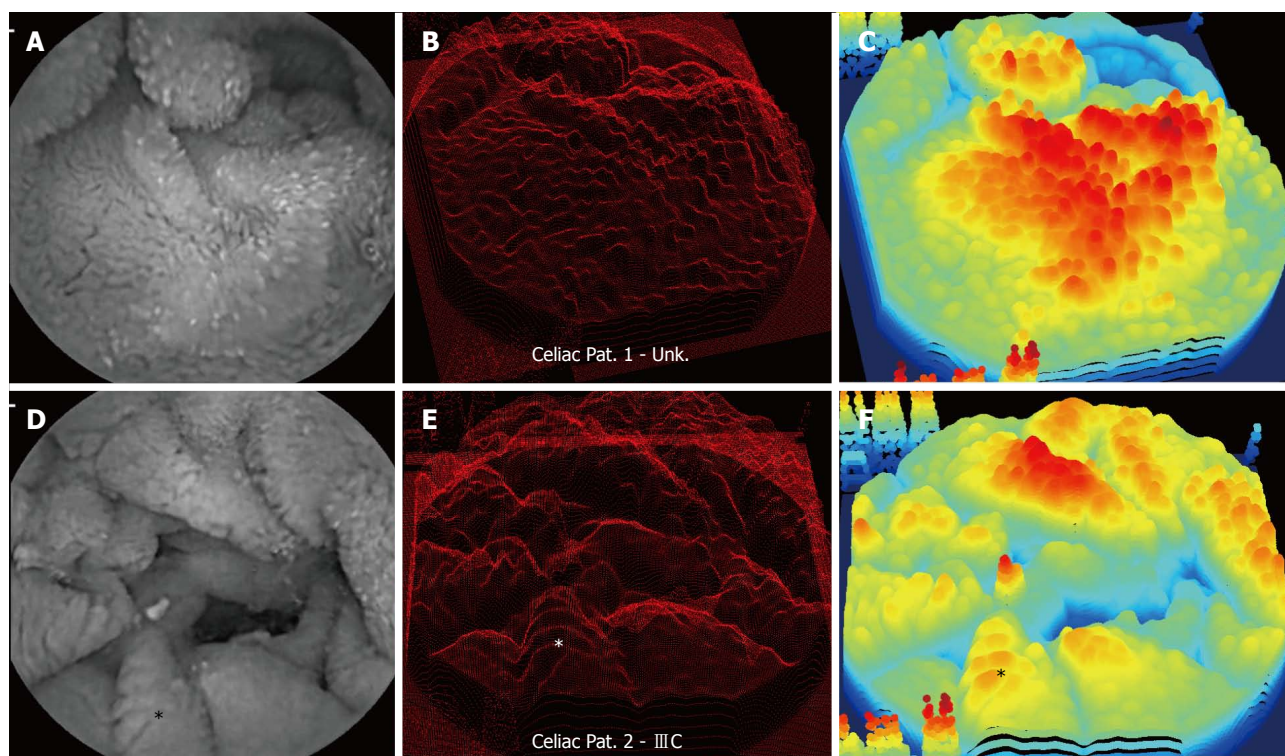


Figure 1 Celiac patient images. A-C: Patient 1; D-F: Patient 2; A, D: The grayscale endoscopic images; B, E: The three-dimensional projections; C, F: Projections in false color. Colors from blue to yellow, orange, and red represent areas with progressively greater amplitude along the Z-axis (vertical axis). Patient 1 did not have a biopsy obtained due to hemophilia but was thought to have a Marsh score III C. Patient 2 also had a Marsh score III C. Note the prominent protrusions evident in the three-dimensional projections of both patients, and the similar appearance of texture in the original two-dimensional endoscopic images.

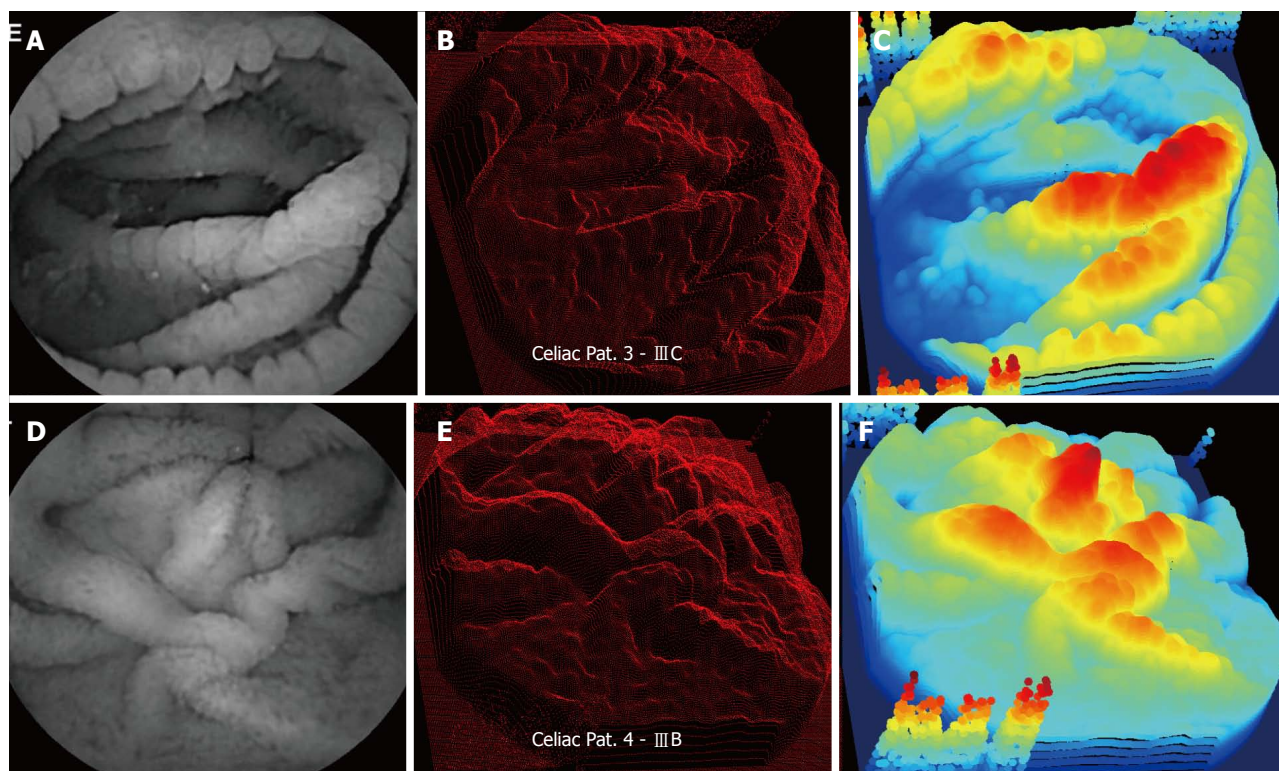


Figure 2 Celiac patient images. A-C: Patient 3 (Marsh III C score); D-F: Patient 4 (Marsh IIIB pathology); A, D: The grayscale endoscopic images; B, E: The three-dimensional projections; C, F: Projections in false color. Colors from blue to yellow, orange, and red represent areas with progressively greater amplitude along the Z-axis (vertical axis). Again note the prominent protrusions evident in the three-dimensional projections of both patients, even though the appearance of texture is somewhat dissimilar in the original two-dimensional endoscopic images.

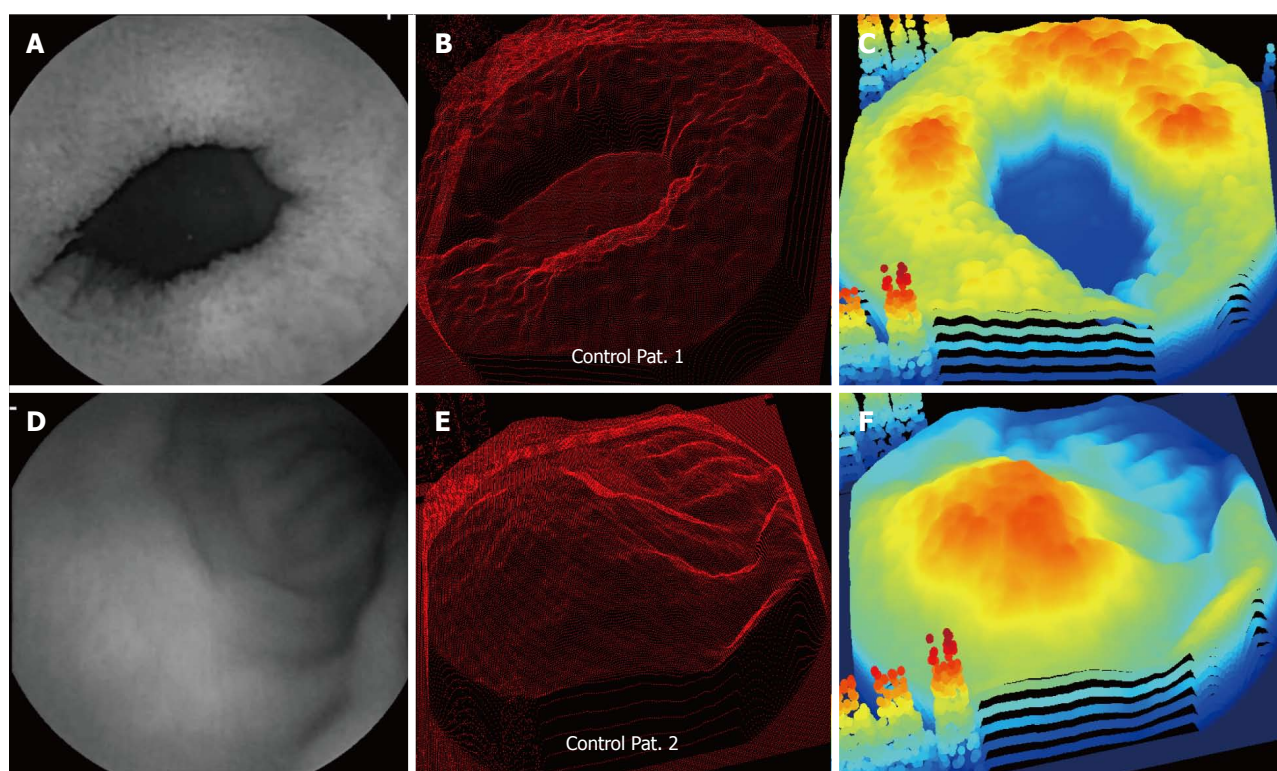


Figure 3 Control patient images. A-C: Patient 1 (no villous atrophy); D-F: Patient 2 (no villous atrophy); A, D: The grayscale endoscopic images; B, E: The three-dimensional projections; C, F: Projections in false color. Note the lack of prominent protrusions evident in the three-dimensional projections of both patients, even though there is a dissimilar appearance of texture in the original two-dimensional endoscopic images.

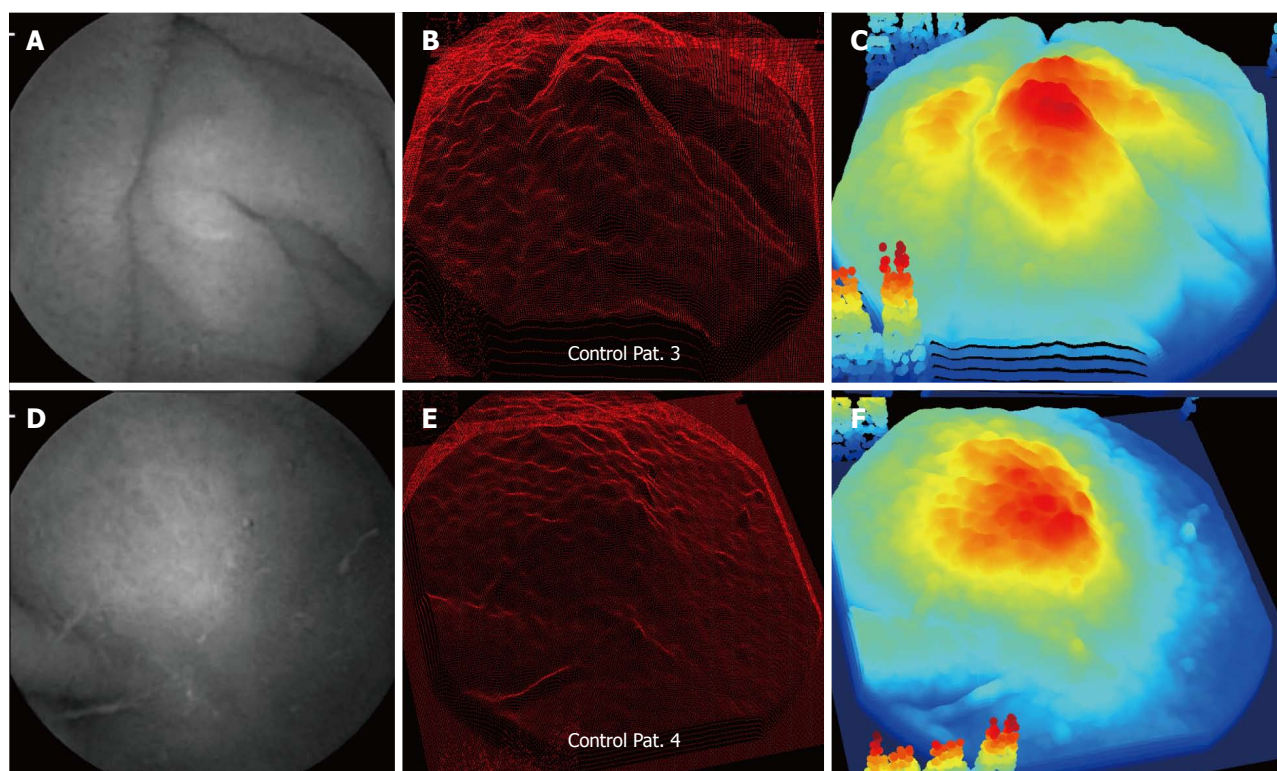


Figure 4 Control patient images. A-C: Patient 3 (no villous atrophy); D-F: Patient 4 (no villous atrophy); A, D: The grayscale endoscopic images; B, E: The three-dimensional projections; C, F: Projections in false color. Note the lack of prominent protrusions evident in the three-dimensional projections of both patients, even though there is a dissimilar appearance of texture in the original two-dimensional endoscopic images.

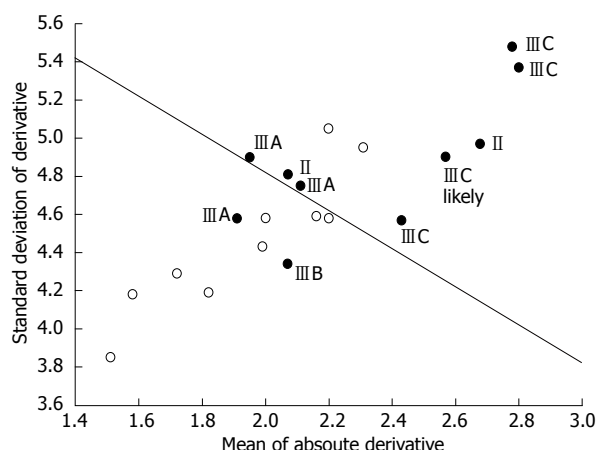


Figure 5 Scatterplot of celiac (black circles) vs control (open circles) patient topographic data. The ordinate scale gives the standard deviation of the derivative in elevation. The abscissa shows the absolute value of the derivative in elevation. A linear discriminant function mostly separates celiac vs control patient parameter values (black line). Based on the scatterplot, the topography of celiac three-dimensional constructs is typically greater than for controls.

based on both the absolute derivative and the standard deviation from the mean. The mean absolute derivative in elevation was 2.34 ± 0.35 brightness units for celiac images vs 1.95 ± 0.28 for controls ($P = 0.014$). The standard deviation of the derivative in elevation was 4.87 ± 0.35 brightness units for celiac images vs 4.47 ± 0.36 for controls ($P = 0.023$).

DISCUSSION

Comparison with prior work

The study findings and observations are in accord with prior scanning electron microscopy studies conducted by Michael Marsh^[16], and our prior work showing that the protrusions, when modeled syntactically, tend to be taller in height for celiac patients as compared with controls^[13,14]. The mean height of protrusions was previously found to be 3.10 ± 2.34 grayscale levels in celiac patients with villous atrophy vs 2.70 ± 0.43 grayscale levels for controls ($P < 0.001$). The prominence of the mucosal protrusions in celiac patients, particularly III C patients, is evident in the three-dimensional constructs of Figures 1 and 2, and the resulting large variation in topography as measured *via* automated computerized means is evident in Figure 5. Large mucosal protrusions, when villous atrophy is present in celiacs, which likely corresponds to clumping of villi^[13,14], translates to greater topographic variation (Figure 5). By comparison, control patient biopsies with normal villi tend to possess narrowed, smaller topographic structures (Figures 3 and 4) corresponding to individual villi, which reduces the overall degree of topographic change as compared with celiac patients with villous atrophy. In the false-color celiac images of Figures 1 and 2C, topographic structure often appears to include more high-elevation areas (combined red-orange false-color regions) as compared to controls (Figures 3 and 4), in agreement with the quantitative topographic results

presented in Figure 5 and in the summary statistics. The mechanism by which the prominent three-dimensional architectural alterations occur in the celiac patient small intestinal mucosa is an interesting topic for further research.

Three-dimensional printing

The three-dimensional projections shown in the center panels of Figures 1-4 only provide a single snapshot of the tissue structure. A 3D printer would be useful in this regard to provide additional perspective. By printing the structure in three dimensions, the observer could view it from any perspective. Three-dimensional tissue reconstruction of intestinal villi has been demonstrated previously^[17]. This could potentially be helpful for improved understanding concerning the relationship of small intestinal architecture with other disease features in celiacs. It would also be useful to improve syntactic modeling of structure. Protrusions can be modeled as square objects^[13,14]. Although not a strictly correct interpretation of structure, the syntax utilized is sufficiently accurate to detect most or all mucosal protrusions automatically, and to estimate the height and width of each. Using a 3D printer for guidance, it would be possible to improve modeling of the projection features, as well as the syntactic modeling of any other pathologic structures embedded in the mucosa. Structural characteristics could be incorporated into the algorithm for improved, automated detection and measurement of the quantitative tissue structural characteristics in suspected and actual celiac patients.

