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World Journal of Gastrointestinal Endoscopy

Contents

Biweekly Volume 7 Number 17 November 25, 2015

EDITORIAL

1233 Use of blood based biomarkers in the evaluation of Crohn's disease and ulcerative colitis

Barnes EL, Liew CC, Chao S, Burakoff R

TOPIC HIGHLIGHT

1238 Endoscopic resection of tumors in the lower digestive tract

Cai SL, Shi Q, Chen T, Zhong YS, Yao LQ

ORIGINAL ARTICLE

Retrospective Cohort Study

1243 Endoscopic submucosal dissection *vs* laparoscopic colorectal resection for early colorectal epithelial neoplasia

Hon SSF, Ng SSM, Wong TCL, Chiu PWY, Mak TWC, Leung WW, Lee JFY

Retrospective Study

1250 Feasibility of cold snare polypectomy in Japan: A pilot study

Takeuchi Y, Yamashina T, Matsuura N, Ito T, Fujii M, Nagai K, Matsui F, Akasaka T, Hanaoka N, Higashino K, Iishi H, Ishihara R, Thorlacius H, Uedo N

CASE REPORT

1257 Duodenal polyposis secondary to portal hypertensive duodenopathy

Gurung A, Jaffe PE, Zhang X

World Journal of Gastrointestinal Endoscopy
Volume 7 Number 17 November 25, 2015

Contents

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EDITORIAL

Use of blood based biomarkers in the evaluation of Crohn's disease and ulcerative colitis

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Abstract

Despite significant improvements in our understanding of Crohn's disease (CD) and ulcerative colitis (UC) in recent years, questions remain regarding the best approaches to assessment and management of these chronic diseases during periods of both relapse and remission. Various serologic biomarkers have been used in the evaluation of patients with both suspected and documented inflammatory bowel disease (IBD), and while each has potential utility in the assessment of patients with IBD, potential limitation remain with each method of assessment. Given these potential shortcomings, there has been increased interest in other means of evaluation of patients with IBD, including an expanding interest in the role of gene expression profiling. Among patients with IBD, gene expression profiles obtained from whole blood have been used to differentiate active from inactive CD, as well as to differentiate between CD, UC, and non-inflammatory diarrheal conditions. There are many opportunities for a non-invasive, blood based test to aid in the assessment of patients with IBD, particularly when considering more invasive means of evaluation including endoscopy with biopsy. Furthermore, as the emphasis on personalized medicine continues to increase, the potential ability of gene expression analysis to predict patient response to individual therapies offers great promise. While whole blood gene expression analysis may not completely replace more traditional means of evaluating patients with suspected or known IBD, it does offer significant potential to expand our knowledge of the underlying genes involved in the development of these diseases.

Key words: Inflammatory bowel disease; Ulcerative colitis; Gene expression analysis; Whole blood gene expression analysis; Biomarkers; Crohn's disease; Gene

profiling

Core tip: Questions remain regarding the best approaches to the assessment and management of patients with inflammatory bowel disease (IBD) during periods of both relapse and remission. Given the existing limitations of other serologic biomarkers, the development of whole blood gene expression profiling as a non-invasive method of assessment of patients with IBD is appealing. In an era of increased focus on personalized medicine, the potential expansion of our understanding of the genes underlying these diseases and their potential utility in predicting an individual's disease course or response to therapy offers great promise.

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INTRODUCTION

Though great strides have been made in our understanding of Crohn's disease (CD) and ulcerative colitis (UC) in recent years, questions remain regarding the best approaches to assessment and management of these chronic diseases during periods of both relapse and remission. These two subtypes of inflammatory bowel disease (IBD) have a presumed genetic predisposition, which when combined with multiple environmental exposures including changes to the gut microbiome, lead to clinically evident CD or UC. While the traditional evaluation of patients with IBD has been largely centered on endoscopic and radiographic examination, along with histological assessment of biopsy specimens, newer techniques focusing on gene expression profiling have been increasingly utilized to examine the differential expression of genes between disease states and normal. The use of gene expression profiling has significant potential within the field of IBD, both in differentiating CD and UC from non-IBD conditions, as well as determining activity of disease and response to treatment.

CURRENT APPROACHES TO EVALUATION

Various serologic biomarkers have been used in the evaluation of patients with both suspected and documented IBD. Erythrocyte sedimentation rate and C-reactive protein (CRP) are non-specific markers of inflammation that can be elevated in patients with active CD and UC. Although CRP can be useful in differentiating IBD from other non-inflammatory gastrointestinal conditions[1], given their non-specific nature, reliance on these biomarkers alone can be problematic. While CRP is an acute phase protein thought to increase in patients with active IBD, up to 50% of patients with an active flare of UC can demonstrate normal CRP levels[2]. In patients with clinically active CD, normal CRP levels can be noted[3,4], as biomarker levels are not necessarily correlated with mucosal lesions noted on endoscopy[3]. Additionally, certain populations of patients with CD can demonstrate persistently low CRP levels in the setting of active disease, including patients with an ileal disease distribution or low body mass index[5].

Other strategies have been developed in attempts to use serologic testing to differentiate CD from UC, such as the tests for anti-Saccharomyces cerevisiae antibodies (ASCAs) and perinuclear antineutrophil cytoplasmic antibodies (pANCAs). Increased titers of ASCA have been associated with CD, whereas increased levels of pANCA are more commonly seen in patients with UC[6]. However, when evaluated in a meta-analysis of 60 studies, the sensitivity and specificity of a $ASCA^+/pANCA^-$ pattern for identification of CD was only 55% and 93% respectively[7]. In addition to ASCA, multiple other antibodies to bacterial proteins (Omp-C and I2), flagellin (CBir1), and bacterial carbohydrates have been studied and associated with CD, including laminaribioside (ALCA), chitobioside (ACCA[2]) and mannobioside (AMCA). These existing serological markers tend to have low sensitivity and specificity due to the potential for elevation in levels caused by autoimmune diseases, infectious processes, and inflammation outside the GI tract[8].

In contrast to the serologic biomarkers, fecal markers such as fecal calprotectin (FC) and fecal lactoferrin are more specific for intestinal inflammation. FC serves as an indirect estimate of the neutrophil infiltrate in the bowel mucosa. When evaluating a patient with suspected IBD, one meta-analysis concluded that measuring FC can be used as a screening tool for identifying patients who are likely to need endoscopy for further evaluation of suspected IBD[9]. Among patients with previously diagnosed IBD, FC serves as a reliable indicator of disease activity, though it's greatest utility may be in the evaluation of UC[10]. While FC has demonstrated significant utility in differentiating IBD from other chronic abdominal syndromes such as Irritable Bowel Syndrome[1,11], FC does not reliably differentiate between UC and CD[12].

DEVELOPMENT OF NEW BIOMARKERS

Given the shortcomings of these established serologic and fecal biomarkers in the evaluation of a patient with suspected or documented IBD, there has been an increased interest in other means of evaluation, including gene expression profiling. One of the more recent advances in this field has been the development of techniques allowing for the evaluation of mRNA extracted from whole blood[13,14]. The use of whole blood

mRNA gene expression methodology has been validated and utilized to stratify an individual into high and low risk groups for the development of colorectal cancer[15], as well as to predict an individual's current risk for having colorectal cancer[16], Additionally, RNA expression profiles obtained from whole blood have been used to identify patients with other conditions such as lung cancer[17], bladder cancer[18], kidney diseases[19,20], cardiovascular diseases[21-23], osteoarthritis[24], and psychiatric disorders such as schizophrenia and bipolar disorder[25,26]. Among patients with IBD, gene expression profiles obtained from whole blood have demonstrated the ability to differentiate active from inactive CD[27], as well as the ability to differentiate between CD, UC, and non-inflammatory diarrheal conditions[28].

The ability of a blood based biomarker to differentiate active from inactive disease states, as well as the ability to differentiate between CD, UC, and non-inflammatory conditions, holds great promise as a clinical tool in the evaluation of patients with suspected or known IBD. While mucosal biopsy and histologic evaluation remains a gold standard in the traditional evaluation of patients with IBD, the ability of a non-invasive, blood based test to differentiate disease states could indicate significant promise as a tool for monitoring IBD disease activity and predicting response to therapy.

Few studies have evaluated whole blood gene expression analysis as a biomarker and clinical tool in the evaluation of patients with UC and CD. One recent study utilized Affymetrix GeneChip technology to generate genome-wide expression profiles used in the prediction of disease activity in patients with UC and CD[8]. In this study, whole blood gene panels reliably distinguished UC and CD, in addition to determining the activity of disease with high sensitivity and specificity[8]. As previously noted, whole blood gene panels have previously demonstrated the ability to differentiate active CD from CD in remission[27], as well as UC from CD and non-inflammatory diarrhea[28]. One early study utilized transcriptional profiling of peripheral blood mononuclear cell RNA to distinguish UC from CD with high accuracy[29]. Another study used peripheral blood-derived mononuclear cells to evaluate mRNA expression levels among patients with IBD, rheumatoid arthritis, and psoriasis[30]. Using this technique, the authors were able to identify disease specific gene panels that could differentiate each disease type and could separate the disease state from healthy controls[30]. Other authors have used peripheral blood MicroRNAs (miRNAs) to distinguish active CD and UC from healthy controls[31]. Finally, in an evaluation of pediatric patients with IBD, patients in clinical remission had distinct gene expression profiles obtained from peripheral blood leukocytes when compared to healthy controls[32].

Gene expression profiling from mucosal biopsies has also been an area of increasing interest. One prior study utilized gene expression profiling from mucosal biopsies to differentiate between normal mucosa, adenoma, colorectal cancer and IBD[33]. Other studies have utilized gene expression profiles obtained from mucosal biopsies to differentiate patients with UC from controls[34], patients with IBD from infectious colitis[35], and patients with IBD from normal controls[36]. Arijs *et al*[37,38] have published data demonstrating the ability of mucosal gene expression profiles to predict response to infliximab in patients with UC and CD. While each of these studies is indicative of the significant promise for gene expression analysis as a clinical tool in predicting disease activity, response to therapy, and disease course in patients with IBD, the fact that they require mucosal biopsy for analysis makes the non-invasive option for gene expression analysis *via* whole blood potentially more attractive.

When evaluating specific patterns identified by gene expression profiling, trends along biological processes have been identified. In an evaluation of response to infliximab among patients with UC[37] using mucosal biopsies, patterns along several biological functions were identified including immune response, cell to cell signaling, cellular movement, cell death and tissue morphology and development. In addition, there was considerable overlap when the gene sets used in this study were compared to the gene sets identified in patients with the colitis subtype of CD[38]. When evaluating patterns identified by whole blood gene expression analysis, a similar trend around immune functions has been demonstrated. A four gene panel used to differentiate UC from CD included *CD300A* which potentially plays a role in modulating proinflammatory stimuli among neutrophils, as well as *IL1R2* which is involved in cytokine-cytokine receptor interactions[28]. In an evaluation of the ability of biomarkers to predict disease activity among patients with UC and CD, some of the genes that were identified within groups of patients with active disease had previously been associated with UC and CD[39]. These target genes included *NLRP12* (a member of the Nod-like receptor family) and *TAGAP*, which is one of 22 genes previously identified as downregulated at week 8 and week 30 among responders to infliximab in the Active Ulcerative Colitis Trial 1 (ACT 1)[39].

