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Postoperative Outcomes and Strategic Refinement in Intraductal Papillary Mucinous Neoplasm Management: A Single Academic Cancer Center Experience

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Abstract

Background/Aim: Intraductal papillary mucinous neoplasm (IPMN) of the pancreas is a precursor lesion with variable malignant potential. Due to its heterogeneity, optimal treatment strategies remain controversial, especially regarding surgical resection and surveillance indications. We reviewed our institutional outcomes to reassess the current postoperative strategy and refine management guidelines.

Patients and Methods: This study retrospectively and consecutively analyzed the data of 49 IPMN patients who underwent pancreatectomy at an academic institution from 2015 to May 2025.

Results: Diagnostic mismatch between preoperative and final pathological findings was observed in 39% of cases, with overdiagnosis (downgrade group) being more common than underdiagnosis. Overdiagnosed cases were significantly associated with main pancreatic duct dilation (>5 mm) (p=0.012) and elevated amylase levels (p=0.031), while the only upgraded case involved invasive carcinoma with mural nodule and Sonazoid enhancement. Histological grade strongly influenced prognosis: Patients with adenoma or carcinoma *in situ* showed favorable outcomes (5-year OS ≥89%), whereas those with invasive IPMN had markedly worse survival (5-year OS 36%; p<0.001). Elevated CA19-9 was a significant negative prognostic factor (p=0.031), while lymph node metastasis (p=0.035) and advanced tumor stage (p=0.0014) were also associated with poor outcomes. Tumors located in the pancreatic tail and those classified as mixed-type IPMN tended to have inferior survival, though without statistical significance. Cancer recurrence occurred in 18% of patients, primarily *via* peritoneal and hepatic routes.

Conclusion: Preoperative diagnostic inaccuracies remain common in IPMN, and invasive transformation, elevated CA19-9, lymph node metastasis, and tumor stage are key prognostic factors. A multimodal diagnostic approach is needed to improve risk stratification and guide appropriate surgical management.

Keywords: Intraductal papillary mucinous neoplasm (IPMN), pancreatectomy, postoperative outcomes, surveillance strategy, malignant potential.

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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas represent a heterogeneous group of cystic lesions with varying malignant potential. Over the past decade, international consensus guidelines have been refined to optimize the surgical management of IPMNs and reduce overtreatment (1-3). However, in real-world clinical practice, several challenges remain in accurately selecting patients who benefit from surgical resection.

In our institutional experience at a single academic cancer center, we identified three major issues despite adherence to current guidelines. There remains a high rate of discrepancy between preoperative cytological diagnosis using endoscopic ultrasound-guided fine-needle aspiration or biopsy (EUS-FNA or -FNB) and final postoperative histopathology. This often leads to unnecessary pancreatectomy for lesions that ultimately prove to be low-grade adenomas (4-6). While, the incidence of remnant pancreatic recurrence was extremely low among patients who underwent partial pancreatectomy, raising questions about the necessity of total pancreatectomy in cases without high-risk stigmata (7-9). Total pancreatectomy remains a radical surgical option for IPMN associated with significant physiological and quality-of-life burdens. From a quality-of-life perspective, the dual burden of diabetes and digestive insufficiency often results in marked reductions in postoperative independence and well-being (7). Importantly, in IPMNs, the incidence of recurrence in the remnant pancreas following partial pancreatectomy is low, raising concerns about the potential overtreatment of total pancreatectomy. For IPMNs that have progressed to invasive carcinoma, the lack of an established neoadjuvant chemotherapy strategy continues to correlate with dismal postoperative outcomes (10-12).

