

Colorectal laterally spreading tumours : subtype evaluation by EUS and BLI and outcome of ESD

W. Yue¹, Y. Liu¹, J. Huang¹, X. Jiang¹, J. Liu¹

(1) Department of Digestive Diseases, Huashan Hospital, Fudan University, 200040 Shanghai, People's Republic of China.

Abstract

Background and study aims : Colorectal laterally spreading tumour (LST) is a specific type of colonic space-occupying lesion unlike other common polypoid lesions. Here, we explored the diagnostic values of endoscopic ultrasonography (EUS) and blue laser image (BLI) in LST subtypes, their relationship with histopathological characteristics and the therapeutic effect of endoscopic submucosal dissection (ESD) for LST.

Patients and methods : A prospective study of 138 patients with LST was conducted. All LSTs were explored for invasion depth and superficial microstructure through EUS and BLI before ESD. Histopathological characteristics of LSTs were demonstrated through pre-operative biopsy and post-operative specimen detection. Finally, the correlations among varied morphologies, manifestations of EUS and BLI, and histopathological characteristics of LSTs were analysed comprehensively. All patients underwent follow-up after ESD.

Results : Nodular-mixed and pseudodepressed subtypes were more likely to invade the submucosa, and BLI revealed a greater proportion of types B and C than the homogeneous or flat-elevated subtypes. These endoscopic features were consistent with and proved by histopathological results. Pathological severity of LST on post-ESD specimen detection was greater than that on pre-ESD biopsy analysis. En bloc R0 resection was achieved in 128 cases, and only two patients suffered recurrence during follow-up.

Conclusions : Pre-operative evaluation through EUS and BLI examination provided clues of possible pathological features and helped guide the treatment of LST. ESD is a safe and effective therapy for colorectal LST. (*Acta gastroenterol. belg.*, 2019, 82, 19-26).

Keywords : laterally spreading tumour, blue laser image, endoscopic ultrasonography, endoscopic submucosal dissection, subtype.

Introduction

Concomitantly with the widespread performance of endoscopy examination and combined chromoendoscopy and magnifying endoscopy in clinical practice, the discovery rate of neoplastic lesions in the colon has been gradually increasing. Colorectal laterally spreading tumour (LST), unlike common colorectal polypoid lesion, is characterized by spreading along the mucosa surface of colon with diameters often greater than 10mm. LST usually invades the mucosal or submucosal layer of the colon and rarely develops towards colonic lumen or muscularis (1). LST has varied potential for malignant transformation depending on pathological subtypes. Therefore, it is important to detect and treat LST in its early stages.

Endoscopic submucosal dissection (ESD) had been regarded the optimum method to cure LST since the lesion can be removed completely for pathological analysis,

providing guidance for further practice and prognosis⁽²⁾. Furthermore, performance of chromoendoscopy, magnifying endoscopy and endoscopic ultrasonography (EUS) prior to ESD can provide information regarding the extension, invasion depth and possible characteristics of LST, thus ensuring integrity and safety of the ESD process. The blue laser image (BLI) technique has characteristics of both chromoendoscopy and magnifying endoscopy and can observe the microvascular pattern and microsurface pattern of digestive tract, estimating potential properties of lesions.

Therefore, in this study, we aimed to investigate the manifestations of various subtypes of LST by EUS and BLI, to analyse the consistency of pre-surgical evaluation and post-surgical pathological results, as well as to assess the outcome of ESD, providing useful suggestions for LST in clinical practice.

Materials and methods

Patients

We conducted a prospective cohort study of one hundred thirty-eight patients presenting with LST from November 2015 to May 2017 in Huashan Hospital affiliated to Fudan University, Shanghai, China. All patients underwent examination with white light endoscopy, endoscopic ultrasonography and blue laser image prior to and following ESD in our endoscopy unit. All patients were given a detailed explanation of the entire surgical process as well as possible complications such as bleeding, perforation and possibility of further surgery depending on pathological results. All patients provided written informed consent. The study was approved by the ethics committee of Huashan Hospital, Fudan University. Patients were excluded from this study if one or more of the following criteria were met : (1) lesion showed negative elevation sign ; (2) severe coagulation dysfunction ; (3) severe cardiovascular or respiratory disease ; and (4) intolerance of anaesthesia.

Correspondence to : Yi Liu, Department of Digestive Diseases, Huashan Hospital, 12# Middle Wulumuqi Road, Shanghai, 200040, People's Republic of China.

