Analysis of Factors Associated with Pathological Upgrading after Endoscopic Submucosal Dissection for Gastric Mucosal Lesions (Postprint)

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Abstract

Objective To investigate the pathological upgrade rate following endoscopic submucosal dissection (ESD) for gastric mucosal lesions in five hospitals in Northern Shaanxi and to analyze factors associated with pathological upgrade. Methods A retrospective analysis was performed on data from patients who underwent ESD for gastric mucosal lesions in five hospitals between January 1, 2016 and December 30, 2021. The pathological upgrade rate was calculated, and statistical methods were employed to analyze related factors. Results Among the 241 cases collected, the overall pathological upgrade rate after ESD was 31.54%. The CIC group had an upgrade rate of 32.14%, with endoscopic classification (OR: 0.134, CI: 0.029-0.617) and surface ulceration (0R: 3.596, CI: 1.226-10.536) being associated with pathological upgrade. The LGIN group had an upgrade rate of 32%, with age (OR: 3.961, CI: 1.071-14.650), endoscopic classification (OR: 0.331, CI: 0.127-0.765), surface redness (OR: 5.830, CI: 1.591-21.355), and number of biopsies (OR: 234, CI: 0.063-0.872) being associated with pathological upgrade. The HGIN group had an upgrade rate of 38.46%, with lesion size (OR: 3.143, CI: 1.003-9.852) being an independent factor associated with pathological upgrade. Conclusion If preoperative biopsy suggests CIC but the endoscopic classification is flat or depressed type and the lesion exhibits surface ulceration, the possibility of pathological underestimation should be considered. If preoperative biopsy suggests LGIN but the patient is older than 60 years, the lesion is of flat type, the lesion surface shows redness, and only one biopsy was obtained, the possibility of preoperative pathological underestimation cannot be excluded, and ESD should be considered when necessary. When lesion size exceeds 2 cm, lesions diagnosed as HGIN by preoperative biopsy are likely to be early gastric cancer (EGC), and ESD is recommended.

Full Text

Analysis of Related Factors for Pathological Upgrading after Endoscopic Submucosal Dissection of Gastric Mucosal Lesions

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Abstract

Objective: To investigate the pathological upgrading rate after endoscopic submucosal dissection (ESD) for gastric mucosal lesions in five hospitals in Northern Shaanxi and to analyze the related factors for pathological upgrading.

Methods: We retrospectively analyzed data from patients who underwent ESD for gastric mucosal lesions in five hospitals between January 1, 2016, and December 30, 2021. The pathological upgrading rate was calculated, and related factors were analyzed using statistical methods.

Results: Among the 241 cases collected, the overall pathological upgrading rate after ESD was 31.54%. In the chronic inflammatory change (CIC) group, the upgrading rate was 32.14%; endoscopic classification (OR: 0.134, CI: 0.029-0.617) and surface ulceration (OR: 3.596, CI: 1.226-10.536) were associated with pathological upgrading. In the low-grade intraepithelial neoplasia (LGIN) group, the upgrading rate was 32%; age (OR: 3.961, CI: 1.071-14.650), endoscopic classification (OR: 0.331, CI: 0.127-0.765), surface redness (OR: 5.830, CI: 1.591-21.355), and number of biopsies (OR: 0.234, CI: 0.063-0.872) were associated with upgrading. In the high-grade intraepithelial neoplasia (HGIN) group, the upgrading rate was 38.46%, with lesion size (OR: 3.143, CI: 1.003-9.852) identified as an independent factor.

Conclusion: For lesions with preoperative biopsy suggesting CIC but endoscopically classified as flat or depressed types with surface ulceration, clinicians should be alert to possible underestimation. For preoperative LGIN in patients over 60 years old with flat lesions showing surface redness and only one biopsy specimen, preoperative pathology may be underestimated, and ESD should be

considered when necessary. When lesion size exceeds 2 cm, HGIN diagnosed by preoperative biopsy is likely to be early gastric cancer (EGC), and ESD is recommended.