Despite advances in international guidelines for managing IPMNs, significant uncertainty remains in real-world surgical decision-making, particularly regarding the indications for resection and the extent of pancreatectomy. Although oncologically definitive, total pancreatectomy imposes profound metabolic burdens that may not be justified in all cases, especially when the risk of remnant pancreatic recurrence is low. Furthermore, the discrepancy between preoperative cytologic findings and final pathology continues to lead to potentially avoidable surgeries for non-invasive disease. In this context, a focused analysis of a single-institution cohort, where patient selection, surgical strategy, and postoperative outcomes can be examined in a consistent and controlled clinical framework, offers a unique opportunity to reassess the appropriateness of surgical indications and to identify parameters predictive of overtreatment or undertreatment. Such data can provide valuable insight into refining operative strategies for IPMN and potentially contribute to the evolution of personalized surgical guidelines. We hypothesize that in a single-institution cohort of resected IPMN cases, 1) a significant proportion of patients underwent surgery for non-invasive disease due to limited diagnostic accuracy of preoperative cytology; 2) recurrence in the remnant pancreas after partial pancreatectomy is infrequent, suggesting limited indications for total pancreatectomy; and 3) patients with invasive IPMN demonstrate poor postoperative outcomes in the absence of neoadjuvant therapy, underscoring the need for integrated oncologic strategies.

To clarify this hypothesis, we retrospectively analyzed 49 patients who underwent surgical resection for IPMNs at our single academic cancer center. We evaluated clinical, radiologic, cytologic, and histopathologic features to assess the appropriateness of surgical indication and the diagnostic concordance between preoperative and postoperative findings. Furthermore, a survival analysis was performed with complete follow-up data to investigate long-term outcomes, particularly recurrence patterns and prognostic factors in invasive *versus* non-invasive IPMN. This study aims to clarify the current challenges in IPMN management and to provide evidence for more refined surgical decision-making.

Patients and Methods

Patients' background. All 49 patients with IPMN who underwent surgical treatment at the Department of

Surgery, Faculty of Medicine, University of Miyazaki, were examined consecutively over a 10-year period from April 2015 to May 2025. Clinical and perioperative data were retrospectively retrieved from patient medical records, including anesthetic charts, electronic hospital records, and institutional databases. The study protocol was approved by the Ethics Review Board of the University of Miyazaki (approval number: O-1802; approval date: October 26, 2025). In accordance with institutional ethical standards, patient consent was obtained through an opt-out process announced publicly in the outpatient clinic and on the institutional website for one month. This study was conducted in compliance with the Declaration of Helsinki, including the principles governing research involving identifiable human materials and data. Data for the duration of the initial hospitalization following radical surgery, as well as information recorded in electronic medical records at the participating institutes, were reviewed. Patient outcomes were determined using these collected data and verified by the co-authors.

Comparative measurement of tumor markers and histological findings. Patients' clinicopathological data were retrieved from our institute's archives. Peripheral blood samples were collected from each patient early in the morning before surgery, when the patient was stable. Tumor-related factors were compared with the histopathological findings of the resected specimen. For the clinicopathological assessment of pancreatic cancer (PC), we used the 7th edition of *General Rules for the Study of Pancreatic Cancer by the Japan Pancreas Society* (13). As a surgical strategy of our institute, IPMN indicating findings of high-risk stigmata (7-9), and those of worrisome features are carefully observed. In certain cases, patients proceeded to surgery when their worrisome features evolved toward findings consistent with high-risk stigmata.

Statistical analysis. Differences in categorical data between groups and prevalence were assessed using the chi-square test, Fisher's exact test, or Dunnett's multiple comparison test. Differences in continuous data between groups were evaluated using Student's *t*-test or the Mann-Whitney test. A two-tailed *p*-value of <0.05 was considered statistically significant. The Kaplan-Meier method was used to analyze survival, and the log-rank test was used to compare survival curves. Statistical analyses were performed using SPSS version 23 (Statistical Package for the Social Sciences Inc., Chicago, IL, USA).

