THE NATURAL HISTORY OF INTRADUCTAL PAPILLARY MUCINOUS NEOPLASM OF THE PANCREAS: REAPPRAISAL OF THE INDOLENT PRECURSOR OF PANCREATIC CANCER

ABSTRACT

INTRODUCTION

Evidences from surgical series have been condensed into several guidelines for the management of Intraductal Papillary Mucinous Neoplasms of the pancreas (IPMNs). However, still a gap must be filled to better understand their biological behavior. Aim of the present study is to describe the natural history of IPMNs observed at a high-volume center for thirty years.

METHODS

All patients with a radiological or pathological diagnosis of IPMN referred to The Pancreas Institute, University of Verona Hospital Trust, from 1985 to 2016 were included. Growth rates were analyzed through a linear-mixed model. The development of worrisome features (WF), high-risk stigmata (HRS), and pancreatic cancer (PC), survival and risk for surgery were also analyzed.

RESULTS

Of 2189 observed patients, 1529 were included in the analysis. The overall median follow-up was 43 months. Three hundred and thirteen patients were sent to surgery upfront, while 181 after initial surveillance. The overall growth rate was 1mm/year. For about half of cases any dimensional change was documented. The presence of high risk stigmata (HRS), age <75 years, and cyst size >30mm at diagnosis were associated to a faster growth rate. During follow-up, trivial IPMNs developed WF in 6.5% of cases and HRS in 0.6%. Overall, 3.5% of patients developed PC after a median time of 28 months. Of these patients, 72% previously developed HRS/WF. Of 1043 initially observed trivial branch duct (BD) IPMNs, 16 eventually developed PC with 10% occurring after 15 years of follow-up. HRS and growth rate were independent predictors of PC. Growth rate was the only difference between IPMNs developing PC and those remaining stable after more than 5 years of follow-up (n=399). The mean estimated disease specific survival (DSS) for the overall population exceeded 19 years. Only 1.9% of BD-IPMNs developed PC, with a resulting 5-years DSS rate of 99.3%. Standardized incidence ratio of PC for patients with trivial BD-IPMN was 21 (95% CI 10 – 38), whereas was only 1.8 (95% CI 0.5 – 4.7) considering patients > 65 years.

CONCLUSIONS

IPMN of the pancreas is the indolent precursor of PDAC that will not show a detectable growth during follow-up in half of the cases. Those rapidly growing (>2.50 mm/year) will likely progress to pancreatic cancer through the development of WF and HRS during the first year of follow-up. In patients > 65 y/o, the presence of a BD-IPMN without WF or HRS at diagnosis might not increase the risk of developing PC than in the general population.

INTRODUCTION

At the time of their discovery in 1980s[1], intraductal papillary mucinous neoplasms of the pancreas (IPMNs) were considered as a rare disease. Soon they have been recognized as a premalignant lesion leading to development of pancreatic cancer (PC) raising a great interest for the potential prevention of a highly lethal disease[2–4]. Due to the large availability of cross-sectional imaging, however, there are increasing data showing that the prevalence of asymptomatic pancreatic cysts is actually higher, ranging from 1.2 to 36.7% of the general population[5–9], with IPMNs being at least 80% of them[10]. This made necessary to draft guidelines able to balance from effective PC prevention and unrequested high-risk surgery[11–15].

International Association of Pancreatology (IAP) guidelines[13], European Expert Consensus guidelines[15] and American Gastroenterological Association (AGA) guidelines[14] are inconsistent and give different recommendations in terms of diagnostic work-up, indication for surgical treatment and follow-up schedule. Moreover, these guidelines and their recommendations are often based on expert opinion after the collection and revision of evidence coming basically from surgical series. This selection bias has prevented to gain an overall perspective that is essential to understand the actual risk of malignant progression of IPMNs, leading to a clinical management characterized by a high sensitivity, but a low specificity in identifying progression towards PC[16,17]. Cyst size, mural nodules, main pancreatic duct (MPD) dilatation, elevation of serum Ca19.9 and symptoms have been variably correlated with the risk of malignancy in many surgical series, but their role in the overall population affected by IPMNs is unknown.