Other rendering methods

Use of endoscopy for patient diagnosis and intervention is based on image sequences that are acquired *via* a video-camera. Yet, the sequence of images lacks depth information. Recognition and evaluation of pathology therefore becomes more difficult. In this study, a straightforward method was described for rendering three-dimensional surfaces, which can be useful in real time during endoscopic procedures, as well as for retrospective analysis. More complex procedures for three-dimensional rendering of the mucosa include one that solves the structure-from-motion problem using parallax, *i.e.*, camera motion is estimated, and it is used to reconstruct the three-dimensional scene^[18]. Another method is to use an optical fiber to act as a probe to transmit three-dimensional information regarding the internal landscape^[19]. Volumetric images are obtained by using a spectrally encoded endoscopy system. The resulting images provide depth information, although the process would be slow to complete for all areas where villous atrophy is suspected, due to the need to direct the probe across small areas at a time. An advantage of syntactic and textural-based methods for videocapsule analysis is the speed of computation, which would be useful for real-time analysis^[20,21]. These methods, like the calculation done in this study to generate Figure 5, are entirely automated, thus

eliminating observer bias.

Limitations

The method uses shape-from-shading as a linear function. Thus depth was as a first approximation, linearly dependent on brightness. However, this is not precisely correct, as the actual function will be nonlinear. Construction and update of the three-dimensional projections in real-time by computerized means could be done during the endoscopic procedure, but was not included in this study. Small intestinal pathology is patchy in celiac patients, thus the results obtained from analysis of selected videocapsule images may differ from histopathologic findings, as the sites chosen for biopsy do not correspond to the images and they only represent limited sampling of the mucosa. The series of patients used for celiac vs control cohorts, $n = 8$ each, should be increased for confirmation of the results. Use of a larger sample size in subsequent studies may assist in clarifying the specific clinical settings in which this methodology will be useful. The Marsh scoring of celiac patient data shown in Figure 5 is not entirely aligned with the magnitude of the x and y variables, perhaps suggesting that there is a lag between cellular-level phenomena and gross architectural structure.

COMMENTS

Background

Celiac disease is prevalent throughout the world and affects approximately 1% of the population. Patients with celiac disease are reactive to the protein gluten, which is present in wheat, rye, and barley grains. Currently, the only treatment is a lifelong gluten-free diet. It is a disease with often occult symptoms that differ from one individual to the next. Diagnosis of celiac disease is difficult owing to the fact that symptoms are highly varied from one individual to another, both in their type and severity. In some patients with celiac disease, no symptoms may be evident. Diagnosis is made by a positive antibody test, which is followed by biopsy of the abnormal appearing mucosa and confirmation of atrophy by light microscopy. Utilizing light microscopy, the small intestinal mucosa is evaluated for presence and degree of villous atrophy and an increase in intraepithelial lymphocytes. Mucosal alterations in celiac disease are assigned a Marsh score, which varies from 1 (normal villous architecture but increased intraepithelial lymphocytes) to IIIA-C (severe degrees of villous atrophy accompanied by crypt hyperplasia and increased intraepithelial lymphocytes).

Research frontiers

Recent advances in imaging technology have enabled visualization of the small intestinal mucosa via a videocapsule to assess areas of villous atrophy, which is convenient to use and is minimally invasive. Analysis of two-dimensional videocapsule endoscopy images by quantitative means can assist in determining areas of pathology in these patients. A difficulty with the use of videocapsule technology, is that areas of pathology are not always clearly identifiable on review of the images. The two-dimensional images provide a very limited perspective of the actual three-dimensional structure of the substrate. It's difficult to determine the precise regions and boundaries of any abnormality that is present in the images. In prior quantitative studies, a method was introduced to estimate three-dimensional structure from two-dimensional endoscopic images, which uses the principle of shape-from-shading. As a first approximation, image brightness is linearly related to image depth. Thus a third spatial axis, the Z-axis, is obtained so that a map of the three-dimensional structure of the substrate can be constructed. The purpose of this study is to show that visualization of the three-dimensional architecture can be useful to detect pathology in the small intestinal mucosa when the presence of patchy villous atrophy is suspected.

Innovations and breakthroughs

In this study, the visual manifestations of three-dimensional image projection are shown for celiac patients with various levels of villous atrophy, vs controls. Special attention is paid to the types of structures that are evident in the projections, and their variation from one patient to the next, which can be helpful to detect the presence and severity of villous atrophy during the diagnosis of celiac disease, and to evaluate treatment efficacy.

Applications

This study showed that visualization of the three-dimensional architecture can be useful to detect pathology in the small intestinal mucosa when the presence of patchy villous atrophy is suspected.

Peer-review

This study shows an interesting new approach to be validated in a prospective way and bigger sample size in order to clarify the potential use in specific clinical situations of celiac patients.

REFERENCES

- 1 Sapone A, Bai JC, Ciacci C, Dolinsek J, Green PH, Hadjivassiliou M, Kaukinen K, Rostami K, Sanders DS, Schumann M, Ullrich R, Villalta D, Volta U, Catassi C, Fasano A. Spectrum of gluten-related disorders: consensus on new nomenclature and classification. *BMC Med* 2012; **10**: 13 [PMID: 22313950 DOI: 10.1186/1741-7015-10-13]
- 2 Alaedini A, Green PH. Narrative review: celiac disease: understanding a complex autoimmune disorder. *Ann Intern Med* 2005; **142**: 289-298 [PMID: 15710962 DOI: 10.7326/0003-4819-142-4-200502150-00011]
- 3 Lee SK, Lo W, Memeo L, Rotterdam H, Green PH. Duodenal histology in patients with celiac disease after treatment with a gluten-free diet. *Gastrointest Endosc* 2003; **57**: 187-191 [PMID: 12556782 DOI: 10.1067/mge.2003.54]
- 4 Lo W, Sano K, Lebowitz B, Diamond B, Green PH. Changing presentation of adult celiac disease. *Dig Dis Sci* 2003; **48**: 395-398 [PMID: 12643621 DOI: 10.1023/A:]
- 5 Green PH, Jabri B. Coeliac disease. *Lancet* 2003; **362**: 383-391 [PMID: 12907013 DOI: 10.1016/S0140-6736(03)14027-5]
- 6 Fasano A, Berti I, Gerarduzzi T, Not T, Colletti RB, Drago S, Elitsur Y, Green PH, Guandalini S, Hill ID, Pietzak M, Ventura A, Thorpe M, Kryszak D, Fornaroli F, Wasserman SS, Murray JA, Horvath K. Prevalence of celiac disease in at-risk and not-at-risk groups in the United States: a large multicenter study. *Arch Intern Med* 2003; **163**: 286-292 [PMID: 12578508 DOI: 10.1001/archinte.163.3.286]
- 7 Gonzalez S, Gupta A, Cheng J, Tennyson C, Lewis SK, Bhagat G, Green PH. Prospective study of the role of duodenal bulb biopsies in the diagnosis of celiac disease. *Gastrointest Endosc* 2010; **72**: 758-765 [PMID: 20883853 DOI: 10.1016/j.gie.2010.06.026]
- 8 Biagi F, Rondonotti E, Campanella J, Villa F, Bianchi PI, Klersy C, De Franchis R, Corazza GR. Video capsule endoscopy and histology for small-bowel mucosa evaluation: a comparison performed by blinded observers. *Clin Gastroenterol Hepatol* 2006; **4**: 998-1003 [PMID: 16814612 DOI: 10.1016/j.cgh.2006.04.004]
- 9 Scapa E, Jacob H, Lewkowicz S, Migdal M, Gat D, Gluckhovski A, Gutmann N, Fireman Z. Initial experience of wireless-capsule endoscopy for evaluating occult gastrointestinal bleeding and suspected small bowel pathology. *Am J Gastroenterol* 2002; **97**: 2776-2779 [PMID: 12425547 DOI: 10.1111/j.1572-0241.2002.07021.x]
- 10 Rondonotti E, Spada C, Cave D, Pennazio M, Riccioni ME, De Vitis I, Schneider D, Spruevnik T, Villa F, Langelier J, Arrigoni A, Costamagna G, de Franchis R. Video capsule enteroscopy in the diagnosis of celiac disease: a multicenter study. *Am J Gastroenterol* 2007; **102**: 1624-1631 [PMID: 17459022 DOI: 10.1111/j.1572-0241.2007.01238.x]
- 11 Ciaccio EJ, Bhagat G, Lewis SK, Green PH. Suggestions for automatic quantitation of endoscopic image analysis to improve detection of small intestinal pathology in celiac disease patients. *Comput Biol Med* 2015; **65**: 364-368 [PMID: 25976612 DOI: 10.1016/j.cbm.2015.05.005]

- 10.1016/j.combiomed.2015.04.019]
- 12 **Ciaccio EJ**, Bhagat G, Lewis SK, Green PH. Trends in celiac disease research. *Comput Biol Med* 2015; **65**: 369-378 [PMID: 26095989 DOI: 10.1016/j.combiomed.2015.05.023]
- 13 **Ciaccio EJ**, Tennyson CA, Bhagat G, Lewis SK, Green PH. Use of shape-from-shading to estimate three-dimensional architecture in the small intestinal lumen of celiac and control patients. *Comput Methods Programs Biomed* 2013; **111**: 676-684 [PMID: 23816252 DOI: 10.1016/j.cmpb.2013.06.002]
- 14 **Ciaccio EJ**, Tennyson CA, Bhagat G, Lewis SK, Green PH. Implementation of a polling protocol for predicting celiac disease in videocapsule analysis. *World J Gastrointest Endosc* 2013; **5**: 313-322 [PMID: 23858375 DOI: 10.4253/wjge.v5.i7.313]
- 15 map3d: Interactive scientific visualization tool for bioengineering data. Scientific Computing and Imaging Institute (SCI). Available from: URL: <http://www.sci.utah.edu/cibc/software.html>
- 16 **N Marsh M**, W Johnson M, Rostami K. Mucosal histopathology in celiac disease: a rebuttal of Oberhuber's sub-division of Marsh III. *Gastroenterol Hepatol Bed Bench* 2015; **8**: 99-109 [PMID: 25926934]
- 17 **Niess JH**, Brand S, Gu X, Landsman L, Jung S, McCormick BA, Vyas JM, Boes M, Ploegh HL, Fox JG, Littman DR, Reinecker HC. CX3CR1-mediated dendritic cell access to the intestinal lumen and bacterial clearance. *Science* 2005; **307**: 254-258 [PMID: 15653504 DOI: 10.1126/science.1102901]
- 18 **Thormahlen T**, Broszio H, Meier PN. Three-dimensional endoscopy. Falk Symposium, Chapter 22. Hagenmüller F, editor. Medical Imaging in Gastroenterology and Hepatology. *Falk Symposium* 2002; **95**: 151-152
- 19 **Yelin D**, Rizvi I, White WM, Motz JT, Hasan T, Bouma BE, Tearney GJ. Three-dimensional miniature endoscopy. *Nature* 2006; **443**: 765 [PMID: 17051200 DOI: 10.1038/443765a]
- 20 **Ciaccio EJ**, Bhagat G, Lewis SK, Green PH. Extraction and processing of videocapsule data to detect and measure the presence of villous atrophy in celiac disease patients. *Comput Biol Med* 2016; **78**: 97-106 [PMID: 27673492 DOI: 10.1016/j.combiomed.2016.09.009]
- 21 **Ciaccio EJ**, Bhagat G, Lewis SK, Green PH. Recommendations to quantify villous atrophy in video capsule endoscopy images of celiac disease patients. *World J Gastrointest Endosc* 2016; **8**: 653-662 [PMID: 27803772 DOI: 10.4253/wjge.v8.i18.653]

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Retrospective Study

Use of volumetric laser endomicroscopy for dysplasia detection at the gastroesophageal junction and gastric cardia

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Author contributions: Gupta N designed and performed the research, performed the statistical analysis, and wrote the paper; Siddiqui U, Waxman I and Chapman C provided clinical advice and contributed to the data set; Koons A and Valuckaite V provided administrative support for VLE system use and patient participation; Xiao SY, Setia N and Hart J performed histologic analysis; Konda V designed the research and supervised the report

Institutional review board statement: This study was reviewed and approved by the IRB committee of the University of Chicago.

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 the patient agreed to treatment and VLE imaging by written consent.

Conflict-of-interest statement: We have no relevant financial relationships to disclose.

Data sharing statement: No additional data are available.

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Abstract**AIM**

To determine specific volumetric laser endomicroscopy (VLE) imaging features associated with neoplasia at the gastroesophageal junction (GEJ) and gastric cardia.

METHODS

During esophagogastroduodenoscopy for patients with known or suspected Barrett's esophagus, VLE was performed before biopsies were taken at endoscopists' discretion. The gastric cardia was examined on VLE scan from the GEJ (marked by top of gastric folds) to 1 cm distal from the GEJ. The NinePoints VLE console was used to analyze scan segments for characteristics previously found to correlate with normal or abnormal mucosa. Glands were counted individually. Imaging features identified on VLE scan were correlated with biopsy results from the GEJ and cardia region.

RESULTS

This study included 34 cases. Features characteristic of the gastric cardia (gastric rugae, gastric pit architecture, poor penetration) were observed in all (100%) scans. Loss of classic gastric pit architecture was common and there was no difference between those with neoplasia and without (100% *vs* 74%, *P* = NS). The abnormal VLE feature of irregular surface was more often seen in patients with neoplasia than those without (100% *vs* 18%, *P* < 0.0001), as was heterogeneous scattering (86% *vs* 41%, *P* < 0.005) and presence of anomalous glands (100% *vs* 59%, *P* < 0.05). The number of anomalous glands did not differ between individual histologic subgroups (ANOVA, *P* = NS).

CONCLUSION

The transition from esophagus to gastric cardia is reliably identified on VLE. Histologically abnormal cardia mucosa produces abnormal VLE features. Optical coherence tomography algorithms can be expanded for use at the GEJ/cardia.

Key words: Volumetric laser endomicroscopy; Cardia; Gastroesophageal junction; Barrett's; Optical coherence tomography; Neoplasia

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Core tip: This is a retrospective study to explore volumetric laser endomicroscopy (VLE) imaging features associated with neoplasia at the gastroesophageal junction (GEJ) and gastric cardia. Histologically abnormal mucosa due to inflammation or neoplasia more often produces abnormal VLE imaging. Specifically, VLE imaging features of irregular surface, heterogeneous scattering and presence of anomalous glands were more often seen in cases of neoplasia than those without. The GEJ and gastric cardia can be difficult to assess endoscopically for dysplasia, and VLE imaging in this area can aid in a "red-flag" biopsy technique.

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INTRODUCTION

Barrett's esophagus (BE) has been well established as a precursor to esophageal adenocarcinoma (EAC)^[1,2]. Management of patients diagnosed with BE includes surveillance endoscopy^[3]. Using the Seattle protocol, targeted biopsies of visible lesions should be taken followed by 4-quadrant biopsies at 2 cm intervals along

the length of the BE segment^[4]. In cases of known dysplasia, the random 4-quadrant biopsies should be taken every 1 cm^[3].

Though currently the standard of care, these techniques are subject to sampling error since random biopsies may miss areas of high-grade dysplasia (HGD) or intramucosal carcinoma (IMC)^[5,6]. There has been increasing interest in evaluating advanced imaging modalities which may allow for better visualization of the entire upper GI mucosal surface and subsurface in order to increase diagnostic yield with targeted biopsies^[7,8].

Optical coherence tomography (OCT) is an imaging technique that utilizes low-coherence interferometry to produce high resolution images of biologic tissue by measuring back-scatter light intensity from a near-infrared light source^[9]. Recently, an OCT based technology called Fourier-domain OCT or volumetric laser endomicroscopy (VLE) is now commercially available and offers higher imaging speed and improved sensitivity as compared to traditional OCT^[10]. The system allows for real time cross-sectional imaging of the esophagus and proximal stomach as an adjuvant to esophagogastroduodenoscopy (EGD). Surface and subsurface architecture such as mucosal layers, gastric pits, and gland morphology can be identified^[11]. Several studies have analyzed the correlation between OCT images and histology from biopsy specimens. Specifically, a blinded prospective study found OCT to have an 81% specificity for diagnosing squamous intestinal metaplasia (SIM) at the squamocolumnar junction (SCJ)^[12].

Due to the limited knowledge about VLE findings at the gastroesophageal junction (GEJ) and gastric cardia, the purpose of this study is to correlate VLE imaging characteristics with histology in this area in order to determine specific features associated with neoplasia.

MATERIALS AND METHODS

Study design

This was a retrospective study conducted at a tertiary care center with a referral BE practice. Patients with known or suspected Barrett's esophagus presented for EGD and VLE. During EGD, biopsies were taken with cold forceps in a targeted and random fashion. Using the NinePoints VLE console, a segment of the VLE scan was delineated from the GEJ (marked by top of gastric folds) to 1 cm distal from the GEJ in order to approximate the gastric cardia. These segments were analyzed frame-by-frame to determine the presence of various imaging features. This analysis was done by a trained reviewer who was initially blinded to the corresponding pathology. Once the image analysis was completed, biopsy results from the GEJ to 1 cm distal to the GEJ were reviewed in order to determine the highest level of pathology found in the segment. Patients were then grouped according to the highest level of pathology indicted on biopsy

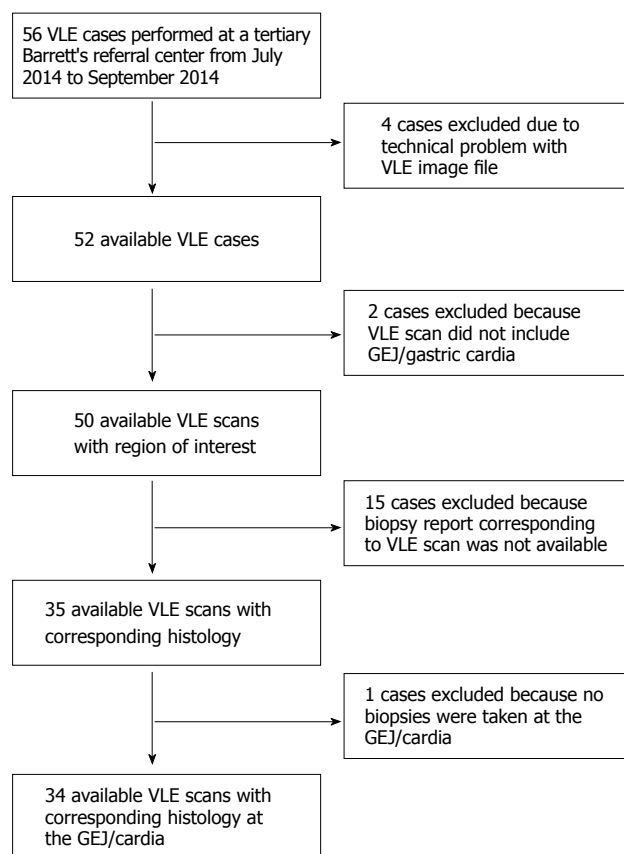


Figure 1 Inclusion and exclusion criteria flowchart. VLE: Volumetric laser endomicroscopy; GEJ: Gastroesophageal junction.

report: neoplasia, Barrett's with no dysplasia, inflamed cardia, and normal mucosa. Within these histologic subgroups, the frequency of each imaging characteristic was calculated based on the VLE scan analysis that had been done.

