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Retrospective Study

Predictors for malignant potential and deep submucosal invasion in colorectal laterally spreading tumors

Hao XW *et al*. Risk assessments for colorectal LST subtypes

Abstract

BACKGROUND

Colorectal laterally spreading tumors (LSTs) with malignant potential require *en bloc* resection by endoscopic submucosal dissection (ESD), but lesions with deep submucosal invasion (SMI) are endoscopically unresectable.

AIM

To investigate the factors associated with high-grade dysplasia (HGD)/carcinoma and deep SMI in colorectal LSTs.

METHODS

The endoscopic and histological results of consecutive patients who underwent ESD for colorectal LSTs in our hospital from June 2013 to March 2019 were retrospectively analyzed. The characteristics of LST subtypes were compared. Risk factors for HGD/carcinoma and deep SMI (invasion depth $\geq$ 1000 µm) were determined using multivariate logistic regression.

RESULTS

A total of 323 patients with 341 colorectal LSTs were enrolled. Among the four subtypes, non-granular pseudodepressed (NG-PD) LSTs (85.5%) had the highest rate of HGD/carcinoma, followed by the granular nodular mixed (G-NM) (77.0%), granular homogenous (29.5%), and non-granular flat elevated (24.2%) subtypes. Deep SMI occurred commonly in NG-PD LSTs (12.9%). In the adjusted multivariate analysis, NG-PD [odds ratio (OR) = 16.8, P < 0.001) and G-NM (OR = 7.8, P < 0.001) subtypes, size $\geq$ 2 cm (OR = 2.2, P = 0.005), and positive non-lifting sign (OR = 3.3, P = 0.024) were independently associated with HGD/carcinoma. The NG-PD subtype (OR = 13.3, P < 0.001) and rectosigmoid location (OR = 8.7, P = 0.007) were independent risk factors for deep SMI.

CONCLUSION

Because of their increased risk for malignancy, it is highly recommended that NG-PD and G-NM LSTs are removed *en bloc* through ESD. Given their substantial risk for deep SMI, surgery needs to be considered for NG-PD LSTs located in the rectosigmoid, especially those with positive non-lifting signs.

Key Words: Colorectal laterally spreading tumors; Subtype; Deep submucosal invasion; Endoscopic submucosal dissection

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Core Tip: The incidence of laterally spreading tumors (LSTs) is continually increasing; however, the optimal strategy for resecting large colorectal LSTs is still under debate. Endoscopic submucosal dissection (ESD) and surgery each have their pros and cons. In this work, we demonstrated that it is highly recommend that non-granular pseudodepressed (NG-PD) and granular nodular mixed LSTs are removed through ESD, and given their substantial risk for deep submucosal invasion, surgery needs to be considered in NG-PD LSTs located in the rectosigmoid, especially those with positive non-lifting signs.

INTRODUCTION

Colorectal laterally spreading tumors (LSTs) are lesions 10 mm or greater in diameter characterized by lateral and circumferential extension with a low vertical axis along the colorectal wall[1]. LSTs are easily missed during colonoscopy and constitute an important contributor to post-colonoscopy colorectal cancer[2,3]. LSTs are morphologically categorized into the granular type (LST-G), which has a nodular surface, and non-granular type (LST-NG), which has a smooth surface[1,3]. The LST-G

type can be divided into a granular nodular mixed subtype (G-NM) and homogeneous subtype (G-H), according to the existence of irregular and large nodules. The LST-NG type can be further subclassified into the non-granular pseudodepressed (NG-PD), presenting a gently sloping central depression, and the flat elevated subtype (NG-FE), characterized by a flat and smooth surface[1,3]. Although some studies have reported that the four subtypes of LSTs have varying clinicopathological features, previous analyses have not been adjusted for confounding factors, and the risk of deep submucosal invasion (SMI) and endoscopic resectability have not been evaluated[4-7].

