United European Gastroenterology Journal

WILEY | ueg journal

ORIGINAL ARTICLE OPEN ACCESS

Survival After Pancreatic Resection for Intraductal Papillary Mucinous Neoplasm: Supporting Selective Surgery

Marcus Holmberg[1,2] | Tomaso Dall'Olio[3] | Mohamed Marwa[4] | Carsten Palnaes Hansen[5] | Dyre Berg Kleive[6] | Gennaro Nappo[7,8] | Lam Shi[9] | Per Sandström[10] | Dennis Björk[10] | Parsa Hadesi[11] | Raffaele Vincenzo De Rosa[12] | Bodil Andersson[13] | Daniel Ansari[13] | Bhargava Chikkala[14] | Letizia Todeschini[15] | Charlotte Leseman[16,17] | Job Schuitema[16,17] | Yentl Lodewijks[18] | Christopher Månsson[19] | Spiros Delis[20] | Frederik Berrevoet[21] | Fabio Giannone[22] | Sofia Xenaki[23] | Elizabeth Pando[24] | Claude Bertrand[25] | Konstantinos Vasileiadis[26] | Patrick Kirchweger[27] | Calogero Ciulla[28] | Claudio Luchini[28] | Misha Luyer[18] | Marc G. Besselink[16,17] | Giovanni Marchegiani[15] | Sanjay Pandanaboyana[14] | Bobby Tingstedt[13] | Laurent Sulpice[12] | Johanna Wennerblom[11] | Bergthor Björnsson[10] | Anita Balakrishnan[9] | Knut Jørgen Labori[6] | Stefan Kobbelgaard Burgdorf[5] | Motaz Qadan[4] | Ernesto Sparrelid[1,29] | Antonio Pea[3] | Yasmin G. Hernandez-Barco[4] | Roberto Salvia[3] | Poya Ghorbani[1,29]

[1]Department of Clinical Science, Intervention, and Technology, Karolinska Institute, Stockholm, Sweden | [2]Department of Surgery and Oncology, Capio St. Gorans Hospital, Stockholm, Sweden | [3]Department of General and Pancreatic Surgery, The Pancreas Institute, University of Verona Hospital Trust, Verona, Italy | [4]Massachusetts General Hospital, Boston, Massachusetts, USA | [5]Department of Digestive Diseases, Transplantation and General Surgery, Rigshospitalet. Copenhagen University Hospital, Copenhagen, Denmark | [6]Department of Hepato-Pancreato-Biliary Surgery, Oslo University Hospital, and Institute of Clinical Medicine, University of Oslo, Oslo, Norway | [7]Department of Biomedical Sciences, Humanitas University, Milan, Italy | [8]Pancreatic Surgery Unit, Humanitas Clinical and Research Centre, IRCCS, Milan, Italy | [9]Addenbrooke's Hospital, Cambridge, UK | [10]Department of Surgery in Linköping and Institution for Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden | [11]Department of Surgery, Institute of Clinical Sciences, Sahlgrenska Academy at the University of Gothenburg and Region of Västra Götaland, Sahlgrenska University Hospital, Gothenburg, Sweden | [12]Hepatobiliary and Digestive Surgery Department, University Hospital of Rennes, Rennes, France | [13]Department of Clinical Sciences Lund, Surgery, Lund University and Skåne University Hospital, Lund, Sweden | [14]Freeman Hospital, Newcastle, UK | [15]Hepato Pancreato Biliary and Liver Transplant Surgery, Department of Surgery, Oncology and Gastroenterology DiSCOG-Padova University, Padova, Italy | [16]Department of Surgery, Amsterdam UMC, Location University of Amsterdam, Amsterdam, the Netherlands | [17]Cancer Center Amsterdam, Amsterdam, the Netherlands | [18]Catharina Hospital, Eindhoven, the Netherlands | [19]Department of Surgical Sciences, Uppsala University, Uppsala, Sweden | [20]Konstantopouleio Hospital, Athens, Greece | [21]Department for General and HPB Surgery and Liver Transplantation, Ghent University Hospital, Gent, Belgium | [22]Department of Visceral and Digestive Surgery, University Hospital of Strasbourg, Strasbourg, France | [23]Bundesamt für Gesundheit BAG - Abteilung für Allgemein- und Viszeralchirurgie, Liebefeld, Switzerland | [24]Department of General and Abdominal Surgery, Liver Transplantation, Hospital Universitari Vall D'Hebron, Autonomous University of Barcelona, Barcelona, Spain | [25]Centre Hospitalier Universitaire UCL, Namur, Belgium | [26]Papageorgiou General Hospital, Thessaloniki, Greece | [27]Department of Surgery, Ordensklinikum Linz, Johannes Keppler, Linz, Austria | [28]Department of Diagnostics and Public Health, Section of Pathology, University of Verona, Verona, Italy | [29]Department of Upper Gastrointestinal Diseases, Karolinska University Hospital, Stockholm, Sweden

Correspondence: Marcus Holmberg (marcus.holmberg@ki.se)

Received: 6 December 2025 | **Revised:** 27 February 2026 | **Accepted:** 3 March 2026

Keywords: IPMN | outcome | preventive | resection

History: The results of this article have not been previously submitted. The study was orally presented as two abstracts by Marcus Holmberg at the E-AHPBA Congress, Dublin on June 10th, 2025.

ABSTRACT

Introduction: Resection of intraductal papillary mucinous neoplasm (IPMN) aims to prevent progression to invasive pancreatic cancer. However, the risks of pancreatic surgery and frequent findings of low-grade dysplasia (LGD) raise concerns about overtreatment. This EAHPBA-endorsed multinational study evaluated short- and long-term overall survival (OS) following preventive resection for IPMN (without pre-operative signs of cancer).

Methods: Adult patients with resected IPMN showing LGD, high grade dysplasia (HGD) or T1-staged invasive carcinoma from 2008–2023 were identified from the OPTIMAL-IPMN database. Estimated OS rates at one, five and 10 years in patients undergoing preventive pancreatic resection were assessed using Kaplan-Meier analyses and predictors for mortality were evaluated using parametric survival regressions.

Results: Among 2275 patients in the OPTIMAL-IPMN database, 1728 (77%) had undergone preventive pancreatic resection for IPMN. Of those were 61% resected without prior surveillance. Final pathology revealed LGD in 63%, HGD in 27% and T1a-c-staged invasive cancer in 10% (7.3% T1a-b, 2.8% T1c). Estimated 1-year OS rate was 97%. Estimated 5-year OS rates (landmark analysis at 1 year) for LGD, HGD, T1a-b, and T1c was 97%, 99%, 96% and 91% respectively. Independent predictors for long-term mortality included age $\geq$ 75 versus < 75 years (HR 1.97) and T1c versus LGD (HR 8.12).

Conclusion: This multinational study confirms excellent survival after preventive IPMN resection but reveals many upfront resections yielding LGD with unknown survival benefit. Future studies should aim to determine which patients can be followed safely with monitoring to avoid unnecessary immediate resection.

