Elevated PGE2 and COX-2 expression in villous adenoma: Implications for electrolyte depletion syndrome

SHIKI FUJINO[1,2*], HIROYUKI FUKUDA[1*], KATSUKI DANNO[1], TAKASHI TAKEDA[1], MASAYA HIGASHIGUCHI[1], KOZO NOGUCHI[1], TAKEFUMI HIRAO[1], AYA ITO[2], NORIKATSU MIYOSHI[2] and YOSHIO OKA[1]

[1]Department of Surgery, Minoh City Hospital, Minoh, Osaka 562-0014, Japan; [2]Department of Innovative Oncology Research and Regenerative Medicine, Osaka International Cancer Institute, Osaka 541-8567, Japan

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Abstract. The present study aimed to clarify the role of prostaglandin E2 (PGE2) signaling in the pathogenesis of electrolyte depletion syndrome (EDS) in colorectal villous adenomas (VAs), which are characterized by excessive mucus secretion and higher malignant potential compared with tubular adenomas (TAs). A retrospective analysis was conducted on 40 colorectal adenoma cases (20 VAs and 20 TAs) resected between January 2011 and September 2021. Clinicopathological factors such as age, sex, tumor location and size were compared. In addition, immunohistochemical staining for PGE2, COX-1 and COX-2 was performed, and the percentage of positive glands was quantified. Associations between PGE2 and COX isoform expression were then analyzed. The results revealed that VAs were more prevalent in female patients (P=0.022) and exhibited a significantly larger tumor size than TAs (21.3±22.5 mm vs. 9.6±7.8 mm, P=0.018). Furthermore, PGE2 and COX-2 expression were significantly elevated in VAs compared with in TAs (P<0.001 and P=0.022, respectively), whereas COX-1 levels were similar. In VAs, PGE2 expression was weakly-to-moderately associated with COX-1 and associated with COX-2 (trend), whereas no associations were observed in TAs. In conclusion, PGE2 upregulation may contribute to EDS in VAs, underscoring the need for early recognition and targeted therapeutic approaches.

Introduction

Although villous adenomas (VAs) are an uncommon subtype of colonic adenomas, they are clinically important due to their tendency to grow large, produce copious mucus, and induce fluid and electrolyte disturbances (1,2). This mucinous and electrolyte-rich secretory activity is thought to be driven by elevated levels of prostaglandins, especially prostaglandin E2 (PGE2), which can stimulate intracellular cAMP and promote fluid secretion (3,4). Despite this established mechanism, direct comparative analyses of PGE2 and its related enzymatic pathways between VAs and other adenoma subtypes remain limited.

VAs account for approximately 5 to 15% of all colonic adenomas and are predominantly located in the rectosigmoid colon (1,2). The reported incidence of coexistent carcinoma in VAs is high. When these tumors reach a substantial size, they may produce excessive mucin, leading to electrolyte disturbances, renal dysfunction, and, in some cases, neuropsychiatric symptoms (2,5). In certain cases, VAs can secrete large amounts of mucus, resulting in dehydration and severe electrolyte imbalance, a condition referred to as Electrolyte Depletion Syndrome (EDS). Originally documented by McKittrick and Wheelock in 1954 (6), this condition, commonly referred to as McKittrick-Wheelock Syndrome, is typified by potassium-rich, tumor-derived mucus. The pathogenesis is believed to involve upregulated PGE2 production with consequent increases in intracellular cAMP, both contributing to the exaggerated secretory response (3,4). Reports of symptomatic improvement with indomethacin, a PGE2 synthesis inhibitor, suggest its potential usefulness as a temporary bridging therapy prior to definitive resection (4,7). Moreover, clinical case reports have described the characteristic features of McKittrick-Wheelock Syndrome associated with VAs, emphasizing the importance of early recognition and appropriate management (8).

This study aims to characterize the differential expression of PGE2, COX-1, and COX-2 in villous vs. tubular adenomas (TAs), with the goal of elucidating their roles in mucin hypersecretion and identifying potential therapeutic implications.