Endoscopic resection is widely used to treat colorectal neoplasms with a negligible risk of lymph node metastasis. *En bloc* resection is indicated for early colorectal cancer[8]. In Eastern countries, early colorectal cancer includes carcinoma *in situ*, tumors with a SMI depth less than 1000 μm (superficial SMI or T1a), and tumors with a SMI depth greater than 1000 μm (deep SMI or T1b)[9]. Given their high risk of lymph node metastasis, lesions with deep SMI are endoscopically unresectable and require surgery[10]. Endoscopic methods for achieving *en bloc* resection includes endoscopic mucosal resection (EMR) (for lesions < 2 cm) and endoscopic submucosal dissection (ESD) (for larger lesions)[9,11]. ESD is also indicated when the likelihood of superficial SMI is high[8].

LSTs are good candidates for endoscopic resection owing to their low overall rate of SMI[3]. However, each morphologic subtype of LSTs is associated with a distinct risk of SMI. Tumor size is known to have various additional effects on SMI among the four subtypes[1,3]. Therefore, morphologic subtype is the initial consideration when selecting treatments for LSTs. Risk stratification of carcinogenesis and invasiveness according to morphologic subtype in combination with other factors remains to be fully elucidated. The aim of our study was to determine the predictors for carcinoma, invasion depth and endoscopically unresectable lesions for colorectal LSTs and to perform risk assessments for each morphologic subtype.

MATERIALS AND METHODS

The endoscopic and histological results of consecutive patients who underwent ESD for colorectal LSTs at Beijing Friendship Hospital between June 2013 and March 2019 were retrospectively reviewed. In our centre, ESD is the standard treatment for LSTs. Patients with familial adenomatous polyposis or inflammatory bowel disease were excluded. This study was approved by the Ethics Committee of Beijing Friendship Hospital, Capital Medical University.

Because of the retrospective nature of this study, decisions regarding study inclusion were made by two endoscopists after reviewing all colonoscopy findings. LSTs were defined as lesions ≥ 1 cm in diameter that extended laterally and circumferentially along the colorectal wall rather than perpendicular to it. All lesions were reviewed and classified by two endoscopists (HYS and YX) using Kudo's classification. All lesions were subclassified as follows: G-NM subtype, which had a granular surface with giant nodules; G-H subtype, which had an even more granular surface; NG-PD subtype, characterized by a mixture of elevated and depressed flat regions in each lesion; or NG-FE subtype, exhibited an elevated flat and smooth surface[1].

In pathological evaluations, high-grade dysplasia was regarded as carcinoma *in situ*, according to the Japanese classification[9]. Carcinomas included carcinoma *in situ* and tumors with SMI. Lesions with a SMI depth ≥ 1000 μm were defined as having deep SMI. If the pathologic diagnosis was adenocarcinoma, in addition to invasion depth, the degree of carcinoma differentiation and tumor budding, as well as the presence of lymphovascular invasion, were evaluated. Endoscopically resectable lesions were defined as those without any of the following features: Poorly differentiated, deep SMI invasion, lymphovascular invasion, and high-grade tumor budding. Demographic and clinicopathologic data, including sex, age, LST subtype (G-NM, G-H, NG-PD, NG-FE), location, size, and pathological features, were recorded.

Statistical analysis
Categorical variables were analysed using the χ^2 test or Fisher's exact test where appropriate. Continuous data were analysed using Student's *t* test if they were

normally distributed or the Mann-Whitney U test if they followed a skewed distribution. Variables found to be significant in univariate analysis were entered into multivariate logistic regression to determine the independent factors for carcinoma, SMI, deep SMI and endoscopically unresectable lesions. Two-sided P values < 0.05 were considered significant. Statistical analyses were performed with IBM SPSS Statistics 20.0.

RESULTS

Characteristics of the patients and lesions

A total of 323 patients with 341 LSTs were included. The mean age was 64.7 years (range 26-88 years), and 56.0% were men. The median size of the lesions was 20 (range 10-100) mm. Most (52.5%) LSTs were located in the right colon, and 41.1% of the lesions were located in the rectosigmoid region. G-NM was the predominant subtype (44.6%). Up to 59.8% of the LSTs were carcinoma, among which 84.4% (173/204) were carcinoma in situ. The proportions of SMI, deep SMI and endoscopic unresectable lesions were 9.1%, 3.5% and 4.7%, respectively (Table 1).

