European Journal of Surgical Oncology 49 (2023) 113–121

Contents lists available at ScienceDirect

European Journal of Surgical Oncology

journal homepage: www.ejso.com

Presence of low-grade IPMN at the pancreatic transection margin does not have prognostic significance after resection of IPMN-associated pancreatic adenocarcinoma

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ARTICLE INFO

Article history:
Received 20 May 2022
Received in revised form
12 July 2022
Accepted 3 August 2022
Available online 9 August 2022

Keywords:
IPMN-Associated carcinoma
Pancreatic transection margin
IPMN dysplasia
Pancreatic ductal adenocarcinoma

ABSTRACT

Introduction: Resection margin status is a well-established prognosticator in pancreatic cancer. The prognostic impact of IPMN dysplasia at the pancreatic transection margin in IPMN-associated carcinoma (IPMN-Ca) remains unclear, hence institutional practices on additional resections vary.
Methods: Patients undergoing partial pancreatectomy or attempted partial pancreatectomy converted to total pancreatectomy for IPMN-Ca between 04/2002 and 12/2018 were identified. Final pathology of the definitive pancreatic transection margin was identified. The association between the presence of IPMN dysplasia at the margin and overall survival (OS) was assessed.
Results: Of 302 patients with IPMN-Ca, 181 (59.9%) patients received partial pancreatoduodenectomy, 61 (20.2%) distal pancreatectomy, and 60 (19.9%) were converted to total pancreatectomy. Median OS was 98.6 months in R0 (≥1 mm), 39.3 months in R1 (<1 mm), and 22.0 months in R1(direct) resected patients, respectively ($p < 0.0001$). No IPMN dysplasia at the definitive margin was present in 103 (34.1%), low-grade in 131 (43.4%), and high-grade/R1 in 8 (2.6%) patients. Low-grade dysplasia or total pancreatectomy were not associated with shorter OS compared to dysplasia-free margin across the entire cohort. Sensitivity analyses confirmed a lack of prognostic relevance of low-grade IPMN dysplasia at the pancreatic margin in R0 resected IPMN-Ca and in R0 resected UICC stage IA/IB IPMN-Ca.
Conclusions: Low-grade IPMN at the transection margin is not associated with shorter overall survival after partial pancreatectomy for IPMN-Ca. Additional resections for low-grade dysplasia, up to total pancreatectomy do not result in a survival benefit and should be omitted. Due to limited sample size, high-grade dysplasia could not be analyzed.

1. Introduction

Intraductal papillary mucinous neoplasm (IPMN) can presents with a wide spectrum of dysplasia, all of which are regarded as neoplastic [1]. Traditionally, the World Health Organization (WHO) classified noninvasive IPMN dysplasia into a three-tier system consisting of low-grade, intermediate-grade, as well as high-grade dysplasia [2]. To account for the uncertain prognostic relevance of low-grade versus intermediate-grade IPMN dysplasia, in 2019 the WHO adapted its classification from a three-tier system to a two-tier grading system, omitting the category of intermediate-grade dysplasia and now only distinguishing between low and high-grade dysplasia, based on the highest grade of dysplasia detected [1,3].

Presence of high-grade dysplasia in resected noninvasive IPMN is associated with a significantly lower 5-year survival compared to low- and intermediate-grade dysplasia [4]. The degree of dysplasia has been implicated as the most important risk factor for recurrence of noninvasive IPMN [5]. A large single-center study reported

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https://doi.org/10.1016/j.ejso.2022.08.003

that progression of low or intermediate-grade dysplasia to invasive cancer in the pancreatic remnant occurred after a median of 69 months, while in patients with high-grade dysplasia progression only took a median of 47 months [6].

Resection margin status regarding the invasive component is a well-established prognosticator in classical PDAC as well as in IPMN-Ca [7–9]. During resections of noninvasive IPMN and IPMN-Ca, IPMN with varying grades of dysplasia is frequently encountered at the pancreatic transection margin [4,10]. Several studies addressed the prognostic impact in noninvasive IPMN, yet controversy remains. A recent multicenter study comprising 330 patients with resected noninvasive IPMN failed to detect a significant association between margin positivity and recurrence at the resection margin itself [4]. Of note, definition of margin positivity consisted of low as well as high-grade dysplasia. In contrast, a large single center study reported a 25% recurrence rate independent of the exact location if IPMN was present at the margin versus 14% if no IPMN was present ($p = 0.008$). High-grade dysplasia at the margin had a significantly increased risk of recurrence compared to negative margins, while this was not observed in cases of low- and intermediate grade dysplasia [11]. Further series provided evidence that high-grade dysplasia at the margin is associated with earlier recurrence and shortened overall survival [12–14].

In resected IPMN-Ca, there is a lack of data regarding the prognostic impact of IPMN dysplasia at the pancreatic transection margin. Interestingly, a recent single-center study described that the degree of IPMN dysplasia at the pancreatic transection margin was independently associated with recurrence only in noninvasive IPMN, while in IPMN-Ca presence of high-grade dysplasia was associated with recurrence only on univariable analysis [11]. A limited number of patients and a lack of consensus what constitutes a positive margin has contributed to these conflicting results in the literature [15]. While some consider the presence of low-grade dysplasia as a negative margin, others consider all grades of dysplasia including invasive carcinoma as a positive margin [14].