Results

Perioperative parameters. The basic data of 49 patients are indicated as follows: male gender was 28 (57%), and a mean age of 68.8±8.9 years at the time of surgery (ranging from 45 to 82 years old). The disease was adenoma (IPMA) in 26 (53%), carcinoma *in situ* (IPMC) in 11 (23%), and invasive IPMC in 12 (24%). The primary tumor location was the head in 19 patients (39%), the head and body in five (10%), the body in 13 (27%), the body and tail in six (12%), and the tail in six (12%). Asymptomatic patient were 34 (69%), abdominal pain was observed in seven (14%), jaundice in two, pancreatitis in four, and others in two. Various co-morbid diseases were observed in 35 patients (71%). Multiple cancers were observed in 16 (33%), including metachronous pancreatic head carcinoma in two patients, synchronous gastric cancer in two, uterine cancer in four, breast cancer in five, and others. Preoperative laboratory data included carcinoembryonic antigen (CEA) (mean 3.7±4.0 ng/ml) and CA19-9 (mean 183±970 U/ml), elastase-1 level (mean 228±347 ng/dl), DUPAN-II (mean 77±112 U/ml), red cell count (mean $428±55×10^4/mm^3$), hemoglobin level (mean 13.3±1.5 g/dl), and amylase level (mean 85±33 mg/dl).

Concerning pancreatectomy, subtotal stomach-preserving pancreaticoduodenectomy was performed in 21 patients (43%), and laparoscopic distal pancreatectomy was performed in six patients (12%). The mean blood loss was 606±497 ml, and the mean operative time was 447±156 min. The type of IMPN was the main duct type in 10 patients (20%), the branch type in 24 (49%), and the

Table I. *Relationship between diagnostic mismatch of intraductal papillary mucinous neoplasm (IPMN) and clinicopathological findings.*

	Matching			Significance
	Match (n=29)	Downgrade (n=19)	Upgrade (n=1)	*p*-Value
Age (years)	68.5±9.8	68.8± 7.6	76	
Sex, Male/Female	16/13	11/8	1/0	0.67
Final diagnosis, Adenoma	8	18	0	<0.001
IPMC in situ or microinvasion	10	1	0	
Invasive IPMC	11	0	1	
Tumor location, Head	11	13	0	0.012
Body	13	6	0	
Tail	5	0	1	
Co-malignancy				
Pancreatic cancer, No/yes (n=1)	28/1	19/0	1/0	0.703
Other cancers, No/yes (n=15)	19/10	14/5	1/0	0.667
CEA (ng/dl)	3.9±4.8	3.5±2.5	1.8	
CA19-9 (U/ml)	274±1253	52±136	19	
WBC (/mm^3)	5,817±1,826	4,978±1,219	7,200	
RBC (×10^4/mm^3)	416±50	445±60	456	
Hemoglobin (g/dl)	13.1±1.3	13.7±1.9	13.8	
Platelet count (×10^4/mm^3)	23.1±6.5	21.6±7.8	26.8	
Amylase level (mg/dl)	73.6±21.8	100.8±40.7*	90	
Pancreatic duct dilation >5 mm, No/yes (n=29)	16/13	3/16	1/0	0.012
Pancreatic duct size (mm)	6.2±4.6	8.1±5.1		
Mural nodule, No/yes (n=46)	2/27	1/18	0/1	0.877
Mural nodule size (mm)	16.0±10.4	15.3±4.7	21.4	
Enhancement by Sonazoid[#], No/yes (n=22)	0/11	2/10	0/1	0.336
Pancreaticoduodenectomy, No/yes (n=24)	17/12	7/12	1/0	0.206
Type of IPMN, Main duct type (n=12)	10	2	0	0.151
Branch type (n=22)	13	9	0	
Mixed type (n=15)	6	8	1	
Tumor size (mm)	28.6±19.9	35.3±20.4	21	
Lymph node metastasis, No/yes (n=4)	16/3	7/0	0/1	0.031
Tumor stage	3	0	0	0.275
0 (n=3)[$]				
1 (n=9)	9	0	0	
2a (n=6)	5	1	0	
2b (n=3)	2	0	1	
4 (n=2)	2	0	0	
Recurrence, No/yes (n=9)	20/9	19/0	1/0	0.022
Cancer death, No/yes (n=2)	27/2	19/0	1/0	0.487

*$p<0.05$ *vs.* match group. [#]Sonazoid was used in 24 patients. [$]Cancer was observed in 23 patients.

mixed type in 15 (31%). The main pancreatic duct dilatation over 5 mm was observed in 29 patients (59%, mean 6.9±4.8 mm). The mean cystic lesion was 60±129 mm, and the mural nodule in the cystic lesion was observed in 37 patients (76%, mean 15.9±8.8 mm). Organ invasion was observed in one patient (stomach and spleen, 2%). The maximum IPMN size of the resected specimen was 31±20 mm. T factor of IPMC (n=22) was T1 in two (4.1%), T3 in one patient, lymph node metastasis in four patients (8.2%), and M factor in one patient.

