Original Article

Lesion size, elevated morphology, and non or closed-type atrophy are predictive factors for gastric adenocarcinoma of the fundic gland type rather than oxyntic gland adenoma

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Background: An oxyntic gland neoplasm confined to the mucosal layer (T1a) is classified as an oxyntic gland adenoma, whereas that with submucosal invasion (T1b) is defined as gastric adenocarcinoma of the fundic gland type (GA-FG).

Methods: To reveal the differences in clinical features between them, we retrospectively investigated 136 patients with 150 oxyntic gland adenoma and GA-FG lesions.

Results: The univariate analysis revealed that the mean size (GA-FG *vs.* oxyntic gland adenoma, 7.7±5.4 *vs.* 5.5±3.1 mm), the prevalence of elevated morphology (79.1% *vs.* 51.8%), black pigmentation within the lesion (23.9% *vs.* 9.6%), and non or closed-type atrophy (81.2% *vs.* 65.1%) were different between the two groups. A multivariate logistic regression analysis revealed that ≥5 mm lesion size (odds ratio, 2.96; 95% confidence interval: 1.21–7.23), elevated morphology (odds ratio, 2.40; 95% confidence interval: 1.06–5.45), and no or closed-type atrophy (odds ratio, 2.49; 95% confidence interval: 1.07–5.80) were factors in distinguishing GA-FG from oxyntic gland adenoma. When oxyntic gland neoplasms with no or one feature were judged as oxyntic gland adenomas and those with two or three features were judged as GA-FG, the sensitivity and specificity were 85.1% and 43.4% for GA-FG, respectively.

Conclusions: We identified three possible distinctive features of GA-FG compared to oxyntic gland adenoma: lesion size ≥5 mm, elevated morphology, and no or closed-type atrophy.

Keywords: Gastric adenocarcinoma of the fundic gland type (GA-FG); gastric neoplasms; oxyntic gland adenoma; submucosal invasion

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Introduction

The first case of gastric adenocarcinoma of the fundic gland type (GA-FG) was reported in 2007 as a well-differentiated adenocarcinoma occurring in the cardia of the remnant stomach (1). Subsequently, several researchers collected similar cases and proposed a new concept of disease entities (2-12). Currently, oxyntic gland neoplasms confined to the mucosal layer (T1a) are classified as oxyntic gland adenomas, and oxyntic gland neoplasms with submucosal invasion (T1b) are defined as GA-FG (13). Compared with conventional gastric cancers, oxyntic gland adenoma and GA-FG have unique clinicopathological features, including frequent development in *Helicobacter pylori* (*H. pylori*) infection-negative patients and endoscopic appearance of subepithelial lesion-like morphology with superficial vascular dilatation (14). Additionally, a higher prevalence of submucosal invasion is well-known in this disease as well (13). However, to the best of our knowledge, there is no prediction model for differentiating tumors confined to the mucosa (i.e., oxyntic gland adenoma) from tumors invading the submucosa (i.e., GA-FG). Therefore, in the current study, we analyzed the differences in features between oxyntic gland adenomas and GA-FG. We present the following article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-870/rc).

Highlight box

Key findings

- We revealed the differences in clinical features between oxyntic gland adenoma and gastric adenocarcinoma of the fundic gland type.

What is known and what is new?

- There is no prediction model for differentiating oxyntic gland neoplasms confined to the mucosa from tumors invading the submucosa.
- Lesion size ≥5 mm, elevated morphology, and non- or closed-type atrophy are predictive factors for gastric adenocarcinoma of the fundic gland type.

What is the implication, and what should change now?

- Our predictive model will serve as a practical guide for the management of oxyntic gland neoplasms.

Methods

This study is a subgroup analysis of our recently published article reporting the clinicopathologic features of 165 patients with 180 oxyntic gland adenomas and GA-FG lesions (15). We excluded 24 patients for whom *H. pylori* infection status was not available. We further excluded five patients in whom the depth of invasion was not available because the tumor was not resected. Finally, 136 patients with 150 oxyntic gland adenomas and GA-FG lesions were enrolled in this study.