Large observational series, including both resected and surveilled IPMNs coming from high-volume centers[18–23] have been recently published trying to fill the gap created in the last decade by mostly surgical series. Thereby, in the near future, we will be able to better understand the biological behavior of IPMNs producing eventually more accurate guidelines.

The aim of the present paper is to describe the natural history of IPMNs defining the most evidence-based policy for their management.

METHODS

Study Design

The study was approved by the Institutional review board and followed the statements developed by the "Strengthening the Reporting of Observational Studies in Epidemiology" (STROBE) guidelines (Fig.1). All patients evaluated in the Pancreatic Cystic Neoplasms outpatient clinic of the Department of General and Pancreatic Surgery – The Pancreas Institute, University of Verona Hospital Trust from 1985 to 2016 who underwent surgery after the first evaluation, who underwent surgery after an initial follow-up period and who were entered in a clinical and radiological surveillance program, were considered eligible

for the study. Patients resected before 6 months from the first visit were considered upfront resected, while patients resected after 6 months or conservatively managed were considered as initially followed.

Indication for surgery were more aggressive in the first years of the study as no guidelines existed. From 2006, IAP Sendai criteria[11] were applied and from 2012 the Fukuoka guidelines[12]. Patients presenting with a suspected IPMN and obstructive jaundice, enhancing mural nodules or an associated solid component and those with a MPD $\geq$ 10mm were considered for surgery. With regards to follow-up, we have always applied the internal policy of submitting patients to abdominal magnetic resonance imaging (MRI) with and without contrast enhancement and with cholangiopancreatography after 6 months from diagnosis and then each 12 months if stable[24].

In presence of other possible predictors of malignancy, also developed after an initial follow-up period, patients were further assessed with endoscopic ultrasounds (EUS) and sent to surgery in presence of mural nodules or solid components, in presence of malignancy at cytology or in presence of signs of direct involvement of the MPD.

Data were prospectively collected in the institutional database including patients' demographics, clinical and radiological characteristics, pathologic diagnosis and follow-up data derived from clinics. Telephonic interviews were used only to collect data about survival. All patients included in the growth rate analysis underwent at least two abdominal MRI with and without contrast enhancement and with cholangiopancreatography. Only patients affected by presumed IPMNs, as defined in presence of a cyst with a clear connection with the MPD detected at MRI or with EUS, in presence of multifocal disease even without a clear connection with the MPD and in presence of MPD dilatation without other reasons for MPD dilatation, were considered for further evaluation. Branch duct IPMNs (BD-IPMN) were defined in presence of a pancreatic cyst with a clear connection with the MPD through a secondary duct, without MPD dilatation; mixed type IPMNs (Mixed-IPMN) were defined in presence of a cyst connected to an enlarged MPD (> 5mm in size); main duct IPMNs (MD-IPMN) were defined in presence of a MPD > 5mm without other focal cystic lesions and without other clinical reasons for MPD obstruction or enlargement. BD-IPMN without WF/HRS at diagnosis and during follow-up were defined as trivial BD-IPMN.

Clinical reports focused on specific IPMNs-related features: cyst size, number of cysts, site of the cyst in the pancreatic gland, wall thickness and enhancement, mural nodules, septa and MPD size. Pathological evaluation was performed by specialized pancreatic pathologists and reported as suggested in the Baltimore[25] and Verona[3] consensus meetings.

Statistical Analysis

Continuous variables were expressed as means with standard deviation (SD) or as medians with range, as appropriate. Categorical variables were expressed as frequencies with percentages. Chi-square test with Yates correction in 2x2 contingency tables was used for categorical data, Student's T test was used to compare means whereas Mann Whitney U test to compare medians, all tests were 2-tailed. For the analysis on the development of pancreatic cancer, a logistic regression model was used for multivariable analysis using all the variables resulting significant ($P \leq 0,050$) at the univariate analysis. The goodness of fit of the model was verified using the Hosmer and Lemeshow test. For the survival analysis time

was calculated from the date of the first visit to the date of death or to the last follow-up, and for the disease specific survival (DSS) only a death related to the IPMN was considered as an event.

