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Real life management of intraductal papillary mucinous neoplasms of the pancreas: Final data from the prospective Italian pancreatic cysts (PANCY) registry

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ABSTRACT

Background: Studies on surveillance of Intraductal Papillary Mucinous Neoplasms (IPMNs) are mainly retrospective with inherited bias.
Aim: To identify factors associated with the development of relevant changes in low risk IPMN under surveillance.
Methods: This study analysed IPMN patients enrolled between 2015–2017 in the prospective observational multicentric registry PANcreatic CYsts (PANCY), focusing on brunch duct (BD). Extension of surveillance until December 31st, 2021 was proposed to the recruited patients. Relevant changes were defined as: worrisome features/high risk stigmata/pancreatic cancer, pancreatectomy, death due to IPMN/pancreatic cancer.

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Results: At diagnosis, from 647 IPMNs, 547 (60%) were BD, 87 (9%) mixed type, and 13 (1%) main duct. 57 (8.8%) underwent immediate surgery and 590 (91.2%) active surveillance. Of them 34 (5.7%) underwent surgery with 2/3 malignancy. Malignancy rates for BD- and mixed-IPMNs under surveillance were 2.7% and 12.5%. Smoking (OR 2.2) and cyst size >15 mm at diagnosis (OR 7.1) were independent risk factors for relevant changes at multivariate analysis. The combination of cyst size ≤15 mm & age >65 was a protective factor at univariate analysis (OR 0.1), mainly in no smokers (OR 0.2, $p < 0.01$).
Conclusions: BD-IPMN progression risk is low for lesions <15 mm in non-smokers, >65 years patients. Surgery and follow-up criteria are still imperfect, leading to inappropriate utilization of resources.

1. Introduction

The prevalence of asymptomatic pancreatic cysts, ranges from 1.2 to 36.7 %, and it is due to the widespread use of cross-sectional imaging [1–5]. Most studies focusing on pancreatic cysts are retrospective with their inherited selection bias. In this context a prospective Italian Survey on PANcreatic CYsts (PANCY) was created. This Survey was launched in 2014 by the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO) and the Italian Association for the Study of the Pancreas (AISP) and the interim analysis was published in 2020 [6]. This prospective survey was created to assess the performance and application of guidelines pertaining to pancreatic cystic neoplasms, as well as the diagnostic workup and management of these lesions in real-world settings. Most pancreatic cysts are intraductal papillary mucinous neoplasms (IPMNs), which make at least 80 % of the overall cyst population [7], being branch-duct (BD) IPMNs the most frequent [8]. Over the years, numerous guidelines have been developed for the management of IPMN [9–13]. It was evident that the majority of BD-IPMN lack worrisome features (WF) and high-risk stigmata (HRS), that represents two categories of risk for malignancy development, and active surveillance is recommended. Of note most "low-risk" IPMNs will never develop WF/HRS nor malignancy [14]. In this context, it is essential to establish a surveillance policy that should be cost-effective, including surveillance discontinuation in some cases. The parameters that can guide this choice are related to the patient's characteristics, such as age and comorbidities [15], and to the characteristics of IPMN, such as cyst size and morphological and dimensional changes after a follow-up period [16]. A concrete example of the combination of these criteria is the suggested discontinuation of follow-up for patients over 65 with trivial cysts [17], namely those ≤15 mm for a minimum of five years [18]. The aim of the present work is to analyse the fate of a large cohort of patients with IPMNs in the prospective PANCY registry, with a specific focus on low-risk BD-IPMN.

2. Methods

2.1. Study design

This study analyses data from the PANCY (PANcreatic CYsts) prospective observational multicentric registry that began on January 1st 2015 after the publication of the Italian guidelines for the management of pancreatic cystic lesions [19]. After two years of active enrolment (January 1st 2015 – December 31st 2017), an amendment was authorised in 2019 to extend the study's follow-up until December 31st 2021, for a total of five years of follow-up. In 2020, the comprehensive registry data were published after an interim analysis [6]. Only 25 (35.8 %) of the 65 participating centres — which covered most geographical areas in Italy from North to South with a slight prevalence for the norther regions— actually enrolled patients in the study.