Comparisons among LST subtypes

Table 2 shows that the four LST subtypes had distinct clinicopathological features. G-NM [median 25 mm, interquartile range (IQR) 18-40 mm] was the largest subtype (vs any of the other three subtypes, $P < 0.001$), and NG-FE (median 15 mm, IQR 13-19 mm) was the smallest subtype (vs NG-PD subtype, $P = 0.009$; vs G-H subtype, $P = 0.002$). A higher percentage of the G-H (68.9%), NG-PD (51.6%) and NG-FE (66.7%) subtypes were located in the right colon, whereas the majority (56.6%) of the G-NM LSTs were located in the rectosigmoid region. The carcinoma rates of the G-NM and NG-PD LSTs were 77.0% and 85.5%, respectively, and both were significantly higher than those of the G-H (vs 29.5%, $P < 0.001$) and NG-FE (vs 24.2%, $P < 0.001$) LSTs. Of the tumors that were carcinoma, carcinoma in situ accounted for 90.6% (106/117), 100% (18/18), 66.0% (35/53) and 87.5% (14/16) of G-NM, G-H, NG-PD and NG-FE lesions, respectively.

Among the four subtypes, the NG-PD subtype had the highest risk for having SMI (*vs* any of the other three subtypes, *P* < 0.001), having deep SMI (12.9% *vs* 2.6% of the G-NM subtype, *P* = 0.004; 12.9% *vs* 0% of the G-H/NG-FE subtype, *P* = 0.002), and being endoscopically unresectable (14.5% *vs* 4.6% of the G-NM subtype, *P* = 0.016; 14.5% *vs* 0% of the G-H/NG-FE subtype, *P* = 0.001).

Predictors for carcinoma

As shown in Table 3, in univariate analysis, the G-NM subtype, NG-PD subtype, rectosigmoid location, size ≥ 2 cm, and positive non-lifting sign were associated with a higher risk for carcinoma. In the adjusted multivariate analysis, the G-NM [odds ratio (OR) = 7.8, 95% confidence interval (CI): 3.8-16.1, *P* < 0.001) subtype, NG-PD subtype (OR = 16.8, 95%CI: 6.5-43.5, *P* < 0.001), size ≥ 2 cm (OR = 2.2, 95%CI: 1.3-3.9, *P* = 0.005), and positive non-lifting sign (OR = 3.3, 95%CI: 1.2-9.2, *P* = 0.024) remained independent predictors. We further performed subgroup analysis according to LST subtype. For the G-NM subtype, a larger size was associated with a higher risk of carcinoma (85.1% of lesions ≥ 3 cm *vs* 70.6% of those < 3 cm, *P* = 0.035). Almost all (96.0%) of the NG-PD lesions located in the rectosigmoid region were carcinoma.

Predictors for SMI and deep SMI

The NG-PD subtype (OR = 9.1, 95%CI: 3.9-21.0, *P* < 0.001), rectosigmoid location (OR = 3.2, 95%CI: 1.4-7.6, *P* = 0.007), and positive non-lifting sign (OR = 3.0, 95%CI: 1.2-8.0, *P* = 0.023) were independent predictive factors for SMI in the adjusted multivariate analysis (Table 4). The NG-PD subtype, rectosigmoid location and positive non-lifting sign were associated with an increased risk for deep SMI. In the adjusted multivariate analysis, the NG-PD subtype (OR = 13.3, 95%CI: 3.7-47.9, *P* < 0.001) and rectosigmoid location (OR = 8.7, 95%CI: 1.8-42.3, *P* = 0.007) were independent predictors for deep SMI (Table 4).

