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Surgical Intervention and Prognosis of Intraductal Papillary Mucinous Adenoma in Elderly Patients: A Single Center Retrospective Study

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ABSTRACT

Objective: The incidence of intraductal papillary mucinous neoplasm (IPMN) is rising among elderly patients. This study aims to investigate the clinical features of IPMN in elderly patients (≥60 years), analyze risk factors for high-grade dysplasia (HGD) and invasive cancer (IC), and provide treatment recommendations for elderly patients with IPMN.

Methods: In this single-center retrospective case–control study, 58 consecutive elderly patients (≥60 years) who underwent IPMN surgery at Beijing Hospital between January 2014 and November 2023 were included. Clinical characteristics across IPMN subtypes were compared, risk factors were analyzed, and the predictive values of the 2017 Fukuoka and 2023 Kyoto guidelines were evaluated. Follow-up and survival outcomes were also examined.

Results: The proportion of patients with main-duct IPMN (MD-IPMN) and mixed-type IPMN (MT-IPMN) who had diabetes was significantly higher than among those with branch-duct IPMN (BD-IPMN) ($p < 0.05$). The average postoperative hospital stay for patients with low-grade dysplasia (LGD) was 17.7 days (range, 6–53 days), while for patients with HGD/IC, it was 25.5 days (range, 9–90 days), with a statistically significant difference ($p < 0.05$). Jaundice, elevated CA19-9, elevated CEA, main duct (MD) > 10 mm, and IPMN subtype were significant predictors of HGD/IC ($p < 0.05$), with elevated CA19-9 and IPMN subtype identified as independent risk factors ($p < 0.05$). The 2023 Kyoto guidelines showed higher sensitivity but lower specificity than the 2017 Fukuoka guidelines for detecting HGD/IC ($p < 0.05$ for both). There was a statistically significant difference in overall survival between patients with LGD and those with HGD/IC following surgery ($p < 0.05$), while no significant difference in postoperative survival was observed between HGD/IC patients with and without lymph node metastasis ($p > 0.05$).

Conclusions: Surgical resection is recommended for elderly patients with MD-IPMN or MT-IPMN combined with elevated CA19-9. The 2017 Fukuoka guidelines are preferable to the 2023 Kyoto guidelines for managing elderly IPMN patients.

Tianhan Sun and Meilan Liu should be considered joint first author.

1 | Introduction

With the advancement and increased use of radiological diagnostic modalities, more and more pancreatic cysts are being identified, and the incidence increases with age. Among these pancreatic cysts, pancreatic intraductal papillary mucinous neoplasm (IPMN) is the most common and exhibits a notably aggressive behavior. The prevalence rate of IPMN is 8.3%, 11.6%, 21.2%, and 26.0% among individuals aged 60–69, 70–79, 80–89, and 90 years or older, respectively [1]. IPMN is morphologically categorized into three subtypes: main-duct IPMN (MD-IPMN), branch-duct IPMN (BD-IPMN), and mixed-type IPMN (MT-IPMN) [2]. Pathologically, IPMN is further classified by the degree of dysplasia, which includes low-grade dysplasia (LGD), high-grade dysplasia (HGD), and invasive cancer (IC) [3]. The prevalence of HGD or IC in MD-IPMN ranges from 60% to 92%, substantially higher than the prevalence observed in BD-IPMN, which ranges from 6% to 46% [4]. Consequently, identifying risk factors associated with HGD and IC has become essential to informing treatment strategies, particularly for elderly patients with IPMN.

2 | Methods

2.1 | Patients

This single-center retrospective case–control analysis included 58 consecutive elderly patients (≥ 60 years) who underwent IPMN surgery at Beijing Hospital between January 2014 and November 2023. Patient demographic information, blood examination results, cross-sectional imaging findings, and pathological features were retrieved from the Beijing Hospital database.

