

# World Journal of *Gastrointestinal Surgery*

*World J Gastrointest Surg* 2017 July 27; 9(7): 161-173





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*World Journal of Gastrointestinal Surgery*

Volume 9 Number 7 July 27, 2017

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*World Journal of Gastrointestinal Surgery* (*World J Gastrointest Surg*, *WJGS*, online ISSN 1948-9366, DOI: 10.4240) is a peer-reviewed open access academic journal that aims to guide clinical practice and improve diagnostic and therapeutic skills of clinicians.

*WJGS* covers topics concerning micro-invasive surgery; laparoscopy; hepatic, biliary, pancreatic and splenic surgery; surgical nutrition; portal hypertension, as well as associated subjects. The current columns of *WJGS* include editorial, frontier, diagnostic advances, therapeutics advances, field of vision, mini-reviews, review, topic highlight, medical ethics, original articles, case report, clinical case conference (Clinicopathological conference), and autobiography. Priority publication will be given to articles concerning diagnosis and treatment of gastrointestinal surgery diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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*World Journal of Gastrointestinal Surgery*

#### ISSN

ISSN 1948-9366 (online)

#### LAUNCH DATE

November 30, 2009

#### FREQUENCY

Monthly

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#### PUBLICATION DATE

July 27, 2017

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## Retrospective Cohort Study

**Perforation associated with endoscopic submucosal dissection for duodenal neoplasm without a papillary portion**

Yasuhiro Matsuda, Kazuki Sakamoto, Naoki Kataoka, Tomoyuki Yamaguchi, Masafumi Tomita, Shinichiro Makimoto

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**Author contributions:** Matsuda Y designed the research and wrote the paper; Sakamoto K designed the research and provided treatment; Sakamoto K, Kataoka N, Yamaguchi T, Tomita M and Makimoto S provided treatment and analyzed the data.

**Institutional review board statement:** The study was reviewed and approved by the Institutional Review Board of Kishiwada Tokushukai Hospital for ethical issues.

**Informed consent statement:** Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment without additional invasion.

**Conflict-of-interest statement:** The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.

**Data sharing statement:** Dataset available from the corresponding author at [my-salsa@air.ocn.ne.jp](mailto:my-salsa@air.ocn.ne.jp).

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**Manuscript source:** Unsolicited manuscript

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Received: December 27, 2016

Peer-review started: December 30, 2016

First decision: January 28, 2017

Revised: May 26, 2017

Accepted: June 6, 2017

Article in press: June 8, 2017

Published online: July 27, 2017

**Abstract****AIM**

To investigate predictors of perforation after endoscopic resection (ER) for duodenal neoplasms without a papillary portion.

**METHODS**

This was a single-center, retrospective, cohort study conducted between April 2003 and September 2014. A total of 54 patients (59 lesions) underwent endoscopic mucosal resection (EMR) ( $n = 36$ ) and endoscopic submucosal dissection (ESD) ( $n = 23$ ). Clinical features, outcomes, and predictors of perforation were investigated.

**RESULTS**

Cases of perforation occurred in eight (13%) patients (95%CI: 4.7%-22.6%). Three ESD cases required surgical management because they could not be repaired by clipping. Delayed perforation occurred in two ESD cases, which required surgical management, although both patients underwent prophylactic clipping. All patients with perforation who required surgery had no postoperative complications and were discharged at an

average of 13.2 d after ER. Perforation after ER showed a significant association with a tumor size greater than 20 mm ( $P = 0.014$ ) and ESD ( $P = 0.047$ ).

### CONCLUSION

ESD for duodenal neoplasms exceeding 20 mm may be associated with perforation. ESD alone is not recommended for tumor treatment, and LECS should be considered as an alternative.

**Key words:** Duodenal neoplasm; Endoscopic submucosal dissection; Laparoscopic and endoscopic cooperative surgery

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**Core tip:** Duodenal neoplasms are relatively rare, and endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) of the duodenum poses a high risk of complications. In our study, 54 patients (59 lesions) underwent EMR ( $n = 36$ ) and ESD ( $n = 23$ ). Cases of perforation occurred in eight (13%) patients (95%CI: 4.7%-22.6%), and perforation showed a significant association with a tumor size greater than 20 mm ( $P = 0.014$ ) and ESD ( $P = 0.047$ ). ESD for duodenal neoplasms exceeding 20 mm may be associated with perforation. ESD alone is not recommended as a treatment for tumor treatment, and laparoscopic and endoscopic cooperative surgery should be considered as an alternative.

Matsuda Y, Sakamoto K, Kataoka N, Yamaguchi T, Tomita M, Makimoto S. Perforation associated with endoscopic submucosal dissection for duodenal neoplasm without a papillary portion. *World J Gastrointest Surg* 2017; 9(7): 161-166 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v9/i7/161.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v9.i7.161>

## INTRODUCTION

Duodenal neoplasms are relatively rare. Duodenal polyps are found in 4.6% of patients referred for upper gastrointestinal endoscopy<sup>[1]</sup>. Primary adenocarcinoma represents only 0.3% of all gastrointestinal tract malignant neoplasms and 0.042% of all malignant neoplasms<sup>[2,3]</sup>. Therefore, no method of treatment for duodenal neoplasm has been established.

Recently, cases of endoscopic resection (ER) for superficial neoplasms without lymph node metastasis have been reported. ER may consist of endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD). However, ER for the duodenum poses a high risk of complications, such as perforation and bleeding, due to the abundant blood vessels in the submucosal layer and thin muscle layer in the duodenum compared with the digestive tract<sup>[4-7]</sup>. Specifically, patients with perforation undergo emergency

surgery in many cases, and it is unclear whether ER for duodenal tumors is appropriate. In this study, we investigated predictors of perforation after ER for duodenal neoplasms without a papillary portion.