Keywords: Gastric mucosal lesion; Endoscopic submucosal dissection; Pathological upgrading

Introduction

Early gastric cancer (EGC) is typically asymptomatic, and symptoms often indicate advanced disease, making gastric cancer a significant global health threat. Early diagnosis is crucial for improving survival rates, and endoscopic screening has become an important method for detecting gastric cancer. Through endoscopic screening, we can identify carcinoma in situ and precancerous lesions at early stages. Conventional forceps biopsy (CFB) typically samples areas with atrophy, erosion, ulceration, or polyps. When CFB pathologically diagnoses carcinoma in situ, low-grade intraepithelial neoplasia (LGIN), or high-grade intraepithelial neoplasia (HGIN), gastroenterologists usually recommend endoscopic submucosal dissection (ESD) to completely resect the lesion and prevent further carcinogenesis. However, CFB cannot represent the entire lesion because only a small portion is sampled. Lu et al. reported that the concordance rate between preoperative biopsy and postoperative pathology was 68.92% [1], while Dae et al. found a discrepancy rate of 31.1% between preoperative pathological biopsy and post-ESD diagnosis [2], suggesting that CFB may underestimate the severity of gastric mucosal lesions. Although ESD is minimally invasive compared with surgery, it still carries potential complications including bleeding and perforation. Therefore, evaluating the pathological diagnosis from CFB before ESD is essential. In this study, we investigated the pathological upgrading rate after ESD for gastric mucosal lesions in five hospitals in Northern Shaanxi and analyzed the related factors for pathological upgrading to identify lesion characteristics associated with upgrading and provide clinical guidance.

1.1 Study Subjects

We collected data from patients who underwent ESD for gastric mucosal lesions between January 1, 2016, and December 30, 2021, in five hospitals and met the inclusion criteria. Inclusion criteria were: (1) meeting indications or expanded indications for gastric ESD; (2) signed informed consent before ESD; and (3) underwent conventional biopsy before ESD. Exclusion criteria were: (1) incomplete clinical or pathological records; and (2) cases where conventional biopsy diagnosed mild inflammation but endoscopic ultrasonography highly suspected gastrointestinal stromal tumor, ectopic pancreas, or neuroendocrine tumor, and ESD final diagnosis confirmed these conditions.

1.2 Histological Evaluation

Histological diagnoses were based on the WHO Classification of Tumors [3] and the Chinese Ministry of Health Guidelines for Diagnosis and Treatment of Gastric Cancer [4]. LGIN referred to mild, mild-to-moderate, and moderate dysplasia; HGIN referred to moderate-to-severe, severe dysplasia, and carcinoma in situ; EGC was defined as cancer invasion not exceeding the submucosal layer regardless of lymph node metastasis; and advanced gastric cancer was defined as invasion beyond the submucosal layer into the muscularis propria or deeper. In our study, pathological types were categorized into five groups: chronic inflammatory change (CIC), including hyperplastic and adenomatous polyps; LGIN; HGIN; EGC; and advanced gastric cancer.

1.3 Statistical Methods

Data were analyzed using SPSS 26.0 statistical software. The chi-square test was used for univariate analysis. For fourfold table data with $n \geq 40$ but $1 \leq T < 5$, the corrected chi-square formula was applied. For $R \times C$ table data, when more than 20% of cells had $1 \leq T < 5$, Fisher' s exact test was used. Variables with statistical significance ($P < 0.05$) were included in a binary logistic regression model to calculate P values, odds ratios (OR), and 95% confidence intervals (CI). $P < 0.05$ was considered statistically significant. For multiple group comparisons, chi-square test for $R \times C$ contingency tables was used.

Results

2.1 General Characteristics

This study included 241 cases with a mean age of 61 years; 130 cases (53.9%) were older than 60 years. Male patients accounted for 61.4% (148/241) and female patients for 38.6% (93/241). Helicobacter pylori positivity was found in 27% (65/241) of cases. Lesion locations were: cardia 12.9% (31/241), fundus 2.1% (5/241), body 22.4% (54/241), angularis 11.6% (28/241), and antrum 51% (123/241).