2.2 | Preoperative Examinations

All patients underwent a comprehensive physical evaluation and blood examination, including measurements of blood glucose, serum bilirubin, and serum tumor markers, specifically carbohydrate antigen 19–9 (CA19-9) and carcinoembryonic antigen (CEA). Elevated CA19-9 was defined by CA19-9 > 37 U/mL. Elevated CEA was established as CEA > 5.0 ng/mL. Preoperative imaging was performed using magnetic resonance imaging (MRI) or computed tomography (CT) to assess the main pancreatic duct (MPD) and the maximum size of branch duct cysts in all 58 patients. Additionally, 11 patients underwent endoscopic ultrasound (EUS), including 7 cases with endoscopic ultrasound-guided fine-needle aspiration.

Tumors were classified according to the Kyoto guidelines established by the International Association of Pancreatic Diseases (IAP) as MD-, BD-, or MT-IPMN based on preoperative imaging. MD-IPMN was defined by segmental or diffuse dilation of the MPD > 5 mm without other causes of obstruction. BD-IPMN was characterized by pancreatic cysts > 5 mm in diameter that communicated with the MPD, while MT-IPMN met the criteria for both MD-IPMN and BD-IPMN [2].

2.3 | Inclusion and Exclusion Criteria

Inclusion criteria: (1) Elderly patients (≥ 60 years) with imaging findings suggestive of IPMN; (2) Patients who underwent surgical resection at Beijing Hospital.

Exclusion criteria: (1) Patients who underwent surgical resection at Beijing Hospital but had pathological results indicating other pancreatic cystic diseases; (2) Patients with incomplete clinical data.

2.4 | Surgical Indications

Before 2015, patients with "Fukuoka positive" findings [5] were recommended for surgery. After 2015, surgical indications were expanded to include: (1) all surgically fit patients diagnosed with MD-IPMN or MT-IPMN by radiography; (2) BD-IPMN cases with risk factors identified on MRI, CT, or EUS, including cyst size ≥ 3 cm, presence of mural nodules, MPD diameter > 10 mm, positive cytology, related symptoms, cyst growth rate ≥ 2 mm/year, or elevated CA19-9 levels, in accordance with the Guidelines for Diagnosis and Treatment of Pancreatic Cystic Disease from the Pancreatic Surgery Group of the Surgery Branch of the Chinese Medical Association [6].

2.5 | Pathological Diagnosis

Pathological grades were classified as LGD, high-grade dysplasia (HGD), or invasive cancer (IC) based on the degree of cytoarchitectural dysplasia, according to the World Health Organization classification system published in 2019 [3]. When more than one grade was present, the highest degree of dysplasia was recorded.

2.6 | Data Analysis and Statistics

Data analysis was conducted using SPSS Version 27.0. Continuous variables were expressed as median ± standard deviation or median (range) and were compared using the Mann–Whitney test. Categorical variables were analyzed using the χ^2 test. Multivariate analysis was performed with a multiple logistic regression model that included factors with $p < 0.05$ in the univariate analysis. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated to evaluate predictive values. Overall survival was calculated using the Kaplan–Meier method and compared with the log-rank test. A statistically significant difference was indicated by $p < 0.05$.

3 | Results

3.1 | Patient Characteristics

Table 1 presents the demographic information, blood examination results, and cross-sectional imaging findings for the 58 elderly patients (55.2% male; median age, 71 years; range, 60–90 years) included in the study. Surgical procedures performed included

20 (34.5%) distal pancreatectomies, 17 (29.3%) total pancreatectomies, 14 (24.1%) pancreaticoduodenectomies, 5 (8.6%) segmental pancreatectomies, and 2 (3.4%) duodenum-preserving pancreatic head resections. Initial lesion locations were in the head of the pancreas for 26 (44.8%) patients, in the body and tail for 24 (41.4%) patients, and in the entire pancreas for 8 (13.8%) patients. Among the patients, 10 (17.2%) were diagnosed with MD-IPMN, 18 (31.0%) with BD-IPMN, and 30 (51.7%) with MT-IPMN. No tumor residue was found at the surgical margins in any of the 58 IPMN patients, with 38 cases classified as LGD, all without lymph node involvement, and 20 cases as high-grade dysplasia/invasive cancer (HGD/IC), including 14 cases negative and 6 cases positive for lymph node metastasis. Typical pathological features of LGD, HGD, and IC are shown in Figure 1.