## MATERIALS AND METHODS

### Patients

This study included a retrospective cohort of 54 patients (59 lesions) in a single center. We recruited patients (without ampullary duodenal tumors) who underwent ER between April 2003 and September 2014. These patients were preoperatively diagnosed with adenoma or carcinoma. The database included patient information such as age, sex, treatment method (EMR or ESD), prophylactic clipping (applied or not applied), and tumor characteristics, such as histological diagnosis (adenoma or carcinoma), location (pre-ampulla or post-ampulla), size (under 20 mm or over 20 mm), and type (polypoid or superficial). When a patient had multiple duodenal tumors, the largest lesion was included in the analysis. When a tumor was located on the opposite side of the ampulla of Vater, it was categorized as post-ampullary. The clinical features of complications (perforation and bleeding) were investigated.

All patients were provided with an explanation of the endoscopic procedure before treatment, including complications and alternative treatments, and written informed consent was obtained.

### Endoscopic resection techniques

The endoscopic procedures were performed with a single-channel endoscope (GIF-Q240 or PCF-PQ260I; Olympus Medical Systems Co., Tokyo, Japan) or a double balloon sigmoid scope (EN-450T5/W; FUJIFILM, Saitama, Japan) by carbon dioxide insufflation. The choice of scope depended on the distance to the lesion.

EMR was indicated for small lesions ( $< 2$  cm) or pedunculated lesions. Simple snarectomy was performed after the injection of 0.4% sodium hyaluronate solution (MucoUp; Johnson and Johnson K.K., Tokyo, Japan). The mucosa bulge is important for the safety of the procedure because the wall of the duodenum is thin. ESD was indicated for large lesions ( $\geq 2$  cm) or flattened lesions. The ESD technique consisted of three steps. First, the periphery of the lesion was marked using a 2.0 mm short needle knife with a water jet function (Flush Knife, DK2618JB20; FUJIFILM, Saitama, Japan). Second, MucoUp was injected into the submucosal layer to achieve sufficient mucosal elevation. Third, a mucosal incision and submucosal dissection were performed with the Flush Knife (1.5 mm or 2.0 mm). Additionally, an electric current generator (VIO300D; ERBE, Tübingen, Germany) was used for hemostasis.

Prophylactic clipping using hemoclips (HX-110/610; Olympus Medical Systems Co.) was performed for mucosal defects after ER.



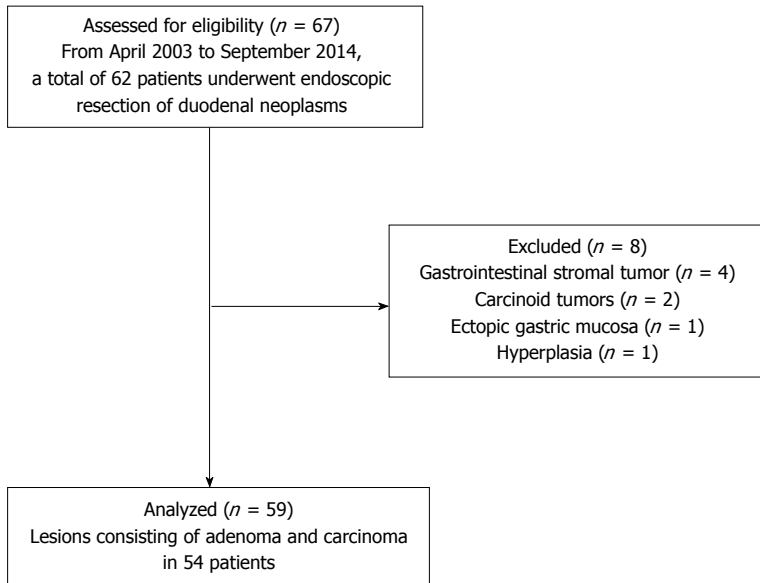


Figure 1 Flow diagram of patients with duodenal neoplasms treated by endoscopic resection.

### Definition of complications

Intraoperative perforation was defined as the ability to recognize a perforation during the EMR and ESD procedures. Delayed perforation was defined as the inability to recognize a perforation during the EMR and ESD procedures, and patients had no symptoms immediately after the procedures. The diagnosis of delayed perforation is reached using enhanced computed tomography, which was performed for patients with abdominal pain. Delayed bleeding was defined in patients who required endoscopic hemostasis or transfusion after ER.

### Statistical analysis

All statistical analyses were performed with the Statistical Package for the Social Sciences (SPSS 22.0 Package; SPSS Inc., Chicago, Illinois, United States). Continuous variables are expressed as the means and were analyzed using Student's *t* test. Categorical variables were compared with a  $\chi^2$  test or, if appropriate, Fisher's exact test. A probability value of  $< 5\%$  was considered statistically significant.

## RESULTS

From April 2003 to September 2014, a total of 62 patients underwent ER of duodenal tumors. Four cases with gastrointestinal stromal tumors, two cases with carcinoid tumors, one case with an ectopic gastric mucosa, and one case with a hyperplasia were excluded. As a result, 59 lesions due to adenoma and carcinoma in 54 patients were analyzed (Figure 1).

The 59 cases included 39 males and 20 females. The average age was 61.3 years (range 40-79 years). Thirty-eight lesions were diagnosed as adenoma, and 21 lesions were diagnosed as carcinoma. The accuracy of the preoperative biopsy was 96.6% (57/59). Thirty-five lesions were located in the pre-ampulla region,

and 24 were in the post-ampulla region. The average tumor size was 14.2 mm (95%CI: 11.6-16.8 mm). The macroscopic types included 12 polypoid and 47 superficial tumors. All lesions were confined to the mucosa. Thirty-six lesions underwent EMR. Piecemeal EMR was performed in four cases, and en-bloc EMR was performed in 32 cases. Among the piecemeal EMR cases, three lesions were removed in two pieces, and one lesion was removed in four pieces. Twenty-three lesions underwent ESD. Prophylactic clipping was applied in 46 patients.

