Potential factors predicting histopathologically upgrade discrepancies between endoscopic forceps biopsy of the colorectal low-grade intraepithelial neoplasia and endoscopic resection specimens

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Abstract

Background: It was gradually accepted that endoscopic fragment biopsy (EFB) diagnosis cannot accurately guarantee the absence of higher-grade neoplasms within the lesion of digestive tract. There are no well-established predictors for histopathologically upgrade discrepancies between EFB diagnosing colorectal low-grade intraepithelial neoplasia (LGIN) and endoscopic resection (ER) specimens demonstrating higher-grade diseases.

Methods: A total of 918 colorectal LGINs was histopathologically diagnosed by EFB, including 162 cases with histopathologically upgrade discrepancy and 756 concordant cases. We compared clinicopathological data and relevant pathologic results of EFB and ER specimen between these two groups. Multivariate analysis was performed to investigate predictors for this upgrade histopathology.

Results: The predominant upgrade discrepancy of LGINs diagnosed by EFB was upgrades to high-grade dysplasia (n = 114, 70.4%), followed by upgrades to intramucosal carcinoma (n = 33, 20.3%), submucosal adenocarcinoma (n = 10, 6.2%) and advanced adenocarcinoma (n = 5, 3.1%). NSAID history (OR 4.83; 95 % CI, 2.27-10.27; P < 0.001), lack of standardization of EFB number (OR 2.99; 95 % CI, 1.91-4.68; P < 0.001), ≥ 1.0 cm maximum diameter of the target adenoma (OR 6.18; 95% CI, 1.32-28.99; P = 0.021), lobulated shape (OR 2.68; 95 % CI, 1.65-4.36; P < 0.001), erythema (OR 2.42; 95 % CI, 1.50-3.91; P < 0.001), erosion (OR 7.12; 95 % CI, 3.91-12.94; P < 0.001), surface unevenness (OR 2.31; 95 % CI, 1.33-4.01; P = 0.003) and distal location of the target adenoma (OR 3.29; 95% CI, 1.68-6.41; P < 0.001) were associated with the histologically upgrade discrepancies.

Conclusion: NSAID history, lack of standardization of EFB number, adenoma size and location, abnormal macroscopic patterns are significant predictors for potentially upgrade histopathology of LGINs diagnosed by EFBs. The standardization of EFB and advanced imaging techniques could minimize the risk of neglecting potential this upgrade histopathology.

Background

Among all individuals worldwide in 2018, colorectal cancer (CRC) has become the third most commonly diagnosed cancer for incidence and the second leading cause for cancer death [1]. Early detection and removal of adenomatous polyps (a precancerous lesions) can contribute to reduce the occurrence of colorectal cancer [2, 3]. As the monoclonal derivatives of a mutated epithelial stem cell, adenomas, the most common type in colorectal polyp, are benign neoplasms that up to 50% of all individuals will develop in their lifetime [4]. Endoscopic resection (ER) for colorectal adenomas is a feasible and safe way with less morbidity, mortality and costs compared to surgical resection [5]. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) are currently the most used techniques for the resection of large distal colorectal polyps [6, 7].

For the intraepithelial neoplasia in the digestive tract, it has been reported that there are some histopathological discrepancies between endoscopic forceps biopsy (EFB) and pathological outcomes of

ER specimens, such as superficial esophageal squamous neoplasm, gastric epithelial neoplasia and colorectal polyps [8–10]. Whereas, little specific research has been conducted to analyze the factors predicting histopathologically upgrade discrepancies between EFBs of colorectal low-grade intraepithelial neoplasia (LGIN) and ER specimens demonstrating high-grade intraepithelial neoplasia (HGIN) or adenocarcinoma. Therefore, the aim of the present study was to explore these discrepancies and intend to elucidate the potential risk factors and traits contributing to this type of upgrade histopathological diagnosis for the colorectal adenomas with LGIN forceps biopsy, which could suggest us to make further accurate diagnosis and guide the optimal clinical management for these lesions.

Methods

Participants

This retrospective study was based on standard documentation of patients undergoing EMR and ESD in The First Affiliated Hospital of Nanchang University from January 1, 2013 to September 9, 2018.