CONCLUSION

Given these recent successes, there remain many opportunities for further utilization of whole blood gene expression analysis to evaluate and treat patients with IBD. Current work is ongoing to evaluate the ability of whole blood gene expression analysis to predict response to biologic therapy for UC and CD. Additionally, given the initial success in differentiating UC from CD and other non-inflammatory diarrheal illnesses, further attention will be paid to the potential clinical utility of whole blood gene expression as a clinical biomarker used in the assessment of patients with IBD. Recent work has demonstrated the utility of whole blood gene expression analysis as a measure of effectiveness of

novel therapies such as leukocytopharesis for UC[40], and further studies will be necessary to evaluate the utility of gene expression biomarkers in monitoring clinical improvement in that population.

Despite the recent successes, some limitations of this expanding area of research must be identified. To date, the majority of the studies evaluating the use of whole blood gene expression analysis in the evaluation of patients with IBD have examined small populations. These small study populations may lead to evaluations of heterogenous patient groups, including patients with varying degrees of disease activity. This introduces heterogeneity into the ultimate population of cells used for the sample analysis, and thus larger studies are still necessary for further exploration. In addition, when target genes have been identified in IBD and other inflammatory conditions, difficulty in the evaluation of which genes represent underlying etiologies and which represent consequences of the disease remains[30].

Each of the significant developments outlined indicates the potential for this non-invasive serologic test to become an important blood based biomarker in the evaluation of patients with IBD. While we do not expect whole blood gene expression analysis to completely replace the traditional means of evaluating patients with suspected or known IBD, it does offer significant potential to expand our knowledge of the underlying genes involved in the development of these diseases. Perhaps most promising, whole blood gene expression analysis offers a non-invasive method of evaluation that may ultimately lead to personalized predictions of disease activity, disease course, and response to therapy.

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TOPIC HIGHLIGHT

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Endoscopic resection of tumors in the lower digestive tract

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Abstract

As endoscopic technology has developed and matured, the endoscopic resection of gastrointestinal tract polyps has become a widely used treatment. Colorectal polyps are the most common type of polyp, which are best managed by early resection before the polyp undergoes malignant transformation. Methods for treating colorectal tumors are numerous, including argon plasma coagulation, endoscopic mucosal resection, endoscopic submucosal dissection, and laparoscopic-endoscopic cooperative surgery. In this review, we will highlight several currently used clinical endoscopic resection methods and how they are selected based on the characteristics of the targeted tumor. Specifically, we will focus on laparoscopic-endoscopic cooperative surgery.

Key words: Colorectal tumor; Endoscopic resection

Core tip: The best case scenario for patients with lower digestive tract tumors is to detect and resect the tumor before it undergoes malignant transformation. However, modern technologies for tumor resection are numerous and there may be specific indications for the implementation of one technology over another. Therefore, we will discuss the current clinical endoscopic resection methods and the process for selecting specific interventions. We wish to highlight laparoscopic-endoscopic cooperative surgery, because it may be of assistance in endoscopic treatment and could remarkably decrease the rate of later surgical repair.

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INTRODUCTION

Colorectal tumors are common in modern society and

although numerous new technologies have become available to locate, identify, and treat these tumors, early detection and removal (*e.g.,* during the polyp stage before malignant transformation) are still the key to long term survival and a favorable overall prognosis[1,2]. As a result, endoscopic methods have steadily developed to better meet these requirements. A study by Winawer *et al*[3] showed that endoscopic removal of colorectal adenomas can reduce the incidence rate of colorectal cancer by about 76%-90%. The current clinical endoscopic polypectomy methods are numerous and varied. Through careful observation of the distribution, size, morphology, and pathological features of colorectal polyps, clinicians/endoscopists can select the appropriate endoscopic resection treatment to avoid repeated unsuccessful procedures and improve the quality of life of the patient[2].

ENDOSCOPIC DIAGNOSIS BEFORE RESECTION

Before endoscopic resection, a comprehensive evaluation of the lesion is required. Ordinary endoscopy, magnifying endoscopy, or narrow-banding imaging (NBI) can be used to make a preliminary observation[4]. If the pathology confirms that the lesion is an adenoma, endoscopic resection can be performed. Pedunculated adenomas can be removed easily by endoscopic resection, regardless of the size of tumor; if the adenoma is sessile, the resection will be based on relevant patient parameters (age, body condition, and the patient's wishes)[5]. If pathological examination shows that the lesion is malignant, a "lifting sign" should be judged by injecting normal saline and indigo dye at the basal submucosal layer of the lesion. If the "lifting sign" is negative, the tumor has invaded and extended into the submucosa or even below[6]. Research has confirmed that for lesions confined to the mucosal layer, lymph node metastasis generally does not occur. Tumors that extend deeper into the submucosal layer can be divided into categories SM1-SM3. SM1 tumors (submucosal invasion < 1000 μm) have a low risk of lymph node metastasis, while the SM2 and SM3 tumors (submucosal invasion more than 1000 μm) have a higher lymphatic metastasis risk-up to 12.5%[7-9]. Tumors with a negative "lifting sign" should be surgically removed, rather than removed endoscopically.

ENDOSCOPIC RESECTION METHODS

Argon plasma coagulation

The principle of argon plasma coagulation (APC) is to use a specialized device to deliver ionization energy from argon; this high frequency energy can be implemented to solidify the tissue surface. Presently, APC plays an important role in maintaining hemostasis and cauterizing lesions during surgical and endoscopic procedures taking place in the human gastrointestinal tract[10]. The advantages of APC for treating colorectal lesions are that it is a rapid and efficient procedure that produces only a small vulnus and is generally well-tolerated by patients[11]. Some studies show that the most outstanding advantage of APC is its self-limited solidification depth. The damage of solidification generally does not extend more than 3 mm, minimizing the risk of perforation[12]. Based on the characteristics of the laser and the high frequency electric knife, APC can effectively be used to stop bleeding during a gastrointestinal procedure. Furthermore, during the operation, the probe does not need to contact the tissue, reducing the risk for adhesions or hemorrhages[13]. However, APC does have some limitations. Mainly, it is difficult to obtain pathological specimens with this technique, making it nearly impossible to determine the invasion depth, such that the cutting edge of the polyps is unclear.

Endoscopic mucosal resection

Endoscopic mucosal resection (EMR) has become a routine method for the treatment of early gastrointestinal mucosal lesions[14]. The general method of EMR is adapted to the submucosal injection of liquid saline to separate the lesions from the underlying muscle layer, after which lesions can be completely removed with a snare. The method is simple, safe, produces a small vulnus, is easily adaptable, and fairly easier to master, even for less experienced endoscopists[15,16]. However, there is the risk for rare and serious complications, such as intestinal perforation and bleeding, although these can be remedied by endoscopy or surgery. The incidence of perforation is very low (0.7%-1.3%), and the risk for bleeding is also fairly low (5.0%-8.1%)[17,18]. Some studies show that effective/optimized submucosal injection can help to prevent complications and ensure the safety of EMR[19]. Compared to APC, EMR has some advantages. Namely, EMR allows for pathological examination of the lesion after EMR to determine invasion depth and the cutting edge. However, due to the likelihood for electrocoagulation through snaring, EMR is only suitable for the complete resection of tumors with diameters that are less than 20 mm. Here, the complete resection rate is 64.3%-77.4%, and the recurrence rate is very low (0%-3.6%)[20,21]. If the tumor is larger than 20 mm, the complete resection rate drops significantly to 48.1%-32.9%, while the recurrence increases to 16%-25.7%[22,23]. Therefore, EMR is not an appropriate choice for the treatment of particularly large (greater than 20 mm) gastrointestinal tumors.

Endoscopic submucosal dissection

Endoscopic submucosal dissection (ESD) was developed based on EMR techniques and was named after it was approved as a new resection method in 2003. In this procedure, an insulation tipped knife (knife IT) is

instrumental for performing ESD. Compared to EMR, ESD can not only provide complete specimens for more reliable pathological examination, but it can also be used to fully resect the tumor with a low rate of recurrence[24]. For tumors less than 20 mm, the complete resection rate is 82.6%-97.7% and the recurrence rate is nearly 0%[21,25,26]. However, if the tumor is larger than 20 mm, the complete resection rate drops a little to 74%-91.8%, but the recurrence rate remains 0%-1%[17,22,23,25]. During the ESD procedure, the operator should pay attention to the "lifting sign" after submucosal injection, which can be used to determine the lesion depth. If the lesion is located in the mucous layer with a proper boundary to the muscularis propria and has a positive "lifting sign," it can be removed by ESD[27,28]. However, the rate of perforation in ESD is higher than that for EMR, because the submucosal layer is nearer to the muscularis. For this procedure, which is more complicated than EMR, the incidence of complications also correlates with the operator's technical proficiency[29]. Nonetheless, in some studies, the bleeding rate of ESD remains low (0.4%-2.5%), although the risk of perforation is slightly higher (2.9%-5.3%)[30,31].

Laparoscopic-endoscopic cooperative surgery

At present, endoscopic therapy is not only applied to resecting colorectal polyps, but also to the treatment of early colorectal cancers that are located in the mucosal layer. Through endoscopic resection, patients can avoid laparotomy, sustain lesser injury, and recover quickly[32]. However, the colonoscopy field of vision is limited in the intestinal lumen, such that the condition of the bowel wall or abdominal cavity is unclear. Some lesions located in the splenic or hepatic flexure can make endoscopic resection difficult. Laparoscopic-endoscopic cooperative surgery (LECS) takes advantage of characteristics of both laparoscopic and colonoscopic procedures. LECS is often implemented when the lesion is difficult to be removed or cannot be completely resected by endoscopic methods alone[33]. Under the guide of a colonscope, the laparoscope can look for and identify the intestinal site where the lesion is located and dissociate it from this site if necessary. By pulling and pushing the laparoscope upward, the lesion may be exposed so that endoscopists can use EMR or ESD to remove the lesion. During this process, the operator can focus on the complete excision of the lesion and does not need to be concerned with possibility of perforation. If perforation or bleeding occurs, laparoscopy can be used to repair the perforation and return to hemostasis immediately. However, no randomized controlled trials have been performed to evaluate LECS in the treatment of lower digestive tract tumors. Nonetheless, select published LECS cases suggest that it is a feasible procedure for the *en bloc* resection of some colonic lateral spreading tumors that would be otherwise difficult to resect using exclusively endoscopic methods[34-36].

CHOOSING THE ENDOSCOPIC TREATMENT

Tumors with a diameter less than 3 mm

For small tumors less than 3 mm in diameter, APC can be used for solidification of the lesion. However, as this technique cannot be used to collect pathological specimens, long-term endoscopic follow-up is required[37].

Tumors with a diameter less than 20 mm

For lesions in this size category, according to a study by Lee *et al*[26], there are no significant differences in the complete resection rate between EMR (82.6%) and ESD (64.3%) techniques. Although EMR has a recurrence rate of 3.6%, the risk of cancer progression for small tumors is minimal and the main pathological type for this size tumor is adenoma; therefore, EMR is suitable for the removal of small lesions and is a fairly easy technique to master, even for less experienced endoscopists. The risk of perforation with EMR is lower than that with ESD, and it is regarded as a quicker and safer choice for lesions with a relatively smooth surface without signs of bleeding and erosion[18,38]. However, there are some exceptions. If the endoscopic diagnosis (NBI or magnifying endoscope) strongly indicates that the lesion is malignant and the pathological examination shows the same results, the tumor must be excised by ESD and the patients should undergo close follow-up in the future.

