

Histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in nonampullary duodenal epithelial tumors

Da Mi Kim, MD^a, Gwang Ha Kim, MD^{a,b,*}, Bong Eun Lee, MD^a, Kyungbin Kim, MD^c, Kyung Un Choi, MD^c, Seung Min Hong, MD^a, Moon Won Lee, MD^a, Geun Am Song, MD^a

Abstract

For patients with nonampullary duodenal epithelial tumors (NADETs), endoscopic forceps biopsy results that reflect the final histopathologic results of the entire lesion are indispensable for accurate diagnosis and appropriate treatment modality selection. This study aimed to investigate the histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in NADETs and to elucidate the factors contributing to such discrepancies.

This retrospective observational study included 105 patients (105 lesions) who underwent endoscopic resection for NADETs at the Pusan National University Hospital between May 2006 and October 2019. NADETs were classified as low-grade intraepithelial neoplasms (LGINs), high-grade intraepithelial neoplasms (HGINs), or adenocarcinomas. Following slide reviews, the histopathologic concordance between endoscopic forceps biopsy and endoscopic resection specimens was assessed for each case.

The histopathologic discrepancy rate between endoscopic forceps biopsy and endoscopic resection specimens was 19.0% (20/105 lesions). Among the 20 diagnostically discordant lesions, up- and downgrade of the histopathologic diagnosis occurred in 17 and 3 lesions, respectively. The predominant discrepancies involved upgrades from LGIN to HGIN (n = 14) and upgrades from LGIN to adenocarcinomas (n = 2). The 3 downgraded cases included 2 from LGIN to inflammation and 1 from HGIN to LGIN. In the multivariate analyses, the old age (>67 years) was the only factor significantly associated with histopathologic upgrade (odds ratio 4.553, 95% confidence interval 1.291–15.939; P = .018).

Considerable histopathologic discrepancies were observed between endoscopic forceps biopsy and endoscopic resection specimens in NADETs. Older age was significantly associated with these discrepancies.

Abbreviations: ADCs = adenocarcinomas, Cls = confidence intervals, EMR = endoscopic mucosal resection, EMR-L = EMR with a ligation device, ESD = endoscopic submucosal dissection, HGINs = high-grade intraepithelial neoplasms, IQRs = interquartile ranges, LGINs = low-grade intraepithelial neoplasms, NADETs = nonampullary duodenal epithelial tumors, ORs = odds ratios.

Keywords: endoscopic resection, histopathologic discrepancy, nonampullary duodenal epithelial tumors

1. Introduction

Nonampullary duodenal epithelial tumors (NADETs) are relatively rare and are found in 0.3% to 1.5% of patients referred for upper gastrointestinal endoscopy.^[1–3] However, the detection rate of NADETs has been increasing with the

widespread use of endoscopy in recent years.^[4] Because they are considered precancerous lesions, NADETs require early treatment.^[5,6] Pancreaticoduodenectomy has been recommended as the standard treatment for NADETs in the past, but it has a notably high rate of adverse events and mortality.^[7,8]

Editor: Bülent Kantarçeken.

Copyright © 2021 the Author(s). Published by Wolters Kluwer Health, Inc.

Received: 25 July 2021 / Received in final form: 9 November 2021 / Accepted: 23 November 2021

http://dx.doi.org/10.1097/MD.00000000028307

This study was supported by the Medical Research Center Program through the National Research Foundation Grant funded by the Korean Government (NRF-2015R1A5A2009656).

The funders had no role in the design, execution, or writing of the study.

The authors have no conflicts of interest to disclose.

Supplemental Digital Content is available for this article.

The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

^a Department of Internal Medicine, Pusan National University College of Medicine, Busan, South Korea, ^b Biomedical Research Institute, Pusan National University Hospital, Busan, South Korea, ^c Department of Pathology, Pusan National University College of Medicine, Busan, South Korea.

^{*} Correspondence: Gwang Ha Kim, Department of Internal Medicine, Pusan National University College of Medicine, and Biomedical Research Institute, Pusan National University Hospital, 179 Gudeok-ro, Seo-gu, Busan 49241, South Korea (e-mail: doc0224@pusan.ac.kr)

This is an open access article distributed under the terms of the Creative Commons Attribution-Non Commercial License 4.0 (CCBY-NC), where it is permissible to download, share, remix, transform, and buildup the work provided it is properly cited. The work cannot be used commercially without permission from the journal.