Complications included perforation and bleeding (Table 1). Perforation occurred in eight (13%) patients (95%CI: 4.7%-22.6%). Four lesions were located in the pre-ampulla region, and four lesions were in the post-ampulla region. The mean size of lesion in cases of perforation was 22.9 mm, which was significantly different from the non-perforated group ( $P < 0.05$ ). Intraoperative perforation occurred in six cases, and delayed perforation occurred two cases. Intraoperative perforation occurred in two EMR cases and ESD four cases. All cases in the EMR group and one case in the ESD group underwent conservative management after clipping. Three ESD cases required surgical management because they could not be repaired by clipping. Delayed perforation occurred in two ESD cases, and these patients required surgical management, even though both patients received prophylactic clipping. Perforation after ER was significantly associated with tumor size greater than 20 mm and ESD (Table 2). Bleeding occurred in two (3.4%) cases. One required endoscopic hemostasis, and the other patient received a transfusion after ER.

For the surgical procedures, three cases consisted of suturing and covering with omentum. Two patients underwent Billroth I anastomosis after pyloric ring resection and partial duodenum resection. No patients with perforation who required surgery had postoperative

**Table 1 Clinical features and outcomes of patients with complications**

Case	Age (yr)	Sex	Method	Complication	Clipping	Treatment	Hospital stay after ER (d)	Tumor characteristics		
								Location	Size (mm)	Type
1	65	M	EMR	IP	Possible	Conservative	7	Post-ampulla	17	Is
2	60	M	EMR	IP	Possible	Conservative	6	Post-ampulla	9	Ila
3	55	M	ESD	DP	Possible	Surgical	12	Post-ampulla	24	Ila
4	60	M	ESD	Bleeding	Possible	Transfusion	9	Pre-ampulla	20	Ila
5	67	M	EMR	Bleeding	Possible	Hemostasis	11	Pre-ampulla	55	Isp
6	40	M	ESD	IP	Impossible	Surgical	11	Pre-ampulla	20	Ila
7	55	M	ESD	IP	Possible	Conservative	18	Pre-ampulla	13	Iic
8	64	M	ESD	IP	Impossible	Surgical	16	Post-ampulla	30	Ila
9	44	F	ESD	IP	Impossible	Surgical	12	Pre-ampulla	30	Ila
10	72	F	ESD	DP	Possible	Surgical	15	Pre-ampulla	40	Ila

ER: Endoscopic resection; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; IP: Intraoperative perforation; DP: Delayed perforation.

**Table 2 Predictors of perforation**

		Perforation		P value
		Did not occur	Occurred	
Sex	M	33	6	0.704
	F	18	2	
Histological diagnosis	Adenoma	33	5	1.000
	Carcinoma	18	3	
Tumor location	Pre-ampulla	31	4	0.704
	Post-ampulla	20	4	
Tumor size	Under 20 mm	42	3	0.014
	Over 20 mm	9	5	
Macroscopic type	Polypoid	11	1	0.482
	Superficial	40	7	
Resection method	EMR	34	2	0.047
	ESD	17	6	
Prophylactic clipping <sup>1</sup>	Not applied	10	0	1.000
	Applied	41	5	

<sup>1</sup>Excluded three cases in which clipping were impossible due to perforation. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; M: Male; F: Female.

complications. The patients were discharged at an average of 13.2 d after ER.

## DISCUSSION

The reported incidence of malignant degeneration of duodenal tubulovillous polyps ranges from 35% to 85%, and accurately differentiating cancer from adenoma is difficult based on biopsy findings alone<sup>[8]</sup>. Even if the histopathological examination of a biopsy specimen reveals an adenoma, it is possible to diagnose an adenoma as carcinoma after ER. In our study, the accuracy of preoperative biopsy was 96.6% (57/59). An ER should be performed if no metastasis is present in the lymph nodes and distant organs; however, an adenoma in the duodenum presents the possibility of carcinoma. Nagatani *et al.*<sup>[9]</sup> reported that the incidence of lymph node metastasis was 0% in cases of intramucosal cancer and 5% in cases of submucosal cancer. Shinoda *et al.*<sup>[10]</sup> reported no cases of lymph node metastasis among 273 cases of early duodenal cancer. Therefore, an early duodenal neoplasm can

be treated by ER, unless lymph node metastasis is revealed.

Some reports address ER for duodenal tumors, but none address standard therapy. The surgical methods include piecemeal EMR, *en-bloc* EMR, and ESD. Piecemeal EMR is possible in most tumors that exceed 20 mm, but commonly results in recurrence<sup>[11,12]</sup>. *En-bloc* EMR can be performed for tumors exceeding 10 mm, although the resection margins may be histologically positive<sup>[8]</sup>. Additionally, lesions larger than 20 mm cannot be safely removed *en-bloc* and closed by any currently available method<sup>[4,6,13]</sup>. Therefore, EMR is not an ideal treatment for duodenal neoplasms larger than 20 mm. ESD can be performed for tumors exceeding 20 mm and achieves higher rates of *en-bloc* and curative resection than EMR<sup>[5]</sup>. In one study, the negative margin rate was 100% for the lateral resection margin in ESD<sup>[8]</sup>. However, ESD is associated with a higher rate of complications, such as perforation and bleeding, than EMR<sup>[5]</sup>. Jung *et al.*<sup>[14]</sup> reported that the perforation rates after ESD were very high (35.7%). For example, perforation rates associated with gastric ESD have been reported to be between 1.2% and 8.7%. Inoue *et al.*<sup>[7]</sup> reported that the incidence of delayed perforation was significantly associated with post-ampullary tumor location and resection method (both piecemeal EMR and ESD). In our study, ER of tumors exceeding 20 mm and ESD presented a high risk of perforation. We examined EMR and ESD because piecemeal EMR was only performed in four cases, and therefore the statistical power was insufficient. Additionally, the results were not significantly different according to the tumor location.