Tumors with a diameter more than 20 mm

Some studies report that the proportion of adenocarcinomas significantly increases in tumors larger than 20 mm in diameter, since the degree of tumor malignancy is often associated with the relative tumor size[39]. Other studies report that the size of the tumor can be at least partly used as an index to predict the degree of malignancy. The possibility of recurrence for tumors greater than 10 mm diameter is relatively high[26]. Early adenocarcinomas have characteristics of invasion, recurrence, and metastasis, and due to a lower complete resection rate and high recurrence rate, EMR is not suitable for these kinds of tumors. Fortunately, ESD can be used to remove larger tumors with much higher complete resection rates and lower recurrence rates. However, ESD still has some limitations, especially for larger laterally spreading tumors. Here the excised area is often too large, translating to an extremely high risk of perforation[40]. Once a perforation occurs, a surgical repair or intestinal resection is needed to repair the large defect left by ESD. Therefore, LECS may be a better choice to ensure a complete resection, while minimizing the risk of serious complications. Based on the assistance of a laparoscope, the visibility of lesion is greatly enhanced and the operator can focus on the complete excision of the lesion while not worrying about the possibility of perforation, which can easily

and rapidly be repaired using the laparoscope to stitch the perforated area. Rapid detection and repair of any perforations greatly reduce the risk of abdominal infection. Therefore, in certain situations, LECS can not only be minimally invasive, but also offers better and safer therapeutic effects[41,42].

CONCLUSION

Endoscopic resection presents a great technological leap in the diagnosis and treatment of colorectal tumors, as well as an important preventive measure to remove polyps in their premalignant stages. In recent years, some new technologies, such as magnifying endoscopy and NBI have improved the detection rate of early colorectal cancers, which improves long term survival and the resulting quality of life. At the same time, with the continuous development of endoscopic treatment equipment and the introduction of new technologies, most colorectal polyps and early cancers can now be resected by minimally invasive EMR, ESD, or LECS techniques, which can now achieve the same effects as surgery. However, when endoscopic treatment is to be used, the indications should be carefully considered following evaluation of the relevant patient and pathological parameters, along with the likelihood of complete resection and risk for complications. Therefore, initial colonscopy examination is crucial. Although minimally invasive and often successful in full resection, endoscopic resections do have some limitations. If the cancer invades deep into the submucosal layer, belongs to the lower differentiation, or contains a lymphatic or venous tumor thrombus, additional radical surgical operation will still be required.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Endoscopic submucosal dissection *vs* laparoscopic colorectal resection for early colorectal epithelial neoplasia

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Informed consent statement: Consent from the participants was not obtained but the presented data are anonymized and risk of identification is low.

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Abstract

AIM: To compare the short term outcome of endoscopic submucosal dissection (ESD) with that of laparoscopic colorectal resection (LC) for the treatment of early colorectal epithelial neoplasms that are not amenable to conventional endoscopic removal.

METHODS: This was a retrospective cohort study. The clinical data of all consecutive patients who underwent ESD for endoscopically assessed benign lesions that were larger than 2 cm in diameter from 2009 to 2013 were collected. These patients were compared with a cohort of controls who underwent LC from 2005 to 2013. Lesions that were proven to be malignant by initial endoscopic biopsies were excluded. Mid and lower rectal lesions were not included because total mesorectal excision, which bears a more complicated postoperative course, is not indicated for lesions without histological proof of malignancy. Both ESD and LC were performed by the same surgical unit with a standardized technique. The patients were managed according to a standard protocol, and they were closely monitored for complications after the procedures. All hospital records were reviewed, and the following data were compared between the ESD and LC groups: patient demographics, size and location of the lesions, procedure time, short-term clinical outcomes and pathology results.

RESULTS: From 2005 to 2013, 65 patients who underwent ESD and 55 patients who underwent LC were included in this study. The two groups were similar in terms of sex (P = 0.41) and American Society of Anesthesiologist class (P = 0.58), although patients in the ESD group were slightly older (68.6 ± 9.4 *vs* 64.6 ± 9.9, P = 0.03). ESD could be accomplished with a shorter procedure time (113 ± 66 min *vs* 153 ± 43 min, P < 0.01) for lesions of comparable size (3.0 ± 1.2 cm *vs* 3.4 ± 1.4 cm, P = 0.22) and location (colon/rectum:

59/6 *vs* colon/rectum: 52/3, $P = 0.43$). ESD appeared to be associated with a lower short-term complication rate, but the difference did not reach statistical significance (10.8% *vs* 23.6%, $P = 0.06$). In the LC arm, a total of 22 complications occurred in 13 patients. A total of 7 complications occurred in the ESD arm, including 5 perforations and 2 episodes of bleeding. All perforations were observed during the procedure and were successfully managed by endoscopic clipping without emergency surgical intervention. Patients in the ESD arm had a faster recovery than patients in the LC arm, which included shorter time to resume normal diet (2 d *vs* 4 d, $P = 0.01$) and a shorter hospital stay (3 d *vs* 6 d, $P < 0.01$).

CONCLUSION: ESD showed better short-term clinical outcomes in this study. Further prospective randomized studies will be required to evaluate the efficacy and superiority of colorectal ESD over LC.

Key words: Early colorectal neoplasia; Laparoscopic colectomy; Endoscopic submucosal dissection

Core tip: This is the first study that compares endoscopic submucosal dissection (ESD) *vs* laparoscopic colorectal resection (LC) for endoscopically benign lesions that could not be adequately removed by conventional polypectomy. Case inclusion was based purely on the pre-operative/pre-procedure endoscopic findings. Although the difference in morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved were much higher in the LC arm. The current study provided evidence that surgeons are capable of performing high-quality colorectal ESD procedures. We expect that the participation of the surgeons as well as the close collaboration with gastroenterologists will play a pivotal role in the formulation of a management plan for patients with early colorectal neoplasms.

Hon SSF, Ng SSM, Wong TCL, Chiu PWY, Mak TWC, Leung WW, Lee JFY. Endoscopic submucosal dissection *vs* laparoscopic colorectal resection for early colorectal epithelial neoplasia. *World J Gastrointest Endosc* 2015; 7(17): 1243-1249 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i17/1243.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i17.1243

INTRODUCTION

Laparoscopic colorectal resection (LC) is currently a widely accepted treatment for colorectal neoplasms that are deemed not amenable to endoscopic removal[1-4]. However, LC carries an inherent complication rate of over 15%[1,2]. Therefore, one could argue that surgery may be too invasive or aggressive as a treatment for early colorectal neoplasms. The potential risks of laparoscopic resection may outweigh the estimated risk of lymph node metastasis if the neoplasms are not resected[5-7]. On the contrary, endoscopic piecemeal removal of large sessile or flat polyps by conventional polypectomy or by endoscopic mucosal resection (EMR), although it is less invasive, is known to be associated with a high local recurrence rate of 14%-19.5%[8,9]. Endoscopic submucosal dissection (ESD) is a novel technique that was originally developed in Japan more than 10 years ago. ESD was developed to achieve an *en bloc* mucosal resection with wider margins[10-13]. Currently, an increased number of endoscopists throughout the world have acquired this skill and have published promising outcomes of ESD[14-19]. The recent retrospective analysis reported by Kiriyama *et al*[20] that compared ESD for colorectal intramucosal or slightly submucosal invasive cancers *vs* LC for T1 cancer demonstrated a lower complication rate in the ESD group. Another similar prospective study also compared ESD for adenoma or T1 cancer with less than SM-s (superficial submucosal invasion) *vs* LC for SM-d (deep submucosal invasion)[21]. Until now, no worldwide consensus has been adopted as to whether the treatment of benign colorectal neoplasms with advanced endoscopic techniques (*i.e.*, ESD) is superior to surgical approaches[22]. From the very beginning of the development of colorectal ESD, the procedure was performed primarily by gastroenterologists. No published data exists on the comparison of the clinical outcomes of ESD *vs* those of LC when both procedures were performed by the same group of surgeons. Surgeons who can perform both procedures may be in an advantageous position in that they can balance the risks and benefits of the endoscopic approach *vs* the surgical approach. Therefore, we performed a retrospective cohort study that aimed to compare ESD *vs* LC for endoscopically benign lesions that could not be adequately removed by conventional polypectomy. This is the first comparative study of a similar topic, and this is also the first series where both procedures were performed by the same group of surgeons.

MATERIALS AND METHODS

This was a retrospective cohort study conducted at Prince of Wales Hospital at, The Chinese University of Hong Kong. Since 2005, LC has been the gold standard surgical treatment for all colorectal lesions that are not amenable to endoscopic removal. Colorectal ESD was first established at our centre in 2008, and since that time, it has enriched the armamentarium of endoscopic interventions. Consecutive patients who underwent ESD or LC for early colorectal neoplasms (endoscopically benign lesions larger than 2 cm in diameter) from 2005 to 2013 were included.

Lesions were excluded when endoscopic signs of massive submucosal invasion were present as evidenced by the existence of excavated/depressed morphology or

Kudo's pit pattern type Ⅴ. Lesions proven to be malignant by initial endoscopic biopsies were also excluded. Mid and lower rectal lesions were not included because total mesorectal excision, which intrinsically bears a more complicated post-operative course and has a negative impact on gastrointestinal function, would not be offered to patients who were diagnosed with benign lesions by endoscopy. Nevertheless, the input of the patients would also influence the selection between ESD and LC because ESD was a relatively new procedure at that time.

Patients were instructed to eat a low residue diet two days before ESD or laparoscopic colectomy. They received four litres of polyethylene glycol solution as a mechanical bowel preparation on the day of ESD or one day before LC. Both ESD and LC were performed by surgeons who were capable of executing these procedures independently.

All hospital records were reviewed, and the following data were compared between the ESD and LC groups: patient demographics, size and location of the lesions, procedure time, short-term clinical outcomes and pathology result.

The ESD procedure and postoperative care

Our techniques for colorectal ESD have been previously reported[23]. In short, all ESDs were performed when the patients were under conscious sedation after intravenous administration of midazolam and pethidine. Intravenous Buscopan was used if significant colonic spasms were encountered during the ESD procedure. All procedures were performed with a water-jet gastroscope or with a paediatric colonoscope with a transparent cap attached to the tip. Carbon dioxide insufflation was routinely used to reduce patient discomfort. The margins of the lesions were determined by either dye (0.4% indigo carmine spray) or digital (narrow band imaging) chromoendoscopy. Submucosal cushions were created by a mixture of normal saline, adrenaline, indigo-carmine and sodium hyaluronate. Circumferential mucosal incision and submucosal dissection were performed by dual knife or insulated tip knife (Olympus Medical System, Tokyo, Japan), depending on the location of the lesion and the preference of the endoscopists. Haemostasis after ESD was achieved by Coagrasper (Olympus Co. Ltd., Tokyo, Japan).

When perforations were encountered during the ESD procedure, they were immediately closed by endoscopic clips; otherwise, salvage surgery was arranged. For optimal procedures without significant bleeding, a diet would be resumed on the following day. Stable patients who managed to tolerate a full diet were discharged. For those patients with perforations that were managed by endoscopic clipping, they were kept nil per oral and monitored closely for signs of sepsis including fever, tachycardia, leukocytosis and peritonism. Depending on the clinical parameters, parenteral antibiotics were given and diet was gradually introduced. Salvage surgery was offered in cases of persistent or deteriorating sepsis.

All patients were encouraged to maintain mobility, and a diet was introduced gradually as tolerated. Patients were discharged when they could tolerate a full diet without signs of sepsis and the absence of rectal bleeding.