E-mail: liuyi8476@163.com

Submission date : 05/12/2017

Acceptance date : 04/09/2018

Acta Gastro-Enterologica Belgica, Vol. LXXXII, January-March 2019

Lesion subtypes

LST was diagnosed under white light endoscopy for flat bulging lesions with diameters over 10mm. All discovered LSTs were classified into two subtypes in terms of morphology: LST-G, with even or uneven nodules or granules on lesion surface; and LST-NG, with smooth surfaces without nodules or granules. LST-Gs were further subcategorized into homogeneous and nodular mixed, and LST-NGs were further subcategorized into flat-elevated and pseudodepressed (3). According to the Paris classification, the homogeneous subtype was characterized as 0-IIa with an evenly granular surface, and the nodular mixed subtype was characterized as 0-IIa or 0-Is with uneven nodules or granule surfaces, respectively. The flat-elevated subtype was defined as 0-IIa with flat smooth surface, while the pseudodepressed subtype was defined as 0-IIa+IIc with regional depression on a smooth surface (4).

Endoscopy examination before ESD

All LSTs discovered by white light endoscopy were further examined by EUS and BLI. The size and depth of lesions were recorded if lesions invaded the mucosal or submucosal layers. BLI results were shown

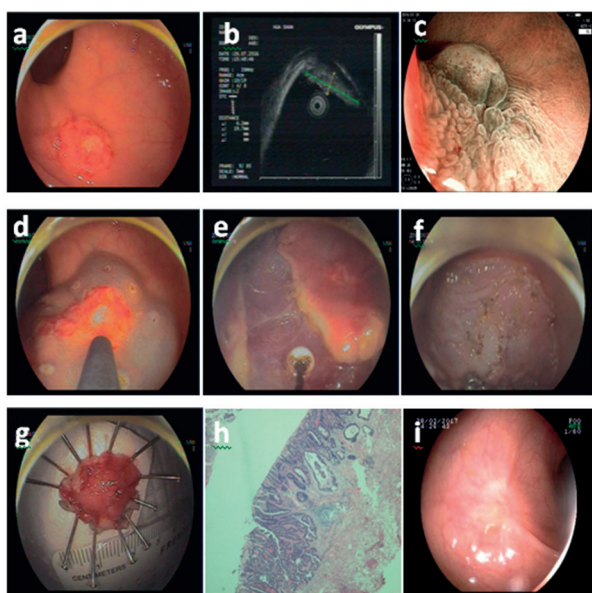


Fig. 1. — ESD procedure of a rectal LST a. one LST of nodular mixed subtype in rectum found by white light endoscopy ; b. the LST was derived from mucosal layer as per EUS observation ; c. the LST was type C as per BLI observation ; d. the boundary of the lesion was marked by APC, and submucosal injection elevated the lesion ; e. the lesion was gradually separated by an IT knife ; f. wound surface after complete dissection of the lesion ; g. the size of the resected specimen was about 20mm*20mm ; h. histological analysis indicated low to high grade intraepithelial neoplasia with local malignant transformation, and no residual tumour at margin or base(40X magnification) ; i. colonoscopy at 6 months after ESD showed scar like manifestation at the original surgical site.

as type A, type B or type C, which were defined as invisible microvascular pattern on surface, regularly reticular microvascular and microsurface pattern or inhomogeneous distribution of microvascular and microsurface pattern, respectively.

ESD procedure

Regular bowel preparation was undertaken 4-5 hours before ESD. Anti-platelet agents or anti-coagulants were discontinued 5-7 days before surgery. Intravenous anaesthesia with propofol was administered with cardiopulmonary monitoring. ESD procedure: the boundary of the lesion was outlined by indicarmine solution, and then argon plasma coagulation (APC) was used to mark the operation scope. A mixed solution of 0.5% indicarmine, 0.01% adrenaline and 100ml glycerol fructose was injected into the submucosal layer to elevate the lesion. A hook knife and IT knife were alternately used to separate the lesion completely. Bleeding during surgery was controlled by electric coagulation or hot biopsy forceps, while the local perforation site was immediately closed with haemostatic clips. After the lesion was resected totally, hot biopsy forceps and haemostatic clips were used to treat the surgical wound to prevent delayed bleeding and perforation. Intravenous antibiotics were given in all cases to prevent secondary infection for 24h under close observation (Fig. 1).

Histopathological examination

Biopsy analysis before ESD was performed in a routine manner. The biopsy site was identified as the most serious part of the LST under BLI observation. The resected specimen after ESD was immediately stretched and fixed in formalin. Histopathological reports included histological type according to the World Health Organization classifications (5), whether the tumour invaded peripheral margin or basal margin of specimen and whether the tumour invaded blood vessels. Low- or high-grade intraepithelial neoplasia (IN) was defined as a lesion with morphological characteristics of low- or high-grade dysplasia or adenocarcinoma that was confined to the glandular epithelium or the lamina propria without submucosal invasion (6). En bloc R0 resection was histologically defined as a tumour removed as a single contact piece with no residual tumorous tissue at the lateral or basal margins.