Histological diagnoses were based on endoscopic biopsy, endoscopic mucosal resection, endoscopic submucosal dissection, or surgical resection (14,15). We compared the patient's sex, age at diagnosis, *H. pylori* infection status, lesion size, location, morphology, and other endoscopic features between oxyntic gland adenoma and GA-FG. The morphology of the neoplastic lesions was classified according to the Japanese Classification of Gastric Carcinoma (16). In the current study, we defined an "elevated lesion" as a tumor with 0–I (polypoid-protruding tumors), 0–IIa (slightly elevated superficial tumors), or 0–IIa+IIc morphology (slightly elevated superficial tumors with slightly depressed area). *H. pylori* infection status was classified as active gastritis (patients with current *H. pylori* infection), inactive gastritis (patients with past infection), or uninfected (*H. pylori*-uninfected patients).

This study was conducted in accordance with the Declaration of Helsinki (as revised in 2013) and was approved by the ethics committees of Okayama University Hospital (No. 2107-011) and other participating institutions. The requirement for written informed consent was waived because of the observational, noninterventional, and retrospective study design. All investigations were performed in accordance with relevant guidelines and regulations.

Statistical analysis

For univariate analysis, variables were analyzed by using a *t*-test, chi-square test or Fisher's exact test. Factors

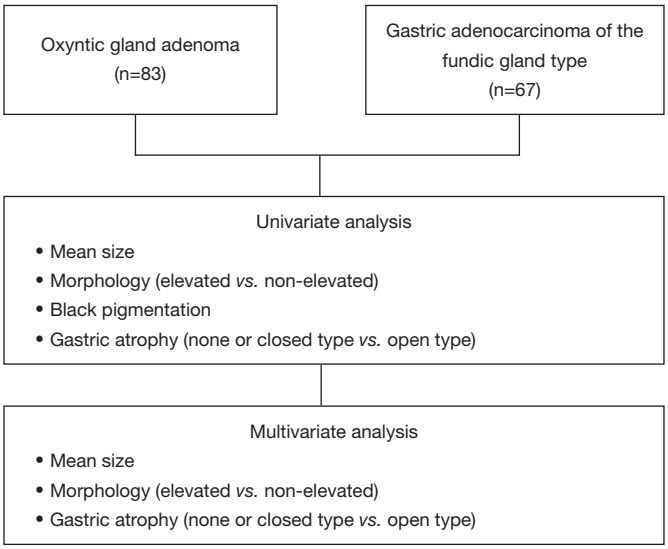

Figure 1 Visual summary of the key study findings.

exhibiting significant values in the univariate analysis were further analyzed by multivariate analysis using logistic regression analysis. Statistical analyses were performed by JMP Pro 14.0.0 software (SAS Institute, Cary, NC, USA), and P<0.05 was considered significant.

Results

Eight patients had two lesions: one patient had two oxyntic gland adenomas, four patients had two GA-FGs, and the remaining three patients had one oxyntic gland adenoma and one GA-FG. Additionally, two patients had four lesions: one patient had four oxyntic gland adenomas, and the other patient had three oxyntic gland adenomas and one GA-FG lesion. The current study included a total of 136 patients with 150 oxyntic gland adenomas and GA-FG lesions (*Figure 1*). Representative endoscopic images of GA-FG and oxyntic gland adenoma are shown in *Figures 2,3*.

A comparison of lesion characteristics between oxyntic gland adenomas and GA-FG is summarized in *Table 1*. The mean size of GA-FG (7.7±5.4 mm) was significantly larger than that of oxyntic gland adenoma (5.5±3.1 mm). GA-FG showed an elevated morphology (79.1%) and a higher prevalence than that of oxyntic gland adenomas (51.8%). GA-FG more frequently had black pigmentation within the lesion (23.9%) than oxyntic gland adenomas (9.6%) (*Figure 4*). Open-type atrophy was less frequently observed in GA-FG (18.8%) than oxyntic gland adenomas (34.9%). No differences were observed in other features such as sex, mean age at diagnosis, lesion location, subepithelial lesion-like morphology, lesion color, vascular dilatation on the surface, and *H. pylori* infection status.