The LC procedure and postoperative care

All LCs were performed under general anaesthesia by the same group of colorectal surgeons, as described in our previous study[24]. In short, the colon or rectum was mobilized laparoscopically from the lateral to the medial area. The isolated lymphovascular pedicles were then transected with either laparoscopic linear staplers or with self-locking plastic clips. One of the working ports was later extended for specimen retrieval. Extracorporeal anastomosis was fashioned for a right-sided resection, while intracorporeal stapled anastomosis was performed for a left-sided resection.

After surgery, the patients were allowed to ingest oral fluid on day one. Diet was resumed gradually during the days following the surgery and depended on the progression of the patients. All patients received regular physiotherapy and were mobilized as soon as possible after surgery. Pain control was achieved by either regular analgesics or by patient-controlled analgesia. Ambulatory patients were discharged if they could tolerate a full diet with no signs of sepsis.

Histological assessment

All ESD specimens were mounted on a foam board for pathological examination by a designated pathologist. Deep and peripheral margins, cellular differentiation as well as the depth of submucosal invasion were recorded. R0 resection was defined as a complete *en bloc* resection with deep and circumferential margins that were free of adenomatous proliferation or dysplasia. Colectomy specimens were evaluated after fixation in 10% formalin and after staining with haematoxylin and eosin. Macroscopic and microscopic examinations for histological type, depth of invasion, lymph node status and resection margins were performed. Malignant lesions were classified according to the AJCC Cancer Staging Manual, 7th Edition (2010)[25].

Outcomes measurement

In regards to the short-term clinical outcomes, we studied the procedure time, the time to resume diet, the time to full ambulation, the duration of the total hospital stay and the complication rate.

Lesions that were located in the colon and at the rectosigmoid junction were defined as "colon", while lesions in the upper rectum were defined as "rectum".

Complications were defined as any event that required re-intervention, re-operation, re-admission or a prolonged hospital stay (namely, Clavien-Dindo Grade Ⅱ or above). Bleeding from the ESD procedure was defined as any bleeding episodes after ESD that warranted

Table 1 Demographic background

	Lap colectomy	ESD	*P* value
Number of patients	55	65	
Age (yr), mean ± SD	64.6 ± 9.9	68.6 ± 9.4	0.03
Sex	Female: 27 Male: 28	Female: 27 Male: 38	0.41
ASA	< 3 *vs* ≥ 3 : 43 *vs* 12	< 3 *vs* ≥ 3 : 48 *vs* 17	0.58
Size of lesion (cm), mean ± SD	3.4 ± 1.4	3.0 ± 1.2	0.07
Location of lesion	Colon: 52 Rectum: 3	Colon: 59 Rectum: 6	0.43

ASA: American Society of Anaesthesiology; ESD: Endoscopic submucosal dissection.

Table 2 Comparisons of the short-term outcome

	Lap colectomy	ESD	*P* value
OT/procedure time (min), mean ± SD	153 ± 43	113 ± 66	0.000
Post-op stay (d), median (range)	6 (3-41)	3 (1-13)	0.000
Days to diet, median (range)	4 (1-13)	2 (0-5)	0.000
Short-term complications	13/55 (23.6%)	7/65 (10.8%)	0.06
Pathology	Benign: 39 T1: 16	Benign: 56 T1: 9	0.04

ESD: Endoscopic submucosal dissection; OT: Operation time.

re-intervention, readmission, or a blood transfusion. ESD-related perforations were either detected during the procedure or were diagnosed radiologically by the presence of intra-peritoneal free gas.

Statistical analysis

Categorical data were analysed using χ^2 or Fisher's exact test, while continuous variables were analysed by *t* test, as appropriate. *P* values < 0.05 were considered statistically significant. All calculations were conducted with SPSS statistical software package (SPSS version 15.0, Chicago, IL, USA). Data analysis was based on the intention to treat principle.

RESULTS

From 2005 to 2013, 55 patients who underwent LC and 65 patients who underwent ESD were included in this study. The mean age of the patients in the ESD group was slightly higher than that of the patients in the LC group. The two groups shared comparable sex and ASA class distributions (Table 1).

No statistically significant differences were observed in terms of lesion size or location, yet ESD could be accomplished with a significantly shorter procedure time (113 ± 66 min *vs* 153 ± 43 min, *P* < 0.01) and a faster recovery course, as illustrated by earlier resumption of a full diet (2 d *vs* 4 d, *P* = 0.01) and a shorter hospital stay (3 d *vs* 6 d, *P* < 0.01) (Table 2).

The overall short-term complication rate for ESD and LC was 10.8% and 23.6%, respectively. Although we could not demonstrate a significant difference between the two groups (*P* = 0.06), the ESD group exhibited a trend towards a lower short-term complication rate. In the LC arm, a total of 22 complications occurred in 13 patients (Table 3). These included 1 anastomotic leak, which necessitated a laparotomy and stoma formation, 1 mechanical small bowel obstruction, which required re-operation, 6 wound infections, 1 chest infection, 4 urinary tract infections, 1 acute urine retention, 6 cases of prolonged ileus, 1 deep vein thrombosis and 1 mental confusion. A total of 7 complications occurred in the ESD arm, including 5 perforations and 2 bleeding episodes. The remainder of the patients in the ESD arm experienced a smooth intra- and post-procedure course without complications. All of the perforations were observed during the procedure and were successfully managed by endoscopic clipping. Therefore, no emergency surgical intervention was needed. One of the bleeding episodes was successfully stopped during the procedure, and blood transfusion was required. Unfortunately, the other incident was encountered during the removal of a caecal lateral spreading tumour (LST). As a result of malfunction in the water-jet, a clear endoscopic view could not be achieved for safe haemostasis and dissection. Hence, the procedure was abandoned and was followed by emergency LC. The patient was discharged home 4 d after surgery. No delayed perforation, bleeding or other post-procedure complications were recorded in the ESD arm (Table 4).

En bloc resection was achieved in 81.5% (53/65) of the ESD procedures. For the remaining 12 lesions, 6 were completely removed by piecemeal EMR. Endoscopic removal had to be abandoned for the other six lesions due to instrumental failure in one case and the presence of dense adhesions in five cases. Amongst the 5 lesions that harboured these dense adhesions, 3 were confirmed T1 adenocarcinomas.

In this study, histological analysis revealed the presence of T1 adenocarcinomas in 25 lesions (LC: 16 and ESD: 9). The proportion of invasive neoplasms was significantly higher in the LC arm (29.1% *vs* 15.3%, *P* = 0.04. *En bloc* ESD resection was successfully achieved in 4 of 9 malignant lesions, and all four of these patients were subsequently managed according to the level of submucosal (sm) invasion and other associated histological features. Although salvage surgery was offered to the two patients with sm2 lesions, they both rejected this procedure. On the contrary, one patient with an sm3 lesion agreed to undergo LC, and the pathology of the resected specimen showed no residual primary tumour; however, one metastatic lymph node was identified. The remaining patient with an sm1 lesion was put under close surveillance in light of an adequate resection margin and the absence of lymphovascular permeation. ESD was abandoned in 3 of 9 malignant lesions due to dense submucosal adhesion, of which 2 were salvaged by LC and 1 by TEO (transanal endoscopic operation).

Table 3 Complications of laparoscopic colectomy (22 events in 13 patients)

	Number of complications	Surgical intervention required
Anastomotic leak	1	1
Mechanical small bowel obstruction	1	1
Wound infection	6	0
Chest infection	1	0
Urinary tract infection	4	0
Urinary retention	1	0
Ileus	6	0
Deep vein thrombosis	1	0
Confusion	1	0

Table 4 Performance indicators of endoscopic submucosal dissection

	n	(%)
En bloc resection	53	81.5
R0 resection	47	72.3
Perforation	5	7.7
bleeding	2	3.1

No other complication apart from perforation and bleeding were observed.

Piecemeal resection was performed in the other 2 of 9 lesions, of which one refused salvage surgery and the other one accepted salvage LC.

DISCUSSION

Since the development of colorectal ESD, its feasibility, safety and oncological outcome have been reported in numerous contemporary studies[14-20]. Currently, nearly 3000 colorectal ESDs are performed each year in Japan[26]. The Japanese healthcare insurance system has also approved a reimbursement scheme for colorectal ESD[26]. On the contrary, the adoption rate of ESD is variable in the rest of the world, especially among surgical societies. To explain this, two potential hurdles have been identified. First, the technique of LC had already been widely practised and supported by a high level of evidence at the time when colorectal ESD was introduced outside of Japan. Second, the volume of cases did not justify a large number of endoscopists having to learn and master the technique of ESD. Moreover, current literature that directly compares LC *vs* ESD for early colonic neoplasms is not available. Two recent studies compared ESD for mucosal or slight submucosal invasive lesions *vs* LC for T1/deep submucosal invasive lesions[20,21], but the pathological nature of the two comparative groups was different.

This is a retrospective cohort study that compared ESD *vs* LC for endoscopically confirmed benign lesions that could not be adequately removed by conventional polypectomy. Case inclusion was based purely on the pre-operative/pre-procedure endoscopic findings, and no crossover of abandoned ESD to LC occurred. The results of this study suggested that ESD was superior to LC with respect to short-term outcomes and that ESD leads to a faster recovery. Despite the fact that perforation and bleeding did occur in the ESD arm, all but one of these events could be managed endoscopically. The post-operative course of the only patient who underwent salvage surgery for complications was also uneventful. Although the difference in morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved are much higher in the LC arm.

Moreover, all ESD procedures were performed when the patients were under conscious sedation without general anaesthesia. This definitely avoided the risks of general anaesthesia and post-operative wound pain. Almost immediate mobilization was feasible once the sedative effect subsided. Therefore, we believe that ESD might be more reasonable and acceptable for patients with early colorectal neoplasia or LSTs.

The ESD perforation rate in this study was 7.7%, which was comparable with quoted figures in the literature. In a recent meta-analysis, the highest reported perforation rate was 12%[18], and most of the reported rates in published series were well below 10%[27]. Although these perforation rates might be considered higher than those at some of the high-volume Japanese centres[14,28,29], they were comparable with large series that have been conducted outside of Japan[30,31]. This cohort study only reflected the early phase of our learning curve, and we expect a further reduction in morbidity in the future. Due to the increasing popularity of screening colonoscopy and image-enhanced endoscopy, a greater number of early colorectal lesions might be detected. Therefore, we expect a higher ESD throughput and an improved performance at our centre.

In reality, whether an endoscopically assessed benign lesion is subjected to ESD or colectomy depends to a large extent on who detects the lesion. For instance, if a gastroenterologist who is capable of performing ESD detects an LST, then an ESD procedure might be attempted. Likewise, if the same lesion is detected by a surgeon who does not possess the skills to perform ESD, then colectomy would be offered instead. In our locality, it is rather unique that surgeons actively participate in advanced diagnostic and therapeutic endoscopies. At our centre, we have a group of surgeons who have acquired the skills to perform both LC and colorectal ESD, and who can confidently counsel patients and offer them both options (ESD *vs* LC). One can also comprehensively balance the risks and benefits between conservative management *vs* salvage surgery for histologically confirmed malignant lesions that are removed by ESD. The current study provided evidence that surgeons are capable of performing high-quality colorectal ESD. We expect that the participation of the surgeons as well as the close collaboration with gastroenterologists will pay a pivotal role in the formulation of a management plan for

patients with early colorectal neoplasms.

The major limitation of the current study was its retrospective nature that extended through a period of eight years, during which time major advances in both laparoscopic and endoscopic technology occurred. Most of the LC cases were recruited prior to the availability of image-enhanced endoscopy (2005-2008), when endoscopic diagnoses were less accurate. This explained why patients in the LC arm had more malignant lesions, which was also a major bias of the current study. During the past few years, we have introduced enhanced recovery protocols in our unit, and thus the same LC group may experience a faster recovery and potentially fewer morbidities. To address these biases, a randomized controlled trial is necessary to provide a higher level of evidence to compare these two intervention modalities. We are currently awaiting the results of our randomized controlled trial.