Pancreatic T factor was 1 in 13%, 2a in three, 2b in three, and 4 in two. Accompanied pancreatic adenocarcinoma was observed in two patients. Adjuvant chemotherapy was given in two patients as S-1. Cancer recurrence was observed in nine patients (18%), including peritoneal dissemination in five, liver metastasis in two, local

recurrence in one, and remnant pancreas in one (remnant total pancreatectomy was performed, and the patient survived). Cancer death was observed in two patients (4%), and three patients died of other diseases.

Relationship between misdiagnosis of preoperative findings and histological diagnosis. Table I shows the diagnostic mismatch between preoperative findings and histological findings. The study compares three diagnostic categories for IPMN: Match group (n=29): Pathological diagnosis matched preoperative diagnosis; Downgrade group (n=19): Final pathology showed a less severe disease than expected; and Upgrade (n=1): Final pathology showed a more severe disease than initially diagnosed. The downgrade group had more adenomas (18 cases) than the matched group (n=8) (p<0.01). Invasive carcinoma was only seen in one upgraded case, which suggests a tendency toward overestimation in some diagnoses. Pancreatic duct dilation >5 mm was significantly more common in the downgrade group (16/19) than in the match group (13/29) (p=0.012), which indicates duct dilation may mislead toward malignancy. Amylase levels were significantly higher in the downgrade group (100.8±40.7 mg/dl) than in the match group (73.6±21.8 mg/dl) (p=0.031), which suggests that elevated amylase may not correlate with malignancy. Sonazoid-enhanced mural nodules were identified in the upgraded case; nevertheless, because Sonazoid was applied in only 24 patients (p=0.022), its diagnostic value remains uncertain and may merit further study. Age, tumor location, CEA/CA19-9, blood counts, pancreatic duct size, mural nodule size, and tumor stage did not differ significantly among groups. Tumor size was larger in the downgrade group (35.3±20.4 mm) than in the match group (28.6±19.9 mm), but the difference was not statistically significant. Co-malignancy and lymph node metastasis mainly occurred in the matched group. Recurrence and cancer-related death were seen only in match or upgrade groups. The only upgraded case had invasive IPMC in the tail with a mural nodule and Sonazoid enhancement, suggesting an underdiagnosis risk in such cases. Overestimation of malignancy (downgrade) was more frequent and associated with features like duct dilation and high amylase, which may not reliably indicate malignancy. Underestimation (upgrade) was rare but potentially dangerous, as seen in the single case with invasive cancer.

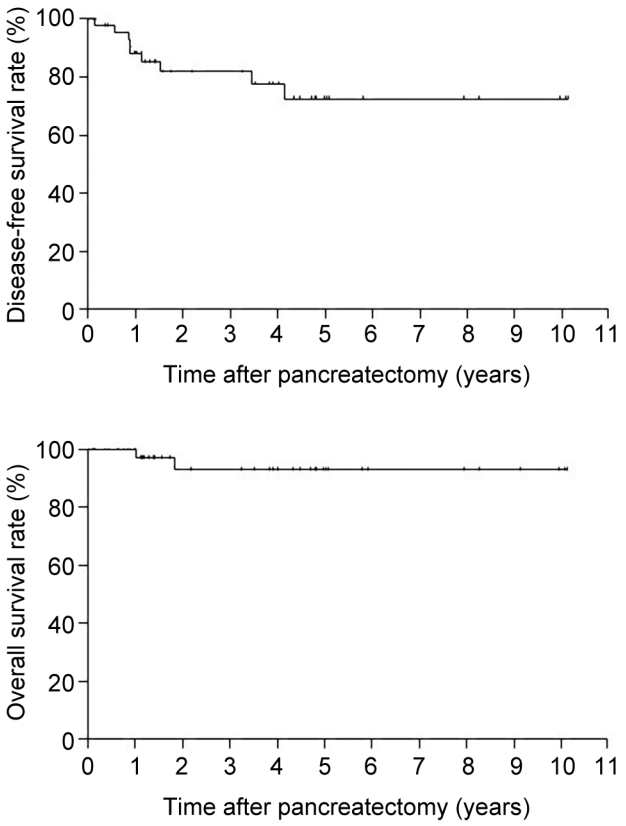

Figure 1. *Disease-free survival (DFS) and overall survival (OS) curves for 49 patients who underwent pancreatectomy for intraductal papillary mucinous neoplasm (IPMN).*