The participants are patients who were diagnosed with by EFBs demonstrating colorectal adenoma of LGIN. The primary exclusion criteria were endoscopic intolerance with severe cardiopulmonary dysfunction, coagulation disorders, low healing capacity with diabetes mellitus, other severe complications and refusal to receive endoscopy treatment. Identified by postoperative pathology, patients diagnosed with the colorectal adenomas of HGIN or adenocarcinoma were selected as the case group (histopathologically upgrade group). Patients still diagnosed with colorectal adenoma of LGIN were selected as control group (histopathologically concordant group). Patients with incomplete data for adenoma characteristics and laboratory examination at baseline were excluded in both groups. After exclusion, 162 cases and 756 controls were identified (Figure 1).

Data definition and collection

We recorded patients' demographics including age, gender, personal medical history of hypertension (HT), diabetes mellitus (DM), using nonsteroidal anti-inflammatory drug (NSAID), colorectal polyps, CRC, familial adenomatous polyposis (FAP), ulcerative colitis (UC), Crohn's disease (CD) and the number of polyps (single or multiple). We also obtained patients' blood lipid level including triglyceride (TG), total cholesterol (TC), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) and carcino-embryonic antigen (CEA).

We established the principle of selecting a target adenoma from one patient. The adenoma with larger size or abnormal macroscopic characteristics was selected as target if there are multiple adenomas in one individual. We also recorded the clinicopathologic data of target adenomas: site (proximal or distal), size of adenomas (diameter), shape pattern (Yamada I+II or Yamada III+IV), the proportion of laterally spreading tumor (LST), macroscopic patterns (lobulation, erythema, erosion, surface unevenness), standardization for EFB number, EFB histopathology (tubular or tubulovillous or villous) and

postoperative pathology (LGIN or HGIN or adenocarcinoma). Based on the consensus, Yamada classification is our reference for assessing the macroscopic type of targeted adenomas [11]. The definition of LST is sessile and flat, ≥ 10 mm polyps on the basis of the original Kudo classification. Adenomas in the cecum to the transverse colon are defined as 'proximal' and those in the rectum through the splenic flexure are defined as 'distal' [12]. The adenoma size was recorded by the maximum diameters of the specimens. The definition of the standardization for the EFB number is at least the integer part of the maximum diameter of a target adenoma. EFB histopathology and postoperative pathology of target adenomatous specimens were based on World Health Organization (WHO) classification [13]. EFB demonstrated that adenomas with 25 to 75% villous features were defined as tubulovillous adenomas, and those with villous architecture $\geq 75\%$ were classified as villous adenomas [14]. HGIN was classified into high-grade dysplasia (HGD) and intramucosal carcinoma. Adenocarcinoma was classified into submucosal adenocarcinoma (submucosa invasion) and advanced adenocarcinoma (muscularis invasion).

Colonoscopy, ER and histopathological reports

Bowel preparation and were abstracted on the report forms [15, 16]. Conventional white light colonoscopes (CF-H260 series; Olympus, AIZU, Japan/EC-450HL5, EC-450WM5 or EC-590ZW series; Fujinon, Saitama, Japan) were used in performance of all procedures. Colonoscopy, EMR and ESD had been randomly allocated to endoscopists who experienced >10,000 colonoscopies (at least 1,500 polypectomies) and scrupulously implemented based on European Society of Gastrointestinal Endoscopy (ESGE) Clinical Guideline [17-19]. The withdrawal times of each colonoscopy were guaranteed at least 6 minutes for adequate inspection [20].

In the cases of EMR, we injected a saline solution containing 0.5 % methylene blue and 0.1 % epinephrine into the mucosa underneath the basal part of colorectal neoplasms to lift the neoplasm. Then the neoplasm was snared by the elastic band and resected by blended electrosurgical current. In the cases of ESD, we injected a saline solution containing 0.5 % methylene blue and 0.1 % epinephrine in the circumferential edge of targeted neoplasm into submucosal space to lift the neoplasm. A circumferential incision was carefully executed using a needle knife (KD-610L, Olympus, Tokyo, Japan), or a needle knife plus an insulated-tip knife (KD-611L, Olympus, Tokyo, Japan) with subsequent continuous submucosal dissection. For prophylaxis of delayed bleeding, hemostatic forceps (FD-410LR, Olympus) and argon plasma coagulation (APC) were taken to coagulate visible active bleeding vessels in the resected surface of EMR and ESD. For the closure of the wound, titanium clip and rope were utilized dependent on the condition of the wound undergoing EMR and ESD.