As described earlier, ER of a duodenal tumor tends to cause complications (especially perforation), and appropriate treatments for perforation are lacking. Abundant blood vessels in the submucosal layer and a thin muscle layer in the duodenum are thought to be related to a high risk of complications. In addition, exposure of the duodenal wall to pancreatic juice and bile may increase the risk of delayed perforation<sup>[5]</sup>. Taku *et al.*<sup>[15]</sup> reported that conservative treatment is possible

when patients with perforation are stable. Krishna *et al.*<sup>[16]</sup> reported that if perforation is suspected, abdominal CT should be performed to evaluate the indication for surgery. We have suggested that patients could be evaluated immediately by abdominal CT and receive emergency surgery, if necessary, when abdominal pain or high fever is present.

Prophylactic clipping is not sufficient to prevent perforation after ESD. Recently, a new device (the over-the-scope clip) has been developed for the prevention of perforation after ER, but this method requires further evaluation<sup>[17]</sup>. We suggest that laparoscopic and endoscopic cooperative surgery (LECS) should be the therapeutic strategy for tumors exceeding 20 mm.

Toyonaga *et al.*<sup>[18]</sup> reported the use of an endo linear stapler for wedge resection. However, it is not possible to appropriately resect tumors of the posterior duodenum using this method (*i.e.*, resection with an inappropriate margin or unnecessary resection of the duodenal wall)<sup>[18,19]</sup>. Sato *et al.*<sup>[20]</sup> reported LECS of a duodenal carcinoid tumor. Recently, others have reported laparoscopic local excision of a tumor followed by closure of the defect using a hand-sewn technique<sup>[21-25]</sup>. We performed endoscopic total layer resection or ESD of a duodenal tumor followed by this procedure in three cases. All patients had no complications and were discharged in approximately one week. More cases should be evaluated in the future because the sample size of duodenal neoplasms was relatively small.

In conclusion, ESD for a duodenal tumor exceeding 20 mm may be associated with complications (especially perforation). ESD alone is not recommended for tumor treatment, and LECS should be considered as an alternative.

## COMMENTS

### Background

Duodenal neoplasms are relatively rare. Primary adenocarcinoma represents only 0.3% of all gastrointestinal tract malignant neoplasms and 0.042% of all malignant neoplasms. Therefore, no method of treatment for duodenal neoplasm has been established.

### Research frontiers

Recently, cases of endoscopic resection (ER) for superficial neoplasms without lymph node metastasis have been reported. ER may consist of endoscopic mucosal resection or endoscopic submucosal dissection (ESD). However, ER for the duodenum poses a high risk of complications. Patients with perforation undergo emergency surgery in many cases. It is unclear whether ER for duodenal tumors is appropriate.

### Innovations and breakthroughs

The authors investigated predictors of perforation after ER for duodenal neoplasms without a papillary portion.

### Applications

ESD for a duodenal tumor exceeding 20 mm may be associated with complications (especially perforation). ESD alone is not recommended for tumor treatment, and LECS should be considered as an alternative.

### Peer-review

This paper presents a unique comparison of endoscopic mucosal dissection

with endoscopic submucosal dissection in the management of non-ampullary duodenal tumours.

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**P- Reviewer:** Dumitrascu DL, Tovey FI **S- Editor:** Kong JX  
**L- Editor:** A **E- Editor:** Wu HL



Retrospective Study

# Analysis of risk factors - especially different types of plexitis - for postoperative relapse in Crohn's disease

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**Institutional review board statement:** This study was reviewed and approved by the Ethics Committee of University of Szeged.

**Informed consent statement:** Patients were not required to give informed consent to the study because the data were collected retrospectively, and the analysis used anonymous clinical data. Each patient gave their informed consent to the treatment.

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

**Data sharing statement:** No additional data are available.

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Manuscript source: Invited manuscript

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Received: January 27, 2017

Peer-review started: February 6, 2017

First decision: March 13, 2017

Revised: April 25, 2017

Accepted: May 22, 2017

Article in press: May 24, 2017

Published online: July 27, 2017

## Abstract

### AIM

To evaluate the presence of submucosal and myenteric plexitis and its role in predicting postoperative recurrence.

### METHODS

Data from all patients who underwent Crohn's disease (CD)-related resection at the University of Szeged, Hungary between 2004 and 2014 were analyzed retrospectively. Demographic data, smoking habits, previous resection, treatment before and after surgery, resection margins, neural fiber hyperplasia, submucosal and myenteric plexitis were evaluated as possible predictors of postoperative recurrence. Histological samples were analyzed blinded to the postoperative outcome and the clinical history of the patient. Plexitis was evaluated based on the appearance of the most severely inflamed ganglion or nerve bundle. Patients underwent regular follow-up with colonoscopy after surgery. Postoperative



recurrence was defined on the basis of endoscopic and clinical findings, and/or the need for additional surgical resection.

## RESULTS

One hundred and four patients were enrolled in the study. Ileocecal, colonic, and small bowel resection were performed in 73.1%, 22.1% and 4.8% of the cases, respectively. Mean disease duration at the time of surgery was 6.25 years. Twenty-six patients underwent previous CD-related surgery. Forty-three point two percent of the patients were on 5-aminosalicylate, 20% on corticosteroid, 68.3% on immunomodulant, and 4% on anti-tumor necrosis factor- $\alpha$  postoperative treatment. Postoperative recurrence occurred in 61.5% of the patients; of them 39.1% had surgical recurrence. 92.2% of the recurrences developed within the first five years after the index surgery. Mean disease duration for endoscopic relapse was 2.19 years. The severity of submucosal plexitis was a predictor of the need for second surgery (OR = 1.267, 95%CI: 1.000-1.606,  $P$  = 0.050). Female gender (OR = 2.21, 95%CI: 0.98-5.00,  $P$  = 0.056), stricturing disease behavior (OR = 3.584, 95%CI: 1.344-9.559,  $P$  = 0.011), and isolated ileal localization (OR = 2.671, 95%CI: 1.033-6.910,  $P$  = 0.043) were also predictors of postoperative recurrence. No association was revealed between postoperative recurrence and smoking status, postoperative prophylactic treatment and the presence of myenteric plexitis and relapse.

## CONCLUSION

The presence of severe submucosal plexitis with lymphocytes in the proximal resection margin is more likely to result in postoperative relapse in CD.