1 | Introduction

Intraductal papillary mucinous neoplasm (IPMN) is a premalignant pancreatic cystic lesion that accounts for 5%–15% of pancreatic ductal adenocarcinoma (PDAC) [1, 2]. Improved imaging [3, 4], heightened awareness [5], and possibly rising incidence [6] have increased diagnosis and resections [5, 7, 8].

Current guidelines recommend resection in a subgroup of IPMN to prevent invasive progression while advocating surveillance for low-risk lesions. However, two thirds of resected IPMN display low grade dysplasia (LGD) [9, 10], and pancreatic surgery carries risks, including up to 5% 1-year mortality in LGD patients [8], raising concerns about overtreatment. Enhancing patient selection is needed.

Balancing the surgical risks against the inherent risk of invasive transformation during surveillance remains a challenge for lesions without invasive traits. The main goal with preventive resection is to avoid too late surgery and evolution to invasive carcinoma, and to aim for high-grade dysplasia (HGD) in final pathology [11]. Resections yielding LGD have hitherto been accepted but may be considered overtreatment. However, recent evidence suggests that outcomes for early invasive lesions < 1 cm may be comparable to LGD lesions [10]. A definite histological upper threshold for intervention has not yet been established or validated.

This retrospective multi-center OPTIMAL-IPMN study evaluates short-term and long-term overall survival (OS) of a low-risk group following preventive IPMN resection.

2 | Material and Methods

2.1 | Study Setting

This was a retrospective cohort study including all adult patients (age $\geq$ 18 years) who had undergone *preventive* (i.e., without pre-operative signs of cancer) pancreatic resection between January 1, 2008, and December 31, 2023, with a final pathology revealing IPMN, classified as LGD, HGD or T1 invasive carcinoma.

Patients were identified through the OPTIMAL-IPMN database, an E-AHPBA-endorsed multi-center project designed to optimize the timing of resection for IPMN lesions that do not require immediate surgery, currently including data from 23 European and one American pancreatic center. Lesions were classified according to the WHO-classification (5th ed.) [12] and invasiveness was assessed using the AJCC TNM-classification (8th ed.) [13, 14]. Lesions that previously had been classified under earlier editions were re-defined. Postoperative complications within 90 days were graded using to the Clavien-Dindo classification [15].

2.2 | Endpoints

The primary endpoint was overall survival (OS), defined as the time from surgery to death or last follow-up whichever came first, and assessed at one, five and 10 years according to dysplasia grade and invasive tumor stage. The secondary endpoint was predictors for short- and long-term mortality.

2.3 | Preoperative Imaging

All patients underwent preoperative magnetic resonance imaging (MRI), contrast-enhanced computer tomography scans (CT) and/or endoscopic ultrasound (EUS) with or without fine needle aspiration/biopsy. Pre-operative multi-disciplinary team discussions were not required, although we assumed that they had taken place.

2.4 | Guideline Adherence

During the study period, radiologic interpretation and surgical decision-making was influenced by various guidelines and

Key Summary

- Summarise the established knowledge on this subject:
  - IPMNs are precursor lesions for invasive pancreatic cancer.
  - Current guidelines recommend resection when certain radiologic features emerge.
  - Pancreatic resection carries significant risk for morbidity and mortality.
  - A substantial proportion of resected IPMNs ultimately show only LGD.
- What are the significant and/or new findings of this study?
  - Large cohort (n = 1728) showed excellent 1- and 5-year overall survival after preventive IPMN resection, from LGD to early invasive (T1a-b) lesions.
  - Only T1c cancer and age ≥ 75 independently predicted worse long-term survival.
  - 63% of resections yielded LGD and 61% were performed without prior surveillance, indicating frequent overtreatment and need for better patient selection or safe monitoring.

consensus statements, including Sendai (2006) [16], Fukuoka (2012, 2017) [7, 17] European (2013, 2018) [18, 19] and American Gastroenterological Association (2015) [20]. Although the updated Kyoto (2024) guidelines [21] were published after the end of the study period for this cohort study, their definitions were considered to enhance alignment with current standards. For instance, the terms "enhancing mural nodule" and "solid component", which varied across earlier guidelines, were jointly analyzed according to Kyoto 2024 [21]. Patients with solid masses or tumors were excluded, as this typically indicate invasive disease.

Radiological features were primarily defined according to European 2018 guidelines, in which surgical indications are classified as *absolute* (solid mass, positive cytology for malignancy, IPMN-related jaundice, enhancing mural nodule ≥ 5 mm and main pancreatic duct [MPD] diameter ≥ 10 mm) and *relative* (cyst diameter ≥ 40 mm, cystic growth ≥ 5 mm/year, MPD dilatation between 5 and 9.9 mm, enhancing mural nodule < 5 mm and acute pancreatitis caused by IPMN) [19].

Additional radiological features highlighted in AGA and Fukuoka guidelines (e.g., abrupt MPD caliber change, lymphadenopathy, or thickened/enhancing cyst walls) were occasionally found to have triggered surgery. Further, it is plausible that some resections may have been performed without strict indications for surgery according to current guidelines (e.g., double-duct sign, stenosis/stricture of MPD, pain, weight loss).

2.5 | Surveillance Strategies

Surveillance was guided by abovementioned guidelines with the discretion of each center's routine and clinical expertise in pancreatic disease management. We acknowledge that practices varied.

2.6 | Pre- and Postoperative Decision-Making

Surgical decisions were also guided by abovementioned guidelines and each center's clinical expertise and judgment. IPMN lesions with features suggestive of invasive cancer (visible/suspected tumor or solid mass) that naturally require immediate resection were excluded from this study. Lesions without such features are managed by either surveillance or *preventive* resection. This study focused on the latter group, who thus underwent surgery for a suspected premalignant lesion in order to mitigate the risk of invasive progression. We acknowledge that these resections were often driven by a combination of guideline adherence and clinical judgment that may have varied between centers, and that some resections—in retrospect—may have been unnecessary. Procedures included pancreatoduodenectomy, left pancreatectomy, total pancreatectomy, or other. Resected patients returned to surveillance program. For the 174 patients with invasive disease (10%), data on chemotherapy was lacking.

2.7 | Data Collection

Demographic, radiological, peri-operative, pathology and survival data were collected via the Research Electronic Data Capture (REDCap) system by each centra. No identifiable information was uploaded. Follow-up followed local protocols. Ethical approval was obtained from Stockholm ethical committee, with local approvals on each site. The study followed the Declaration of Helsinki and STROBE guidelines [22]. Informed consent was not required.

2.8 | Covariates

Collected covariates included: demographical, radiologic, laboratory and clinical variables. Pancreatic cancer < 1 cm was in some centers occasionally not subcategorized into T1a or T1b, and were grouped to T1a-b to avoid exclusion. As T1a and T1b lesions showed similar short- and long-term outcomes, they were jointly analyzed to increase statistical power.

2.9 | Statistical Analyses

Clinical and radiologic variables were compared across LGD, HGD and T1-lesions using Wilcoxon rank-sum test for continuous covariates and Chi-square or Fisher's exact test (when appropriate) for categorical variables. Results are presented as medians and interquartile ranges (IQR) or frequencies (n) and percentages (%).