Patients and methods

Patients and tissue samples. VA cases were first identified by reviewing all patients who underwent endoscopic or surgical resection at Minoh City Hospital (Minoh, Japan) between January 2011 and September 2021. During this period, twenty consecutive VA cases met the inclusion criteria and

Correspondence to: Dr Shiki Fujino, Department of Innovative Oncology Research and Regenerative Medicine, Osaka International Cancer Institute, 3-1-69 Ohtemae, Chuo, Osaka 541-8567, Japan
E-mail: sfujino@gesurg.med.osaka-u.ac.jp

*Contributed equally

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had adequately preserved formalin-fixed, paraffin-embedded (FFPE) tissue suitable for immunohistochemical analysis. To allow for a balanced comparison, an equal number of TA cases were then selected consecutively from the same database, matched to the availability of high-quality FFPE tissue. Clinicopathological data, including patient age, sex, tumor location, and tumor size (maximum diameter measured endoscopically or pathologically), were collected and compared between groups. Patients with conditions that could potentially influence prostaglandin metabolism or mucosal inflammatory status were excluded. Specifically, exclusion criteria consisted of: i) Long-term regular use of nonsteroidal anti-inflammatory drugs (including low-dose aspirin or COX-2 inhibitors); ii) systemic immunosuppressive therapy such as chronic corticosteroids, calcineurin inhibitors, or anti-TNF agents; iii) a history of inflammatory bowel disease (ulcerative colitis or Crohn's disease); iv) hereditary colorectal cancer syndromes including familial adenomatous polyposis or Lynch syndrome; and v) inadequate or poorly fixed tissue unsuitable for immunohistochemical evaluation. No patients in this cohort met any of these exclusion criteria, allowing all eligible consecutive cases to be included in the final analysis. This study was conducted in accordance with The Declaration of Helsinki and was approved by the Ethics Committee of Minoh City Hospital (approval no. R0311B64). As a retrospective study, written informed consent was waived, and an opt-out approach was implemented by publicly disclosing study information on the hospital website to provide patients with the opportunity to decline participation.

Immunohistochemistry. Immunohistochemical staining was performed using 3-μm FFPE sections. Antigen retrieval was carried out by heating the sections in citrate buffer (pH 6.0) in a pressure cooker for 15 min. The primary antibodies used were anti-PGE2 (ab2318, Abcam, Cambridge, UK; dilution 1:100), anti-COX-1 (ab109025, Abcam, Cambridge, UK; dilution 1:150), and anti-COX-2 (ab15191, Abcam, Cambridge, UK; dilution 1:100). Sections were incubated with primary antibodies overnight at 4˚C, followed by incubation with appropriate secondary antibodies (Vector Laboratories, Burlingame, CA, USA) and visualization using the ImmPACT DAB substrate kit (SK-4105, Vector Laboratories, Burlingame, CA, USA). Counterstaining was performed with hematoxylin. Negative controls were prepared by omitting the primary antibody. As no standardized or universally accepted cutoff for COX-1, COX-2, or PGE2 immunohistochemical positivity has been established in colorectal neoplasia, a threshold was determined *a priori* based on both morphological clarity and interobserver reproducibility. Immunostaining was evaluated manually, without the use of image-analysis software, by three independent investigators. The percentage positivity was estimated on an area basis by visually assessing the proportion of the glandular area exhibiting cytoplasmic or membranous staining within the entire adenomatous component. Glands were classified as positive when ≥10% of the glandular area exhibited cytoplasmic or membranous staining. Staining below this level was consistently interpreted as minimal and lacked biological significance. This threshold was supported by the high concordance of independent assessments performed by three investigators. For each case, at least 50 glands were evaluated to determine the percentage of positive glands.

Table I. Clinicopathological characteristics of patients with tubular and villous adenomas.

Characteristic	Tubular adenoma (n=20)	Villous adenoma (n=20)	P-value
Age, years	68.8±9.9	72.5±9.6	0.203
Sex, Male/Female	16/4	8/12	0.022
Location, A/T/D/S/R	2/3/5/6/4	1/2/3/6/8	-0.729
Size, mm	9.6±7.8	21.3±22.5	0.018

Data are presented as mean ± standard deviation or as absolute numbers. A, ascending colon; T, transverse colon; D, descending colon; S, sigmoid colon; R, rectum.

Statistical analysis. Comparisons of clinicopathological factors and immunohistochemical expression between the VA and TA groups were performed using the Wilcoxon rank-sum test or Fisher's exact test, as appropriate. Associations between PGE2 and COX-1/COX-2 expression were assessed using simple linear regression to illustrate the direction and magnitude of the association. All statistical tests were two-tailed, and $P<0.05$ was considered to indicate a statistically significant difference. Statistical analyses were conducted using JMP Student Edition 18.2.2 (SAS Institute).