**Key words:** Submucosal plexitis; Postoperative recurrence; Crohn's disease; Stricturing disease behavior; Isolated ileal disease

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**Core tip:** This is a retrospective study to evaluate the presence of submucosal and myenteric plexitis and its role in predicting postoperative recurrence (POR) in Crohn's disease. Demographic data, smoking habits, previous resection, treatment before and after surgery, and histological findings were evaluated as possible predictors of POR. We found that the severity of submucosal plexitis was a predictor of the need for second surgery. Other predictors of POR were female gender, stricturing disease behavior, and isolated ileal localization. Our results did not confirm the hypothesis that myenteric plexitis can be predictive of postoperative relapse.

Analysis of risk factors - especially different types of plexitis - for postoperative relapse in Crohn's disease. *World J Gastrointest Surg* 2017; 9(7): 167-173 Available from: URL: <http://www.wjgnet.com/1948-9366/full/v9/i7/167.htm> DOI: <http://dx.doi.org/10.4240/wjgs.v9.i7.167>

## INTRODUCTION

Surgery is not curative in Crohn's disease (CD), hence postoperative recurrence still remains a significant problem in the treatment of CD. More than 70% of all patients with CD require surgery in the course of their disease. A second surgery is required in 34%-53% of the cases; the highest recurrence rate has been observed in the ileocolic disease location<sup>[1]</sup>. Farmer *et al*<sup>[2]</sup> also demonstrated that operative incidence was the highest (91.5%) among patients with ileocolic disease. Therefore it is important to identify the predictors of postoperative recurrence in order to optimize treatment and surveillance after surgery. Currently conflicting data are available on the different risk factors. The IBSEN study group found that the probability of surgery was 37.9% in a 10-year follow-up. Terminal ileal location, stricturing, penetrating behavior, and age younger than 40 years at diagnosis were independent risk factors of subsequent surgery<sup>[3]</sup>. A large meta-analysis of 2962 patients with CD revealed that smoking significantly increases the risk of clinical and surgical recurrence. This high risk of postoperative relapse and reoperation is significantly reduced if a patient quits smoking<sup>[4]</sup>. A recently published study only identified preoperative steroid use as a risk factor for early postoperative endoscopic recurrence<sup>[5]</sup>, while another study found a higher risk for postoperative endoscopic recurrence in case of previous use of two or more anti-tumor necrosis factor (TNF)- $\alpha$  agents<sup>[6]</sup>.

Histological changes in the enteric nervous system are common in CD. The major structural abnormalities are irregular hypertrophy and hyperplasia of nerve fibers and alterations of neuronal cell bodies and enteric glial cells in the ganglia of the submucosal and myenteric plexus<sup>[7]</sup>. Ferrante *et al*<sup>[8]</sup> showed that the presence of myenteric plexitis in proximal resection margins of ileocolonic resection specimens is highly associated with postoperative CD recurrence, and the severity of myenteric plexitis in the proximal resection margin correlated with the severity of endoscopic recurrence<sup>[8-10]</sup>. Sokol *et al*<sup>[11]</sup> revealed an association between submucosal plexitis and early clinical recurrence, moreover lymphocytic plexitis in the proximal surgical margin was related to a higher risk of endoscopic or surgical recurrence after ileocolonic resection<sup>[12,13]</sup>.

Our aim was to evaluate the frequency and predictors of postoperative recurrence and the role of submucosal and myenteric plexitis in predicting postoperative recurrence on the basis of endoscopic findings

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and/or the need for additional surgical resection.

## MATERIALS AND METHODS

### Patients and data collection

Patients were selected retrospectively from the database of the Department of Pathology, University of Szeged (Hungary). All patients who underwent CD-related surgery between 2004 and 2014 were included in the study.

Diagnosis of CD was based on clinical, endoscopic and histological findings. The following data were extracted retrospectively from the medical chart of each patient: Age, sex, year of the diagnosis of CD, phenotype of CD according to the Montréal classification<sup>[14]</sup>, smoking habits, date of the CD-related surgery, type of the anastomosis, CD-related therapy before and after surgery, and the presence of postoperative relapse. Postoperative relapse was defined on the basis of endoscopic and clinical findings, and/or the need for additional surgical resection. Patients were regularly followed up with colonoscopy after the surgery. Postoperative endoscopy findings were classified on the basis of the Rutgeerts score in case of ileocolonic resection<sup>[15]</sup>; remission was defined as Rutgeerts endoscopic score i0-i1, and recurrence as a score of i2-i4<sup>[15]</sup>.

Postoperative recurrences were defined on the basis of the work of Ng *et al.*<sup>[10]</sup> Clinical recurrence was defined as the presence of CD-related symptoms associated with radiologic or endoscopic findings, considered severe enough to change the current therapy (requires steroid treatment or an increase in existing treatment). Surgical recurrence was defined as a need for further operation (refractory to medical treatment or new complications developed)<sup>[10]</sup>.

### Pathologic examination

Histological samples were analyzed retrospectively by two expert pathologists, blinded to the postoperative outcome and the clinical history of the patient. Both resection margins (ileal and colonic margins) were investigated for typical CD lesions (inflammatory infiltrates, granuloma, etc). Further investigations focused on the proximal resection margin. Special attention was given to the enteric nervous system, namely to the myenteric and submucosal plexuses. Proctitis was evaluated based on the appearance of the most severely inflamed ganglion or nerve bundle<sup>[12]</sup>. The severity of proctitis was graded according to the classification proposed by Ferrante *et al.*<sup>[8]</sup>: Mild proctitis if the ganglion or nerve bundle contained 0-4 inflammatory cells ( $G_1$ ), moderate proctitis if it contained 4 to 9 cells ( $G_2$ ), or severe if containing  $\geq 10$  cells ( $G_3$ ). Evaluation was performed independently for each cellular type: Mast cell, plasmacyte, lymphocyte, eosinophil and neutrophil cell counts were also evaluated<sup>[12]</sup>. Each sample was fixed in buffered formalin and analyzed using hematoxylin-eosin staining. Some examples are demonstrated in Figure 1.