Follow up after ESD

Patients whose histopathological result indicated undifferentiated cancer or tumour invasion of basal margins or vessels needed further curative surgery. Those without these characteristics underwent follow up by endoscopic examination at 3, 6 and 12 months after ESD. Recurrence was defined as visible tumour at or

adjacent to a previous ESD site. Biopsy and further ESD were performed if recurrence was suspected.

Endoscopic equipment and ancillary devices

A single-operator colonoscope (Olympus, Japan) was used during all examination and surgical procedures. EUS (EU-M2000, Olympus, Japan) and BLI (VP-4450HD, FUJINON, Japan) were used for evaluation of LST before ESD. Other ancillary devices included an APC unit (APC300, ERBE), a Hook knife (KD-620QR, Olympus), an IT knife (KD-611L, Olympus), hot biopsy forceps (HDBF-24-230-S, Cook), haemostatic clips (HX-610-135L, Olympus) and an injection needle (VIN-25, Cook).

Statistical analysis

Continuous variables are presented as the mean±SD, and statistical comparisons between two groups were performed with Student's t-test. Categorical variables are presented as frequency and percentage for description, and statistical comparison was performed with Pearson's chi-square test. The SPSS 17.0 package was used. Differences were considered statistically significant when the p-value was < 0.05.

Results

Overall clinical characteristics of LSTs

Demographic data

As shown in Table 1, a total of 138 patients with a mean age of 65.8±6 years were enrolled, sixty of whom were male. The most common complaints for colonoscopy were medical examination (43.5%) and changed defecation habits (39.1%). The average diameter of LSTs was 19.5±5.5mm. Most LSTs were located in the rectum (30.4%) or sigmoid colon (26.1%). The nodular-mixed subtype (60 cases, 43.5%) accounted for the majority. Most LSTs (71%) were derived from the mucosal layer as per EUS observation. Types B (43.4%) and C (34.8%) accounted for the majority as per BLI observation.

Histological analysis of LSTs

Pre-operative pathological biopsy results showed that tubular adenoma accounted for the majority (47.8%), and approximately 52.2% had varying grades of IN. Post-operative histological results showed that tubular adenoma also accounted for the majority (30.4%), and approximately 56.5% had varying grades of IN, some of which were accompanied by intra-mucosal carcinoma (15.9%) (Table 1).

Follow-up of LSTs after ESD

The en bloc R0 resection rate of all LSTs was 92.7%. Among the exceptional ten cases, piecemeal resection was performed in eight, and high-grade IN was detected

Table 1 — Demographic data and clinical characteristics of LST patients

Age(mean±sd,year)	65.8±6.0 (59-76)
Gender(male/female)	60/78
complaint(n,%)	
abdominal pain	24(17.4)
defecation habit or feces property change	4(39.1)
physical examination	60(43.5)
Diameter of LST(mean±sd, mm)	19.5±5.5(10-30)
Subtypes of LST (n,%)	
granular	84(60.9)
homogeneous	24(17.4)
nodular mixed	60(43.5)
non-granular	54(39.1)
flat-elevated	30(21.7)
pseudodepressed	24(17.4)
Location of LST(n,%)	
rectum	42(30.4)
sigmoid colon	36(26.1)
descending colon	6(4.3)
transverse colon	30(21.7)
ascending colon	18(13.0)
cecum	6(4.3)
EUS feature(n,%)	
mucosal layer	98(71.0)
submucosal layer	40(29.0)
BLI feature(n,%)	
typeA	30(21.7)
typeB	60(43.4)
typeC	48(34.8)
Pre-operative biopsy analysis (n,%)	
inflammatory	18(13.0)
tubular adenoma	66(47.8)
villous adenoma	30(21.7)
villous tubular adenoma	24(17.4)
LGIN/HGIN	72(52.2)
Post-operative pathological result (n,%)	
inflammatory	24(17.4)
tubular adenoma	42(30.4)
villous adenoma	36(26.1)
villous tubular adenoma	36(26.1)
LGIN/HGIN	78(56.5)
intramucosal carcinoma	22(15.9)
Outcome of ESD (%)	
en bloc R0 resection rate	92.7(128/138)
post-operative bleeding rate	2.9(4/138)
perforation rate	1.4(2/138)
recurrence rate	1.4(2/138)

LST : laterally spreading tumour ; EUS : endoscopic ultrasonography ; BLI : blue laser image ; ESD : endoscopic submucosal dissection ; LGIN : low grade intraepithelial neoplasia ; HGIN : high grade intraepithelial neoplasia.