In conclusion, by a comparison of LC and ESD performed by the same group of surgeons for the treatment of early colorectal neoplasms, ESD produced better short-term clinical outcomes with respect to a shorter procedure time and an earlier recovery. Therefore, ESD may be superior to LC for the treatment of this specific type of colorectal lesion.

COMMENTS

Background

Before the development of colonic endoscopic submucosal dissection (ESD), colorectal lesions that were not deemed to be suitable for conventional endoscopic removal were classically treated by colorectal resection. Currently, although minimally invasive surgery can often be performed, the risks associated with surgery should be considered especially for the treatment of benign lesions. While colorectal ESD has become popular in Japan, its adoption rate and its performance quality are still variable in all other areas of the world. It is unknown whether ESD leads to a better short-term outcome for the treatment of early colorectal epithelial neoplasms.

Research frontiers

Results from this study may help surgeons to appreciate the potential benefits of ESD, which has not yet been widely adopted by surgical societies outside of Japan for the treatment of early colorectal epithelial neoplasms.

Innovations and breakthroughs

To date, no worldwide consensus has been adopted as to whether the treatment of benign colorectal neoplasms with ESD is superior to the use of colorectal resection. Moreover, there is no published data on the clinical outcomes of ESD *vs* laparoscopic colorectal resection (LC), where both procedures were performed by the same group of clinicians. In this retrospective study, the authors compared the short-term outcomes between ESD and LC and focused on the immediate recovery course and the complications.

Applications

This retrospective cohort study suggested that ESD produced better short-term clinical outcomes. The results from future randomized controlled trials would be expected to provide a higher level of evidence in regards to the potential superiority of ESD.

Terminology

In this study, early colorectal epithelial neoplasms referred to lesions without endoscopic signs of massive submucosal invasion, as evidenced by the absence of an excavated/depressed morphology or Kudo's pit pattern type Ⅴ.

Peer-review

The authors evaluated one hundred and twenty patients (ESD: 65, LC: 55) who underwent treatment for early colorectal epithelial neoplasms. ESD could be accomplished in a shorter time, and patients experienced a faster recovery. Although the difference in the occurrence of morbidities did not reach statistical significance, the absolute number of complications and the number of patients involved were much higher in the LC arm. Therefore, the option of ESD should be seriously considered in the contemporary management of early colorectal epithelial neoplasms.

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ORIGINAL ARTICLE

Retrospective Study

Feasibility of cold snare polypectomy in Japan: A pilot study

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Institutional review board statement: The Local Ethics Committee of Osaka Medical Center for Cancer and Cardiovascular Diseases approved the protocols of this study.

Informed consent statement: Written informed consent was obtained from all patients upon inclusion.

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Data sharing statement: The technical appendix, statistical code and data set are available from the corresponding author.

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Abstract

AIM: To investigate the feasibility of cold snare polypectomy (CSP) in Japan.

METHODS: The outcomes of 234 non-pedunculated polyps smaller than 10 mm in 61 patients who underwent CSP in a Japanese referral center were retrospectively analyzed. The cold snare polypectomies were performed by nine endoscopists with no prior experience in CSP using an electrosurgical snare without electrocautery.

RESULTS: CSPs were completed for 232 of the 234 polyps. Two (0.9%) polyps could not be removed without electrocautery. Immediate postpolypectomy bleeding requiring endoscopic hemostasis occurred in eight lesions (3.4%; 95%CI: 1.1%-5.8%), but all were easily managed. The incidence of immediate bleeding after CSP for small polyps (6-9 mm) was significantly higher than that of diminutive polyps (≤ 5 mm; 15% *vs* 1%, respectively). Three (5%) patients complained of minor bleeding after the procedure but required no intervention. The incidence of delayed bleeding requiring

endoscopic intervention was 0.0% (95%CI: 0.0%-1.7%). In total, 12% of the resected lesions could not be retrieved for pathological examination. Tumor involvement in the lateral margin could not be histologically assessed in 70 (40%) lesions.

CONCLUSION: CSP is feasible in Japan. However, immediate bleeding, retrieval failure and uncertain assessment of the lateral tumor margin should not be underestimated. Careful endoscopic diagnosis before and evaluation of the tumor residue after CSP are recommended when implementing CSP in Japan.

Key words: Colonoscopy; Endoscopic gastrointestinal surgery; Colorectal neoplasm; Polypectomy; Cold snare polypectomy

Core tip: Cold snare polypectomy (CSP) was completed for 232 of the 234 polyps. Immediate postpolypectomy bleeding requiring endoscopic hemostasis occurred in eight lesions (3.4%), but all were easily managed. The incidence of immediate bleeding after CSP for small polyps (6-9 mm) was significantly higher than that for diminutive polyps (≤ 5 mm; 15% *vs* 1%, respectively). Three (5%) patients complained of minor bleeding after the procedure but required no intervention. In total, 12% of the resected lesions could not be retrieved for pathological examination. Tumor involvement in the lateral margin could not be histologically assessed in 70 (40%) lesions.

Takeuchi Y, Yamashina T, Matsuura N, Ito T, Fujii M, Nagai K, Matsui F, Akasaka T, Hanaoka N, Higashino K, Iishi H, Ishihara R, Thorlacius H, Uedo N. Feasibility of cold snare polypectomy in Japan: A pilot study. *World J Gastrointest Endosc* 2015; 7(17): 1250-1256 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i17/1250.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i17.1250

INTRODUCTION

Colorectal cancer is one of the most common causes of cancer-related death worldwide[1]. The adenoma-carcinoma sequence is thought to be the main route of colorectal cancer development[2], and the removal of colorectal adenomas is known to reduce the risk of subsequent colorectal cancer development and colorectal cancer death[3,4]. Endoscopic removal of all detected adenomas during colonoscopy screening is the standard strategy for the prevention of colorectal cancer, although more than 90% of the polyps are less than 10 mm in size, and most will never develop into cancer during the lifetime of the patient[5]. However, in this context, it is important to note that endoscopic resection is associated with potential complications that include bleeding and perforation[6-8]. Thus, endoscopists should always consider the most likely natural history of the lesion and balance those considerations against the risks associated with endoscopic resection[5]. Indeed, Japanese guidelines do not recommend the removal of diminutive (≤ 5 mm) colorectal polyps[9], and most Japanese endoscopists follow up diminutive colorectal polyps that are not endoscopically removed based on their experience[10].

Several techniques are available for the removal of diminutive or small (6-9 mm) (subcentimetric) polyps, although the optimal method remains unclear, and the method selection is often based on expert opinion. One approach that is used in Western countries for the removal of subcentimetric polyps is cold polypectomy, *i.e.*, removal without electrocautery. This approach seems to minimize the risks of complications when removing subcentimetric lesions[11]. Two different cold polypectomy techniques are available. Cold forceps polypectomy (CFP) is a simple and easy procedure using endoscopic forceps without electrocautery[12]. The second technique is cold snare polypectomy (CSP), which uses snare resection without electrocautery and has been reported to be a safe method for the removal of subcentimetric polyps[13]. Although CSP appears to be a promising procedure for endoscopic removal of subcentimetric colorectal polyps, CSP is not yet widely used in Japan because of the lack of sufficient data about this procedure. Therefore, the purpose of the present study was to examine the feasibility of the use of CSP in a Japanese center.

MATERIALS AND METHODS

Study design

This retrospective study was performed at the endoscopy unit of the Osaka Medical Center for Cancer and Cardiovascular Diseases. The study protocol was approved by the center's local ethics committee. Patients with colorectal polyps larger than 5 mm who were recommended to undergo polypectomy and all polyps detected during screening colonoscopies were included in the study. All consecutive patients who underwent colorectal CSP for a subcentimetric polyp between November 2012 and March 2013 were included in a prospectively maintained database. CSP was not performed in patients who were undergoing anticoagulant and antiplatelet therapy. Additionally, CSP was not performed for lesions with suspected intramucosal or invasive carcinomas based on endoscopic assessments. Written informed consent was obtained from all patients upon inclusion.

Procedures

All procedures were performed by nine experienced colonoscopists who had each conducted more than 100 colorectal polypectomies. None of the colonoscopists had performed CSP prior to this trial. A standard type colonoscope (EVIS CF-240I or CF-260DI; Olympus

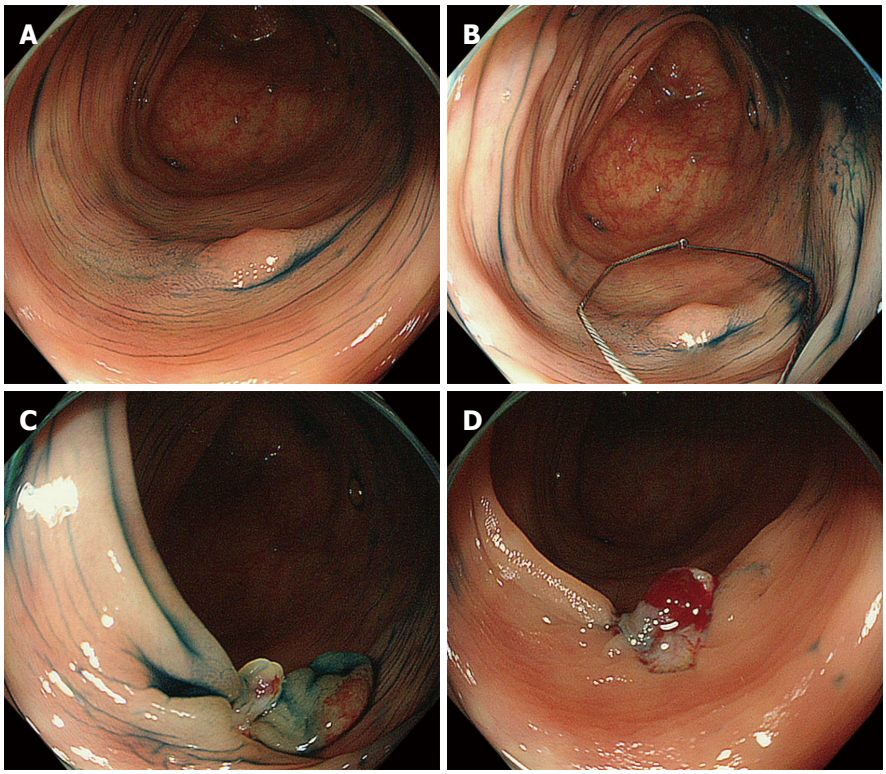

Figure 1 Actual cold snare polypectomy procedure. A: A 5-mm flat adenoma located in the sigmoid colon; B: The electrosurgical snare is opened and pressed against the colonic wall; C: The lesion and surrounding normal non-neoplastic mucosa are grasped and cut without electrocautery; D: Mucosal defect after cold snare polypectomy. Oozing immediately occurred after the procedure but stopped within a few minutes.