The revised 2017 international consensus Fukuoka guideline recommends additional resection if high-grade dysplasia or invasive carcinoma is present at the pancreatic resection margin during resection of IPMN without explicitly referring to cases of IPMN-Ca. Resection should be extended until low-grade dysplasia or dysplasia-free margins are obtained. In cases of low-grade dysplasia, no further resection is advised [16]. Similarly, the evidence-based European guidelines advocate no further resection in cases of low-grade IPMN at the margin (GRADE 2C recommendation), but point out as limitation that the data in the literature on this topic are variable [17]. Of note, additional resection up to total pancreatectomy is associated with increased morbidity and a reduced quality of life due to pancreatic endocrine and exocrine insufficiency with the necessity of life-long insulin and pancreatic enzyme substitutions [18,19]. Importantly, despite the obvious clinical relevance, these recommendations do not specifically address the scenario of IPMN dysplasia at the margin during resections for IPMN-Ca. In particular, no data exists on the prognostic relevance of IPMN dysplasia at the pancreatic transection margin in resected IPMN-Ca in the context of the R status of the invasive component.

As no specific guidelines exist for this specific situation, institutional practices to address the presence of dysplasia at the pancreatic resection margin for IPMN-Ca resections vary. While in most institutions, high-grade dysplasia at the resection margin is addressed by an additional resection, institutional practices vary for the presence of low-grade dysplasia. The aim of this study was to investigate the association between IPMN dysplasia at the pancreatic transection margin in resected IPMN-Ca and overall survival in consideration of the R status of the invasive cancer.

2. Methods

2.1. Study design and study population

This study was approved by the ethics committee at Heidelberg University Hospital (Approval S-069/2016) and conducted according to the STROBE recommendations for observational studies [20]. All patients with pathologically confirmed IPMN-Ca who underwent partial pancreatectomy or attempted partial pancreatectomy converted to total pancreatectomy between 04/2002–12/2018 were identified from a prospectively maintained database at the Department of General Surgery, Heidelberg University Hospital.

Exclusion criteria consisted of pancreatic tumors other than IPMN-Ca, M1 stage other than paraaortic lymph node metastasis, presence of other tumors on pancreatic transection margins, R2 resection and indeterminable margin status (Rx) resection. Since overall survival dependent on margin status was the primary outcome, patients who died within the same hospital stay and patients who were lost to follow-up were also excluded.

Data on patient's demographics, type of resection, tumor localization, tumor size, grading, TNM classification, IUCC staging, and lymph node status were extracted from a prospectively maintained data base. Data on pancreatic resection margins were extracted from pathology reports available for all patients through the electronical hospital record system. Classification of IPMN into main-duct IPMN; branch-duct IPMN, and mixed-type IPMN based on preoperative cross-sectional imaging was retrieved from medical records.

Survival data was collected through consultations in our pancreas outpatient clinic, by contacting general practitioners as well as from regional and national tumor registries. The last update of follow-up data was performed in 07/2020.

2.2. Surgical and oncological management

Primary resection was attempted if patients were deemed fit for surgery and tumors regarded as resectable or borderline resectable based on preoperative cross-sectional imaging. Resectability was defined according to the International Study Group of Pancreatic Surgery criteria [21]. In cases of locally advanced unresectable tumors, neoadjuvant chemotherapy was performed. In the event of tumor contact with the celiac trunk or superior mesenteric artery, an artery-first approach was employed to assess resectability and to avoid R2 resections [22]. If infiltration of portal vein or superior mesenteric vein was suspected, venous resection was performed. Intraoperative frozen section examination of the pancreatic transection margin was routinely performed; while the gastric margin, bile duct margin, and duodenal transection margins were examined dependent on tumor location and according to the surgeon's discretion. Invasive cancer or high-grade dysplasia on intraoperative frozen section examination were routinely addressed by additional resections up to total pancreatectomy. In cases of low-grade IPMN dysplasia and a lack of clinical evidence, additional resection was carried out as part of an individualized therapy.

2.3. Pathologic workup

A standardized pathology protocol was used to evaluate resected specimens [23]. Pancreatic neck, bile duct, gastric and duodenum transection margins were reported separately, while the anterior, posterior, medial and uncinate margins were each analyzed separately but margin status was reported combined. Resection margin was reported according to the revised R status definition with R0 corresponding to a 1 mm tumor-free margin [8]. Additionally, R1(<1 mm) and R1 (direct) with tumor cell directly at the resection margin were reported separately.

Tumors were classified according to the current TNM staging system [24]. T stage was defined based on the maximum diameter of the invasive component. Grading of the carcinoma component followed WHO recommendations [3]. Prognostic staging was performed according the 8th edition of the AJCC/UICC cancer staging manual [25].

Epithelial dysplasia at the pancreatic transection margin was classified according to the contemporary WHO criteria at the time of surgery and pathological evaluation into dysplasia-free margin, low-grade IPMN dysplasia, intermediate-grade IPMN dysplasia, high-grade IPMN dysplasia, and invasive IPMN/R1[2]. To reflect the revised 2019 WHO classification criteria, low-grade and intermediate-grade IPMN were subsequently combined as low-grade IPMN dysplasia [3]. Similarly, high-grade IPMN and R1 at the transection margin were grouped together due to a low number of patients. If different degrees of dysplasia existed, the highest degree was recorded. Definitive pancreatic transection margin was defined as the margin after any type of additional resection independent of its reason.