Table 2 — Clinical characteristics of LST subtypes

	LST-G				LST-NG				P
	homogeneous	nodular-mixed	P1	total	flat-elevated	pseudodepressed	P2	total	
Lesion number (n)	24	60		84	30	24		54	
Lesion diameter (mm)	16.2±4.8	17.8±6.0	NS		16.6±4.2	15.7±2.9	NS		NS
Location (n)									
rectum	12	18	NS	30	6	6	NS	12	NS
sigmoid colon	6	18	NS	24	6	6	NS	12	NS
descending colon	-	6	NS	6					0.045
transverse colon		18	0.002	18	12		0.000	12	NS
ascending colon	6		0.000	6	6	6	NS	12	0.01
cecum						6	0.004	6	0.002
EUS feature (n)									
mucosal layer	22	40	0.019	62	26	10	0.000	36	NS
submucosal layer	2	20	0.019	22	4	14	0.000	18	NS
BLI feature (n)									
typeA	6	6	NS	12	18		0.000	18	0.008
typeB	18	24	0.004	42	8	10	NS	18	NS
typeC		30	0.000	30	4	14	0.000	18	NS
Pre-operative biopsy analysis									
inflammatory	2	6	NS	8	6	4	NS	10	NS
tubular adenoma	18	30	0.036	48	12	6	NS	18	0.006
villous adenoma	2	8	NS	10	10	10	NS	20	0.000
villous tubular adenoma	2	16	0.035	18	2	4	NS	6	NS
LGIN/HGIN	6	36	0.004	42	10	20	0.000	30	NS
Post-operative pathological result									
inflammatory	12		0.000	12	6	6	NS	12	NS
tubular adenoma	12	8	0.000	20	10	12	NS	22	NS
villous adenoma		24	0.000	24	6	6	NS	12	NS
villous tubular adenoma		28	0.000	28	8		0.006	8	0.016
LGIN/HGIN	8	42	0.002	50	12	16	NS	28	NS
intramucosal carcinoma		16	0.005	16		6	0.004	6	NS
Outcome of ESD									
en bloc R0 resection	24/24	54/60	NS	78/84	28/30	22/24	NS	50/54	NS
post-operative bleeding	-	2/60	NS	2/84	-	2/24	NS	2/54	NS
perforation	-	-	-	0/84	-	2/24	NS	2/54	NS
recurrence	-	2/60	NS	2/84	-	-	-	0/54	NS

LST : laterally spreading tumour ; EUS : endoscopic ultrasonography ; BLI : blue laser image ; ESD : endoscopic submucosal dissection ; LGIN : low grade intraepithelial neoplasia ; HGIN : high grade intraepithelial neoplasia ; P1 : comparison of homogeneous and nodular-mixed ; P2 : comparison of flat-elevated and pseudodepressed ; P : comparison of LST-G and LST-NG.

at basal margins in two. Delayed bleeding occurred in four patients with small amounts of haemorrhage that was controlled with intravenous haemostatic drugs. Local perforation occurred during surgery in two patients and was treated immediately by haemostatic clips. No infection or acute abdominal pain occurred due to use of antibiotics. There was no delayed perforation in any patient. Two patients (as mentioned above) with high-grade IN at the basal margin refused surgery, and

recurrence was considered when polypoid proliferation was found adjacent to former wound scars at the 6-month and 12-month follow-ups. Therefore, secondary ESD was performed, and no further abnormal lesion was detected 3 months later. The remaining 136 patients underwent colonoscopy every 3 months after ESD, and no recurrent lesions were discovered during the follow-up period of three months to eighteen months (Table 1).

Clinical characteristics of the subtypes of LSTs

Demographic data

There were no significant differences in lesion diameter between the LST-G and LST-NG groups nor among their subtypes. Homogeneous and nodular-mixed were mostly located in the rectum and sigmoid colon. Flat-elevated types were mostly seen in the transverse colon, while pseudodepressed lesions were distributed throughout the colon (Table 2).

EUS and BLI features of LST subtypes

Under EUS observation, homogeneous, nodular-mixed and flat-elevated subtypes mainly invaded the mucosal layer, while pseudodepressed mainly invaded the submucosal layer, indicating that pseudodepressed types were more likely to invade the deep layer. As per BLI observation, type B accounted for the majority in homogeneous types without any of type C, while type B and type C accounted for the majority in the nodular-mixed subtype ($p < 0.01$), implying that the latter was more severe than the former. Meanwhile, type A was in the majority among flat-elevated subtypes, while types C and B were in the majority among pseudodepressed subtypes without any of type A ($p < 0.01$), also implying that the latter was more severe than the former. Overall, there was no significant difference in BLI features between LST-NG and LST-G (Table 2, Fig. 2).