For the assessment of the risk of being operated during follow-up, time was calculated from the first visit to surgery or to the last available follow-up. Both for the analysis of survival and for the risk of being operated, univariate analysis was carried out with the method of Kaplan Meyer. Log-Rank test was used to compare differences. Cox proportional hazard regression model was used for multivariable analysis.

A linear-mixed model was used to assess cyst growth rate and factors associated with cyst growth rate. The model is based on the restricted maximum likelihood method and handles correlated data with unequal variance (ie, repeated measurement on each subject) as well as unbalanced designs (ie, studies with an unequal number of repetitions between subjects). Response from a subject (ie, tumor growth) is thought to be the sum of fixed and random effects. Fixed effects were presence of high risk stigmata at diagnosis as a dichotomic variable. Age and maximum tumor diameter at the time of diagnosis were considered to be random effects and were handled as covariates. Random effects were fitted by introducing an 'effect by subject' interaction term to account for possible subject variations. Type III tests for fixed effects and covariance parameters were used for the interpretation of potential predictors of tumor growth. Tumor growth rate was calculated using difference in size, obtained by size at diagnosis and size at last follow-up, divided by the numbers of years of follow-up. Age specific and age standardized incidence was assessed through the age specific and the standardized incidence ratios (SIRs) defined as the ratio of the observed to the expected number of patients developing malignancies. The 95% confidence interval (CI) of the SIR was estimated using the Wilson and Hilferty approximation of the exact Poisson distribution. The SIR was considered significant when all values in the 95% CI did not contain unity. The expected number of cases of PC was calculated using sex-specific, age-standardized and age specific data on the incidence of cancer in Italy for the study period, obtained from the EUREG-EUCAN projects of the International Agency for Research on Cancer[26]. P value < 0.05 were considered to be statistically significant. The analysis was conducted using SPSS v.22 (SPSS Inc., an IBM company, Chicago, IL).

RESULTS

1 - Overall population

During the study period, a total of 4686 clinical records belonging to 2189 patients affected by presumed and pathologically confirmed IPMNs were documented at our dedicated pancreatic cysts outpatient clinic (Table 1 and Figure 1). Most of patients were female and in the sixth decade of life. Only one patient out of three experienced symptoms, and these were more frequently associated with a significantly larger cyst (20 *vs.* 16mm, p< 0.001). According to imaging features, 1718 (78.4%) cases were classified as presumed BD-IPMNs, 271 (12.4%) as presumed Mixed-IPMNs and 200 (9.1%) as presumed MD-IPMNs.

Most patients (n= 1876, 85.7%) entered a clinical and radiological surveillance program, whereas 313 (14.3%) underwent surgery upfront. Among initially followed patients, 181 crossed over to resection after a median of 21 months (range 7-237) of follow-up.

A complete and reliable follow-up was available for 1529 (69.8%) patients accounting for a median time of 43 months (range 1 – 281 months).

1.1- Growth rate

Among 1529 patients with available follow-up, 1180 had at least two different cyst size measurement (figure 1). Considering all types of IPMNs, the overall growth rate during follow-up was 1mm/year (range -5 – 45mm/year). The 50° percentile of the growth rate was 0 mm/year, as half of cases showed no dimensional change during follow-up. The highest growth rate (≥ 2mm/year) was recorded only over the 90° percentile.

Considering only BD-IPMN (n= 1077), median growth rate was zero, while the 90° percentile was 2.4 mm/year. According to the test of fixed effects, the presence of high-risk stigmata (HRS), according to IAP guidelines[13], was significantly associated with a higher growth rate (0.91 vs 3.6mm/year, p< 0.001). According to the test of random effects, an older age and cyst size at first observation were significantly related with a higher growth rate (table2). In particular, comparing a baseline cyst size of <30mm with ≥30mm, the growth rate was significantly different (0.96mm/year vs. 1.33mm/year, respectively). Patients younger than 75 years showed a significantly higher growth rate when compared to older than 75 (1.06 vs. 0.76 mm/year).