2.4. Statistical analysis

Quantitative parameters are expressed as median and interquartile range (IQR), unless otherwise indicated. Categorical parameters are depicted as absolute numbers and relative frequencies. Comparisons between the three R status groups and categorical histopathological parameters were performed using the chi square test, if appropriate, or the Fisher's exact test. Survival curves were created according to Kaplan-Meier method [26]. Survival differences were assessed using the log-rank test. Overall survival was defined as the time from resection to either death from any cause or last follow-up. Patients alive at last follow-up were censored. Due to the exploratory nature of the analyses performed, all p-values were interpreted descriptively. Statistical significance was set at $p < 0.05$. SAS® release 9.4 (SAS Institute, Cary, North Carolina, USA) was used for statistical analysis.

3. Results

3.1. Clinicopathologic characteristics

In total, 332 patients undergoing partial pancreatectomy or attempted partial pancreatectomy converted to total pancreatectomy for IPMN-Ca between 04/2002 and 12/2018 were identified (Fig. 1). Some 28 patients were excluded because of distant metastases other than paraaortic lymph nodes (n = 14), loss to follow-up (n = 12), presence of additional pancreatic neuroendocrine carcinoma (n = 1), and Rx resection (n = 1). In-hospital mortality was 0.6% (n = 2) and these two patients were also excluded.

The final study cohort consisted of 302 patients with IPMN-Ca including 151 males (50.0%) and 151 females (50.0%) with a median age of 68.3 years (Table 1). Of 302 patients, 181 (59.9%) patients underwent a classical or pylorus-preserving partial pancreatoduodenectomy, while 61 (20.2%) patients underwent a distal pancreatectomy and in 60 (19.9%) patients an attempted partial pancreatectomy was converted to a total pancreatectomy. Median OS was 41.5 months with a 5-year survival rate of 42.2% and a median follow-up of 51.9 months (IQR: 28.2–102.8 months). In total, 237 (78.5%) patients had IPMN-Ca of the tubular subtype, whereas 65 (21.5%) patients had IPMN-Ca of the colloid subtype.

3.2. Resection margin and overall survival

Of 302 patients, R0 resections were achieved in 134 (44.4%) patients, whereas 60 (19.9%) patients had an R1(<1 mm) resection and 108 (35.8%) patients an R1 (direct) resection. R0 resections were associated with a significantly longer median OS of 98.6 months and a 5-year survival of 58.5% compared to R1(<1 mm) resections (median OS 39.2 months; 5-year survival 39.6%) and R1 (direct) resections (median OS 22.0 months; 5-year survival 23.1%), respectively (Fig. 2a, $p < 0.0001$). The distribution of prognostic factors in the subgroups of different resection margin status is depicted in Table 2. Histological subtype of IPMN-Ca as well as AJCC/UICC stage differed significantly between R0, R1(<1 mm), and R1 (direct) groups ($p < 0.0001$).

3.3. Prognostic relevance of IPMN dysplasia at the pancreatic transection margin

Of 242 patients with partial pancreatectomy, 103 (42.6%) patients had no evidence of dysplasia at the definitive pancreatic transection margin, 131 (43.4%) had low-grade IPMN, and 8 (2.6%) had high-grade IPMN or R1 status (Table 2). Kaplan-Meier survival analysis did not reveal a significant difference in OS between the subgroups (log-rank $p = 0.48$) (Fig. 2b). Of note, due to the surgical strategy employed, cases of high-grade IPMN (n = 4) and R1 (n = 4) at the resection margin were rare. Hence, survival data for this group has to be interpreted with caution.

Conversion of partial pancreatectomy to total pancreatectomy based on intraoperative findings was performed in 60 patients, primarily due to R1 status (n = 20, 36.4%) or presence of IPMN with high-grade dysplasia (n = 17, 30.9%) at the pancreatic transection margin. In 23 (38.3%) patients, conversion to total pancreatectomy was performed for low-grade and intermediate-grade IPMN.

As there was no prognostic relevance of IPMN dysplasia at the pancreatic transection margin in the univariable analysis of the entire study cohort, multivariable survival analyses were not performed. However, several subgroup analyses were performed to investigate if IPMN dysplasia at the pancreatic transection margin may be relevant in specific subgroups with favorable prognosis.

3.3.1. Subgroup analysis of IPMN dysplasia and survival according to R status

First, survival analyses for the subgroups of R0, R1(<1 mm) and R1 (direct) resection margin status of the IPMN-Ca were performed. Of note, frequency of additional parenchymal resection as well as total pancreatectomy did not differ significantly between the 3 subgroups (Table 2).

Of the 134 patients with R0 resections, 51 had no dysplasia at the definitive pancreatic transection margin, 55 had low-grade IPMN dysplasia, and 28 were converted to a total pancreatectomy. Only one patient had high-grade dysplasia and was analyzed together with the low-grade group for the purpose of this analysis due to low patient number. In patients with R0 resection of IPMN-Ca, no significant difference in OS was observed between the subgroup with or without low-grade IPMN or with total pancreatectomy (Fig. 3a, $p = 0.75$).