TABLE 1 | Characteristics of the included patients.

Variables	Patients with IPMN, $n = 58$
Male	32 (55.2%)
Age (years)	71.0 ± 8.1
Weight loss	6 (10.3%)
Symptoms	30 (51.7%)
Abdominal pain	12 (20.7%)
Jaundice	9 (15.6%)
Diabetes	24 (41.4%)
Pancreatitis	18 (31.0%)
Elevated CA19-9	14 (24.1%)
Elevated CEA	9 (15.6%)
Surgical procedures	
Distal pancreatectomy	20 (34.5%)
Total Pancreatectomy	17 (29.3%)
Pancreaticoduodenectomy	14 (24.1%)
Segmental pancreatectomy	5 (8.6%)
Duodenum-preserving pancreatic head resection	2 (3.4%)
Predominant location of tumor	
Head	26 (44.8%)
Body/tail	24 (41.4%)
Diffuse	8 (13.8%)
IPMN type	
MD-IPMN	10 (17.2%)
BD-IPMN	18 (31.0%)
MT-IPMN	30 (51.7%)
Histopathology	
LGD	38 (65.5%)
HGD/IC	20 (34.5%)

3.2 | Clinical Features of MD-IPMN and MT-IPMN Compared to BD-IPMN

The prevalence of diabetes was significantly higher among patients with MD-IPMN and MT-IPMN compared to those with BD-IPMN ($p < 0.05$) (Table 2).

3.3 | Perioperative Surveillance

One perioperative death occurred due to postoperative hemorrhage, and three patients required reoperation for postoperative hemorrhage. A total of 14 cases of postoperative complications were observed, including 5 cases (8.6%) of delayed gastric emptying (DGE), 2 cases (3.4%) of postoperative pancreatic fistula (POPF), 5 cases (8.6%) of postoperative hemorrhage, and 2 cases (3.4%) of abdominal infection. DGE and POPF were defined according to international guidelines [7, 8], while other complications were categorized based on the Clavien-Dindo classification (Table 3) [9].

The average length of hospital stay for the cohort was 28.8 days (range, 11–114 days). Patients with LGD had a mean hospital stay of 25.7 days (range, 11–68 days), while those with HGD/IC had a significantly longer mean hospital stay of 34.5 days (range, 16–114 days) ($p < 0.05$). The average postoperative hospital stay was 20.4 days (range, 6–90 days). For patients with LGD, the mean postoperative stay was 17.7 days (range, 6–53 days), whereas patients with HGD/IC had a longer mean postoperative stay of 25.5 days (range, 9–90 days) ($p < 0.05$) (Table 3).

3.4 | Risk Factors for HGD/IC

Univariate and multivariate analyses of risk factors predictive of HGD/IC are presented in Table 4. Univariate analysis identified

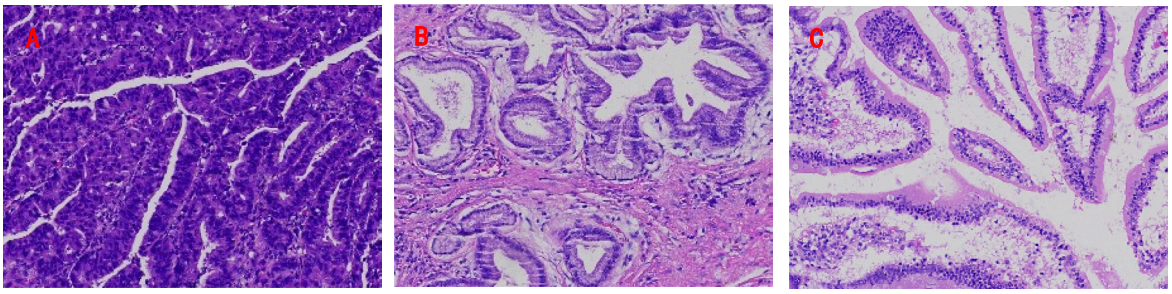

FIGURE 1 | Typical pathological features of IPMN. (A) LGD, (B) HGD, and (C) IC.

