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Retrospective Cohort Study

Disparities in colonoscopy utilization for lower gastrointestinal bleeding in rural *vs* urban settings in the United States

Nagapratap Ganta, Mina Aknouk, Dina Alnabwani, Ivan Nikiforov, Veera Jayasree Latha Bommu, Vraj Patel, Pramil Cheriyath, Christopher S Hollenbeak, Alan Hamza

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Abstract

BACKGROUND

Lower gastrointestinal bleeds (LGIB) is a very common inpatient condition in the United States. Gastrointestinal bleeds have a variety of presentations, from minor bleeding to severe hemorrhage and shock. Although previous studies investigated the efficacy of colonoscopy in hospitalized patients with LGIB, there is limited research that discusses disparities in colonoscopy utilization in patients with LGIB in urban and rural settings.

AIM

To investigate the difference in utilization of colonoscopy in lower gastrointestinal bleeding between patients hospitalized in urban and rural hospitals.

METHODS

This is a retrospective cohort study of 157748 patients using National Inpatient Sample data and the Healthcare Cost and Utilization Project provided by the Agency for Healthcare Research and Quality. It includes patients 18 years and older hospitalized with LGIB admitted between 2010 and 2016. This study does not differentiate between acute and chronic LGIB and both are included in this study. The primary outcome measure of this study was the utilization of colonoscopy among patients in rural and urban hospitals admitted for lower gastrointestinal bleeds; the secondary outcome measures were in-hospital mortality, length of stay, and costs involved in those receiving colonoscopy for LGIB. Statistical analyses were all performed using STATA software. Logistic

regression was used to analyze the utilization of colonoscopy and mortality, and a generalized linear model was used to analyze the length of stay and cost.

RESULTS

Our study found that 37.9% of LGIB patients at rural hospitals compared to approximately 45.1% at urban hospitals received colonoscopy, (OR = 0.730, 95%CI: 0.705-0.7, $P > 0.0001$). After controlling for covariates, colonoscopies were found to have a protective association with lower in-hospital mortality [OR = 0.498, 95%CI: 0.446-0.557, $P < 0.0001$], but a longer length of stay by 0.72 d (95%CI: 0.677-0.759 d, $P < 0.0001$) and approximately $2199 in increased costs.

CONCLUSION

Although there was a lower percentage of LGIB patients that received colonoscopies in rural hospitals compared to urban hospitals, patients in both urban and rural hospitals with LGIB undergoing colonoscopy had decreased in-hospital mortality. In both settings, benefit came at a cost of extended stay, and higher total costs.

Key Words: Lower gastrointestinal bleeding; Rural-urban disparities; Colonoscopy; Utilization of colonoscopy; Length of stay; Inpatient admission costs

Core Tip: Colonoscopy utilization is lower in rural hospitals than in urban hospitals in the United States for all acute and chronic lower gastrointestinal bleeding. Patients in both rural and urban hospitals who present with lower gastrointestinal bleeds that undergo colonoscopy have decreased in-hospital mortality, an extended length of hospital stay, and higher total costs.

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INTRODUCTION

Gastrointestinal (GI) bleeding is the most common cause of hospitalization due to gastrointestinal disease in the United States and is responsible for 2%-4% of hospital mortality[1]. Approximately 30% to 40% of all cases of GI bleeding are from a lower GI source[2]. Over the past decade, there has been a progressive change in GI bleeding patterns that lead to hospitalization, with a clear decreasing trend in upper GI events and a significant increase in lower GI events[3]. Unfortunately, even though lower gastrointestinal bleeding (LGIB) is a common indication for admission to the hospital, it has received relatively little attention in the literature[4]. The estimated hospitalization rate for LGIB is 33-87 per 100000 population[3] with mortality rates of 2%-4% during hospitalization and rebleeding rates of 13%-19% after one year[4] . Diverticular bleeds are the leading cause of LGIB and account for approximately 30%-50% of all cases[5]. In patients 50 years or younger, the leading cause of LGIB is hemorrhoids, which often present as minor bleeding. Increased incidence of LGIB with age is likely secondary to increased diverticulosis and angiodysplasia[1]. Other conditions that are commonly associated with LGIB include angiodysplasia, ischemic colitis, colon cancer/polyps, post-polypectomy bleeding, inflammatory bowel disease, solitary rectal ulcer, radiation colitis/proctitis, and rectal varices[6]. Colonoscopy is a minimally invasive procedure that improves clinical outcomes which include- decreased rebleeding, decreased duration of hospital stay, and decreased need for major surgery[7].

Primary intervention in diagnosing LGIB is receiving a colonoscopy and it is important that the procedure is performed with minimal delay[8]. Currently the large majority of diagnostic and therapeutic procedures in Gastroenterology is the colonoscopy. In 2015, approximately 11.5 million colonoscopies were performed compared to 6.1 million upper endoscopies and a significantly lower rate of flex sigmoidoscopies at 313000 annually[2]. Urgent Golytely preparation and colonoscopy is the most direct and cost effective approach to diagnose hematochezia[7].

Several factors might contribute to rural-urban disparities in utilizing colonoscopy. Major factors may be rural provider distribution and scarcity, challenges that have persisted despite significant attempts by federal and state governments to address them over the last three decades[9]. The increased disparity is also linked to fewer specialist visits and a greater reliance on generalists in rural regions. Therefore,

examining differences in rural hospitals and the benefits of colonoscopy among patients with lower gastrointestinal bleeds can lead to better patient outcomes.

This study is aimed to determine whether there were rural disparities in colonoscopy utilization in hospitalized patients with lower GI bleeding (LGIB) and the benefits of receiving a colonoscopy.

MATERIALS AND METHODS

Study design

This is a retrospective cohort study.

Data source

Data used in this study were from the National Inpatient Sample (NIS), Healthcare Cost and Utilization Project (HCUP), provided by the Agency for Healthcare Research and Quality (AHRQ). The NIS is the most extensive all-payer administrative discharge data set in the US and contains information on discharges from community hospitals[10]. Cohorts of hospitalized patients can be identified in the NIS using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9) codes for the third quarter of 2015 and earlier, and International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10) codes for the fourth quarter of 2015 and later.

Cohort

This study examined 157748 patients from the United States aged 18 and older in the NIS hospitalized with a principal diagnosis of LGIB between 2010 and 2016. There is no differentiation between acute or chronic bleeding. The algorithm described by Strate *et al*[4] was used to define the cohort. While Strate *et al*[4] defines a cohort of patients with LGIB ICD-9 diagnosis and procedure codes, the general equivalence mappings (GEM) from the Centers for Medicare and Medicaid Services (CMS) were used to extend their algorithm to ICD-10 diagnosis and procedural classification system (PCS) codes[11-13].

Patients with a principal ICD-9 diagnosis code indicating lower gastrointestinal bleeding were included in the cohort, including 562.12 (Diverticulosis of colon with hemorrhage), 562.13 (Diverticulitis of colon with hemorrhage), 569.85 (Angiodysplasia of the intestine with bleeding), 569.3 (Hemorrhage of rectum and anus), 455.2 (Internal hemorrhoids with other complication), 455.5 (External hemorrhoids with further complication) and 455.8 (Unspecified hemorrhoids with other complication). We also included patients with a secondary ICD-9 code that indicated a source of bleeding in the lower gastrointestinal tract (Supplementary material). Furthermore, patients were excluded if the source of bleeding appeared to be in the upper gastrointestinal tract or if they had an ICD-9 procedure code or ICD-10 PCS code suggestive of a surgical procedure in the upper gastrointestinal tract or small intestine. ICD-9 diagnosis and procedure codes were used for inclusion or exclusion criteria, and comparable ICD-10 codes are listed in Supplementary material. Since we have based our study on administrative data obtained from NIS, which is further based purely on ICD codes, we cannot comment with certainty as to the clinical details on why colonoscopy was not done in some patients with LGIB and if any other diagnostics were used. A study based on a medical chart review would be able to better answer the questions related to the final diagnosis or cause of LGIB or why colonoscopy was not done in some patients, and we would definitely want to conduct a study in the future to analyze these details.

The primary outcome of this study was the utilization of colonoscopy. This was identified using a principle or secondary ICD-9 procedure code of 45.23 (colonoscopy) or a principle or secondary ICD-10 PCS code of 0DJD8ZZ (Inspection of Lower Intestinal Tract, Via Natural or Artificial Opening Endoscopic). In addition, three secondary outcomes were studied, including in-hospital mortality, length of stay, and costs. Length of stay was defined as total days from admission to discharge or death. Costs were estimated from the hospital perspective from hospital-level ratios of costs-to-charges. All charges were adjusted to the year 2018 US dollars using the medical care component of the consumer price index.

Covariates

All multivariable analyses controlled for the patient and hospital characteristics. Models controlled for age (18-64, 65-74, 75-84, 85+), sex (male, female), race (white, black, Hispanic, Asian, other), and primary payer (Medicare, Medicaid, commercial, other). We controlled the size of the hospital (small, medium, large) and the teaching status of the hospital. Teaching hospitals have at least one Accreditation Council for Graduate Medical Education (ACGME) approved residency program or are members of the Council of Teaching Hospitals (COTH). Comorbidities were controlled using the Charlson Comorbidity Index, a weighted index of 17 comorbidities[14,15]. Finally, we controlled for the geography of the hospital (rural, urban). Geography was based on the county where the hospital is located. Rural hospitals were identified as those located in counties with a core-based statistical area designated as micropolitan or non-core. This classification of rural-urban is based on the site's zip code.

Statistical analysis

Statistical analyses were designed to determine whether there was a significant association between rural hospital designation and utilization of colonoscopy among patients admitted for gastrointestinal bleeding. In addition, we tested whether patients who received colonoscopy had significantly different rates of in-hospital mortality, length of hospital stay, and hospital costs. Characteristics of patients were compared between those who received care at rural *vs* urban hospitals using *t*-tests for continuous variables and chi-square tests for binary and categorical variables. Utilization of colonoscopy was modeled using logistic regression, controlling for patient and hospital characteristics. Mortality was also modeled using logistic regression. Length of stay and costs were modeled using linear regression, controlling for patient and hospital characteristics. A propensity score analysis matched patients who received care at a rural hospital to those at an urban hospital. Matching was performed using a 1:1 nearest neighbor approach and a caliper restriction of 0.2 times the standard deviation. Statistical analyses were performed using STATA software (version 15, College Station, TX, United States). Statistical significance was defined as $P < 0.05$.

RESULTS

Rates of colonoscopy utilization stratified by rurality are presented in Figure 1. Approximately 37.9% of patients with lower gastrointestinal bleeding received colonoscopy at rural hospitals compared to 45.1% at urban hospitals. Rural hospitals had a consistently lower rate of colonoscopy utilization relative to urban hospitals from 2010 through 2015. The difference was mediated to a large degree in 2016. Also, there was a trend for decreasing colonoscopy utilization in both settings.

As seen in Table 1, patients differed significantly in demographics and comorbidities. However, much of the significance was due to the considerable sample size. For example, patients treated at rural hospitals tended to be slightly older (74.4 years *vs* 73.0 years, $P < 0.0001$), more likely to be female (53.7% *vs* 51.9%, $P < 0.0001$), and significantly more likely to be white (74.6% *vs* 63.9%). Instead of other payers, they were more likely to be insured by Medicare (78.8% *vs* 74.3%). Hospital characteristics also differed significantly. For example, all rural hospitals are non-teaching hospitals, and bed size varies by region and rurality in the NIS[10]. A large hospital in a rural area in the Northeast has 100 or more beds, while a large, urban teaching hospital has 425 or more beds. A large hospital in a rural area in the West has 45 or more beds, while a large, urban teaching hospital has 325 or more beds.