How to cite this article: Kim DM, Kim GH, Lee BE, Kim K, Choi KU, Hong SM, Lee MW, Song GA. Histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in nonampullary duodenal epithelial tumors. Medicine 2021;100:51(e28307).

Recently, endoscopic resection has been performed for other gastrointestinal neoplasms such as those in the esophagus, stomach, and colon. Endoscopic resection is a minimally invasive procedure and is an ideal replacement treatment modality for surgical resection of NADETs without lymph node metastasis.^[9,10] In fact, a previous study reported that 17 cases of early duodenal cancer had no recurrence during an average follow-up period of 52 months after endoscopic resection.^[11]

Early and accurate preoperative diagnosis of NADETs is important for making appropriate therapeutic decisions. However, endoscopic forceps biopsy often does not allow for the histopathologic diagnosis of an entire lesion. Several previous studies have reported histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in duodenal lesions.^[6,12–14] However, these studies had small sample sizes, focused on endoscopic forceps biopsy rather than the discrepancies between endoscopic forceps biopsy and endoscopic resection specimens, and did not analyze the factors associated with the discrepancies. Therefore, we aimed to investigate discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in NADETs, and to identify the clinicopathologic factors contributing to these discrepancies.

2. Methods

2.1. Subjects

We retrospectively analyzed a database of patients who underwent endoscopic resection at Pusan National University Hospital (Busan, Korea) between May 2006 and October 2019. The inclusion criteria of the study were the presence of a tumor located in the duodenum and of an epithelial tumor according to the endoscopic forceps biopsy results. The exclusion criteria were the presence of a tumor located at the ampulla of Vater, presence of subepithelial lesions, or absence of endoscopic forceps biopsy results prior to the endoscopic resection. We identified 109 patients with 111 lesions who underwent endoscopic resection for NADETs. Of these, 6 lesions in 4 patients were excluded due to unclear biopsy results or the absence of a biopsy before the endoscopic resection. A total of 105 patients with 105 lesions who underwent endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) were included in the analysis. NADETs were defined as low-grade intraepithelial neoplasms (LGINs), high-grade intraepithelial neoplasms (HGINs), and adenocarcinomas (ADCs) limited to the mucosal or submucosal layers of the duodenum.^[15] All patients with ADC underwent abdominal computed tomography prior to endoscopic resection to evaluate the presence of lymph node or distant metastases. Indications of endoscopic resection for duodenal ADCs are not well established; therefore, we performed endoscopic resection for duodenal ADCs confined to the mucosa without lymph node metastasis.^[11,16] This study was reviewed and approved by the Institutional Review Board of Pusan National University Hospital (IRB number: E-2103-023-101).

2.2. Endoscopic resection

Endoscopic resection was performed under intravenous, conscious sedation with midazolam (5–10 mg) and meperidine (25 mg) under continuous cardiorespiratory monitoring, and propofol was administered if necessary. Endoscopic resection was performed by 1 of 3 methods: standard EMR, EMR with a ligation device (EMR-L), or ESD, as previously reported.^[17,18] First, dots marking the incision were placed 2mm outside the tumor with argon plasma coagulation. Then, saline solution containing a small amount of epinephrine and indigo carmine dye was injected into the submucosal layer. For standard EMR, snare resection was performed using a blended electrosurgical current. EMR-L was performed by aspirating the lesion into the ligation device (Stiegmann-Goff ClearVue, ConMed, Boston, MA), followed by the deployment of the elastic band and then snare resection. For ESD, a circumferential incision was made with a flex knife (Olympus, Tokyo, Japan) or an insulation-tipped knife (ESD-Knife, MTW Endoskopie, Wesel, Germany). After an additional injection of saline beneath the lesion to sufficiently separate the lesion from the muscularis propria, the submucosal layer was dissected directly using a flex knife or insulation-tipped knife. In the case of bleeding during the procedure, immediate endoscopic hemostasis was performed. A high-frequency electrosurgical current generator (Erbotom VIO 300D; ERBE, Tübingen, Germany) was used during the procedure.