The diagnosis of EFBs and ER specimens was assessed and determined by two independent expert gastrointestinal pathologists in the pathology department.

Statistical Analysis

Continuous variables were calculated by using the student t test and expressed as means $\pm$ SD. Age, maximum diameters of adenoma and blood lipid level were not distributed normally and were expressed as median and inter-quartile range (IQR) of 25th, 75th percentiles. Mann-Whitney U test were used for statistical analysis of these data. The significance of difference for categorical variables were assessed by Chi-square tests or Fisher's exact tests, which were described using the odd ratio (OR) and 95% confidence interval (CI). Statistical significance was determined at an α level of 0.05 by utilizing two-sided tests. Multiple logistic regression was used to identify the significant factors for the phenomenon of this inconsistent pathology.

Post hoc testing was used when measuring the predictive significance of the EFB diagnosis and Macroscopic type. Multiple variables with $P < 0.05$ in the univariate analysis were selected as potential risk factors in the multivariate forward stepwise logistic regression analysis. All statistical analyses were performed using the Statistical Package for Social Science software suite (version 25.0; SPSS, Inc., Chicago, IL, USA)

Results

Baseline characteristics of 918 patients suffering LGIN diagnosed by EFBs

Table 1 summarizes baseline characteristics of 918 included patients suffering LGIN diagnosed by EFBs. Of the 918 patients, 584 were male and 332 were female, with a median age of 58y (IQR: 50–66). 34.7% patients (319/918) did not have adequate EFB number. The predominant macroscopic shapes were Yamada III or IV (490/918, 53.4%). 42 (4.6%) lesions were LSTs. Most lesions (721/918, 78.5%) were located in the distal large intestine. Lobulated, erythema, erosion and surface unevenness patterns were observed in 192 (20.9%), 461 (50.2%), 102 (11.1%), 149 (16.2%) patients, respectively. And 553 cases (60.2%) just suffered single colorectal polyp. Further, the median maximum diameter of the target adenoma is 1.5 cm (IQR: 1, 2). <1.0 cm, 1.0-1.9 cm, 2.0-2.9 cm and ≥ 3.0 cm maximum diameters of target adenoma were found in 92 (10%), 487 (53.1%), 233 (25.4%), 106 (11.5%) patients.

Table 1
Baseline characteristics of 918 patients with colorectal LGIN diagnosed by EFB

Baseline Characteristics	Value
Median Age, y (IQR)	58 (50, 66)
Gender, n (%)	
Male	586 (63.8)
Female	332 (36.2)
Lack of standardization of EFB number, n (%)	
Yes	319 (34.7)
No	599 (65.3)
Shape pattern of the target adenoma, n (%)	
Yamada I + II	428 (46.6)
Yamada III + IV	490 (53.4)
LST	42 (4.6)
Location, n (%)	
Proximal	197 (21.5)
Distal	721 (78.5)
Lobulated shape, n (%)	192 (20.9)
Erythema, n (%)	461 (50.2)
Erosion, n (%)	102 (11.1)
Surface unevenness, n (%)	149 (16.2)
Number of colorectal polyps	
Single	553 (60.2)
Multiple	366 (39.8)
Median largest diameter of the target, cm (IQR)	1.5 (1, 2)
Largest diameter of the target adenoma, n (%)	
<1.0 cm	92 (10)
1.0-1.9 cm	487 (53.1)

LGIN, low-grade intraepithelial neoplasia; IQR, inter-quartile range; EFB, endoscopic fragment biopsy; LST, laterally spreading tumor

Baseline Characteristics	Value
2.0-2.9 cm	233 (25.4)
≥3.0 cm	106 (11.5)
LGIN, low-grade intraepithelial neoplasia; IQR, inter-quartile range; EFB, endoscopic fragment biopsy; LST, laterally spreading tumor	

Clinicopathological and endoscopic characteristics of patients in the histopathologically upgrade group and the histopathologically concordant group

Clinicopathologic characteristics of 918 patients were presented in Table 2 between the histopathologically upgrade and concordant groups. Clinical details of 15 patients who have an initial EFB diagnosis of LGIN and ER specimen histopathology of the adenocarcinoma was shown in Supplement Table 1. Figure 2 shows a typical case with upgrade histopathologically discrepancies between the histological results of EFBs and the ER specimen. This patient was initially diagnosed as LGIN by EFBs and finally confirmed as HGIN and adenocarcinoma by ER, respectively.