2.2 Comparison of CFB and Post-ESD Pathological Results

The overall pathological upgrading rate between preoperative CFB diagnosis and postoperative pathology was 31.54% (76/241) . Among 84 lesions diagnosed as CIC on preoperative biopsy, 15 were upgraded to LGIN, 7 to HGIN, and 5 to EGC postoperatively, yielding an upgrading rate of 32.14% (27/84). Among 75 lesions diagnosed as LGIN preoperatively, 33 maintained the original diagnosis, 13 were upgraded to HGIN, and 11 to EGC, with an overall upgrading rate of 32% (24/75); 18 cases were downgraded to CIC, representing a downgrading rate of 24% (18/75). Among 65 lesions diagnosed as HGIN preoperatively, 25 were upgraded to EGC, with an upgrading rate of 38.46% (25/65); 16 cases

were downgraded, representing a downgrading rate of 24.62%. No cases were upgraded to advanced gastric cancer after ESD in this study.

2.3 Analysis of Related Factors for Pathological Upgrading after ESD

Cases undergoing ESD were grouped according to differences between preoperative biopsy diagnosis and postoperative pathology. Cases with upgraded postoperative pathology were assigned to the upgrading group, and those without upgrading to the non-upgrading group. Separate comparisons were made for the CIC, LGIN, and HGIN groups to analyze factors related to pathological upgrading.

2.3.1 Univariate Analysis of Pathological Upgrading Analysis revealed that pathological upgrading in the CIC group was associated with endoscopic classification and surface ulceration. In the LGIN group, upgrading was associated with age, endoscopic classification, surface redness, surface ulceration, and number of biopsies. Lesion size was associated with pathological upgrading in the HGIN group .

2.3.2 Multivariate Analysis of Pathological Upgrading Variables with statistical significance in univariate analysis were entered into a binary logistic regression model for multivariate analysis. The results showed that endoscopic classification and surface ulceration were independent factors for pathological upgrading in the CIC group. Age, endoscopic classification, surface redness, and number of biopsies were independent factors for upgrading in the LGIN group. Lesion size was an independent factor for upgrading in the HGIN group .

Discussion

This retrospective study of 241 cases from five hospitals in Northern Shaanxi found an overall pathological upgrading rate of 31.54% between CFB and post-ESD diagnosis, which increased to 33.93% when cases diagnosed as EGC by CFB were excluded. These results are consistent with intermediate levels reported in similar domestic and international studies.

Among 84 lesions diagnosed as CIC by CFB, 27 (32.14%) were ultimately upgraded, including 5 cases upgraded to EGC. Univariate analysis indicated that pathological upgrading was associated with endoscopic classification and surface ulceration, both of which were independent factors. Compared with the non-upgrading group, the upgrading group had more cases with flat or depressed types and surface ulceration. The upgrading rate for CIC in our study was slightly lower than the 43.1% reported by Baek et al. for gastritis or hyperplasia after ESD [5]. However, overall, this upgrading rate for CIC lesions remains relatively high, possibly due to: (1) CIC lesions selected for ESD were those considered by endoscopists to have carcinogenic potential, representing a secondary

selection that may not reflect all CIC lesions; and (2) these lesions may represent mixed pathology of inflammation, hyperplasia, and neoplasia, with CFB only representing the biopsied area rather than the entire lesion, as pathology may be focal. These findings suggest that a CFB diagnosis of CIC (including inflammation and polyps) cannot completely exclude the possibility of EGC or precancerous lesions. Cases with endoscopic features of flat or depressed types and surface ulceration warrant attention, and repeat endoscopy with biopsy may be necessary when indicated.

Intraepithelial neoplasia is a recognized precancerous lesion with malignant potential, classified as LGIN or HGIN. HGIN is currently recommended for endoscopic mucosal resection (EMR) or ESD, while LGIN is recommended for follow-up or surgical treatment in China [6]. Patients without upgrading-related factors can be followed, while those with such factors should undergo ESD. However, clear standards for upgrading-related factors remain undefined. In a study by Lim et al. [7], the concordance rate between preoperative and postoperative pathology for intraepithelial neoplasia was 31.7% (587/1850), with upgrading rates of 24.0% for LGIN and 52.7% for HGIN. LGIN upgrading was associated with maximum lesion diameter >1.8 cm (P=0.001), uneven surface (P=0.014), and depressed endoscopic type (P=0.001). A study by Choi et al. [8] on diagnostic accuracy of HGIN before ESD reported an upgrading rate of 66.5%, with surface ulceration (OR 4.151), surface nodularity (OR 5.582), surface redness (OR 2.926), and location in the upper third of the stomach (OR 3.894) as related factors. In a study by Wu et al. [9], the upgrading rate for lesions diagnosed as LGIN was 29.5%, with surface redness and ulceration associated with post-ESD upgrading (P<0.05). Li and Qiu [10] reported that fewer biopsies, lesion diameter >1 cm, and elevated or ulcerative types were factors for misdiagnosing EGC as HGIN. Chen [11] found that among lesions diagnosed as HGIN by preoperative CFB, the post-ESD upgrading rate was 50.4%, with lesion diameter >3 cm (OR, 2.61) and male sex (OR, 3.371) as related factors.