TABLE 2 | Clinical features among patients with MD-IPMN and MT-IPMN compared with those with BD-IPMN.

Variables	MD- and MT- IPMN, $n=40$	BD-IPMN, $n=18$	Statistic value	p
Male:Female	23:17	9:9	$\chi^2=0.282$	0.595
Age (years)	71.0 ± 7.8	71.0 ± 8.8	$M=345.000$	0.801
Weight loss	4	2	$\chi^2=0.017$	0.898
Symptoms	24	6	$\chi^2=3.535$	0.060
Abdominal pain	11	1	$\chi^2=3.643$	0.056
Jaundice	8	1	$\chi^2=1.976$	0.160
Diabetes	21	3	$\chi^2=6.571$	0.010
Pancreatitis	12	6	$\chi^2=0.064$	0.800
Elevated CA19-9	10	4	$\chi^2=0.052$	0.819
Elevated CEA	6	3	$\chi^2=0.026$	0.871
Cystic size (cm)	3.2 ± 2.2	2.5 ± 2.3	$M=321.000$	0.512

TABLE 3 | Postoperative complications, hospital stay, and postoperative hospital stay.

Histopathology	DGE ≥ grade B	POPF ≥ grade B	Clavien-Dindo classification ≥ IIIa	Hospital stay	Postoperative hospital stay
LGD	5.3% (2/38)	5.3% (2/38)	5.6% (2/38)	25.7 ± 14.0	17.7 ± 12.6
HGD/IC	15.0% (3/20)	0 (0/20)	5.0% (1/20)	34.5 ± 22.1	25.5 ± 19.5
Statistic value	$\chi^2=1.577$	$\chi^2=1.090$	$\chi^2=0.002$	$M=256.000$	$M=257.000$
p	0.209	0.296	0.966	0.042	0.044

jaundice, elevated CA19-9, elevated CEA, and IPMN type as significant predictors of HGD/IC ($p<0.05$). Multivariate analysis revealed that elevated CA19-9 and IPMN type were independent risk factors for HGD/IC ($p<0.05$).

3.5 | Predictive Value of the 2017 Fukuoka and 2023 Kyoto Guidelines for HGD/IC

The 2017 Fukuoka guidelines showed a sensitivity of 70.0%, specificity of 70.3%, positive predictive value (PPV) of 56.0%, and negative predictive value (NPV) of 81.3% for detecting HGD/IC. The 2023 Kyoto guidelines demonstrated a significantly higher sensitivity of 95.0% but a lower specificity of 47.4%, with a PPV of 48.7% and NPV of 94.7% ($p<0.05$ for both sensitivity and specificity comparisons with the 2017 Fukuoka guidelines) (Table 5).

3.6 | Follow-Up and Survival

Out of the 58 patients, 55 underwent follow-up through telephone or outpatient visits, including 37 patients with LGD and 18 with HGD/IC. The follow-up period ranged from 7 to 125 months, with a median duration of 38 months. For patients with LGD, the 1-, 3-, and 5-year overall survival rates were 85.7%, 81.5%, and 71.4%, respectively. One individual died from postoperative hemorrhage, one died from surgical site infection, one died from pneumonia, and one died from intra-abdominal hemorrhage. Additionally, two individuals died as a result of other malignant neoplasms, while three others experienced mortality due to tumor progression. In contrast, the overall survival rates for patients with HGD/IC were 78.6%, 40.0%, and 14.3% at 1, 3, and 5 years, respectively. All deaths were due to tumor progression. A statistically significant difference in survival was observed between the LGD and HGD/IC groups post-surgery ($p<0.05$) (Figure 2).

Within the HGD/IC group, 12 patients without lymph node metastasis showed overall survival rates of 82.5%, 58.9%, and 58.9% at 1, 3, and 5 years, respectively. Meanwhile, six patients with lymph node metastasis had survival rates of 66.7%, 33.3%, and 33.3% at the same intervals. Statistical analysis indicated no significant difference in overall survival based on lymph node metastasis status within the HGD/IC patient subgroup ($p>0.05$) (Figure 3).