2.2. Ethics

Protocol number 375 of the study was approved by the Crema Hospital's Ethical Committee on December 11, 2014. Every patient who was part of the study gave a written, informed consent. The institution's human research committee has given the study protocol a priori approval, indicating that it complies with the ethical principles of the 1975 Declaration of Helsinki [6].

2.3. Patient eligibility

Main inclusion criteria for the PANCY registry were already published [6] and are here summarized: (1) being at least eighteen years old; (2) having a therapy opportunity that was appropriate at the time of diagnosis or during the follow-up; (3) having one or more non-inflammatory pancreatic cysts; and (4) signing a consent form to participate in the study. The patient's refusal of a diagnostic work-up or ineligibility for any treatment was the sole exclusion criterion. In this specific study, we selected from the registry population only those patients who had at least two follow-ups over time in order to focus on the evolution and to avoid potential misdiagnosis with an interval follow-up time of at least six months.

2.4. Data collection

For each patients enrolled 127 items were collected including [6]: i) personal information, ii) clinical information, iii) imaging information, iv) cystic lesion characteristics, v) the final diagnosis, vi) surgical information, vii) associated hereditary syndromes, viii) the medications each patient took, and ix) follow-up data. In general, patients underwent an annual MRI scan. Endoscopic ultrasonography (EUS) was recommended based in the event of major changes (development of WF/HRS).

Development of WFs and HRS at the end of the study was defined according to the latest update of the IAP guidelines [13]. The largest-sized cyst was taken into consideration for investigation in patients with numerous lesions. Cyst size was reported using the largest diameter. The time between the diagnosis and the date of the last follow-up, operation, or death was known as the surveillance duration. The onset of WF and HRS, pancreatectomy for IPMN/Pancreatic carcinoma (PDAC), and mortality for IPMN/PDAC were considered relevant changes in relation to BD-IPMN [15]. Mortality unrelated to IPMN progression or pancreatic cancer development was not considered as a relevant change. The two IPMN categories that were previously suggested for follow-up discontinuation if stable after 5 years were also examined among our BD IPMNs population: i) cyst <30 mm in size in patients older than 75 years, and ii) cyst ≤15 mm in size in patients older than 65 years.

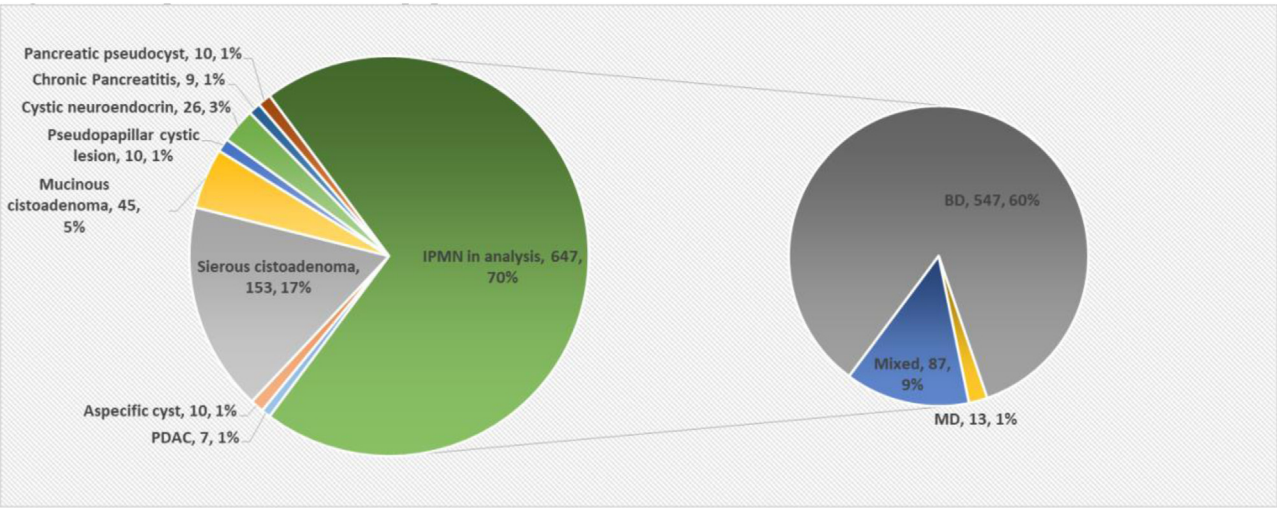

Fig. 1. Graphic of the PANCY population.