Histological features of LST subtypes

Pre-operative biopsy results showed that tubular adenoma accounted for the majority of homogeneous and nodular-mixed subtypes, and the proportion of concomitant IN was higher in the latter ($p < 0.01$). Meanwhile, tubular adenoma and villous adenoma accounted for the majority of flat-elevated and pseudodepressed subtypes, and the proportion of concomitant IN was also higher in the latter ($p < 0.01$). This result indicated that the nodular-mixed and pseudodepressed types were more severe than the homogeneous and flat-elevated types. Furthermore, post-operative histological assessment showed that the nodular-mixed and pseudodepressed subtypes, both accompanied by a higher incidence of intra-mucosal carcinoma, were more severe than the homogeneous and flat-elevated subtypes ($p < 0.01$). There were no significant differences in terms of overall pathological features between LST-NG and LST-G (Table 2, Fig. 2).

Post-ESD follow-up of LST subtypes

En bloc R0 resection was performed in all patients with homogeneous subtypes without any complications. Six patients with the nodular-mixed subtype did not undergo en bloc R0 resection, among which the two who were found to have high-grade IN at the basal margin

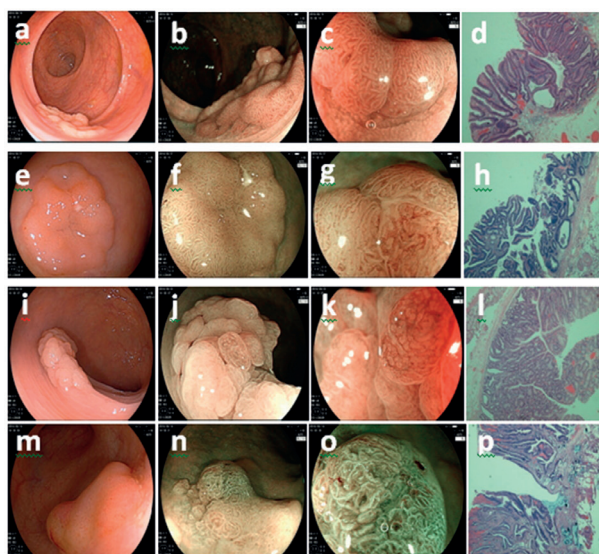


Fig. 2. — Characteristics of varied forms of LSTs in terms of white light endoscopy (a, e, i, m), BLI (b, c, f, g, j, k, n, o) and histopathological examination (d, h, l, p, 40X magnification) a-d. one LST of homogeneous subtype. BLI showed type B feature and histopathological result was tubular adenoma with low grade intraepithelial neoplasia and focal high grade intraepithelial neoplasia ; e-h. one LST of pseudodepressed subtype. BLI showed main type B with local type C1 feature and histopathological result was villous tubular adenoma with low grade intraepithelial neoplasia ; i-l. one LST of nodular mixed subtype. BLI showed type C2 feature and histopathological result was tubular adenoma with low grade intraepithelial neoplasia ; m-p. one LST of flat-elevated subtype. BLI showed type C1 feature and histopathological result was high grade intraepithelial neoplasia and local malignant transformation without residual tumour at margin.

underwent secondary ESD due to recurrence at the 6-month and 12-month follow-ups. All but two patients with the flat-elevated subtype underwent en bloc R0 resection without any post-operative complications. Two patients with pseudodepressed subtypes did not undergo en bloc R0 resection, and acute perforation occurred in two cases. Four patients with delayed bleeding had the nodular-mixed or pseudodepressed subtypes (Table 2).

Correlation analysis of EUS features and histopathological characteristics

EUS provides information regarding invasion depth of LST. We next investigated the relationship between LST depth and pathological findings. As shown in Figure 3, in each LST subtype, the proportion of accompanying IN was higher in those invading the submucosa than in those invading the mucosa ($p < 0.05$). Similar results were obtained for the proportion of accompanying intramucosal carcinomas in the nodular-mixed and pseudodepressed subtypes. This implied that LST involving the submucosa more easily tended towards carcinogenesis and thus needed complete dissection during ESD.

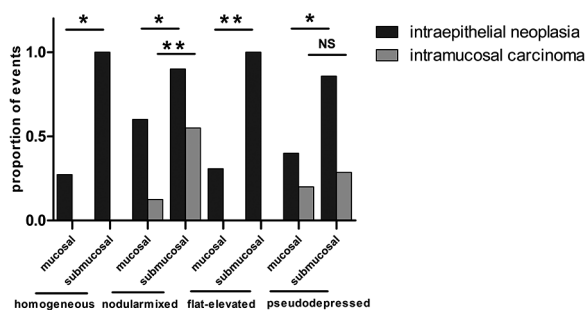


Fig. 3. — Correlation analysis of EUS features and histopathological characteristics. ** $p < 0.01$, * $p < 0.05$, NS=no significant.