**Table 1 Patient characteristics *n* (%)**

Baseline characteristics of patients	<i>n</i> = 104
Mean age at diagnosis (yr)	41.3 $\pm$ 14.047
Mean disease duration at the time of the operation (yr)	6.25 $\pm$ 6.12
Sex	
Female	50 (48)
Male	54 (52)
Age at index resection (yr)	
Younger than 40	74 (71.2)
40 and older	30 (28.8)
Smoking history at index surgery	
Current smoker	32 (30.8)
Never smoked	68 (65.4)
Ex-smoker	4 (3.8)
Montréal classification	
A1 (< 16 yr)	15 (14.4)
A2 (between 17 and 40 yr)	71 (68.3)
A3 (> 40 yr)	18 (17.3)
B1 (nonstricturing, nonpenetrating)	12 (11.5)
B2 (stricturing)	52 (50)
B3 (penetrating)	40 (38.5)
L1 (isolated ileal disease)	51 (49)
L2 (isolated colonic disease)	22 (21.2)
L3 (ileocolonic disease)	31 (29.8)
L4 (isolated upper disease)	0 (0)
p (perianal disease modifier)	14 (13.5)
Type of index resection	
Ileocolonic resection	76 (73.1)
Colonic resection	23 (22.1)
Small bowel resection	5 (4.8)
Previous resection before index surgery	26 (25)

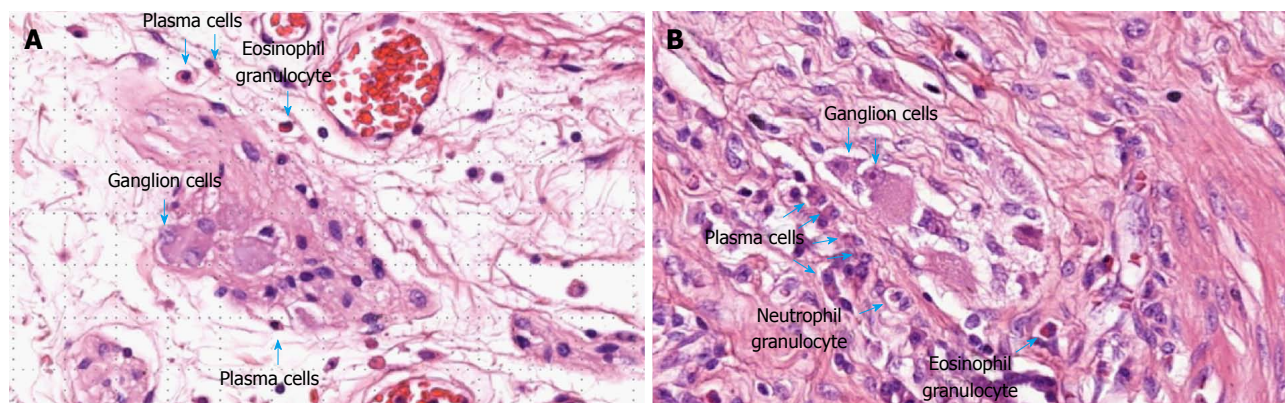
### Statistical analysis

The statistical analysis of the data was performed by a biomedical statistician using SPSS. To identify predictors of postoperative recurrence (clinical recurrence or surgical recurrence) among patients' baseline characteristics, histological findings such as severity of myenteric and submucosal proctitis univariable logistic regression analysis was used. *P* values < 0.05 were considered statistically significant. Survival was examined with the Kaplan-Meier method.

## RESULTS

### Patient characteristics

One hundred and four patients with CD were enrolled in the study. The baseline characteristics of the patients are reported in Table 1. Mean age at index CD-related surgery was 34.8  $\pm$  13.24 years, mean disease duration at the time of the index surgery was 6.25  $\pm$  6.12 years. 86.5% of the patients were on specific CD-related treatment at the time of the index surgery; 37.5% of patients were on aminosaliclates, 13.5% on anti-TNF- $\alpha$  therapy, 51% on corticosteroid, 12.5% on budesonide, 43.3% on azathioprine, 6.7% on methotrexate, and 35.6% on antibiotics. Operations were performed for specific reasons: abscess (20.2%), fistulas (13.5%), perforation (4.8%), stenosis (67.3%) and other (1%). Ileocecal, colonic and small bowel



**Figure 1** Submucosal plexitis (A) with plasma cells, eosinophil granulocyte surrounding the ganglion cell (hematoxylin-eosin staining); and myenteric plexitis (B) with plasma cells, neutrophil granulocyte, eosinophil granulocyte surrounding the ganglion cell (hematoxylin-eosin staining) in a Crohn's disease resection specimen.

resection were performed in 73.1%, 22.1% and 4.8% of the cases, respectively. Twenty-six patients had undergone previous CD-related surgery. Forty-three point two percent of the patients were on 5-aminosalicylate, 20% on corticosteroid, 68.3% on immunomodulant, and 4% on anti-TNF- $\alpha$  postoperative treatment. Postoperative recurrence occurred in 61.5% of the patients; of them 39.1% had surgical recurrence. 92.2% of the recurrences developed within the first five years after the index surgery. Mean disease duration for postoperative relapse was  $2.70 \pm 2.11$  years.

### Histological findings

Typical Crohn's lesions, such as inflammatory cell infiltration, architectural alterations, crypt abscesses, ulcers, and granulomas were detected in both resection margins. Typical CD lesions were found in proximal resection margins (5.8%), distal resection margins (5.8%), and in both resection margins (16.3%). Neural fiber hyperplasia was present in 37.5% of proximal resection margins. The pathological examination focused on proximal resection margins with quantitative evaluation of myenteric and submucosal plexitis. Inflammatory cell count (mastocyte, plasmocyte, lymphocyte, eosinophil and neutrophil granulocyte) for myenteric and submucosal plexuses are summarized in Table 2. Median severity of submucosal plexitis was 1 and median severity of myenteric plexitis was 2. Submucosal plexitis was mainly constituted by lymphocytes (median: 2), while myenteric plexitis was mainly constituted by lymphocytes (median: 2) and plasmocytes (median: 2). Other cell types, such as mastocytes, eosinophils and neutrophil granulocytes were less frequently observed.