2.5. Endpoints

The primary endpoint was the identification of factors associated with the development of relevant changes in low-risk BD-IPMNs undergoing surveillance. Secondary aims do include: the evaluation of patients' attrition to a structured follow-up; the evaluation of natural history of all IPMNs in a prospective study and the rate of death due to IPMN/PDAC.

2.6. Statistical analysis

Statistical analyses were performed using the Stata software. The clinicopathologic data of patients in the cohort study were summarized using descriptive statistics. Categorical variables were presented as numbers and percentages and were compared among groups using Chi-square *t*-test Continuous variables were reported as median and interquartile range (IQR) and were compared using Mann-Whitney U test. Multivariate logistic regression analysis, adjusted for possible confounders, will be performed to identify factors associated with the occurrence of relevant change, with results presented as Odds Ratio (OR) with a 95 % Confidence Interval. Statistical significance was predefined as $p < 0.05$.

3. Results

In the study period, 1427 patients were initially enrolled. Due to inadequate/missing data at diagnosis, 42 patients were excluded. Of the remaining 1385, 468 patients were excluded from the present study as they did not have a single follow-up evaluation, and 917 patients were analysed. The type of presumed cystic lesion is depicted in Fig. 1. Six hundred forty- seven (70 %) patients had an IPMN at diagnosis, of which 547 (60 %) were BD-IPMNs, 87 mixed type IPMN (9 %) and 13 (1 %) main duct (MD) IPMN. The remaining 270 (30 %) patients had a different diagnosis, including serous cystoadenoma, $n = 153$ (17 %), mucinous cystoadenoma $n = 45$, and cystic neuroendocrine tumours $n = 26$ (3 %). Main characteristics of the IPMN population at the time of diagnosis are presented in Table 1. Among 647 patients with IPMN, 249 were male (38.5 %) and the median age was 67 years. Overall, only 68 patients were active smokers (10.5 %), while 87 were ex-smokers (13.5 %). Fifty-seven patients (8.8 %) underwent immediate surgical resection while the rest of patients underwent surveillance. Of the 57 patients who underwent immediate surgery (Supplementary Table 1), 22 (38.6 %) were submitted to pancreaticoduodenectomy, while 20 to a total pancreatectomy (35.1 %) and only 15 to a distal pancreatectomy (26.3 %). Histological examinations showed that 26 (45.6 %) patients had a PDAC arising in the context of an IPMN, while three (5.3 %) had a pure PDAC. Overall, a noninvasive IPMN was detected in 28 patients (49.1 %), with high grade dysplasia in $n = 3$ of them (5.3 %) and with low grade dysplasia in $n = 25$ (43.9 %) of them. Among patients who underwent immediate surgery, 21 (36.8 %) had BD-IPMN, (Supplementary Table 2). Of these 21 patients, fiveunderwent pancreaticoduodenectomy, eight distal pancreatectomy and eight a total pancreatectomyConsidering final histology, 13 were IPMN with low-grade dysplasia (LGD) and 8 were PDAC arising in the context of an IPMN.

Fig. 2 represents timing of surveillance as well as patients' attrition to every control. Median time of first follow-up was 13 months and at this timepoint 12 patients underwent surgery while 5 patients died for non-pancreatic reasons. Of these 12 resected patients, six were branch-duct (BD) IPMN and 6 with mixed type IPMN. Among the six BD-IPMN, the final histology showed LGD in two cases and adenocarcinoma arising in the context of an IPMN in four, (Supplementary Table 3).

After that time 573 patients remained under active surveillance. More than one-third-of the overall population ($n = 247/590$, 41.8 %) remained still under active surveillance after a median follow-up time of 61 months.