Cases (Figure 1)

From July 2014 to September 2015, forty-six patients underwent a total of fifty-six procedures with VLE scan at a tertiary care center with referral Barrett's practice. These patients were undergoing screening or had known BE and were undergoing endoscopic follow-up. Cases were included in the study if they had a VLE scan available for review and had biopsies taken specifically at the GEJ/gastric cardia.

Cases were excluded if the VLE scan did not include imaging of the GEJ/gastric cardia, biopsies were not taken in this region, or if there was a technical problem with the VLE scan.

Of the fifty-six cases, thirty-four met criteria for inclusion in the study. This study was approved by the Institutional Review Board.

Endoscopy

All endoscopic procedures were performed by 3 expert endoscopists with experience in detection and management of BE. EGD procedures were performed using the high resolution Olympus GIF-HQ190 gastro-

scope. After insertion of the gastroscope, the esophagus, GEJ and gastric cardia were first examined by WLE for gross evidence of BE. Narrow band imaging features with near focus was also used. Following this, VLE ODFI imaging was performed using the NinePoints system described below. Lastly, biopsies were taken with cold forceps and/or endoscopic mucosal resection at the endoscopist's discretion.

VLE system

The NinePoints Medical VLE optical frequency domain imaging (ODFI) system was used in this study. Technical specifications of ODFI imaging are described in detail in previous publications^[12]. Briefly, the NinePoints VLE system includes a balloon centered probe and user console with monitor. The probe consists of a transparent balloon surrounding a laser light source and optical system. Commercially available probe sizes range from 14–25 mm. These are compatible with endoscope channels 2.8 mm and larger. After the balloon is placed into the esophagus and inflated, the central component helically scans while simultaneously retracting throughout the length of the balloon (6 cm). A data set is generated using interferometry and measurement of optical reflection delay from the laser light source. The scan takes 90 s to complete and produces circumferential cross-sectional images of the tissue abutting the edge of the inflated balloon probe. In total, 1200 cross sectional images are obtained from the mucosa to a depth of 3 mm. These images have a resolution of 7 μ m making it comparable to low-power microscopy.

VLE images were analyzed on a console that allows for simultaneous cross-sectional and longitudinal views. Additionally, a zoom view was available for both dimensions.

VLE image assessment

All VLE scans were viewed using the NinePoints VLE console. For each scan included in the study, the corresponding endoscopy report was reviewed to determine the centimeter marking at which the top of gastric folds was seen. The corresponding centimeter marking was found on the VLE scan and this was designated as the GEJ. Each scan was assessed frame by frame from the GEJ to 1 cm below the GEJ. Each frame was viewed circumferentially for presence of the specified features which have been found in previous studies to correlate with normal or abnormal mucosa (Table 1). The features of interest were based on OCT criteria set forth by Evans *et al.*^[12] and included gastric rugae, gastric pit architecture, image penetration, homogenous or heterogeneous scattering, surface to subsurface intensity, and surface irregularity. Following this, another review was done during which the number of typical, atypical, and septated glands were counted individually. Glands were deemed to be atypical if they were dilated or had irregular morphology, similar to the definition used in previous publications^[13].

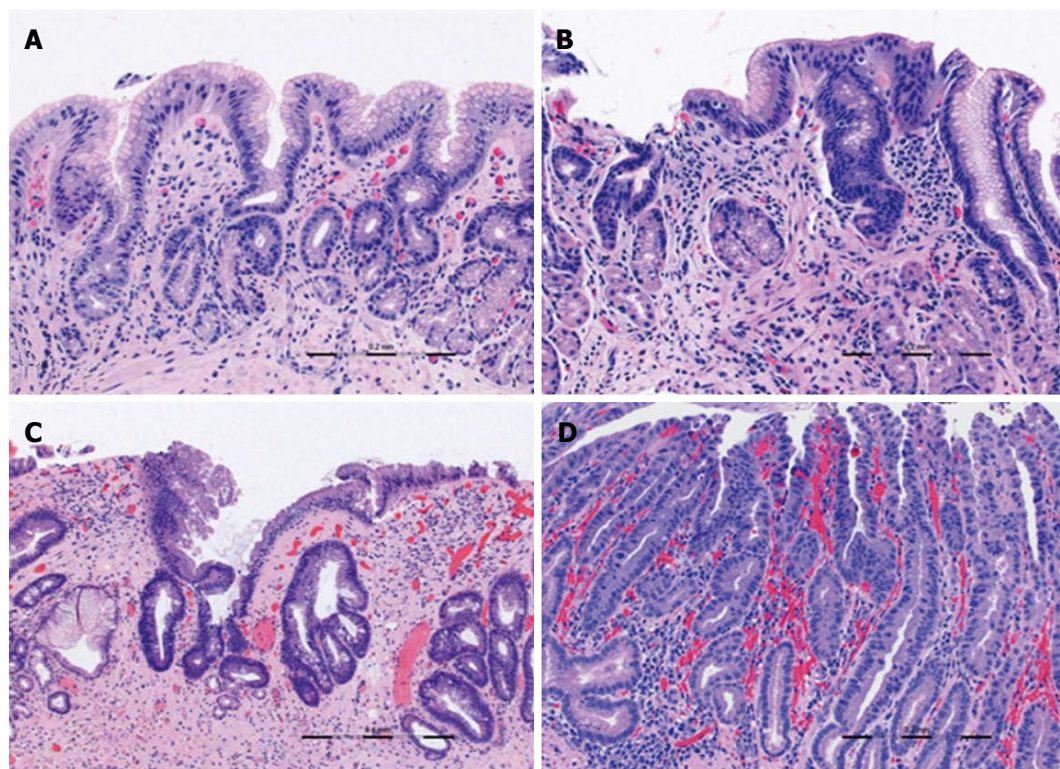


Figure 2 Correlating histology. A: Normal gastric cardia with regular gastric pit architecture; B: Inflamed gastric cardia with chronic inflammatory infiltrate and loss of structured gastric pits; C: Low grade dysplasia in Barrett's mucosa with a prominent atypical septated gland; D: High grade dysplasia with cytologic and architectural atypia extending to the surface.

Table 1 Validated criteria for interpretation of volumetric laser endomicroscopy Images of gastroesophageal tissue^[12]

Diagnosis	Imaging criteria on volumetric laser endomicroscopy
Squamous epithelium	Layered horizontal architecture Absence of glands
Gastric cardia	Vertical pit architecture Regular glandular architecture Poor image penetration Homogeneous scattering Regular, broad gastric rugae
Metaplasia	Lack of layered or vertical pit architecture Heterogeneous scattering Irregular surface Atypical glandular structure

Statistical analysis

Statistical analysis was performed using Microsoft Excel software for Windows. χ^2 test was used when comparing the proportion of each group that exhibited a particular imaging feature. The *t*-test was used when determining if the number of typical and atypical glands differed between two groups. Analysis of variance (ANOVA) analysis was performed comparing the number of atypical glands between all histologic subgroups. A *P*-value of < 0.05 was considered statistically significant in this study. The statistical methods of this study were reviewed by a biostatistician through the University of Chicago Biostatistics Laboratory which is part of the Department of Public Health Sciences.

RESULTS

Patients

Thirty-four patients with VLE imaging and cardia level biopsies were included in the study and had an average age of 63 years (SD 9). Twenty-two patients had undergone prior therapy while twelve had not. Of the 22 patients who had undergone prior treatment, 4 patients had undergone endoscopic mucosal resection (EMR), 6 radiofrequency ablation (RFA), 12 hybrid therapy.

Endoscopy review

Hiatal hernias were present in 20 cases. In two cases, the patient was status post a fundoplication and in one case the patient was status post a duodenal switch surgery. Visible BE was seen during EGD in 22 cases of which 14 had short segment BE and 8 had long segment BE. Visible lesions at the GEJ/gastric cardia such as nodularity or abnormal vascularity were seen in 4 cases.

Pathology review (Figure 2)

In patients who had no prior treatment for BE, the highest pathology identified from the GEJ and cardia region was intramucosal carcinoma (IMC)/high grade dysplasia (HGD) in one case, Barrett's with low grade dysplasia (LGD) in four cases, Barrett's without no dysplasia (NDBE) in four cases, and normal mucosa (NL) in three cases.

Among the 22 patients who had previously under-

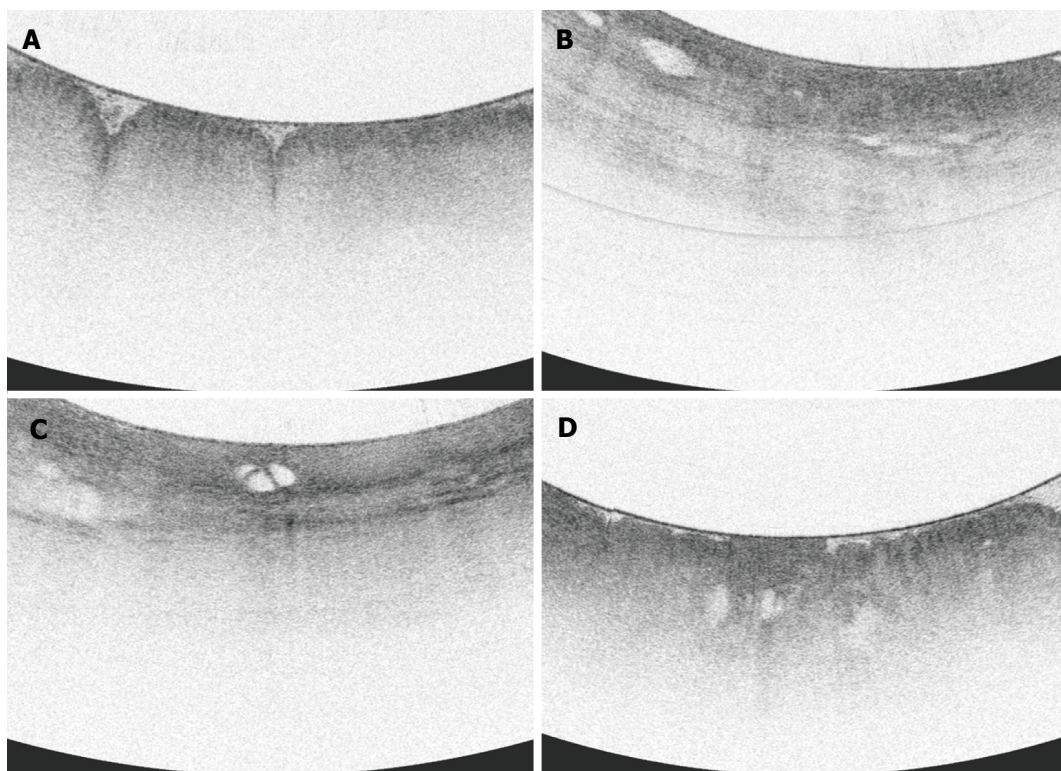


Figure 3 Volumetric laser endomicroscopy imaging snapshots. A: Normal gastric cardia with gastric rugae and gastric pit architecture; B: Inflamed gastric cardia with loss of gastric pit architecture and anomalous glands; C: Low grade dysplasia with loss of gastric pit architecture, heterogeneous scattering, anomalous septated gland; D: High grade dysplasia with irregular surface and anomalous glands.

gone treatment, the pre-treatment pathology was IMC in 1 case, HGD in 11 cases, LGD in 8 cases and NDBE in 2 cases and study procedure pathology was LGD in 2 cases, NDBE in 2 cases, inflamed gastric cardia (IGC) in 9 cases, and NL in 9 cases.

VLE findings (Table 2 and Figure 3)

Of the fifty-six VLE cases available for this study, twelve cases were excluded due to inadequate VLE imaging of the GEJ/cardia or because corresponding biopsies were not taken in that region.

Features characteristic of the gastric cardia (gastric rugae, gastric pit architecture, and poor penetration) were observed in all (100%) scans. A focal area with loss of normal gastric pit architecture was also a prevalent finding, seen in 79.4% of total patients. Heterogeneous scattering was found in exactly half (50%) of patients. Irregular surface was less common, seen in 35% of patients. Similarly, subsurface intensity greater than surface intensity was a rare finding, also occurring only in 6 of 34 patients (17.6%).

All 34 cases showed some typical epithelial glands with a range of 3-56 glands in the GE junction and cardia region examined. Anomalous glands were found in 25 of 34 scans (73.5%) and the number of anomalous glands ranged from 2 to 39.

Focal loss of normal gastric pit architecture was a prevalent finding, notably in patients with neoplasia, non-dysplastic Barrett's, and inflamed cardia. There was no difference of this feature between those with

neoplasia and those without (100% vs 74%, $P = \text{NS}$). However, patients with all types of abnormal cardia (IMC/HGD, LGD, NDBE, IGC) more frequently had loss of normal gastric pit architecture than patients with no mucosal abnormality (90.0% vs 58.3%, $P < 0.05$).

Irregular surface was more often seen in patients with neoplasia than those without neoplasia (100% vs 18.5%, $P < 0.0001$). Irregular surface was also more often seen in those patients with neoplasia compared to those with IGC (100% vs 11.1%, $P < 0.001$).

A greater proportion of patients with neoplasia had heterogeneous scattering as compared to patients without neoplasia (85.7% vs 40.7%, $P < 0.005$). Additionally, patients with neoplasia or non-dysplastic BE analyzed together more often had heterogeneous scattering compared to those with inflamed cardia or normal mucosa (84.6% vs 28.5%, $P < 0.005$).

Anomalous glands were more commonly found in patients with neoplasia as opposed to those without (100% vs 59.2%, $P < 0.05$). When analyzed together, patients with either neoplasia or non-dysplastic BE were found to have anomalous glands more often than those with inflammation or normal mucosa (92.3% vs 52.4%, $P < 0.05$).

In terms of the number of anomalous glands found, ANOVA analysis did not reveal a difference between individual histologic subgroups ($P = \text{NS}$). When grouped, patients with neoplasia did not have a significantly higher number of anomalous glands than all patients without neoplasia (t -test $P = \text{NS}$). However, patients

Table 2 Frequency of volumetric laser endomicroscopy imaging features in histologic subgroups *n* (%)

	IMC/HGD (<i>n</i> = 1)	LGD (<i>n</i> = 6)	NDBE (<i>n</i> = 6)	Inflamed cardia (<i>n</i> = 9)	No diagnostic abnormality (<i>n</i> = 12)	Neoplastic ¹ (<i>n</i> = 7)	Non-neoplastic ² (<i>n</i> = 27)	<i>P</i> -value ³
Gastric rugae	1 (100)	6 (100)	6 (100)	9 (100)	12 (100)	7 (100)	27 (100)	NS
Gastric pit architecture	1 (100)	6 (100)	6 (100)	9 (100)	12 (100)	7 (100)	27 (100)	NS
Poor penetration	1 (100)	6 (100)	6 (100)	9 (100)	12 (100)	7 (100)	27 (100)	NS
Loss of normal gastric pit architecture	1 (100)	6 (100)	5 (83)	8 (89)	7 (58)	7 (100)	20 (74)	NS
Irregular surface	1 (100)	6 (100)	2 (33)	1 (11)	2 (20)	7 (100)	5 (19)	< 0.0001
Heterogeneous scattering	1 (100)	5 (83)	5 (83)	6 (67)	3 (25)	6 (86)	14 (52)	< 0.005
Epithelial glands	1 (100)	6 (100)	6 (100)	9 (100)	12 (100)	7 (100)	27 (100)	NS
Anomalous glands	1 (100)	6 (100)	5 (83)	6 (67)	5 (42)	7 (100)	16 (59)	< 0.05

¹Neoplastic: HGD + IMC; ²Non-neoplastic: NDBE + IGC + NL; ³*P* value: Neoplastic *vs* non-neoplastic. IMC: Intramucosal carcinoma; HGD: High-grade dysplasia; LGD: Low grade dysplasia; NDBE: Barrett's without no dysplasia; IGC: Inflamed gastric cardia; NL: Normal mucosa; NS: Not significant.

with neoplasia did have significantly more anomalous glands than the subgroup of patients with no mucosal abnormality (*t*-test *P* < 0.05). Septated glands were seen in 8 patients across histology subtypes and did not appear to be associated with higher levels of pathology.

Notably, WLE or narrow band imaging (NBI) failed to detect suspicious lesions within BE at the GEJ or cardia in 3 cases of LGD.

DISCUSSION

This is the first study to analyze the correlation between imaging features and histology specifically in the GEJ and gastric cardia region. Our first main finding was that all scans exhibited features such as broad based rugae, gastric pits, and poor penetration. These features have been previously described in the gastric cardia, and our findings confirm that these are reliable markers for identifying the transition from tubular esophagus to gastric cardia.

We found that patients with neoplasia at the GEJ and gastric cardia more frequently have abnormal features on VLE imaging. In fact, the loss of normal gastric pit architecture was the only abnormal feature that did not differ significantly between those with neoplasia and those without. This is likely because this feature was loosely defined, and any deviation from the normal gastric pit architecture was counted. In the tubular esophagus, loss of layering is found in cases of NDBE. Thus, it was already known that NDBE can appear with an irregular architecture. In addition, gastric pit architecture appears as subtle alternation of vertical dark and light bands at the mucosal surface and this imaging feature could have been easily disturbed by artifact.

Other studies of VLE have similarly shown this imaging modality to be a safe and useful adjuvant to endoscopy. The safety and feasibility of VLE imaging was evaluated by Wolfson *et al.*^[14] who were able to successfully perform VLE imaging in 87% of a 100 patient cohort. Probe and console issues were the reason for unsuccessful VLE imaging in 13 patients.

Two minor mucosal lacerations occurred in the study and neither required therapy. The diagnostic utility of VLE has been explored by several groups. Trindade *et al.*^[15] presented a small case series which found that targeted biopsy by VLE upstaged or diagnosed dysplasia in several patients who then became candidates for ablation or resection. VLE has even been found to detect dysplasia missed by other advanced imaging techniques such as NBI^[16] and missed on random biopsy^[17]. Currently, two validated OCT image assessment algorithms exist. The OCT-scoring index (OCT-SI) created in 2005 by Evans *et al.*^[13] focuses on signal intensity and glandular architecture whereas the newer VLE diagnostic algorithm (VLE-DA) from Leggett *et al.*^[18] is based on degree of mucosal effacement, surface intensity, and atypical glands. The OCT scoring index (score > 2) was found to have an 83% sensitivity and 75% specificity for dysplasia detection when tested *in-vivo*^[13]. The VLE-DA performed slightly better with 86% sensitivity, 88% specificity, and 87% diagnostic accuracy, though this is based on an *ex-vivo* study^[18]. Based on our results, we propose adding "red-flag" features of irregular surface and heterogeneous scattering in the GEJ region to the current protocols in order to capture areas of dysplasia which may otherwise be missed.

