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Research Article | **Pathology**

Comparative Diagnostic Performance of Endoscopic Classifications for Predicting Histopathology in Large Laterally Spreading Colorectal Tumors

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Abstract

Introduction. Colorectal cancer is a major cause of cancer-related mortality worldwide, and early, accurate diagnosis is essential for effective management. Optical diagnosis using image-enhanced endoscopy and standardized classifications has improved real-time assessment of lesion morphology, yet the optimal approach for large laterally spreading tumors (LSTs), especially granular mixed type, remains under debate. This study aimed to compare the diagnostic performance of the JNET, Kudo, Modified Sano, Hiroshima classifications, and forceps biopsy in predicting histopathology for large LSTs, with a focus on differentiating between granular (LST-G) and non-granular (LST-NG) subtypes.

Methods. Ninety-five patients with LSTs > 20 mm were enrolled, with the largest lesion per patient selected for analysis. Patients were stratified into LST-G and LST-NG groups using the Paris classification. Lesions were evaluated using optical diagnosis based on four endoscopic classifications: Kudo, JNET, Modified Sano, and Hiroshima. Targeted forceps biopsies were obtained from areas of the most pronounced changes, and subsequent endoscopic resection specimens served as the histopathological reference standard. The diagnostic performance metrics were calculated, including sensitivity, specificity, predictive values, and diagnostic accuracy.

Results. In the LST-G group, the Modified Sano classification achieved the highest sensitivity (92.31%) but had low specificity (52.38%). In contrast, the Hiroshima classification exhibited low sensitivity (65.22%) but achieved superior specificity (100%), along with the highest positive predictive value (100%), negative predictive value (82.22%), and overall diagnostic accuracy (86.67%). Forceps biopsy demonstrated a balanced diagnostic performance, slightly surpassing JNET in sensitivity (79.49% vs. 71.79%), specificity (95.24% vs. 90.48%), negative predictive value (96.88% vs. 93.33%), positive predictive value (71.43% vs. 63.33%), and diagnostic accuracy (85% vs. 78.3%). In contrast, for LST-NG lesions, the JNET classification outperformed other modalities across most diagnostic metrics, with the highest sensitivity (71.43%), specificity (100%), and positive predictive value (100%); however, it had a slightly lower negative predictive value and diagnostic accuracy compared to the Hiroshima classification (84% vs. 93.75% and 88.57% vs. 94.29%, respectively).

Conclusions. Among the evaluated endoscopic classifications, JNET proved to be the most effective for large LST-NG, while for LST-G, the Modified Sano classification demonstrated the highest sensitivity, and the Hiroshima classification excelled in other diagnostic metrics. Although further improvements in optical diagnosis are warranted, targeted forceps biopsy provides no additional diagnostic benefits before resection.

Keywords
Laterally Spreading Tumor; Colorectal Neoplasia; Optical Biopsy; Image-Enhanced Endoscopy; Colonoscopy

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Introduction

Colorectal cancer remains one of the leading causes of cancer-related mortality worldwide, with an increasing incidence in many regions. Early and accurate histologic diagnosis of colorectal lesions is critical for effective patient management and improved clinical outcomes [1].

Image-enhanced endoscopy has emerged as a valuable tool in the morphological assessment of colorectal neoplasms. Standardized endoscopic classifications are integral to this approach, as they facilitate the optical biopsy process by enabling real-time histologic predictions [2]. Among the most widely recommended classifications are the Kudo [3], Narrow-Band Imaging (NBI)

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International Colorectal Endoscopic (NICE) [4], and Japan NBI Expert Team (JNET) [5, 6] systems. Each of these systems has a distinct development history and clinical focus. For example, the Kudo classification was originally developed to correlate lesion pit patterns with histology [3]. In contrast, the JNET classification was designed as a universal NBI magnifying endoscopic system that addresses inconsistent terminology, incorporates surface patterns, and accounts for differences between elevated and superficial lesions [5]. Meanwhile, the NICE classification was established as a practical and straightforward system based on color, vascular, and surface pattern features, and it is particularly suited for use without optical magnification [4].