Results

Clinicopathological features. The clinicopathological characteristics of the 40 colorectal adenoma cases, comprising 20 TA and 20 VA, are summarized in Table I. Patients with VA tended to be older (mean age 72.5±9.6 years) than those with TA (68.8±9.9 years), although this difference did not reach statistical significance (P=0.203). A significant sex difference was observed between the groups: the TA group had a predominance of male patients (16 males, 4 females), whereas the VA group showed a female predominance (8 males, 12 females), a difference that was statistically significant (P=0.022). The anatomical distribution also differed slightly. VAs were more frequently located in the distal colon, especially in the rectum and sigmoid colon, although the statistical power for segment-based comparison was limited due to small subgroup sizes. Notably, VAs were significantly larger than TAs, with mean lesion diameters of 21.3±22.5 mm vs. 9.6±7.8 mm, respectively (P=0.018).

Immunohistochemical findings. Fig. 1 presents representative immunohistochemical staining for PGE2, COX-1 and COX-2. Each gland was assessed based on the proportion of the stained area. Glands in which the stained area comprised less than 10% were considered negative, whereas those in which the stained area exceeded 10% were considered positive. The proportion of positive glands was calculated as follows: (number of positive glands/total number of glands) x100. The

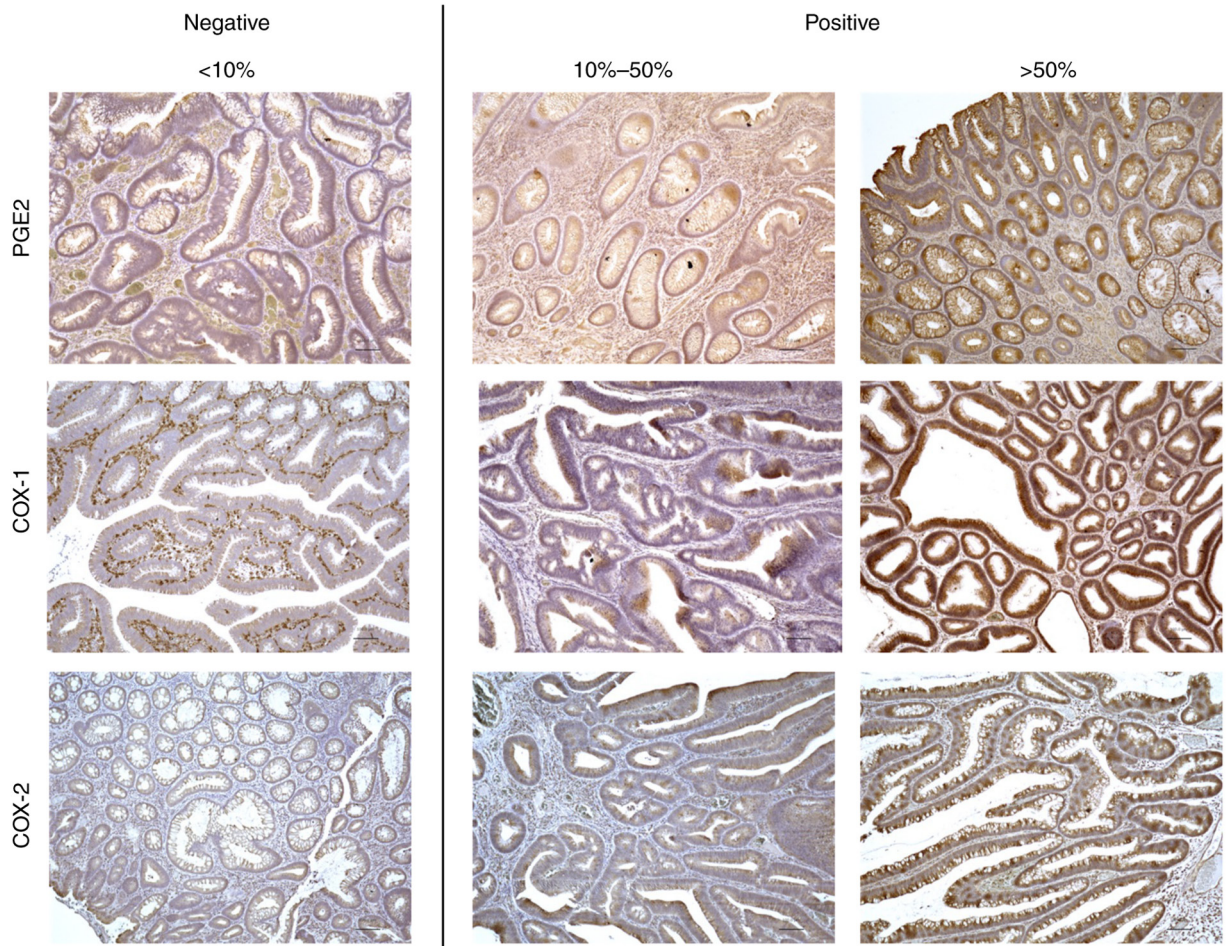

Figure 1. Representative immunohistochemical staining for PGE2, COX-1 and COX-2. Formalin-fixed, paraffin-embedded sections were immunostained for PGE2, COX-1 and COX-2 (brown), and counterstained with hematoxylin (blue). Images illustrate the staining categories used for scoring (negative, 10-50, and >50%) and are intended as examples of staining intensity, not as specific TA or VA cases. The representative images include TA and VA samples. Scale bars: 100 μm. PGE2, prostaglandin E2.