These interpretation systems are focused on the tubular esophagus. However, there is a role for expanding the applicability of these criteria to the GEJ/cardia region since this is a difficult place to assess endoscopically and can harbor SIM or dysplasia^[19]. Cardia tissue may be present at the anatomical region of the cardia but may also be present in a mosaic pattern in Barrett's esophagus amidst intestinal type mucosa and fundic type mucosa. The appearance of cardia type tissue within this mosaic pattern in the tubular esophagus is a potential confounder and may be a cause for false positives in VLE interpretation.

One limitation of this study is that exact correlation of biopsy location to VLE scan location was unable to be performed in this retrospective study. Rather, a circumferential area scanning 1 cm in length was

designated as the GEJ/gastric cardia region and biopsy and imaging features from this area were compared. Currently, general location correlation can be done by matching a registration line on the probe to one of the cross-sectional image. This allows for clock-face orientation. However, to allow for even more precise targeting Suter *et al.*^[20] validated the recently developed method for using a cautery marking laser coupled into the VLE balloon catheter's optical fiber to mark areas of interest with simultaneously acquiring a VLE image.

The results of this study show a promising role for VLE as an adjuvant for endoscopic assessment of the GEJ and gastric cardia region. The current OCT-scoring algorithms may be expanded to include GEJ/cardia assessment in order to target areas that exhibit irregular surface, heterogeneous scattering, or anomalous glands. A prospective study validating these features utilizing 1:1 histologic correlation will be required. With *in-vivo* laser marking soon to be commercially available, we anticipate with this be a feasible study in the near future. Ultimately, the clinical comparison of yield of VLE targeted biopsy protocol compared with a standard Seattle protocol biopsy protocol will be needed to assess clinical impact.

COMMENTS

Background

Barrett's esophagus can lead to the development of esophageal adenocarcinoma. Because of this, patients with known Barrett's esophagus are recommended to have surveillance upper endoscopies. Biopsies are taken of visible lesions as well as in a random fashion according to the Seattle Protocol. However, this technique is suboptimal because occult dysplasia may still be missed. Several adjuvant modalities have been explored to help identify potentially dysplastic areas and allow for more targeted biopsies. Targeted biopsies improve dysplasia detection rates. volumetric laser endomicroscopy (VLE) is a type of OCT imaging modality that produces cross sectional images of the esophagus and proximal stomach. It is currently used for Barrett's surveillance and biopsy targeting in the tubular esophagus. This study explores the use of VLE specifically at the gastroesophageal junction (GEJ) and gastric cardia to determine the correlation of imaging features with neoplasia in this region.

Research frontiers

In Barrett's esophagus, there is increasing interest in a moving toward targeted biopsies by identifying abnormal "red-flag" areas. The correlation of VLE imaging with histology is increasingly being studied, however many of these studies are *ex-vivo* and their applicability may be limited. Additionally, most studies of VLE are limited to the tubular esophagus even though VLE scans also image the GEJ and gastric cardia. The results of this *in-vivo* study contribute to understanding the applicability of VLE imaging at the GEJ/cardia, as well as contributing to knowledge of correct VLE image interpretation.

Innovations and breakthroughs

This is the only study known to date which focus on VLE imaging characteristics specifically at the GEJ and gastric cardia. This is important because dysplasia can occur in this region just as it can in the tubular esophagus. Similar to prior VLE studies, this study found that VLE features of abnormal surface architecture and atypical glands are associated with dysplasia. However, this study also found that the scattering pattern of the VLE image (heterogeneous vs homogeneous) was correlated with dysplasia and should be considered in the image assessment.

Applications

This study suggests that VLE imaging is useful for assessing the GEJ and

gastric cardia. Current OCT scoring systems can be expanded for use in this region.

Terminology

Barrett's esophagus: A pre-cancerous cellular change in the esophagus that is often the result of longstanding acid reflux. Optical coherence tomography (OCT): An imaging technique that produces high resolution images of biologic tissue by measuring back-scatter light intensity from a near-infrared light source. Volumetric laser endomicroscopy (VLE): A specific type of OCT that is probe-based and produces cross sectional images of the esophagus and gastric cardia.

Peer-review

This retrospective study correlates VLE imaging characteristics with histology at the GEJ and gastric cardia, which is helpful to determine specific features associated with neoplasia. The authors investigated a new area of invasive gastroenterology field. Their findings have some novel findings and also lead new investigations as a prospective designed.

REFERENCES

- 1 **Drewitz DJ**, Sampliner RE, Garewal HS. The incidence of adenocarcinoma in Barrett's esophagus: a prospective study of 170 patients followed 4.8 years. *Am J Gastroenterol* 1997; **92**: 212-215 [PMID: 9040193]
- 2 **Sharma P**, Falk GW, Weston AP, Reker D, Johnston M, Sampliner RE. Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. *Clin Gastroenterol Hepatol* 2006; **4**: 566-572 [PMID: 16630761 DOI: 10.1016/j.cgh.2006.03.001]
- 3 **Evans JA**, Early DS, Fukami N, Ben-Menachem T, Chandrasekhara V, Chathadi KV, Decker GA, Fanelli RD, Fisher DA, Foley KQ, Hwang JH, Jain R, Jue TL, Khan KM, Lightdale J, Malpas PM, Maple JT, Pasha SF, Saltzman JR, Sharaf RN, Shergill A, Dominitz JA, Cash BD. The role of endoscopy in Barrett's esophagus and other premalignant conditions of the esophagus. *Gastrointest Endosc* 2012; **76**: 1087-1094 [PMID: 23164510 DOI: 10.1016/j.gie.2012.08.004]
- 4 **Shaheen NJ**, Falk GW, Iyer PG, Gerson LB. ACG Clinical Guideline: Diagnosis and Management of Barrett's Esophagus. *Am J Gastroenterol* 2016; **111**: 30-50; quiz 51 [PMID: 26526079 DOI: 10.1038/ajg.2015.322]
- 5 **Cameron AJ**, Carpenter HA. Barrett's esophagus, high-grade dysplasia, and early adenocarcinoma: a pathological study. *Am J Gastroenterol* 1997; **92**: 586-591 [PMID: 9128304]
- 6 **Pohl J**, Pech O, May A, Manner H, Fissler-Eckhoff A, Ell C. Incidence of macroscopically occult neoplasias in Barrett's esophagus: are random biopsies dispensable in the era of advanced endoscopic imaging? *Am J Gastroenterol* 2010; **105**: 2350-2356 [PMID: 20664531 DOI: 10.1038/ajg.2010.280]
- 7 **Thosani N**, Abu Dayyeh BK, Sharma P, Aslanian HR, Enestvedt BK, Komanduri S, Manfredi M, Navaneethan U, Maple JT, Pannala R, Parsi MA, Smith ZL, Sullivan SA, Banerjee S. ASGE Technology Committee systematic review and meta-analysis assessing the ASGE Preservation and Incorporation of Valuable Endoscopic Innovations thresholds for adopting real-time imaging-assisted endoscopic targeted biopsy during endoscopic surveillance of Barrett's esophagus. *Gastrointest Endosc* 2016; **83**: 684-98.e7 [PMID: 26874597 DOI: 10.1016/j.gie.2016.01.007]
- 8 **Muthusamy VR**, Kim S, Wallace MB. Advanced Imaging in Barrett's Esophagus. *Gastroenterol Clin North Am* 2015; **44**: 439-458 [PMID: 26021204 DOI: 10.1016/j.gtc.2015.02.012]
- 9 **Testoni PA**. Optical coherence tomography. *ScientificWorldJournal* 2007; **7**: 87-108 [PMID: 17334603 DOI: 10.1100/tsw.2007.29]
- 10 **Vakoc BJ**, Shishko M, Yun SH, Oh WY, Suter MJ, Desjardins AE, Evans JA, Nishioka NS, Tearney GJ, Bouma BE. Comprehensive esophageal microscopy by using optical frequency-domain imaging (with video). *Gastrointest Endosc* 2007; **65**: 898-905 [PMID: 17383652 DOI: 10.1016/j.gie.2006.08.009]
- 11 **Sauk J**, Coron E, Kava L, Suter M, Gora M, Gallagher K, Rosenberg M, Ananthakrishnan A, Nishioka N, Lauwers G, Woods K, Brugge W, Forcione D, Bouma BE, Tearney G. Interobserver agreement for

- the detection of Barrett's esophagus with optical frequency domain imaging. *Dig Dis Sci* 2013; **58**: 2261-2265 [PMID: 23508980 DOI: 10.1007/s10620-013-2625-x]
- 12 **Evans JA**, Bouma BE, Bressner J, Shishkov M, Lauwers GY, Mino-Kenudson M, Nishioka NS, Tearney GJ. Identifying intestinal metaplasia at the squamocolumnar junction by using optical coherence tomography. *Gastrointest Endosc* 2007; **65**: 50-56 [PMID: 17137858 DOI: 10.1016/j.gie.2006.04.027]
 - 13 **Evans JA**, Poneros JM, Bouma BE, Bressner J, Halpern EF, Shishkov M, Lauwers GY, Mino-Kenudson M, Nishioka NS, Tearney GJ. Optical coherence tomography to identify intramucosal carcinoma and high-grade dysplasia in Barrett's esophagus. *Clin Gastroenterol Hepatol* 2006; **4**: 38-43 [PMID: 16431303 DOI: 10.1016/S1542-3565(05)00746-9]
 - 14 **Wolfsen HC**, Sharma P, Wallace MB, Leggett C, Tearney G, Wang KK. Safety and feasibility of volumetric laser endomicroscopy in patients with Barrett's esophagus (with videos). *Gastrointest Endosc* 2015; **82**: 631-640 [PMID: 25956472 DOI: 10.1016/j.gie.2015.03.1968]
 - 15 **Trindade AJ**, George BJ, Berkowitz J, Sejjal DV, McKinley MJ. Volumetric laser endomicroscopy can target neoplasia not detected by conventional endoscopic measures in long segment Barrett's esophagus. *Endosc Int Open* 2016; **4**: E318-E322 [PMID: 27004250 DOI: 10.1055/s-0042-101409]
 - 16 **Atkinson C**, Singh S, Fisichella PM. Volumetric laser endomicroscopy in the detection of neoplastic lesions of the esophagus. *Dig Liver Dis* 2016; **48**: 692 [PMID: 26976783 DOI: 10.1016/j.dld.2016.02.013]
 - 17 **Trindade AJ**, Vamadevan AS, Sejjal DV. Finding a needle in a haystack: use of volumetric laser endomicroscopy in targeting focal dysplasia in long-segment Barrett's esophagus. *Gastrointest Endosc* 2015; **82**: 756; discussion 757 [PMID: 26005011 DOI: 10.1016/j.gie.2015.03.1984]
 - 18 **Leggett CL**, Gorospe EC, Chan DK, Muppa P, Owens V, Smyrk TC, Anderson M, Lutzke LS, Tearney G, Wang KK. Comparative diagnostic performance of volumetric laser endomicroscopy and confocal laser endomicroscopy in the detection of dysplasia associated with Barrett's esophagus. *Gastrointest Endosc* 2016; **83**: 880-888.e2 [PMID: 26344884 DOI: 10.1016/j.gie.2015.08.050]
 - 19 **Pascarenco OD**, Boeriu A, Mocan S, Pascarenco G, Drasoveanu S, Găleanu M, Dobru D. Barrett's esophagus and intestinal metaplasia of gastric cardia: prevalence, clinical, endoscopic and histological features. *J Gastrointest Liver Dis* 2014; **23**: 19-25 [PMID: 24689092]
 - 20 **Suter MJ**, Gora MJ, Lauwers GY, Arnason T, Sauk J, Gallagher KA, Kava L, Tan KM, Soomro AR, Gallagher TP, Gardecki JA, Bouma BE, Rosenberg M, Nishioka NS, Tearney GJ. Esophageal-guided biopsy with volumetric laser endomicroscopy and laser cautery marking: a pilot clinical study. *Gastrointest Endosc* 2014; **79**: 886-896 [PMID: 24462171 DOI: 10.1016/j.gie.2013.11.016]

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Observational Study

All ileo-cecal ulcers are not Crohn's: Changing perspectives of symptomatic ileocecal ulcers

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Institutional review board statement: This study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent for the treatment and colonoscopy was obtained from all patients. We did not seek individual ethical approval by the Committee because this was an observational study without interpositions and with the medical practice necessary for therapeutic purposes.

Informed consent statement: Informed consent from the included patients was not obtained to participate in the study. However, each patient provided written informed consent for undergoing colonoscopy and treatment.

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Abstract**AIM**

To investigate clinical, endoscopic and histopathological parameters of the patients presenting with ileocecal ulcers on colonoscopy.

METHODS

Consecutive symptomatic patients undergoing colonoscopy, and diagnosed to have ulcerations in the ileocecal (I/C) region, were enrolled. Biopsy was obtained and their

clinical presentation and outcome were recorded.

RESULTS

Out of 1632 colonoscopies, 104 patients had ulcerations in the I/C region and were included in the study. Their median age was 44.5 years and 59% were males. The predominant presentation was lower GI bleed (55, 53%), pain abdomen \pm diarrhea (36, 35%), fever (32, 31%), and diarrhea alone (9, 9%). On colonoscopy, terminal ileum was entered in 96 (92%) cases. The distribution of ulcers was as follows: Ileum alone 40% (38/96), cecum alone 33% (32/96), and both ileum plus cecum 27% (26/96). The ulcers were multiple in 98% and in 34% there were additional ulcers elsewhere in colon. Based on clinical presentation and investigations, the etiology of ulcers was classified into infective causes (43%) and non-infective causes (57%). Fourteen patients (13%) were diagnosed to have Crohn's disease (CD).

CONCLUSION

Non-specific ileocecal ulcers are most common ulcers seen in ileo-cecal region. And if all infections are clubbed together then infection is the most common (> 40%) cause of ulcerations of the I/C region. Cecal involvement and fever are important clues to infective cause. On the contrary CD account for only 13% cases as a cause of ileo-cecal ulcers. So all symptomatic patients with I/C ulcers on colonoscopy are not Crohn's.

Key words: Ileocecal; Crohn's disease; Diffuse large B-cell non-hodgkin's lymphoma

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Core tip: This is one of the largest studies till date defining etiology, endoscopic and histological features of ileocecal (I/C) ulcers. Non-specific ileocecal ulcers are most common ulcers seen in ileo-cecal region. And if all infections are clubbed together then infection is the the most common (> 40%) cause of ulcerations of the IC region. On the contrary Crohn's disease (CD) account for only 13% cases as a cause of ileo-cecal ulcers. So all symptomatic patients with I/C ulcers on colonoscopy are not CD. Also, we conclude that with increasing use of Colonoscope in diagnosis and treatment, majority of the patients with ileo-cecal ulcers can be managed conservatively without surgery.

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INTRODUCTION

Term ileocecum pertains to the cecum and the terminal filament of ileum including the region where they are connected by the ileocecal (I/C) valve^[1]. Due to distinct anatomy and physiology this region is affected by various diseases like ulcerative colitis, Crohn's disease (CD), non-specific ulcers, Malignancies, Amoebiasis, Enteric fever and Tuberculosis (TB)^[2-6]. CD in particular affect Ileum alone or ileo-colonic region in about 60%-70% cases^[7]. But whether 60%-70% of I/C ulcers are CD needs evaluation. I/C ulcers may manifest as small bowel obstruction, abdominal pain, perforation, acute or chronic gastrointestinal blood loss, cachexia, fever or malabsorption syndrome^[8]. There is paucity of data on etiology, clinical profile and histopathological correlation of patient with I/C ulcerations. To evaluate the etiology of ileocecal ulcers is challenging for Clinician, Endoscopist and Histopathologist alike^[9-13]. In the present study, clinical, endoscopic and histopathological parameters of the patients presenting with ileocecal ulcers on colonoscopy, were summarized, and investigated.

MATERIALS AND METHODS

This study was conducted at Sir Ganga Ram Hospital, New Delhi. This was an observational study conducted over a period of 18 mo from May 2010 to October 2011. Colonoscopy was done with fibro-optic colonoscope (Olympus, Japan 180 cf or 160 cf). Colonic preparation was done using a polyethylene glycol-electrolyte-based solution (Peglec, Tablets India Ltd, Chennai). The procedure was performed under conscious sedation with intravenous diazepam (5-10 mg) and pentazocine (25-50 mg). During colonoscopy a careful search was made for the presence of ulcers in cecum, ileocecal valve or terminal ileum. If any ulcer was present then multiple biopsies were obtained from the lesion and the margins for histopathological examination. Exclusion criteria included patients < 18 years of age and asymptomatic patients undergoing screening colonoscopy. The data was prospectively collected. This study was conducted in accordance with the principles of the Declaration of Helsinki, and written informed consent for the treatment and colonoscopy was obtained from all patients. We did not seek individual ethical approval by the Committee because this was an observational study without interpositions and with the medical practice necessary for therapeutic purposes. Descriptive statistics was used for data analysis. Continuous variables were presented as mean or median (range). Categorical variables were expressed as frequencies and percentages. SPSS 17 for windows statistics package (Microsoft corp. Richmond, VA) was used for analysis. One hundred and four patients with ileo-cecal ulcerations and biopsy specimen

Table 1 Etiology of ileo-cecal ulcers *n* (%)

Infective causes <i>n</i> = 45 (43%)	Amoebic	13 (12)
	Tubercular	11 (11)
	Typhoid	4 (4)
	Pseudomembranous colitis	2 (2)
	Unspecified bacterial infections	15 (14)
Non-infectious causes <i>n</i> = 59 (57%)	CD	14 (13)
	NSAID induced	6 (6)
	Malignant	6 (6)
	Miscellaneous	4 (4)
	Non-specific	29 (28)

CD: Crohn's disease; NSAID: Nonsteroidal antiinflammatory drug.

subjected to histopathological examination were included in the study.

Definitions

(1) Amoebic ulcers were diagnosed if the biopsy specimen demonstrated trophozoites of *E. histolytica* or test for amoebic serology was positive in blood sample; (2) enteric or typhoid ulcers were diagnosed either on histology or if widal titer was positive or blood culture was positive for *Salmonella typhi*; (3) unspecified infective ulcers were diagnosed if patient presented with acute onset diarrhea or dysentery with febrile illness and tests for other infections like amoebiasis; enteric fever were negative; or by histopathological evidence; (4) tubercular ulcers were diagnosed if tubercle bacilli was demonstrated in biopsy specimen or by presence of caseating granuloma in biopsy specimen or if there was evidence of extra-intestinal tuberculosis; or past history of tuberculosis; (5) Crohn's ileocecal disease was diagnosed by presence of skip lesions, pseudopolyps or fistulas on endoscopic or radiological examination with presence of cryptitis or cryptic abscesses or non-caseating granulomas on biopsy. Use of data and criterias from past studies was made to differentiate between TB and CD^[9-11,13]; (6) NSAID induced ileocecal ulcers were diagnosed either on histology or if patient had history of NSAID intake; (7) malignant ileocecal ulcers were diagnosed if malignancy was demonstrated on biopsy from ulcers or biopsy/fine needle aspiration cytology from surrounding lymphnode; (8) pseudomembranous colitis was diagnosed if stool examination demonstrated the presence of *C. difficile* toxin A and B; (9) eosinophilic enteritis was diagnosed as per standard criteria^[14]; (10) non-specific ileocecal ulcer was diagnosis of exclusion; where other causes were ruled out and biopsy demonstrated the same; (11) small ulcers were ulcers with maximum diameter < 1.5 cm; and (12) large ulcers were ulcers with maximum diameter of > 1.5 cm.