Medical Systems, Co., Ltd., Tokyo, Japan) or a high-definition magnifying colonoscope (CF-FH260AZI or CF-H260AZI; Olympus) with a light source (EVIS CLV-260SL; Olympus) and video processor (EVIS LUCERA CV-260SL; Olympus) were used for all patients. A transparent hood (D-201 series; Olympus) was attached to the tip of the colonoscope[14]. All patients were prepared the day before colonoscopy with a low fiber diet and preparatory medicines. Bowel preparation and sedation were administered as previously described in detail[15]. The colonoscope was first inserted into the cecum using the conventional white light mode. In cases of incomplete total colonoscopy (*e.g.*, stenosis with advanced colorectal cancer, pain or discomfort or difficult insertion caused by looping), any detected lesions were recorded and removed within the range of observation. The location, size, and macroscopic type of all of the lesions were documented according to the Paris classification[16,17]. The size was determined using biopsy forceps with a 2.2-mm outer diameter (Radial Jaw 3; Boston Scientific, Natick, MA, United States) or a 13-mm small hexagonal electrosurgical snare (Captivator; Boston Scientific). Magnifying endoscopy was performed to predict the tumor histology when available. CSP was performed using an electrosurgical snare (Captivator; Boston Scientific) without electrocautery (Figure 1, videos). The polyp was snared including normal surrounding mucosa to maintain a non-neoplastic mucosal margin around the lesion. Blood oozing was usually observed immediately after CSP. In the first 10 cases, we observed the resection sites until the oozing stopped. After these 10 cases, oozing wounds were left behind, and endoscopic hemostasis was only performed when spurting or massive bleeding occurred. If the polyps were unresectable with CSP, electrocautery was used for their removal. The removed lesions were suctioned and retrieved after CSP. The retrieved specimens were immersed in 20% formalin without pinning on a plate and examined using standard hematoxylin and eosin staining. Two experienced histopathologists who were blinded to the endoscopic findings evaluated all of the specimens according to the Japanese classification of colorectal carcinomas[18].

Statistical analysis

The procedural details were prospectively recorded in a database, and the medical records were thoroughly investigated. The collected data included patient age, gender, polyp location (*i.e.*, cecum, ascending colon, transverse colon, descending colon, sigmoid colon, or rectum), polyp size, endoscopist (expert or senior resident), morphological type (*i.e.*, protruded/sessile or superficial/elevated), histological diagnosis, incidence of immediate postpolypectomy bleeding requiring endoscopic hemostasis, incidence of delayed bleeding (clinically evident after examination) and any abdominal symptoms. Endoscopic hemostasis was usually performed for delayed postpolpectomy bleeding

Table 1 Baseline data of the participants (n = 61)

Male/female (%)	44 (72%)/17 (28%)
Median age	65
(range, yr)	(40-86)
Total detected lesion	234
Median detected lesion per patient (range)	3 (1-16)
Location	
Cecum	19 (8%)
Ascending colon	61 (26%)
Transverse colon	56 (24%)
Descending colon	33 (14%)
Sigmoid colon	52 (22%)
Rectum	13 (6%)
Morphology	
Protruded, sessile	205 (88%)
Superficial, elevated	29 (12%)
Median detected polyp size	4
(range, mm)	(1-9)
Endoscopist	
Expert	79 (34%)
Senior resident	155 (66%)
Histological type	
Not retrieved	28 (12%)
Non-neoplastic polyp	28 (12%)
Neoplastic polyp	176 (76%)
Horizontal margin (neoplastic lesion only)	
HM 0	104 (59%)
HM 1	2 (1%)
HM X	70 (40%)

HM X: Tumor involvement of the lateral margin could not be assessed; HM 0: No tumor identified at the lateral margin; HM 1: Tumor identified at the lateral margin.

when patients experienced repetitive bloody bowel discharges or became hemodynamically unstable. The study investigators assessed the symptoms in the outpatient department during follow-up appointments. Because this was a pilot feasibility study, the sample size was not estimated. The results related to non-parametric data are reported as the medians (ranges) and were compared by Wilcoxon test. The incidence (%) was used for the categorical variables, which were compared using the Yates' χ^2 test. The data analyses were conducted using the statistical package JMP 10 (SAS Institute, Cary, NC, United States).

RESULTS

Baseline data

Two-hundred patients underwent colorectal endoscopic resection (including conventional polypectomy, endoscopic mucosal resection, and endoscopic submucosal dissection) between November 2012 and March 2013. CSP was attempted in 61 patients in this study. The baseline data of the participants are shown in Table 1. The median age (range) of the patients was 65 (40-86) years. The patients comprised 44 (72%) men and 17 (28%) women. In total, 234 subcentimetric lesions were detected during colonoscopy screening. The median and maximum numbers of polyps detected per patient were 3 and 16, respectively. Thirteen (21%) patients presented with only one subcentimetric polyp, and 48 (79%) patients presented with at least two subcentimetric lesions. Two hundred five (88%) of the lesions were protruded/sessile (0-Ⅰs), and 29 (12%) were superficial/elevated (0-Ⅱa). The median (range) size of the polyps was 4 (1-9) mm. Among these lesions, 186 (80%) were diminutive (≤ 5 mm), and 48 (20%) were small (6-9 mm). One hundred and thirty-six (58%) polyps were located proximal to the splenic flexure, and 98 (42%) were situated distal to the splenic flexure. In total, 79 (34%) CSP procedures were performed by four experts, and 155 (66%) were performed by five senior residents.

Procedures for and outcomes of CSP

CSP was attempted for 234 subcentimetric polyps in 61 patients. Two (0.9%) polyps could not be resected without electrocautery and were thus removed by conventional polypectomy with electrocautery. One of these was a 2-mm protruded type inflammatory polyp that was located near a scar from a previous polypectomy in the transverse colon. The other polyp was an 8-mm protruded type adenoma located in the rectum. Thus, CSP was completed for 232 polyps in 61 patients. Immediate postpolypectomy bleeding requiring endoscopic hemostasis occurred in eight lesions (3.4%; 95%CI: 1.1%-5.8%). Although no differences were observed in sex, age, location, morphology, endoscopist or histological type between the lesions with and without immediate bleeding, the median lesion size with immediate bleeding was larger than that of the lesions without immediate bleeding (7.5 mm *vs* 4.0 mm, respectively, P = 0.002), and the incidence of immediate bleeding after CSP was greater for the small than the diminutive polyps (15% *vs* 1%, respectively, P = 0.001) (Table 2). All eight cases of immediate postpolypectomy bleeding were easily managed by endoscopic clipping alone. All patients who underwent CSP visited our outpatient department 7-35 d (median, 14 d) after the procedures. Three (5%) patients complained of minor bleeding after the procedure that stopped without any intervention. Therefore, the incidence of delayed bleeding requiring endoscopic intervention after CSP without prophylactic clipping was 0.0% (95%CI: 0.0%-1.7%). No other complications, such as perforation or postpolypectomy syndrome, were observed. Twenty-eight (12%) of the 232 lesions could not be retrieved after resection for pathological analysis. The remaining 204 (88%) polyps underwent histopathological assessments that revealed 176 (76%) neoplastic polyps (163 low-grade adenomas, 1 tubulovillous adenoma, 4 high-grade adenomas, 5 sessile serrated adenomas/polyps and three serrated adenomas) and 28 (12%) non-neoplastic lesions. The horizontal margins (HMs) of the neoplastic lesions that were removed by CSP underwent pathological assessments. One hundred four (59%) lesions were classified as HM 0 (*i.e.*, no tumor identified at the lateral margin),

Table 2 Procedure-related outcomes

	Immediate bleeding (n = 8)	Non-immediate bleeding (n = 224)	P-value
Male/female	8/0	146/78	0.10[a]
Median age	64.5	68	0.27[b]
(range, years)	(50-76)	(40-86)	
Location			0.40[a]
Proximal to splenic flexure	3 (38%)	132 (59%)	
Distal from splenic flexure	5 (62%)	92 (41%)	
Morphology			0.59[a]
Protruded, sessile (0-Is or Isp)	7 (88%)	196 (88%)	
Flat, elevated (0-IIa)	1 (12%)	28 (12%)	
Median size	7.5 (3-9)	4 (1-9)	0.002[b]
(range, mm)			
≤ 5 mm (%)	2 (22%)	183 (82%)	0.001[a]
> 6 mm (%)	6 (78%)	41 (18%)	
Endoscopist			0.54[a]
Expert	4 (50%)	74 (33%)	
Senior resident	4 (50%)	150 (67%)	
Histological type			
Not retrieved	0 (0%)	28 (12.5%)	
Non-neoplastic polyp	0 (0%)	28 (12.5%)	0.53[a]
Neoplastic polyp	8 (100%)	168 (75%)	

[a]Yates' χ^2 test; [b]Wilcoxon test.

2 (1%) were classified as HM 1 (*i.e.*, tumor identified at the lateral margin), and 70 (40%) were classified as HM X (*i.e.*, tumor involvement at the lateral margin could not be assessed).

DISCUSSION

Although CSP has been reported to minimize the risk of complications when removing subcentimetric polyps in Western countries[19,20], this technique has not yet been widely implemented in Japan. The present study represents one of the largest patient samples regarding CSP from any Japanese institution to date[21-23]. Our results indicate that CSP is a safe and effective method for resecting small colorectal lesions and suggest that CSP is also a feasible method for the removal of subcentimetric polyps in Japan.

Herein, we observed that the incidence of immediate bleeding requiring endoscopic treatment after CSP was 3.4%, which is somewhat higher than that reported in the prospective multicenter study conducted by Repici *et al*[11] (1.8%). However, only 37% of the procedures were CSPs, and the others were CFPs in the study by Repici *et al*[11]. Thus, the incidence of immediate bleeding after CSP might be different from that after CFP. In this context, it should also be mentioned that none of participating endoscopists herein had performed CSP prior to this study, and some of them might have been cautious about oozing that occurred after CSP and unnecessarily used endoscopic clips. Regardless, all cases of immediate CSP-associated bleeding were easily managed endoscopically. Caution might be required when adopting CSP, especially for small (6-9 mm) polyps because these polyps exhibited a higher incidence of immediate bleeding compared to the diminutive (≤ 5 mm) polyps. We observed no CSP cases involving delayed bleeding, perforation or postpolypectomy syndrome that required treatment in this trial, which is perhaps one of the greatest advantages of CSP.

Many Japanese patients who undergo polypectomy are currently hospitalized for a few days, and the number of hospitals that can perform polypectomy is insufficient to treat all of the patients with colorectal polyps. Considering this limited access to polypectomy in Japan and the fact that more than 90% of polyps are subcentimetric, it is possible that the implementation of CSP could increase the availability of a safe and easy procedure for the removal of subcentimetric polyps in outpatients, which could not only the decrease medical expenses associated with hospitalization but also shorten the waiting time for polyp removal in large groups of patients in Japan. Nonetheless, it should be noted that minor bleeding (that did not require endoscopic hemostasis) was observed in 3 patients (5%) after CSP. Although we rarely experience such minor bleeding after conventional polypectomy with electrocautery, this information is important when adopting CSP in daily practice.

Notably, we observed that CSP was associated with a retrieval failure of 12%. Deenadayalu and Rex[24] reported no cases of retrieval failure after CSP in their study, whereas Komeda *et al*[25] reported a retrieval failure of 19% after CSP. The relatively higher incidence of retrieval failure associated with CSP might be an issue of concern for endoscopists who do not currently apply CSP in clinical practice. However, because the indication for CSP is limited to subcentimetric polyps, which have low risks for invasive carcinomas, this aspect is perhaps not a major concern. Additionally, the "resect and discard" policy, which omits formal pathological examination, is now regarded as a promising strategy for decreasing the cost and labor associated with screening and surveillance colonoscopy[26,27]. Therefore, retrieval failure will not be a major obstacle for the generalization of CSP in the future especially if a "resect and discard" strategy is adopted. Of course, careful endoscopic assessment before CSP is essential to avoid removing and discarding invasive carcinomas. Magnifying narrow-band imaging may be a promising tool to secure the safety of both CSP (*i.e.*, by preventing the removal of subcentimetric invasive carcinomas) and the "resect and discard" strategy because pretreatment assessment using magnifying endoscopy allows for the selection of lesions with advanced histologies[28,29]. Therefore, we believe that the combination of CSP and the "resect and discard" strategy using magnifying narrow-band imaging could provide a more efficient (*i.e.*, simple, safe, and cost-effective) strategy for screening and surveillance colonoscopy.