Correlation between various clinicopathological, intraoperative, and postoperative parameters and patient survival. Figure 1 shows the survival of all 49 patients with IPMN. Nine patients (18%) experienced disease recurrence, and the 1-, 3-, 5-, and 8-year disease-free survival (DFS) rates were 88, 82, 73, and 73%, respectively. The mean DFS period was 95.6 months. Two patients died of IPMN-related status, and the 1-, 3-, 5-, and 8-year overall survival (OS) rates were 100, 93, 93, and 93%, respectively. The mean OS

Table II. Disease-free and overall survival in the clinicopathological findings.

		Disease-free survival rate (%)			Significance
		1-year	3-year	5-year	*p*-Value
Age (years)	<60 (n=7)	100	83	83	0.586
	≥60 (n=42)	86	82	71	
Sex	Male (n=28)	91	86	78	0.554
	Female (n=21)	85	77	66	
Final diagnosis	Adenoma (n=26)	100	100	100	
	IPMC *in situ* or microinvasion (n=11)	89	89	89	<0.001
	Invasive IPMC (n=12)	61	40	20	
Tumor location	Head (n=24)	90	83	83	0.061
	Body (n=19)	94	87	74	
	Tail (n=6)	60	60	30	
Co-malignancy					
Pancreatic cancer	No (n=48)	88	84	74	0.031
	Yes (n=1)	100	0	0	
Other cancers	No (n=34)	89	81	74	0.959
	Yes (n=15)	85	85	71	
CEA (ng/dl)	<5 (n=38)	91	84	79	0.113
	≥5 (n=9)	73	73	36	
CA19-9 (U/ml)	<37 (n=37)	97	89	83	0.0014
	≥37 (n=12)	61	61	30	
Hemoglobin (g/dl)	<12 (n=9)	88	49	-	0.161
	≥12 (n=38)	88	88	76	
Platelet count ($\times 10^4/mm^3$)	<15 (n=2)	100	100	-	0.507
	≥15 (n=47)	88	80	71	
Amylase level (mg/dl)	<130 (n=46)	88	81	72	0.567
	≥130 (n=3)	100	100	100	
Pancreatic duct dilation (mm)	<5 (n=20)	76	76	76	0.597
	≥5 (n=29)	96	86	71	
Mural nodule (mm)	No (n=2)	100	100	100	0.686
	Yes (n=47)	85	85	85	
Pancreaticoduodenectomy	No (n=25)	86	86	69	0.773
	Yes (n=24)	91	78	78	
Type of IPMN	Main duct type (n=10)	100	100	71	0.163
	Branch type (n=24)	82	73	73	
	Mixed type (n=15)	100	100	100	
Tumor size (mm)	<30 (n=29)	87	78	78	0.113
	≥30 (n=20)	94	94	94	
Lymph node metastasis	No (n=45)	84	75	63	0.105
	Yes (n=4)	67	33	33	
Tumor stage,	0 (n=3)	100	100	100	0.035
	1 (n=9)	78	78	0	
	2a (n=6)	100	100	100	
	2b (n=3)	50	50	-	
	4 (n=2)	50	0	0	
Cancer death	No (n=47)	90	87	77	<0.001
	Yes (n=2)	50	0	0	

period was 115.6 months. To evaluate how clinicopathological factors affect DFS and OS at 1, 3, and 5 years in patients with IPMN, we analyzed the variables summarized in Table II. The adenoma group had excellent outcomes (100% DFS/OS at all timepoints), IPMC in situ/microinvasion had stable survival (89% at 5 years), and the invasive IPMC had poor survival (20% 5-year DFS, 36% OS). Final pathological severity significantly affects prognosis