2.9.1 | Parametric Survival Regression

Covariates associated with short- and long-term mortality were initially identified using univariable and multivariable Cox proportional hazard regression. However, as Schoenfeld residual tests revealed violation of the proportional hazards assumption ($p < 0.05$ for three variables), we instead employed parametric survival regression using the Gompertz distribution,

which accommodates non-proportional hazards through its time-varying baseline hazard. Model selection was based on Akaike Information Criterion (AIC) corrected for sample size.

Two separate models were developed for short term (1-year) and long-term (10-year) mortality. Covariates were selected a priori based on clinical relevance. The 1-year model assessed perioperative mortality and included age (< 75 vs ≥ 75 years), comorbidity (ASA class 1–2 vs 3–4), and surgical procedure type (pancreatoduodenectomy vs left and total pancreatectomy). The 10-year model included a landmark analysis at 12 months to minimize confounding from perioperative mortality, excluding patients who died within 12 months. The remaining 1557 patients (79 events) were initially assessed with age (< 75 vs ≥ 75 years), comorbidity (ASA class 1–2 vs 3–4), pre-operative CA19-9 levels (≤ 37 vs > 37 U/mL) and pathologic grade (LGD, HGD, T1a-b, T1c). CA19-9 was not significant ($p = 0.459$) and excluded from final model. Hazard ratios (HR) with 95% confidence intervals (CI) were reported; $p < 0.05$ indicated statistical significance.

All tests were two-sided, with statistical significance set at $p < 0.05$. Analyses were performed in R version 4.5.0 (GUI 1.81 Big Sur ARM build). SuperGrok by xAI and Claude Sonnet 4.5 by Anthropic were used to refine R-code, as well as to enhance flow, grammar and spelling of this manuscript.

2.9.2 | Kaplan-Meier Analyses and Sensitivity Analyses

Short- and long-term survival outcomes were depicted using Kaplan-Meier analyses. As for in the regression, the long-term model also included a landmark analysis at 12 months excluding patients who died within 12 months. OS rates at one, five and 10 years were estimated using the Kaplan Meier methods, with pairwise comparisons conducted using Z-tests to focus on fixed time point differences, rather than log rank tests for entire survival curve differences.

Based on predictors retrieved from the two models, sensitivity analyses were performed to assess OS in high-risk individuals. To minimize confounding from perioperative mortality, the long-term model also included a landmark analysis at 12 months.

3 | Results

The 24 OPTIMAL-IPMN centers contributed 2275 patients (median of 58, IQR 28–114; range 4–360) over a16-year period, with median center participation of 10 years, IQR 8–13.

3.1 | Baseline Characteristics

Out of the 2275 included patients from the OPTIMAL-IPMN cohort, three quarters ($n = 1728$) underwent *preventive* resection and included in this study. Half ($n = 917$) were of male sex and median age was 70 (IQR 63–74) years. One-third ($n = 521$) were critically comorbid (ASA 3–4). Overall, 61% ($n = 1059$) underwent resection at discovery without prior surveillance, while an additional 15% underwent resection within 1 year of initial diagnosis (Table 1). Resections upon discovery decreased over study cohort periods: 68% in 2008–2015%, to 65% in 2016–2019%, and 48% in 2020–2023 ($p < 0.001$).

3.2 | Indications for Surgery

Radiologic diagnosis was branch-duct (35%), main-duct (25%) and mixed-type (40%). The most common surgical indications were main duct (61%) and branch duct (55%), whereas the presence of tissue proliferation (i.e., enhancing mural nodule and/or solid component) was not as common (16%). Presentation with symptoms and increased CA19-9 ≥ 37 U/mL occurred in 21% and 17% respectively. With the exception of branch-duct involvement (57%), all indications were more frequent in invasive lesions: main duct involvement (73%), solid part (34%), symptoms (39%) and CA19-9 ≥ 37 (25%) ($p \leq 0.005$ for all). Almost half ($n = 787$) underwent pancreatoduodenectomy, 38% ($n = 634$) left pancreatectomy and 16% ($n = 269$) total pancreatectomy. Surgical indications (absolute, high-risk features/stigmata) according to AGA, European and Kyoto guidelines respectively were present in a third of the resections, and final pathology revealed LGD in 44%–48%, HGD 33.5%–40% and T1 in 16%–17%.

3.3 | Clinical Outcome

Major morbidity (Clavien-Dindo ≥ 3a) within 90-day occurred in a quarter ($n = 507$) for non-invasive lesions, but in 15% for invasive lesions ($p = 0.004$). Major morbidity was mainly due to grade 3a/3b complications (20% vs 12%, $p = 0.013$). Postoperative 90-day mortality occurred in 2.0%, with no significant group differences. Major morbidity remained stable over time periods. Of the 46 patients (2.7%) that died within the first year and excluded from Landmark analysis, 24 (52%) were LGD, 17 (37%) HGD and 5 (11%) T1-disease. Information on cause of death was lacking.

3.4 | Postoperative Pathology

Pathology revealed LGD in 63% ($n = 1085$), HGD in 27% ($n = 469$) and invasive T1-carcinoma in 10% ($n = 174$). In the study period 2020–2023, LGD, HGD and T1 were found in 58%, 29% and 13%, respectively. T1c frequency was 1.7%, 3.3% and 3.2% across study periods. Among lesions resected at discovery, 62% were LGD, and 9% T1 (6.5% T1a-b and 2.6% T1c).

3.5 | Follow Up and Overall Survival

Median follow-up was 156 months (IQR 79.1–237), with 949 patients (54.9%) followed beyond 10 years. Overall, 284 deaths (16.4%) occurred during follow-up. Estimated five- and 10-year OS rates were 94.3% and 87.9%, respectively.

TABLE 1 | Descriptive statistics of the resected cohort.