2.3. Histopathologic evaluation

The macroscopic shapes of the lesion were classified as protruding (I), nonprotruding and nonexcavated (II), or excavated (III). Based on the Paris classification,^[19] the type II was divided into 3 subtypes: slightly elevated (IIa), flat (IIb), or slightly depressed (IIc). The lesions were then classified into 3 groups: elevated (I and IIa), flat (IIb), or depressed (IIc and III).

The resected specimen was fixed in formalin and sectioned at 2mm intervals. Tumor size, depth of invasion, lymphovascular invasion, and degree of differentiation were evaluated according to the 7th edition of the American Joint Committee on Cancer's TNM staging system for small bowel adenocarcinoma.^[20] Endoscopic biopsy and resected specimen slides were examined by 2 expert pathologists (KK and KUC). Following the slide reviews, the concordance between the endoscopic biopsy and resection specimen results was assessed for each case. In discordant cases, the histopathologic findings were adjudicated by consensus between the 2 pathologists. An upgraded histopathologic diagnosis was defined when a lesion described as an LGIN in the endoscopic biopsy was determined to be an HGIN or ADC in the endoscopic resection specimen, or when an HGIN in the endoscopic biopsy was reassessed as an ADC in the endoscopic resection specimen.^[21] Conversely, a downgraded histopathologic diagnosis was defined when a lesion described as an ADC in the endoscopic biopsy was confirmed to be either an LGIN or HGIN in the endoscopic resection specimens, or when a lesion described as an HGIN in the endoscopic biopsy was reclassified as an LGIN in the endoscopic resection specimen.^[21]

2.4. Statistical analysis

Categorical variables are presented as counts and percentages, whereas continuous variables are expressed as medians with interquartile ranges (IQRs). The Mann–Whitney *U* test, chisquared test, and Fisher exact test were performed to compare the clinicopathologic characteristics between the inflammation/ LGIN and HGIN/ADC groups and between the histopathologically concordant and upgraded groups, respectively. Multivariate logistic regression analyses were performed to evaluate factors related to the final advanced histopathology and histopathologic upgrade, respectively. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the relative risks of the final advanced histopathology and histopathologic upgrade. Cutoff values were determined using a receiver operating characteristic curve to determine whether age and maximum tumor diameter contributed to the final advanced histopathology above a certain value. The intersection of sensitivity and specificity was determined to be the optimal cut-off value. A *P* value <.05 was considered statistically significant. Statistical calculations were performed using the SPSS version 25.0 for Windows software (SPSS Inc, Chicago, IL).

3. Results

3.1. Baseline characteristics of patients with nonampullary duodenal epithelial tumors

The clinicopathologic characteristics of 105 patients (105 lesions) who underwent endoscopic resection for NADETs are summarized in Table 1. Of the 105 patients, 65 were men and 40 were women, with a median age of 58 years (IQR, 50-66 years). Most lesions (80/105, 76%) were located in the second portion of the duodenum, and the predominant macroscopic shape was elevated (84/105, 80%). Regarding lesion color, 56 were similar to the surrounding normal mucosa, 39 were discolored, and 10 were red. The endoscopic forceps biopsy diagnoses indicated the presence of LGIN in 99 lesions, HGIN in 4 lesions, and ADC in 2 lesions. Endoscopic resection was performed within 3 months after the diagnosis of NADETs by endoscopic forceps biopsy in 103 lesions and after 6 months in 2 lesions. The median maximum tumor size was 10 mm (IQR, 6-15 mm). Eighty-seven lesions were treated using standard EMR, 4 using EMR-L, and 14 using ESD. The final pathologic diagnoses were inflammation for 2 lesions, LGIN for 82 lesions, HGIN for 16 lesions, and ADC for 5 lesions.