Demographic, exposome, clinical and IPMN features divided according to the management selected at diagnosis (surgery versus follow-up) are reported in Table 1. Patients who underwent immediate surgery were more symptomatic at diagnosis ($n = 26/57$, 45.6 % versus $n = 161/590$, 27.3 %, $p < 0.01$) being jaundice ($n = 6/57$, 10.5 %) and diabetes ($n = 6/57$, 10.5 %) the most common symptoms. Vague abdominal pain was more common in IPMN who underwent surveillance ($n = 99/590$, 16.8 % versus $n = 3/57$, 7.2 %, $p < 0.01$). All main duct IPMN underwent surgery while 64/87 (73.5 %) presumed mixed type underwent non operative management and follow-up, of which only 12/64 (18.7 %) developed a surgical indication during follow-up, while some of them were "downgraded" to BD IPMN during follow-up and thus are excluded from the further analysis. Overall, 34 patients underwent surgery during surveillance and in Table 2 are depicted their characteristics and their final histology. The rate of malignancy in the overall initial population of the study, combining all types of IPMN (BD, mixed and main duct) was 7.8 % (51/647).

Table 1
Demographic, exposome and clinical characteristics of IPMN enrolled in the study (n = 647), divided according to the management selected at diagnosis.

	Total n (%)	Surgery n (%)	Surveillance n (%)	p
Gender (male vs. female)	249 (38.5)	19 (33.3)	230 (39)	0.40
Age, median (IQR)	67 (58 – 65)	69 (59 – 75)	67 (58 – 73)	0.24
BMI, median (IQR)	24 (20 – 27)	24 (20 – 30)	24 (20 – 28)	0.60
Alcohol assumption (>24 gr. die)	21 (3.2)	0	21 (3.2)	0.15
Smoker (yes vs no)	68 (10.5)	7 (12.3)	61 (10.3)	0.74
Ex smoker (yes vs. no)	87 (13.5)	6 (10.5)	81 (13.7)	
First family member with pancreatic disease	36 (5.6)	2 (3.5)	34 (5.8)	0.45
Family history of neoplasms	182 (28.1)	14 (24.6)	168 (28.5)	0.53
Aspirin/statins assumption	107 (16.5)	9 (15.8)	98 (16.6)	0.87
Drugs assumption	295 (45.6)	22 (38.6)	273 (46.3)	0.27
Type of IPMN				
BD	547 (84.5)	21 (36.8)	526 (82.9)	
MD	13 (2.0)	13 (22.8)	0 (0)	**<0.01**
Mixed	87 (13.5)	23 (40.4)	64 (10.9)	
Symptoms (yes vs. no)	187 (28.9)	26 (45.6)	161 (27.3)	**<0.01**
Diabetes (yes vs. no)	24 (3.7)	6 (10.5)	18 (3.1)	**<0.01**
Abdominal pain (yes vs. no)	103 (15.9)	3 (7.2)	99 (16.8)	**<0.01**
Jaundice (yes vs. no)	17 (2.6)	6 (10.5)	11 (1.9)	**<0.01**
Pancreatitis (yes vs. no)	41 (6.4)	4 (7.0)	37 (6.3)	0.82
Enhancing nodules	41 (6.3)	19 (33.3)	33 (3.7)	**<0.01**
Cyst diameter (mm), mean(sd)	17.5 (11.2)	24.4 (17.2)	16.8 (10.29	**<0.01**
Site				
Diffuse	176 (27.2)	20 (35.1)	156 (26.4)	
Body tail	205 (31.7)	23 (40.4)	182 (30.9)	0.07
Head	265 (41)	14 (24.6)	251 (42.5)	