4 | Discussion

As the population ages, the diagnosis of IPMN has increased significantly, sparking interest in research on surgical indications for tumor resection and treatment strategies informed by the histopathological characteristics of IPMN, classified as borderline tumors.

TABLE 4 | Univariate and multivariate analyses of risk factors predictive of HGD/IC.

		Univariate analysis			Multivariate analysis		
Variable	**Total *n* (HGD/IC *n*)**	**OR**	**95% CI**	***p***	**OR**	**95% CI**	***p***
Gender							
Male	32 (13)	1.000					
Female	26 (7)	0.538	0.176–1.646	0.275			
Age							
< 65	18 (4)	1.000					
≥ 65	40 (16)	2.333	0.650–8.381	0.188			
Weight loss							
Negative	52 (17)	1.000					
Positive	6 (3)	2.059	0.375–11.292	0.398			
Symptoms							
Negative	28 (7)	1.000					
Positive	30 (13)	2.294	0.749–7.027	0.142			
Abdominal pain							
Negative	46 (16)	1.000					
Positive	12 (4)	0.938	0.244–3.598	0.925			
Jaundice							
Negative	49 (14)	1.000			1.000		
Positive	9 (6)	5.000	1.096–22.820	0.027	4.918	0.714–33.848	0.106
Pancreatitis							
Negative	40 (15)	1.000					
Positive	18 (5)	0.641	0.190–2.158	0.471			
Diabetes							
Negative	34 (10)	1.000					
Positive	24 (10)	1.714	0.573–5.133	0.334			
Elevated CA19-9							
Negative	44 (10)	1.000			1.000		
Positive	14 (10)	8.500	2.188–33.021	< 0.001	17.507	1.651–185.664	0.018
Elevated CEA							
Negative	49 (14)	1.000			1.000		
Positive	9 (6)	5.000	1.096–22.820	0.027	6.688	0.467–95.687	0.162
Cyst > 30 mm							
No	33 (10)	1.000					
Yes	25 (10)	1.533	0.515–4.567	0.442			
MD > 10 mm							
No	48 (12)	1.000			1.000		
Yes	10 (8)	12.000	2.233–64.489	< 0.001	6.318	0.697–57.277	0.101

(Continues)

TABLE 4 | (Continued)

Variable	Total *n* (HGD/IC *n*)	Univariate analysis			Multivariate analysis		
		OR	95% CI	*p*	OR	95% CI	*p*
IPMN type							
MD-IPMN	10 (5)	17.000	1.594–181.362	0.006	46.566	1.637–1324.646	0.025
MT-IPMN	30 (14)	14.875	1.749–126.497	0.003	84.737	1.809–3970.010	0.024
BD-IPMN	18 (1)	1.000			1.000		

TABLE 5 | Predictive value of 2017 Fukuoka guidelines and 2023 Kyoto guidelines for HGD/IC.

Variables	2017 Fukuoka guidelines	2023 Kyoto guidelines	χ^2	*p*
Sensitivity	70.0% (14/20)	95.0% (19/20)	4.329	0.037
Specificity	70.3% (26/37)	47.4% (18/38)	4.055	0.044
PPV	56.0% (14/25)	48.7% (19/39)	0.323	0.570
NPV	81.3% (26/32)	94.7% (18/19)	1.831	0.176

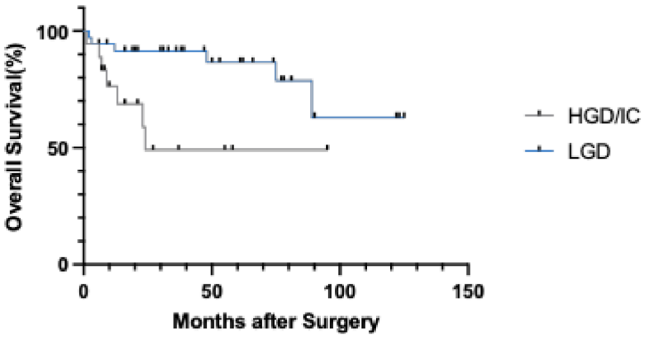

FIGURE 2 | Patients with HGD/IC showed worse overall survival than patients with LGD.