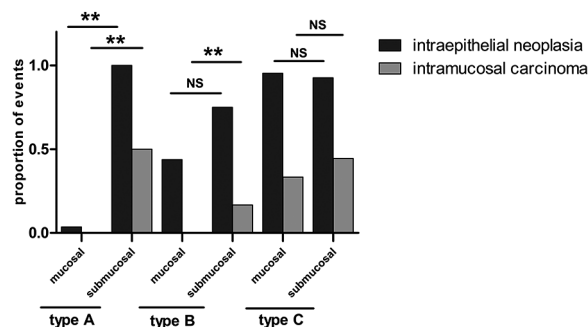


Fig. 5. — Added value of EUS to BLI in prediction of histopathological characteristics. ** $p < 0.01$, NS=no significant.

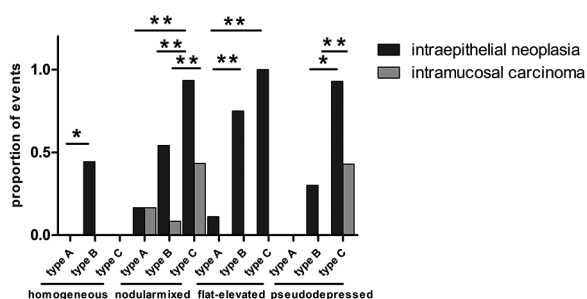


Fig. 4. — Correlation analysis of BLI features and histopathological characteristics. ** $p < 0.01$, * $p < 0.05$.

Correlation analysis of BLI features and histopathological characteristics

BLI provides information regarding the superficial microstructure of LST; therefore, we investigated the relationship between BLI description and pathological findings. As shown in Figure 4, in each LST subtype, the proportion of accompanying IN findings was higher in those of types B or C than in those of type A ($p < 0.05$). Similar results were obtained for the proportion of accompanying intramucosal carcinoma in the nodular-mixed and pseudodepressed subtypes ($p < 0.01$). This implied that the pathological severity of LST accorded with BLI features, and thus, careful surgery was especially needed for LSTs of type C during ESD to prevent residual tumour.

Added value of EUS to BLI in prediction of histopathological characteristics

Because we proved the role of EUS and BLI in evaluating the nature of LST, we further investigated the added value of EUS to BLI for such predictions. As shown in Figure 5, the proportion of accompanying IN and intramucosal carcinoma was higher in those invading the submucosa than in those invading the mucosa in LSTs of types A and B ($p < 0.01$). However, there was no similar finding in LSTs of type C. This implied that EUS provided more information regarding LST characteristics in types A and B.

Discussion

Colorectal LST is a special type of neoplastic lesion in the colon whose growth characteristics are quite different from those of other common colonic lesions that grow towards the colonic lumen or wall (1). LST usually spreads along the surface of the bowel wall and possesses a malignant tendency. Therefore, early treatment is needed to prevent it from undergoing malignant transformation. It has been reported that the local lymph node metastasis rate of LST is rather low; accordingly, endoscopic therapy is a reasonable method for LST (7).

It was worth noting that the average age of our 138 LST patients was above fifty, and most patients were diagnosed with LST when undergoing routine colonoscopy without specific symptoms. Hence, LST might develop with concealed manifestations, and more attention should be paid during routine colonoscopy. We found that LSTs were mostly found in the distal colon, including the rectum and sigmoid colon, a finding that differed from those of a Japanese study (8). Due to its specific characteristics, LST is rather difficult to differentiate from normal mucosa under white light endoscopy. However, chromoendoscopy and magnifying endoscopy are helpful to detect superficial neoplastic lesions such as LST (9). In our study, we performed EUS and BLI on LSTs before ESD in order to evaluate the scope and nature of LSTs, offering guidance for LST treatment.

In our study, LST-G outnumbered LST-NG, and the nodular-mixed subtype was most common in LST-G. Among LST-Gs, the nodular-mixed type was more likely than the homogeneous subtype to invade the submucosa, implying that the invasion degree of the nodular-mixed type was higher, which was consistent with the report from Kudo *et al* (10). In addition, among LST-NGs, the pseudodepressed type was more likely than the flat-elevated subtype to invade the submucosa, which was in accordance with previous findings (11). Furthermore, we found that LST involving the submucosa was more likely to have pathological manifestations of IN or

intramucosal carcinoma. Therefore, we believe that thorough dissection is needed for LST of nodular-mixed and pseudodepressed subtype during ESD in order to prevent recurrence from residual neoplastic tissue at basal margins.