RESULTS

Total 1632 colonoscopies were performed during the study period. One hundred and four (7%) patients with ulcer in cecum, ileo-cecal valve or terminal ileum

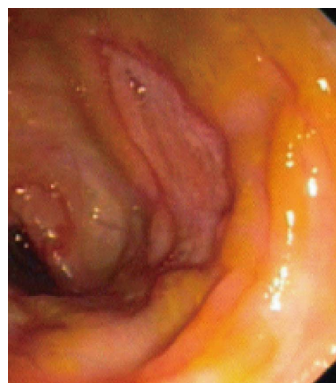


Figure 1 Amoebic ulcer in cecum.

and biopsy specimen subjected for histopathological examination formed the study group. The median age was 44.5 years with a range of 18-85 years. Sixty-one (59%) patients were males. The predominant presentation was lower Gastro-intestinal (GI) bleed (*n* = 55), Pain abdomen with or without diarrhoea (*n* = 36), weight loss (*n* = 20), constipation (*n* = 10), diarrhoea alone (*n* = 9). Associated fever was present in 33 patients. On colonoscopy, terminal ileum could be entered in 96 (92%) cases. The distribution of ulcers was as follows: Ileum alone 38 (40%), cecum alone 32 (33%), and both ileum plus cecum 26 (27%). In the 8 patients in whom ileum could not be entered ulcerations were present on the cecum and the IC valve. The ulcers were multiple in 99 (98%). In 35 (34%) there were additional ulcers elsewhere in colon. One patient left the hospital against medical advice. Three patients expired. Eight patients required surgical treatment. Remaining 92 patients had uneventful recovery. Various causes of Ileo-cecal ulcers are summarised in Table 1.

Amoebic ulcers (*n* = 13) predominantly affected males. Most common presentation was lower gastro-intestinal (GI) bleeding. Twelve patients had multiple ulcers. Ileum was affected in only one case but cecum (Figure 1) was involved in twelve cases. Ulcers were large, multiple, necrotic, with inflammatory edges. Amoebic serology was positive in all patients. Amoebic trophozoites (Figure 2) were seen on biopsy in 1 patient. Six patients had active ooze from ulcers. Two patients required surgery in form of right hemicolectomy to control the bleed. Rest were managed with conservative treatment including antibiotics.

Eleven patients had I/C ulcers due to tuberculosis (Figure 3). Presenting complaints were weight loss and pain abdomen. Cecum was cicatrised in 8 patients and I/C valve was deformed in four. Ulcers were small and multiple. Biopsy (Figure 4) was diagnostic in 7. In view of persistent obstruction 1 patient required surgery while the remaining 10 patients were managed with anti-tubercular treatment.

Fifteen patients were diagnosed as unspecified infective ulcers. GI bleed and fever were most common presentation. Ileum was involved in 10 and cecum in 8 patients. Ulcers were small, large, multiple and with

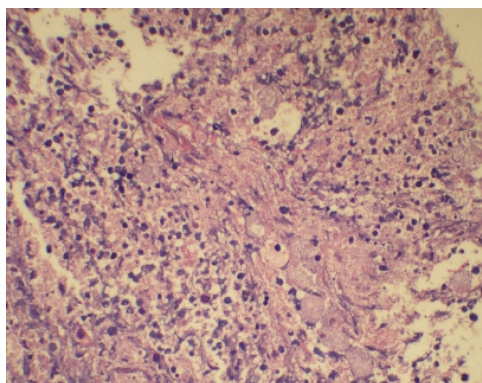


Figure 2 Amoebic trophozoites on histopathology.

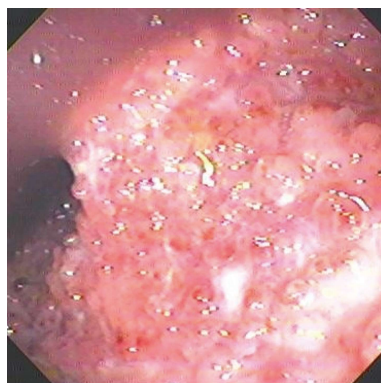


Figure 5 Pseudopolyps in Crohn's disease.

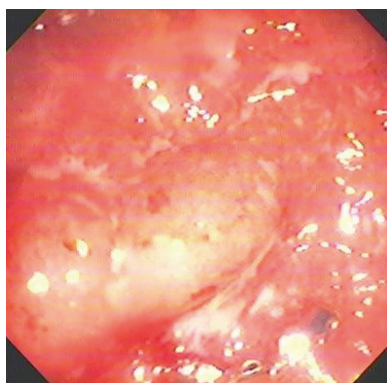


Figure 3 Tubercular ulcers in ileum.



Figure 6 Ulcer on ileo-cecal valve ileocecal-lymphoma.

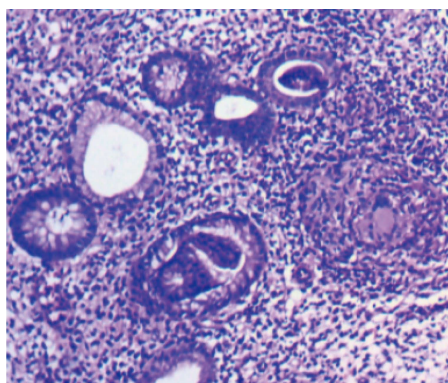


Figure 4 Tubercular granuloma.

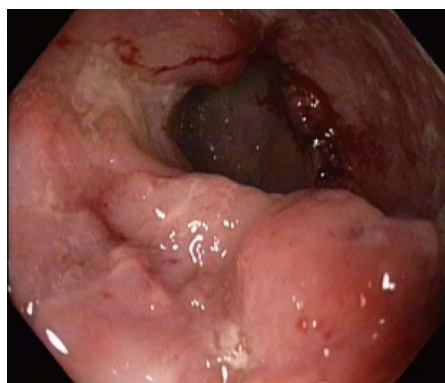


Figure 7 Ileal ulcer-lymphoma.

various morphologies. Ten patients had active ooze or stigmata of recent bleed, on colonoscopy. Biopsy was diagnostic in 9 patients. One patient expired due to sepsis and renal failure. One patient left the hospital against medical advice.

Fourteen patients were diagnosed as ileocecal Crohn's. Eleven were females. Most common presenting complaints were pain abdomen or gastrointestinal bleed. Ileum was involved in 12, cecum in 6 and I/C valve in only one. Ulcers were small or large. Skip lesion were present in 3 cases. Pseudopolyps (Figure 5) were present in two cases. Biopsy was diagnostic in 6 patients. No patient required surgical intervention.

Six patients had non-steroidal anti-inflammatory drugs (NSAID) induced I/C ulcers. All had history of NSAID intake ranging for 5 d to 24 mo prior to presentation. Presenting complaints were gastrointestinal bleed, diarrhea, pain abdomen. No patient had fever. Ileum was involved in 5 patients and cecum in 3. Biopsy was diagnostic in 1 patient. All patients recovered without the need for surgery.

Six patients were diagnosed to have malignancies-3 adenocarcinoma cecum and 3 ileocecal diffuse large B-cell non-hodgkin's lymphoma (DLBCL) (Figures 6 and 7). Colonic biopsy (Figure 8) was diagnostic in 4 cases. Two patients of adenocarcinoma were operated, while

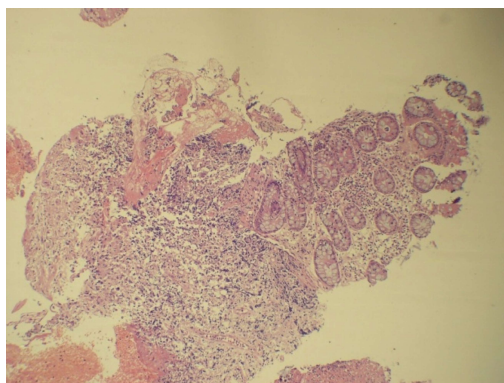


Figure 8 Biopsy demonstrating lymphoma.

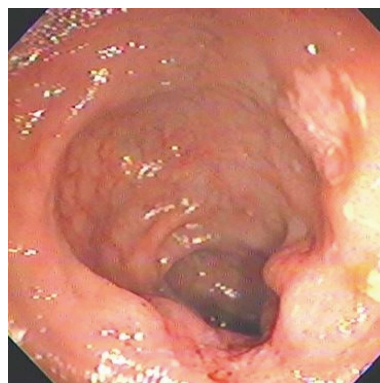


Figure 9 Non-specific ileal ulcer.

1 was treated with chemotherapy. The later expired. Of the 3 DLBCLall were treated with chemotherapy.

Four patients had I/C ulcers secondary to enteric fever. Presenting complaints were fever, pain abdomen, GI bleed. Ileum was involved in 3 cases and cecum in 2 cases. Ulcers were large (> 1.5 cm) with necrotic slough; associated with active ooze in 2 cases. Biopsy was diagnostic in one. Haemostasis by endoscopic therapy was achieved in one patient while one patient underwent right hemicolectomy.

Two patients were diagnosed with eosinophilic enteritis with ileal ulcers on colonoscopy. Both presented with pain abdomen.

Two patients were diagnosed as pseudomembranous colitis with I/C involvement. Biopsy was diagnostic in one patient whereas stool for *Clostridium difficile* toxin A and B was positive for both. On endoscopy Ulcers were multiple with necrotic slough.

Twenty-nine patients were diagnosed with non-specific ileocecal ulcers (Figure 9). Presenting complaints were GI bleed in 14, pain abdomen in 11 and diarrhea in 7 patients. No patient had fever. Ileum was involved in 21 patients. Ulcers were small or large and with various morphologies. Active ooze was noted in eight patients of whom six were managed by Endoscopic therapy. Two required surgery. One expired due to massive bleeding.

With infective cause, fever was significantly more common (47% vs 19%, $P < 0.01$) and cecum was preferentially involved (82% vs 45%, $P < 0.01$).

DISCUSSION

This is one of the largest study till date defining etiology, colonoscopic and histo-pathological features of ileo-cecal ulcers. This study is interesting for several reasons.

First, Crohn's disease in particular affect ileum or ileum along with colon in about 60%-70% patients^[7]. However, the converse is not true, *i.e.*, 80% of ileo-cecal ulcers are not Crohn's. In our study CD was cause for ileo-cecal ulcers in 13% of patients. Ileum was affected in 90% cases. Pain abdomen and GI bleed were

common presentations. Absence of fever and sparing of ileo-cecal valve were helpful in diagnosing Crohn's.

Second, in our study most common etiology of ileo-cecal ulcers was non-specific ulcers. Clinically these ulcers manifest without fever. They are pleomorphic in nature on colonoscopy and predominantly involve the ileum. They can cause massive GI bleed and result in mortality. However, if treated promptly hemostasis can be achieved by endoscopic treatment. These results were comparable to studies by Boydstun *et al*^[6] and Thomas *et al*^[15] in terms of, presenting complaints and site of ulcers. However, as they conducted studies when endoscopic methods of hemostasis were not practiced. So surgery was the only curative treatment for their patients.

Third, Infections, if clubbed together, was most common cause of ulcerations in Ileo-cecal region. Findings were comparable with a Chinese study^[8]. Both these studies demonstrated that most common cause of ileocecal ulcers is infection especially in tropics. We also hypothesize that infection can be most common etiology of ulcers in other parts of world. Though, Amoeba and Tuberculosis are uncommon in Europe and America, bacterial infections are common worldwide.

Amoebic serology was useful diagnostic tool to differentiate amoebic ileocecal ulcers from other causes of ileocecal ulcers. Male sex, fever, gastrointestinal bleed, and large necrotic ulcers involving the cecum with ileal sparing favored amoebic ulcers. Findings were comparable to other studies^[16].

Multiple ulcers with cicatrization of Cecum and deformed I/C valve suggest tubercular etiology. Biopsy is always not diagnostic. Abdominal pain, weight loss, fever, and a lump in the abdomen are common presentations. Clinical features combined with colonoscopy need to be considered to start treatment. Cai *et al*^[8] even suggested that based on these findings anti-tubercular treatment can be started and response to treatment can be evaluated after 6-8 wk of treatment.

In enteric fever, patients are febrile with widal test or blood culture positive for *S. typhi*. Large ileal ulcers with necrotic slough; associated with active ooze is common colonoscopic findings. Majority of them can be treated

by conservative treatment including antibiotic therapy.

Unspecified bacterial infections was most common cause of infective ileocecal ulcers. Febrile patients with multiple ileal ulcers and associated oozing of blood are common findings. Tests for other infective causes are negative. These findings were comparable to other studies but in these studies causative bacteria were defined^[17,18].

And lastly, NSAIDs, Eosinophilic enteritis and malignancies have been described in literature as cause of ulcerations in ileo-cecal region^[3,14,19]. These causes were also noted in our study. But, they were cause of ulcerations in minor group of patients. Findings of our study were comparable with literature.

To conclude, non-specific ileocecal ulcers are most common ulcers seen in ileo-cecal region. And if all infections are clubbed together then infection is the the most common (> 40%) cause of ulcerations of the IC region. Cecal involvement and fever are important clues to infective cause. On the contrary CD account for only 13% cases as a cause of ileo-cecal ulcers. So all symptomatic patients with I/C ulcers on colonoscopy are not Crohn's. And with increasing use of Colonoscope in diagnosis and treatment, majority of the patients with ileo-cecal ulcers can be managed conservatively without need for surgery.

COMMENTS

Background

Evaluation of ileocecal ulcers is challenging for Clinician, Endoscopist and Histopathologist. Data on ileocecal ulcers, from Asian countries, differ from western world. In this study, all these parameters of the patients presenting with ileocecal ulcers on colonoscopy, were summarized, and investigated.

Research frontiers

Colonoscopy is a novel tool that allows evaluation as well as treatment of ileocecal ulcers in majority of cases. It has largely replaced surgery for evaluation and treatment of these ulcers. The present study confirmed this hypothesis in Indian patients.

Innovations and breakthroughs

The present study showed that symptomatic ileo-cecal ulcers, are mainly caused by infections; specially in tropical Asian countries. Non-specific ulcers also predominate the list and are cause of significant morbidity and mortality. Fortunately, with the use of colonoscope for achieving hemostasis majority of these patients can be managed conservatively.

Applications

This study suggests that Crohn's disease is cause of ulcers in ileo-cecal region in a very small subset of patients. Majority of ulcers are caused by infections. Involvement of cecum and fever are important clues to diagnoses these infective ulcers.

Terminology

Ileo-cecal (I/C) ulcers are ulcers located in terminal ileum, cecum or on ileocecal valve noted during colonoscopic examination.

Peer-review

I/C ulcers were evaluated in this study. Jay Toshniwal *et al* evaluated their patients undergoing colonoscopy. It was detected that 104 patients (of 1632 colonoscopies) had ulcerations in the I/C region and non-specific ileocecal

ulcers are most common ulcers seen in ileo-cecal region. The results may be meaningful for interested specialists.

REFERENCES

- 1 Barret KE. Lange Gastrointestinal Physiology. 1st ed. USA: The McGraw-Hill Companies, 2006: 196
- 2 Alvares JF, Devarbhavi H, Makhija P, Rao S, Kottoor R. Clinical, colonoscopic, and histological profile of colonic tuberculosis in a tertiary hospital. *Endoscopy* 2005; **37**: 351-356 [PMID: 15824946 DOI: 10.1055/s-2005-861116]
- 3 Zhai L, Zhao Y, Lin L, Tian Y, Chen X, Huang H, Lin T. Non-Hodgkin's lymphoma involving the ileocecal region: a single-institution analysis of 46 cases in a Chinese population. *J Clin Gastroenterol* 2012; **46**: 509-514 [PMID: 22105183 DOI: 10.1097/MCG.0b013e318237126c]
- 4 Wanke C, Butler T, Islam M. Epidemiologic and clinical features of invasive amebiasis in Bangladesh: a case-control comparison with other diarrheal diseases and postmortem findings. *Am J Trop Med Hyg* 1988; **38**: 335-341 [PMID: 2895590]
- 5 Lee JH, Kim JJ, Jung JH, Lee SY, Bae MH, Kim YH, Son HJ, Rhee PL, Rhee JC. Colonoscopic manifestations of typhoid fever with lower gastrointestinal bleeding. *Dig Liver Dis* 2004; **36**: 141-146 [PMID: 15002823 DOI: 10.1016/j.dld.2003.10.013]
- 6 Boydston JS, Gaffey TA, Bartholomew LG. Clinicopathologic study of nonspecific ulcers of the small intestine. *Dig Dis Sci* 1981; **26**: 911-916 [PMID: 7285731 DOI: 10.1007/BF01309496]
- 7 Santana GO, Souza LR, Azevedo M, Sá AC, Bastos CM, Lyra AC. Application of the Vienna classification for Crohn's disease to a single center from Brazil. *Arg Gastroenterol* 2008; **45**: 64-68 [PMID: 18425231 DOI: 10.1590/S0004-28032008000100012]
- 8 Cai J, Li F, Zhou W, Luo HS. Ileocecal ulcer in central China: case series. *Dig Dis Sci* 2007; **52**: 3169-3173 [PMID: 17404880 DOI: 10.1007/s10620-006-9548-8]
- 9 Makharia GK, Srivastava S, Das P, Goswami P, Singh U, Tripathi M, Deo V, Aggarwal A, Tiwari RP, Sreenivas V, Gupta SD. Clinical, endoscopic, and histological differentiations between Crohn's disease and intestinal tuberculosis. *Am J Gastroenterol* 2010; **105**: 642-651 [PMID: 20087333 DOI: 10.1038/ajg.2009.585]
- 10 Yu H, Liu Y, Wang Y, Peng L, Li A, Zhang Y. Clinical, endoscopic and histological differentiations between Crohn's disease and intestinal tuberculosis. *Digestion* 2012; **85**: 202-209 [PMID: 22354097 DOI: 10.1159/000335431]
- 11 Pulimood AB, Amarapurkar DN, Ghoshal U, Phillip M, Pai CG, Reddy DN, Nagi B, Ramakrishna BS. Differentiation of Crohn's disease from intestinal tuberculosis in India in 2010. *World J Gastroenterol* 2011; **17**: 433-443 [PMID: 21274372 DOI: 10.3748/wjg.v17.i4.433]
- 12 Gan HT, Chen YQ, Ouyang Q, Bu H, Yang XY. Differentiation between intestinal tuberculosis and Crohn's disease in endoscopic biopsy specimens by polymerase chain reaction. *Am J Gastroenterol* 2002; **97**: 1446-1451 [PMID: 12094863 DOI: 10.1111/j.1572-0241.2002.05686.x]
- 13 Pulimood AB, Peter S, Ramakrishna B, Chacko A, Jeyamani R, Jeyaseelan L, Kurian G. Segmental colonoscopic biopsies in the differentiation of ileocolic tuberculosis from Crohn's disease. *J Gastroenterol Hepatol* 2005; **20**: 688-696 [PMID: 15853980 DOI: 10.1111/j.1440-1746.2005.03814.x]
- 14 Freeman HJ. Adult eosinophilic gastroenteritis and hypereosinophilic syndromes. *World J Gastroenterol* 2008; **14**: 6771-6773 [PMID: 19058302 DOI: 10.3784/wjg.14.6771]
- 15 Thomas WE, Williamson RC. Nonspecific small bowel ulceration. *Postgrad Med J* 1985; **61**: 587-591 [PMID: 4022891 DOI: 10.1136/pgmj.61.717.587]
- 16 Nagata N, Shimbo T, Akiyama J, Nakashima R, Nishimura S, Yada T, Watanabe K, Oka S, Uemura N. Risk factors for intestinal invasive amebiasis in Japan, 2003-2009. *Emerg Infect Dis* 2012; **18**: 717-724 [PMID: 22515839 DOI: 10.3201/eid]
- 17 Shigeno T, Akamatsu T, Fujimori K, Nakatsuji Y, Nagata A. The clinical significance of colonoscopy in hemorrhagic colitis due to enterohemorrhagic *Escherichia coli* O157: H7 infection. *Endoscopy* 2002; **34**: 311-314 [PMID: 11932787 DOI: 10.1055/s-2002-23644]