After controlling for other factors, patients treated at rural hospitals had 27% lower odds of receiving colonoscopy relative to patients treated at urban hospitals (OR = 0.73, $P < 0.0001$) (Table 2). There were several other factors associated with receiving a colonoscopy. For example, women had 4.4% lower odds of receiving colonoscopy (OR = 0.96, $P < 0.0001$), and non-white patients were more likely to receive a colonoscopy. Patients with more comorbidities were less likely to receive colonoscopy; each additional one-point increase in the Charlson comorbidity index was associated with 5.1% lower odds of colonoscopy. Patients who were receiving care at small (OR = 0.90, $P < 0.0001$) and medium (OR = 0.92) sized hospitals were less likely to receive colonoscopy relative to patients receiving care at large hospitals.

Patients who received colonoscopy had a significantly lower likelihood of in-hospital mortality (Table 3). After controlling for other factors, colonoscopy was associated with a 50% lower odds of mortality (OR = 0.50, $P < 0.0001$). In addition, patients treated at rural hospitals had a 5% greater odds of mortality (OR = 1.05, $P = 0.58$), but this association was not statistically significant after controlling for colonoscopy utilization. Several other factors were associated with more significant in-hospital mortality, including age and comorbidities. Other factors were protective for mortality, including the female sex, which was associated with 17% lower odds of mortality (OR = 0.83, $P < 0.0001$).

Utilization of colonoscopy was associated with a longer length of hospital stay of 0.72 days ($P < 0.0001$) (Table 4). In addition, patients treated at rural hospitals had a shorter stay of 0.37 d ($P < 0.0001$). Colonoscopy was also associated with higher hospital costs. Patients treated at rural hospitals incurred lower costs of $853 ($P < 0.001$) independent of colonoscopy. Patients admitted for lower gastrointestinal bleeding who received colonoscopy incurred an additional $2,199 in costs ($P < 0.0001$) (Table 5).

To control for potential selection bias in patients receiving treatment at rural hospitals, a propensity score matching analysis was used to match 16177 patients treated at rural hospitals with 16177 similar patients treated at urban hospitals. After matching, there were no significant differences in inpatient or hospital characteristics. Results of the propensity score analysis confirmed the multi-variable model. In the overall (unmatched) cohort, 37.9% of patients treated at rural hospitals received a colonoscopy, while 46% of patients treated at urban hospitals received a colonoscopy ($P < 0.0001$). After matching, 44.7% of patients treated at urban hospitals received colonoscopy ($P < 0.0001$), suggesting that the utilization of colonoscopy between urban and rural hospitals is not related to patient characteristics.

Table 1 Characteristics of patients admitted for lower gastrointestinal bleeding, stratified by geography

Variable	Urban (*n* = 141571)	Rural (*n* = 16177)	*P* value
Age	73.01	74.35	< 0.0001
18-64	24.2%	20.3%	
65-74	22.2%	22.3%	
75-84	27.6%	29.6%	
85+	22.9%	24.5%	
Sex			< 0.0001
Male	48.1%	46.3%	
Female	51.9%	53.7%	
Race			< 0.0001
White	63.9%	74.6%	
Black	18.5%	10.8%	
Hispanic	8.2%	2.3%	
Asian	2.7%	1.9%	
Other	2.1%	1.0%	
Missing	4.6%	9.4%	
Payer			< 0.0001
Medicare	74.3%	78.8%	
Medicaid	5.4%	4.3%	
Commercial	16.0%	12.4%	
Other	4.3%	4.4%	
Missing	0.1%	0.3%	
Comorbidities			
Number	1.38	1.32	< 0.0001
Charlson index	1.89	1.77	< 0.0001
Colonoscopy			< 0.0001
Yes	45.1%	37.9%	
No	54.9%	62.1%	
Hospital bed size			< 0.0001
Small	15.5%	10.8%	
Medium	29.5%	18.9%	
Large	54.9%	70.2%	
Region			< 0.0001
Northeast	33.2%	21.8%	
Midwest	44.2%	20.8%	
South	50.0%	39.9%	
West	28.4%	17.4%	
Teaching			< 0.0001
No	45.5%	100.0%	
Yes	54.5%	0.0%	

DISCUSSION

Patients who present with gastrointestinal bleeds should undergo a thorough history, physical examination, lab work, and diagnostic procedure to determine the source of bleeding (upper GI tract, colon, or small bowel) and identify the pathology of the bleed. Colonoscopy is the most popular procedure for diagnosing, risk stratifying, and treating colonic bleeding[16]. It is often challenging to manage lower GI bleeding because of the wide variety of pathology that can lead to a lower gastrointestinal bleed. With advancements in endoscopic technology it is modality of choice for lower gastrointestinal bleeds as it allows for diagnosis and treatment simultaneously[17]. Approximately 15% of patients with presumed LGIB are ultimately found to have an upper GI source for their bleeding, highlighting the importance of receiving a timely colonoscopy[18].

Our study demonstrates that patients with LGIB admitted to rural hospitals are less likely to receive colonoscopy for the diagnosis and management, with an odds ratio of 0.73 (95%CI: 0.71-0.76, $P < 0.0001$). Results also showed that the disparity gap has narrowed over the past few years, but we should continue to improve availability of colonoscopy in rural hospitals.

Colonoscopy utilization in rural *vs.* urban LGIB patients could be due to several factors. One of the major factors is the lack of specialists, such as gastroenterologists, in rural hospitals. For this reason, colonoscopies in hospitals that are short on subspecialists are often performed by family medicine physicians that are trained in the procedure. Despite the lower rate of colonoscopies, the safety and quality of family physicians performing colonoscopies are highly comparable to specialists performing the same procedure[19]. These findings suggest that increasing the training opportunities for family physicians in performing colonoscopies could potentially alleviate the scarcity of subspecialists in rural hospitals. Rural provider distribution and scarcity challenges have persisted despite significant attempts by federal and state governments to address them over the last three decades[9].

Lack of insurance and the barrier of financial hardship in rural populations may also partly explain the lower rate of colonoscopies performed in rural hospitals. The disproportion of colonoscopies performed in rural *vs* urban hospitals does however show a downward trend after implementing the Affordable Care Act (ACA)[20]. Insufficient public transportation and increased distance and time to travel to urban hospitals to get colonoscopy and specialist health care can also explain the lower rates of colonoscopy utilization in rural patients. Access to primary care is one of the most significant determinants of up-to-date screening status. However, cost barriers and other factors such as poor broadband internet services limit rural residents' access to finding a primary provider[21].

According to the United States census bureau, in 2017, rural counties continued to have higher uninsured residents than urban areas. In entirely rural counties, 12.3% of the population lacked health insurance, compared to 11.3 percent in primarily rural counties (more than half of the people in rural areas) and 10.1 percent in most urban counties (less than half of the population in rural areas)[22]. According to the Medical Expenditure Panel Survey (MEPS), in 2014-2015, 37.0% of rural people and 33.6% of urban people aged 65 years and older were covered by medicare[23].

In a cross-sectional analysis of Center for Disease Control (CDC) data by Cole *et al*[24], rural residents had lower colorectal cancer screening rates (48%; 95%CI: 48%-49%) than urban residents (54%; 95 %CI: 53%- 55%) from 1998 to 2005 after accounting for demographic and health factors. However, the total number of colonoscopy or flexible sigmoidoscopy screenings increased in urban and rural populations from 1998 to 2005[24]. The rural disparity is also shown in a systematic review by Castellanos *et al*[21], who examined studies of patients suffering from cardiovascular diseases between 1990 and 2017. Most published clinical trials showed that patients from rural communities had significantly lower cardiac rehabilitation referral and participation rates than the general population[21].

Our study also showed that older people aged 85 years and above with LGIB were less likely to receive a colonoscopy, perhaps because current guidelines do not recommend routine screening after 75 years. Women with LGIB are less likely to receive a colonoscopy, most likely because lower GI bleeding is more common in men than in women, and men are more likely to undergo colonoscopy[25]. A study by Devani *et al*[26] showed that women were more likely to delay colonoscopy than males, and women were more likely to ignore bleeding than men (Table 2).

The odds of mortality were reduced in all patients who received a colonoscopy, irrespective of rural or urban location, and the mortality was not significantly different in rural and urban hospitals for patients who received a colonoscopy. This supports our observation that colonoscopy utilization is associated with decreased mortality in all patients, and thus it should be offered to all LGIB patients. As shown in our study, there is, however, a statistically significant difference in colonoscopy utilization between rural and urban hospitals. Thus, by increasing colonoscopy availability in rural hospitals, we anticipate a reduction in mortality in rural hospitals. In general, rural populations in the United States are, on average, older and sicker than their urban counterparts[27]. Our study demonstrates that patients with lower gastrointestinal bleeds who underwent colonoscopy had significantly lower mortality than those with LGIB who did not undergo colonoscopy. This effect was observed after controlling for meaningful patient and hospital characteristics (Table 3). This highlights the significant impact colonoscopy can play in patients with LGIB.

Table 2 Results of multivariable model of colonoscopy utilization

Variable	OR	95%CI		*P* value
		Lower	Upper	
Rural	0.730	0.705	0.757	< 0.0001
Age				
18-64	Reference			
65-74	0.978	0.946	1.010	0.177
75-84	0.986	0.954	1.018	0.384
85+	0.826	0.798	0.855	< 0.0001
Sex				
Male	Reference			
Female	0.956	0.937	0.976	< 0.0001
Race				
White	Reference			
Black	1.224	1.191	1.258	< 0.0001
Hispanic	1.206	1.160	1.253	< 0.0001
Asian	1.222	1.148	1.301	< 0.0001
Other	1.158	1.078	1.244	< 0.0001
Missing	1.107	1.057	1.159	< 0.0001
Payer				
Medicare	Reference			
Medicaid	0.986	0.938	1.037	0.590
Commercial	1.068	1.034	1.103	< 0.0001
Other	1.076	1.020	1.135	0.007
Missing	0.763	0.579	1.004	0.053
Hospital bed size				
Small	0.899	0.873	0.925	< 0.0001
Medium	0.919	0.898	0.940	< 0.0001
Large	Reference			
Teaching				
No	Reference			
Yes	0.951	0.931	0.972	< 0.0001
Charlson comorbidity index	0.949	0.944	0.955	< 0.0001

Patients aged 85 years and above with LGIB had higher mortality rates than patients aged 18-64 years. This may partly be explained by the fact that current guidelines do not recommend routine screening after the age of 75 years, and also, they have confounding prognostic factors compared to younger patients (Table 3). Other research has shown that independent predictors of in-hospital mortality include age, intestinal ischemia, comorbid illness, bleeding while hospitalized for a separate process, coagulation defects, hypovolemia, transfusion of packed red blood cells, and male gender[4].

Women with LGIB had lower mortality rates than men regardless of the treatment setting. These results were comparative to a retrospective observational study by Devani *et al*[26], who found that the odds of mortality were almost 17% lower in women with LGIB than in men.