Previously, magnifying chromoendoscopy was used to describe the microvascular and microsurface patterns of the digestive tract according to the classic Kudo and Sano classification, which was of certain value to assess the nature of lesions (12,13). BLI is a novel, recently developed endoscopic imaging technique that combines chromoendoscopy and magnifying endoscopy by adjusting spectral bands. BLI is more likely to discover polypoid lesions than common white light imaging (14). BLI, which has high diagnostic sensitivity similar to that of NBI, can predict the depth of invaded lesions (15). In our study, we found that LSTs of types B and C were more likely to have pathological manifestations of IN or intramucosal carcinoma. It was also interesting to find that EUS provided more information regarding possible malignant transformation in LSTs of types A and B but not of type C. The reason might be that type C itself indicated high potential of malignancy, whether involving the submucosa or not, while types A and B had decreased malignant potential. Furthermore, LSTs of the homogeneous type were mainly types A or B rather than type C, whereas LSTs of the nodular-mixed type were mainly type C, suggesting that the latter were more serious than the former. Pre-operative biopsy results showing that the proportion of concomitant IN was higher in the nodular-mixed type than in the homogeneous type supported the BLI analysis. Furthermore, the proportion of types B and C for the pseudodepressed type was substantially higher than that of the flat-elevated type, implying that the former was more serious than the latter. This was also in accordance with the pre-operative biopsy results showing that the proportion of concomitant IN was higher in the former. From these results, we concluded that BLI provided information regarding the properties of LST comparable to those provided by pathological tests. Additionally, post-operative histological assessment basically agreed with pre-operative biopsy results in that the nodular-mixed and pseudodepressed subtypes with higher proportion of IN were more serious than the homogeneous and flat-elevated subtypes. It is remarkable that post-operative pathological results showed that a portion of specimens had features of intramucosal carcinoma that were not detected before ESD. Although sampling error may cause targeted biopsy to fail to reflect the overall nature of LST, the importance of pre-operative biopsy should not be neglected. The biopsy results accompanied with EUS and BLI manifestations can help to determine further therapy, i.e., whether to proceed to endoscopic resection or surgery. Specimen detection after ESD cannot be replaced by pre-operative biopsy since complete acquisition of specimen after ESD for pathological examination provides detailed evidence

to evaluate treatment effect and prognosis of LST.

Treatment methods for LST have long been controversial. There have been reports that LST could be treated by endoscopic mucosal resection (EMR) safely and with rare recurrences (16). However, multi-centre studies have found that EMR had lower en bloc R0 resection rates and higher recurrence rates than ESD, although EMR had a rather low perforation rate (17). In addition, it was reported that the improved EMR method did not reduce recurrences more than standard EMR for treatment of laterally spreading colorectal lesions (18). Furthermore, it has been believed that only LSTs of homogeneous subtype were suitable for EMR treatment and that LSTs of other subtypes were appropriate for ESD treatment since they were more likely to invade the submucosa (19,20). Therefore, in order to achieve high en bloc R0-resection rates with low incidences of residual or recurrences and to allow en bloc examination for the pathologist, in our study, all enrolled LSTs underwent ESD treatment regardless of LST size. However, only LSTs of the homogeneous type achieved total en bloc R0 resection. The en bloc R0 resection rate was relatively low in the nodular-mixed type, among which two had residual lesions at the basal margin and post-operative recurrence, indicating that the nodular-mixed type usually invades deeply; complete resection by ESD rather than EMR is needed to avoid any residual tumour, as reported previously (21). Four patients had wound bleeding after ESD and intra-operative perforation due to deep depression sites, and substantial submucosal fibrotic tissue occurred in two patients with the pseudodepressed type (22). Such complications could not be avoided completely; however, careful surgery and timely treatment can prevent deterioration, indicating that ESD is comparatively safe. Total LST patients underwent follow-up of three months to eighteen months, and all except two achieved good prognosis without recurrence, indicating that ESD is an ideal way to treat LST.

In summary, LSTs of different types vary in terms of pathological characteristics and prognosis. EUS and BLI examination can help evaluate the possible features and invasion depth of lesions, thus guiding further ESD therapy. ESD is a safe and effective method to treat LSTs. However, the relatively small sample size and short follow-up time were limitations of our study. In future studies, results from more LST samples and longer follow-up times from several centres will be more convincing in terms of assessment of the therapeutic value of ESD for LST.

Acknowledgements

This work was supported by grants from the National Natural Science Foundation of China (No.81630016, to Jie Liu)

Conflicts of interest

None of the authors have a conflicting financial interest.