Variables	Overall $N = 1728$[a]	LGD, $n = 1085$[a]	HGD, $n = 469$[a]	T1, $n = 174$[a]	p-value[b]
History of IPMN					0.139
Not previously known	1059 (61)	661 (61)	301 (64)	97 (56)	
Under surveillance	668 (39)	423 (39)	168 (36)	77 (44)	
Time					0.044
< 1 year	263 (40)	159 (38)	62 (37)	42 (55)	
1–2 years	148 (22)	102 (25)	34 (20)	12 (16)	
2–5 years	155 (23)	90 (22)	49 (29)	16 (21)	
≥ 5 years	94 (14)	65 (16)	22 (13)	7 (9.1)	
Radiologic diagnosis					< 0.001
BD-IPMN	609 (35)	463 (43)	104 (22)	42 (24)	
MD-IPMN	430 (25)	230 (21)	140 (30)	60 (35)	
MT-IPMN	681 (40)	385 (36)	225 (48)	71 (41)	
IPMN-Uns	8 (0)	7 (0)	0 (0)	1 (0)	
Surgical indication[c]					
Absolute indication	542 (31)	238 (22)	218 (46)	86 (49)	< 0.001
High risk features	499 (29)	241 (22)	173 (37)	85 (49)	< 0.001
High risk stigmata	580 (34)	263 (24)	225 (48)	92 (53)	< 0.001
Surgical indication					
Related to main duct	1066 (62)	603 (56)	337 (72)	126 (73)	< 0.001
Dilatation	1061 (61)	599 (55)	337 (72)	125 (72)	< 0.001
Abrupt change of duct	26 (1.5)	18 (1.7)	4 (0.9)	4 (2.3)	0.313
Related branch duct	947 (55)	602 (56)	245 (53)	100 (57)	0.575
Size > 4 cm	806 (47)	508 (47)	212 (45)	86 (49)	0.623
Size progression	203 (12)	151 (14)	44 (9.4)	8 (4.6)	< 0.001
Thickened walls	108 (6.3)	46 (4.2)	36 (7.8)	26 (15)	< 0.001
Related to solid part	270 (16)	122 (11)	89 (19)	59 (34)	< 0.001
Enhancing nodulus	207 (12)	84 (7.7)	74 (16)	49 (28)	< 0.001
Solid component	79 (4.6)	46 (4.2)	20 (4.3)	13 (7.5)	0.155
Symptoms	360 (21)	160 (15)	133 (28)	67 (39)	< 0.001
CA19-9 > 37 (U/mL)	210 (17)	110 (14)	65 (19)	35 (25)	0.005
Operation year					0.039
2008–2015[d]	541 (31)	347 (32)	139 (30)	55 (32)	
2016–2019	724 (42)	470 (43)	195 (42)	59 (34)	
2020–2023	463 (27)	268 (25)	135 (29)	60 (34)	
Procedure					< 0.001
PD	787 (47)	481 (46)	228 (49)	78 (46)	
Left P	634 (38)	468 (44)	127 (27)	39 (23)	
Total P	269 (16)	108 (10)	109 (23)	52 (31)	
Clavien-Dindo 90 days					0.016
0–2	1182 (75)	695 (73)	349 (75)	138 (84)	
3	303 (19)	202 (21)	82 (18)	19 (12)	
4	67 (4.2)	39 (4.1)	24 (5.2)	4 (2.4)	
5	32 (2.0)	18 (1.9)	11 (2.4)	3 (1.8)	

(Continues)

TABLE 1 | (Continued)

Variables	Overall $N = 1728$[a]	LGD, $n = 1085$[a]	HGD, $n = 469$[a]	T1, $n = 174$[a]	p-value[b]
Histopathology					< 0.001
LGD	1085 (63)	1085 (100)	0 (0)	0 (0)	
HGD	469 (27)	0 (0)	469 (100)	0 (0)	
T1a	89 (5.2)	0 (0)	0 (0)	89 (51)	
T1b	26 (1.5)	0 (0)	0 (0)	26 (15)	
T1a-b	11 (0.6)	0 (0)	0 (0)	11 (6.3)	
T1c	48 (2.8)	0 (0)	0 (0)	48 (28)	

Abbreviations: BD, branch duct; CA, Cancer Antigen; HGD, high grade dysplasia; LGD, low grade dysplasia; MD, main duct; MT, mixed type; PD, Pancreatoduodenectomy; PE, Pancreatectomy; T1, T1-stage; Uns, unspecified.
[a]*n* (%).
[b]Pearson's Chi-squared test; Fisher's exact test.
[c]According to American Gastroenterological Association, European and Kyoto guidelines.
[d]32 patients (1.4%) were resected prior to 2010.

Estimated 1-year OS rate for the entire cohort was 97.2% (CI 96.5–98.0) (Figure 1a): LGD 97.7% (CI 96.8–98.6), HGD 96.3% (CI 94.6–98.0), T1a-b 97.5% (CI 94.8–100), and for T1c 95.8% (CI 90.2–100), with no significant differences in pairwise comparisons between groups ($p > 0.1$ for all).

Estimated 5-year OS rate (with landmark analysis at 1 year) was 97.1% (CI 96.3–98.0) across LGD to T1b: LGD 96.6% (CI 95.4–97.8), HGD 98.6% (CI 97.4–99.7), T1a-b 96.2% (CI 92.6–99.9), and for T1c 90.9% (CI 82.9–99.8) (Figure 1b). Significant difference was only found between LGD versus HGD ($p = 0.021$), borderline for HGD versus T1c ($p = 0.081$) but not between other groups ($p > 0.1$ for all).

Estimated 10-year OS rate (with landmark analysis at 1 year) was 91.4% (CI 89.8–93.0) across LGD to T1a-b: LGD 91.9% (CI 90.0–93.8), HGD 90.9% (CI 87.9–94.1), T1a-b 88.5% (CI 82.3–95.2) and T1c 57.1% (CI 43.0–75.8) (Figure 1b). In pairwise comparisons, LGD versus T1c, HGD versus T1c and T1a-b versus T1c were statistically significant ($p < 0.001$), not between other comparisons ($p > 0.2$).

3.6 | Parametric Survival Regression

Among 1728 patients, 46 deaths occurred within the first year. Independent predictors of 1-year mortality included: age ≥ 75 versus < 75 years (HR 2.62, CI 1.40–4.89, $p = 0.003$), ASA 3–4 versus ASA 1–2 (HR 2.95, CI 1.61–5.40, $p < 0.001$), pancreatoduodenectomy versus left pancreatectomy (HR 5.51, 95% CI 2.30–13.2, $p < 0.001$) (Table 2).

Among 1557 non-censored patients surviving beyond one year, 45 and 79 deaths occurred within 5 and 10 years respectively. Independent predictors of 10-year mortality included age ≥ 75 years versus < 75 years (HR 1.97, 95% CI 1.21–3.23, $p = 0.009$) and T1c invasive carcinoma (HR 8.12, 95% CI 4.34–15.2, $p < 0.001$). T1b invasive carcinoma did not reach statistical significance for mortality (HR 3.00, 95% CI 0.91–9.86, $p = 0.071$) (Table 2).

3.7 | Sensitivity Analyses

Individuals ≥ 75 years and/or ASA 3-4 undergoing pancreatoduodenectomy demonstrated an estimated OS-rate at one-year of 91.5% with no significant differences between groups ($p > 0.3$). Individuals ≥ 75 years demonstrated conditional estimated OS-rate (landmark at one year) at five year of 95.4% for entire cohort with no differences within groups, and at 10 year of 87.2%, 92.3% 72.4% and 60% for LGD, HGD, T1a-b and T1c respectively. Pairwise comparisons between LGD, HGD, T1a-b and T1c at 10 year showed only significant differences between HGD and T1a-b ($p = 0.03$) and HGD and T1c ($p = 0.009$).

4 | Discussion

Managing IPMN remains a clinical challenge that requires a careful balance between the potential for invasive transformation during surveillance [23] and the risk for complications of preventive surgery [24]. Despite advances in imaging and updates of guidelines, pre-operative assessment still is imprecise and may lead to premature surgery.

This multinational retrospective study of a Western cohort demonstrated that short-term and landmark adjusted long-term survival after preventive resections for IPMN (without preoperative signs of cancer) were excellent and comparable between patients with non-invasive and small invasive lesions. It also demonstrated a high rate of resections performed without prior surveillance and more than half revealing LGD on final pathology. Although the proportion of resected patients at diagnosis notably decreased in later years (from 68% to 48% across the study periods), resected T1c lesions remained low (~3%) and LGD rates declined only modestly. Consequently, most of the patients with IPMN who underwent upfront preventive resection thus lacked a risk assessment based on longitudinal observation. These findings underscore the need to re-evaluate surgical timing and thresholds, while also emphasizing the importance of involving the patients in the decision-making process.