Table 2
Baseline characteristics of the concordant group and the upgrade group disease after endoscopic resection.

Characteristics	Upgrade group (n = 162)	Concordant group (n = 756)	P value
Age/y, median (IQR)	59 (48.75, 67)	58 (50, 65)	0.449
Female, n (%)	69 (42.6)	263 (34.8)	0.061
Past medical history, n (%)			
HT	48 (29.6)	156 (20.6)	0.012
DM	21 (13.0)	71 (9.4)	0.170
NSAID	22 (13.6)	29 (3.8)	< 0.001
Colorectal polyps	5 (3.1)	27 (3.6)	0.76
FAP	1 (0.6)	2 (0.3)	0.442
CRC	8 (4.9)	48 (6.3)	0.496
Lack of standardization of EFB number, n (%)	102 (63.0)	217 (28.7)	0.001
EFB diagnosis, n (%)			< 0.001
Tubular	126 (77.8)	663 (87.7)	
Tubulovillous	25 (15.4)	77 (10.2)	
Villous	11 (6.8)	16 (2.1)	
Postoperative pathological diagnosis, n (%)			
Tubular adenoma	-	712 (94.2)	
Tubulovillous adenoma	-	34 (4.5)	
Villous adenoma	-	10 (1.3)	
HGD	114 (70.4)	-	
Intramucosal carcinoma	33 (20.3)	-	
Submucosal adenocarcinoma	10 (6.2)	-	
Advanced adenocarcinoma	5 (3.1)	-	

HT, hypertension; DM, diabetes mellitus; NSAID, nonsteroidal anti-inflammatory drug; FAP, familial adenomatous polyposis; CRC, colorectal cancer; HGD, high-grade dysplasia; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein

Characteristics	Upgrade group (n = 162)	Concordant group (n = 756)	P value
Maximum diameter of the target adenoma/cm, median (IQR)	2.44 (1.5, 3)	1.59 (1, 2)	< 0.001
Lobulated pattern, n (%)	85 (52.5)	107 (14.2)	< 0.001
Erythema, n (%)	127 (78.4)	334 (44.2)	< 0.001
Erosion, n (%)	69 (42.6)	33 (4.4)	< 0.001
Surface unevenness, n (%)	80 (49.4)	69 (9.1)	< 0.001
Blood biochemistry, median (IQR)			
TG, mmol/L	1.14 (0.80, 1.63)	1.27 (0.89, 1.84)	0.025
TC, mmol/L	4.33 (3.73, 5.08)	4.6 (4.03, 5.24)	0.002
HDL, mmol/L	1.27 (1.03, 1.49)	1.25 (1.05, 1.52)	0.742
LDL, mmol/L	2.56 (2.04, 3.10)	2.79 (2.25, 3.30)	0.001
Shape pattern, n (%)			0.547
Yamada I + II	79 (48.8)	349 (46.2)	
Yamada III + IV	83 (51.2)	407 (53.8)	
LST, n (%)	5 (3.1)	37 (4.9)	0.318
Multiple colorectal polyps	73 (45.1)	293 (38.8)	0.137
Distal location of the target adenoma, n (%)	143 (88.3)	578 (76.5)	< 0.001
HT, hypertension; DM, diabetes mellitus; NSAID, nonsteroidal anti-inflammatory drug; FAP, familial adenomatous polyposis; CRC, colorectal cancer; HGD, high-grade dysplasia; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein			