- 18 **Khuroo MS**, Mahajan R, Zargar SA, Panhotra BR, Bhat RL, Javid G, Mahajan B. The colon in shigellosis: serial colonoscopic appearances in *Shigella dysenteriae* I. *Endoscopy* 1990; **22**: 35-38 [PMID: 2407526 DOI: 10.1055/s-2007-1012784]
- 19 **Hayashi Y**, Yamamoto H, Kita H, Sunada K, Sato H, Yano T,

Iwamoto M, Sekine Y, Miyata T, Kuno A, Iwaki T, Kawamura Y, Ajibe H, Ido K, Sugano K. Non-steroidal anti-inflammatory drug-induced small bowel injuries identified by double-balloon endoscopy. *World J Gastroenterol* 2005; **11**: 4861-4864 [PMID: 16097059 DOI: 10.3748/wjg.v11.i31.4861]

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Prospective Study

Endoscopic submucosal dissection of gastric adenomas using the clutch cutter

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Abstract**AIM**

To evaluate the efficacy and safety of endoscopic submucosal dissection (ESD) using the clutch cutter (CC) (ESD-CC) for gastric adenoma (GA).

METHODS

From June 2007 to August 2015, 122 consecutive patients with histological diagnoses of GA from specimens resected by ESD-CC were enrolled in this prospective study. The CC was used for all ESD steps (marking, mucosal incision, submucosal dissection, and hemostatic treatment), and its

therapeutic efficacy and safety were assessed.

RESULTS

Both the *en-bloc* resection rate and the R0 resection rate were 100% (122/122). The mean surgical time was 77.4 min, but the time varied significantly according to tumor size and location. No patients suffered perforation. Post-ESD-CC bleeding occurred in six cases (4.9%) that were successfully resolved by endoscopic hemostatic treatment.

CONCLUSION

ESD-CC is a technically efficient, safe, and easy method for resecting GA.

Key words: Endoscopic submucosal dissection; Clutch cutter; Gastric adenoma

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Core tip: The clutch cutter (CC) was developed to reduce risk of complications related to endoscopic submucosal dissection (ESD) using conventional knives. The CC can grasp, pull, coagulate and/or incise targeted tissue using electrosurgical current, as with a bite biopsy. The CC can be used in all ESD steps (marking, mucosal incision, submucosal dissection, and hemostatic treatment). ESD using the CC (ESD-CC) for gastric adenoma (GA) gave a 100% R0 resection rate in this study, with no perforation. ESD-CC is a technically efficient, safe, and easy method for resecting GA.

Akahoshi K, Kubokawa M, Gibo J, Osada S, Tokumaru K, Yamaguchi E, Ikeda H, Sato T, Miyamoto K, Kimura Y, Shiratsuchi Y, Akahoshi K, Oya M, Koga H, Ihara E, Nakamura K. Endoscopic submucosal dissection of gastric adenomas using the clutch cutter. *World J Gastrointest Endosc* 2017; 9(7): 334-340 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v9/i7/334.htm> DOI: <http://dx.doi.org/10.4253/wjge.v9.i7.334>

INTRODUCTION

Endoscopic submucosal dissection (ESD) has considerable advantages regarding rates for local recurrence, and *en-bloc* and R0 resections, compared with conventional endoscopic mucosal resection (EMR)^[1,2]. Worldwide, ESD gradually increases in its indication share instead of EMR. However, the major disadvantages of ESD with conventional knives is its technical difficulty; Therefore, it has a high complication incidence and protracted procedural time, requiring advanced endoscopic skills and many devices^[3-5]. Conventional devices (such as IT and needle knives) are gently pushed to the targeted tissue; then, these tissues are cut using electrosurgical current. Because these cutting mechanisms cannot grasp or pull at the targeted tissue, accurate targeting, compressive hemostasis and the ability to draw the

targeted tissue away from the muscle layer are lacking, causing the risk of serious adverse events including gastric perforation and hemorrhage^[6,7]. In order to resolve the hazards of ESD using conventional knives, the Clutch Cutter (CC) was developed and can precisely grasp, pull, coagulate, and/or resect the targeted tissue using high frequency current^[5-9]. In our previous prospective study of early gastric cancers (EGCs), we were able to remove cancers safely and easily without unexpected electrical tissue damage by using ESD with the CC (ESD-CC)^[5]. However, until now clinical performance in many patients with GA treated by this new method of ESD-CC has not been sufficiently investigated. In this study, we evaluated the clinical performance of ESD-CC for GA in larger number of patients.

MATERIALS AND METHODS

Inclusion criteria/curability criteria and ethical considerations

We enrolled 122 consecutive patients (78 men, 44 women; mean age: 71.8 years, range: 52-91 years) who were histologically diagnosed with GA using specimens resected by ESD-CC at Aso Iizuka Hospital from June 2007 to December 2015 (Table 1) in this study. R0 resection (*en-bloc* resection with negative horizontal and vertical margins) is considered to be curative. To evaluate the learning curve for ESD-CC, 122 cases were grouped chronologically into four periods: (1) cases 1-30; (2) cases 31-60; (3) cases 61-90; and (4) cases 91-122. This study was carried out at Aso Iizuka Hospital and was approved by its ethics committee. Written informed consent was obtained from all patients in accordance with the Declaration of Helsinki.

Clutch cutter

The clutch cutter (CC) (DP2618DT, FUJIFILM Corporation, Tokyo, Japan; Video 1) has serrated jaws that allow the endoscopist to grasp the targeted tissue securely. The width and length of the jaws is 0.4-mm and 5-mm respectively^[5-9]. The jaws can be rotated 360 degrees and the outer edges are insulated to minimize the electrical risk. The diameter of the insertion portion is 2.7 mm. The CC can manage all steps of ESD. The high-frequency electrosurgical unit is the VIO 300D (Erbe, Tübingen, Germany). The forced coagulation mode (30 W, effect 3) was used for marking. The Endocut-Q mode (effect 2, duration 3, interval 1) was used for mucosal incision and submucosal dissection, whereas the soft coagulation mode (effect 5, 100 W) was used for hemostasis and preventive coagulation (pre-cut and post-ESD).

ESD-CC

The ESD-CC procedures were performed by two endoscopists; one maneuvered the video-endoscope, and the other one operated the CC. The ESD-CC procedure

Table 1 Clinicopathological characteristics (*n* = 122)

Sex, male/female	78/44
mean ± SD (range) age years	71.9 ± 8.4 (52-91)
Locatio	
Lower	44 (36)
Middle	54 (44)
Upper	24 (20)
Macroscopic type	
I (protruded)	10 (8)
II a (flat elevated)	65 (53)
II a + II c	16 (13)
I c + II a	5 (4)
II a + I	2 (2)
II c (shallow depressed)	24 (20)

used a one-channel endoscope with water jet function (EG-450RD5, EG-530RD5, Fujifilm, Tokyo, Japan) or a two-channel multi-bending endoscope with water jet function (GIF-2T240M; Olympus, Tokyo, Japan). A transparent attachment (F-01, Top Co. Ltd., Tokyo, Japan) was fitted onto the tip of the endoscope to obtain an adequate endoscopic view and to create tension on the targeted submucosal tissue during ESD-CC.

The ESD-CC technique

Using the CC in closed mode, dots placed approximately 5 mm outside the lesion margin were made to mark the circumference of the target lesion. Next, 1-2 mL of hyaluronic acid solution (MucoUp; Johnson and Johnson Co., Tokyo, Japan) mixed with small volumes of epinephrine and indigo carmine dye were injected into the submucosal layer; this injection was repeated a few times to obtain sufficient elevation of the mucosa (Videos 2 and 3).

A mucosal incision and subsequent submucosal excision using the CC were repeated to remove the lesion *en-bloc*. The bleeding artery or vein was grasped, pulled or lifted, and coagulated with the CC to stop the bleeding. Finally, the *en-bloc* resection of the lesion was completed. All incisions and excisions consisted of four basic procedures: (1) grasping; (2) pulling or lifting up; (3) initiating pre-cut-coagulation with soft coagulation (if a blood vessel is observed); and (4) cutting with the Endo-cut Q.

Histopathological evaluation

All resected specimens were sectioned into 2-mm wide slices. Histological diagnosis, tumor diameter, infiltration depth, presence of ulcer, and tumor involvement of horizontal and vertical margins were evaluated.

Assessment of the clinical outcomes

Surgical time was calculated as the time from the beginning of the submucosal injection to the end of the submucosal dissection. *En-bloc* resection was defined as the lesion being removed in one piece with macroscopically intact resection margins.

Involvement of the tumor to the resected margins

Table 2 Technical outcomes of endoscopic submucosal dissection procedures using the clutch cutter (*n* = 122)

mean ± SD size of the lesion, mm (range)	15.3 ± 8.8 (2-43)
mean ± SD size of resected specimen, mm (range)	41.4 ± 14.3 (8-90)
En-bloc resection rate (%)	122/122 (100)
R0 resection rate (%)	122/122 (100)
mean ± SD surgical time, min (range)	77.4 ± 52.8 (13-325)
Complication rate	6/122 (4.9)
Intra-ESD perforation rate	0/122 (0)
Intra-ESD uncontrollable bleeding rate	0/122 (0)
Post-ESD bleeding rate	6/122 (4.9)
Post-ESD perforation rate	0/122 (0)

ESD: Endoscopic submucosal dissection.

was determined as R0 (*en-bloc* resection with histologically lateral and basal tumor-free resection margins), R1 (incomplete resection with histologically tumor-positive lateral or basal margins), or Rx (resection with unevaluable histological tumor margins resulting from burning effects or multiple-piece resection). All patients stayed in the hospital for 7 d following the procedure, after which follow-up endoscopic examinations were conducted at 2 d, then at 2 (or 3) mo, and annually thereafter. All patients took proton pump inhibitors for a minimum of 8 wk.

Statistical analysis

All data analysis was conducted with a statistical software package (SAS version 9.2 and JMP version 8.0.1, SAS Institute Inc, NC, United States). The Kruskal-Wallis test was used to evaluate differences with respect to tumor size and location, and ESD-CC surgical time. *P* < 0.05 was considered significant.

RESULTS

Table 1 shows the patients' clinical findings. The ratio between males and females was 1.8: 1 (78/44), and the average age was 71.9 years (52-91 years of age). Table 2 shows technical outcomes. The step of grasping and lifting or pulling before cutting the target tissue facilitated the confirmation of the distance between the grasped tissue and the proper muscle layer and enabled the use of sufficient pre-cut coagulation. All tumors could be removed easily and safely without unexpected incision. The mean diameters of GAs were 15.3 ± 8.8 mm. The mean size of resected specimens were 41.4 ± 14.3 mm. Rates for both *en-bloc* resections and R0 resections were 100%. Mean surgical time was 77.4 ± 52.8 min.

During ESD-CC, we encountered no uncontrollable bleeding. Post-ESD bleeding was observed in 4.9% (6/122) of cases. All postoperative bleeding was successfully treated by endoscopic hemostasis using mechanical clip or electrical hemostatic forceps. No patients suffered perforation. Tumor size and location significantly affected the mean surgical time (Table 3).

Learning curves showed changes in proficiency over

Table 3 Surgical time of endoscopic submucosal dissection using the clutch cutter by tumor size and location (*n* = 122)

Tumor size	
0-20 mm	65.2 ± 41.6 (13-260)
21-mm	116.3 ± 65.6 (29-325)
<i>P</i> value	<i>P</i> < 0.001
Location	
Lower	57.5 ± 32.4 (13-192)
Middle	85.7 ± 58.5 (21-325)
Upper	94.8 ± 60.1 (32-264)
<i>P</i> value	<i>P</i> < 0.005

time (Figure 1). Proficiency was expressed as surgical time only; because we had a 100% R0 resection rate and a 0% perforation rate, these parameters were not used to assess proficiency. The surgical time in the introduction stage of ESD-CC was significantly longer than in later stages (*P* < 0.01).

DISCUSSION

Gastric adenoma is usually a benign localized protruding neoplastic lesion, and is a histopathologically, proliferation of mildly atypical epithelium and tubular and/or papillary structures^[10,11]. Since the prevalence of cancerous change of gastric adenoma is relatively low, it is generally considered that follow-up observation is sufficient if the biopsy result during periodic endoscopic examination is Group III and there is no increase in size or change in morphology of the lesion^[12]. However, non-invasive carcinomas sometimes coexist within GAs and can progress to invasive carcinomas^[12,13]. Generally, if a GA is diagnosed through an endoscopic forceps biopsy, the possibility that the lesion has not been diagnosed correctly or that the presence of cancer lesions is overlooked should be carefully considered^[13]. Therefore, a total biopsy, such as endoscopic resection, is often used to obtain a conclusive diagnosis. Although most GAs are removed by conventional EMR, ESD has a high R0 resection rate regardless of the size of the tumor, it allows for more accurate and detailed histopathological examination compared with the EMR, and the recurrence rate can also be reduced^[2-5]. However, ESD is a more difficult and meticulous procedure than EMR, and occasionally causes serious complications. GA is basically a benign disease, and the aim of ESD for this disease is total biopsy. Therefore, safety is vital for performing ESD, and a new and safer device is wanted in this situation.

To resolve the adverse events associated with conventional ESD using a knife devices, Akahoshi and FujiFilm developed the Clutch Cutter (CC) which can accurately grasp, pull, coagulate, and/or cut targeted tissue using high frequency current^[5,8,9]. The CC has four main mechanical functions: (1) fixation (precise targeting); (2) pulling or lifting up (away from the proper muscle layer); (3) compression (high hemostatic capability); and (4) outside insulation (minimization

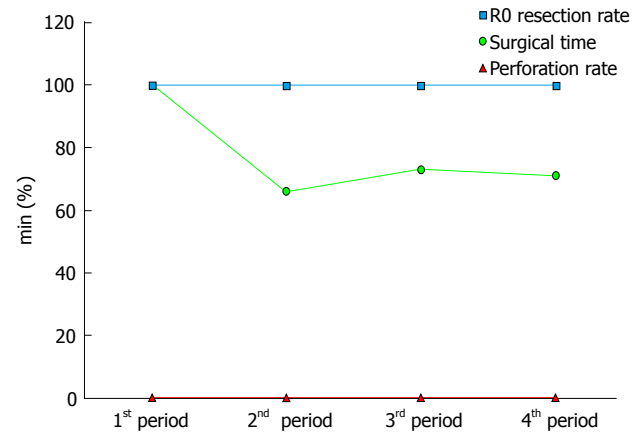


Figure 1 Learning curves. Video 1: The clutch cutter mechanism; Video 2: The basic ESD technique, using the clutch cutter; Video 3: Endoscopic view of ESD using the clutch cutter on gastric adenoma on the greater curvature of the lower gastric body. ESD: Endoscopic submucosal dissection.

of outside electric damage)^[5-9]. In this investigation and in our previous studies^[5-9,14-17], no unintentional incisions were made, and we were able to stop intra-ESD bleeding promptly and without difficulty using the CC without changing devices (Video 2). ESD-CC is performed only by grasping, pulling (or lifting up), and cutting or coagulating procedures; most endoscopists may accept it without difficulty, because ESD-CC is similar to a forceps biopsy (Videos 2 and 3). Moreover, the CC is available for all ESD sub-procedures. These benefits of ESD-CC seem to be effective for reducing the difficulty level of ESD procedures, the frequency of adverse events, and cost^[5-7].

Reported performance ranges for the use of knife devices in EGCs were *en-bloc* resection rate: 94.9%-97.7%; R0 resection rate: 82%-95.5%; and surgical time: 47.8-108.1 min^[2,4,5,18-20]. In our previous study, these rates were *en-bloc* resection rate: 99.7%; R0 resection rate: 95.3%; and mean procedure time using the CC for EGC: 97.2 min^[5], and in this study, these variables were 100%, 100%, and 77.4 min, respectively, using the CC for GA. Thus, rates for *en-bloc* and R0 resection and surgical time of ESD-CC for GAs appears to be slightly better than those of ESD for EGC using a conventional knife. We hypothesize that these better results are because of the CC's fixation mechanism (improving target accuracy), and the fact that GA does not cause ulcerative changes.

Perforation by ESD procedures is of two types, depending on time of onset. The first type is intra-ESD perforation, which is mainly the result of an electrical incision of the proper muscle layer by knife devices. The second fashion is post-ESD perforation that ordinarily shows 1-2 d after the ESD procedure because of deep coagulation. Intra-ESD perforation reportedly occurs in 1.2%-8.2% of gastric ESDs^[3,5,21,22]. Avoiding electric damage to the proper muscle layer is important to avoid unintended incisions. The CC's mechanisms, such as the grasping function (allowing accurate targeting),

pulling function and external insulation are very effective in preventing intra-ESD perforation, and we had none in this ESD-CC study for GAs (0%). Although post-ESD perforation is a rare complication (0.45%), it can lead to serious conditions that often require emergency surgery^[23,24]. Deep thermal damage to the proper muscle layer is considered to be the main cause of perforation after ESD. A gentle push of the knife to the visible vessel using adequate power and duration of electrosurgical coagulation for hemostatic treatment is vital to avoid delayed perforation, a maneuver that requires considerable skill. In addition, there are currently no hemostatic devices with external insulation. These mechanical problems of currently available ESD devices can be associated with Post-ESD perforation. The mechanical advantages of the CC including the pull effect and external insulation are effective to prevent deep thermal tissue damage; we had no post-ESD perforations in this ESD-CC study for GAs.