Our study showed that patients with LGIB admitted to rural hospitals had 8 to 9 h (0.37 d) shorter length of hospital stay than patients admitted to urban hospitals. This can be due to the likelihood that rural populations were less likely to undergo colonoscopy, which extends admissions, as rural hospitals have fewer resources and specialists to perform colonoscopies. Rural populations may also get discharged earlier due to poor insurance benefits and higher inpatient admission costs. Most rural

Table 3 Multivariable model of mortality

Variable	OR	95%CI		*P* value
		Lower	Upper	
Rural	1.050	0.888	1.242	0.567
Colonoscopy				
Yes	0.498	0.446	0.557	< 0.0001
No	Reference			
Age				
18-64	Reference			
65-74	0.939	0.780	1.130	0.504
75-84	1.333	1.121	1.584	0.001
85+	2.132	1.797	2.530	< 0.0001
Sex				
Male	Reference			
Female	0.828	0.749	0.915	< 0.0001
Race				
White	Reference			
Black	0.961	0.835	1.106	0.579
Hispanic	0.694	0.556	0.867	0.001
Asian	1.063	0.784	1.443	0.693
Other	0.960	0.665	1.385	0.826
Missing	0.944	0.750	1.187	0.621
Payer				
Medicare	Reference			
Medicaid	0.941	0.718	1.235	0.662
Commercial	0.834	0.695	1.002	0.052
Other	0.774	0.556	1.077	0.129
Missing	0.538	0.074	3.905	0.540
Hospital bed size				
Small	0.911	0.786	1.057	0.218
Medium	0.966	0.862	1.083	0.552
Large	Reference			
Teaching				
No	Reference			
Yes	0.987	0.887	1.099	0.813
Charlson comorbidity index	1.239	1.215	1.263	< 0.0001

patients (37.01% of patients aged 65 years and older) have Medicare insurance[25] that has a prospective payment system, which pays a predetermined, fixed reimbursement to the hospital for a diagnosis irrespective of the length of stay. This payment system might prompt an earlier discharge for rural patients[28].

Patients with LGIB undergoing colonoscopy had a longer length of hospital stay by 17 h (0.72 d) than those who did not (Table 4). The length of time it takes to perform a colonoscopy is determined by the patients' and endoscopists' characteristics. Even though not all colonoscopies are the same, there is no distinction in the time permitted for each colonoscopy when arranging the procedure in the endoscopy suite. As a result, patient wait times vary, impacting the overall length of stay. Factors determining the length of stay (LOS) include overall time spent preparing for an operation, procedure time, insurance

Table 4 Multivariable model of length of hospital stay

Variable	Coefficient	95%CI		*P* value
		Lower	Upper	
Rural	-0.372	-0.444	-0.300	< 0.0001
Colonoscopy				
Yes	0.718	0.677	0.759	< 0.0001
No	Reference			
Age				
18-64	Reference			
65-74	0.133	0.066	0.201	< 0.0001
75-84	0.382	0.315	0.449	< 0.0001
85+	0.518	0.448	0.588	< 0.0001
Sex				
Male	Reference			
Female	0.067	0.026	0.109	0.001
Race				
White	Reference			
Black	0.590	0.534	0.646	< 0.0001
Hispanic	0.016	-0.064	0.095	0.699
Asian	-0.041	-0.169	0.088	0.534
Other	0.091	-0.057	0.238	0.227
Missing	-0.183	-0.277	-0.089	< 0.0001
Payer				
Medicare	Reference			
Medicaid	-0.047	-0.150	0.055	0.367
Commercial	-0.386	-0.453	-0.319	< 0.0001
Other	-0.403	-0.513	-0.292	< 0.0001
Missing	-0.079	-0.631	0.473	0.779
Hospital bed size				
Small	-0.451	-0.511	-0.391	< 0.0001
Medium	-0.235	-0.283	-0.188	< 0.0001
Large	Reference			
Teaching				
No	Reference			
Yes	0.297	0.253	0.341	< 0.0001
Charlson comorbidity index	0.232	0.221	0.243	< 0.0001
Intercept	3.173	3.097	3.249	< 0.0001

reimbursement, and out-of-pocket expenses, influencing hospital and patient decision-making[29].

Our study showed that rural patients with LGIB incur $853 less in costs than patients treated at urban hospitals which could be due to the fact that rural patients are less likely to undergo colonoscopy, which can be contributory to the reduction of the total inpatient admission cost.

Our study showed that patients with LGIB who undergo colonoscopy incur $2199 in higher costs than those who do not. Procedural costs and longer duration of stay for patients undergoing colonoscopy may be part of the higher costs. A cost-effectiveness analysis study comparing four diagnostic strategies in the evaluation of rectal bleeding in adults by Allen *et al*[30] using a Markov

Table 5 Multivariable model of inpatient admission costs

Variable	Coefficient	95%CI		*P* value
		Lower	Upper	
Rural	-$853.03	-$1059.62	-$646.44	< 0.0001
Colonoscopy				
Yes	$2198.68	$2080.08	$2317.27	< 0.0001
No	Reference			
Age				
18-64	Reference			
65-74	$353.75	$159.71	$547.79	< 0.0001
75-84	$569.47	$377.06	$761.87	< 0.0001
85+	$184.80	-$16.82	$386.42	0.072
Sex				
Male	Reference			
Female	-$487.40	-$606.30	-$368.49	< 0.0001
Race				
White	Reference			
Black	$1065.28	$903.76	$1226.81	< 0.0001
Hispanic	$571.60	$343.11	$800.10	< 0.0001
Asian	$2228.13	$1858.86	$2597.39	< 0.0001
Other	$938.42	$514.93	$1361.92	< 0.0001
Missing	-$223.19	-$492.88	$46.49	0.105
Payer				
Medicare	Reference			
Medicaid	$209.94	-$85.38	$505.27	0.164
Commercial	-$432.66	-$624.55	-$240.77	< 0.0001
Other	-$788.60	-$1105.57	-$471.62	< 0.0001
Missing	-1065.893	-2652.626	520.839	0.188
Hospital bed size				
Small	-$418.08	-$590.47	-$245.70	< 0.0001
Medium	-$305.15	-$440.76	-$169.54	< 0.0001
Large	Reference			
Teaching				
No	Reference			
Yes	$604.62	$477.91	$731.33	< 0.0001
Charlson comorbidity index	$601.63	$570.19	$633.06	< 0.0001
Intercept	$7859.86	$7642.30	$8077.41	< 0.0001

model showed that in addition to being associated with lower mortality, colonoscopy was also cost-effective when compared to flexible sigmoidoscopy, flexible sigmoidoscopy followed by air contrast barium enema (FS+ACBE), and simple observation. Additional research is needed to understand the value proposition of colonoscopy for LGIB other than rectal bleeding. This is perhaps because patients undergoing colonoscopy are more likely to stay longer in the hospital and spend higher costs than those who do not undergo colonoscopy. Increases in LOS per day were linked to a 47% increase in Inpatient admission costs[26]. The total cost of a colonoscopy depends on whether costs are assessed from a societal or a health system perspective[31].

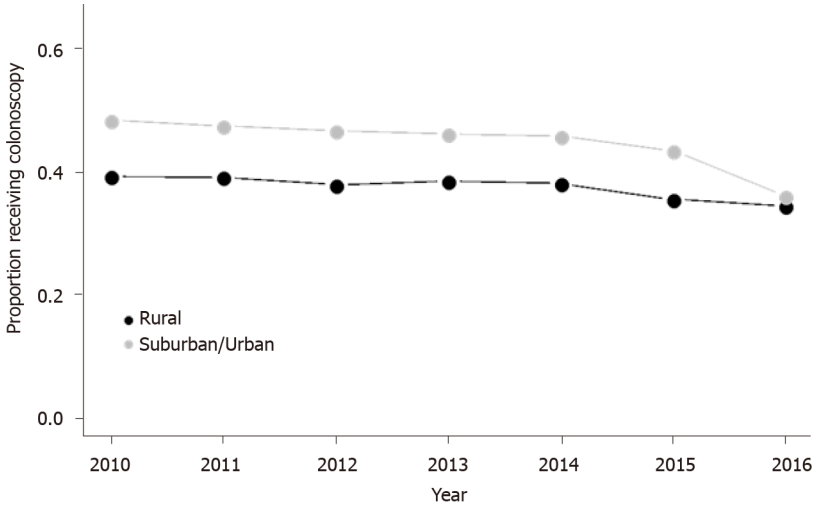

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Figure 1 Trends in utilization of colonoscopy for patients admitted for lower gastrointestinal bleeding.

One strength of the study is that we used data from NIS, HCUP, provided by the AHRQ. This is a nationally representative sample, which enhances the generalizability of our findings.

Limitations of the study

We could not account for the severity of LGIB or the screening status of patients. Also, we studied admissions between 2010 and 2016 which is the most recent database and there is not currently more recent data. A limitation is that the NIS data set is based solely on ICD-9 and ICD-10 diagnoses. Specific colonoscopy findings are not reported in the NIS data set.

CONCLUSION

Our study results demonstrated that the rate of utilization of colonoscopy was significantly lower in rural hospitals compared to urban hospitals. This study also showed that patients with lower gastrointestinal bleeds undergoing colonoscopy had significantly lower in-hospital mortality than those who did not. The study results emphasize the importance of counseling rural patients and educating them about the life-threatening complications of LGIB, which colonoscopy can avoid. Furthermore we would benefit from more access to colonoscopies in rural settings. Internal medicine and family physicians should be trained to perform colonoscopies in rural settings to increase the availability of colonoscopy in these areas. Physicians should be encouraged to improve rural population outreach, hospital resources, and reimbursement. Despite differences in colonoscopy utilization, this study did not show any significant difference in mortality between rural and urban patients with LGIB. Further studies are needed to give more insights into rural-urban disparities in mortality.

ARTICLE HIGHLIGHTS

Research background

Disparities in colonoscopy access in rural and urban hospitals is an understudied topic. The significance of this study is to demonstrate whether or not improved access improves patient mortality.

Research motivation

To improve access to colonoscopies in the United States. We are also interested in the availability of colonoscopy and how it effects patients length of stay and costs.

Research objectives

To discover whether or not there is a disparity in colonoscopy utilization for lower gastrointestinal bleeds between rural and urban hospital areas in the United States. Also to determine whether there is a benefit for mortality in patients with lower gastrointestinal bleeds when they receive colonoscopies.

Research methods

Retrospective cohort study and data analysis of National Inpatient Sample, Healthcare Cost and Utilization Project, provided by the Agency for Healthcare Research and Quality.

Research results

Approximately 37.9% of patients with lower gastrointestinal bleeding received colonoscopy at rural hospitals compared to 45.1% at urban hospitals. Patients treated at rural hospitals had 27% lower odds of receiving colonoscopy relative to patients treated at urban hospitals (OR = 0.73, $P < 0.0001$) After controlling for other factors, colonoscopy was associated with a 50% lower odds of mortality (OR = 0.50, $P < 0.0001$). The problem that remains to be solved is providing patients in rural hospitals access to colonoscopy so more patients can have a mortality benefit when they present with a lower gastrointestinal bleed.

Research conclusions

This study proposes that because there is a decrease in mortality when patients receive a colonoscopy, we should improve access to colonoscopies in rural hospitals. New methods proposed are increased access to specialists and increased training opportunities for primary care providers for colonoscopies.

Research perspectives

Future research should be aimed at determining mortality differences in patients with lower gastrointestinal bleeds that receive colonoscopy between urban and rural hospitals.

FOOTNOTES

Author contributions: Ganta N and Aknouk M contributed equally to this work; Ganta N, Aknouk M, Nikiforov I, Bommu VJL, Patel V, Cheriyath P, Hollenbeak C, and Hamza A, designed the research study; Ganta N, Aknouk M, Alnabwani D, Nikiforov I, Bommu VJL, Patel V, and Hollenbeak C performed the research; Hollenbeak C, Nikiforov I, and Cheriyath P contributed in statistical analysis; Ganta N, Aknouk M, Alnabwani D, Nikiforov I, Bommu VJL, Patel V, and Hollenbeak C analyzed the data and wrote the manuscript.