Assessment of the HMs of tumor specimens that have been resected by CSP is also a potential concern for endoscopists who are skeptical about CSP because we cannot expect the thermal burn effect to eradicate

the neoplastic tissue around the electrosurgical snare during CSP. The incidence of HM 1 was only 1.1% in our trial, but the incidence of HM X was 40%. The main indication for CSP is subcentimetric polyps, and for such lesions, doctors do not usually pay attention to HM X statuses because they expect the thermal burn effect to occur and routinely confirm the absence of tumor residue *via* observations of the surrounding mucosa. Although Lee *et al*[30] reported a significantly higher rate of histologic eradication with CSP than with CFP in their prospective randomized controlled trial, the non-inferiority of CSP for tumor residues compared with conventional polypectomy warrants further investigation of the efficacy of CSP. In the meantime, although it is important to pay attention to the presence of tumor residue after CSP, care must be taken to remove the surrounding non-neoplastic mucosa as well as the targeted lesion when implementing CSP. Moreover, careful observation of the surrounding mucosa after CSP using magnifying endoscopy or chromoendoscopy, the washing out of minor bleeding after CSP, and strict surveillance colonoscopy are recommended until the evidence for tumor residue after CSP is considered to be adequate.

This was only a pilot study and therefore has some limitations. First, although the number of CSP procedures was larger than those of previous reports, the small sample size remains still a major limitation of this trial. A large-scale prospective study investigating the actual incidence of delayed bleeding after CSP should be conducted in the future. Second, we used a conventional electrosurgical snare in this trial because the snare developed for CSP was not available during the study period. The use of this snare may have affected the rates of removal failures or insufficient assessments of the HMs of the resected specimens. Finally, although the CSPs in this study were performed by nine endoscopists with no prior experience in CSP, different results might have been obtained if the endoscopists had experienced at least 20-30 CSPs. Specifically, the 70 (40%) HM X lesions should be carefully assessed.

In conclusion, we found that CSP is effective for removal subcentimetric polyps in the colon and rectum. CSP was safe and resulted in no cases of delayed bleeding or perforation and a 3.4% incidence of manageable immediate bleeding. Attention should be given to the potential risk of bleeding immediately after CSP, particularly for small (6-9 mm), lesions as well as to careful endoscopic diagnosis before CSP and the evaluation of tumor residue after CSP. Other areas of concern when implementing CSP might be retrieval failure and incomplete HM assessment. Nonetheless, we conclude that CSP for subcentimetric colorectal lesions is also a feasible procedure for implementation in Japan.

COMMENTS

Background

Although cold snare polypectomy (CSP) using snare resection without electrocautery has been reported to be a safe method for the removal of subcentimetric polyps, CSP is not currently widely used in Japan.

Research frontiers

CSP is a promising procedure, but there are no detailed data about immediate bleeding or the horizontal margins of the histological specimens from Japanese institutions.

Innovations and breakthroughs

The incidence of immediate bleeding after CSP for small polyps (6-9 mm) was significantly higher than that for diminutive polyps (≤ 5 mm). Histopathological diagnoses can be often insufficient because 12% of the resected lesions could not be retrieved for pathological examination, and tumor involvement in the lateral margin could not be histologically assessed in 70 (40%) lesions.

Applications

The authors need to be cautious in the performance of CSP for small (6-9 mm) polyps due to concerns about immediate bleeding and histopathological assessment.

Terminology

Cold forceps polypectomy is a simple procedure that uses endoscopic forceps without electrocautery. CSP is a procedure that uses snare resection without electrocautery.

Peer-review

This is an important manuscript.

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CASE REPORT

Duodenal polyposis secondary to portal hypertensive duodenopathy

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Author contributions: Jaffe PE performed esophagogastroduodenoscopy; Gurung A and Zhang X performed histopathological examination; Gurung A wrote the initial draft of the manuscript; the final manuscript was reviewed and revised by Jaffe PE and Zhang X.

Institutional review board statement: Case reports do not require examination and are considered exempt by the Yale University Institutional Review Board. Ethical considerations were upheld and patient personal information was protected.

Informed consent statement: Written informed consent was obtained for all interventions and follow up.

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Abstract

Portal hypertensive duodenopathy (PHD) is a recognized, but uncommon finding of portal hypertension in cirrhotic patients. Lesions associated with PHD include erythema, erosions, ulcers, telangiectasia, exaggerated villous pattern and duodenal varices. However, duodenal polyposis as a manifestation of PHD is rare. We report a case of a 52-year-old man who underwent esophagogastroduodenoscopy and was found with multiple small duodenal polyps ranging in size from 1-8 mm. Biopsy of the representative polyps revealed polypoid fragments of duodenal mucosa with villiform hyperplasia lined by reactive duodenal/gastric foveolar epithelium and underlying lamina propria showed proliferating ectatic and congested capillaries. The features were diagnostic of polyps arising in the setting of PHD.

Key words: Cirrhosis; Portal duodenopathy; Polyposis; Portal hypertension

Core tip: Duodenal polyposis secondary to portal hypertensive duodenopathy (PHD) is rare. We report a case of PHD presenting as polyposis.

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INTRODUCTION

Portal hypertensive duodenopathy (PHD) is a recognized, but uncommon finding of portal hypertension in cirrhotic patients. While other associations of portal hypertension such as portal hypertensive gastropathy and portal hypertensive colopathy have been described and studied, data concerning duodenal alterations is relatively scarce. The lesions described in PHD include erythema, erosions, ulcers, telangiectasia, exaggerated villous pattern and duodenal varices[1]. Recently, there have been emerging reports of polyps as a manifestation of PHD[2-5]. Herein, we report a patient with duodenal polyposis secondary to portal hypertension, review the literature and describe the spectrum of histopathologic changes.

CASE REPORT

A 52-year-old man with compensated alcoholic cirrhosis presented for follow up esophagogastroduodenoscopy. Past medical history includes remote T1N0 colon cancer (status post right hemicolectomy 4 years), low-grade gastrointestinal blood loss, iron deficiency anemia, gastric antral vascular ectasia, portal hypertensive gastropathy and hypertension. He was diagnosed with cirrhosis 13 years ago when he presented with jaundice and ascites and had a recent history of hepatic encephalopathy. Abdominal U/S and magnetic resonance imaging showed a large heterogenous liver, recanalization of the umbilical vein, splenomegaly, splenorenal shunt, additional collateral vessels inferior to the left renal vein and scattered renal cysts. Endoscopy revealed numerous small 1-2 mm polyps extending from the duodenal bulb to the second portion of the duodenum. The three largest polyps included a 6 mm polyp in the mid duodenal bulb (Figures 1A and B), 8 mm polyp distal to this along the anterior wall, and 8 mm polyp in the second part of the duodenum (Figure 1C). The esophagus was normal and no esophageal varices were noted. The stomach showed diffuse "snake skin" appearance, an area of friable mucosa with a polypoid appearance and surface erosions in the antrum and pre-pyloric area with spontaneous oozing of blood. The three duodenal largest polyps were biopsied and histologic examination revealed polypoid fragments of duodenal mucosa with villiform hyperplasia lined by reactive duodenal and gastric foveolar epithelium. The underlying lamina propria showed proliferating ectatic and congested capillaries (Figures 2A and B, D and E). The findings were diagnostic of multiple portal hypertensive duodenal polyps.

DISCUSSION

Common gastrointestinal tract manifestations of portal hypertension include esophageal/gastric/anorectal varices and gastric antral vascular ectasia. In addition, less common features include portal hypertensive gastropathy[6-8], congestive jejunopathy[9,10], portal colopathy[11,12] and PHD[1,13]. PHD is commonly defined as the appearance of patchy or diffuse congestion of the duodenal mucosa associated with friability, erosions or ulcerations[14,15]. The prevalence of PHD in cirrhotic patients with portal hypertension ranges from 8.4%[16] to 51.4%[1]. The lesions described in PHD include erythema, erosions, ulcers, telangiectasia, exaggerated villous pattern and duodenal varices[1]. Coexistence of severe gastropathy and higher hepatic venous pressure gradients are more frequent in PHD patients and features of PHD have been reported to disappear after liver transplantation[16].

Duodenal polyps as a manifestation of PHD, an uncommon event, have been reported previously (summarized in Table 1). These include an ulcerated solitary 3 cm polyp in the descending duodenum[3], multiple sessile polyps in the first portion of the duodenum[2] and a recent report documenting two to "several" duodenal or jejuno-ileal polypoid lesions ranging in size from < 5 mm to 15 mm in 5 patients[4]. The spectrum of histopathologic findings in the polyps includes the presence of numerous capillaries with vascular ectasia/congestion/thrombi as well as fibrosis and smooth muscle proliferation. In addition gastric foveolar metaplasia, reactive atypia and ulceration may be seen. Devadason *et al*[5] reported "duodenal capillary hemagiomatous polyps" in 3 pediatric patients (aged 1, 4 and 6 years old). All these 3 patients presented with multiple duodenal polyps in either the 1st or 2nd portion of the duodenum in the setting of extrahepatic portal venous obstruction. Polyps were biopsied in two patients, both of which demonstrated lobular capillary proliferation within the polyps[5]. Although they favored the term "duodenal capillary hemagiomatous polyps", it appears from their description, as well as accompanying image, that the polyps they described share similar morphological features to the polyps in our case and other reported polyps in the setting of PHD.

To date, including our case, there are 11 documented reports of polyps associated with PHD (Table 1). There is no gender predilection (6 male and 5 female), the ages of patients ranges from 1 to 73 years and in the majority of cases (10/11), multiple polyps are seen. The etiology of portal hypertension in adult patients include alcoholic cirrhosis (37.5%, 3/8), hepatitis C cirrhosis (25%, 2/8) and cryptogenic cirrhosis (37.5%, 3/8), while extrahepatic portal venous obstruction accounts for all cases in the pediatric population (100%, 3/3).

Histologically, the PHD associated polyp surface- and crypt-lining epithelium may focally show cells with

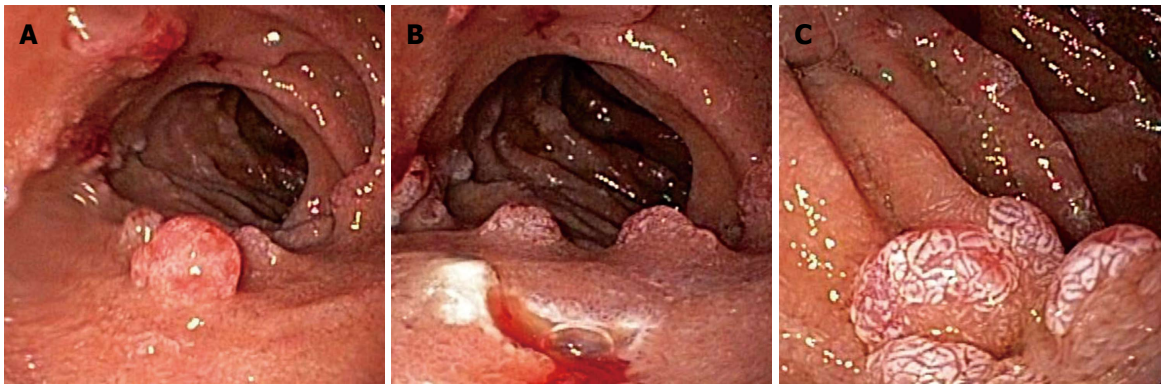

Figure 1 Duodenal polyposis under esophagogastroduodenoscopy. A 6 mm, sessile polyp was seen [prior to removal (A); immediately after removal (B)] in the mid duodenal bulb. A separate 8 mm polyp was seen along the lateral aspect of the second part of the duodenum (C).