Bleeding from ESD procedures is also of two types, depending on the time of onset. The first type is intra-ESD bleeding that usually occurs during mucosal incision and submucosal excision. The second type is post-ESD bleeding that occurs after the ESD procedure. Although intra-ESD bleeding occurs frequently, measuring its severity is difficult. Reportedly, significant intra-ESD bleeding occurs in 7% of procedures^[25]. Its prevention and quick hemostasis are crucial because bleeding can lead to a poor endoscopic view, resulting in increased surgical time and the likelihood of perforation. Prophylactic electrosurgical coagulation of visible blood vessels and quickly stopping any bleeding are critical to safe ESDs. The CC can fix (accurately target), pull or lift-up (decreased deep thermal tissue damage), and compress (high hemostatic capability) the target tissue^[5-7]. Therefore, the CC can perform effective pre-cut coagulation and stop intra-ESD hemorrhage quickly without changing the device. We encountered no uncontrollable intra-ESD bleeding in this study. Reportedly, post-ESD gastric bleeding occurs in 5.3%-15.6% of procedures^[3,21,25-28], usually within a week after ESD. Therefore, patients are hospitalized for seven days after ESDs in our institute. The CC can perform pre-cut coagulation or coagulation for exposed blood vessels of a bottom of ESD ulcer. In our research of GAs, the post-ESD bleeding incidence was 4.9%. We must focus on post-ESD bleeding as well as conventional ESD bleeding.

In the introduction stage of ESD, endoscopist has to overcome its technical difficulties and high rates of complication including perforation and bleeding^[29,30]. Previous studies^[30-32] of learning curves for ESD using knife devices show decreased surgical durations and complication rates and increased rates of successful R0 resections, over time. However, ESD-CC is a simple method that consists of (1) grasping; (2) pulling; and (3) cutting or coagulating, as with a standard bite biopsy. Therefore, we obtained a 100% R0 resection rate and a 0% perforation rate, even at the beginning

of the learning curve, because of the ease of learning the ESD-CC procedure, although we were beginners of conventional ESD method using knives. Based on the results of the learning curve analysis, about 30 cases of experience are needed to master the skills to perform ESD-CC for GAs safely and effectively.

In conventional ESD procedures, several specific knives and devices are needed to accomplish the ESD^[5-7], whereas ESD-CC was carried out using only the CC. Before introducing ESD-CC into our institute, we performed conventional ESD procedures that required a needle knife for marking and creating the starting hole, an insulation-tipped electrosurgical knife for mucosal incision and submucosal dissection and an electric hemostat for intra-ESD hemorrhage^[5-7]. The total number of devices for a single ESD was at least three. In our research, we used only one device, the CC, throughout the ESD. Thus, the ESD-CC significantly reduces the number of devices and the cost of ESD^[5,7].

In conclusion, because of its safety, effectiveness of use, technical ease of operation, and low cost of performance, the ESD-CC represents a promising option in the treatment of GAs.

COMMENTS

Background

Compared with endoscopic mucosal resection (EMR) for early gastric tumors, endoscopic submucosal dissection (ESD) has considerable advantages with regard to the rates for *en-bloc* resection, R0 resection and local recurrence. The main shortcoming of ESD using conventional knives is its technical difficulty. Therefore, it has a high rate of complications, and requires advanced endoscopic skills and many devices.

Research frontiers

Conventional knife devices gently push the knife to the tissue and cut using electrosurgical current. As these cutting methods lack a grasping function (which would allow more accurate targeting and hemostatic effect) and pulling function (to lift tissues away from the proper muscle layer), they carry a risk of major complications such as perforation and bleeding.

Innovations and breakthroughs

To reduce the risk of complications related to ESD using a conventional knife, Akahoshi and FujiFilm developed a new grasping type of scissor/forceps, the clutch cutter (CC), which can accurately grasp, pull (or lift), coagulate, and/or incise targeted tissue using electrosurgical current. The CC can safely perform four characteristic mechanical procedures: (1) fixation for accurate targeting; (2) pulling or lifting tissue away from the proper muscle layer; (3) compressing tissue through high hemostatic capability; and (4) external insulation, which minimizes risk of unintended electric damage.

Applications

The authors performed ESD-CC for 122 patients with gastric adenoma. The *en-bloc* resection rate was 100% and the R0 resection rate was 100%. No patients in this study suffered perforation. Post-ESD-CC bleeding occurred in 6 cases (4.9%), which were successfully treated by endoscopic hemostatic treatment.

Terminology

The CC (DP2618DT, FujiFilm Corporation, Tokyo, Japan) is a grasping type of scissor/forceps (VTR: 1), which can grasp and cut or coagulate a piece of tissue with electrosurgical current. It has a 0.4-mm width and a 3.5-mm or 5-mm long serrated cutting edge to facilitate grasping the tissue. The outer side of the forceps is insulated so that electrosurgical current energy is concentrated at the enclosed blade, to avoid unintentional incision. Furthermore, the forceps can be

rotated to the desired orientation. The diameter of the forceps is 2.7 mm. The CC is disposable and not reusable. The CC is available for all steps of ESD.

Peer-review

This manuscript "Endoscopic submucosal dissection of gastric adenomas using the clutch cutter" is the nice paper and good results with the CC.

REFERENCES

- Kakushima N**, Fujishiro M. Endoscopic submucosal dissection for gastrointestinal neoplasms. *World J Gastroenterol* 2008; **14**: 2962-2967 [PMID: 18494043 DOI: 10.3748/wjg.14.2962]
- Lian J**, Chen S, Zhang Y, Qiu F. A meta-analysis of endoscopic submucosal dissection and EMR for early gastric cancer. *Gastrointest Endosc* 2012; **76**: 763-770 [PMID: 22884100 DOI: 10.1016/j.gie.2012.06.014]
- Chung IK**, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, Hwangbo Y, Keum BR, Park JJ, Chun HJ, Kim HJ, Kim JJ, Ji SR, Seol SY. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest Endosc* 2009; **69**: 1228-1235 [PMID: 19249769 DOI: 10.1016/j.gie.2008.09.027]
- Yamamoto Y**, Fujisaki J, Ishiyama A, Hirasawa T, Igarashi M. Current status of training for endoscopic submucosal dissection for gastric epithelial neoplasm at Cancer Institute Hospital, Japanese Foundation for Cancer Research, a famous Japanese hospital. *Dig Endosc* 2012; **24** Suppl 1: 148-153 [PMID: 22533772 DOI: 10.1111/j.1443-1661.2012.01278.x]
- Akahoshi K**, Motomura Y, Kubokawa M, Gibo J, Kinoshita N, Osada S, Tokumaru K, Hosokawa T, Tomoeda N, Otsuka Y, Matsuo M, Oya M, Koga H, Nakamura K. Endoscopic Submucosal Dissection for Early Gastric Cancer using the Clutch Cutter: a large single-center experience. *Endosc Int Open* 2015; **3**: E432-E438 [PMID: 26528497 DOI: 10.1055/s-0034-1392509]
- Akahoshi K**, Akahane H. A new breakthrough: ESD using a newly developed grasping type scissor forceps for early gastrointestinal tract neoplasms. *World J Gastrointest Endosc* 2010; **2**: 90-96 [PMID: 21160708 DOI: 10.4253/wjge.v2.i3.90]
- Akahoshi K**, Akahane H, Motomura Y, Kubokawa M, Itaba S, Komori K, Nakama N, Oya M, Nakamura K. A new approach: endoscopic submucosal dissection using the Clutch Cutter® for early stage digestive tract tumors. *Digestion* 2012; **85**: 80-84 [PMID: 22269283 DOI: 10.1159/000334647]
- Akahoshi K**, Akahane H, Murata A, Akiba H, Oya M. Endoscopic submucosal dissection using a novel grasping type scissors forceps. *Endoscopy* 2007; **39**: 1103-1105 [PMID: 18072064 DOI: 10.1055/s-2007-966842]
- Akahoshi K**, Honda K, Akahane H, Akiba H, Matsui N, Motomura Y, Kubokawa M, Endo S, Higuchi N, Oya M. Endoscopic submucosal dissection by using a grasping-type scissors forceps: a preliminary clinical study (with video). *Gastrointest Endosc* 2008; **67**: 1128-1133 [PMID: 18355820 DOI: 10.1016/j.gie.2007.12.007]
- Goldstein NS**, Lewin KJ. Gastric epithelial dysplasia and adenoma: historical review and histological criteria for grading. *Hum Pathol* 1997; **28**: 127-133 [PMID: 9023391 DOI: 10.1016/S0046-8177(97)90095-2]
- Ming SC**. Cellular and molecular pathology of gastric carcinoma and precursor lesions: A critical review. *Gastric Cancer* 1998; **1**: 31-50 [PMID: 11957042 DOI: 10.1007/s101209800018]
- Nonaka K**, Arai S, Ban S, Kitada H, Namoto M, Nagata K, Ochiai Y, Togawa O, Nakao M, Nishimura M, Ishikawa K, Sasaki Y, Kita H. Prospective study of the evaluation of the usefulness of tumor typing by narrow band imaging for the differential diagnosis of gastric adenoma and well-differentiated adenocarcinoma. *Dig Endosc* 2011; **23**: 146-152 [PMID: 21429020 DOI: 10.1111/j.1443-1661.2010.01070.x]
- Kim JH**, Kim YJ, An J, Lee JJ, Cho JH, Kim KO, Chung JW, Kwon KA, Park DK, Kim JH. Endoscopic features suggesting gastric cancer in biopsy-proven gastric adenoma with high-grade neoplasia. *World J Gastroenterol* 2014; **20**: 12233-12240 [PMID: 25232257 DOI: 10.3748/wjg.v20.i34.12233]
- Kamiya T**, Morishita T, Asakura H, Miura S, Munakata Y, Tsuchiya M. Long-term follow-up study on gastric adenoma and its relation to gastric protruded carcinoma. *Cancer* 1982; **50**: 2496-2503 [PMID: 7139542]
- Rugge M**, Cassaro M, Di Mario F, Leo G, Leandro G, Russo VM, Pennelli G, Farinati F. The long term outcome of gastric non-invasive neoplasia. *Gut* 2003; **52**: 1111-1116 [PMID: 12865267 DOI: 10.1136/gut.52.8.1111]
- Minoda Y**, Akahoshi K, Otsuka Y, Kubokawa M, Motomura Y, Oya M, Nakamura K. Endoscopic submucosal dissection of early duodenal tumor using the Clutch Cutter: a preliminary clinical study. *Endoscopy* 2015; **47** Suppl 1 UCTN: E267-E268 [PMID: 26099085 DOI: 10.1055/s-0034-1392209]
- Akahoshi K**, Okamoto R, Akahane H, Motomura Y, Kubokawa M, Osoegawa T, Nakama N, Chaen T, Oya M, Nakamura K. Endoscopic submucosal dissection of early colorectal tumors using a grasping-type scissors forceps: a preliminary clinical study. *Endoscopy* 2010; **42**: 419-422 [PMID: 20340070 DOI: 10.1055/s-0029-1243973]
- Min YW**, Min BH, Lee JH, Kim JJ. Endoscopic treatment for early gastric cancer. *World J Gastroenterol* 2014; **20**: 4566-4573 [PMID: 24782609 DOI: 10.3748/wjg.v20.i16.4566]
- Nakamoto S**, Sakai Y, Kasanuki J, Kondo F, Ooka Y, Kato K, Arai M, Suzuki T, Matsumura T, Bekku D, Ito K, Tanaka T, Yokosuka O. Indications for the use of endoscopic mucosal resection for early gastric cancer in Japan: a comparative study with endoscopic submucosal dissection. *Endoscopy* 2009; **41**: 746-750 [PMID: 19681023 DOI: 10.1055/s-0029-1215010]
- Bialek A**, Wiechowska-Kozłowska A, Pertkiewicz J, Karpińska K, Marlicz W, Milkiewicz P, Starzyńska T. Endoscopic submucosal dissection for the treatment of neoplastic lesions in the gastrointestinal tract. *World J Gastroenterol* 2013; **19**: 1953-1961 [PMID: 23569341 DOI: 10.3748/wjg.v19.i12.1953]
- Mannen K**, Tsunada S, Hara M, Yamaguchi K, Sakata Y, Fujise T, Noda T, Shimoda R, Sakata H, Ogata S, Iwakiri R, Fujimoto K. Risk factors for complications of endoscopic submucosal dissection in gastric tumors: analysis of 478 lesions. *J Gastroenterol* 2010; **45**: 30-36 [PMID: 19760133 DOI: 10.1007/s00535-009-0137-4]
- Watairi J**, Tomita T, Toyoshima F, Sakurai J, Kondo T, Asano H, Yamasaki T, Okugawa T, Ikehara H, Oshima T, Fukui H, Miwa H. Clinical outcomes and risk factors for perforation in gastric endoscopic submucosal dissection: A prospective pilot study. *World J Gastrointest Endosc* 2013; **5**: 281-287 [PMID: 23772265 DOI: 10.4253/wjge.v5.i6.281]
- Ikezawa K**, Michida T, Iwahashi K, Maeda K, Naito M, Ito T, Katayama K. Delayed perforation occurring after endoscopic submucosal dissection for early gastric cancer. *Gastric Cancer* 2012; **15**: 111-114 [PMID: 21948482 DOI: 10.1007/s10120-011-0089-2]
- Hanaoka N**, Uedo N, Ishihara R, Higashino K, Takeuchi Y, Inoue T, Chatani R, Hanafusa M, Tsujii Y, Kanzaki H, Kawada N, Iishi H, Tatsuta M, Tomita Y, Miyashiro I, Yano M. Clinical features and outcomes of delayed perforation after endoscopic submucosal dissection for early gastric cancer. *Endoscopy* 2010; **42**: 1112-1115 [PMID: 21120780 DOI: 10.1055/s-0030-1255932]
- Oda I**, Gotoda T, Hatanaka H, Eguchi T, Saito Y, Matsuda T, Bhandari P, Emura F, Saito D, Ono H. Endoscopic submucosal dissection for early gastric cancer: technical feasibility, operation time and complications from a large consecutive series. *Dig Endosc* 2005; **17**: 54-58 [DOI: 10.1111/j.1443-1661.2005.00459.x]
- Tsuji Y**, Ohata K, Ito T, Chiba H, Ohya T, Gunji T, Matsuhashi N. Risk factors for bleeding after endoscopic submucosal dissection for gastric lesions. *World J Gastroenterol* 2010; **16**: 2913-2917 [PMID: 20556838 DOI: 10.3748/WJG.v16.i23.2913]
- Fujishiro M**, Chiu PW, Wang HP. Role of antisecretory agents for gastric endoscopic submucosal dissection. *Dig Endosc* 2013; **25** Suppl 1: 86-93 [PMID: 23368844 DOI: 10.1111/j.1443-1661.2012.01370.x]
- Koh R**, Hirasawa K, Yahara S, Oka H, Sugimori K, Morimoto M, Numata K, Kokawa A, Sasaki T, Nozawa A, Taguri M, Morita S, Maeda S, Tanaka K. Antithrombotic drugs are risk factors for delayed postoperative bleeding after endoscopic submucosal dissection for

- gastric neoplasms. *Gastrointest Endosc* 2013; **78**: 476-483 [PMID: 23622974 DOI: 10.1016/j.gie.2013.03.008]
- 29 **Neuhaus H.** Endoscopic submucosal dissection in the upper gastrointestinal tract: present and future view of Europe. *Dig Endosc* 2009; **21** Suppl 1: S4-S6 [PMID: 19691732 DOI: 10.1111/j.1443-1661.2009.00864.x]
 - 30 **Probst A,** Golger D, Arnholdt H, Messmann H. Endoscopic submucosal dissection of early cancers, flat adenomas, and submucosal tumors in the gastrointestinal tract. *Clin Gastroenterol Hepatol* 2009; **7**: 149-155 [PMID: 19032991 DOI: 10.1016/j.cgh.2008.09.005]
 - 31 **Tanimoto MA,** Torres-Villalobos G, Fujita R, Santillan-Doherty P, Albores-Saavedra J, Chable-Montero F, Martin-Del-Campo LA, Vasquez L, Bravo-Reyna C, Villanueva O, Villalobos JJ, Uribe M, Valdovinos MA. Learning curve in a Western training center of the circumferential en bloc esophageal endoscopic submucosal dissection in an in vivo animal model. *Diagn Ther Endosc* 2011; **2011**: 847831 [PMID: 21976950 DOI: 10.1155/2011/847831]
 - 32 **Coman RM,** Gotoda T, Draganov PV. Training in endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; **5**: 369-378 [PMID: 23951392 DOI: 10.4253/wjge.v5.i8]

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Management of hyperplastic gastric polyp following upper gastrointestinal bleeding in infant with Menkes' disease

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Abstract

We report a case of an infant with Menkes' disease (MD) presented at the age of five months, with coffee ground vomiting, melaena with a significant drop of haemoglobin. Urgent endoscopic assessment revealed a friable bleeding trans-pyloric multi-lobulated sessile polyp. Due to further significant upper gastrointestinal bleeding, polypectomy occurred. Endoscopic mucosal resection was performed with a grasp-and-snare technique using a dual channel operating gastroscope. Haemostasis was achieved by application of argon plasma coagulation where required. No perforation occurred. Repeated debridement was required 6 wk after which the growth was excised completely with no further blood transfusion required after that procedure. Histological examination confirmed ulcerated and inflamed hyperplastic polyp. We discuss our endoscopic technique and discuss the reported gastrointestinal manifestation of MD in the literature.

Key words: Menkes' disease; Gastrointestinal bleeding; Grasp and snare technique; Polypectomy; Gastric polyp

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Core tip: Infant with Menkes' disease can present with a potentially life threatening bleeding from hyperplastic gastric polyp. Removing hyperplastic polyp in those infants using grasp and snare technique is feasible and can avoid unnecessary surgical excision in those children.

Belsha D, Narula P, Urs A, Thomson M. Management of hyperplastic gastric polyp following upper gastrointestinal bleeding in infant with Menkes' disease. *World J Gastrointest Endosc* 2017; 9(7): 341-345 Available from: URL: <http://www.wjgnet>.