In the subgroup analysis by LST subtype, for the G-NM subtype, lesions located in the rectum were more likely to have SMI than those located in the colon (13.8% *vs* 2.3%,

P = 0.009). None of the G-H lesions in our study invaded the submucosal layer. For the NG-PD subtype, 61.5% of LSTs with a positive non-lifting sign (*vs* 22.7% of those without a positive non-lifting sign, *P* = 0.015) had SMI. Deep SMI occurred in 44.4% of NG-PD lesions with a positive non-lifting sign (*vs* 9.3% of lesions without a non-lifting sign, *P* = 0.023) and 30.4% of those located in the rectosigmoid region (*vs* 3.0% of lesions located proximal to the sigmoid colon, *P* = 0.006). Kudo's pit pattern type V (60.0% *vs* 0% of those with type I-IV pit patterns, *P* = 0.027) and JNET type 2B/3 (75.0% *vs* 0% of those with JNET type 1/2A, *P* = 0.033) were associated with a significantly higher risk for deep SMI. For NG-FE lesions, a rectosigmoid location was associated with a higher risk of SMI (15.4% *vs* 0%, *P* = 0.036). None of the NG-FE LSTs in our study invaded the deep submucosal layer.

Predictors for endoscopically unresectable lesions
The NG-PD subtype (OR = 7.1, 95%CI: 2.3-22.0, *P* = 0.001), rectosigmoid location (OR = 10.5, 95%CI: 2.2-49.0, *P* = 0.003), and positive non-lifting sign (OR = 3.5, 95%CI: 1.0-12.0, *P* = 0.045) were independent predictors for endoscopically unresectable lesions (Table 5). For the NG-PD subtype, 33.3% of the lesions in the rectosigmoid region (*vs* 3.0% of those located proximal to the sigmoid colon, *P* = 0.003) and 50.0% of the lesions with positive non-lifting signs (*vs* 9.3% of those without non-lifting signs, *P* = 0.008) were endoscopically unresectable. The risk for being endoscopically unresectable was low in G-NM LSTs. All of the G-H or NG-FE LSTs in our study were endoscopically resectable.

DISCUSSION

Our study revealed that the G-NM subtype, NG-PD subtype, size ≥ 2 cm and positive non-lifting sign were independent predictors for carcinoma. The NG-PD subtype, rectosigmoid location and positive non-lifting sign were independently associated with SMI and endoscopically unresectable lesions. We comprehensively compared the clinicopathological characteristics among the four subtypes of LSTs. G-NM lesions had the largest tumor size among the four subtypes and most commonly occurred in the

rectosigmoid region. Although a substantial proportion of carcinomas (77%) were found among G-NM LSTs, over 90% of the carcinomas were carcinomas *in situ*. Approximately 30% of the G-H LSTs were carcinomas, and all were carcinoma *in situ*. The NG-PD subtype was associated with the highest risks for being malignant (86%), having SMI (29%), having deep invasion (12.9%) and being endoscopically unresectable (16%) among the four subtypes. NG-FE LSTs had the smallest tumor size and a malignancy rate of approximately 25%. None of the malignant lesions considered the NG-FE subtype invaded the deep submucosal layer.

Large non-pedunculated colorectal lesions are traditionally managed by surgical resection[12]. Over the past decade, with the evolution of endoscopic techniques, endoscopic resection has become the first-line therapy for colorectal tumors without deep invasion[13,14]. Compared to surgery, endoscopic resection is associated with significantly lower rates of complications and a much quicker recovery[15-17]. Long-term outcomes including recurrence and survival rates are comparable between endoscopic and surgical treatment[8,18]. Furthermore, endoscopic resection has been shown to be more cost-effective than surgery for the management of superficial colorectal neoplasms[19,20]. *En bloc* resection is indicated for carcinomatous lesions because of its superiority over piecemeal resection in reducing recurrence rates[8,9,23-25]. If superficial SMI is suspected, ESD is recommended to provide complete resection for accurate histological staging and reduced recurrence[8]. LSTs are good candidates for endoscopic resection due to their low risk for deep invasion[21,22]. In our study, approximately 60% of the LSTs were carcinomas, and the majority (approximately 85%) were carcinoma *in situ*.