3.2. Clinicopathologic factors predicting the final advanced histopathology

Differences in clinicopathologic characteristics between the inflammation/LGIN and HGIN/ADC groups are presented in Table 2. To investigate whether the final advanced histopathology (HGIN and ADC) might be predicted by specific values for age and maximum tumor size, receiver operating characteristic curves were used to determine cut-off values. It was fond that the sensitivity and specificity were almost optimized at an age of 67 years and a maximum tumor size of 15 mm; the corresponding areas under the curve values were 0.676 and 0.507, respectively (Supplementary Figure 1, http://links.lww.com/MD/G547). Older age (>67 years) was significantly more frequently observed in the HGIN/ADC group (P < .001). Depressed macroscopic shape was more frequently observed in HGIN/ADC group, but this did not reach statistical significance (P=.125). Other characteristics, such as sex, location, endoscopic color, and maximum tumor size, did not differ between the inflammation/ LGIN and HGIN/ADC groups. In multivariate analyses, older age (>67 years) and depressed macroscopic shape were statistically significant factors for predicting the final advanced histopathology (OR 15.696, 95% CI 3.928-62.718; P<.001 and OR 4.105, 95% CI 1.083–15.555; P=.038, respectively) (Table 3).

Table 1

Baseline clinicopathologic characteristics of 105 patients (105 lesions) undergoing endoscopic resection for nonampullary duodenal epithelial tumors.

Characteristic	Value
Median age, yr (IQR)	58 (50–66)
Sex, n (%)	
Men	65 (62)
Women	40 (38)
Site, n (%)	
Bulb	15 (14)
Second portion	80 (76)
Third portion	10 (10)
Macroscopic shape, n (%)	
Elevated	84 (80)
Depressed	21 (20)
Endoscopic color, n (%)	
Normal	56 (53)
Discolored	39 (37)
Red	10 (10)
Median maximum tumor size, mm (IQR)	10 (6–15)
Endoscopic resection, n (%)	
Standard endoscopic mucosal resection*	87 (83)
Endoscopic mucosal resection with a ligation device	4 (4)
Endoscopic submucosal dissection	14 (13)
Final histopathology, n (%)	
Inflammation	2 (2)
Low-grade intraepithelial neoplasm	82 (78)
High-grade intraepithelial neoplasm	16 (15)
Adenocarcinoma	5 (5)

IQR = interquartile range.

Table 2

Differences in clinicopathologic characteristics between inflammation/LGIN and HGIN/ADC.

	Inflammation/LGIN	HGIN/ADC	
Characteristics	(n = 84)	(n=21)	P value
Sex, n (%)			.615
Men	51 (61)	14 (67)	
Women	33 (39)	7 (33)	
Age, n (%)			<.001
\leq 67 yrs	74 (88)	10 (48)	
>67 yrs	10 (12)	11 (52)	
Location, n (%)			.702
Bulb	13 (16)	2 (9)	
Second portion	62 (74)	14 (86)	
Third portion	9 (11)	1 (5)	
Macroscopic shape, n (%)			.125
Elevated	70 (83)	14 (67)	
Depressed	14 (17)	7 (33)	
Endoscopic color, n (%)			.673
Normal	43 (51)	13 (62)	
Discolored	33 (39)	6 (29)	
Red	8 (10)	2 (10)	
Maximum tumor size, mm (mean±SD)	12.7 ± 8.4	14.3 ± 13.0	.388

ADC = adenocarcinoma, HGIN = high-grade intraepithelial neoplasm, LGIN = low-grade intraepithelial neoplasm.

3.3. Comparison of pretreatment endoscopic forceps biopsy and endoscopic resection specimen diagnoses

The initial endoscopic forceps biopsy diagnoses of the 105 lesions revealed that 99 lesions were LGINs, 4 were HGINs, and 2 were ADCs. When the forceps biopsy diagnoses were compared with Table 4

 Table 3

 Multivariate analyses of clinicopathologic factors predicting the final advanced histopathology.

Variables	Odds ratio (95% confidence interval)	P value
Age >67 yrs	15.696 (3.928-62.718)	<.001
Depressed shape	4.105 (1.083–15.555)	.038
Maximum tumor	1.767 (0.495-6.314)	.381
size >1.5 cm		

the endoscopic resection specimen diagnoses, the histopathologic discrepancy rate was 19.0% (20/105 lesions) (Table 4). Among the 20 diagnostically discordant lesions, an upgrade of the final histopathologic diagnosis was made for 17 lesions, and a downgrade was made for 3 lesions. The predominant discrepancies involved upgrades from LGIN to HGIN (n=14) and upgrades from LGIN to ADC (n=2) (Fig. 1). The 3 cases with downgrade histopathologic diagnoses included 2 from LGIN to inflammation and 1 from HGIN to LGIN.