Subsequently, we performed multivariate logistic regression analysis (*Table 2*), which revealed that lesion size of ≥5 mm (odds ratio, 2.96; 95% confidence interval: 1.21–7.23), elevated morphology (odds ratio, 2.40; 95% confidence interval: 1.06–5.45), and no or closed-type atrophy (odds ratio, 2.49; 95% confidence interval: 1.07–5.80) were factors that differentiated GA-FG from oxyntic gland adenoma. In contrast, the presence of black pigmentation within the lesion was not significant in the multivariate analysis, despite its significance in the univariate analysis.

Based on the multivariate analysis, we considered that a lesion size of ≥5 mm (feature 1), elevated morphology (feature 2), and no or closed-type atrophy (feature 3) are characteristic of GA-FG rather than oxyntic gland adenoma. We assigned one point to each feature, and the overall score was calculated based on the number of these three features. When oxyntic gland neoplasms with no feature or at least one feature were categorized as oxyntic gland adenomas and those with two or three features were categorized as GA-FG, the sensitivity and specificity were 85.1% and 43.4% for GA-FG, respectively.

Discussion

In the present study, the number of oxyntic gland adenoma

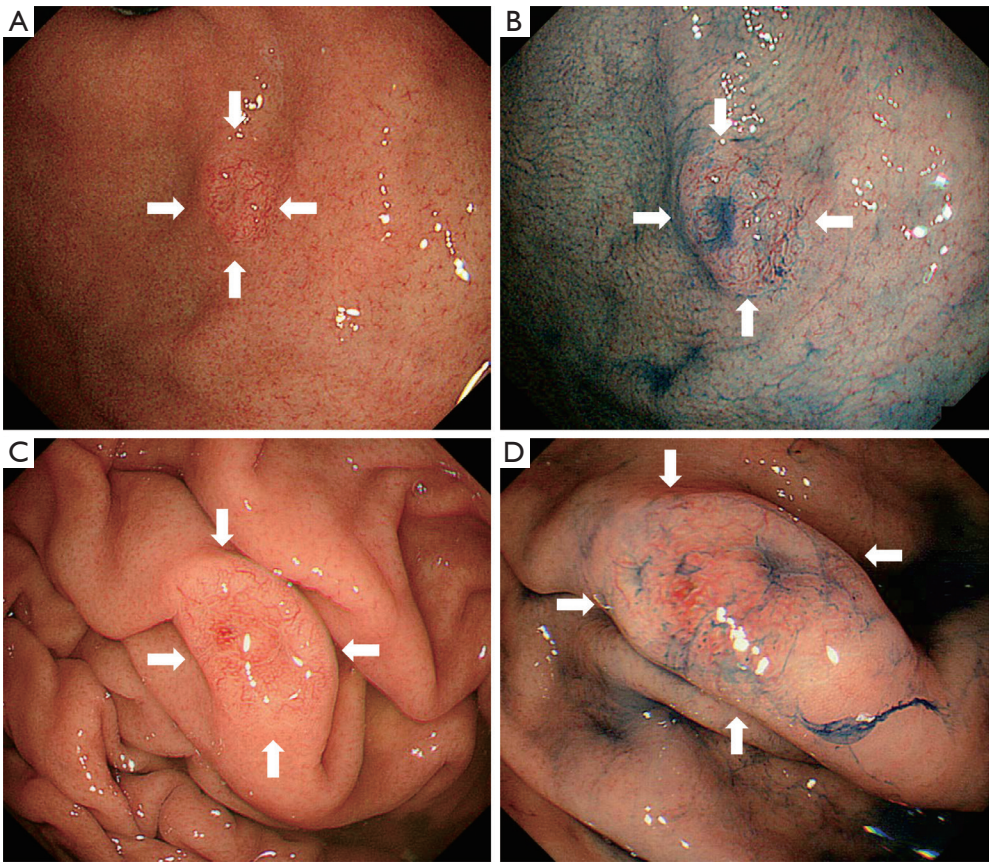

Figure 2 Representative endoscopic images of GA-FG. An elevated tumor of 6 mm in diameter (A,B, arrows) was observed in the non-atrophic mucosa of the gastric fornix (A, white light image; B, after indigo carmine dye spraying). Another patient had an elevated tumor of 10 mm in diameter (C,D, arrows) in the non-atrophic gastric body mucosa (C, white light image; D, after indigo carmine dye spraying). GA-FG, gastric adenocarcinoma of the fundic gland type.