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ORIGINAL ARTICLE

Retrospective Study

Percutaneous transluminal angioplasty balloons for endoscopic ultrasound-guided pancreatic duct interventions

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Abstract

BACKGROUND

Endoscopic ultrasound (EUS)-guided main pancreatic duct (PD) access may be used when conventional endoscopic retrograde cholangiopancreatography (ERCP) techniques fail. The use of a percutaneous transluminal angioplasty balloon (PTAB), originally developed for vascular interventions, can be used to facilitate transmural (*e.g.*, transgastric) PD access and to dilate high-grade pancreatic strictures.

AIM

To describe the technique, efficacy, and safety of PTABs for EUS-guided PD interventions.

METHODS

Patients who underwent EUS with use of a PTAB from March 2011 to August 2021 were retrospectively identified from a tertiary care medical center supply database. PTABs included 3-4 French angioplasty catheters with 3-4 mm balloons designed to use over a 0.018-inch guidewire. The primary outcome was technical success. Secondary outcomes included incidence of adverse events (AEs) and need for early reintervention.

RESULTS

A total of 23 patients were identified (48% female, mean age 55.8 years). Chronic pancreatitis was the underlying etiology in 13 (56.5%) patients, surgically altered anatomy (SAA) with stricture in 7 (30.4%), and SAA with post-operative leak in 3 (13.0%). Technical success was achieved in 20 (87%) cases. Overall AE rate was 26% (n = 6). All AEs were mild and included 1 pancreatic duct leak, 2 cases of post-procedure pancreatitis, and 3 admissions for post-procedural pain. No

patients required early re-intervention.

CONCLUSION

EUS-guided use of PTABs for PD access and/or stricture management is feasible with an acceptable safety profile and can be considered in patients when conventional ERCP cannulation fails.

Key Words: Dilating balloon; Pancreatic duct intervention; Chronic pancreatitis; Anastomotic stricture

Core Tip: Endoscopic ultrasound (EUS)-guided access of the main pancreatic duct (MPD) can be used to perform endotherapy when conventional endoscopic retrograde cholangiopancreatography fails. After access to the MPD is obtained, the tract created between the gastrointestinal lumen and pancreatic duct must be dilated prior to any further intervention. Percutaneous transluminal angioplasty balloons, originally developed for vascular interventions, can be used to access the pancreatic duct effectively and safely, as well as dilate high-grade MPD strictures if needed. Interventional endoscopists should be familiar with these cross-platform balloons as additional tools in the toolbox for EUS-guided MPD endotherapy.

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INTRODUCTION

Obstruction of the main pancreatic duct (MPD) can occur in the context of chronic inflammation and fibrosis due to a variety of clinicopathologic conditions, including both malignant and benign etiologies (*e.g.*, chronic pancreatitis, post-pancreatic surgery). Obstruction of MPD outflow leads to higher resistance to pancreatic secretions, intraductal hypertension, and ultimately ductal dilation[1,2]. Patients can present with chronic abdominal pain, recurrent pancreatitis, steatorrhea, and unexplained weight loss. Decompression of the PD is the mainstay of treatment for symptomatic patients, and endoscopic therapy has become the preferred treatment modality due to its safety profile when compared to surgery[3,4].

Transpapillary or transanastomotic drainage with endoscopic retrograde cholangiopancreatography (ERCP) remains the preferred approach for endoscopic pancreatic duct access and intervention[5]. While successful in the vast majority of cases, 3% to 10% fail due to inability to cannulate the papilla/anastomosis, obstructive stones, high-grade strictures, and surgically-altered anatomy (SAA) that impacts access to the pancreaticobiliary tree, including surgeries like Roux-en-Y gastric bypass and pancreaticoduodenoctomy[6]. In these cases, endoscopic ultrasound (EUS)-guided pancreatic duct drainage has emerged as a potential salvage approach with a favorable safety profile and technical success rate. Technical and clinical success rates range from 63% to 100% and 76% to 100%, respectively, with adverse event rates ranging from as low as 14% up to 37%[7]. Guidelines recommend consideration of EUS-guided access in multidisciplinary, tertiary care settings when conventional therapy fails [8].

As EUS-guided pancreatic duct access becomes more established among experienced operators, there remains significant variation in technique. Specifically, dilation of the access tract can be performed with a variety of devices and currently published studies include the utilization of hydrostatic balloons, tapered catheters, and electrocautery-enhanced catheters[9,10]. No comparative trials exist comparing the success and complication rates of these devices. The hydrostatic balloons which are currently used were designed for biliary intervention, and their size may increase the risk of complications during pancreatic duct access[11].

Percutaneous transluminal angioplasty balloons (PTAB) are smaller caliber, 3 to 4mm diameter balloons initially designed for vascular interventions but can passed over standard 0.018-inch guidewires for use on endoscopic platforms. Initial case reports described the use of these balloons to treat otherwise impassable biliary strictures[12]. Their size makes them well-suited for dilation of the pancreaticogastrostomy/enterostomy as well as high-grade MPD strictures. Reports describe the use of these devices during ERCP; however, experience during EUS is limited to a handful of reported cases

[13,14]. The objective of this study is to describe the use of PTABs during EUS-guided MPD interventions. This includes the technique, efficacy, and safety of their use during these procedures.

MATERIALS AND METHODS

Study overview

This is a retrospective, single-center cohort study approved by the Institutional Review Board at the Mayo Clinic. Consecutive patients who underwent EUS-guided MPD intervention with use of a PTAB between March 2011 to August 2021 were identified from a single tertiary care center using a supply database. Balloons used included 3 and 4 mm diameter SAVVY™ and SABER™ PTA balloons (Cordis, Santa Clara, CA, United States) which were 20 mm in length. Procedure information was extracted *via* manual chart review and included procedure indication, inpatient status, preceding ERCP attempts, indication for EUS-guided approach, maximum diameter of the MPD measured intraprocedurally, site of MPD access, and location of balloon dilation (Figure 1). In patients with SAA, the exact procedure was recorded. Patients with post-surgical pancreatic leaks were classified as biochemical leaks, grade B, or grade C according to the International Study Group for Pancreatic Fistula criteria[15].

The primary outcome was technical success defined by successful MPD access and accomplishing the intent of the procedure. If either of these conditions were not met, the procedure was classified as technical failure. Secondary outcomes included procedural related adverse events (AEs) including pain, bleeding, pancreatitis, leak, new fluid collection, perforation, or death as well as need for early reintervention prior to planned follow-up and clinical success. AEs were classified as mild, moderate, or severe based on American Society of Gastrointestinal Endoscopy (ASGE) lexicon[16]. Clinical response was noted at last follow up. Complete response was noted when there was clear documentation that all clinical symptoms fully resolved after intervention, and partial response if it any improvement in severity or frequency was documented. Patients without any benefit were classified as persistent symptoms.

Procedural technique

All procedures were performed by EUS- and ERCP-trained interventional endoscopists in a dedicated endoscopy unit with patients under general anesthesia. Due to the retrospective nature of this study, the exact technique used in each case was operator dependent. Generally, a linear-array echoendoscope was passed into the stomach and the MPD was identified. The MPD was preferentially accessed through the gastric wall with an FNA needle (19- to 22-gauge); however, the small bowel was also evaluated as an access point if suitable endosonographic windows for duct puncture were not found in the stomach. After EUS-guided ductal access was achieved, an 0.018-inch guidewire was passed under fluoroscopic guidance into the MPD and through the ampulla/anastomosis when possible. When utilized, the PTAB was then advanced over the guidewire and used to dilate the access tract and/or pancreatic duct stricture prior to any additional intervention, including further dilation or stenting (Figure 2).

Statistical analysis

Data management, analysis, and visualization was performed using BlueSky Statistics software (version 7.10, BlueSky Statistics LLC, Chicago, IL, United States). Quantitative variables were described with median value and interquartile range (IQR). Categorical data were reported as relative proportions (%).

RESULTS

Patient characteristics

A total of 23 patients were identified. The median age of the cohort was 55.8 years (IQR 45.0-57.8) with 11 (48%) females and 12 (52%) males. Median body mass index was 25.8 kg/m^2 (IQR 23.9-27.5). Procedural indications included chronic pancreatitis in 13 (57%) patients, SAA with stricture in 7 (30%), and SAA with post-operative leak in 3 (13.0%). Of the 10 patients with SAA, 9 had undergone pancreaticoduodenectomy with antrectomy (*i.e.*, Whipple procedure) and 1 had an en-bloc resection of metastatic cervical cancer requiring hepaticogastrostomy with Roux-en-Y reconstruction. The 3 post-operative leaks were identified as nonspecific peripancreatic fluid on computed tomography and confirmed by ERCP. All cases were classified as grade B and none were associated with organ failure or need for operative reintervention. Indications for an EUS-guided approach included 5 cases with inaccessible anastomosis/ampulla (22%), 5 obstructive anastomotic strictures (22%), 2 failed cannulations (9%), 9 proximal obstructions due to stone or stricture (9, 39%), and 2 disconnected pancreatic ducts (9%).

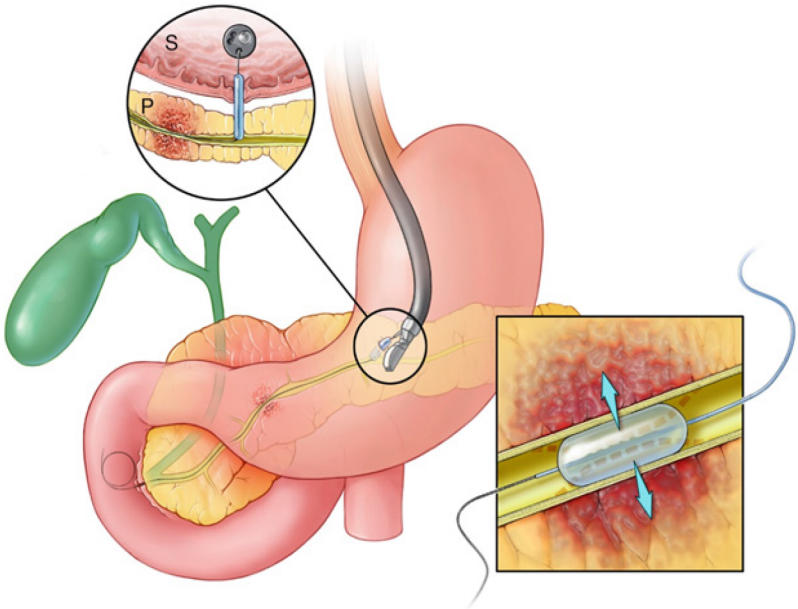

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Figure 1 Illustration of endoscopic ultrasound-guided pancreatic duct access showing balloon dilation of the gastropancreatic fistula.
The balloon can also be passed into the main pancreatic duct to dilate high grade strictures.