(p<0.001). Regarding tumor location, pancreas head tumors had better 5-year OS (83%) compared to body (74%) and tail (30%), though not significant (p=0.061), which showed that tumors in the pancreatic tail may be associated with poorer outcomes. Patients with CA19-9 <37 U/ml showed better 5-year DFS (84%) and OS (79%) than those with ≥37 U/ml (DFS 61%, OS 30%), which showed that elevated CA19-9 is a negative prognostic indicator (p<0.05). CEA ≥5 ng/dl trended toward lower survival (5-year OS 30% *vs*. 74%), but not statistically significant (p=0.113). Survival decreased with advancing stage in 23 patients with IPMC (p<0.001), which showed that tumor staging is a strong predictor of survival. Lymph node involvement tended to worsen the prognosis (p=0.105). Age, sex, hemoglobin, platelet count, amylase level, mural nodule presence, pancreaticoduodenectomy, and tumor size showed no significant association with DFS. Patients with other cancers did not show significantly worse outcomes. Cancer deaths occurred only in the advanced disease groups.

Discussion

IPMN of the pancreas presents a broad histological spectrum ranging from benign adenoma to invasive carcinoma, making accurate preoperative risk assessment essential for guiding appropriate management. Despite the use of established imaging and serological criteria, discrepancies between clinical suspicion and pathological reality remain frequent, leading to both over- and under-treatment. In this study, we examined the clinicopathological characteristics, diagnostic mismatches, and survival outcomes in a cohort of surgically treated patients with IPMN, with particular attention to the factors contributing to diagnostic inaccuracy and prognostic stratification.

In our study, approximately 39% of patients with IPMN experienced a discrepancy between preoperative diagnosis and final pathological findings. The downgrade group, which reflects overdiagnosis, was substantially more frequent than the upgrade group, suggesting a systematic tendency to overestimate malignant potential. This diagnostic overcall was significantly associated with main pancreatic duct dilation (>5 mm) and elevated amylase levels, both of which are traditionally considered high-risk features in consensus guidelines (1). However, our findings and those of others raise concerns about the specificity of ductal dilation as a predictor of malignancy. For instance, Tamura *et al.* demonstrated that although duct dilation is sensitive, it lacks predictive specificity for high-grade dysplasia or invasive carcinoma (14). Similarly, elevated amylase, often linked with mucinous cysts or partial ductal obstruction, may reflect ductal communication rather than neoplastic aggression (15). These insights caution against overreliance on such markers when making surgical decisions, particularly for branch-duct IPMN. Conversely, although underestimation of malignancy was rare in our cohort, the clinical implications were profound. The single upgraded case demonstrated invasive carcinoma in the pancreatic tail, with mural nodules and positive Sonazoid enhancement, aligning with prior studies highlighting mural nodules and contrast enhancement as predictors of malignancy (16, 17). Yet, Sonazoid-enhanced ultrasound remains underutilized in routine diagnostic workup, and its full potential in preoperative risk stratification warrants further exploration (18). Our findings mirror broader diagnostic challenges reported in the literature. For example, a multicenter analysis by Crippa *et al.* found that up to 30-40% of resected branch-duct IPMNs were pathologically low-grade, despite meeting consensus criteria for surgery (19). This suggests a need to refine diagnostic algorithms, incorporating radiomics, molecular profiling, and machine learning-based imaging interpretation, which have shown promise in improving diagnostic precision (3, 20). Our results emphasize the limitations of conventional imaging and serum biomarkers. There is an urgent need to develop more reliable multimodal diagnostic frameworks that balance the risks of overtreatment with the dangers of underdiagnosing high-risk lesions. Future guidelines may benefit from integrating quantitative imaging, novel contrast agents, and genomic alterations (*e.g., GNAS, KRAS* mutations) in cyst fluid analysis to more accurately classify the malignant potential of IPMN.