The advent of high-quality endoscopic imaging and the subsequent classification of lesions have enabled the optical biopsy concept, whereby histologic predictions can be made in real time [7]. This development has facilitated the "resect-and-discard" policy for diminutive ($\leq$ 5 mm) colorectal polyps [2]. Although studies comparing the JNET and NICE classifications suggest that magnifying NBI may offer additional benefits, a key clinical advantage lies in establishing standardized criteria for diagnosing superficial and deep submucosal invasion [8]. Such standardization is essential to guide the choice between en bloc resection and piecemeal endoscopic mucosal resection (EMR).

While the JNET classification has demonstrated adequate accuracy in differentiating neoplastic from non-neoplastic lesions, its performance remains suboptimal for certain lesion types (i.e., Types 2A, 2B, and 3) regardless of the endoscopist's experience [9]. In practice, existing classifications yield the highest diagnostic accuracy for lesions at the extremes of the diagnostic spectrum, whereas distinguishing between low-grade and high-grade dysplasia is considerably more challenging [10–12].

The diagnostic accuracy of histologic prediction is further reduced in laterally spreading tumors (LSTs), particularly in the granular mixed subtype. This limitation is most likely attributable to the difficulties in assessing the extensive and uneven surface architecture of these lesions [8, 13]. Although the JNET system incorporates elements from other established classifications (including Sano, Hiroshima, Showa, and Jikei), this integration has omitted certain parameters that may be useful for predicting progressive changes in large LST neoplasms. Competing systems, such as the Hiroshima and Modified Sano classifications, continue to provide detailed evaluations of both vascular and pit patterns.

Given the current gaps in the literature, especially the lack of comparative studies focusing on large LSTs, a systematic analysis of the diagnostic metrics of these classifications is warranted. Therefore, the objective of this study is to compare the performance of various endoscopic classifications and forceps biopsy in the evaluation of LSTs. By assessing their relative merits, this study may assist clinicians in selecting the most appropriate classification system for their practice.

Materials and Methods

Study Design and Setting

This single-center study was conducted at the University Clinic of Zaporizhzhia. Data were collected retrospectively from 2015 to 2022 and prospectively from 2023 to 2024.

Participants and Eligibility Criteria

A total of 95 patients with LSTs larger than 20 mm were enrolled. For each patient, only the largest lesion was selected for analysis. The inclusion criteria comprised patients aged 18 years or older presenting with an LST meeting the specified size requirement. The exclusion criteria were as follows:

- Age below 18 years,
- Presence of endoscopic signs indicative of deep invasion,
- Concurrent malignant tumors at other sites,
- Contraindications to LST removal.

Group Allocation

Based on macroscopic morphology, patients were categorized according to the Paris classification, as described by Kudo *et al.* [14]. Two primary groups were defined.

Group I comprised 60 patients with the granular type of LSTs (LST-G), with 16 patients classified as granular homogeneous subtype (LST-G-H) and 44 as granular mixed subtype (LST-G-M).

Group II comprised 35 patients with the non-granular type (LST-NG), including 7 patients with pseudo-depressed LSTs (LST-NG-PD) and 28 with non-granular flat-elevated LSTs (LST-NG-FE).

Assessment and Tissue Collection

Upon identification of a lesion that satisfied the inclusion criteria, an expert endoscopist performed an examination using both virtual and vital chromoendoscopy with Indigo Carmine solution. The vascular and pit patterns of the lesions were assessed according to the Kudo, JNET, Modified Sano, and Hiroshima classifications. Optical findings were evaluated based on the criteria detailed in the following references: Modified Sano [15, 16], Kudo [3, 17], Hiroshima [18, 19], and JNET [5].

After a comprehensive evaluation of the lesion surface, targeted forceps biopsies were obtained from the areas exhibiting the most pronounced morphological changes. Lesions were subsequently removed endoscopically following the preliminary histopathological assessment of the biopsy samples. The histopathological evaluation of the resected lesions, which served as the reference standard, was categorized into completely benign lesions, lesions with areas of low-grade dysplasia, lesions exhibiting high-grade dysplasia, and lesions with cancer in situ (adenocarcinomas).

The correspondence between the predicted histopathology and optical assessments in different classifications is summarized in Table 1.

Table 1. Cross-tabulation of histopathology and endoscopic classifications.