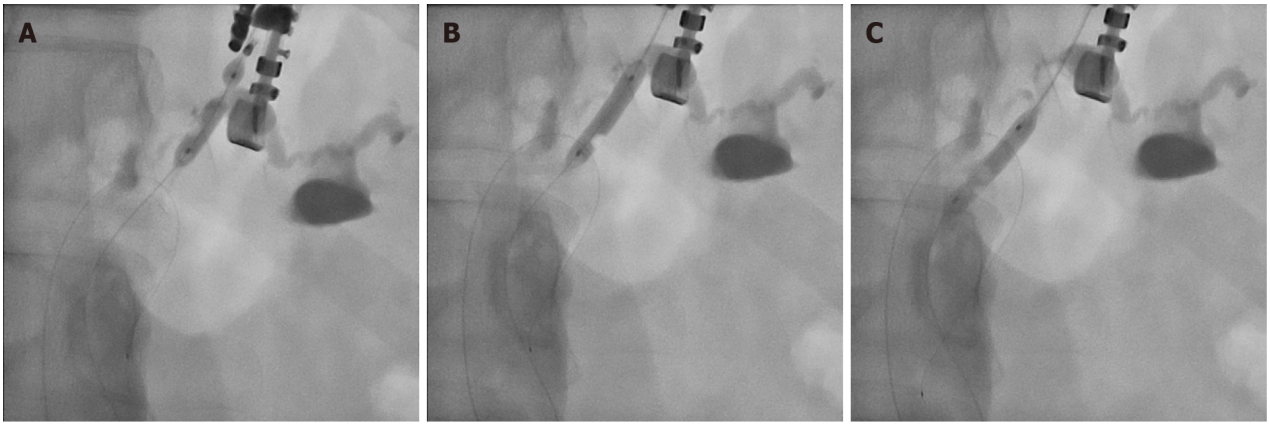

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Figure 2 Fluoroscopy images taken during endoscopic ultrasound showing dilation of access tract and stricture in a patient with chronic pancreatitis and a disconnected duct (A-C).

Procedural details

The majority of procedures were performed as an outpatient (n = 18, 78%). Maximum MPD size as measured during EUS was 5.5 mm (IQR 3.7-8.3 mm). Transgastric access was obtained in 22 cases (96%) with 1 pancreaticoenterostomy performed (4%). A 4 mm diameter PTAB was used in 15 cases (65%) with 3 mm balloons used in the remaining 8 (35%). The pancreatic duct was typically accessed through the body (n = 17, 74%) followed by tail (n = 3, 13%), and head (n = 3, 13%). The balloons were primarily used to dilate the access tract in 21 cases (91.3%), of which 9 were then passed into the pancreas and used for PD dilation. Pancreatic duct dilation alone was performed in 2 cases (10%). Dilation with a PTAB was the initial method used in the majority of cases (n = 21, 91%). In the remaining 2 cases, PTAB was used if needle knife access puncture and a dilating catheter was not successful. Further pancreatic duct intervention with dilation was performed in 5 cases (22%) and stenting in 17 (74%). This included 9 transmural stents terminating in the MPD, 8 stents placed through the stomach which traversed the MPD into the small bowel, and 1 retrograde transpapillary stent terminating in the MPD.

Outcomes

Technical success was achieved in 20 cases (87%). All 3 failed cases occurred in patients with chronic, calcific pancreatitis. In 2 of these cases, the procedure failed due to inability to obtain an adequate

window for MPD access. The third case failed due to a high-grade MPD stricture with calcified stones that prevented the passage of all devices, including the 4 mm PTAB.

AEs were noted in 6 patients (26%) which were all mild in severity, requiring an unplanned hospital admission for ≤ 3 nights. Additional patient and procedural factors that may have impacted AEs are outlined in Table 1. There was 1 case of pancreatic duct leak identified endosonographically during the procedure, which was self-contained and managed conservatively. Additionally, there were two cases of pancreatitis and 3 cases of post-procedural pain requiring hospital admission. There were no AEs related to bleeding from the access site or perforation.

Median post-procedure follow up time was 13.9 mo (IQR 6.9-28.1 mo). No patients required unanticipated, early intervention. In the 20 cases that were technically successful, 14 underwent additional planned interventions prior to stent removal which included routine stent exchange in 7 cases and placement of a parallel stent in the remaining 7. At the time of last follow up, 9 of the 20 (45.0%) technically successful cases were noted to have complete resolution of symptoms, 5 (25.0%) partial resolution, and 3 (15%) persistent symptoms. One patient (4.3%) did not have follow up symptoms documented, and two (8.6%) died during follow up prior to assessment of symptom improvement.

DISCUSSION

The emergence of interventional EUS has given endoscopists the ability to treat pancreatic duct obstruction even when conventional ERCP fails. These interventions require dilation of the gastro- or enteropancreatic fistula created during EUS-guided pancreatic duct drainage. Given the lack of dedicated devices to facilitate EUS-directed drainage interventions, endoscopists rely on other accessories that were not designed for these interventions. These include hydrostatic pancreaticobiliary dilating balloons, tapered dilating catheters, traction sphincterotome, and diathermy-compatible catheters[13]. PTABs are yet another device that can be used to facilitate access with interventional EUS.

Each technique and device carries its own risk-benefit profile. Axial pressure forces created during dilation with a fixed-diameter catheter, cannula or tapered passage dilator can lead to dissection of the tissue planes. On the other hand, balloon dilation may increase the risk of perforation, leakage, and bleeding due to its "all-or-nothing" approach. Standard endoscopic balloon dilators typically have diameters of 5 to 6 French and were designed primarily for intraductal ERCP-guided interventions. The use of smaller diameter balloons theoretically may allow for controlled dilation of the tract while minimizing the risk of perforation and leak. Notably, all AEs in this cohort were mild, without significant bleeding or perforation. There was one, self-contained pancreatic duct leak, but this occurred in a case where a diathermy catheter was used prior to balloon dilation. Electrocautery devices can result in a delayed-burn effect, increasing the risk of developing serious adverse events[17]. The overall AE rate of 26% may seem high compared to other standard endoscopic procedures but is favorable when compared to the morbidity and mortality associated with surgical alternatives, which include AE rates of up to 30% and 2% mortality[18,19]. Our data is similar to published literature on EUS-guided drainage of the MPD with more conventional ERCP accessories, including one of the largest multicenter studies which reported an AE rate of 20%[12].

Technical success of EUS-guided drainage of the MPD ranges from 50%-100% in the literature, approaching 80%-90% in more recent cohorts with experienced operators[10,12]. A technical success rate of 87% is consistent with the higher end of this range. In a previously published case series on the utilization of PTABs during EUS-guided interventions, a very similar technical success rate of 88% was reported with only one mild adverse event[15]. However, this was a very small cohort of 8 patients, contained only 1 case of chronic pancreatitis with stricture, and details regarding other procedural factors that may have impacted outcomes were limited. In this study, we report on a robust cohort with chronic pancreatitis and post-surgical disease. The majority of PTABs were successfully used as first line EUS-guided therapy, as opposed to salvage therapy when other devices failed. Furthermore, two of the three failures were due to limited mobility and inability to secure a safe window for MPD access, which is a limitation of the procedure itself and not the dilation device used.

This study is limited by its retrospective design with slight variations in patient characteristics and procedural technique. However, this heterogeneity also highlights that PTABs can be used in a wide range of clinical scenarios. Furthermore, procedural outcomes were certainly confounded by patient and technical factors unrelated to PTAB use. This study was not designed to evaluate EUS-guided drainage of the MPD outcomes overall, and additional detail was provided regarding cases of technical failure and AEs to allow for careful evaluation of the role the device played in these outcomes.

CONCLUSION

This study suggests that PTABs can be used to successfully and consistently access and drain the pancreatic duct while maintaining a high technical success rate without severe AEs. Additional comparative studies are needed to determine optimal technique; however, these cross-platform devices

Table 1 Procedural adverse event details

	Adverse Event	Severity	Additional devices used for tract dilation	Other procedural detail
1	Post-procedure pain	Mild[1]	None	None
2	Post-procedure pain	Mild[1]	None	Multiple puncture attempts; Needle dislodgement requiring retrieval with forceps
3	Post-procedure pain	Mild[1]	None	Dehiscence of surgical anastomosis noted prior to procedure start
4	Pancreatic duct leak	Mild[1]	Needle knife electrocautery	Electrocautery utilized prior to percutaneous angioplasty balloon dilation; Small, self-contained leak identified sonographically prior to completion of the procedure
5	Pancreatitis	Mild[1]	None	Additional pancreatic duct dilation to 6 mm; Large fragmented pancreatic duct stone cleared in an antegrade fashion with occlusion balloon
6	Pancreatitis	Mild[1]	None	Small endoscopic window with limited mobility; Multiple puncture attempts

[1]Post-procedure hospitalization ≤ 3 d.

can help address the safety and technical limitations of existing endoscopic devices including larger diameter balloons, fixed diameter catheters, tapered passage dilators, and electrocautery-based devices. Interventional endoscopists should be familiar with these devices as additional tools in the toolbox for EUS-guided MPD endotherapy.

ARTICLE HIGHLIGHTS

Research background

While endoscopic retrograde cholangiopancreatography (ERCP) remains the gold standard for main pancreatic duct (MPD) intervention, endoscopic ultrasound (EUS)-guided MPD access has emerged as a safe and effective alternative when ERCP fails. A key step in EUS-guided intervention is dilation of the tract created between the gastrointestinal lumen and pancreatic duct, however there is limited data regarding the optimal dilation device and technique. Furthermore, current tools were designed primarily for biliary intervention, including hydrostatic balloons, tapered bougies, and electrocautery-enhanced catheters.

Research motivation

A small diameter, hydrostatic balloon would theoretically allow for safe dilation while minimizing the risk of adverse events, however commercially available devices are limited. Percutaneous angioplasty balloons (PTABs) are small diameter balloons that were initially designed for vascular interventions. They can be deployed over a standard guidewire and utilized on endoscopic platforms to dilate the access tract created during EUS-guided access as well as high grade strictures. However, data on the use of these devices is limited to a handful of case reports.

Research objectives

The main objective of this study is to describe the efficacy and safety of PTAB use during EUS-guided MPD access. The primary outcome was technical success with secondary outcomes of clinical success and adverse event rate. The objectives of this study provide key, real-word information on the use of PTABs for clinicians as well as preliminary data to inform future prospective studies.

Research methods

This is a retrospective, single center cohort study performed at an academic tertiary care center which includes all patients from 2011 to 2021 who underwent EUS-guided MPD which utilized a PTAB. Patients were identified retrospectively from a procedural supply database and clinical information was extracted from the electronic medical record.

Research results

A total of 23 cases were identified. Intervention was performed in the setting of chronic pancreatitis in 13 (56%), post-surgical stricture in 8 (35%), and post-surgical leak in 2 (9%). Technical success was achieved in 20 (87%) cases with 6 (26%) adverse events. Adverse events were all mild in severity and included 3 admissions for post-procedural pain, 2 pancreatitis, and 1 pancreatic duct leak.

Research conclusions

This study demonstrates that PTABs can be used to consistently access the MPD for EUS-guided interventions with an acceptable safety profile. In the absence of dedicated devices, endoscopists can consider using cross-platform PTABs for initial dilation prior to antegrade interventions.

Research perspectives

Further prospective, randomized studies are needed to compare the efficacy and safety of PTABs to other dilating devices and techniques.

FOOTNOTES

Author contributions: AbiMansour JP collected the data, performed the analysis and wrote the paper; Abu Dayyeh BK, Levy MJ, Storm AC, Martin JA, Petersen BT, Law RJ, and Topazian MD performed the procedures, obtained the data, and critically reviewed the manuscript; and Chandrasekhara VC designed the research and provided supervision, manuscript review, and final approval.

Institutional review board statement: This study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB No. 20-0055740).