(n=83) and GA-FG (n=67) was in a ratio of approximately 4:3. Benedict *et al.* reported that 32 cases of pT1a, 63 cases of pT1b, and two cases of advanced-stage tumors were included in 111 published cases (17). Hence, the prevalence of oxyntic gland adenomas and GA-FG was in the ratio of 1:2. Concerning the difference in prevalence between our study and the previous reports, publication bias might have existed because more lesions with submucosal or deeper invasion (GA-FG) may have been published than lesions confined within the mucosa (oxyntic gland adenomas). Regardless of the prevalence, oxyntic gland neoplasms frequently invade the submucosa. Oxyntic gland adenomas and GA-FG are composed of highly differentiating columnar cells that mainly differentiate into chief cells and, to a lesser extent, parietal cells (12). Gastric chief cells and parietal cells are located at the base of the fundic glands (i.e., oxyntic glands), which constitute the mucosa of the fundus and body of the stomach. These cells reside at any level in the fundic glands, but the chief and parietal cells are most abundant in the deeper and middle regions of the mucosa, respectively. Therefore, the higher incidence of submucosal invasion in oxyntic gland neoplasms may be explained by the cell of origin.

We revealed that a larger lesion size, elevated tumor morphology, and no or closed-type atrophy in the background gastric mucosa were endoscopic features characteristics of GA-FG, rather than oxyntic gland adenoma. Because large lesion size reflects tumor growth in a horizontal direction and elevated morphology reflects tumor growth in a vertical direction, it is reasonable that these two features correspond to submucosal invasion. In contrast, there is no clear explanation for the association between the grade of gastric atrophy and invasion depth. A possible hypothesis is that, since oxyntic gland