INTRODUCTION

Menkes' disease (MD) is a rare metabolic disease secondary to copper deficiency. It usually presents within the first year of life. Failure to thrive, neurological deficits, and seizures, along with subdural haematomas, connective tissue abnormalities and bony changes are classical features of MD^[1]. Gastrointestinal disorder had been reported in MD including gastrointestinal bleeding. Surgical intervention is the only described treatment in the management due to the challenges of endoscopic management in the first year of life.

CASE REPORT

A Caucasian boy was born of an unrelated couple after an uncomplicated pregnancy. He was vaginally delivered at 39-wk gestation with a birth weight of 2880 g. At birth, no abnormal physical findings were recorded. At one month of age, he was referred because of two cephalohaematoma. Further examination revealed mild dysmorphic features including bilateral adducted thumbs, pectus excavatus, lax skin, moderate hypotonia and bilateral inguinal herniae. In view of mild respiratory distress a chest X-ray was performed and revealed two posterior rib fractures. Following that a skeletal survey was performed and revealed a Wormian bone raising the suspicion of MD. Further physical examination showed bronze and steely hair. The diagnosis of MD was made based on a serum copper level of 0.6 (reference range 5.9-16.3 mg/dL), and confirmed by positive genetic testing for the ATP7A gene. He developed epilepsy which was treated with anti-convulsants. In addition, an echocardiogram revealed aortic stenosis and abdominal US showed bladder diverticuli.

Subcutaneous copper histidinate therapy was introduced at around 8 wk of life. He was nasogastrically fed due to concerns regarding safe swallowing. At the age of five months, he presented with multiple coffee ground vomiting episodes and evidence of aspiration. Initially this was assumed to be secondary to gastro-oesophageal reflux disease (GORD). He was managed conservatively with proton pump inhibitors and naso-jejunal feeding. At the age of six months and after a significant drop of haemoglobin from 10 mg/dL to 7.6 mg/dL associated with melaena, urgent endoscopic assessment revealed a friable bleeding trans-pyloric multi-lobulated sessile polyp of around 4 cm in diameter (Figure 1). The lesion was partially obstructing the pylorus but pyloric intubation was easily performed. Histological examination of the biopsied sample was suggestive of hyperplastic polyp.

Due to further significant upper gastrointestinal (GI) bleeding polypectomy occurred. Tissue lifting was



Figure 1 Endoscopic appearance of the hyperplastic polyp.

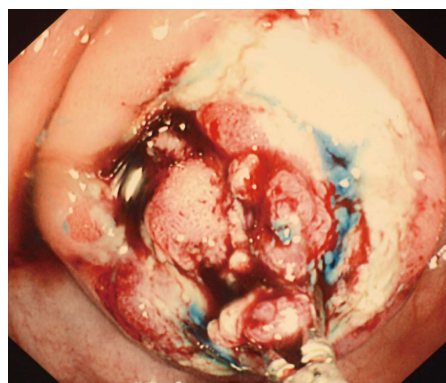


Figure 2 Piecemeal polypectomy.

achieved with plasma expander mixed with adrenaline and methylene blue. Piecemeal polypectomy was the procedure of choice (Figure 2). Due to the difficulty in lifting up such a folded and small area, endoscopic mucosal resection was performed with a grasp-and-snare technique (20 mm eccentric snare and crocodile grasping forceps) using a dual channel operating gastroscope (Erbe Endocut level 1 and 2); the snare was connected to the ERBE and placed down channel one of the dual scope whereas the grasping forceps was down channel two (Figure 3). Table 1 describes the required equipment for the procedure.

Haemostasis was achieved by application of argon plasma coagulation where required (Figure 4). No perforation occurred. Repeated endoscopic debridement was required 6 wk after which finally excised the growth (Figure 5) with no further blood transfusion required after that procedure. Histological examination of the polyp revealed granulation tissue with fibrosis and neovascularisation of the submucosa with evidence of an ulcerated surface and hence the histological confirmation of ulcerated and inflamed hyperplastic polyp.

DISCUSSION

Connective tissue abnormalities in MD are caused by decreased lysyl oxidase (LO) activity. LO is the

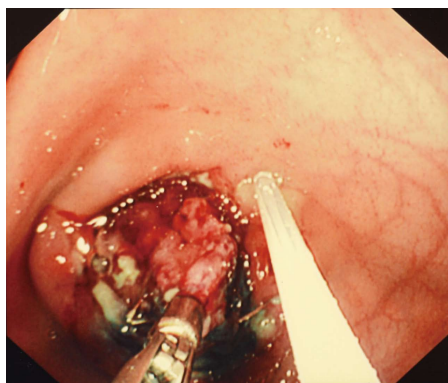


Figure 3 The use of grasp-and-snare technique.

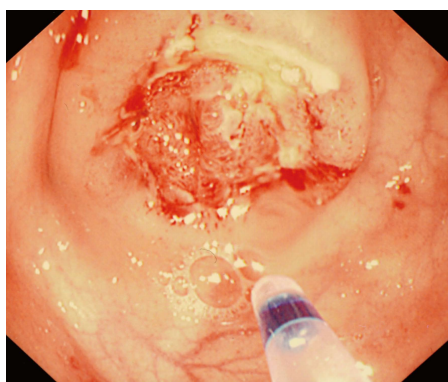


Figure 4 The use of argon plasma coagulation to achieve hemostasis.

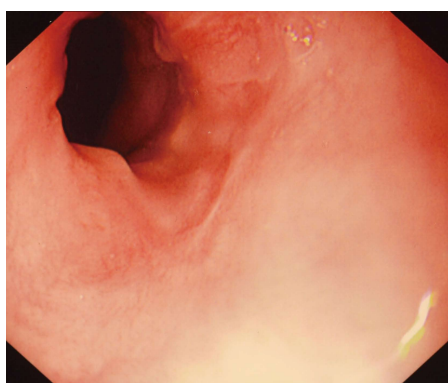


Figure 5 Appearance post procedure.

copper dependent enzyme responsible for oxidative deamination of lysine and hydroxylysine as the first step in collagen cross-link formation and is low in this condition^[2,3].

It has been hypothesized that the connective tissue weakness caused by LO deficiency creates a predisposition toward mucosal redundancy and hypertrophic polyp formation at the pyloric outlet, a site exposed to chronic localized pressure during gastric peristalsis^[4].

Haematemesis in our patient can be explained by the presence of a polyp found in the pyloric region which acted as a ball-valve mechanism, causing inter-

Table 1 The equipments during the procedure

GIF-XQ 260; Olympus Optical Co., Ltd
Dual channel operating scope (2TQ260M), Olympus Optical Co., Ltd
Argon plasma coagulator and ERBE electraucutery
Argon catheter. 1500 A, 1.5 mm, ERBE electraucutery.
Polyloop (2.8 mm channel); Olympus®
25 mm eccentric snare(1.8 mm channel); Quick Clip®
Clip applicators (single use rotatable clip fixing devise), Olympus®
Resolution clip, Boston Scientific®
Rat toothed grasper, Olympus®
Roth net, 2.5 mm, 3 cm, US endoscopy®
Injection needle, 2.8 mm, 155 cm, Olympus®
50 mL syringe
Succinylated Gelatin, Volplex®
Methelionum blue
Adrenaline 1 in 10000

mittent obstruction to the gastric outlet. Exposure of the functional mucosa of this polyp in the alkaline media of the duodenum possibly resulted in continuous gastrin secretion and in turn hypergastrinaemia and erosion of the polyp leading to haematemesis^[3].

Review of the literature reveals 4 similar cases of hypertrophic gastric polyps in MD: EMBASE, PubMed, and google scholar databases were searched from 1970 till now using the keywords "Menkes", "gastrointestinal bleeding", and or "polyp".

First case presented at 3 and a half months with coffee ground emesis, upper GI endoscopy revealed an irregular growth around the posterior wall of the gastric antrum there which was managed conservatively as per his parental wishes. At seven months he had massive GI bleeding with melaena leading to hypovolemic shock and death. Post-mortem revealed an ulcerated polypoid mass obstructing the pyloric opening^[4].

The second case presented at the age of 10 mo with haematemesis managed conservatively followed by large haematemesis eight months later. Endoscopy revealed a large solitary ulcerated polypoid mass, again partially obstructing the pylorus. Surgical excision of the mass was performed successfully^[4].

The third case was discovered at a post mortem examination of an 11-mo-old infant with MD and revealed an isolated hyperplastic gastric polyp located around the pyloric antrum^[5].

The fourth was a Japanese boy with MD who developed multiple gastrointestinal polypoid masses on the palate, the posterior wall of the oropharynx, the gastric body, and pyloric antrum despite normal serum copper levels following copper therapy^[6].

Hyperplastic polyps in infancy of such a large size with extensive involvement of the antrum and pylorus of the stomach are extremely rare^[7]. Two previous report in non MD has been described in infancy period and required surgical resection secondary to hematemesis and obstructive symptoms^[7,8]. Gastric polyps have been described in children receiving long term proton pump inhibitor (PPI) therapy as in our patient^[9]; however, the majority of PPI-associated polyps are small (2-8 mm), with a partly translucent surface and usually located in

the fundus or proximal in the gastric corpus. In most cases, these polyps appear to be fundic gland polyps, although in a minority hyperplastic and inflammatory polyps occur^[10,11].

In Western countries, adults hyperplastic polyps constitute 20% of all gastric polyps and are sessile or pedunculated polyps of usually less than 2 cm in diameter. They can occur as single polyps usually in the antrum or as multiple polyps throughout the stomach^[12]. Hyperplastic polyps of the gastric antrum are a rare but significant cause of gastrointestinal blood loss in older patients. Removal of the polyps using endoscopic or surgical methods may be required for resolution of the blood loss along with iron supplementation^[13].

Though bleeding from hyperplastic gastric polyps is not well documented in adult series, a review by Al-Hadad *et al.*^[14] of all gastric polyps encountered in their centre revealed 1.4% to be hyperplastic polyps in the gastric antrum, of whom 35% presented with melaena and significant iron deficiency anaemia.

The British Society of Gastroenterology (BSG) recommends the removal of hyperplastic polyps > 1 cm whenever possible whilst multiple, or smaller ones can be biopsied and monitored annually. Biopsies should be taken of the intervening or surrounding mucosa and *Helicobacter pylori* eradicated when present^[15].

Endoscopic treatment

To the best of our knowledge our case is the first reported in a child with MD to undergo endoscopic treatment of such a hyperplastic gastric polyp. In addition, and allowed by recent advances in endotherapeutic techniques, this is the first reported case of an infant of a weight of less than 6 kg that has undergone extended endoscopic submucosal dissection (ESD) using the grasp-and-snare technique.

In an adult series of 11 patients: The grasp-and-snare technique was used to perform EMR with good outcomes where sub-mucosal lifting and accessibility were problematic^[16]. Complication rates are known to be higher after EMR and ESD relative to other basic endoscopic interventions^[17]. In an adult series gastric lesions treated with EMR and ESD demonstrated complete resection in 73.9% and a combined complication rate of 1.9% (1.4% bleeding, 0.5% perforation)^[18].

Of note our case also had significant GORD, which is noted to be more frequent in MD and in one case during open Nissen fundoplication, loose connective tissues were noted around the GOJ, especially the crura of the diaphragm^[19]. GOR is probably one of the connective tissue manifestations of MD and may reflect a failure in elastin and collagen crosslinking caused by a decrease in the functional activity of copper-dependent LO. Defective elastic fibres within the internal elastic lamina, tunica media, and intimal layers of arteries and arterioles result in vascular tortuosity and ectasia with greater predisposition to mucosal haemorrhage^[20].

This case identifies an unusual gastrointestinal complication of MD and for the first time shows the

possibility of successful and uncomplicated EEMR even in very small infants.

COMMENTS

Case characteristics

Upper gastrointestinal bleeding in infants with Menkes' disease (MD).

Clinical diagnosis

Hyperplastic gastric polyp.

Differential diagnosis

Upper gastrointestinal endoscopy ruled out other diagnosis of gastrointestinal bleeding like gastric/ duodenal ulcers /erosive oesophagitis/erosive gastritis.

Laboratory diagnosis

Low serum Copper level was documented. Patient had recurrent low haemoglobin level after bleeding episodes necessitating blood transfusions. The diagnosis was confirmed with upper gastroesophageal endoscopy.

Pathological diagnosis

Bleeding from ulcerated hyperplastic gastric polyp in the gastric antrum was the diagnosis as per endoscopic finding and the histological examinations.

Treatment

The patient was treated endoscopically. Piecemeal polypectomy was the procedure of choice. Due to the difficulty in lifting up such a folded and small area, endoscopic mucosal resection was performed with a grasp-and-snare technique. Repeated debridement was required 6 wk after which the growth was excised completely with no further blood transfusion required after that procedure. Histological examination confirmed ulcerated and inflamed hyperplastic polyp.

Related reports

Four similar cases of hypertrophic pyloric gastric polyps in MD were all presented in infancy period, two patients had fatal extensive bleeding and two managed with surgical excision of the pylorus.

Experiences and lessons

Infants with MD can present with a potentially life threatening bleeding from hyperplastic gastric polyp. Endoscopic removal of the polyp infants using grasp and snare technique is feasible and can avoid unnecessary surgical excision in those children.

Peer-review

Nice case. Good literature review.

REFERENCES

- 1 **Bacopoulou F**, Henderson L, Philip SG. Menkes disease mimicking non-accidental injury. *Arch Dis Child* 2006; **91**: 919 [PMID: 17056864]
- 2 **Siegel RC**. Lysyl oxidase. *Int Rev Connective Tiss Res* 1979; **8**: 73-118 [DOI: 10.1016/B978-0-12-363708-6.50009-6]
- 3 **Alper M**, Akcan Y, Belenli O. Large pedunculated antral hyperplastic gastric polyp traversed the bulbous causing outlet obstruction and iron deficiency anemia: endoscopic removal. *World J Gastroenterol* 2003; **9**: 633-634 [PMID: 12632536 DOI: 10.3748/wjg.v9.i3.633]
- 4 **Kaler SG**, Westman JA, Bernes SM, Elsayed AM, Bowe CM, Freeman KL, Wu CD, Wallach MT. Gastrointestinal hemorrhage associated with gastric polyps in Menkes disease. *J Pediatr* 1993; **122**: 93-95 [PMID: 8419622 DOI: 10.1016/S0022-3476(05)83496-1]
- 5 **Wheeler EM**, Roberts PF. Menkes's steely hair syndrome. *Arch Dis Child* 1976; **51**: 269-274 [PMID: 1275538]
- 6 **Sasaki G**, Ishii T, Sato S, Hoshino K, Morikawa Y, Kodama H,

- Matsuo N, Takahashi T, Hasegawa T. Multiple polypoid masses in the gastrointestinal tract in patient with Menkes disease on copper-histidinate therapy. *Eur J Pediatr* 2004; **163**: 745-746 [PMID: 15480778 DOI: 10.1007/s00431-004-1556-0]
- 7 **Too SC**, Sarji S A, Yik Y I, Sithasanan N, Singaravel S. Infantile Hyperplastic gastric polyps: a rare entity. *Internet J of Paediatrics and Neonatology* 2009; In press
- 8 **Brooks GS**, Frost ES, Wesselhoeft C. Prolapsed hyperplastic gastric polyp causing gastric outlet obstruction, hypergastrinemia, and hematemesis in an infant. *J Pediatr Surg* 1992; **27**: 1537-1538 [PMID: 1469565 DOI: 10.1016/0022-3468(92)90498-V]
- 9 **Pashankar DS**, Israel DM. Gastric polyps and nodules in children receiving long-term omeprazole therapy. *J Pediatr Gastroenterol Nutr* 2002; **35**: 658-662 [PMID: 12454582 DOI: 10.1097/00005176-200210000-00013]
- 10 **Stolte M**, Bethke B, Seifert E, Armbrrecht U, Lütke A, Goldbrunner P, Rabast U. Observation of gastric glandular cysts in the corpus mucosa of the stomach under omeprazole treatment. *Z Gastroenterol* 1995; **33**: 146-149 [PMID: 7754645]
- 11 **el-Zimaity HM**, Jackson FW, Graham DY. Fundic gland polyps developing during omeprazole therapy. *Am J Gastroenterol* 1997; **92**: 1858-1860 [PMID: 9382052]
- 12 **Carmack SW**, Genta RM, Schuler CM, Saboorian MH. The current spectrum of gastric polyps: a 1-year national study of over 120,000 patients. *Am J Gastroenterol* 2009; **104**: 1524-1532 [PMID: 19491866 DOI: 10.1038/ajg.2009.139]
- 13 **Stolte M**, Sticht T, Eidt S, Ebert D, Finkenzeller G. Frequency, location, and age and sex distribution of various types of gastric polyp. *Endoscopy* 1994; **26**: 659-665 [PMID: 7859674 DOI: 10.1055/s-2007-1009061]
- 14 **Al-Haddad M**, Ward EM, Bouras EP, Raimondo M. Hyperplastic polyps of the gastric antrum in patients with gastrointestinal blood loss. *Dig Dis Sci* 2007; **52**: 105-109 [PMID: 17151810 DOI: 10.1007/s10620-006-9182-5]
- 15 **Goddard AF**, Badreldin R, Pritchard DM, Walker MM, Warren B; British Society of Gastroenterology. The management of gastric polyps. *Gut* 2010; **59**: 1270-1276 [PMID: 20675692 DOI: 10.1136/gut.2009.182089]
- 16 **de Melo SW**, Cleveland P, Raimondo M, Wallace MB, Woodward T. Endoscopic mucosal resection with the grasp-and-snare technique through a double-channel endoscope in humans. *Gastrointest Endosc* 2011; **73**: 349-352 [PMID: 21295646 DOI: 10.1016/j.gie.2010.10.030]
- 17 **ASGE Technology Committee**, Kantsevoy SV, Adler DG, Conway JD, Diehl DL, Farraye FA, Kwon R, Mamula P, Rodriguez S, Shah RJ, Wong Kee Song LM, Tierney WM. Endoscopic mucosal resection and endoscopic submucosal dissection. *Gastrointest Endosc* 2008; **68**: 11-18 [PMID: 18577472]
- 18 **Kojima T**, Parra-Blanco A, Takahashi H, Fujita R. Outcome of endoscopic mucosal resection for early gastric cancer: review of the Japanese literature. *Gastrointest Endosc* 1998; **48**: 550-554 [PMID: 9831855]
- 19 **Okada T**, Sasaki F, Honda S, Miyagi H, Kubota M, Todo S. Menkes disease with gastroesophageal reflux disease and successful surgical treatment: a case report and literature review. *Turk J Pediatr* 2010; **52**: 333-335 [PMID: 20718197]
- 20 **Mandelstam SA**, Fisher R. Menkes disease: a rare cause of bilateral inguinal hernias. *Australas Radiol* 2005; **49**: 192-195 [PMID: 15845066 DOI: 10.1111/j.1440-1673.2005.01421.x]

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