In our study, 32% of lesions diagnosed as LGIN by CFB were upgraded after ESD. After analyzing sex, age, lesion location, size, endoscopic classification, surface redness, nodularity, ulceration, H. pylori status, and number of biopsies, we found upgrading was associated with age >60 years, flat endoscopic type, surface redness, surface ulceration, and number of biopsies. Multivariate analysis identified age >60 years, flat endoscopic type, surface redness, and number of biopsies as independent factors for LGIN upgrading. For lesions diagnosed as HGIN preoperatively, 38.46% were upgraded after ESD, with lesion size identified as an independent factor. Our overall upgrading rate of 31.54% is intermediate compared with domestic and international studies, and the identified factors are similar to those reported previously. Therefore, for lesions diagnosed as LGIN preoperatively, special attention should be paid to patients >60 years old with flat lesions showing surface redness, and ESD resection should be considered when necessary. For lesions diagnosed as HGIN by CFB, possible carcinogenesis should be suspected when lesion size exceeds 2 cm.

Discordance between CFB and post-ESD pathology has been reported in domestic and international studies. Based on clinical practice, possible reasons for pathological upgrading include: (1) Endoscopist and pathologist factors: Some cases underwent preoperative biopsy at county-level hospitals and post-ESD pathology at higher-level centers. County-level endoscopists and pathologists may have less diagnostic experience. Hosokawa et al. [12] found that endoscopists with >10 years of experience had an EGC miss rate of only 19.5%, compared with 32.4% for those with <10 years, a finding confirmed by Li and Qiu [10]. (2) Lesion factors: Lesions may be focal with uneven distribution, and CFB only samples a small portion that may not represent the entire lesion. (3) Biopsy specimen factors: Biopsies typically sample only small portions of the mucosal and proper layers, rarely reaching the muscularis mucosae. However, Jeon et al. [13] suggested that larger biopsy forceps do not improve accuracy, but increasing the number of biopsies does. In clinical practice, insufficient biopsy numbers may occur. Reports indicate that with seven endoscopic biopsy samples, the diagnostic rate for advanced gastric cancer exceeds 98% [14], but multiple biopsies for superficial gastric tumors, especially small lesions, may hinder endoscopic resection by inducing submucosal fibrosis [15], a major risk factor for post-ESD perforation. Based on this, Chinese consensus guidelines for early gastric cancer screening and management recommend at least two specimens for lesions >1 cm, with one additional specimen for each additional centimeter. When advanced cancer is suspected, 6-8 specimens should be collected from non-necrotic areas, with adequate size and depth reaching the muscularis mucosae. In practice, insufficient numbers or depth may occur due to surface ulceration or difficult lesion locations. (4) Diagnostic criteria differences: Schlemper et al. [16] reported that when Japanese and Western pathologists diagnosed 35 gastric biopsies and resection specimens with suspected early neoplasia, Western pathologists diagnosed suspected or confirmed cancer in <50% of specimens, while Japanese gastrointestinal pathologists made such diagnoses in >80%. Therefore, endoscopists and pathologists should improve their technical and diagnostic skills, pay adequate attention to cases with surface redness, ulceration, and flat lesions, strictly follow guidelines for biopsy number and depth, communicate actively with pathologists to avoid missed diagnoses, and utilize magnification and chromoendoscopy for better lesion observation and improved biopsy representativeness.

This study has several limitations. First, as a retrospective study, it has inherent selection bias and relatively limited data. Second, the included data lacked results from magnification, chromoendoscopy, and endoscopic ultrasonography, limiting the generalizability of our conclusions. Future studies will expand to more centers, increase sample sizes, and incorporate magnification, chromoendoscopy, and endoscopic ultrasonography results to improve representativeness.

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Note: Figure translations are in progress. See original paper for figures.