3.4. Clinicopathologic factors contributing histopathologic upgrade between pretreatment endoscopy forceps biopsy and endoscopic resection specimens

The clinicopathologic characteristics of the histopathologically concordant and upgraded lesions are presented in Table 5. Sex, location, endoscopic color, tumor size, and pretreatment histopathology did not differ between the histopathologically concordant and upgraded lesions. Older age (>67 years) was more frequently observed in the histopathologically upgraded group (P=.043), but depressed macroscopic shape and maximum tumor size >15 mm were not different between the histopathologically concordant and upgraded lesions (P=.335 and P=.363, respectively). In the multivariate analyses, older age (>67 years) was the only factor significantly associated with histopathologic upgrade (OR 4.535, 95% CI 1.291–15.939; P=.018) (Table 6). Depressed macroscopic shape and maximum tumor size >15 mm were not associated with the histopathologic

Comparison	of the histopatho	logic diagnoses be	etween pretreatment	t endoscopic forceps	biopsy and end	oscopic resection	specimens.
oompanoon	or and motopaulo	logio alagnocoo be	othoon productation	i onaoooopio ioi oopo	biopoy and ona	00000010100000000	opeointene

	Final diagnosis of endoscopic resection specimen					
Pretreatment endoscopic forceps biopsy diagnosis	Inflammation (n=2)	LGIN (n=82)	HGIN (n=16)	ADC (n=5)		
LGIN $(n = 99)$	2	81	14	2		
HGIN $(n = 4)$	0	1	2	1		
ADC $(n=2)$	0	0	0	2		

ADC = adenocarcinoma, HGIN = high-grade intraepithelial neoplasm, LGIN = low-grade intraepithelial neoplasm.



Figure 1. A representative case showing a histopathologic discrepancy between pretreatment endoscopic forceps biopsy and endoscopic resection specimens. A, A slightly depressed lesion is seen in the third portion of the duodenum (*arrow*). B, Endoscopic forceps biopsy reveals a low-grade intraepithelial neoplasia (hematoxylin and eosin stain, ×100). C, A complete circumferential incision is made using a flex knife. D, Submucosal dissection is made using an insulated-tip knife, and the lesion is completely removed. E, The resected specimen. F, The endoscopic resection specimen reveals a well-differentiated adenocarcinoma, which invades the submucosa (hematoxylin and eosin stain, ×100).

Table 5

Clinicopathologic factors	contributing to	histopathologic	upgrade	between	pretreatment	endoscopic	forceps biop	sy and	endoscopic
resection specimens.									

Characteristics	Histopathologically concordant group (n=85)	Histopathologically upgraded group (n=17)	P value
Sex, n (%)			.856
Men	52 (61)	10 (59)	
Women	33 (39)	7 (41)	
Age, n (%)			.043
\leq 67 yrs	71 (84)	10 (59)	
>67 yrs	14 (16)	7 (41)	
Location, n (%)			1.000
Bulb	13 (15)	2 (12)	
Second portion	63 (74)	14 (82)	
Third portion	9 (11)	1 (6)	
Macroscopic shape, n (%)			.335
Elevated	69 (81)	12 (71)	
Depressed	16 (19)	5 (29)	
Endoscopic color, n (%)			.929
Normal	44 (52)	9 (53)	
Discolored	33 (39)	6 (35)	
Red	8 (9)	2 (12)	
Maximum tumor size, n (%)			.363
<u>≤</u> 15 mm	65 (76)	11 (65)	
>15 mm	20 (24)	6 (35)	
Pretreatment histopathology, n (%)			.606
Low-grade intraepithelial neoplasm	81 (95)	16 (94)	
High-grade intraepithelial neoplasm	2 (2)	1 (6)	
Adenocarcinoma	2 (2)	0 (0)	

upgrade (OR 2.003, 95% CI 0.541–7.421; *P*=.298 and OR 2.155, 95% CI 0.601–7.725; *P*=.239, respectively).