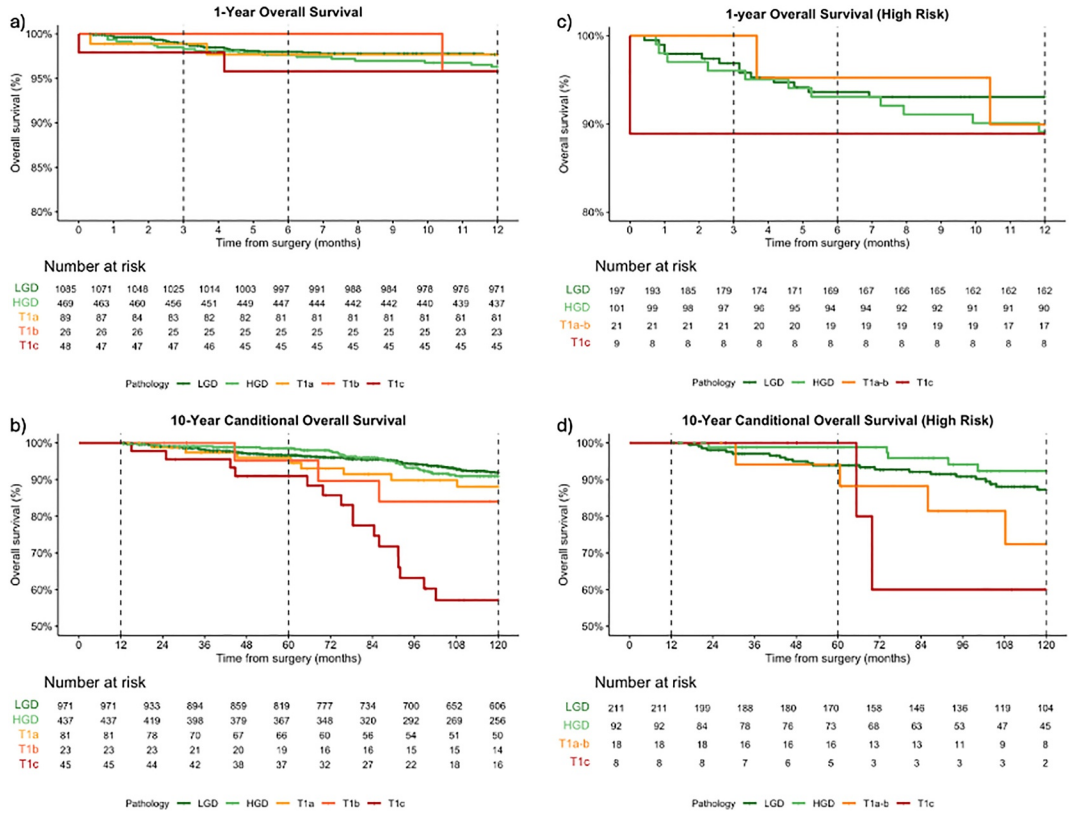

FIGURE 1 | Kaplan Meier overall survival (OS) analysis, short- and long-term (a, b) and sensitivity analyses of high-risk individuals (c, d). (a) One-year OS in all patients stratified by pathology ($n = 1728$). Estimated short-term OS rate at 1 year was 97.2% without significant differences in pairwise comparisons. (b) Ten-year conditional OS with 1-year landmark analysis stratified by pathology ($n = 1557$). Estimated 5-year OS rate for LGD to T1a–b and T1c was 97.1% and 90.9% respectively ($p < 0.001$). Estimated 10-year OS rate for LGD to T1a-b was 91.4% and for T1c 57.1% ($p < 0.001$). (c) Sensitivity analyses of individuals ≥ 75 years and/or ASA 3–4 undergoing pancreatoduodenectomy demonstrated an estimated OS-rate at 1-year of 91.5% with no significant differences between groups ($p > 0.3$). (d) Sensitivity analyses of individuals ≥ 75 years demonstrated conditional estimated OS-rate (landmark at 1 year) at 5 year of 95.4% for LGD to T1c with no differences within groups, and at 10 year of 87.2%, 92.3% 72.4% and 60% for LGD, HGD, T1a–b and T1c respectively.

Whether LGD on final pathology should be considered a failure or rather viewed in the context of preventing cancer-related death, remains a subject of debate. There is limited knowledge about which LGD lesions progress to invasive cancer, and which remain indolent over time. The prevailing strategy, supported by current guidelines, favors early surgery to prevent progression to invasive carcinoma [25] but are largely driven by expert consensus rather than prospective data on natural history [25, 26] and are designed to prioritize high sensitivity in detecting HGD and early invasive carcinoma, with lesser focus on specificity [27]. This may result in premature surgeries and exposing the patients to risks of major short-term morbidity and possibly even long-term effects [28, 29].

Ideally, surgery should be reserved for highly selected cases, targeting HGD [11] *prior to* progression to invasive carcinoma [25]. While adherence to guidelines and a more restrictive approach have led to a reduction in the proportion of resected LGD lesions in later years [30], recent studies still indicate that many resections may be premature [26, 27, 31–34] and that many of these lesions could be safely managed through surveillance [10, 35] and additional work-up [34].

In the present study, 1-year mortality and landmark-adjusted 5-year mortality were comparable at around 3% between non-invasive and T1a-b lesions. Although parametric regression further identified T1c stage as the most important independent predictor of long-term mortality, it constituted less than 3% of the cohort—similar to 1-year mortality—and demonstrated a 5-year OS rate of around 90%. Regression also demonstrated similar outcomes between LGD, HGD and T1a-b-lesions. These findings align with recent single-center studies of long-term outcomes for T1-staged invasive carcinomas [10, 36] and a Swedish national cohort (2010–2019), which reported a non-reached median OS for T1, including T1c [37]. Notably, the Swedish study also demonstrated an approximate 10-percentage-point improvement in five-year OS during 2016–2019 versus earlier periods. Japanese studies have reported even more favorable outcomes for T1a invasive IPMN, with 0% 5-year mortality rates [38, 39]; both Japanese studies analyzed T1b lesions alongside more advanced tumor stages.

These exceptional outcomes contrast with a recent multi-center Western cohort study, which reported median OS (rather than 5-year OS rates): 159 months for T1a ($n = 69$), 129 months for T1b

TABLE 2 | Parametric Regression of short- and long-term mortality.