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

Conflict-of-interest statement: Andrew C Storm is a consultant for Apollo Endosurgery; and received research support from Apollo Endosurgery and Boston Scientific. Ryan J Law is a consultant for ConMed and Medtronic and receives royalties from UpToDate. Bret T Petersen is a consultant for Olympus America and investigator for Boston Scientific and Ambu. Barham K Abu Dayyeh reports consultant roles with Endogenex, Endo-TAGSS, Metamodix, and BFKW; consultant and grant or research support from USGI, Cairn Diagnostics, Aspire Bariatrics, Boston Scientific; speaker roles with Olympus, Johnson and Johnson; speaker and grant or research support from Medtronic, Endogastric solutions; and research support from Apollo Endosurgery and Spatz Medical. Vinay Chandrasekhara is a consultant for Covidien LP, is on the advisory board for Interpace Diagnostics, and is a shareholder in Nevakar, Inc. The remaining authors have no conflicts or funding to disclose.

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ORIGINAL ARTICLE

Observational Study

New application of endocytoscope for histopathological diagnosis of colorectal lesions

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Abstract

BACKGROUND

The endocytoscope with ultra-high magnification (x 520) allows us to observe the cellular structure of the colon epithelium during colonoscopy, known as virtual histopathology. We hypothesized that the endocytoscope could directly observe colorectal histopathological specimens and store them as endocyto-pathological images by the endoscopists without a microscope, potentially saving the burden on histopathologists.

AIM

To assess the feasibility of endocyto-pathological images taken by an endoscopist as adequate materials for histopathological diagnosis.

METHODS

Three gastrointestinal pathologists were invited and asked to diagnose 40 cases of endocyto-pathological images of colorectal specimens. Each case contained seven endocyto-pathological images taken by an endoscopist, consisting of one loupe image, three low-magnification images, and three ultra-high magnification images. The participants chose hyperplastic polyp or low-grade adenoma for 20 cases of endocyto-pathological images (10 hyperplastic polyps, and 10 Low-grade adenomas in conventional histopathology) in study 1 and high-grade adenoma/

shallow invasive cancer or deep invasive cancer for 20 cases [10 tumor in situ/T1a and 10 T1b] in study 2. We investigated the agreement between the histopathological diagnosis using the endocyto-pathological images and conventional histopathological diagnosis.

RESULTS

Agreement between the endocyto-pathological and conventional histopathological diagnosis by the three gastrointestinal pathologists was 100% (95%CI: 94.0%–100%) in studies 1 and 2. The interobserver agreement among the three gastrointestinal pathologists was 100%, and the κ coefficient was 1.00 in both studies.

CONCLUSION

Endocyto-pathological images were adequate and reliable materials for histopathological diagnosis.

Key Words: Cancer; Colon; Endocytoscopy; Histopathology; Specimen

Core Tip: The endocytoscope allows us to observe the histological structure of the colon epithelium, but it is a virtual histopathology. We directly observed pathological specimens by the endocytoscope and evaluated the practical usefulness of endocyto-pathology in this pilot study.

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INTRODUCTION

The endocytoscope, which was launched in early 2018 by Olympus Medical Systems Corporation (Tokyo, Japan), can provide ultra-high magnification (x 520) images in real time during colonoscopy. The endocytoscopy allows us to observe the cellular structure of the colorectal lesions, known as virtual histopathology and has provided high diagnostic performance in estimating their histopathology[1-5]. There is growing evidence that the diagnostic accuracy of endocytoscopy with computer-aided diagnosis (CAD) was greater than that of non-expert and comparable to expert endoscopists[6-12].

Based on the background of the shortage of histopathologists, we have explored a new application of endocytoscope for histopathological diagnosis of colorectal lesions[13]. We hypothesized that the endocytoscope could directly observe colorectal histopathological specimens and store them as endocyto-pathological images by the endoscopists themselves without a microscope. The endocyto-pathological images taken by endoscopists can be stored in the same system as the endoscopic images so that both images can be obtained as needed, making it possible to hold clinicopathological conferences efficiently even in countries with a few pathologists. Furthermore, a combination of endocyto-pathological images and the CAD system may lead to saving the burden of histopathologists in the future.

This pilot study aimed to assess the feasibility of endocyto-pathological images taken by an endoscopist as adequate materials for histopathological diagnosis.

MATERIALS AND METHODS

Endocyto-pathological images

First, each specimen was placed horizontally in a white container filled with water to control the diffuse reflection of the scope light. An endoscopist (FI) took the ultra-magnifying images of the specimens (endocyto-pathological images) with the right hand firmly fixed by touching the edge of the container and holding the tip of the scope using a penhold grip (Figure 1). This method helps bring high-quality endocyto-pathological images into focus. Seven endocyto-pathological images were obtained for each case (one loupe image, three low-magnification images, and three ultra-high magnification images) (Figures 2 and 3).

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Figure 1 How to take the endocyto-pathological images using an endocytoscope: The right hand was firmly fixed by touching the edge of the container, and the tip of the scope was held in the penhold method.

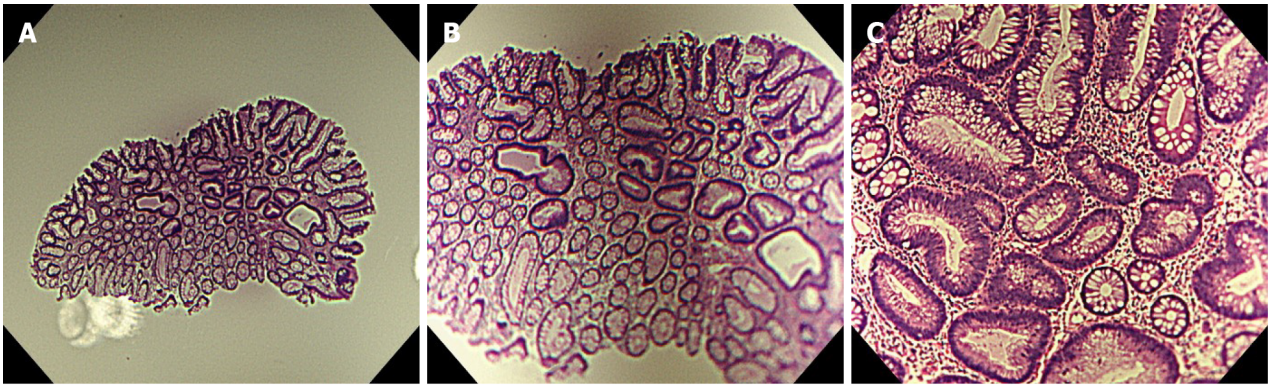

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Figure 2 Endocyto-pathological images of low-grade adenoma. A: Loupe image. B: Low-magnification image. C: Ultra-high magnification image.

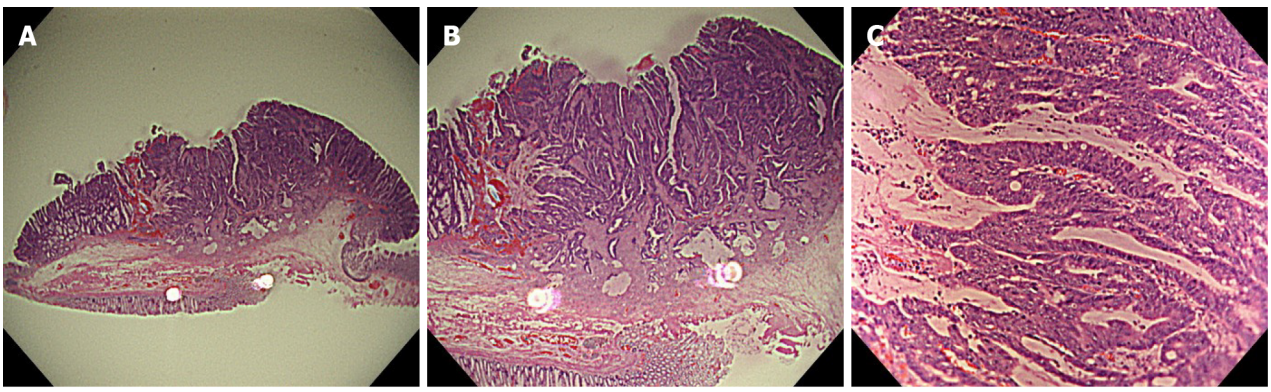

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Figure 3 Endocyto-pathological images of T1b cancer. A: Loupe image. B: Low-magnification image. C: Ultra-high magnification image.

Selection of colorectal specimens

Candidate colorectal specimens were selected from histopathologically-known material obtained by endoscopic or surgical resection at Sano Hospital between January 2017 and January 2021. Candidates samples with poor preservation, incomplete resection of the lesion, or other candidates deemed inappropriate by the investigators were excluded. Among these candidates samples, 10 specimens for each of the following categories hyperplastic polyps, low-grade adenoma, high-grade adenoma/shallow invasive cancer (10 tumor in situ (Tis)/T1a), and deep invasive cancer (T1b) were randomly selected. The number of specimens in each category was masked to the participants.

Evaluation of endocyto-pathological images by gastrointestinal pathologists

Three gastrointestinal pathologists (TS, HK, KI) were invited and asked to read the endocyto-pathological images for 40 cases (7 images for each case) of colorectal specimens from May to July 2021. The participants were asked to choose hyperplastic polyp or low-grade adenoma for 20 cases of endocyto-pathological images (10 hyperplastic polyps and 10 Low-grade adenomas diagnosed by the conventional method) in study 1 and high-grade adenoma/shallow invasive cancer (Tis/T1a) or deep invasive cancer (T1b) for 20 cases (10 Tis/T1a and 10 Tib cancer) in study 2.

The study protocol was reviewed and approved by the Institutional Review Board at Sano Hospital (202106-02). This study was registered with Japan Registry of Clinical Trials (jRCT1050210046).

Outcome measures

The primary outcome measure was the agreement between the histopathological diagnosis using the endocyto-pathological images and conventional histopathological diagnosis.

The secondary outcome measure was the interobserver agreement rate and Fleiss's Kappa statistics among three pathologists.

Statistical analysis

This study was conducted as an exploratory research investigation without calculating sample size due to the lack of data in previous studies.

RESULTS

Tables 1 and 2 show the agreement between the histopathological diagnosis by three gastrointestinal pathologists using the endocyto-pathological images and conventional histopathological diagnosis in differentiating low-grade adenoma from hyperplastic polyp (study 1) and T1b from Tis/T1a cancer (study 2). The agreement between the endocyto-pathological and conventional histopathological diagnosis was 100% (95%CI: 94.0%-100%) in study 1 and 100% (94.0%-100%) in study 2. The interobserver agreement among the three gastrointestinal pathologists was 100%, and the κ coefficient was 1.00 in both studies.

DISCUSSION

To our knowledge, this is the first report of a new clinical application of the endocytoscope for histopathological specimens. The quality of endocyto-pathological images taken by an endoscopist was sufficiently high to make a histopathological diagnosis. We attempted to take pathological images of histopathological specimens by conventional magnifying endoscopy (x 85 maximum optical magnification with approximately 2mm of a minimum depth of observation); however, cytological findings could not be evaluated owing to a lack of resolution power and focus depth. In contrast, the endocytoscope easily enables the evaluation of cytological findings by taking ultra-high power magnification images with contact on the histological slides. For better quality, the specimens were placed horizontally in a white container filled with water to control the diffuse reflection of the diffuse reflection of the scope light.