Predicted Histopathology	Classification			
	JNET	Kudo	Modified Sano	Hiroshima
Benign	1, 2A	I, II, II-O, IIIL, IV	MS I, MS IIo	A, B
Low-grade dysplasia	2A	IIIL, IV	MS II	B
High-grade dysplasia	2B	IIIs	MS IIIa	C1
Cancer in situ	2B	Vi	MS IIIa	C1, C2
Invasive cancer (excluded from the study)	3	Vn	MS IIIb	C2, C3

Table 2. Location and types of resected colorectal lesions.

	LST-G group	LST-NG group
Location		
Caecum	10 (16.66%)	4 (11.43%)
Ascending colon	10 (16.66%)	12 (34.29%)
Transverse colon	4 (6.67%)	16 (45.71%)
Descending colon	1 (1.67%)	1 (2.86%)
Sigmoid colon	4 (6.67%)	2 (5.71%)
Rectosigmoid flexure	4 (6.67%)	-
Rectum	27 (45%)	-
Types of resected colorectal lesions		
Hyperplastic	1 (1.67%)	6 (17.14%)
Tubular adenoma	17 (28.33%)	22 (62.86%)
Tubulo-villous adenoma	41 (68.33%)	1 (2.86%)
Villous adenoma	1 (1.67%)	-
Serrated adenoma	-	6 (17.14%)

Notes: LST-G – granular laterally spreading tumors; LST-NG – non-granular laterally spreading tumors.

Resection Methods

The method of resection varied by group. In the LST-G group, 12 LSTs (20%) were removed en bloc using the method of EMR, 22 (36.67%) by piecemeal EMR (pEMR), 18 (30%) via endoscopic submucosal dissection (ESD), and 8 (13.33%) using the hybrid ESD method. In the LST-NG group, 17 LSTs (48.57%) were removed using en bloc EMR, 16 LSTs (45.71%) via pEMR, and one LST each (2.86%) through ESD and hybrid ESD.

Statistical Analysis

Statistical analysis was performed using Statistica 13 software (StatSoft Inc., Tulsa, OK, USA; License number: JPZ8041382130ARCN10-J). The analysis comprised the following methods.

Descriptive Statistics. Categorical data, such as lesion morphology, location, resection methods, etc., were summarized using percentages. Patient age and lesion size are presented as median values with interquartile range (IQR).

Diagnostic Accuracy Measures. Sensitivity, specificity, positive, and negative predictive values were calculated. Confidence intervals for these proportions were derived using the Wilson Score Interval method. A binomial approximation was applied for overall diagnostic accuracy.

The significance level was set at $p < 0.05$.

Results

In the LST-G group, the median age was 65.5 years (IQR: 60.5–69.25), compared with 68 years (IQR: 57.5–71) in the LST-NG group. The median lesion size was 40 mm (IQR: 25–50) in the LST-G group versus 20 mm (IQR: 20–25) in the LST-NG group. Lesion distribution differed between groups: 60% of LST-G lesions were located in the left colon, whereas 91.43% of LST-NG lesions were localized in the right colon. Regarding types of resected colorectal lesions, tubulo-villous adenomas predominated in the LST-G group (68.33%), while tubular adenomas were most common in the LST-NG group (62.86%). Detailed lesion characteristics are provided in Table 2.

Histopathological examination of the resected specimens classified lesions into four categories. In the LST-G group, 11 lesions (18.33%) were completely benign, 10 (16.67%) exhibited low-grade dysplasia, 16 (26.67%) showed high-grade dysplasia, and 23 (38.33%) contained adenocarcinoma. In the LST-NG group, 16 lesions (45.71%) were benign, 5 (14.29%) exhibited low-grade dysplasia, 10 (28.57%) demonstrated high-grade dysplasia, and 4 (11.43%) were diagnosed as adenocarcinoma in situ.

Table 3 summarizes the diagnostic metrics obtained from target forceps biopsy and optical assessments based on various endoscopic classifications. In the LST-G group, forceps biopsy demonstrated the most balanced performance, followed by the JNET classification. The Modified Sano classification achieved the highest sensitivity at 92.31% (95% CI: 79.13–98.38), albeit with the lowest specificity at 52.38% (95% CI: 31.39–73.08). The Hiroshima classification, in contrast, yielded the highest specificity, positive predictive value, negative predictive value, and overall diagnostic accuracy.