4. Discussion

Since NADETs have the potential to be malignant, an accurate histopathologic diagnosis is essential when selecting an appropriate treatment modality. Endoscopic forceps biopsy is usually performed to diagnose NADETs; however, the current study demonstrates that there is a considerable discrepancy between pretreatment endoscopic forceps biopsy and endoscopic resection specimen diagnoses in NADETs. The overall histopathologic discrepancy rate in the present study was 19.0%, which is consistent with the results of previous studies on duodenal neoplasms (13.5%–41.6%).^[6,13,22,23] Moreover, we found that older age (>67 years) was significantly associated with histopathologic discrepancies. Our results suggest that the diagnosis of NADETs using endoscopic forceps biopsy could not guarantee the absence of foci with advanced histopathology (HGID/ADC) within the lesion and that endoscopic forceps biopsy alone might lack the accuracy needed for diagnosing NADETs.

Of the 20 histopathologically discordant lesions in the present study, 17 (85.0%) were underdiagnosed based on the pretreat-

Table 6

Multivariate analyses of factors predicting histopathologic upgrade between pretreatment endoscopic forceps biopsy and endoscopic resection specimens.

	Odds ratio (95% confidence interval)	P value
Age >67 yrs	4.535 (1.291–15.939)	.018
Depressed shape	2.003 (0.541-7.421)	.298
Maximum tumor size >15 mm	2.155 (0.601-7.725)	.239

ment endoscopic forceps biopsy specimens. Among these cases, 14 LGINs were subsequently confirmed to be HGINs, while 2 LGINs and 1 HGIN were confirmed as ADCs after endoscopic resection. This can be explained as follows. Two pathways are suggested for the carcinogenesis of duodenal cancer: the adenoma-carcinoma sequence and the development of de novo cancer.^[11] Since almost all NADETs are thought to follow the adenoma-carcinoma sequence, these discrepancies might have arisen due to heterogeneity within the tumor; ^[22] in other words, the hidden foci of malignancy might not have been included in the endoscopic forceps biopsy specimens.^[24] In addition, malignant cells might have spread horizontally along the basement membrane and could be misdiagnosed as LGINs if the endoscopic forceps biopsy did not contain enough tissue to include the basement membrane.^[21]

In the present study, there were also 3 cases of over-diagnoses, based on pretreatment endoscopic forceps biopsy specimen histopathology. Two cases were initially diagnosed as LGINs in the biopsy specimens but were subsequently diagnosed as inflammation after endoscopic resection. The other case was first diagnosed as an HGIN via the biopsy specimen, but was later diagnosed as an LGIN after endoscopic resection. These diagnostic differences might be caused by either the complete removal of the lesion via forceps biopsy, or the misinterpretation of one of these samples by the tangential sectioning of the forceps biopsy specimens.

Knowing the potentially predictive clinicopathologic features of advanced histopathology in NADETs during endoscopy is important in clinical practice. Multivariate analyses indicated that older age (>67 years; OR 15.696) and depressed macroscopic shape (OR 4.105) were significantly associated with advanced histopathology. These findings are consistent with the results of previous studies that the risk of duodenal neoplasms increases with age^[25] and that lesions with depressed morphology tend to include carcinomatous components.^[26] Furthermore, older age (>67 years; OR 4.535) was associated with histopathologic upgrade after endoscopic resection. These results suggest that more active treatment is needed for NADETs detected in older persons, especially those with depressed morphology.

Previous studies have reported that large lesions are more likely to develop histopathologic discrepancies,^[6,22] and 2 or more biopsies tend to increase diagnostic accuracy.^[23] However, the maximum tumor size >15 mm was not associated with histopathologic upgrade after endoscopic resection in the present study. Our different results might be caused by heterogeneity in the baseline clinicopathologic features and differences in the number of endoscopic forceps biopsies included in each study. Considering that multiple biopsies could cause more submucosal fibrosis and make endoscopic resection difficult, it would be reasonable to perform the smallest number of endoscopic biopsies possible to maintain histopathologic accuracy. Therefore, further studies evaluating the minimal number of endoscopic biopsies required, based on lesion area, to reduce the likelihood of histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens are needed. Rigorous targeted biopsies for portions with the most invasive histopathology during endoscopy are essential.