Of 60 patients with R1(<1 mm) resections, dysplasia-free margin was present in 18 patients, 26 patients had low-grade dysplasia, and 16 underwent conversion to total pancreatectomy. No patient had high-grade dysplasia at the definitive margin in the R1(<1 mm) group. In patients with R1 (<1 mm) resected IPMN-CA low-grade dysplasia and total pancreatectomy were associated with a significantly worse survival compared to no evidence of dysplasia at the transection margin (Fig. 3b, $p = 0.03$). Further analysis revealed that this survival difference is explained by a worse survival of patients who underwent total pancreatectomy as no difference in survival was detected between patients without dysplasia at the margin (n = 18) versus low-grade dysplasia (n = 26) ($p = 0.15$). In contrast, total pancreatectomy showed a

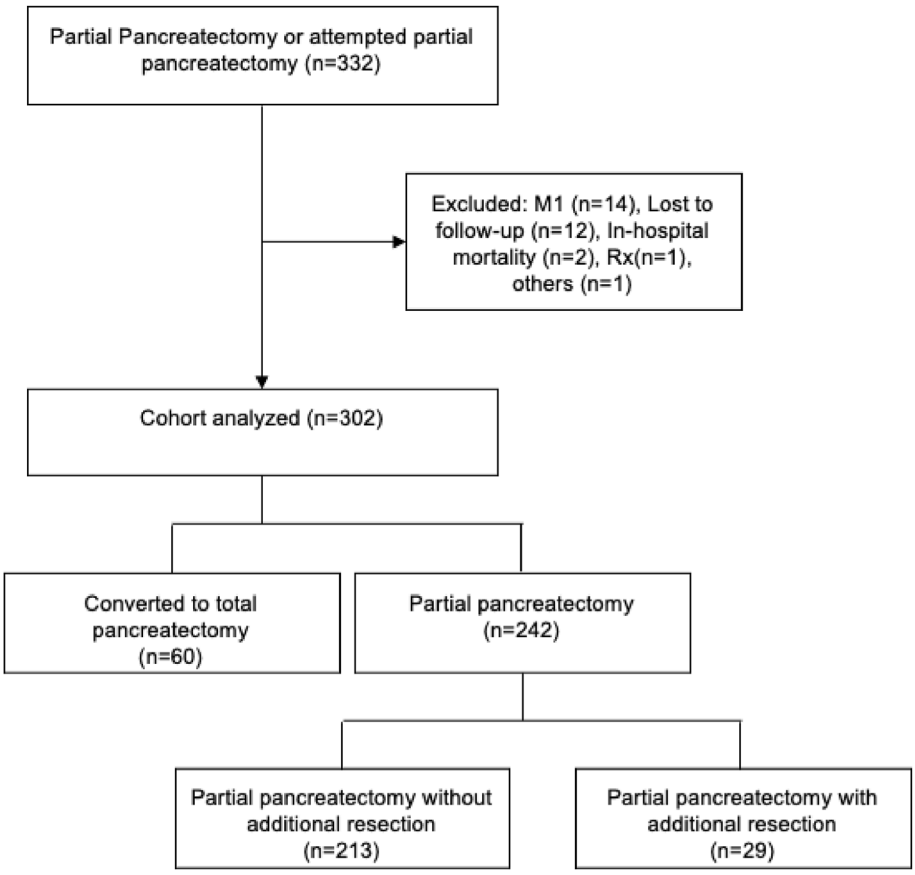

Fig. 1. STROBE flow-chart of study cohort.

significantly worse survival than patients who underwent partial pancreatectomy in the R1(<1 mm) group ($p = 0.02$).

Of 108 patients with R1 (direct) resections, no significant difference in OS stratified according to the definitive pancreatic transection margin was observed (Fig. 3c, $p = 0.39$).

3.3.2. IPMN dysplasia in early-stage pancreatic cancer

Considering its preneoplastic nature, it is conceivable that IPMN dysplasia at the pancreatic transection margin may most likely have an effect in patients with early-stage pancreatic cancer who have a long survival expectation. In total, 67 patients had a stage IA/IB tumor according to the UICC 8th edition and a R0 resection. In these patients, median overall survival was not yet reached with a median follow-up of 86.2 months (IQR 41.6–114.5 months) and the actuarial 5-year survival rate was 76.3%. Among these patients, 27 patients had no evidence of dysplasia at the definitive transection margin, 27 had low-grade IPMN, and 13 underwent total pancreatectomy. Kaplan-Meier survival analysis did not reveal a survival difference associated with IPMN-dysplasia at the pancreatic transection margin in patients with early-stage, R0-resected IPMN-Ca (Fig. 3d, $p = 0.86$).