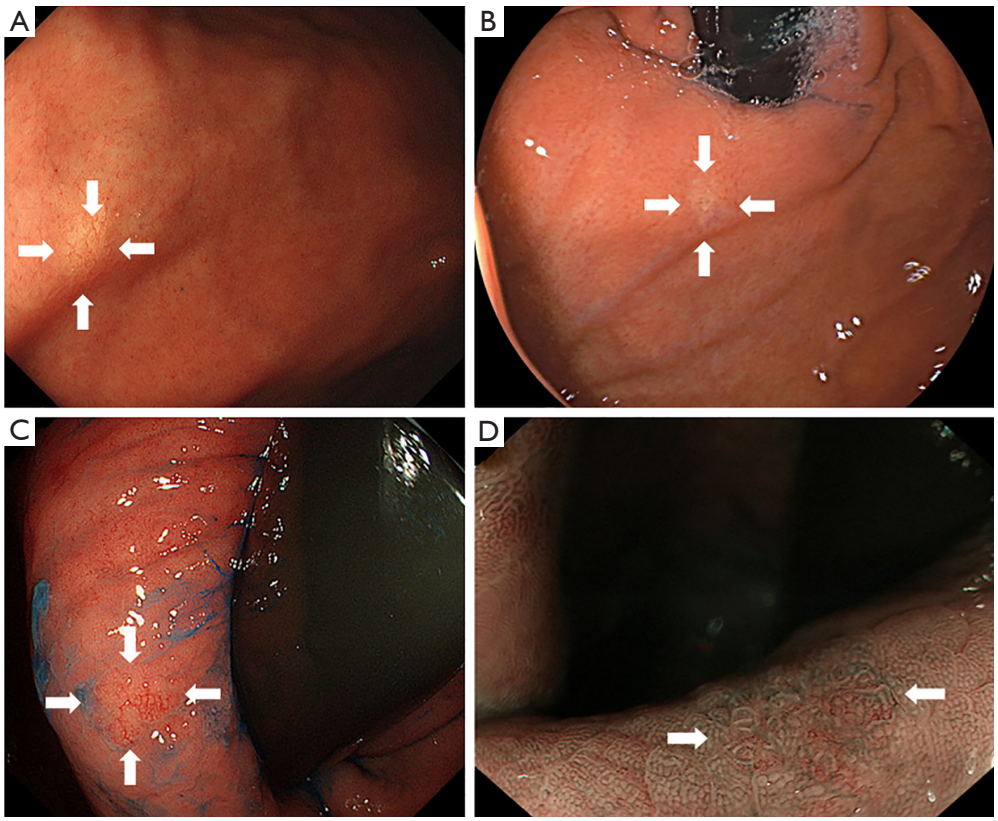

Figure 3 Representative endoscopic images of oxyntic gland adenoma. An elevated, whitish, small tumor of 2 mm in diameter (arrows) was identified in the gastric fornix (A). Open-type atrophy was observed. A flat, whitish lesion of 4 mm in diameter (arrows) was found in the cardia of the stomach with closed-type atrophy (B). Another patient had a slightly depressed lesion of 10 mm in the cardia (C,D, arrows; C, after indigo carmine dye spraying; D, narrow-band imaging observation). The atrophic area was open-type.

neoplasms are generally covered by foveolar epithelium, non or less-atrophic, thick mucosa may conceal the tumor, and small tumors are not easily identified with esophagogastroduodenoscopy.

Based on the results of the present study, we propose a discriminating algorithm to differentiate GA-FG from oxyntic gland adenoma. Our study had several limitations. First, pathologists at various institutions diagnosed the gastric lesions. Interobserver variations and differences in methodologies between the participating pathologists may have resulted in interpretation bias during the analysis of the oxyntic gland adenoma and GA-FG groups. Second, although we proposed a diagnostic algorithm for differentiating GA-FG from oxyntic gland adenoma, a validation study was not conducted. Thirdly, although the sensitivity of our algorithm was relatively high (85.1%), its specificity was low (43.4%). We consider that methods to distinguish between the two diseases are unlikely to be developed because a morphological continuum exists from oxyntic gland adenoma to GA-FG (13). Despite its low specificity, our algorithm can be used to develop appropriate disease management strategies. For instance, en bloc resection with endoscopic submucosal dissection is desirable for preoperatively suspected GA-FG lesions, to evaluate the invasion depth. At the same time, the relatively null result in the present study highlights the morphological continuum between the two categories and the necessity of a thorough pathological evaluation for diagnosis. Although statistical differences were observed in endoscopic findings, such as the size, elevated morphology, and background atrophy, these factors may not be specific for differentiating oxyntic gland adenomas from GA-FGs. Thus, to overcome these issues, validation of our scoring system in a multicenter study with a larger sample size is required.

Table 1 Comparison of oxyntic gland adenoma and GA-FG

Variables	Oxyntic gland adenoma, n (%)	GA-FG, n (%)	P value
Sex			0.508
Male	54 (65.1)	47 (70.1)	
Female	29 (34.9)	20 (29.9)	
Age, mean ± SD, years	66.7±9.1	67.1±8.3	0.784
Size, mean ± SD, mm	5.5±3.1	7.7±5.4	0.002
Location			0.815
Fornix	30 (36.1)	22 (32.8)	
Cardia	10 (12.0)	9 (13.4)	
Body	42 (50.6)	36 (53.7)	
Upper third of the body	21	18	
Middle third of the body	16	14	
Lower third of the body	5	4	
Angle	1 (1.2)	0 (0)	
Antrum	0 (0)	0 (0)	
Pylorus	0 (0)	0 (0)	
Morphology			<0.001
0–I	0 (0)	2 (3.0)	
0–IIa	43 (51.8)	47 (70.1)	
0–IIb	31 (37.3)	12 (17.9)	
0–IIc	9 (10.8)	2 (3.0)	
0–IIa+IIc	0 (0)	4 (6.0)	
0–III	0 (0)	0 (0)	
Macroscopic appearance			0.075
SEL-like	40 (48.2)	42 (62.7)	
Non SEL-like	43 (51.8)	25 (37.3)	
Color			0.288
Similar to the peripheral mucosa	23 (27.7)	24 (35.8)	
Reddish	9 (10.8)	11 (16.4)	
Whitish	27 (32.5)	11 (16.4)	
Yellowish-white	20 (24.1)	17 (25.4)	
Yellowish	4 (4.8)	4 (6.0)	
Vascular dilatation on the surface			0.244
Present	52 (62.7)	48 (71.6)	
Absent	31 (37.3)	19 (28.4)	