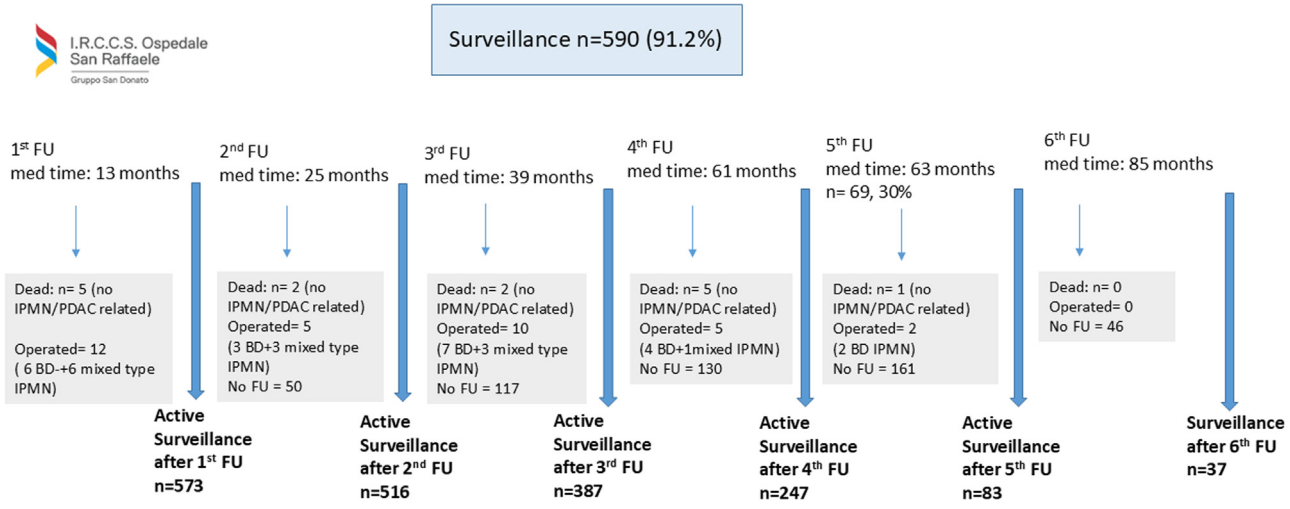

Fig. 2. Timing of surveillance.

3.1. Subgroup of patients with a presumed BD-IPMN at diagnosis

Among the population of patients categorized with a presumed BD IPMN at diagnosis, 21 underwent immediate surgery (3.8 %) and 526 underwent surveillance (96.2 %). Of them, 84 patients developed a relevant change (21.4 %) during follow-up. Within this cohort, 22 patients underwent a surgical procedure (4.1 %). Supplementary Table 3 presents all data concerning surgical indications and histology for those patients. The rate of pancreatic-related malignancy was 2.7 % in low-risk BD-IPMNs (14/526 pts) and 12.5 % (8/64 pts) in mixed IPMNs under initial surveillance. At histological report of resected BD-IPMN the rate of LGD was 61.9 % (13/21) for patients who underwent immediate resection and 27.2 % (6/22) in patients who underwent resection during surveillance, accounting for an overall rate of overtreatment in BD-IPMN of 44.18 % (19/43).

The univariate and multivariate analysis (Table 3) showed that being active smoker (OR 2.2, $p = 0.04$) and a cyst diameter >15 mm (OR 7.1, $p < 0.01$) at diagnosis were independent risk factors of development of relevant changes. A combination of cyst size ≤15 mm and age >65 (trivial cyst) acts as a major protective factor in univariate analysis (OR 0.1, $p < 0.01$) even more so if associated with no smoking habit (OR 0.2, $p < 0.01$), while the other trivial cyst defined as cyst <30 mm combined with age >75 is less effective protective factor (OR 0.5, $p = 0.09$).

4. Discussion

PANCY is one of the few prospective observational registry regarding cystic pancreatic neoplasms. The registry began in 2015 following the publication of the Italian guidelines for the management of pancreatic cystic lesions [19], to evaluate their applicability in real world. The registry, which succeeded in involving 25 different centers from the entire Italian area, had the initial objective to evaluate the diagnostic work-up and management at diagnosis of patients with cystic lesions of the pancreas [6]. The study was subsequently amended to evaluate the outcomes of patients

Table 2
Patients who underwent surgery during surveillance (n = 34).

Variables	N (%)
Type of surgery	
DCP	16 (47.1)
Distal Pancreatectomy	10 (29.4)
Total pancreatectomy	7 (20.6)
Cyst enucleation	1 (2.9)
Final pathological diagnosis	
PDAC	1 (2.9)
PDAC arising on IPMN	21 (61.8)
LGD	10 (29.4)
Other	2 (5.9)
Indication to surgery	
HRS	20 (58.8)
Multiple WF	13 (38.3)
Other	1 (2.9)
TNM[30]	
T0N0M0	7 (20.6)
T1N0M0	15 (44.1)
T2N0M0	11 (32.3)
T3N0M0	1 (2.9)

undergoing surveillance. Most of these patients had an IPMN, in line with the epidemiological data of pancreatic neoplasms/cystic lesions.