We found that perianal disease [odds ratio (OR) = 3.78, 95%CI: 1.164-12.312,  $P = 0.027$ ] and female gender (OR = 2.21, 95%CI: 0.98-5.00,  $P = 0.056$ ) are risk factors for postoperative relapse. Stricturing disease behavior (OR = 3.584, 95%CI: 1.344-9.559,  $P = 0.011$ ) and isolated ileal disease localization (OR = 2.671, 95%CI: 1.033-6.910,  $P = 0.043$ ) increased

the risk of second surgery. Stricturing disease behavior (OR = 6.417, 95%CI: 0.999-41.212,  $P = 0.050$ ) and ileocecal disease (OR = 6.00, 95%CI: 0.832-43.293,  $P = 0.076$ ) also increased the risk of relapse in previously operated CD patients.

Higher lymphocyte cell count in the submucosal plexus was a risk factor for surgical or clinical relapse (OR = 1.267, 95%CI: 1.000-1.606,  $P = 0.050$ ). Moderate submucosal plexitis reduced the risk of second surgery by 85.4% compared to severe submucosal plexitis (OR = 0.146, 95%CI: 0.029-0.738,  $P = 0.020$ ). No association was revealed between postoperative recurrence and smoking status, postoperative prophylactic treatment and the presence of myenteric plexitis and relapse. Figure 2 shows the survival probability without a second CD-related surgery and the probability without clinical recurrence.

## DISCUSSION

We have demonstrated that severity of submucosal plexitis in proximal resection margins, perianal manifestation and stricturing disease behavior, as well as isolated ileal disease were all associated with postoperative recurrence. Over the last few years, several studies focused on plexitis and its role in the postoperative recurrence of CD. Ferrante *et al.*<sup>[8]</sup> demonstrated that inflammation of the myenteric plexus was significantly associated with postoperative CD endoscopic recurrence; moreover they found a positive correlation between the severity of the inflammatory infiltration of the plexus and the severity of endoscopic recurrence. These data are in concordance with the findings of recent studies: Misteli *et al.*<sup>[9]</sup> revealed that severe myenteric plexitis at the proximal resection margin is associated with surgical resection; Ng *et al.*<sup>[10]</sup> demonstrated that myenteric plexitis can be present in otherwise uninvolved proximal resection margins. Sokol *et al.*<sup>[11]</sup> demonstrated an association between submucosal plexitis and early clinical recurrence; they found that mast cell-associated submucosal plexitis



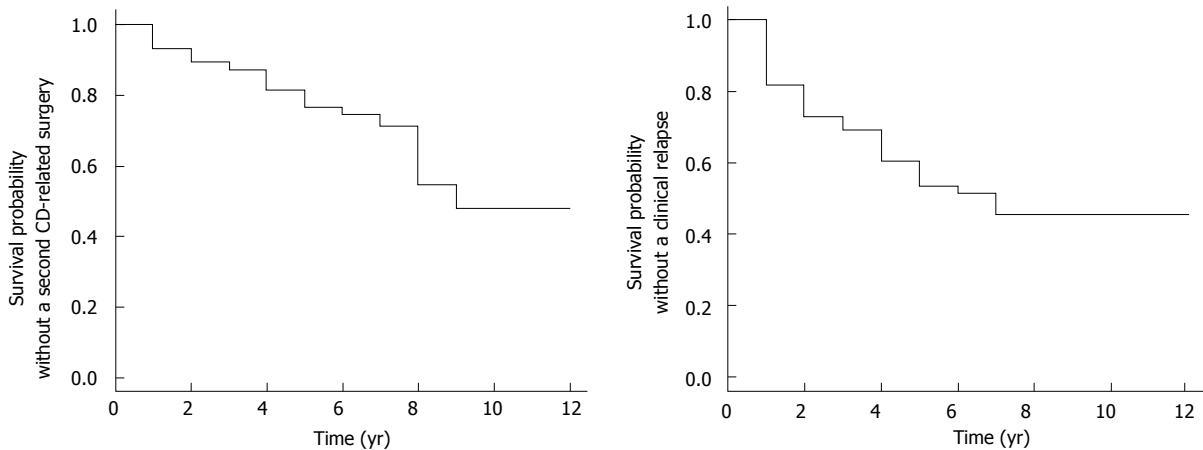


Figure 2 Shows the survival probability without a second Crohn's disease-related surgery and the probability without clinical recurrence with the Kaplan-Meier method. CD: Crohn's disease.

**Table 2** Inflammatory cell count of histopathological findings ( $n = 104$ )

	Median	IQR, 25 <sup>th</sup> to 75 <sup>th</sup>
Myenteric plexus		
Eosinophils	0	0-1
Lymphocytes	2	1-4
Neutrophils	0	0-0
Plasmocytes	2	1-3
Mastocytes	0	0-0
Submucosal plexus		
Eosinophils	0	0-0
Lymphocytes	2	1-3
Neutrophils	0	0-0
Plasmocytes	1	0-3
Mastocytes	0	0-0

in proximal resection margins is a predictor of early postoperative clinical recurrence. Aude *et al*<sup>[12]</sup> revealed that submucosal plexitis of  $> 0$  eosinophils and/or  $> 6$  lymphocytes in proximal resection margins and early surgical revision after the first ileocecal resection are predictive of a second surgery in CD; Lemmens *et al*<sup>[13]</sup> found that submucosal lymphocytic plexitis in the proximal surgical margin was significantly associated with a higher risk of endoscopic recurrence after ileocolonic resection. All these studies found that plexitis is more frequent in the proximal resection margin, but data on the prognostic value of histological factors in postoperative CD recurrence are conflicting. This is the reason why we used a comprehensive approach by analyzing all inflammatory cell types in both submucosal and myenteric plexuses in proximal resection margins. Data of the most severely inflamed plexus were involved in the study.