1.2 – Development of features of malignancy during follow-up

Only patients with BD-IPMN who were initially followed up were extracted for this analysis (n= 1296). Upfront resected patients (n= 28) were subsequently excluded (Figure 1).

To evaluate the occurrence of WF during follow-up, patients with WF at diagnosis (n=192) were excluded, therefore 1076 patients were available for analysis. WF were developed by 70 (6.5%) patients after a median time of 15 months (range 1-157) (Table 3). Of note, 17 (24%) patients developed WF after 5 years of follow-up. Patients developing WF within 5 years from diagnosis presented significantly smaller cysts (25 vs. 40mm, p= 0.007). The cumulative risk of developing WF at 5 years from diagnosis was 6%. Considering only those individuals with more than 5 years of follow-up (n= 393), twenty-two (5.6%) developed a WF after a median time of 77 months (2 – 144).

To evaluate the occurrence of HRS patients with HRS at diagnosis (n=7) were excluded, therefore 1261 patients were available for analysis. During follow-up, 8 (0.6%) patients developed a HRS after a median of 20.5 months (range 3-59): 4 developed jaundice, 2 enhancing mural nodules and 2 a MPD dilatation > 10mm.

1.3 – Development of pancreatic cancer during follow-up

Considering 1417 initially surveilled IPMN available for follow-up (figure 1), 54 (3.5%) developed PC after a median follow-up of 28 months (1 - 275). Of those, 39 (72.2%) developed a WF or a HRS before showing signs of progression to PC. Thirty-

three patients (84.6%) developed WF/HRS within 6 months from diagnosis, while the remaining 6 patients (15.4%) after the first year of follow-up.

Considering only MD-IPMN and mixed IPMN (n=145), 30 (20.7%) developed PC after a median time of 21 months (6 - 226), whereas considering only BD-IPMNs (n=1272), 24 (n= 1.9%) patients developed PC after a median of 31 months (1 – 275). The development of an HRS during follow-up (16.7% vs. 0.4%, p<0.001) and a faster growth rate (median 2.5 mm/year vs. 0 mm/year, p<0.001) were statistically related to the development of PC.

Considering trivial and always stable to follow-up BD-IPMN alone (n= 1002), the incidence of PC was 1.1% (n= 11). This subgroup showed a 5-years disease specific survival (DSS) of 99.7%. About 10% of PC development occurred after more than 10 years of follow-up. Univariate analysis of predictors of malignant progression reveals that a higher growth rate (>2.5 mm/year) was the only predictor of development of PC (Table 4).

Considering trivial BD-IPMN with at least 5 years of follow-up (n= 371), the incidence of PC was 1.6% (n= 6). In this case, a univariate analysis failed to identify any predictor of cancer development due to the small sample size.

Table 5 reports the comparison between the "best" and the "worst" BD-IPMN case scenario. Best cases were trivial BD-IPMNs with at least five years of follow-up that did not progress to cancer (n= 365); worst cases were followed-up BD-IPMNs that eventually developed PC (n= 24). Once again, growth rate was the only independent predictor of malignant progression.

The SIR of PC in the initially followed BD-IPMN group (n=1272) was 37.36 (95% CI 23.93 - 55.59). The SIR of trivial BD-IPMN was 21.74 (95% CI 10.83 - 38.89). The age-specific incidence ratio of PC for patients over 65 years old with trivial BD-IPMN (n=544) was 1.86 (95%CI 0.50-4.76), which resulted as not significant since the 95% confidence interval included the unity.