In the LST-NG group, the JNET classification generally outperformed both forceps biopsy and all other classifications across most diagnostic metrics. Nevertheless, the Hiroshima classification slightly exceeded JNET in terms of negative predictive value (93.75% vs. 84%) and diagnostic accuracy (94.29% vs. 88.57%).

Discussion

Our study indicates that the diagnostic performance of optical classifications for LSTs differs according to lesion subtype. The JNET classification provided the most robust overall performance for LST-NG, whereas, for LST-G, the optimal diagnostic method remains less definitive.

In the LST-G group, targeted forceps biopsy demonstrated relatively high diagnostic metrics, slightly surpassing the JNET classification across all parameters. However, it is essential to note that biopsy results depend on the endoscopist's ability to select the most suspicious areas; malignant regions that are not visibly apparent on the lesion surface may be overlooked, potentially leading to underestimation of dysplasia or carcinoma both in optical and biopsy-based preliminary diagnosis [13].

Table 3. Diagnostic metrics of forceps biopsy and endoscopic classifications for granular and non-granular laterally spreading tumors.

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value	Diagnostic Accuracy	p
Group I (LST-G)						
Forceps biopsy	79.49% (95% CI: 63.54–90.68)	95.24% (95% CI: 76.18–99.88)	96.88% (95% CI: 81.59–99.97)	71.43% (95% CI: 53.75–85.39)	85% (95% CI: 73.39–92.93)	<0.001
Kudo	41.03% (95% CI: 25.63–57.85)	95.20% (95% CI: 76.18–99.88)	94.12% (95% CI: 71.31–99.85)	46.51% (95% CI: 30.63–62.88)	60% (95% CI: 46.18–72.86)	0.003
JNET	71.79% (95% CI: 55.11–85.01)	90.48% (95% CI: 69.62–98.83)	93.33% (95% CI: 77.93–99.18)	63.33% (95% CI: 43.86–80.07)	78.30% (95% CI: 65.56–88.25)	<0.001
Hiroshima	65.22% (95% CI: 42.66–83.58)	100% (95% CI: 90.51–100.00)	100% (95% CI: 80.75–100.00)	82.22% (95% CI: 70.89–90.92)	86.67% (95% CI: 75.41–94.06)	<0.001
Modified Sano	92.31% (95% CI: 79.13–98.38)	52.38% (95% CI: 31.39–73.08)	78.26% (95% CI: 63.01–89.70)	78.57% (95% CI: 49.20–95.34)	78.33% (95% CI: 65.56–88.25)	<0.001
Group II (LST-NG)						
Forceps biopsy	57.14% (95% CI: 28.86–82.34)	100% (95% CI: 83.89–100.00)	100% (95% CI: 63.06–100.00)	77.78% (95% CI: 58.96–90.41)	82.86% (95% CI: 66.35–93.44)	<0.001
Kudo	58.33% (95% CI: 27.67–84.83)	91.30% (95% CI: 71.96–98.93)	77.78% (95% CI: 40.00–97.19)	80.77% (95% CI: 60.65–93.45)	80% (95% CI: 63.06–91.56)	0.003
JNET	71.43% (95% CI: 41.90–91.61)	100% (95% CI: 83.89–100.00)	100% (95% CI: 69.15–100.00)	84% (95% CI: 64.78–95.02)	88.57% (95% CI: 73.26–96.80)	<0.001
Hiroshima	60% (95% CI: 14.66–94.73)	100% (95% CI: 88.43–100.00)	100% (95% CI: 29.24–100.00)	93.75% (95% CI: 79.19–99.23)	94.29% (95% CI: 80.84–99.30)	0.002
Modified Sano	58.33% (95% CI: 27.67–84.83)	91.30% (95% CI: 71.96–98.93)	77.78% (95% CI: 39.99–97.19)	80.77% (95% CI: 60.65–93.45)	80% (95% CI: 61.43–92.29)	0.003

Notes: LST-G – granular laterally spreading tumors; LST-NG – non-granular laterally spreading tumors.

Among the optical methods, the Modified Sano classification achieved the highest sensitivity but at the expense of low specificity. Conversely, the Hiroshima classification provided the highest specificity, positive predictive value, negative predictive value, and diagnostic accuracy, while the Kudo classification yielded the lowest performance across key diagnostic metrics. This variability likely reflects the original design intentions of these systems - with the Kudo, Modified Sano, and Hiroshima classifications developed primarily to predict lesion types, such as hyperplastic, serrated neoplasia, tubular or villous adenoma, or deep invasive cancer rather than gradations of dysplasia.