The predominant LGIN upgrade discrepancies by EFB diagnosis was upgrades to high-grade dysplasia (n = 114, 70.4%), followed by upgrades to intramucosal carcinoma (n = 33, 20.3%), submucosal adenocarcinoma (n = 10, 6.2%) and advanced adenocarcinoma (n = 5, 3.1%). The proportion of patients with HT (29.6 vs 20.6%, P = 0.012), the proportion of patients with NSAID (13.6 vs 3.8%, P < 0.001), lack of standardization of EFB number (63.0 vs 28.7%, P = 0.001), maximum diameter of the target adenoma (2.44 vs 1.59 cm, P < 0.001), lobulated pattern (52.5 vs 14.2%, P < 0.001), erythema (78.4 vs 44.2%, P < 0.001), erosion (42.6 vs 4.4%, P < 0.001), surface unevenness (49.4 vs 9.1%, P < 0.001) and distal location of the target adenoma (88.3 vs 76.5%, P < 0.001) were significantly greater in histopathologically upgrade group. TC (4.33 vs 4.6 mmol/L, P = 0.002) and LDL (2.56 vs 2.79 mmol/L, P = 0.001) were significantly

lower in upgrade group. There was no significant difference in the proportion of patients with DM, colorectal polyps, FAP and CRC history between the groups. Gender, age, TC, HDL, the number of Yamada III + IV lesions, the number of LSTs and the number of patients with multiple colorectal polyps did not differ between two groups.

There are also significantly different in EFB result ($P < 0.001$) between the group. Based on Post hoc testing, the values of Cramer's V in EFB diagnosis is 0.127 ($P = 0.001$), which indicated that they had a small magnitude of effect size. In histopathologically upgrade group, the adjusted standardized residual of tubular, tubulovillous and villous EFB diagnosis were -3.3 , $+1.9$, $+3.2$, respectively.

Predictive risk factors for an initial EFB diagnosis of LGIN being upgraded to a higher-grade histopathologic diagnosis by ER specimen.

Univariate analysis was taken to screen a series of variates including female, age ≥ 60 , HT history, NSAID history, lack of standardization of EFB number, $\geq 25\%$ Villous in EFB diagnosis, ≥ 1.0 cm maximum diameter of the target adenoma, lobulated shape, erythema, erosion, surface unevenness, LST, multiple colorectal polyps, distal location of the target adenoma. Then our multivariate analysis showed that NSAID history (OR 4.83; 95% CI, 2.27–10.27; $P < 0.001$), lack of standardization of EFB number (OR 2.99; 95% CI, 1.91–4.68; $P < 0.001$), ≥ 1.0 cm maximum diameter of the target adenoma (OR 6.18; 95% CI, 1.32–28.99; $P = 0.021$), lobulated shape (OR 2.68; 95% CI, 1.65–4.36; $P < 0.001$), erythema (OR 2.42; 95% CI, 1.50–3.91; $P < 0.001$), erosion (OR 7.12; 95% CI, 3.91–12.94; $P < 0.001$), surface unevenness (OR 2.31; 95% CI, 1.33–4.01; $P = 0.003$) and distal location of the target adenoma (OR 3.29; 95% CI, 1.68–6.41; $P < 0.001$) were significantly associated with the histologically upgrade discrepancies (Table 3).

Table 3

Multivariate analyses for predictive factors demonstrating histopathologically upgrade discrepancies between pretreatment EFB and endoscopic resection specimens

	Univariate analysis		Multivariable analysis	
	OR (95%CI)	P value	OR (95%CI)	P value
Female	1.39 (0.98,1.97)	0.061		0.054
Age $\geq$ 60	1.18 (0.84, 1.66)	0.337		0.256
Past medical history				
NSAID	3.94 (2.20, 7.06)	< 0.001	4.83 (2.27, 10.27)	< 0.001
Colorectal polyps	0.86 (0.33,2.27)	0.760		
FAP	2.34 (0.21,25.98)	0.488		
CRC	0.77 (0.36,1.65)	0.497		
Lack of standardization of EFB number	4.22 (2.96, 6.03)	< 0.001	2.99 (1.91, 4.68)	< 0.001
$\geq$ 25% Villous in EFB diagnosis	2.04 (1.33, 3.13)	0.001		0.845
Maximum diameter $\geq$ 1.0 cm	10.81 (2.64, 44.36)	0.001	6.18 (1.32, 28.99)	0.021
Lobulated shape	6.70 (4.63, 9.69)	< 0.001	2.68 (1.65, 4.36)	< 0.001
Erythema	4.59 (3.07, 6.85)	< 0.001	2.42 (1.50, 3.91)	< 0.001
Erosion	16.26 (10.18, 25.95)	< 0.001	7.12 (3.91, 12.94)	< 0.001
Surface unevenness	9.71 (6.54, 14.42)	< 0.001	2.31 (1.33, 4.01)	0.003
LST	0.62 (0.24, 1.60)	0.322		
Multiple colorectal polyps	1.30 (0.92, 1.83)	0.138		
Distal location of the target adenoma	2.32 (1.40, 3.85)	< 0.001	3.29 (1.68, 6.41)	< 0.001