Magnifying endoscopy using narrow-band imaging (ME-NBI), which enables the observation of differences in the microvascular and microsurface patterns between the tumor and surrounding mucosa, is also useful for diagnosing NADETs and predicting their histopathologic grade.^[27–29] Therefore, targeted biopsies using ME-NBI could reduce the risk of histopathologic discrepancies. However, ME-NBI is not available in most hospitals, and the additional role of ME-NBI in NADETs must first be elucidated via further studies.

This study has several limitations. First, as this was a retrospective study that analyzed the histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in NADETs, selection bias may have influenced our results. Second, the number of HGINs and ADCs included in the present study was relatively small compared with the number of LGINs. Further large-scale multicenter studies are necessary to clarify our results.

In conclusion, based on the present study, considerable histopathologic discrepancies exist between endoscopic forceps biopsy and endoscopic resection specimens in NADETs. Our results suggest that endoscopic forceps biopsies may be insufficient for diagnosing NADETs and that endoscopic resection may be considered not only as a treatment modality but also as a diagnostic modality in patients with NADETs. In particular, endoscopists should consider the possibility that the risk of histopathologic upgrade increases when the lesion is found in elderly persons (>67 years).

Author contributions

Conceptualization: Gwang Ha Kim.

- Data curation: Da Mi Kim, Gwang Ha Kim, Seung Min Hong.
- Formal analysis: Da Mi Kim, Bong Eun Lee, Kyungbin Kim, Kyung Un Choi.
- Methodology: Bong Eun Lee, Seung Min Hong, Moon Won Lee. Software: Da Mi Kim, Gwang Ha Kim.
- Supervision: Gwang Ha Kim, Geun Am Song.
- Writing original draft: Da Mi Kim, Gwang Ha Kim.

Writing – review & editing: Da Mi Kim, Gwang Ha Kim, Bong Eun Lee, Kyungbin Kim, Kyung Un Choi, Seung Min Hong, Moon Won Lee, Geun Am Song.