4. Discussion

This study investigates the association between IPMN dysplasia at the pancreatic transection margin and overall survival in patients undergoing partial pancreatectomy or attempted partial pancreatectomy for IPMN-Ca. We provide evidence that the presence of low-grade IPMN dysplasia at the transection margin does not have prognostic relevance compared to a dysplasia-free transection margin after resection of IPMN-Ca. Moreover, total pancreatectomy in these patients does not confer a survival benefit. The lack of prognostic relevance of low-grade IPMN dysplasia at the pancreatic transection margin was confirmed in sensitivity analysis for early-stage (UICC I) and R0-resected IPMN-Ca. Based on these results, the presence of low-grade IPMN dysplasia at the pancreatic transection margin during resection for an IPMN-Ca does not warrant an additional resection.

Prior to this study, there was a lack of evidence concerning the association between the prognostic effects of IPMN dysplasia at transection margin and survival in IPMN-Ca. However, data from noninvasive IPMN offers critical insights. Several series could show that although recurrence was associated with the degree of dysplasia at the transection margin, it rarely occurred at the margin itself [4,5,14,27,28]. A large multi-center study comprising 330 patients with noninvasive IPMN and a median follow-up of 36 months did not detect an association between IPMN dysplasia at the margin and recurrence or development of invasive IPMN. Interestingly, noninvasive disease recurred after a median of 31 months and invasive disease after a median of 21 months, but 18% recurred after more than 5 years [4]. Further support for a process of field cancerization in IPMN is provided by the finding that concomitant IPMN in patients treated with partial pancreatectomy for classical PDAC was identified as an independent predictive factor for the development of recurrence in the remnant pancreas [29].

Evolutionary timeline analysis based on genomic data indicates that the progression of a cell with high-grade IPMN dysplasia to invasive carcinoma takes at least 3 years [30]. To account for a time-dependent effect in carcinogenesis, subgroup analysis for R0 resected patients with AJCC/UICC 8th stage IA/IB IPMN-Ca was

Table 1
Clinicopathologic characteristics of 302 patients with resected IPMN-associated carcinoma. Values in parentheses are percentages unless indicated otherwise.

Parameter	Category	Total ($n = 302$)
Gender	Male	151 (50.0)
	Female	151 (50.0)
Median age (IQR) [years]		68.3 (61.7–73.8)
Age (years)	<60	61 (20.2)
	60-<70	108 (35.8)
	≥70	133 (44.0)
Median BMI (IQR) [kg/m^2]		24.6 (22.5–26.8)
ASA classification	ASA 1	9 (3.1)
	ASA 2	158 (55.1)
	ASA 3	119 (41.5)
	ASA 4	1 (0.3)
	Missing values	15
Median Ca 19–9 (IQR) [U/mL]		82.9 (18.0–434.4)
Ca 19–9 (U/mL)	<37	102 (34.9)
	37-<400	114 (39.0)
	≥400	76 (26.0)
	Missing values	10
Median CEA (IQR) [g/L]		1.8 (1.0–3.7)
CEA (g/L)	<2.5	174 (60.4)
	≥2.5	114 (39.6)
	Missing values	14
Neoadjuvant chemotherapy	yes	9 (3.0)
Type of surgery	Pancreatoduodenectomy	181 (59.9)
	Distal Pancreatectomy	61 (20.2)
	Total Pancreatectomy	60 (19.9)
Vascular resection	yes	57 (18.9)
Tumor location	head	210 (69.5)
	body	15 (5.0)
	tail	39 (12.9)
	multifocal	38 (12.6)
Median invasive tumor diameter (IQR) [cm]		3.0 (2.0–4.2)
Histology	IPMN associated carcinoma tubulary type	237 (78.5)
	colloid IPMN carcinoma	65 (21.5)
Tumor status (T 8th)	T1	74 (25.9)
	T2	136 (48.2)
	T3	71 (25.2)
	T4	2 (0.7)
	Missing values	20
Lymph nodes status (N 8th)	N0	113 (37.4)
	N1	94 (31.1)
	N2	95 (31.5)
Distant metastasis-status (M)	M0	294 (97.4)
	M1	8 (2.6)
Grading (G)	G1	17 (5.8)
	G2	199 (68.2)
	G3	76 (26.0)
	GX	10
Resection margin status (R)	R0	134 (44.4)
	R1(<1 mm)	60 (19.9)
	R1(direct)	108 (35.8)
AJCC/UICC stage (8th)	IA	52 (17.2)
	IB	36 (11.9)
	IIA	25 (8.3)
	IIB	92 (30.5)
	III	89 (29.5)
	IV	8 (2.6)
Median postoperative hospital stay (IQR) [days]		12 (10–17)
Adjuvant therapy**	Yes	163 (74.4)
	No	56 (25.6)
	Missing data	83

AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control; ASA: American Society of Anesthesiologists Classification; BMI: Body mass index; Ca 19–9: Carbohydrate-Antigen 19–9; CEA: Carcinoembryonic antigen.

performed. Again, no association between IPMN dysplasia at the transection margin and survival could be observed, independent of R status at the other margins.