Discussion

Cancers developing from the adenoma towards carcinoma sequence in an indolent pattern may be more likely to be detected and prevented than aggressive cancers progressing rapidly or developing de novo [21, 22]. Therefore, precise histopathological diagnoses for superficial colorectal neoplasms are indispensable to select appropriate treatment strategies. Samples from EFBs are usually taken to diagnose the histopathologic grade of targeted colorectal adenomas. En-bloc resection of the neoplasms by ER could be a kind of curative treatment and provide definite histological diagnosis. In fact, some colorectal adenomas diagnosed as LGINs by their histopathology of EFBs were eventually confirmed as HGINs or adenocarcinomas diagnosed by their histopathology of ER specimens in actual clinical practice. Some researchers have revealed this kind of significantly upgrade discrepancies in histopathological diagnoses between pretreatment EFB and ER specimen for patients with superficial esophageal squamous neoplasms and gastric epithelial neoplasia [8, 9]. Some studies also reported histology discrepancies of colorectal polyps but failed to figure out significantly useful predictors [23–25]. Recently, a retrospective study analyzing 290 polyps reported histologic discrepancies between pretreatment EFB and EMR specimens of colorectal polyps [10]. But their inclusion criteria are not relatively strict, and their sample size is relatively small. Polyp size > 10 mm was proven as the single most significant predictor for histology discrepancy and under-diagnosis cases. It is necessary for clinicians to figure out the clinicopathologic features that may increase the likelihood of histopathologically upgrade discrepancies between pretreatment EFB and ER specimens. Our study is the first specific study to explore potential factors predicting this kind of histopathological upgrade discrepancies for colorectal LGINs diagnosed by EFBs.

An inverse association between the regular NSAIDs use and the presence of high-risk adenomatous polyps (HRAP), which implied a beneficial and chemopreventive effect of NSAIDs use on the presence of HRAP and recurrence of colorectal adenomas [26, 27]. A multicenter, randomized, double-blind trial with high quality confirmed that aspirin (300 mg per day) did not reduce colorectal adenoma risk in the proportion of participants with at least one adenoma but it does suggest aspirin's chemopreventive activity with adenoma subtype selective and location selective [28–30]. NSAIDs use was a risk factor for upgrade histopathology in our study, which is relatively conflicting to existing data. We considered our result may be reasonable because clinicians are more likely to reduce the number of biopsy fragment against biopsy standardization due to minimize the risk of continuous bleeding in the operation, which increases the possibility of the occurrence of upgrade histopathology. It is required for further investigation whether NSAIDs use could be a predictor for upgrade discrepancies. It is meaningful for clinicians to take the fewest number of EFB, while maintaining histopathologic accuracy. If the diameter of esophagus neoplasms is > 14 mm, at least two endoscopic biopsies are recommended [8]. Despite of few researches reporting no significant relationship between single and multiple biopsies, we recommend a standardization that EFB number should reach at least the integer part of the maximum diameter of a target adenoma, which is valuable experience from the clinical practice in our hospital [31]. We are convinced that the larger size of target lesions could potentially increase rates of histopathologic discrepancies [32]. Our result has verified ≥ 1.0 cm could be a significant cut-off value to predict upgrade histopathology in accordance with the previous studies [10]. 1.0 cm is also considered as a cut-off value