	1-year model			10-year model		
Variables	**HR**	**(95% CI)**	***p*-value**	**HR**	**(95% CI)**	***p*-value**
Age						
< 75 years	Ref			Ref		
≥ 75 years	2.62	(1.40–4.89)	0.003	1.97	(1.21–3.23)	**0.009**
ASA						
1–2	Ref			Ref		
3–4	2.95	(1.61–5.40)	**< 0.001**	1.41	(0.89–2.23)	0.144
Procedure						
Left pancreatectomy	Ref			—	—	
Total pancreatectomy	1.27	(0.32–5.08)	0.737	—	—	
Pancreatoduodenectomy	5.51	(2.30–13.2)	**< 0.001**	—	—	
Pathology						
LGD	—	—		Ref		
HGD	—	—		0.96	(0.55–1.67)	0.885
T1a invasive	—	—		1.15	(0.41–3.23)	0.786
T1b invasive	—	—		3.00	(0.91–9.86)	0.071
T1c invasive	—	—		8.12	(4.34–15.2)	**< 0.001**

Note: Gompertz parametric regressions on short- and long-term mortality. The 1-year model included all patients from surgery and assessed perioperative mortality using age, ASA-class, and surgical procedure as predictors (n = 1,717, 46 events). The 10-year model used a landmark analysis at 12 months to assess long-term mortality using age, ASA class, and pathologic grade as predictors (n = 1,557, 79 events). CA19-9 > 37 U/mL was tested in the 10-year model but was not significant (p = 0.459) and excluded from presentation. Hazard ratios (HR) with 95% confidence intervals (CI) shown.
Abbreviations: "—", variable not included in model; ASA, American Society of Anesthesiologists physical status classification; CI, confidence interval; HGD, high-grade dysplasia; HR, hazard ratio; LGD, low-grade dysplasia; Ref, reference category.

(n = 50) and 78 months for T1c [40]. Spanning 2000 to 2020, this study cohort may have experienced evolving standards in peri-operative care, with the later decade possibly characterized by more refined patient selection, peri-operative management, and follow-up practices. These factors may have influenced both short- and long-term outcomes, independent of tumor biology. It also classified 1 cm lesions as T1b according to the Recommendations of the Verona Consensus Meeting on Pathologic Evaluation and Reporting of IPMN [41] whereas the present study defined T1c according to AJCC TNM-classification, 8th edition [13].

The present study, including 126 T1a-b invasive IPMN-patients, focused on tumor-related survival outcomes in relation to clinical presentation among patients considered for *preventive* resection. We thus specifically focused on lesions resected without malignant signs (which seems to confer better outcomes than lesions resected *with* malignant signs, regardless of final tumor-stage [10]). One-year landmark analyses were performed to exclude deaths related to the post-operative period. Overall, adjusting for year, preventive indication and early mortality may explain similar survival. These findings indicate a low tumor-related death in early-stage cancer. In this context, accepting to miss a very few, small invasive lesions in order to reduce the large number of resected LGD-lesions may be justifiable, particularly since three-quarters of patients undergo resection within a year of lesion detection and that the 5-year incidence rate of pancreatic malignancy for selected IPMN is just 3.3% [42]. For lesions without apparent malignant features at discovery, these findings support safe surveillance until high-risk progression emerges, or at least a period of monitoring and a proper preoperative work-up before deciding on surgical intervention.

However, the decision to proceed with complication-prone surgery to prevent invasive transformation must be carefully weighed against both patient- and procedure-related risks. Our study identifies several factors where ongoing surveillance could be undertaken as the long-term mortality with surgery may be greater. Age ≥ 75 years was independently associated with increased short- and long-term mortality. These findings align with a modeling study suggesting that preventive resection in low-risk IPMN yields a net survival benefit only up to age 60, and up to age 75 in high-risk IPMN [25]. The substantial proportion of critically comorbid patients (ASA 3-4, n = 521; one-third of our cohort) who underwent resection warrants particular consideration. While this reflects real-world practice patterns, it raises questions about patient selection for major *preventive* surgery in those with significant medical burden.

Indeed, comorbidity emerged as an independent risk factor for short-term mortality in our study. This is further supported by a retrospective single-center study of 115 patients with IPMN and high-risk stigmata which found that in the presence of important comorbidity, surgical resection was recommended for only those with a solid component, whereas conservative management may be preferable in the absence of such features [43].

Moreover, pancreatoduodenectomy conferred substantially higher 1-year mortality compared to left pancreatectomy, consistent with the procedure's greater complexity and impact on

complications. This finding emphasizes the importance of tailoring surgical approach to patient risk profile and disease location. Thus, high-risk individuals are exposed to important short-term surgical burden and long-term life expectancy is also affected (Figure 1). Preventive surgery thus seems unjustified in older, comorbid persons, especially if pancreatoduodenectomy is considered.

While current guidelines recommend considering comorbidity and surgical fitness, they may underemphasize age, comorbidity and procedure as standalone factors. Incorporating age, ASA-class and tumor locale more explicitly into surgical decision-making could help avoid unnecessary resections in older and comorbid patients [25], particularly when absolute indications or high-risk features/stigmata are absent.

The principal strength of this study is the large, multinational Western cohort of preventively resected IPMN (without preoperative suspicion of malignancy), one of the largest reported to date, allowing robust stage-stratified and landmark-adjusted survival analyses in a real-world setting. The study also has several limitations. First, variation in practice may have introduced bias. Second, differences in surgical techniques, perioperative management and follow-up protocols over the study periods across centers may have influenced outcomes. Third, pathological assessment was not centralized, which may have introduced interobserver variability. Fourth, patients with disease beyond T1 are not included in the database, which limits our ability to assess the full spectrum of IPMN progression. Nonetheless, we find it implausible that a preventively resected lesion would represent an invasive carcinoma larger than 2 cm. Fifth, the retrospective nature of the study limits causal inference and may be subject to incomplete or inconsistent data capture. Unmeasured confounders, such as endocrine and exocrine insufficiency, could also have impacted long-term survival outcomes. Sixth, Surgical morbidity was assessed using broad Clavien–Dindo categories within 90 days, but detailed data on specific postoperative complications were lacking and were not collected in the original registry form. Finally, our predominantly Western cohort may limit generalizability to other populations.

This multinational study shows that preventive resection of IPMN (i.e., without preoperative signs of malignancy) confers excellent survival, even in early, unexpectedly invasive lesions. It also revealed many resections performed without prior surveillance yielding LGD. Considering the substantial risks of pancreatic surgery, surveillance may be the preferable strategy for many patients. Our findings highlight the need for more individualized operative criteria and improved preoperative risk stratification.

Acknowledgments

We are grateful for valuable input from Biostatistician Nils Hentati Isacsson, Karolinska Institutet as well as for data collection by Christina Biorserud, Thomas Apers, An Verena Lerut and Stavros Antoniou from Sahlgrenska University Hospital, Gothenburg, Sweden, Ghent University Hospital, Belgium, and Papageorgiou General Hospital respectively.

We are also deeply grateful for the endorsement of this OPTIMAL-IPMN project by the European-African Hepato-Pancreato-Biliary Association (EAHPBA).

Funding

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

References

1. A. D. Singhi, E. J. Koay, S. T. Chari, and A. Maitra, "Early Detection of Pancreatic Cancer: Opportunities and Challenges," *Gastroenterology* 156, no. 7 (May 2019): 2024–2040, https://doi.org/10.1053/j.gastro.2019.01.259.

2. T. Muraki, K. T. Jang, M. D. Reid, et al., "Pancreatic Ductal Adenocarcinomas Associated With Intraductal Papillary Mucinous Neoplasms (IPMNs) Versus Pseudo-IPMNS: Relative Frequency, Clinicopathologic Characteristics and Differential Diagnosis," *Modern Pathology* 35, no. 1 (January 2022): 96–105, https://doi.org/10.1038/s41379-021-00902-x.