References

1. KUDO S. Endoscopic mucosal resection of flat and depressed types of early colorectal cancer. *Endoscopy*, 1993, 25 : 455-461.
2. MATSUDA T., GOTODA T., SAITO Y., NAKAJIMA T., CONIO M. Our perspective on endoscopic resection for colorectal neoplasms. *Gastroenterol Clin Biol*, 2010, 34 : 367-370.
3. VLEUGELS JLA., HAZEWINKEL Y., DEKKER E. Morphological classifications of gastrointestinal lesions. *Best Pract Res Clin Gastroenterol*, 2017, 31 : 359-367.
4. No authors listed. The Paris endoscopic classification of superficial neoplastic lesions: esophagus, stomach, and colon : November 30 to December 1, 2002. *Gastrointest Endosc*, 2003, 58 (Suppl): S3-S43.
5. FENOGLIO CM., HAGGITT RC., HAMILTON SR., LUMB G., PASCAL RR., RIDDELL RH. Colonic dysplasia. *Pathol Annu*, 1981, 16 : 181-213.
6. DIXON MF. Gastrointestinal epithelial neoplasia: Viennare visited. *Gut*, 2002, 51 : 130-131.
7. NGUYEN-TANG T., GENEVAY M., DUMONCEAU JM. Endoscopic resection of digestive tumors: indications, quality criteria and results. *Rev Med Suisse*, 2010, 6: 1642-1648.
8. KAKU E., ODA Y., MURAKAMI Y., GOTO H., TANAKA T., HASUDA K *et al*. Proportion of flat- and depressed-type and laterally spreading tumor among advanced colorectal neoplasia. *Clin Gastroenterol Hepatol*, 2011, 9: 503-508.
9. KONISHI K., KANEKO K., KURAHASHI T., YAMAMOTO T., KUSHIMA M., KANDA A *et al*. A comparison of magnifying and non magnifying colonoscopy for diagnosis of colorectal polyps: a prospective study. *Gastrointest Endosc*, 2003, 57: 48-53.
10. KUDO S., LAMBERT R., ALLEN JL, FUJII H., FUJII T., KASHIDA H *et al*. Nonpolypoid neoplastic lesions of the colorectal mucosa. *Gastrointest Endosc*, 2008, 68: S3-S47.
11. URAOKA T., SAITO Y., MATSUDA T., IKEHARA H., GOTODA T., SAITO D *et al*. Endoscopic indications for endoscopic mucosal resection of laterally spreading tumours in the colorectum. *Gut*, 2006, 55: 1592-1597.
12. KANAO H., TANAKA S., OKA S., HIRATA M., YOSHIDA S., CHAYAMA K. Narrow-band imaging magnification predicts the histology and invasion depth of colorectal tumors. *Gastrointest Endosc*, 2009, 69: 631-636.
13. HUANG Y., LIU S., GONG W., ZHI F., PAND., JIANG B. Clinicopathologic features and endoscopic mucosal resection of laterally spreading tumors: experience from China. *Int J Colorectal Dis*, 2009, 24: 1441-1450.
14. YOSHIDA N., HISABE T., HIROSE R., OGISO K., INADA Y., KONISHI H *et al*. Improvement in the visibility of colorectal polyps by using blue laser imaging. *Gastrointest Endosc*, 2015, 82: 542-549.
15. YOSHIDA N., HISABE T., INADA Y., KUGAI M., YAGI N., HIRAI F *et al*. The ability of a novel blue laser imaging system for the diagnosis of invasion depth of colorectal neoplasms. *J Gastroenterol*, 2014, 49: 73-80.
16. LEE EY., BOURKE MJ. EMR should be the first-line treatment for large laterally spreading colorectal lesions. *Gastrointest Endosc*, 2016, 84: 326-328.
17. DE CEGLIE A., HASSAN C., MANGIAVILLANO B., MATSUDA T., SAITO Y., RIDOLA L *et al*. Endoscopic mucosal resection and endoscopic submucosal dissection for colorectal lesions: A systematic review. *Crit Rev Oncol Hematol*, 2016, 104: 138-155.
18. BAHIN FF., PELLISE M., WILLIAMS SJ., BOURKE MJ. Extended endoscopic mucosal resection does not reduce recurrence compared with standard endoscopic mucosal resection of large laterally spreading colorectal lesions. *Gastrointest Endosc*, 2016, 84: 997-1006.e1.
19. IMAI K., HOTTA K., YAMAGUCHI Y., TANAKA M., KAKUSHIMA N., TAKIZAWA K *et al*. Should laterally spreading tumors granular type be resected en bloc in endoscopic resections? *Surg Endosc*, 2014, 28: 2167-2173.
20. MESSMANN H. Endoscopic resection: when is EMR/ESD sufficient? *Recent Results Cancer Res*, 2014, 203: 25-30.
21. XU MD., WANG XY., LI QL., ZHOU PH., ZHANG YQ., ZHONG YS *et al*. Colorectal lateral spreading tumor subtypes: clinicopathology and outcome of endoscopic submucosal dissection. *Int J Colorectal Dis*, 2013, 28: 63-72.
22. KIM ES., CHO KB., PARK KS., LEE KI., JANG BK., CHUNG WJ *et al*. Factors predictive of perforation during endoscopic submucosal dissection for the treatment of colorectal tumors. *Endoscopy*, 2011, 43: 573-578.