4.1 | Diagnosis of IPMN

The considerable variability in the potential for HGD/IC among MD-, MT-, and BD-IPMN underscores the need to clarify IPMN classification to advance diagnosis and treatment planning. This study found a higher prevalence of diabetes among patients with MD-IPMN and MT-IPMN than in those with BD-IPMN, while other clinical features lacked statistical significance—likely due to the limited sample size. Future studies with larger samples could better elucidate these relationships. Since the publication of the first international consensus on IPMN treatment in 2006, MRI/magnetic resonance cholangiopancreatography (MRCP) has been advocated as the optimal imaging technique for distinguishing BD-IPMN from MCN [10]. As MRI offers enhanced visualization of the pancreatic duct and identification of enhancing mural nodules or internal septations and eliminates the risk associated with repeated exposure to ionizing radiation, it remains the preferred imaging modality per clinical guidelines. Studies indicate that MRI's diagnostic accuracy for identifying HGD/IC ranges from 75% to 80% [11, 12]. A 2021 meta-analysis of 17 studies found no significant differences in sensitivity ($p=0.822$) and specificity ($p=0.096$) between MRI and CT in distinguishing LGD from HGD/IC [13]. However, studies suggest that combining MRI with CT improves diagnostic accuracy over using either modality alone [14, 15]. Given the cost-effectiveness and accessibility of both MRI and CT, it is advisable for medical institutions in China to employ a combination of imaging methods for more accurate IPMN diagnoses.

With technological advances, endoscopic ultrasound (EUS) combined with other imaging techniques can further enhance IPMN diagnostic accuracy [16]. The 2023 Kyoto guidelines recommend EUS for IPMN cases suspected of HGD/IC when available [2]. Likewise, European guidelines advise using EUS as a supplement to other imaging techniques to identify IPMN features that may indicate surgical resection [17]. Studies show EUS has comparable accuracy to MRI in predicting HGD/IC in IPMN [18, 19], with the advantage of a dynamic, close-up sonographic view that accurately characterizes internal structures, including septa and mural nodules [20, 21]. According to the Chinese guidelines for pancreatic cystic neoplasms (2022), EUS is recommended for further evaluation when imaging reveals: (1) cysts > 3 cm or enhancing mural nodules > 5 mm; (2) thickened/enhanced cyst walls; (3) MPD diameter > 5 mm; (4) abrupt changes in duct caliber with distal pancreatic atrophy; (5) lymphadenopathy; (6) elevated CA19-9; or (7) cyst growth rate ≥ 5 mm/2 years [16]. EUS-guided fine-needle aspiration/biopsy (EUS-FNA/FNB) can also be used to collect cystic fluid for cytological and biochemical analysis, aiding in diagnosing IPMN and differentiating it from other PCNs [16]. Due to its invasiveness, EUS is not advised when MRI/CT reveals high-risk stigmata (HRS) [2].

In this study, all IPMN patients underwent MRI or CT, with EUS added for 11 patients who did not meet surgical criteria based on MRI or CT findings alone. This additional examination allowed for a definitive diagnosis, ensuring all patients met surgical criteria prior to surgery.

4.2 | Surgical Indications

Our findings show that the 2023 Kyoto guidelines have higher sensitivity but lower specificity than the 2017 Fukuoka

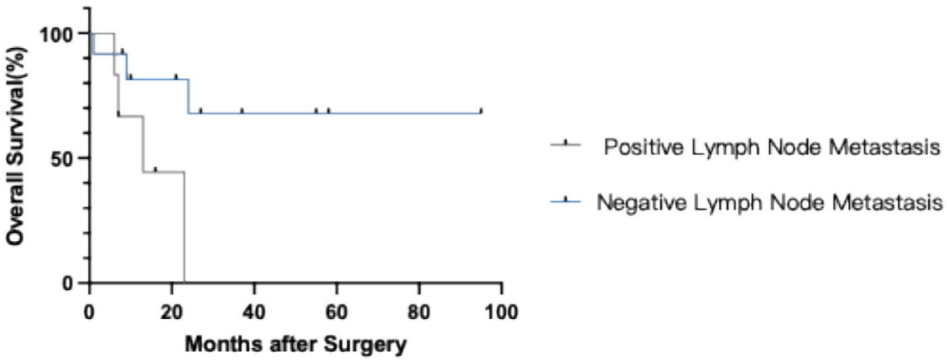

FIGURE 3 | No significant difference was shown in overall survival of patients with negative lymph node metastasis and positive lymph node metastasis.