3. O. Basturk, S. M. Hong, L. D. Wood, et al., "A Revised Classification System and Recommendations From the Baltimore Consensus Meeting for Neoplastic Precursor Lesions in the Pancreas," *American Journal of Surgical Pathology* 39, no. 12 (December 2015): 1730–1741, https://doi.org/10.1097/PAS.0000000000000533.

4. M. L. Kromrey, R. Bulow, J. Hubner, et al., "Prospective Study on the Incidence, Prevalence and 5-Year Pancreatic-Related Mortality of Pancreatic Cysts in a Population-Based Study," *Gut* 67, no. 1 (January 2018): 138–145, https://doi.org/10.1136/gutjnl-2016-313127.

5. D. A. Klibansky, K. M. Reid-Lombardo, S. R. Gordon, and T. B. Gardner, "The Clinical Relevance of the Increasing Incidence of Intraductal Papillary Mucinous Neoplasm," *Clinical Gastroenterology and Hepatology* 10, no. 5 (May 2012): 555–558, https://doi.org/10.1016/j.cgh.2011.12.029.

6. L. Aronsson, R. Andersson, and D. Ansari, "Intraductal Papillary Mucinous Neoplasm of the Pancreas - Epidemiology, Risk Factors, Diagnosis, and Management," *Scandinavian Journal of Gastroenterology* 52, no. 8 (August 2017): 803–815, https://doi.org/10.1080/00365521.2017.1318948.

7. M. Tanaka, C. Fernandez-Del Castillo, T. Kamisawa, et al., "Revisions of International Consensus Fukuoka Guidelines for the Management of IPMN of the Pancreas," *Pancreatology* 17, no. 5 (September–October 2017): 738–753, https://doi.org/10.1016/j.pan.2017.07.007.

8. L. Aronsson, B. Andersson, R. Andersson, B. Tingstedt, S. O. Bratlie, and D. Ansari, "Intraductal Papillary Mucinous Neoplasms of the Pancreas: A Nationwide Registry-Based Study," *Scandinavian Journal of Surgery* 107, no. 4 (December 2018): 302–307, https://doi.org/10.1177/1457496918766727.

9. H. Aziz, A. W. Acher, S. G. Krishna, J. M. Cloyd, and T. M. Pawlik, "Comparison of Society Guidelines for the Management and Surveillance of Pancreatic Cysts: A Review," *JAMA Surgery* 157, no. 8 (June 22 2022): 723, https://doi.org/10.1001/jamasurg.2022.2232.

10. Y. Djoumi, O. Sadr-Azodi, M. Vujasinovic, et al., "Pre-Emptive Resection for Intraductal Papillary Mucinous Neoplasia - Long-Term Outcome is Similar Between Non-Invasive and Early Invasive Lesions

in a Tertiary Single Center," *Pancreatology* 23, no. 4 (March 2023): 389–395, https://doi.org/10.1016/j.pan.2023.03.007.

11. R. Salvia, A. Burelli, G. Perri, and G. Marchegiani, "State-of-The-Art Surgical Treatment of Ipmns," *Langenbeck's Archives of Surgery* 406, no. 8 (December 2021): 2633–2642, https://doi.org/10.1007/s00423-021-02349-9.

12. I. D. Nagtegaal, R. D. Odze, D. Klimstra, et al., "The 2019 WHO Classification of Tumours of the Digestive System," *Histopathology* 76, no. 2 (January 2020): 182–188, https://doi.org/10.1111/his.13975.

13. M. B. Amin, F. L. Greene, S. B. Edge, et al., "The Eighth Edition AJCC Cancer Staging Manual: Continuing to Build a Bridge From a Population-Based to a More "Personalized" Approach to Cancer Staging," *CA: A Cancer Journal for Clinicians* 67, no. 2 (March 2017): 93–99, https://doi.org/10.3322/caac.21388.

14. G. A. Margonis, A. Pulvirenti, V. Morales-Oyarvide, et al., "Performance of the 7 Th and 8 Th Editions of the American Joint Committee on Cancer Staging System in Patients With Intraductal Papillary Mucinous Neoplasm-Associated PDAC: A Multi-Institutional Analysis," *Annals of Surgery* 277, no. 4 (April 2023): 681–688, https://doi.org/10.1097/SLA.0000000000005313.

15. D. Dindo, N. Demartines, and P. A. Clavien, "Classification of Surgical Complications: A New Proposal With Evaluation in a Cohort of 6336 Patients and Results of a Survey," *Annals of Surgery* 240, no. 2 (August 2004): 205–213, https://doi.org/10.1097/01.sla.0000133083.54934.ae.

16. M. Tanaka, S. Chari, V. Adsay, et al., "International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas," *Pancreatology* 6, no. 1–2 (2006): 17–32, https://doi.org/10.1159/000090023.

17. M. Tanaka, C. Fernandez-del Castillo, V. Adsay, et al., "International Consensus Guidelines 2012 for the Management of IPMN and MCN of the Pancreas," *Pancreatology* 12, no. 3 (May–June 2012): 183–197, https://doi.org/10.1016/j.pan.2012.04.004.

18. M. Del Chiaro, C. Verbeke, R. Salvia, et al., "European Experts Consensus Statement on Cystic Tumours of the Pancreas," *Digestive and Liver Disease* 45, no. 9 (September 2013): 703–711, https://doi.org/10.1016/j.dld.2013.01.010.

19. European Study Group on Cystic Tumours of the P. "European Evidence-Based Guidelines on Pancreatic Cystic Neoplasms," *Gut* 67, no. 5 (May 2018): 789–804, https://doi.org/10.1136/gutjnl-2018-316027.

20. S. S. Vege, B. Ziring, R. Jain, and P. Moayyedi, and Clinical Guidelines Committee; American Gastroenterology Association, "American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Asymptomatic Neoplastic Pancreatic Cysts," *Gastroenterology* 148, no. 4 (April 2015): 819–822: quize12–3, https://doi.org/10.1053/j.gastro.2015.01.015.

21. T. Ohtsuka, C. Fernandez-Del Castillo, T. Furukawa, et al., "International Evidence-Based Kyoto Guidelines for the Management of Intraductal Papillary Mucinous Neoplasm of the Pancreas," *Pancreatology* 24, no. 2 (March 2024): 255–270, https://doi.org/10.1016/j.pan.2023.12.009.

22. E. E. von, D. G. Altman, M. Egger, et al., "The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies," *International Journal of Surgery* 12, no. 12 (December 2014): 1495–1499, https://doi.org/10.1016/j.ijsu.2014.07.013.

23. J. Yu, A. L. Blackford, M. Dal Molin, C. L. Wolfgang, and M. Goggins, "Time to Progression of Pancreatic Ductal Adenocarcinoma From Low-to-High Tumour Stages," *Gut* 64, no. 11 (November 2015): 1783–1789, https://doi.org/10.1136/gutjnl-2014-308653.

24. P. Sanchez-Velazquez, X. Muller, G. Malleo, et al., "Benchmarks in Pancreatic Surgery: A Novel Tool for Unbiased Outcome Comparisons," *Annals of Surgery* 270, no. 2 (August 2019): 211–218, https://doi.org/10.1097/SLA.0000000000003223.