References

- Hochter W, Weingart J, Seib HJ, Ottenjann R. [Duodenal polyps. Incidence, histologic substrate and significance]. Dtsch Med Wochenschr 1984;109:1183–6.
- [2] Jung SH, Chung WC, Kim EJ, et al. Evaluation of non-ampullary duodenal polyps: comparison of non-neoplastic and neoplastic lesions. World J Gastroenterol 2010;16:5474–80.
- [3] Jepsen JM, Persson M, Jakobsen NO, et al. Prospective study of prevalence and endoscopic and histopathologic characteristics of duodenal polyps in patients submitted to upper endoscopy. Scand J Gastroenterol 1994;29:483–7.
- [4] Kakushima N, Ono H, Takao T, Kanemoto H, Sasaki K. Method and timing of resection of superficial non-ampullary duodenal epithelial tumors. Dig Endosc 2014;26(suppl 2):35–40.
- [5] Seifert E, Schulte F, Stolte M. Adenoma and carcinoma of the duodenum and papilla of Vater: a clinicopathologic study. Am J Gastroenterol 1992;87:37–42.
- [6] Okada K, Fujisaki J, Kasuga A, et al. Sporadic nonampullary duodenal adenoma in the natural history of duodenal cancer: a study of follow-up surveillance. Am J Gastroenterol 2011;106:357–64.
- [7] Lee CHA, Shingler G, Mowbray NG, et al. Surgical outcomes for duodenal adenoma and adenocarcinoma: a multicentre study in Australia and the United Kingdom. ANZ J Surg 2018;88:E157–61.
- [8] van Heumen BW, Mul K, Nagtegaal ID, van Kouwen MC, Nagengast FM. Management of sporadic duodenal adenomas and the association with colorectal neoplasms: a retrospective cohort study. J Clin Gastroenterol 2012;46:390–6.
- [9] Ceppa EP, Burbridge RA, Rialon KL, et al. Endoscopic versus surgical ampullectomy: an algorithm to treat disease of the ampulla of Vater. Ann Surg 2013;257:315–22.
- [10] Bourke MJ. Endoscopic resection in the duodenum: current limitations and future directions. Endoscopy 2013;45:127–32.
- [11] Oka S, Tanaka S, Nagata S, et al. Clinicopathologic features and endoscopic resection of early primary nonampullary duodenal carcinoma. J Clin Gastroenterol 2003;37:381–6.
- [12] Takahashi TAT, Kabeshima Y, Kawakubo H, Shito M, Sugiura H, Omori T. Borderline cases between benignancy and malignancy of the duodenum diagnosed successfully by endoscopic submucosal dissection. Scand J Gastroenterol 2009;44:1377–83.
- [13] Lepilliez V, Chemaly M, Ponchon T, Napoleon B, Saurin JC. Endoscopic resection of sporadic duodenal adenomas: an efficient technique with a substantial risk of delayed bleeding. Endoscopy 2008;40:806–10.
- [14] Endo M, Abiko Y, Oana S, et al. Usefulness of endoscopic treatment for duodenal adenoma. Dig Endosc 2010;22:360–5.
- [15] Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut 2002;51:130–1.
- [16] Hirasawa SIH, Tatsuta M, Ishiguro S. Clinicopathologic features and endoscopic resection of duodenal adenocarcinoma and adenomas with the submucosal saline injection technique. Gastrointest Endosc 1997; 46:507–13.
- [17] Hwang KL, Kim GH, Lee BE, Lee MW, Baek DH, Song GA. Long-term outcomes of endoscopic resection for non-ampullary duodenal epithelial tumors: a single-center experience. Turk J Gastroenterol 2020;31:49–57.
- [18] Kim GH, Kim JI, Jeon SW, et al. Endoscopic resection for duodenal carcinoid tumors: a multicenter, retrospective study. J Gastroenterol Hepatol 2014;29:318–24.
- [19] Endoscopic Classification Review Group. Update on the Paris classification of superficial neoplastic lesions in the digestive tract. Endoscopy 2005;37:570–8.
- [20] Edge SB, Compton CC. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. Ann Surg Oncol 2010;17:1471–4.
- [21] Park YJ, Kim GH, Park DY, et al. Histopathologic discrepancies between endoscopic forceps biopsy and endoscopic resection specimens in superficial esophageal squamous neoplasms. J Gastroenterol Hepatol 2019;34:1058–65.
- [22] Kakushima N, Kanemoto H, Sasaki K, et al. Endoscopic and biopsy diagnoses of superficial, nonampullary, duodenal adenocarcinomas. World J Gastroenterol 2015;21:5560–7.

- [23] Kinoshita S, Nishizawa T, Ochiai Y, et al. Accuracy of biopsy for the preoperative diagnosis of superficial nonampullary duodenal adenocarcinoma. Gastrointest Endosc 2017;86:329–32.
- [24] Kim JH, Kim SH, Park WH, et al. Predictable factors of histologic discrepancy of gastric cancer between the endoscopic forceps biopsy and endoscopic treatment specimen. Korean J Gastroenterol 2012;59:354–9.
- [25] Raghav K, Overman MJ. Small bowel adenocarcinomas—existing evidence and evolving paradigms. Nat Rev Clin Oncol 2013;10:534–44.
- [26] Yamanaka TYN, Konishi F. Clinico-pathological study of duodenal adenoma. Gastroenterol Endosc 1987;29:3070–9.
- [27] Tanaka K, Toyoda H, Inoue H, et al. Depressed-type early duodenal carcinoma (carcinoma in situ) observed by enhanced magnification endoscopy. Endoscopy 2007;39(suppl 1):E125–6.
- [28] Tsuji S, Doyama H, Tsuji K, et al. Preoperative endoscopic diagnosis of superficial non-ampullary duodenal epithelial tumors, including magnifying endoscopy. World J Gastroenterol 2015;21:11832–41.
- [29] Kikuchi D, Hoteya S, Iizuka T, Kimura R, Kaise M. Diagnostic algorithm of magnifying endoscopy with narrow band imaging for superficial nonampullary duodenal epithelial tumors. Dig Endosc 2014;26(suppl 2): 16–22.