guidelines. These results suggest that surgical indications for elderly patients should be carefully considered, taking into account not only the risk of HGD/IC but also the patient's overall condition, comorbidities, and life expectancy, given the Kyoto guidelines' lower specificity. For elderly patients, we recommend surgical resection in cases of MD-IPMN or MT-IPMN with elevated CA19-9. Conversely, for elderly patients without worrisome features (WF) or HRS as per the 2023 Kyoto guidelines [2], conservative treatment is suggested, given the high negative predictive value (NPV) of these guidelines.

4.3 | Prognosis and Follow-Up of Elderly Patients With IPMN

Our findings indicate that overall survival in patients with LGD is longer than in those with HGD/IC. Among patients with HGD/IC, survival was similar regardless of lymph node metastasis, while a previous study indicates that increased rates of recurrence were associated with lymph node spread, which could further influence survival [22]. Prior research shows that the proportion of patients with non-invasive IPMN who experienced disease progression after a median follow-up of 42 months was 22% [23]. Within this cohort, a new cystic lesion > 1 cm developed in 79% of patients, 14% of patients experienced a doubling in the diameter of preexisting cysts, and 16% of patients developed invasive cancer in the pancreatic remnant after a median of 28 months from initial resection [23]. In a study with a median follow-up of 33 months post-IPMN resection, 58.0% of BD-IPMN patients who did not have a worrisome feature or HRS at diagnosis developed a worrisome feature [24]. Another study with a median postoperative follow-up of 32 months found that 15.0% had recurrent tumors. The 1-, 3-, and 5-year recurrence-free survival rates were 89.3%, 82.8%, and 82.8%, respectively [25]. Collectively, these studies support the tendency of IPMN to progress to HGD/IC. A study indicates that overall survival in a group with an observation interval of 6 months or less was better than that in a group with an observation interval of more than 6 months, indicating that IPMN patients benefit from follow-up [26]. Notably, 9.2% of patients who did not have a worrisome feature or HRS at diagnosis developed a worrisome feature after 5 years of postoperative surveillance [24], which means IPMN patients need long-term surveillance even after the tumors have been wholly resected. Given elderly patients' frequent comorbidities, limited mobility, and shorter life expectancy, postoperative follow-up should be individualized. We recommend imaging follow-up 1–2 times per year for elderly patients with LGD pathology postoperatively. For those with HGD/IC, we suggest imaging follow-up every 3–6 months during the first two postoperative years, followed by 1–2 annual follow-ups.

5 | Limitations

This study has limitations. As a single-center retrospective analysis with a limited patient sample, our findings may be affected by selection bias. Additionally, some postoperative imaging details were unavailable due to patients seeking follow-up care at other institutions. Furthermore, our study focused exclusively on elderly patients, which limits the generalizability of our findings to the broader IPMN patient population.

6 | Conclusions

Surgical resection is recommended for elderly patients with MD-IPMN or MT-IPMN combined with elevated CA19-9. The 2017 Fukuoka guidelines are preferable to the 2023 Kyoto guidelines for managing elderly IPMN patients.

Author Contributions

Tianhan Sun: data acquisition, data analysis, writing – original draft. **Meilan Liu:** data acquisition, data analysis. **Qing Wang, Boyue Jiang, Tong Li, and Jianfu Cao:** data acquisition. **Jinghai Song:** writing – review. **Jingyong Xu**: writing – review. **Hongyuan Cui:** conceptualization, methodology, writing – review.

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Ethics Statement

The study protocol was approved by the Institutional Review Board of Beijing Hospital (Approval No. BJYYEC2024-H457). All patients or

their family members provided informed consent for surgery prior to the procedures.

Conflicts of Interest

The authors declare no conflicts of interest.

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