An analysis of the literature reveals both similarities and notable differences compared to our study. For example, Vosko *et al.* reported higher sensitivity for non-granular lesions when assessing submucosal invasive cancer [13], whereas our study considered the full spectrum of histopathological stages. Similarly, Shahidi *et al.* [20] and Bogie *et al.* [21] have demonstrated relationships between lesion size, subtype, and malignant potential, with reported malignancy frequencies considerably lower than those observed in our granular group. These discrepancies may be attributed to differences in lesion selection criteria, the exclusion of lesions with deep invasion, and variations in sample size.

Our analysis excluded the NICE classification due to its three-tier system, which inadequately discriminates among the wide range of histopathological changes observed in large LSTs. Type 2 encompasses a broad spectrum of histopathological outcomes, ranging from completely benign to intramucosal carcinoma, and fails to provide sufficient guidance for selecting an endoscopic resection method [4, 8]. Previous reports have also highlighted the limited sensitivity of the NICE classification for detecting deep invasive lesions, with its accuracy being affected by depressed areas or nodular mixed subtypes [22], reinforcing our decision to rely on classifications that offer more detailed stratification.

Our findings regarding the Hiroshima classification are consistent with prior studies. A multicenter study from the Netherlands reported a sensitivity of 78.7% and a specificity of 94.2% for resectable T1 lesions [23]. In our study, although the sensitivity was slightly lower (65.22% in granular and 60% in non-granular lesions), the specificity reached

100% in both groups. These differences probably reflect variations in patient populations and inclusion criteria. Considering the strong statistical performance of this classification in the LST-G group, it seems appropriate to use it as a supplementary tool in complex diagnostic cases.

The JNET classification emerged as the most balanced system, comparable to forceps biopsy in predicting histopathology, and demonstrated overall better results in LST-NG, despite its inherent limitations. For instance, its grouping of lesions - where Type 1 includes both hyperplastic and serrated lesions and Type 2B encompasses both high-grade dysplasia and carcinoma in situ - may obscure subtle histopathological differences. This limitation was also noted by Sumimoto *et al.*, who suggested that adjunctive chromoendoscopy could enhance diagnostic precision in ambiguous cases [24]. However, all the classifications under review were developed in Japan, where high-grade dysplasia is considered equivalent to cancer [25]. Consequently, the recommended endoscopic treatment for lesions with a 2B capillary pattern is only en bloc resection [6, 10, 26].

In complex scenarios, such as granular mixed lesions or cases with indeterminate features (e.g., pseudo-depression or ambiguous vascular patterns), the supplementary use of the Kudo pit pattern classification has been recommended to differentiate invasive from non-invasive lesions [26]. Furthermore, emerging modalities such as blue laser imaging have demonstrated diagnostic accuracy comparable to NBI [27], potentially broadening the clinical applicability of the JNET system even among less experienced endoscopists.

While the JNET classification demonstrated strong diagnostic performance for large LST-NG, the optimal approach for LST-G remains unclear. Given the variability in classification performance, a multimodal approach incorporating supplementary classification systems may offer a more reliable strategy, particularly for challenging cases.

Limitations

This study has several limitations. It was a single-center study, where only two expert endoscopists assessed the lesions in real time, and interobserver agreement was not measured. Additionally, diagnostic metrics were not evaluated separately for each stage of every classification or for the four LST subtypes due to the relatively small sample size of the LST-G-H (16/95) and LST-NG-PD (7/95) groups.

Conclusions

JNET was the most effective in predicting histopathology and guiding treatment strategies for large non-granular laterally spreading lesions among the endoscopic classifications evaluated. The Modified Sano classification showed the highest sensitivity for LST-G, while the Hiroshima classification was the leader in other statistical indicators. Although there is room for improvement in the optical diagnosis, pre-resection forceps biopsy provides no additional diagnostic benefits.

Ethical Statement

All procedures in this study were performed in accordance with the ethical standards of the institutional research committee, the Declaration of Helsinki, and its later amendments.

Informed Consent

Informed consent was obtained from all the study participants.

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of Interest

The authors declare no potential conflicts of interest.

Financial Disclosure

The authors declare no financial conflicts of interest.

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