of advanced adenomas, which is another reason we used [33]. Our study also supports a growing body of literature surprisingly demonstrating a significant relationship between a higher possibility of histopathologically upgrade discrepancy and all four endoscopic features including lobulated shape, erythema, erosion, surface unevenness. Flat-type early cancer may be a precursor of advanced cancer in the right colon [34]. And sessile serrated adenomas (SSAs) have been generally considered to associate with microsatellite instability of DNA repair defects. A meta-analysis reported that 8.5% LSTs contained submucosal invasion (SMI) and a higher risk of SMI was observed in non-granular pseudodepressed LSTs [35]. Hence, we expected that Yamada classification and LST may predict this upgrade discrepancy, but our result did not show any significance. Further research with bigger sample size should be designed to investigate the predictive role of shape pattern in upgrade histopathology of LGINs diagnosed by EFB. There are a series of evidence showing a more distal distribution of colorectal adenomas and advanced adenomas in Asia compared with U.S. [36–38]. We also found distal location of the colorectal adenoma potentially increases the risk of the upgrade histopathology we discussed, which may support this conclusion. Besides, villous $\geq 25\%$ (tubulovillous and villous) did not reach the significance in our multivariable analysis. However, villous adenomas are more commonly sessile and are more likely to have severe atypia or dysplasia. Villous component may imply a risk of rapid growth and malignant trend so that we expect a predictive role of EFB diagnosis [39]. Post hoc testing was taken for measuring the predictive significance of EFB diagnosis and macroscopic type. For residuals, we set ± 3 as a cut-off value indicating the existence of statistical significance on the basis of general consensus [40–42]. So our results implied that villous EFB diagnosis significantly contributes to histopathologically upgrade discrepancies. Tubulovillous EFB diagnosis is also likely to predict upgrade histopathology though they did not reach statistically significance.

We also recorded the level of plasma lipid level as some evidence showed plasma cholesterol levels may be associated with advanced adenoma [43]. It has been reported that adenoma risk is positively correlated with plasma TG levels and negatively correlated with plasma HDL cholesterol levels [44]. We found that there are some differences of plasma lipid level between the group but the medians of two group are within normal range. Consequently, we did not consider plasma lipid level as a sensitive indicator for predicting upgrade histopathology of LGINs diagnosed by EFB and screening colorectal early cancer. Of the 162 histopathologically upgrade lesions in our present study, invasive adenocarcinomas were subsequently confirmed in 15 cases including 5 advanced adenocarcinomas and 10 submucosal adenocarcinomas after the definite diagnosis of ER specimens. All lesions are larger than 1.0 cm. 93.3% (14/15) lesions had abnormal macroscopic patterns. 86.7% (13/15) lesions were distally distributed and had single piece of EFB. All adenocarcinomas except one were moderately differentiated or well differentiated. Further detailed study could be designed to identify predictors for LGIN to adenocarcinoma upgrade discrepancy.

The purpose of our study is to figure out high-risk colorectal adenoma and early cancer in time and achieve early accurate diagnosis. After procuring predictors for these histopathologically upgrade discrepancies, we are conducted to a consideration of what strategies we should do to minimize the risk of neglecting this upgrade discrepancies and to First, the experience in our institution elucidates that

multi-layered biopsies should be clamped apically to basally (especially at the nodular, erythematous portion) for high-risk lesions in order to avoid the neglect of malignant lesions if we aim to gain a smaller biopsy specimen with highly accurate histologic diagnosis. Second, advanced imaging including narrow band imaging (NBI), magnifying chromoendoscopy (MCE) has been proven to be more accurate in predicting deep submucosal invasive carcinoma and promoting early diagnosis of T1 CRC dependent on their precise evaluation of the surface pattern, pit pattern and capillary vessels [45–47]. And these advanced imaging techniques could approximately contribute to three-fold better diagnosis of T1 CRC and twofold better diagnosis for tumor invasive depth than conventional diagnosis by macroscopic morphology, which is also meaningful for diagnoses of LGIN with our verified risk factors [45]. In addition to NBI and MCE, confocal laser endomicroscopy (CLE) and blue laser imaging (BLI) could accomplish a thousand-fold magnification (optical biopsy) and multiple observation mode, respectively [46]. These advanced imaging techniques will lead to fewer endoscopic biopsies and a decreased risk of histopathologic discrepancies, but high expense and experience variance of inter-operator limit their wide spreading. There is still no consensus on the use of computed tomography (CT) and endoscopic ultrasound (EUS) to recognizing early carcinoma or carcinoma micro-original foci due to lack of sensitivity of screening lymph node metastasis and depth of invasion in early stage of adenoma-carcinoma sequence.