Table II. Proportion of positive glands in tubular and villous adenoma.

Protein	Tubular adenoma (n=20)	Villous adenoma (n=20)	P-value
PGE2	24±4.8	83±4.1	<0.001
COX1	33±5.8	33±5.7	0.480
COX2	41±6.3	59±6.2	0.022

Data are presented as mean ± standard deviation.

proportion of positive glands was significantly higher in VAs compared to TAs for PGE2 (83±4.1% vs. 24±4.8%, P<0.001) and COX-2 (59±6.2% vs. 41±6.3%, P=0.022), while COX-1 expression did not differ between the two groups (33±5.7% vs. 33±5.8%, P=0.48) (Table II). Association analyses were performed to assess the relationships between PGE2 expression and COX-1/COX-2 in tubular and VAs (Fig. 2). In VAs, PGE2 expression demonstrated a weak-to-moderate association with COX-1, which was statistically significant (R^2=0.325, P=0.009), and a weak association with COX-2, with only a trend toward significance (R^2=0.193, P=0.053). In TAs, no meaningful associations were observed (R^2=0.082, P=0.220 for COX-1; R^2=0.014, P=0.619 for COX-2). These findings indicate that PGE2-COX associations are more pronounced in VAs than in TAs.

Discussion

In this study, we observed that VAs exhibited substantially higher expression of PGE2 and COX-2 compared to TAs, while COX-1 expression showed no notable differences. Association analyses further revealed that in VAs, PGE2 expression showed a weak-to-moderate association with COX-1 and a weak association with COX-2, whereas such associations were not observed in TAs. These findings suggest a distinct upregulation of the PGE2 signaling pathway in VAs, potentially contributing to their unique biological and clinical characteristics (9,10). Previous reviews have reported that VAs tend to occur more frequently in the distal colon, which is consistent with our findings (2). Case-based literature often describes VAs as large lesions associated with marked clinical manifestations, such as electrolyte disturbances seen in McKittrick-Wheelock syndrome (2). In contrast, many VAs in our cohort were incidentally detected and did not present with