25. J. H. Chang, C. Wehrle, M. S. Hossain, et al., "A Practical Strategy to Reduce Surgical Overtreatment of Intraductal Papillary Mucinous Neoplasms of the Pancreas," *Annals of Surgery* 280, no. 1 (July 2024): 32–34, https://doi.org/10.1097/SLA.0000000000006133.

26. F. De Stefano, R. Pellegrini, G. Marchegiani, and S. Crippa, "Reducing the Burden of Pancreatic Cancer by Surveilling Mucinous Cystic Neoplasms: Are We There Yet?," *Best Practice & Research Clinical Gastroenterology* 74 (February 2025): 101998, https://doi.org/10.1016/j.bpg.2025.101998.

27. S. Crippa, A. Fogliati, R. Valente, et al., "A tug-of-war in Intraductal Papillary Mucinous Neoplasms Management: Comparison Between 2017 International and 2018 European Guidelines," *Digestive and Liver Disease* 53, no. 8 (August 2021): 998–1003, https://doi.org/10.1016/j.dld.2021.03.009.

28. J. M. Sharib, A. L. Fonseca, D. S. Swords, et al., "Surgical Overtreatment of Pancreatic Intraductal Papillary Mucinous Neoplasms: Do the 2017 International Consensus Guidelines Improve Clinical Decision Making?," *Surgery* 164, no. 6 (December 2018): 1178–1184, https://doi.org/10.1016/j.surg.2018.07.014.

29. H. V. Wundsam, C. S. Rosch, P. Kirchweger, et al., "Long-Term Quality of Life After Pancreatic Surgery for Intraductal Papillary Mucinous Neoplasm," *European Surgical Research* 62, no. 2 (2021): 80–87, https://doi.org/10.1159/000515459.

30. F. Aleotti, S. Crippa, G. Belfiori, et al., "Pancreatic Resections for Benign Intraductal Papillary Mucinous Neoplasms: Collateral Damages From Friendly Fire," *Surgery* 172, no. 4 (October 2022): 1202–1209, https://doi.org/10.1016/j.surg.2022.04.036.

31. M. A. Attiyeh, C. Fernandez-Del Castillo, E. M. Al, et al., "Development and Validation of a Multi-Institutional Preoperative Nomogram for Predicting Grade of Dysplasia in Intraductal Papillary Mucinous Neoplasms (IPMNs) of the Pancreas: A Report From the Pancreatic Surgery Consortium," *Annals of Surgery* 267, no. 1 (January 2018): 157–163, https://doi.org/10.1097/SLA.0000000000002015.

32. M. Del Chiaro, R. Beckman, Z. Ateeb, et al., "Main Duct Dilatation is the Best Predictor of High-Grade Dysplasia or Invasion in Intraductal Papillary Mucinous Neoplasms of the Pancreas," *Annals of Surgery* 272, no. 6 (December 2020): 1118–1124, https://doi.org/10.1097/SLA.0000000000003174.

33. R. E. Khoury, C. Kabir, V. K. Maker, M. Banulescu, M. Wasserman, and A. V. Maker, "What is the Incidence of Malignancy in Resected Intraductal Papillary Mucinous Neoplasms? An Analysis of over 100 US Institutions in a Single Year," *Annals of Surgical Oncology* 25, no. 6 (June 2018): 1746–1751, https://doi.org/10.1245/s10434-018-6425-6.

34. F. Giannone, S. Crippa, F. Aleotti, et al., "Improving Diagnostic Accuracy and Appropriate Indications for Surgery in Pancreatic Cystic Neoplasms: The Role of EUS," *Gastrointestinal Endoscopy* 96, no. 4 (October 2022): 648–656.e2, https://doi.org/10.1016/j.gie.2022.05.009.

35. G. Marchegiani, S. Andrianello, G. Morbin, et al., "Importance of Main Pancreatic Duct Dilatation in IPMN Undergoing Surveillance," *British Journal of Surgery* 105, no. 13 (December 2018): 1825–1834, https://doi.org/10.1002/bjs.10948.

36. P. Addeo, G. Canali, C. Paul, P. de Mathelin, G. Averous, and P. Bachellier, "Long-Term Survival After Resection of Invasive Pancreatic Intraductal Papillary Mucinous Neoplasm," *Langenbeck's Archives of Surgery* 409, no. 1 (November 2024): 361, https://doi.org/10.1007/s00423-024-03550-2.

37. M. Holmberg, C. Radkiewicz, C. Stromberg, et al., "Outcome After Surgery for Invasive Intraductal Papillary Mucinous Neoplasia Compared to Conventional Pancreatic Ductal Adenocarcinoma - A Swedish Nationwide Register-Based Study," *Pancreatology* 23, no. 1 (January 2023): 90–97, https://doi.org/10.1016/j.pan.2022.12.003.

38. Y. Takeda, H. Imamura, J. Yoshimoto, et al., "Survival Comparison of Invasive Intraductal Papillary Mucinous Neoplasm Versus Pancreatic Ductal Adenocarcinoma," *Surgery* 172, no. 1 (July 2022): 336–342, https://doi.org/10.1016/j.surg.2022.01.013.

39. S. Nara, K. Shimada, T. Kosuge, Y. Kanai, and N. Hiraoka, "Minimally Invasive Intraductal Papillary-Mucinous Carcinoma of the Pancreas: Clinicopathologic Study of 104 Intraductal Papillary-Mucinous Neoplasms," *American Journal of Surgical Pathology* 32, no. 2 (February 2008): 243–255, https://doi.org/10.1097/PAS.0b013e3181484f1e.

40. J. R. Habib, I. F. Rompen, B. A. Campbell, et al., "An International Multi-Institutional Validation of T1 Sub-Staging of Intraductal Papillary Mucinous Neoplasm-Derived Pancreatic Cancer," *Journal of the National Cancer Institute* 116, no. 11 (November 1 2024): 1791–1797, https://doi.org/10.1093/jnci/djae166.

41. V. Adsay, M. Mino-Kenudson, T. Furukawa, et al., "Pathologic Evaluation and Reporting of Intraductal Papillary Mucinous Neoplasms of the Pancreas and Other Tumoral Intraepithelial Neoplasms of Pancreatobiliary Tract: Recommendations of Verona Consensus Meeting," *Annals of Surgery* 263, no. 1 (January 2016): 162–177, https://doi.org/10.1097/SLA.0000000000001173.

42. H. Oyama, M. Tada, K. Takagi, et al., "Long-Term Risk of Malignancy in Branch-Duct Intraductal Papillary Mucinous Neoplasms," *Gastroenterology* 158, no. 1 (January 2020): 226–237.e5, https://doi.org/10.1053/j.gastro.2019.08.032.

43. H. Hasegawa, M. Fukasawa, S. Takano, et al., "New Surgical Criteria for Intraductal Papillary Mucinous Neoplasm Based on the Age-Adjusted Charlson Comorbidity Index Values and Presence of Solid Component," *Diagnostics* 14, no. 22 (November 2024): 2582, https://doi.org/10.3390/diagnostics14222582.