Studies found myenteric plexitis in 42.5%-69.7%-88% of proximal surgical margins<sup>[8-10]</sup>. We could evaluate myenteric and submucosal plexitis of different severity in every sample, in accordance with Aude *et al*<sup>[12]</sup>, while the rate of typical CD-lesions was low (5.7%) in proximal resection margins. A higher lymphocyte cell count in the submucosal plexus was a risk factor for

surgical or clinical relapse ( $P = 0.050$ ), while moderate submucosal plexitis reduced the risk of a second surgery by 85.4% compared to severe submucosal plexitis ( $P = 0.020$ ), which is in accordance with other studies. No association was revealed between postoperative recurrence and the presence of myenteric plexitis.

We found no relationship between the presence of granulomas and clinical or surgical recurrence; however, we could find granulomas only in approximately half of the samples. A few studies found a positive association between the presence of granulomas and the likelihood of recurrence or a more aggressive disease process<sup>[16-18]</sup>, while other studies suggested the opposite<sup>[19,20]</sup>. It has also been reported that the need for immunosuppressive therapy and surgical interventions were significantly higher in patients with granulomas.

We found no association between postoperative recurrence and neural hypertrophy. Ferrante *et al*<sup>[8]</sup> found that patients who had both neural hypertrophy in the terminal ileum and myenteric plexitis in the proximal resection margin had a tendency to develop a higher endoscopic recurrence rate compared with patients who only had myenteric plexitis.

Postoperative recurrence occurred in 61.5% of patients with a median duration of 2 years between the index surgery and relapse; of them 39.1% had surgical recurrence. Ninety-two point two percent of the recurrences occurred within five years. Our data are similar to previously published data: Surgical recurrence was reported in 11%-32% of patients at 5 years<sup>[21]</sup>. Mean disease duration for endoscopic relapse on the basis of the Rutgeerts score was 2.70 years. Postoperative recurrence was divided into two groups on the basis of the paper of Ng *et al*<sup>[10]</sup>. Clinical recurrence was defined as the presence of CD-related symptoms associated with radiologic or endoscopic findings considered severe enough to change the current therapy (requires steroid treatment or an increase in existing treatment). Surgical recurrence was defined as a need for further operation if the

disease was refractory to medical treatment or new complications developed.

No association was revealed between postoperative recurrence and preoperative or postoperative prophylactic treatment. Forty-three point two percent of patients were on 5-aminosalicylate, 20% on corticosteroid, 68.3% on immunomodulant, and 4% on anti-TNF- $\alpha$  postoperative treatment. 5-aminosalicylic acid (5-ASA) has been extensively studied in the postoperative management of CD. Studies showed that the early administration of oral mesalazine following surgery is effective in preventing postoperative endoscopic recurrence in CD over a 2-year period<sup>[22]</sup> and it can also decrease the rate and severity of endoscopic recurrences<sup>[23]</sup>. In a meta-analysis, 5-ASA significantly reduced the risk of symptomatic relapse<sup>[24]</sup>. In a prospective, open-label randomized study, azathioprine was more effective than mesalazine in preventing clinical relapse in patients with previous intestinal resections<sup>[25]</sup>. These studies suggest that 5-ASA is safe in postoperative CD prophylaxis, even if it seems to provide only a small reduction in clinical and endoscopic recurrence<sup>[26]</sup>.

Our study has certain limitations including its retrospective nature, although it is one of the largest series looking at myenteric and submucosal plexitis. As the course of CD may differ from one patient to another, many studies have looked for potential predictors of CD recurrence as these can modify the intensity of surveillance and the type of medical therapy.

In conclusion, the presence of severe submucosal plexitis with lymphocytes in the proximal resection margin is more likely to result in postoperative relapse. Postoperative assessment of plexitis could be performed routinely by every pathologist in every center as proximal resection margins are systematically analyzed. This requires no special immunostaining. Histological analysis of the proximal resection margin may be useful when making a decision on early postoperative treatment without a postoperative follow-up colonoscopy, thus possibly modifying the natural course of CD. However, further studies with a prospective design and a longer follow-up period are needed.

## COMMENTS

### Background

Crohn's disease (CD) can affect the entire gastrointestinal tract, but the most commonly affected sites are the ileum and the ascending colon. More than 70% of all patients with CD require surgery in the course of their disease, which is not curative; the disease recurs in most cases. Currently, there are no reliable tools to predict when and in whom the disease will recur.

### Research frontiers

In the last decade, particular attention was paid to histological features to assess the risk of postoperative relapse (POR). Inflammatory changes in the enteric nervous system (myenteric and submucosal plexus) of the resection margins are probably the most promising factors.

### Innovations and breakthroughs

The authors confirmed the significant value of investigating the presence of

submucosal plexitis in the proximal resection margin of ileo-colonic resection specimens; the severity of submucosal plexitis (higher lymphocyte cell count in the submucosal plexus) was a risk factor for surgical and clinical POR of CD. These investigations can be performed by analyzing proximal resection margins with routine staining.

### Applications

All available data, including ours, suggest that lymphocyte cell count plays the most important role in predicting the POR of CD. Routine histological analysis of the proximal resection margin for submucosal plexitis can be useful to stratify patients according to their risk to decide the need for early postoperative treatment.

### Terminology

POR was defined as the reappearance of lesions after complete surgical resection. Clinical recurrence was defined as the presence of CD-related symptoms associated with radiologic or endoscopic findings, considered severe enough to change the therapy (requires steroid treatment or an increase in existing treatment). Surgical recurrence was defined as a need for further operation.

### Peer-review

In the article, the clinical and pathological data of 140 postoperative patients with CD were analyzed, so as to study the risk factors of postoperative recurrence of CD.

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P- Reviewer: Zhong YQ S- Editor: Qi Y L- Editor: A  
E- Editor: Wu HL





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