The present study confirmed that histological grade is the most critical determinant of long-term prognosis over eight years in IPMN. Patients with non-invasive lesions, including adenomas and carcinoma *in situ* or microinvasion IPMC, exhibited excellent survival outcomes, with 5-year DFS and OS rates of ≥89%. In stark contrast, those with invasive IPMC demonstrated a 5-year DFS of 20%, indicating a significantly worse prognosis. This prognostic disparity highlights the natural history of IPMN, where progression from low-grade dysplasia to invasive carcinoma results in a dramatic loss of curability. Multiple studies have reported similar survival trends. For example, Fukushima *et al.* showed that patients with non-invasive IPMN had a 5-year survival rate >90%, while those with invasive IPMN had rates between 30-50%, depending on the depth of invasion (21). Similarly, a multicenter European cohort reported a higher 5-year OS for non-invasive IPMN compared to invasive carcinoma, reinforcing the clinical importance of early-stage surgical intervention (22). Notably, the poor prognosis in invasive cases appears comparable to that of conventional pancreatic ductal adenocarcinoma (PDAC), particularly when lymph node metastasis or advanced T-stage is present (23). This observation has prompted some to suggest that once invasive transformation occurs, IPMN-associated carcinoma should be managed similarly to PDAC, including consideration for adjuvant therapy. Our findings support the argument that timely surgical resection, especially for high-risk lesions (*e.g*., mural nodules, the main duct IPMN, mixed type), remains critical to prevent progression. However, since many low-grade IPMNs are indolent and non-lethal, overtreatment must also be avoided. Accurate preoperative stratification of histologic grade is the cornerstone of balancing curability and surgical risk. Recent developments in genomic and transcriptomic profiling have revealed potential markers (*e.g.,* TP53, SMAD4, KRAS, and GNAS mutations) that may distinguish invasive from non-invasive IPMN, aiding risk prediction (24). Moreover, radiomics and AI-based image analysis have shown early promise in predicting invasive behavior before surgery (25). Integrating these innovations into clinical workflows may help refine indications for surgery and better personalize management.

Although not statistically significant in our cohort, a noteworthy trend was observed regarding tumor location and prognosis. Patients with IPMN located in the pancreatic tail had a markedly worse 5-year OS of 30%, compared to those with tumors in the head or body of the pancreas, whose survival exceeded 70%. This disparity, though subtle in numbers, may carry clinical relevance. One possible explanation is that pancreatic tail tumors often present later in the disease course. Unlike lesions in the pancreatic head, which may trigger early symptoms, tail-located lesions tend to remain clinically silent until they reach a more advanced stage. Several reports support this anatomical disparity. For instance, IPMN in the body/tail was more frequently associated with invasive carcinoma and nodal metastasis than head lesions (26). Similarly, distal IPMN-associated carcinomas often presented at a later T-stage and with worse survival, even after curative resection (27). These findings emphasize the need for enhanced imaging surveillance protocols that ensure the entire pancreatic parenchyma, especially the tail, is adequately visualized, particularly in high-risk or surveillance populations. Additionally, the surgical threshold for distal lesions may need to be adjusted based on evolving risk prediction models and enhanced imaging.

CA19-9 demonstrated a significant prognostic value among the preoperative serum biomarkers evaluated in our cohort. Patients with CA19-9 levels over 37 U/ml had a statistically significantly reduced 5-year OS compared to those with lower levels, with. This finding underscores CA19-9's utility as a negative prognostic indicator, even in resectable IPMN. CA19-9 is widely recognized as a tumor-associated antigen elevated even in high-grade IPMNs (28). Its elevation is believed to reflect either invasive transformation or the presence of mucin-producing, high-risk epithelium. Previous studies have confirmed the association between preoperative CA19-9 levels and IPMN malignancy or recurrence risk (29). In particular, Takahashi *et al.* demonstrated that CA19-9 levels >37 U/ml independently predicted poor outcomes following

resection for IPMN-associated carcinoma (29). In addition, CEA over 5 ng/ml also trended toward worse survival in our analysis, but without reaching statistical significance. It is worth noting that both markers can be falsely elevated in cases of biliary obstruction or inflammation, and some individuals cannot produce CA19-9, limiting its utility in a subset of patients.