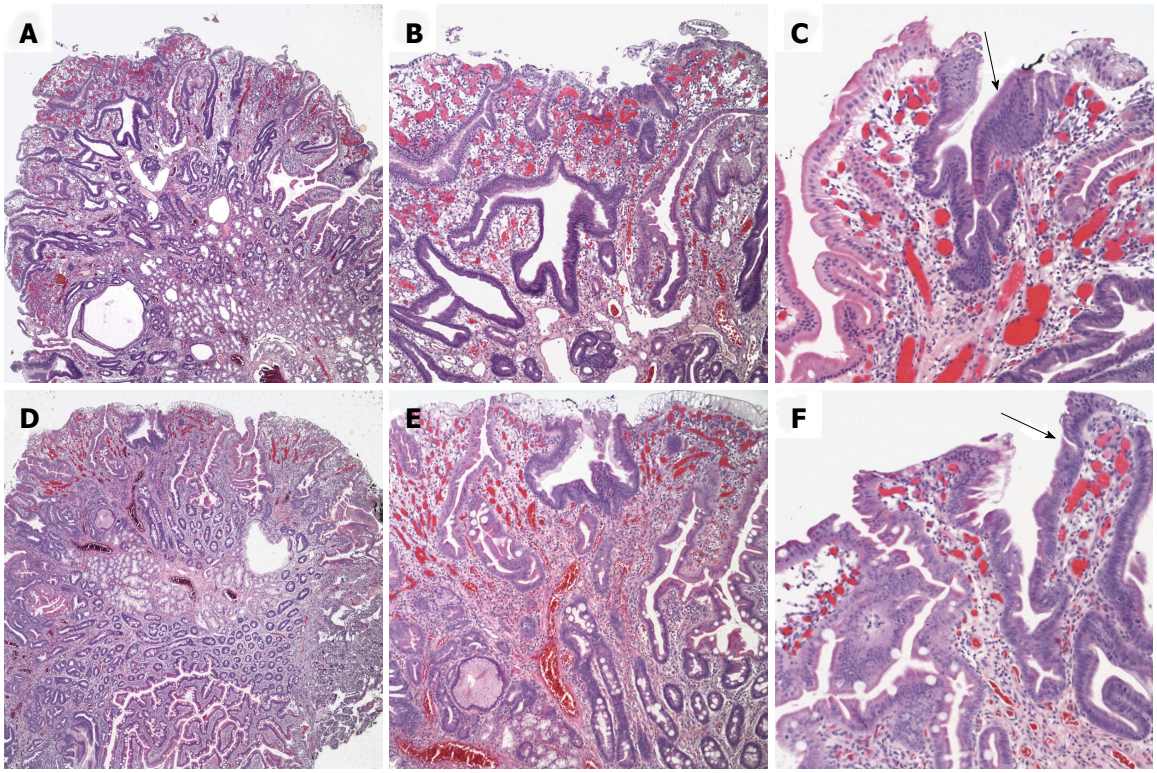

Figure 2 Histopathologic findings. Biopsies from the mid duodenal bulb polyp showed villiform hyperplasia of intestinal and gastric foveolar epithelium with numerous capillaries demonstrating congestion and vascular ectasia (A and B). Similar changes seen in the polyp from the second part of the duodenum (D-E). The epithelium lining the surface and crypts focally (arrows) showing cells with mucin depletion and slightly pencillate nuclei with hyperchromasia (C and F). Representative images of hematoxylin and eosin stained slides taken at 40 × (A, D: 4 × objective and 10 × ocular magnification), 100 × (B, E: 10 × objective and 10 × ocular magnification) and 200 × (C, F: 20 × objective and 10 × ocular magnification).

mucin depletion and contain slightly pencillate nuclei with mild hyperchromasia (Figures 2C and F). These features may mimic duodenal adenomatous polyp, a precancerous lesion in the duodenum. Our current case was previously diagnosed as "duodenal adenomas" at an outside institution. The initial diagnosis of duodenal adenoma in our patient's prior biopsy highlights the challenges that the reactive atypia may pose during histological evaluation. The differential diagnosis of polypoid lesions in the duodenum is diverse (Table 2) and we limit our discussion to more commonly seen and lesions with similar histologically features to PHD associated polyps. While duodenal adenomas with low-grade dysplasia (which are histologically similar to those seen in the colon) are typically composed of mucin depleted cells with hyperchromatic pencillate nuclei, compared to the reactive atypia seen in polyps associated with PHD, nuclei show a greater degree of enlargement, hyperchromasia and stratification. PHD polyps differ from duodenal hamartomatous polyps seen in Peutz-Jegher syndrome as polyps in the latter typically show disorganized mucosa with thick arborizing

Table 1 Reported small intestinal polyps secondary to portal hypertension (including current case)

Ref.	Age (yr)/ gender	Location(s)	Number/sizes of polyps	Pathologic findings	Etiology of portal hypertension
Current report	52/M	Duodenal bulb to second portion	Greater than 7, majority 1-2 mm, largest 8 mm	Villiform hyperplasia of reactive intestinal and gastric foveolar epithelium, proliferating ectatic and congested lamina propria vessels	Alcoholic cirrhosis
Pillai *et al*[2]	55/M	1st portion of duodenum	"multiple sessile polyps", sizes NS	Polypoid muocsa lined by small intestinal and gastric foveolar type epithelium with ectatic capillaries, fibrosis and smooth muscle proliferation of lamina propria	Alcoholic cirrhosis
Zeitoun *et al*[3]	70/M	2nd portion of duodenum	Single polyp, 3 cm	Numerous thick-walled capillaries with vascular ectasia in lamina propria	Alcoholic cirrhosis
[1]Lemmers *et al*[4]	50/F	Jueuno-ileal	"Several", > 5 mm	Lamina propria vascular dilation and thrombi without epithelial atypia	Hepatitis C cirrhosis
	73/M	Jejunal	Two "bumps", < 5 mm	Not biopsied	Cryptogenic cirrhosis
	67/M	Duodenal	"Several", 5 mm	Lamina propria vascular dilation and inflammation with epithelial atypia and ulceration	Alcoholic cirrhosis
	74/F	Antral/duodenal	"Several", 15 mm	Lamina propria vascular dilation and epithelium with crenellated glands	Hepatitis C cirrhosis
	66/F	Duodenal/jejuno-ileal	"Several", 5/< 5 mm	Not biopsied	Cryptogenic cirrhosis
Devadason *et al*[5]	6 yr/M	1st and 2nd portion of duodenum	"polyps", sizes NS	Lobular capillary proliferation in a hemagiomatous pattern in lamina propria	EHPVO
	4 yr/F	2nd portion of duodenum	"numerous", sizes NS	Lobular capillary proliferation in a hemagiomatous pattern in lamina propria	EHPVO
	1 yr/F	2nd portion of duodenum	"polyps", sizes NS	Polyp not biopsied, mucosa adjacent to polyp with ecatsia and congestion of lamina propria with smooth muscle hypertrophy	EHPVO

[1]Data obtained from Table 1 (provided by Dr. Lemmers, personal communication). EHPVO: Extrahepatic portal venous obstruction; NS: Not specified.

Table 2 Histological differential diagnosis of polyps in the duodenum

Primary	Epithelial
	Duodenal adenoma/adenocarcinoma
	Ampullary adenoma/adenocarcinoma
	Hyperplasia, heterotopias, ectopias, inflammatory
	Brunners gland hyperplasia/hamartoma
	Gastric/pancreatic hetertopia/ectopia
	IBD associated inflammatory pseudopolyps
	Inflammatory fibroid polyp
	Peutz Jegher polyps
	Juvenile polyps (JPS or PTEN associated)
	Cronkhite-Canada syndrome polyps
	Neuroendocrine/neural
	Neuroendocrine tumors
	Mixed adenocarcinoma neuroendocrine carcinoma
	Gangliocytic paranglioma
	Neurofibroma
	Ganglioneuroma
	Schwannoma
	Perinerioma
	Mesenchymal
	Gastrointestinal stromal tumor
	Leiomyoma
	Lipoma
	Hemangioma
	Granular cell tumor
	Kaposi sarcoma
	Lymphoid
	Lymphoid hyperplasia
	B and T cell lymphomas
Secondary	Metastases
Miscellaneous	Malakoplakia, mucosal prolapse related, lymphangiectasia, xanthoma

IBD: Inflammatory bowel disease.

smooth muscle fibers of the muscularis mucosa. Although there may be histologic overlap between Juvenile polyps, inflammatory bowel disease (IBD) associated inflammatory polyps and PHD associated polyps, Juvenile polyps are characterized by dilated mucin filled crypts, while IBD associated polyps tend to have prominent glandular architectural distortion in the background of IBD.

In summary, duodenal polyps secondary to PHD is uncommon. With our case, the total number of patients reported in the literature to date is 11. The finding of multiple polyps in a patient with portal hypertension should raise suspicion for this entity and careful histopathologic examination is necessary to render the appropriate diagnosis.

COMMENTS

Case characteristics

A 52-year-old man with compensated alcoholic cirrhosis presented for follow up esophagogastroduodenoscopy and multiple duodenal polyps were found.

Clinical diagnosis

Cirrhosis and duodenal polyps.

Differential diagnosis

Duodenal adenomatous polyp, polyposis syndrome, duodenal pancreatic or gastric ectopia, or other benign neoplasms.

Imaging diagnosis

Endoscopy revealed numerous small 1-2 mm polyps extending from the duodenal bulb to the second portion of the duodenum. The three largest polyps

included a 6 mm polyp in the mid duodenal bulb, 8 mm polyp distal to this along the anterior wall, and 8 mm polyp in the second part of the duodenum.

Pathological diagnosis

Portal hypertensive duodenal polyps.

Related reports

Duodenal polyps as a manifestation of portal hypertensive duodenopthy (PHD), an uncommon event, have been reported previously. The prevalence of PHD in cirrhotic patients with portal hypertension ranges from 8.4% to 51.4%. However, manifestation as multiple duodenal polyps is rare.

Term explanation

Portal hypertensive duodenal polyps are seen in patients with cirrhosis and portal hypertension. The spectrum of histopathologic findings in the polyps includes the presence of numerous capillaries with vascular ectasia/congestion/thrombi as well as fibrosis and smooth muscle proliferation. In addition gastric foveolar metaplasia, reactive atypia and ulceration may be seen.

Experiences and lessons

PHD is a recognized, but uncommon finding of portal hypertension in cirrhotic patients. Multiple duodenal polyps can be an endoscopic finding of PHD.

Peer-review

The authors reported a 52-year-old patient with cirrhosis and portal hypertension who underwent endoscopy and was found with multiple portal hypertensive duodenal polyps. This is an interesting case report and literature review. It is very well written with excellent images. The article highlights the clinical characteristics of PHD and provides information about differential diagnosis of portal hypertensive duodenal polyps.

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