An accurate preoperative diagnosis to identify carcinoma and determine the depth of invasion is essential for selecting an appropriate therapeutic strategy. We investigated independent factors for carcinoma, SMI, deep SMI and endoscopically unresectable lesions. The G-NM subtype, NG-PD subtype, large lesion size and positive non-lifting sign were predictors for carcinoma in our study, which was in line with previous studies[5-8,27]. For SMI, we found that the NG-PD subtype, positive non-lifting sign and

rectosigmoid location were predictive factors. Although the NG-PD subtype and positive non-lifting sign are well acknowledged markers for SMI[5-8,21,27], the rectosigmoid location is a newly identified predictor for SMI. A large prospective multicentre study from Australia reported that rectosigmoid location was an independent factor for SMI, and the significance of this parameter remained among lesions without obvious high-risk features for SMI (type V Kudo pit pattern and Paris 0-IIc components)[28]. Rectal lesions accounted for a greater proportion of lesions with SMI in a few previous studies[4,29]. This may suggest different pathways of carcinogenesis between distal and proximal LSTs. Endoscopic resection of lesions located in the distal colorectum, particularly in the rectum, is technically easier and is associated with a lower risk of complications than that of lesions located in the proximal colon[30]. Endoscopically assessing the depth of SMI is extremely important in deciding whether to perform ESD or refer the patient to surgery. However, research investigating predictors for deep SMI is limited. Yamada et al[31] reported that a depressed component was strongly associated with deep SMI both in LST-G and LST-NG. In our study, the NG-PD subtype and rectosigmoid location were also independent factors for deep SMI. We also confirmed that NG-PD, rectosigmoid location and positive non-lifting sign were independent factors for endoscopic unresectability. In addition to deep SMI, factors including lymphovascular invasion also determine endoscopic resectability. There were 4 cases of lymphovascular invasion on pathological examination without deep SMI in our study. The other risk factors for being endoscopically unresectable are very large lesion size (size > 40 mm), special location (lesions involving the ileocaecal valve, appendix, diverticulum), prior failed attempt at resection or recurrence at site of previous resection, and non-lifting sign after submucosal injection[26].

The risk of carcinoma, invasion depth and endoscopic unrespectability in each LST subtypes was further assessed. G-H LSTs are good candidates for EMR due to their relatively small tumor size and very low risk for SMI. For G-NM lesions, the overall rate of carcinoma was high, and this rate increased with as lesion size increased. A rectal location was associated with a high risk for SMI. Therefore, en bloc resection is desirable

for the G-NM subtype, whereas ESD is preferred for large lesions and those located in the rectum. NG-FE LSTs had a small tumor size and low overall risk for SMI. However, the risk for SMI increased significantly if the lesions were located in the rectosigmoid region, suggesting ESD in such cases. A consensus has been reached that the NG-PD subtype is an indicator for ESD[8,11,32]. The high rate of SMI in our study supported this consensus. However, the NG-PD subtype is also associated with a high risk of being endoscopically unresectable. The decision between performing ESD and referring the patient to surgical treatment should be cautiously considered in this scenario. Our results showed that a rectosigmoid location, positive non-lifting sign and type V Kudo pit pattern were associated with a significantly higher risk for having deep SMI and being endoscopically unresectable. Before treating lesions with these risk features, the endoscopists' experience and patients' preferences should be cautiously considered. Despite improvements in endoscopic diagnosis, the sensitivity of endoscopic techniques for identifying SMI remains unsatisfactory[28]. In recent years, *en bloc* ESD prior to surgery as a total excisional biopsy for early colorectal carcinoma has been introduced in clinical practice[33]. A recent multicentre study on the influence of preoperative ESD on the prognosis of patients with early colorectal carcinomas (T1) found that *en bloc* ESD did not adversely affect the long-term clinical outcomes[34]. As a more cost-effective method than surgery, ESD is a reasonable first option for early colorectal carcinomas without obvious features of deep invasion.