Therefore, the fondamental strength of analysis of IPMN patients from the PANCY registry is the opportunity to get long-term, real-life data, prospectively collected.

Of the 647 patients with an initial diagnosis of IPMN, 57 (8.8 %) underwent immediate surgery and 590 (91.2 %) active surveillance, including mainly low-risk BD-IPMNs, but also mixed-IPMNs. Adherence to the registry was very good in the first 24 months. Of the 590 patients, 17 (2.8 %) underwent surgery, seven (1.1 %) died from other causes, while no follow-up data was available for 50 (8.4 %) patients and 516 patients (87.4 %) were under surveillance. In the following years, the rate of patients with no follow-up data significantly increased reaching around half % (n = 297) of the overall population after a median follow-up time of 61 months. Reasons for study attrition in patients undergoing longitudinal studies/registries are heterogeneous and they can be mortality-related (i.e., cancer patients), or related to logistic, physical, and psychological factors [20,21]. In our context, attrition may be linked to the presence of a diagnosis perceived as benign by the patient, with low likelihood of progression, so that many patients have undergone subsequent checks over time in community hospitals - this is especially true for high-volume centers.

An important result of the study is that no patient in the surveillance cohort developed an advanced, unresectable pancreatic cancer. During surveillance 34/590 patients (5.7 %) underwent surgery mainly because the development of high-risk stigmata or multiple worrisome features. The percentage is further diminished when including the proportion of patients who received surgery among the lesions referred for follow-up as suspected BD IPMNs (22/547, 4 %). Only one patient had an IPMN-independent pancreatic cancer while most of resected patients had malignant IPMNs (61.8 %) and a remarkable 29.4 % had only low-grade dysplasia. Focusing on invasive lesions, most had “early” cancers with no lymph node metastases, underlying the benefit of a correct surveillance. The overall pancreatic malignancy rate was 2.7 % for low-risk BD-IPMNs and 12.5 % for mixed-IPMN undergoing initial surveillance. Despite the involvement of main duct by the IPMN increases the risk of harboring cancer [12,13,22], the vast majority of patients with presumed mixed IPMNs did not display malignancy, and some were also “downgraded” to pure BD-IPMNs, suggesting that some mild main pancreatic duct dilations are not related to the presence of an IPMN but to other reasons including ductal hypertension due to mucus [23,24]. Therefore, a surveillance policy for mixed IPMN with single WF and/or in patients with advanced age or major comorbidities seems a reasonable approach. Considering the entire group of 91 patients resected at diagnosis or during follow-up, more than one-third-(n = 35, 38.4 %) overall and around 44 % in the BD IPMN subgroup had exclusively low-grade dysplasia and they could be theoretically spared from a surgical resection. This is particularly relevant because postoperative morbidity and mortality can occur in patients with benign histology who could have avoided surgery [25].

The presence of invasive carcinomas (although pN0) operated during surveillance and of a significant number of resected low-grade underline that we are still far from the optimal goal of accurately identifying IPMN with high-grade dysplasia alone.

In low-risk BD-IPMNs we defined as “clinically relevant change” a composite outcome consisting of onset of WF and HRS and/or pancreatectomy for IPMN/PDAC and/or and mortality for

Table 3
Factors influencing a relevant change onset (univariate and multivariate analyses) on BD IPMN (n = 526) patients under active surveillance.