Linking endoscopic and histopathological images is a clinically essential step for endoscopists to improve endoscopic diagnosis for estimating the histopathology of gastrointestinal lesions. In situations where pathologists are scarce, it would be better to have endoscopists obtain histopathological images using a microscope. However, most endoscopists do not have microscopes in their institutions or are generally unfamiliar with using them. In this context, we considered it meaningful to have endoscopists obtain histopathological images using endocytoscopes. Additionally, our endocyto-pathological images have the advantage of being stored with endoscopic images in the same endoscopic system, which is helpful when holding clinicopathological conferences. We believe the endocyto-pathological diagnosis will reduce the growing burden on histopathologists, including their time and cost, when especially made with the CAD system. Further studies will be required to prove the hypothesis.

This study has limitations. First, knowledge of histopathology is required for endoscopists to take diagnosable ultra-high magnification images, especially for cancer depth diagnosis. Taking inadequate images would lead to the wrong endocyto-pathological diagnosis. Second, endocytoscopes have not yet been disseminated worldwide. However, the results of this study may encourage the spread of the endocytoscopes, especially in countries with a few pathologists.

Table 1 The agreement between endocyto-pathological and conventional histopathological diagnosis for differentiating low-grade adenoma from hyperplastic polyp by three gastrointestinal pathologists

	Conventional pathological diagnosis	
	Low-grade adenoma (*n* = 30)	Hyperplastic polyp (*n* = 30)
Endocyto-pathological diagnosis		
Low-grade adenoma	30	0
Hyperplastic polyp	0	30

Table 2 The agreement between endocyto-pathological and conventional histopathological diagnosis for differentiating T1b from Tis/T1a cancer by three gastrointestinal pathologists

	Conventional pathological diagnosis	
	T1b cancer (*n* = 30)	Tis/T1a cancer (*n* = 30)
Endocyto-pathological diagnosis		
T1b cancer	30	0
Tis/T1a cancer	0	30

CONCLUSION

In conclusion, endocyto-pathological images of colorectal lesions were adequate and reliable materials for histopathological diagnosis. Endocytoscopes will be disseminated in the future and have the potential for endocyto-pathology worldwide.

ARTICLE HIGHLIGHTS

Research background

Based on the background of the shortage of histopathologists, we explore the new application of endocytoscope for directly observing histopathological specimens of colorectal lesions and storing them as endocyto-pathological images with their endoscopic images.

Research motivation

Endocyto-pathological images taken by endoscopists potentially reduce the burden of histopathologists and facilitate holding clinicopathological conferences more simply.

Research objectives

To assess the feasibility of endocyto-pathological images taken by an endoscopist as adequate materials for histopathological diagnosis.

Research methods

This was a single-center prospective pilot study. Three gastrointestinal pathologists were asked to diagnose 40 cases of endocyto-pathological images of colorectal specimens (Each case contained seven images: one loupe image, three low-magnification images, and three ultra-high magnification images). The participants chose hyperplastic polyp or low-grade adenoma for 20 cases of endocyto-pathological images (10 hyperplastic polyps, and 10 Low-grade adenomas in conventional histopathology) in study 1 and high-grade adenoma/shallow invasive cancer or deep invasive cancer for 20 cases [10 tumor in situ (Tis)/T1a and 10 T1b] in study 2.

Research results

Agreement between the endocyto-pathological and conventional histopathological diagnosis by the three gastrointestinal pathologists was 100% (95%CI: 94.0%–100%) in studies 1 and 2. The interobserver agreement among the three gastrointestinal pathologists was 100%, and the κ coefficient was 1.00 in both studies.

Research conclusions

Endocyto-pathological images were adequate and reliable materials for histopathological diagnosis.

Research perspectives

Endocyto-pathological images taken by endoscopists will reduce the growing burden on histopathologists, including their time and cost, when especially used with the computer-aided diagnosis system.

FOOTNOTES

Author contributions: Inoue F, Hirata D, Iwatate M, Hattori S, Fujita M, Sano W and Sano Y contributed to the study concept and design; Sugai T, Kawachi H and Ichikawa K contributed to read endocytopathological images; Inoue F, Hirata D, Iwatate M and Sano Y contributed to the data analysis and interpretation; Inoue F contributed to draft the manuscript; and Sugai T, Kawachi H, Ichikawa K and Sano Y contributed to the critical revision of the manuscript for intellectual content.

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CASE REPORT

Hidden local recurrence of colorectal adenocarcinoma diagnosed by endoscopic ultrasound: A case series

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Abstract

BACKGROUND

Almost half of the patients with colorectal cancer (CRC) will experience local-regional recurrence after standard surgical excision. Many local recurrences of colorectal cancer (LRCC) do not grow intraluminally, and some may be covered by a normal mucosa so that they could be missed by colonoscopy. Early detection is crucial as it offers a chance to achieve curative reoperation. Endoscopic ultrasound (EUS) is mainly used in CRC staging combined with cross-section imaging study. EUS can provide an accurate assessment of sub-mucosal lesions by demarcating the originating wall layer and evaluating its echostructure. EUS fine-needle aspiration (FNA) provides the required tissue examination and confirms the diagnosis.

CASE SUMMARY

We report a series of five cases referred to surveillance for LRCC with negative colonoscopy and/or negative endoscopic biopsies. EUS-FNA confirmed LRCC implanted deep into the third and fourth wall layer with normal first and second layer.

CONCLUSION

Assessment for LCRR is still problematic and may be very tricky. EUS and EUS-FNA may be useful tools to exclude local recurrence.

Key Words: Colorectal cancer; Endoscopic ultrasound; Local recurrence; Fine-needle aspiration; Deep implanted CRC; Case report

Core Tip: The local recurrence of colorectal adenocarcinoma that has been implanted deeply in the submucosal layers is usually missed by colonoscopy, despite that some cases show submucosal elevation. Endoscopic biopsies often give negative results, so endoscopic ultrasound fine-needle aspiration can be used to confirm the diagnosis and give patients a better chance for proper management.

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INTRODUCTION

In patients with curatively resected colorectal cancer (CRC), local recurrence is often considered a clinical dilemma difficult to treat, may cause markedly disabling symptoms, and usually has a bad prognosis[1,2]. Several factors were incriminated in the recurrence as positive surgical margins, especially with inadequate excision, inadequate nodal dissection, implantation of exfoliated malignant cells into the deep layers, and changed biological characters at the site of large bowel anastomosis[3]. However, while colonoscopy remains the gold standard method of detecting local recurrences of colorectal cancer (LRCC) and metachronous lesions, it is considered an imperfect tool even in the best hands, with missing rates of adenocarcinoma ranging from 1% to 3%[4,5]. Unfortunately, not all local recurrences are detectable at the mucosal surface with false-negative colonoscopy. In these cases, endoscopic ultrasound (EUS) plays an irreplaceable role allowing highly detailed visualization of all the bowel wall layers with all the surrounding structures[6].

The great value of EUS in the evaluation for possible CRC recurrence nowadays comes from its ability to direct fine-needle aspiration (FNA) and fine needle biopsy, thus allowing the acquisition of tissue samples for histological and immunohistochemical examination, and providing a definitive diagnosis.

There are two studies on EUS FNA that showed its high accuracy in the diagnosis of subepithelial and extra-luminal lesions of the colon and rectum[7,8]. In both studies, the accuracy of EUS-FNA was 90%-95% compared with an 82% accuracy for imaging alone[8].

CASE PRESENTATION

All patients gave their informed written consent before the procedure. All patients had MRI examination before EUS examination.

All examinations were done under deep sedation with IV propofol. All cases had ano-rectal lesions, maximum 15-20 cm from the anal verge, which are easy to be scanned by the side view scope. No right hemicolon masse were included as they are very difficult to be approached by the side view scope. For EUS-FNA, we used Cook 22G needles (Echotip, Wilson-Cook) (Figure 1).

Chief complaints

Case 1: This was a 70-year-old male patient. During LRCC surveillance, no lesions were detected by colonoscopy. The patient experienced unexplained weight loss and was referred for EUS assessment.

Case 2: This was a 45-year-old male patient. LRCC surveillance colonoscopy revealed a submucosal lesion at the rectal anastomotic line, and multiple endoscopic biopsies got negative results repeatedly. The patient was referred for EUS examination.

Case 3: This was a 45-year-old female patient who presented with difficult defecation. Colonoscopy revealed narrowed rectal anastomotic line, but biopsies were negative.

Case 4: This was a 48-year-old male patient. During LRCC surveillance, submucosal elevation at the sigmoido-colonic anastomotic line was noticed by colonoscopy, and endoscopic biopsies showed

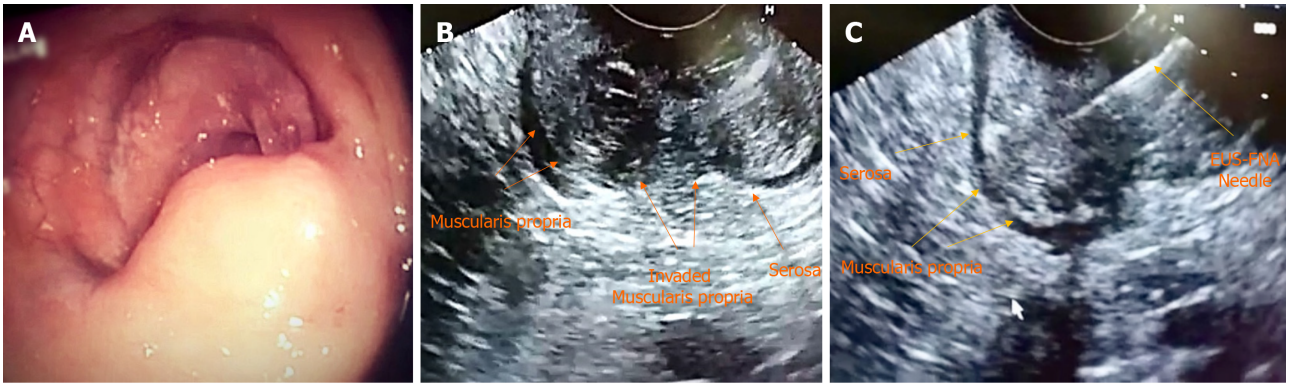

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Figure 1 Colonoscopy and endoscopic ultrasonography. A: Colonoscopic appearance of submucosal lesion at the anastomotic line at the recto-sigmoid junction; B: Endoscopic ultrasound appearance of a hypoechoic mass arising from the 3rd layer with interruption of the fourth layer at its base; C: Endoscopic ultrasound guided fine-needle aspiration acquisition. EUS: Endoscopic ultrasound; FNA: Fine-needle aspiration.

negative results.

Case 5: This was a 46-year-old male patient. During LRCC surveillance, colonoscopy showed a submucosal lesion with negative endoscopic biopsies.

History of present illness

Case 1: The patient experienced unexplained weight loss and was referred for EUS assessment.

Cases 2, 4, and 5: The patients underwent LRCC surveillance.

Case 3: The patient presented with difficult defecation.

History of past illness

Cases 1-5: The patients had a history of CRC surgical excision.

Personal and family history

Cases 1-5: No notable personal or family medical history.

Physical examination

Case 1: Unremarkable apart from unexplained weight loss.

Cases 2-5: Unremarkable physical examination.

Laboratory examinations

Case 1: No other abnormalities were noted apart from mild microcytic hypochromic anemia.

Cases 2-5: No other abnormalities noted.

Imaging examinations

Case 1: EUS assessment revealed a 2.8 cm × 4 cm homogenous mass at the rectal anastomotic line, arising from the fourth wall layer. FNA was performed, and pathological examination confirmed adenocarcinoma.