In our study, the type of pancreatectomy performed, the presence of mural nodules, and the tumor size did not demonstrate a statistically significant association with DFS. While these features are commonly used in preoperative assessments and risk models, their prognostic implications may be context-dependent and affected by other histopathological variables (30). For example, mural nodules have traditionally been associated with malignancy risk. Still, as shown in our findings and supported by others, their mere presence is not sufficient to predict outcome without considering size, enhancement, or cytology. In contrast, lymph node metastasis and advanced tumor stage emerged as significant predictors of poor prognosis, confirming their well-established roles in oncologic outcomes for IPMN-associated carcinoma. Previous large-scale studies have shown that nodal involvement in invasive IPMC is associated with a 3- to 4-fold increase in recurrence and mortality, even after curative resection (31). Of particular note, our cohort's patients with mixed-type IPMN experienced inferior outcomes. While traditionally classified alongside main duct and branch duct types, emerging evidence suggests that mixed-type IPMN may represent a biologically distinct and more aggressive entity. Mixed-type IPMN exhibits a higher incidence of both invasive carcinoma and multifocality, thereby supporting the need for intensified surveillance or consideration of proactive resection (32). Cancer recurrence occurred in 18% of our patients, with patterns primarily involving peritoneal dissemination and liver metastasis, even in some cases of presumed early-stage disease. This highlights the systemic potential of IPMN-associated carcinoma, which may behave similarly to conventional pancreatic ductal adenocarcinoma once invasion occurs. Notably, all cancer-related deaths occurred in the matched or upgraded diagnostic groups, reinforcing the clinical consequences of underestimating malignancy. These cases underscore the need for accurate preoperative risk stratification and the potential benefit of adjuvant chemotherapy, especially in patients with lymph node involvement or margin positivity (33). Furthermore, the recurrence pattern emphasizes that local resection alone may be insufficient in invasive cases. A more multidisciplinary approach should be incorporated into treatment planning for high-risk patients with IPMN, including postoperative surveillance and systemic therapy considerations.

Strengths of this study: This study provides a detailed comparison between preoperative assessments and postoperative pathological diagnoses. It enables an in-depth analysis of diagnostic mismatch in IPMN and its clinical consequences. By correlating multiple clinical, imaging, and histopathological variables with DFS, the study offers robust insight into prognostic determinants, including tumor grade, location, biomarkers, and lymph node status. *Limitations:* As a retrospective study from a single institution, the findings are susceptible to selection bias, and results may not be generalizable to broader populations or community-based settings. The overall cohort size (n=49) limits the statistical power, particularly in subgroup analyses (*e.g*., upgrade group n=1, lymph node positive n=4), which may underpower some comparisons or lead to overestimating trends. Although Sonazoid-enhanced imaging was referenced, it was used in only a subset of patients. Broader application of contrast-enhanced harmonic EUS or radiomic analysis could have enriched the diagnostic evaluation. Follow-up duration, recurrence monitoring, and use of adjuvant chemotherapy (only two patients received S-1) were not standardized, possibly affecting long-term outcome data and limiting survival comparisons.

Conclusion

In this retrospective analysis of 49 surgically resected IPMN cases, we found that diagnostic mismatch occurred

in nearly 40% of patients, with a predominance of overdiagnosis associated with pancreatic duct dilation and elevated amylase levels, potentially leading to unnecessary surgery. Conversely, the rare underestimation of malignancy carries serious clinical consequences, emphasizing the limitations of current preoperative diagnostic criteria. Survival outcomes were strongly linked to pathological grade, with excellent prognosis in non-invasive lesions and significantly poorer outcomes in invasive carcinoma. Elevated CA19-9, lymph node metastasis, and advanced tumor stage were significant predictors of worse prognosis, while tumor location in the pancreatic tail and mixed-type IPMN also showed trends toward poor survival. These findings reinforce the need for refined risk stratification tools, potentially integrating molecular, radiologic, and clinical features, to improve diagnostic accuracy and guide optimal management strategies for IPMN.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Surgical and Medical Practices-Concept: AN; Design: AN; Data Collection or Processing: MH, NI, TH, YT, TW; Analysis or Interpretation: AN, AH, HK; Literature Search: AN; Writing: AN.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

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