To the best of our knowledge, the present work is one of the largest studies comprehensively comparing the clinicopathological features, including risk of carcinoma, depth of invasion and endoscopic resectability, among the four subtypes of LSTs. With a relatively large number of cases involved, we were able to perform multivariate analyses and determine the independent predictors for carcinoma, SMI, deep SMI and endoscopic unresectability. Subgroup analyses were also conducted to identify distinct risks for the four subtypes of LSTs. We also proposed a treatment strategy for each subtype of LST, according to the risks of carcinoma and deep SMI based on our findings. Additionally, ESD is the standard therapy for LSTs in our centre

and enables accurate pathological evaluation with detailed information on the depth of invasion and other risk factors for lymph node metastasis.

Several limitations of our study should be acknowledged. First, as this was a single-centre retrospective study based on clinical records, regional or institutional bias may exist. Second, because ESD was the commonly used treatment for LSTs in our centre and to allow for accurate histopathological assessment, only lesions that were resected *en bloc* by ESD were included in this study; thus, there were no data on LSTs resected by EMR and surgery. However, the number of these lesions was relatively small. Third, it has previously been reported that magnifying observation (pit pattern diagnosis) and image-enhancement technology (*e.g.,* narrow band imaging) are reliable and effective methods for predicting the depth of tumor invasion; however, due to the inherent limitations of retrospective studies, some lesion records on JNET and Kudo pit pattern type were missing.

CONCLUSION

In conclusion, the clinicopathological characteristics of LSTs varied according to subtypes in terms of size, distribution, malignant potential, depth of invasion and endoscopic resectability. Because of their increased risk for malignancy, it is highly recommended that NG-PD and G-NM LSTs are removed *en bloc* through ESD. Given their substantial risk for deep SMI, surgery needs to be considered in NG-PD subtype LSTs located in the rectosigmoid, especially those with a positive non-lifting sign.

ARTICLE HIGHLIGHTS

Research background

The incidence of laterally spreading tumors (LSTs) is continually increasing; however, the optimal strategy for resecting large colorectal LSTs is still under debate. Endoscopic submucosal dissection (ESD) is associated with a high *en bloc* resection rate, low risk of recurrence and perfect pathological analysis. However, the possibility of a positive postoperative pathological resection margin exists, which would require additional

surgical procedures. Surgery has a high complication rate, high mortality and prolonged hospital stays.

Research motivation

Accurate preoperative assessment based on various risk factors to identify carcinoma and invasion depth is essential for selecting an appropriate therapeutic strategy.

Research objectives

This study aimed to identify the predictors of carcinoma, invasion depth and endoscopically unresectable lesions for colorectal LSTs and to facilitate appropriate preoperative selection.

Research methods

This retrospective study analysed the endoscopic and histological results of consecutive patients who underwent ESD for colorectal LSTs in our hospital during a six-year period. The characteristics of the LSTs were compared by subtypes. Risk factors for high-grade dysplasia (HGD)/carcinoma and deep submucosal invasion (SMI) (invasion depth ≥ 1000 μm) were determined for each morphologic subtype.

Research results

Among the four subtypes, non-granular pseudodepressed (NG-PD) LSTs had the highest rate of HGD/carcinoma and deep SMI (invasion depth ≥ 1000 μm). NG-PD subtype and rectosigmoid location were the independent risk factors for deep SMI in adjusted multivariate analysis.

Research conclusions

We demonstrated that it is highly recommend that NG-PD and granular nodular mixed (G-NM) LSTs are removed through ESD; given their substantial risk for deep SMI,

surgery needs to be considered in NG-PD LSTs located in the rectosigmoid, especially those with positive non-lifting signs.

Research perspectives

A risk score chart, which can determine the risk for carcinoma, invasion depth and endoscopically unresectable lesions for colorectal LSTs should be developed. It can help endoscopists in selective use of different types of endo-resection or to proceed to surgery instead of endoscopy.

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