Table 1 (*continued*)

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Variables	Oxyntic gland adenoma, n (%)	GA-FG, n (%)	P value
Black pigmentation			0.018
Present	8 (9.6)	16 (23.9)	
Absent	75 (90.4)	51 (76.1)	
H. pylori infection status			0.541
Uninfected	27 (32.5)	25 (37.3)	
Active gastritis	10 (12.0)	5 (7.5)	
Inactive gastritis	46 (55.4)	37 (55.2)	
Gastric atrophy			0.028
None or closed type	54 (65.1)	52 (81.3)	
Open type	29 (34.9)	12 (18.8)	

GA-FG, gastric adenocarcinoma of the fundic gland type; SD, standard deviation; SEL, subepithelial lesion.

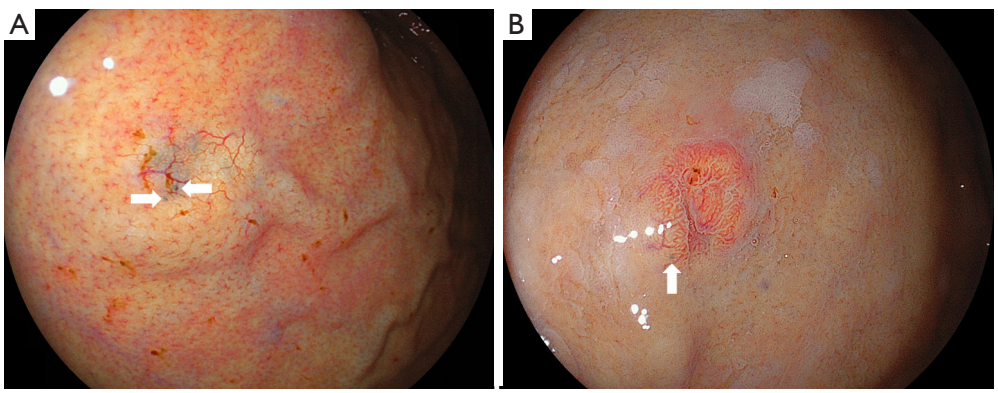

Figure 4 Representative endoscopic images of black pigmentation observed in gastric adenocarcinoma of the fundic gland type. A white, mildly elevated, 10 mm-diameter, superficial tumor was observed in the gastric fornix (A, linked color image). Black pigmentation (arrows) and vascular dilatation were seen on the lesion surface. A reddish, slightly elevated, 5 mm-diameter, superficial tumor was observed in the gastric fornix (B, linked color image) in another patient. Black pigmentation (arrow) and vascular dilatation were seen on the lesion surface.

Table 2 Multivariate logistic regression analysis for differentiating GA-FG from oxyntic gland adenoma

Factor	Comparison	Odds ratio	95% LCL	95% UCL	P value
Lesion size	≥5 *vs.* <5 mm	2.96	1.21	7.23	0.017
Morphology	Elevated *vs.* non-elevated	2.40	1.06	5.45	0.036
Gastric atrophy	None or closed type *vs.* open type	2.49	1.07	5.80	0.034
Black pigmentation	Present *vs.* absent	1.89	0.68	5.30	0.224

GA-FG, gastric adenocarcinoma of the fundic gland type; LCL, lower confidence limit; UCL, upper confidence limit.

Conclusions

In conclusion, we investigated the differences between oxyntic gland adenomas and GA-FG. We identified three possible distinctive features of GA-FG compared to oxyntic gland adenoma: lesion size ≥5 mm, elevated morphology, and no or closed-type atrophy. Oxyntic gland neoplasms with two or three features were judged as GA-FG, with 85.1% sensitivity and 43.4% specificity for GA-FG diagnosis. Future studies with larger sample sizes are required to determine whether GA-FGs have distinct endoscopic features that differentiate it from oxyntic gland adenomas.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-870/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-870/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-22-870/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the ethics committees of Okayama University Hospital (No. 2107-011) and other participating institutions. The requirement for written informed consent was waived because of the observational, noninterventional, and retrospective study design.

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