The nature limitations of retrospective studies are inevitable in our study. And the pathologic diagnosis of EFB and ER specimens was assessed by different pathologists even different institutions. It probably resulted in inter-observer variability, which could be an independent predictor of histological discrepancies for colorectal polyps [31]. Besides, there is an inevitable selection bias because analyzed individuals were not consecutive due to some exclusion of patients with insufficient clinical data.

Conclusions

Our results imply that EFB diagnosis of colorectal adenomas with LGINs cannot accurately guarantee the absence of higher-grade neoplasms or carcinoma foci within the lesion. NSAID history, lack of standardization of EFB number, tumor size and location, abnormal macroscopic patterns are significant predictors for potentially upgrade histopathology of LGINs diagnosed by EFBs. And upgrade histopathology would be far more likely if more risk factors simultaneously existed. Improving the standardization and skills of EFB, advanced imaging techniques could help the accurate detection and diagnosis of colorectal lesions.

Abbreviations

EFB: endoscopic fragment biopsy; LGIN: low-grade intraepithelial neoplasia; ER: endoscopic resection; CRC: colorectal cancer; EMR: endoscopic mucosal resection; ESD: endoscopic submucosal dissection; HGIN: high-grade intraepithelial neoplasia; HT: hypertension; DM: diabetes mellitus; NSAID: nonsteroidal anti-inflammatory drug; FAP: familial adenomatous polyposis; CD: Crohn's disease; TG: triglyceride; TC: total cholesterol; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CEA: carcino-embryonic

antigen; OR: odd ratio; CI: confidence interval; HRAP: high-risk adenomatous polyps; LST: laterally spreading tumors; SMI: submucosal invasion; SSA: sessile serrated adenomas; NBI: narrow band imaging; MCE: magnifying chromoendoscopy; BLI: blue laser imaging; CT: computed tomography; EUS: endoscopic ultrasound

Declarations

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Authors' Contributions

Junbo Hong, Wei Zuo and Youxiang Chen contributed to the study design. Junbo Hong and Jiangshan Deng contributed to the collection of data. Junbo Hong contributed to the analysis and interpretation of data. Junbo Hong, Anjiang Wang, Xiaodong Zhou, Xiaojiang Zhou, Guohua Li, Xu Shu, Yin Zhu, Nonghua Lv, Youxiang Chen contributed to endoscopic treatment. Yi Tu and Shan Xu contributed to pathological diagnosis. Junbo Hong and Youxiang Chen contributed to the revision of the article and statistical analysis. All authors read and approved the final version of the article.

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Data Availability

The data used to support the findings of this study are available from all authors upon request.

Ethics approval and consent to participate

All procedures in our study were performed in accordance with the Declaration of Helsinki. This study was approved by the Ethics Committee of the First Affiliated Hospital of Nanchang University, Nanchang, China. The informed consents were obtained from all patients.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Figures

Figure 1

Flow diagram for selecting eligible individuals into histopathologically upgrade and concordant group

Figure 2

(A) A 20-mm sessile lobulated lesion with erythema and surface unevenness on the rectum. (B) The lesion was excised by endoscopic submucosal dissection. (C) Microscopic features of initial EFB. The biopsy specimen showed mild glandular disarray and stratified epithelial cells with rod-like nuclei. These characteristics were diagnosed with “tubular” low-grade intraepithelial neoplasm (H&E, original magnification X4). (D) Microscopic features of initial EFB (H&E, original magnification X20). (E)

Microscopic features of ER specimen. The glandular structure on the left side is severely distorted and fused by marked proliferation of disarrayed glands and epithelial cells showed enlarged and irregular nuclei with nucleoli. These characteristics were consistent with moderately-differentiated adenocarcinoma with submucosal invasion (H&E, original magnification X4). No residual was observed in tumor margin and base. (F) Microscopic features of ER specimen (H&E, original magnification X20).

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