Case 2: EUS examination showed a 1.9 cm × 2.9 cm homogenous mass, arising from the fourth layer. FNA was performed, and pathological assessment confirmed adenocarcinoma recurrence.

Case 3: EUS was conducted and revealed a homogeneous mass measuring 3 cm × 3.3 cm, arising from the fourth layer. FNA was carried out, and adenocarcinoma local recurrence into the deep submucosal layers confirmed.

Case 4: EUS revealed a heterogeneous mass measuring 2.3 cm × 4.2 cm arising from the third layer. FNA was performed, and pathological studies confirmed adenocarcinoma recurrence.

Case 5: EUS was carried out and revealed a 1.2 cm × 2.4 cm homogeneous mass, arising from the fourth layer at the ano-rectal anastomotic line. FNA was performed, and the result confirmed adenocarcinoma.

FINAL DIAGNOSIS

We report five case series referred to surveillance for LRCC with negative colonoscopy and/or negative endoscopic biopsies. EUS-FNA confirmed LRCC implanted deep into the third and fourth wall layer with normal first and second layer.

TREATMENT

Case 1: The patient underwent Lt hemi-colectomy for local recurrence and was referred to medical oncology.

Case 2: Partial colectomy was carried out.

Case 3: The patient received chemotherapy for cancer colon.

Case 4: The patient was referred to medical oncology.

Case 5: The patient received chemo-radiotherapy for ano-rectal cancer.

OUTCOME AND FOLLOW-UP

In all cases, the patients were referred to medical cancer institute.

DISCUSSION

CRC is one of the common and lethal malignancies worldwide and is considered the second leading cause of cancer deaths in the United States[9]. Most of CRC patients underwent surgical excision aiming at curative treatment, and up to 40% of patients with the locoregional disease will develop recurrent cancer, of which 90% will occur within 5 years[10,11].

The postoperative surveillance of patients treated for CRC is a clinical challenge, first due to distorted anatomy and scarring and second because of intent to prolong survival by diagnosing recurrent and metachronous cancers at a curable stage. LRCC surveillance strategies combined different modalities, including clinical assessment, tumor marker carcinoembryonic antigen, computed tomography (CT) scans, and endoluminal imaging, including colonoscopy, sigmoidoscopy, EUS, and CT colonography. The optimal surveillance strategy is still not clearly defined.

A number of studies have shown EUS to be very accurate in detecting LCRR, with EUS-FNA being able to provide tissue confirmation[12,13].

Several guidelines and organizations recommend EUS in post-treatment surveillance for resected colon and rectal cancer. The NCCN guidelines state that flexible sigmoidoscopy with EUS or MRI should be done every 3 to 6 mo for 2 years, then every 6 mo to complete 5 years for patients with rectal cancer undergoing transanal excision only[14]. The United States Multi-Society Task Force include EUS as an alternative to sigmoidoscopy in the testing strategy for patients at higher risk of recurrence[15].

In patients with a curative resection for rectal cancer, the current US Multi-Society Task Force recommendation suggests EUS at 3-6 mo for the first 2 years after resection as a reasonable option[16]. It is noteworthy that not all recurrences are evident at the mucosal surface, so in those cases the benefit of EUS will be restricted in highly detailed visualization and assessment of all the bowel wall layers with all the surrounding structures[6].

Our study showed a rare clinical scenario of hidden implanted adenocarcinoma in the third and fourth layer with an intact mucosal layer, so it was not evident intraluminally and missed by colonoscopy, and endoscopic biopsies were false-negative repeatedly. This may be explained by the presence of cancer cells at the anastomotic line or trapping of cancer cells in the staple line, resulting in local recurrence, especially in patients who underwent double-staplinganastomosis[6,17].

Therefore, EUS-FNA gained the optimal diagnostic procedure and defined the proper treatment plan.

EUS can act not only as a method for the evaluation of precancerous polyps and subepithelial lesions found during screening of CRC, but also it has a great role in follow-up after resection of rectal carcinoma for early detection and tissue confirmation of locally recurrent cancer colon, by allowing the collection of specimens for histological and immuno-histochemical analysis, and overcoming some of the inherent user bias[18].

CONCLUSION

Assessment for LCRR is still problematic and may be very tricky, so we recommend using EUS-FNA to exclude local recurrence, since it could be deeply implanted and missed by routine imaging tools and colonoscopy.

FOOTNOTES

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LETTER TO THE EDITOR

Laparoscopic and endoscopic cooperative surgery for full-thickness resection and sentinel node dissection for early gastric cancer

Serafino Vanella, Maria Godas, Joaquim Costa Pereira, Ana Pereira, Ivano Apicella, Francesco Crafa

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Abstract

The endoscopic submucosal dissection (ESD) technique has become the gold standard for submucosal tumors that have negligible risk of lymph node metastasis (LNM), due to its minimal invasiveness and ability to improve quality of life. However, this technique is limited in stage T1 cancers that have a low risk of LNM. Endoscopic full thickness resection can be achieved with laparoscopic endoscopic cooperative surgery (LECS), which combines laparoscopic gastric wall resection and ESD. In LECS, the surgical margins from the tumor are clearly achieved while performing organ-preserving surgery. To overcome the limitation of classical LECS, namely the opening of the gastric wall during the procedure, which increases the risk of peritoneal tumor seeding, non-exposed endoscopic wall-inversion surgery was developed. With this full-thickness resection technique, contact between the intra-abdominal space and the intragastric space was eliminated.

Key Words: Endoscopic submucosal dissection; Laparoscopic endoscopic cooperative surgery; Non-exposed endoscopic wall-inversion surgery; Early gastric cancer; Nodal basin evaluation

Core Tip: The initial indication for laparoscopic endoscopic cooperative surgery (LECS) was gastric submucosal tumors (SMTs) without ulcerative features. Later, the LECS procedure was expanded to include gastric SMTs with ulceration and gastric cancer (GC) with negligible risk of lymph node metastasis. Currently, LECS can be applied to early GC in which sentinel node (surgical nodal basin) dissection can be performed with intra-operative evaluation by one-step nucleic acid amplification. Modified LECS procedures have been developed, such as inverted LECS, non-exposed endoscopic wall-inversion surgery, a combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique, and closed LECS.

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TO THE EDITOR

We read with great interest the retrospective study by Inokuchi *et al*[1], which evaluated the feasibility and efficacy of gastric endoscopic submucosal dissection (ESD) in patients aged ≥ 80 years. The study was based on 172 sessions of gastric ESD in 124 patients, with a final diagnosis of gastric cancer (GC) in 175 Lesions. The patients were studied retrospectively to evaluate short-term outcomes (procedure-related mortality, complications, curative dissection and rates of *en bloc* dissection) and survival. In the study, there was a high *en bloc* dissection rate (97.1%) and a curative dissection rate of 77.1%. Complications occurred in 8 patients (4.7%). There were 6 cases (3.4%) of postoperative bleeding, 2 (1.1%) of intraoperative perforation, and 1 (0.6%) of aspiration pneumonitis after ESD. There were no procedure-related deaths[1]. The significant risk factors that increased the rates of bleeding were tumor location in the lower third of the stomach, lesions > 40 mm, presence of a depressive component, and ulcerative features. The main risk factor for perforation was the site in the upper third of the stomach[1]. To evaluate long-term outcomes, the patients were divided into two groups: curative group (n = 87) and non-curative (without additional surgery) ESD group (n = 33). The overall survival rate was strongly predicted by the Charlson Comorbidity Index (CCI). Patients with CCI ≥ 2 had a poor prognosis, regardless of curability. The conclusion of the study underlines that ESD is feasible even in elderly patients aged > 80 years, without an increase in complications.

It is clear why, over the years, the ESD technique has become the gold standard for submucosal tumors with negligible risk of lymph node metastasis (LNM), namely its minimal invasiveness and ability to improve quality of life. We agree with the importance of ESD, but this technique is limited in stage T1 cancers that have a low risk of developing LNM.

The laparoscopic endoscopic cooperative surgery (LECS) approach was melt, for the treatment of gastric submucosal tumors (SMTs), from fusion of ESD and surgery to endoscopic identification of the resection line and laparoscopic resection of gastric wall[2-4]. LECS begins with the endoscopic pre-cut around the tumor and section of the gastric wall. Then, with a laparoscopic approach, the tumor is excised and the gastric wall defect is reconstructed with a mechanical stapler. The advantage is that there are no limitations on tumor location[5]. LECS was used initially for the SMTs without ulceration [6]. Subsequently, the indication was expanded to also include lesions with ulcerative features and GC with very low risk of LNM[7,8]. The limitation of classical LECS includes the possibility of tumor and gastric content contamination into the peritoneal cavity because of the opening of the gastric wall during the procedure, increasing the risk of peritoneal tumor seeding. Therefore, some modified LECS procedures have been developed, such as inverted LECS[7], non-exposed endoscopic wall-inversion surgery (NEWS)[9-11], a combination of laparoscopic and endoscopic approaches to neoplasia with a non-exposure technique[12], and closed LECS[13].

The NEWS technique allows full thickness resection avoiding contamination of the intra-abdominal region with intragastric material.This procedure does not require intentional perforation, avoiding the risk of tumor seeding. Saline solution is injected endoscopically into the submucosa to mark the lesion margins. In the next step, the section of the outer layers of the wall and their suture are performed laparoscopically in such a way as to invert the early GC (EGC) towards the inside of the stomach. The last step is represented by the removal of the specimen by the ESD approach and closure of the defect with clips or nets. NEWS has the advantage of avoiding peritoneal contamination and cancer cell seeding. The limitations are represented by the long duration due to the combination with ESD and endoscopic closure of the mucosal defect. It is also difficult to perform for lesions of the esophagogastric junction and pylorus. The main disadvantage of this technique is the size of the tumor. Since the lesion must be extracted orally, this approach is limited for gastric SMTs greater than 3 cm[5]. The indication

for NEWS is gastric SMTs and lymph node-negative EGC, where there is some technical contraindication to ESD.

The Japanese National Health Insurance Plan recently approved the LECS procedure for GC for insurance coverage. Postoperative gastrectomy syndrome and post-procedure physical weakness are negligible with LECS.

LECS was recently performed in an elderly patient who refused radical surgery as a palliative treatment[14].

Currently, the main indications for modified LECS are EGCs not amenable to endoscopic treatment by endoscopic mucosal resection (EMR)/ESD, again with negligible risk of LNM. The suspicion of LNM requires a gastrectomy with lymphadenectomy[15].

The combination of the NEWS technique with sentinel node (SN) navigation surgery for the treatment of EGCs was reported by Goto *et al*[10,16]. A previous prospective multicenter study had already validated SN navigation surgery for GC[17]. The combined use of modified LECS and SN navigation surgery in the case of EGC allows for oncologically adequate resections with minimally invasive approaches, and can represent a valid alternative in elderly patients. Currently, this combination technique can be applied to EGC in which SN (surgical nodal basin) dissection can be performed with intra-operative evaluation by the one-step nucleic acid amplification assay[8].

Moreover, as suggested by the authors, this new cooperative technique can be applied even to EGC, which has features that significantly increase the risk of bleeding and/or perforation. Careful selection of indications and careful post-operative follow-up is required. No cases of disseminated GC recurrence have been described after LECS[7,15,18,19]. Randomized clinical trials on long-term oncological outcomes are needed to better clarify the future indications of ESD and modified LECS with SN navigation surgery.

FOOTNOTES

Author contributions: Vanella S designed the study; Godas M, Pereira AM, and Apicella I conducted the study; Crafa F and Pereira JC revised the letter.

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