Variables	Tot n (%)	Univariate analysis		Multivariable analysis	
		OR	p	OR	p
Gender (male vs. female)	210 (39.9)	1.0 (0.6 – 1.6)	0.89		
Age (>65 yr vs. <65 yr)	365 (56.4)	0.9 (0.6 – 1.3)	0.50	0.9 (0.5 – 1.5)	0.63
Age (>75 yr vs. <75 yr)		1.0 (0.6 – 1.9)	0.92		
BMI, 25?	264 (50.2)	1.1 (0.6 – 1.3)	0.66		
BMI, 28?	175 (33.3)	0.8 (0.5 – 1.3)	0.42		
Alcohol assumption (>24 gr. die)	17 (3.2)	3.0 (1.1 – 7.2)	**0.03**	1.8 (0.6 – 5.2)	0.59
Smoker (yes vs no)	55 (10.5)	2.2 (1.2 – 4.0)	**<0.01**	2.1 (1.1 – 4.3)	**0.04**
Ex smoker (yes vs. no)	72 (13.7)	1.2 (0.6 – 2.4)	0.60	1.1 (0.5 – 2.1)	0.91
First family member with pancreatic disease	31 (5.9)	0.8 (0.6 – 2.1)	0.60		
Family history of neoplasms	145 (27.6)	1.3 (0.7 – 1.8)	0.30		
Aspirin/statins assumption	86 (16.4)	1.0 (0.6 – 1.8)	0.88		
Drugs assumption	295 (45.6)	1.1 (0.7 – 1.8)	0.65		
Diabetes	18 (3.4)	0.3 (0.1 – 2.3)	0.24		
Stable cyst (yes vs. no)	236 (44.9)	0.6 (0.4 – 1.3)	0.43		
Trivial Cysts (yes vs. no)	146 (27.8)	0.1 (0.1 – 0.3)	**<0.01**		
Cyst >15mm	254 (48.3)	7.1 (3.8 – 9.8)	**<0.01**	6.7 (3.7 – 12.4)	**<0.01**
Cyst ≤15 mm& age >65	166 (31.6)	0.1 (0.1 –0.3)	**<0.01**		
Cyst <30 & age >75	83 (15.8)	0.5 (0.3–1.1)	0.09		
Cyst ≤15 mm & age >65 & no smoke	137 (26.1)	0.2 (0.1 – 0.4)	**<0.01**		
Cyst ⟨30 & age⟩ 75 & no smoke	70 (13.3)	0.6 (0.2 – 1.4)	0.27		

IPMN/PDAC. At multivariate analysis we found that being active smoker (OR 2.2) and a cyst diameter >15 mm (OR 7.1) at diagnosis were independent risk factors of development of relevant changes. These data are in keeping with the current literature. Several Authors found an association between cigarette and IPMN progression [15,26–29], and a synergic role of nicotine metabolites and some mutations (i.e., *KRAS* mutations) has been proposed. Therefore, in accordance with previous research [26], this study confirmed the appropriateness of recommending cessation of cigarette smoking in patients with IPMN. BD-IPMNs <15 mm in size have been associated with a very low risk or no risk of progression in different studies [14,15,17,30–32].

We also applied the definitions of Trivial IPMN to our Cox model. Although not significant at multivariate analysis, the combination of cyst size ≤15 mm & age >65 was a significant protective factor at univariate analysis (OR 0.1), mainly in no smokers (OR 0.2), while the combination of cyst <30 mm & age >75 did not. From a practical point of view, it is appropriate to suggest a cessation of cigarette smoking in patients with IPMN; the risk of progression is low in BD-IPMN < 15 mm in general and in particular in patients and in patients over 65 years of age (trivial IPMN) and our data confirm the possibility of discontinuing surveillance in this setting.

This study has numerous limitations, the most significant being that it was initially conceived as a registry study to emphasize prevalence within an Italian population and was subsequently modified into a follow-up study; consequently, data for a substantial number of patients were not updated by the participating centers due to insufficient research resources. Moreover, as a real-world study, even patients who were continually monitored over time experienced difficulty to comply with the prescribed time frames for radiological examinations due to various factors, including expected logistical challenges (such as difficulties in scheduling the examination) and unforeseen circumstances like the COVID pandemic in 2020.

All these reasons resulted in decreased adherence to surveillance, thus leading to a loss of daa, particularly on patients who were no longer monitored. Consequently, it is challenging to generalize the findings of this study to a broader international population.

In conclusion, the PANCY study provided useful information about the natural history of patients with IPMN. In low-risk BD-IPMN the risk of progression is particularly low in lesions <15 mm found in patients >65 years of age who are non-smokers. In patients undergoing surgery, one-third-had benign lesions that did not require intervention with absolute indication but most patients with malignant IPMN had an invasive component at final histology. This suggests the need for a precision medicine approach to optimize the management of patients with IPMN.

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Declaration of competing interest

No conflicts of interest

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.dld.2026.02.007.

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