Although no association between OS and degree of dysplasia at the pancreatic transection margin was detected across the entire study cohort, R0 resections were associated with a significantly improved OS compared to R1 (direct) resections. This emphasizes the importance of achieving a R0 resection in IPMN-Ca. The revised R status definition was applied in this study with R0 corresponding to ≥1 mm clear margin as previous studies in pancreatic cancer were able to show that it identifies a group of patients with favorable prognosis [7,8]. In our cohort, R1(<1 mm) resected

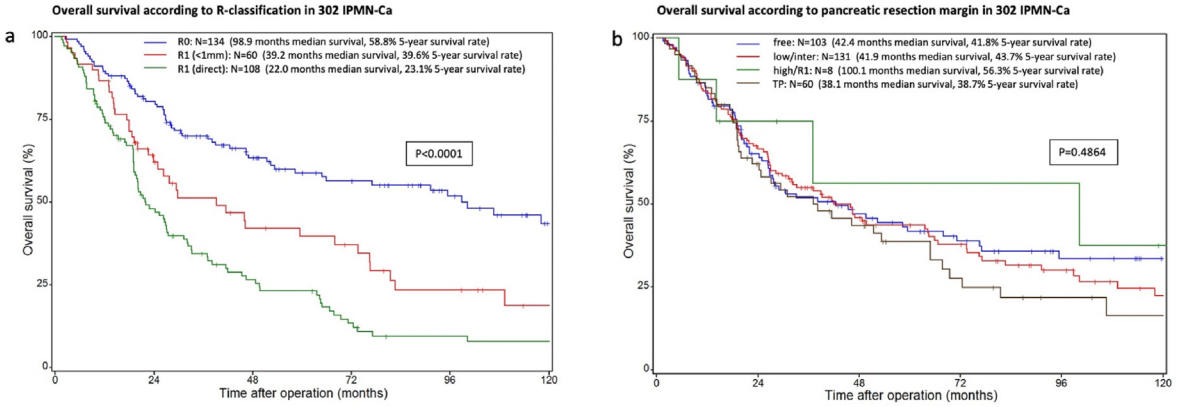

Fig. 2. Kaplan-Meier curves for overall survival according to R status (a) and according to pancreatic transection margin (b) in 302 IPMN-Ca patients.

Table 2
Pathological parameters according R-classification in the study cohort. Values in parentheses are percentages unless indicated otherwise.

Parameter	R0	R1(<1 mm)	R1 (direct)	P Value
n	134	60	108	
AJCC/UICC (8th)				<0.0001
IA	48 (35.8)	3 (5.0)	1(0.9)	
IB	19 (14.2)	6 (10.0)	11 (10.2)	
IIA	18 (13.4)	2 (3.3)	5 (4.6)	
IIB	31 (23.1)	30 (50.0)	31 (28.7)	
III	15 (11.2)	19 (31.7)	55 (50.9)	
IV	3 (2.2)	0 (0.0)	5 (4.6)	
Histology				<0.0001
Tubular IPMN-Ca	86 (64.2)	57 (95.0)	94 (87.0)	
Colloid IPMN-Ca	48 (35.8)	3 (5.0)	14 (13.0)	
Pancreatectomy after frozen section (TP)	28 (20.9)	16 (26.7)	16 (14.8)	0.1678
Pancreas resection margin without TP	106	44	92	0.0589
Tumor-free	51 (48.1)	18 (40.9)	34 (37.0)	
Low-grade	54 (50.9)	26 (59.1)	51 (55.4)	
High grade/R1	1 (0.9)	0 (0.0)	7 (7.6)	
Further resection without TP	14 (13.2)	3 (6.8)	12 (13.0)	0.5685

AJCC/UICC: American Joint Committee on Cancer/Union for International Cancer Control; IPMN-Ca: IPMN- associated pancreatic adenocarcinoma.

patients had a significantly better prognosis and a median OS of 39.2 months versus 22.0 months for R1 (direct) resected patients, providing evidence that the revised R status carries prognostic significance in IPMN-Ca.

Interestingly, subgroup analysis according to R status revealed significantly worse survival in R1(<1 mm) resected patients with presence of low-grade IPMN as well as total pancreatectomy compared to a dysplasia-free transection margin ($p = 0.03$). However, patient numbers in the R1(<1 mm) subgroup ($n = 60$) were smaller than in the R1 (direct) ($n = 108$) and R0 ($\geq$1 mm) ($n = 134$) groups. Additionally, no difference in survival was detected when separately analyzing patients with low-grade dysplasia at the margin versus no evidence of dysplasia. Worse survival was due to the 16 patients who underwent total pancreatectomy. Considering the relatively low patient number and the fact that worse survival was primarily related to worse outcome in the total pancreatectomy group, this result should be interpreted with caution.

In 2015, the Baltimore consensus conference proposed a simplified two-tier classification system of IPMN dysplasia combining low-grade dysplasia and intermediate-grade dysplasia to low-grade dysplasia [1,31]. In 2019 the WHO adopted this classification [3]. A lack of prognostic relevance associated with the presence of low-grade IPMN at the pancreatic transection margin during resection of IPMN-Ca support this revised classification system.

The results of this study are in agreement with studies investigating the association between pancreatic intraepithelial neoplasia (PanIN) at the pancreatic transection margin and overall survival in patients resected for classical PDAC. Similar as our findings suggest, no association between survival and grade of low-grade dysplasia could be observed [31,32]. Moreover, Matthaei and co-workers did not detect any significant differences in survival between high-grade PanIN and low-grade PanIN [32].