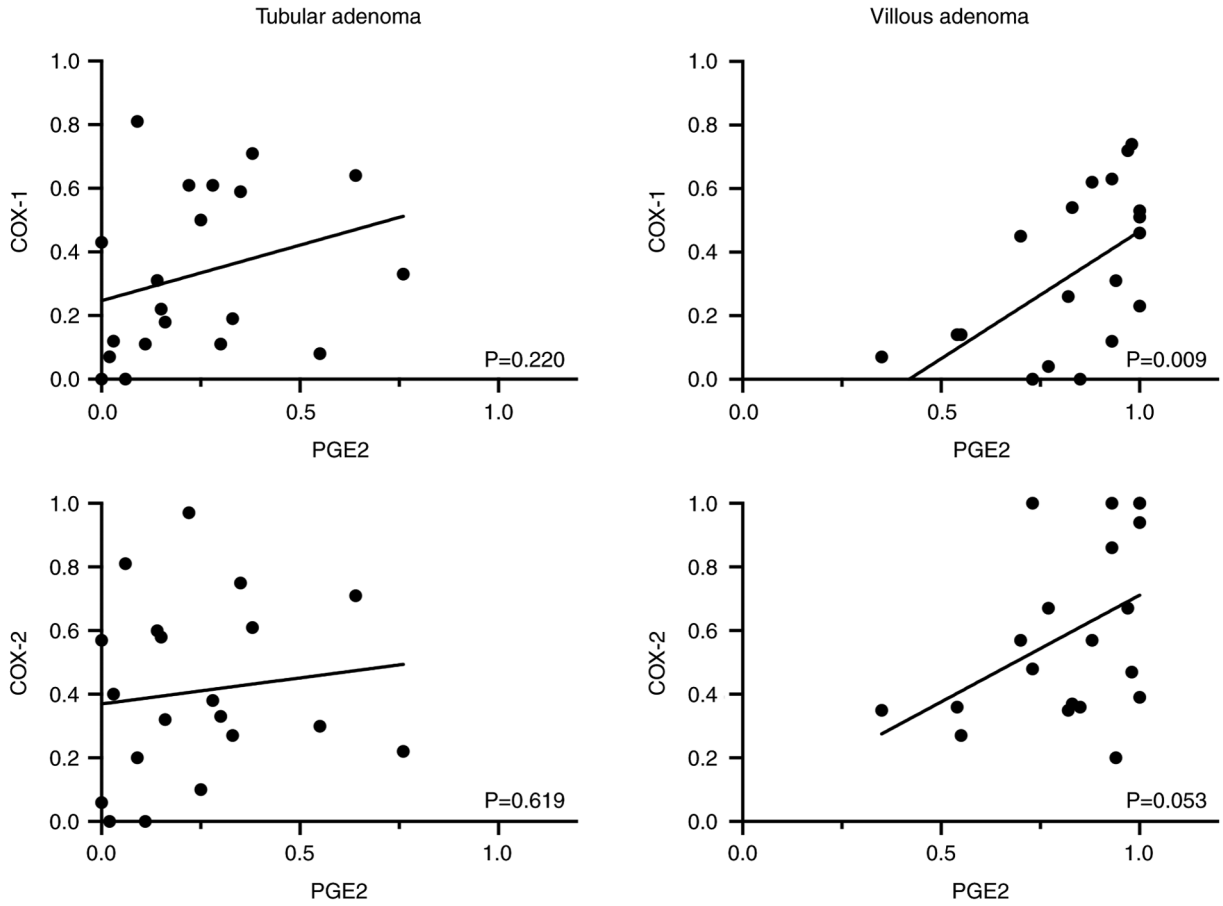

Figure 2. Association analysis between PGE2 expression and COX-1/COX-2 expression in tubular and villous adenomas. Scatter plots and linear regression lines illustrate the relationships between PGE2 and COX-1 (top panels) or PGE2 and COX-2 (bottom panels) in tubular adenomas (left) and villous adenomas (right). In villous adenomas, association analysis revealed a weak-to-moderate positive association between PGE2 and COX-1 expression (R^2=0.325, P=0.009) and a weak positive trend with COX-2 (R^2=0.193, P=0.053). By contrast, no significant associations were detected in tubular adenomas.

overt symptoms, which likely explains their comparatively smaller size despite still being significantly larger than TAs. In our institutional experience, larger VAs showed a tendency to develop electrolyte derangements (data not shown), supporting the notion that lesion size may contribute to the likelihood of clinically significant secretory activity.

The pivotal role of the PGE2 signaling axis in colorectal tumorigenesis and progression has been well documented (9,10). PGE2, primarily produced via COX-2-mediated catalysis, promotes colorectal carcinogenesis by enhancing cell proliferation, angiogenesis, and immune evasion (9-11). Our findings of elevated PGE2 and COX-2 expression in VAs align with this understanding, suggesting that VAs may represent lesions with a more aggressive molecular phenotype compared to TAs. In contrast, the absence of significant associations in TAs indicates that PGE2 signaling is less active in these lesions, consistent with their generally lower malignant potential (1).