Omitting additional resection for low-grade IPMN at the margin did not carry prognostic relevance in our cohort, yet we were unable to investigate the effects on local recurrence. Notably, approximately 15–30% of patients with IPMN-Ca experience with local recurrence at the pancreatic remnant-either by itself or in combination with distant recurrence [5,33,34]. Winter et al. reported that after resection of IPMN-Ca with an invasive component of <20 mm, 17 patients (24.3%) experienced recurrence within the follow-up time of which two-third had distant recurrence (either by itself or in combination with local recurrence) and one-third isolated local recurrence [35].

Subclinical foci of different degrees of dysplasia can coexist in the remnant pancreas independent of margin status, consistent with a theory of field cancerization and the reported multifocal nature of IPMN [36]. Almost 20% of co-occurring IPMN and PDAC appear to be genetically unrelated despite close physical proximity, hinting to a multifocal carcinogenic process [37].

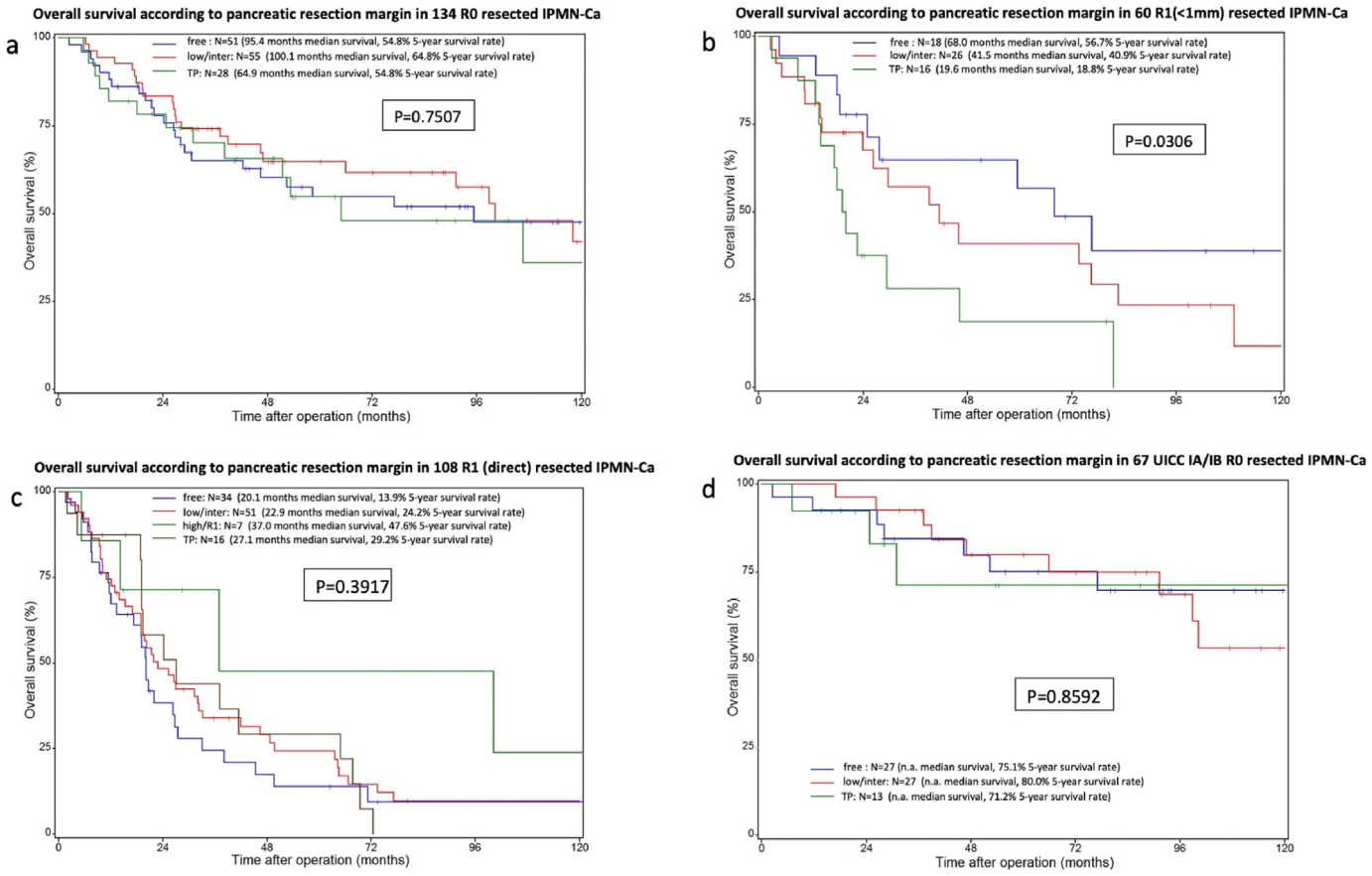

Fig. 3. Kaplan-Meier curves for overall survival according to pancreatic transection margin in 134 R0 (a), 60 R1 (<1 mm) (b) and 108 R1 (direct) (c) resected IPMN-Ca patients and in 67 R0 resected AJCC/UICC stage IA/IB IPMN-Ca patients (d).