Previous studies have also indicated that COX-1 may participate in PGE2 biosynthesis and colorectal neoplasia, particularly in the early stages of adenoma development (12). This is further supported by evidence showing that combined COX-1 and COX-2 activity is elevated in non-neoplastic colonic mucosa from patients with colorectal neoplasia (13). These data suggest that COX-1, traditionally considered a constitutive enzyme, may play a complementary role alongside COX-2 in the biology of VAs. Although COX-1 is classically regarded as a constitutive isoform, emerging evidence suggests that its functional contribution may be selectively amplified in pre-neoplastic and neoplastic contexts without a corresponding increase in protein abundance. In intestinal tumorigenesis models, COX-1-derived PGE2 production has been shown to drive the early phase of polyp initiation before COX-2 induction (14). In our study, COX-1 expression levels were comparable between TAs and VAs; however, a significant association with PGE2 was observed only in VAs. This may reflect the villous architecture, characterized by a large surface area, high secretory activity, and rapid epithelial turnover, facilitating more efficient coupling between constitutively expressed COX-1 and downstream prostanoid synthesis.

Clinically, our findings underscore the importance of early colonoscopic evaluation and timely intervention in patients with suspected EDS. VAs are well recognized as the principal cause of EDS due to their copious secretion of potassium- and chloride-rich mucus, driven in part by PGE2-mediated mechanisms (3,4,8). The markedly elevated PGE2 and COX-2 expression observed in our VA cohort reinforces the mechanistic link between PGE2 overproduction and the secretory diarrhea and electrolyte imbalance

characteristic of EDS (4,8). Although VAs are typically managed with endoscopic or surgical resection (1,7), our findings highlight the need for prompt recognition and early treatment in patients presenting with secretory diarrhea, dehydration, or electrolyte disturbances suggestive of EDS. Short-term COX inhibition has been reported to ameliorate PGE2-driven secretory symptoms and may serve as a bridging measure before definitive resection.

The use of COX-2 selective inhibitors or NSAIDs could also be considered as temporary supportive therapy to mitigate secretory symptoms by suppressing PGE2 synthesis (15), although this must be balanced against the known gastrointestinal and cardiovascular risks associated with long-term COX-2 inhibition (16,17).

Beyond these immediate implications, understanding the distinct PGE2 signaling patterns in VAs may provide insights into early tumorigenic processes, as VAs represent an intermediate stage between benign adenomas and malignant transformation (9,10). Advances in digital pathology (18) and molecular profiling, including liquid biopsy (19), may further enhance the precision of VA characterization in future studies.

This study has several limitations. First, the retrospective single-center design and small sample size limit the generalizability of our findings. The number of evaluable VAs was constrained by the availability of well-preserved archival tissue, reducing statistical power, particularly for subgroup and association analyses, and likely contributing to some nonsignificant results. Second, the 10% positivity cutoff for immunohistochemistry is not universally standardized and remains an empirical threshold, although interobserver agreement was high. Third, we evaluated only PGE2, COX-1, and COX-2 expression and did not assess downstream pathways or additional regulatory molecules, limiting mechanistic interpretation. Finally, the lack of multicenter validation and functional assays underscores the need for further studies to confirm and expand upon these findings.

In conclusion, this study demonstrates that VAs exhibit marked activation of the PGE2 signaling pathway, driven by increased COX-2 expression and strengthened functional coupling with COX-1. This coordinated upregulation provides a mechanistic explanation for both the secretory phenotype and the development of EDS in affected patients. These findings underscore the importance of early recognition and timely intervention for suspected EDS and suggest that short-term modulation of PGE2 synthesis may serve as a potential perioperative strategy to alleviate severe secretory symptoms prior to definitive resection.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

SF conceived and designed the study, performed data analysis and drafted the manuscript. HF contributed to data acquisition, assisted in writing and participated in patient management. KD, TT, MH, KN and TH were responsible for reviewing the patients' postoperative clinical course, acquisition of data and data verification. AI and NM conducted immunohistochemistry and performed laboratory analyses. YO made a substantial contribution to the conception of the study, provided overall supervision and critically revised the manuscript. SF and HF confirm the authenticity of all the raw data. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with The Declaration of Helsinki and was approved by the Ethics Committee of Minoh City Hospital (approval no. R0311B64). The requirement for written informed consent for the use of residual specimens was waived due to the retrospective design, and study information was disclosed on the hospital website to provide patients the opportunity to decline participation (opt-out procedure).

Patient consent for publication

The requirement for individual patient consent for publication was waived, as this study was conducted under an institutional opt-out policy.

Competing interests

The authors declare that they have no competing interests.

Use of artificial intelligence tools

During the preparation of this work, an AI tool was used to improve the readability and language of the manuscript, and subsequently, the authors revised and edited the content produced by the AI tool, taking full responsibility for the ultimate content of the present manuscript.

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