Of note, local recurrence might be amenable to re-resection. In classical PDAC re-resection for isolated local recurrence has been associated with encouraging survival [38]. Similarly, a large study from the Japan Pancreas Society analyzed 247 resected IPMN-Ca patients, out of which 107 (43.4%) developed recurrence within the follow-up period. Median OS was significantly better in patients who underwent re-resection for local recurrence versus patients who did not ($p = 0.04$) [39]. Interestingly, higher UICC stage was associated with increased tendency of extra-pancreatic recurrence ($p < 0.001$). Another series by the same authors could show that while invasive IPMN, mixed-type IPMN, and high CA19-9 values were independent risk factors for extrapancreatic recurrence, a positive transection margin including LGD, HGD and invasive IPMN were independently predictive of recurrence in the pancreas remnant. Importantly, median OS differed significantly for recurrence in the pancreas versus extrapancreatic recurrence (21.8 vs. 110.6 months), supporting the hypothesis that the relevance of recurrence differs between invasive and noninvasive IPMN and in the former, prognosis is primarily determined by systemic recurrence [9,40].

This study has several key strengths: (1) It is the first study to systematically assess the prognostic relevance of IPMN dysplasia at the pancreatic resection margin in resected IPMN-Ca. (2) It describes for the first time the clinical significance of the revised R classification specifically in IPMN-Ca. (3) A large patient cohort enabled us to include patients who were converted to total pancreatectomy in the Kaplan-Meier survival analysis and therefore allowed a direct evaluation of its prognostic impact. (3) Subgroup analysis of early-stage IPMN-Ca patients accounted for a potential time-dependent effect of malignant transformation in IPMN dysplasia and therefore strengthens validity of results. (4) As a single-center study indications for resections and techniques of pathological evaluation of specimen were uniformly applied to all patients, thus circumventing variability associated with different surgical approaches and pathology protocols.

There are several limitations. On one hand, the retrospective nature is associated with an inherent selection bias. On the other hand, due to the surgical strategy there was a low number of high-grade dysplasia/R1 at the final transection margin. While this is to be expected as high-grade dysplasia/R1 results in further resection in most institutions including our own, it prevented us from investigating the association between high-grade dysplasia at the margin and OS in IPMN-Ca patients. Of note, in our cohort patients with high-grade dysplasia/R1 status at the transection margin tended to have longer survival compared to low-grade IPMN. However, this effect is most likely associated with a total sample size of only 8 patients.

Moreover, contemporary German guidelines do not recommend regular cross-sectional imaging after resection of pancreatic cancer [41]. Therefore, we were not able to assess patterns of recurrence and recurrence-free survival in this study. Similarly, although the median follow-up of 51.9 months is rather long it potentially could have been too short to detect a prognostic effect in low-grade IPMN as transformation from IPMN dysplasia to invasive carcinoma takes several years [42]. Although desirable given different risks of malignant transformation, we were not able to separately assess the prognostic effects of epithelial subtype of IPMN [10].

In summary, low-grade (formerly low and intermediate-grade) IPMN dysplasia at the pancreatic transection margin in patients

resected for IPMN-Ca does not have prognostic relevance. Based on these data, it can be recommended to abstain from additional resection and total pancreatectomy to address low-grade IPMN at the pancreatic transection margin during resection for IPMN-Ca, including resection for early stage UICC IA/IB tumors. Based on the available data from the literature, the presence of invasive IPMN at the pancreatic transection margin, constituting an R1 situation, should result in additional resection [9]. The data available in the literature and from our study do not allow a data-driven recommendation on how high-grade dysplasia at the pancreatic margin should be addressed. Rigorous pathological assessment including intraoperative frozen section analysis of the transection margin to obtain information on the presence of invasive cancer and IPMN with its grade of dysplasia remain essential to guide surgical decision-making during resection of IPMN-Ca. The results have a direct clinical relevance and considerably add to the growing body of literature on surgical management of IPMN-Ca.

5. Conclusion

Low-grade IPMN dysplasia is frequently encountered at the pancreatic transection margin during resection of IPMN-Ca, yet no evidence exists regarding intraoperative management. This study provides evidence that low-grade IPMN at the transection margin is not associated with shorter overall survival after partial pancreatectomy for IPMN-Ca. Additional resections up to total pancreatectomy for low-grade dysplasia do not seem to result in a survival benefit and should therefore be omitted.

Source of funding

None;

Declaration of competing interest

None.

CRediT authorship contribution statement

Carl-Stephan Leonhardt: Conceptualization, Methodology, Data curation, Writing – original draft, Writing – review & editing, Investigation. **Ulf Hinz:** Methodology, Formal analysis, Visualization, Writing – review & editing. **Jörg Kaiser:** Data curation, Writing – review & editing, Investigation. **Thomas Hank:** Data curation, Writing – review & editing, Investigation. **Christine Tjaden:** Data curation, Writing – review & editing. **Frank Bergmann:** Data curation, Resources, Writing – review & editing. **Thilo Hackert:** Conceptualization, Writing – review & editing. **Markus W. Büchler:** Conceptualization, Supervision, Funding acquisition, Project administration, Writing – review & editing. **Oliver Strobel:** Conceptualization, Supervision, Funding acquisition, Project administration, Writing – review & editing.

Declaration of competing interest

No competing interests to declare.

Acknowledgements

None.

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