1.4 – Crossing over to surgery during follow-up

Of the 1417 initially followed IPMN, 151 (10.7%) were resected after a median time of 21 months (1 – 237). Presumed BD-IPMN had a significantly lower risk of being resected during follow up compared to MD-IPMN and mixed IPMN (5 years cumulative risk 5.1% *vs* 52.9%, p<0.001). Considering only BD-IPMN (n=1272), at univariate analysis, being under 65 years of age was associated with an increased risk of crossing over to surgery (p=0.026), as well as being symptomatic at diagnosis (p<0.001), growing more than 2.50 mm/year (p<0.001) and developing a WF during FU (p<0.001). At multivariate analysis, the presence of symptoms at diagnosis (HR=2.477, CI95% 1.312-4.676, p=0.005), a growth rate > 2.50mm/year (HR=9.642, CI95% 5.199-17.881, p<0.001) and the development of WF during FU (HR=2.721, CI95% 1.489-4.971, p=0.001) were independent predictors of the risk of need for surgical resection during follow-up.

2 – Survival analysis

The overall mortality rate was 4.8% (n= 74), whereas disease specific mortality was 2.6% (n= 40). Mean estimated overall survival and mean estimated disease specific survival were 231 (215 – 247) and 251 (236 – 268) months respectively. Figure 3 shows Kaplan-Meier disease specific survival curves stratified by clinical and radiological features. Patients younger than 75 years experienced a longer estimated DSS (5yrs DSS 98.3% vs 94.6%, p=0.003), as well as patients with IPMN smaller than 30mm (5yrs DSS 98.8% vs 92.2%, p<0.001), patients with a growth-rate under the 90° percentile (>2.75mm/year) of the entire population (5yrs DSS 99.7% vs 93.9%, p< 0.001), without symptoms at diagnosis (5yrs DSS 99.1% vs 92.4%, p<0.001),

without HRS at diagnosis (5yrs DSS 98.7% vs 68.1%, p< 0.001), without WF at diagnosis (5yrs DSS 99.3% vs 94.1%, p< 0.001) or with a presumed diagnosis of BD-IPMN (5yrs DSS 98.8% vs 91.1%, p<0.001). Overall, independent predictors of disease specific survival were the presence of symptoms at diagnosis (HR 2.72, 95%CI 1.24 – 5.97, p= 0.013), a diameter ≥ 30mm (HR 2.41 95%CI 1.17-4.96, p=0.017) the presence of HRS at diagnosis (HR 5.96, 95%CI 2.70 – 13.18, p< 0.001) and a presumptive diagnosis of BD-IPMN (HR 0.37 95%CI 0.16 – 0.88, p=0.024).

Considering 1270 initially surveilled BD-IPMNs, only 12 (1%) died due to PC. Extracting from the original population only those cases with more than 5-years of follow-up (n= 583), 2.7% (n=16) died of PC. At univariate analysis, a cyst size larger than 30 mm, the absence of symptoms at diagnosis, the absence of WF or HRS at diagnosis and a presumptive radiological diagnosis of BD-IPMN were all related to a longer DSS (p<0.05). At multivariable analysis, only a presumptive diagnosis of BD-IPMN (HR 0.077 95%CI 0.02 – 0.29, p<0.001) was an independent predictor of DSS.

DISCUSSION

The fear of the unknown has historically led to aggressive active responses in terms of medical treatments. When first facing cysts in the pancreas in the mid-1980s[1], the surgical community reacted with a radical interventional approach without a precision knowledge about their biology. As the surgical series have been expanded worldwide, retrospective analyses of pathological and survival data were carried out, and disappointing results in terms of cost-effectiveness (pancreatectomy related morbidity and mortality vs. actual rate of malignancy) became available. These surgical data were incorporated into guidelines[13–15], able to provide useful recommendations for clinicians.

With the last year, we are now entering into a new era. Thanks to the information collected in decades of experience, Institutions worldwide are re-analyzing observational data mostly on observed individuals harboring IPMNs. These data are re-writing the natural history of the disease, providing neglected points of view about their actual biology.

The present paper is inscribed into this new chapter of IPMN literature, with the strength of analyzing the thirty-year long experience of a dedicated outpatient cyst clinic at a single high-volume center. As a result, patients have been referred from an entire country and managed homogeneously. The single pictures of each observation summed up into a movie provided a longitudinal appraisal of the natural history of the disease. We found that IPMNs of the pancreas usually present as small cystic lesions in asymptomatic individuals in their 6th decade of life. They are indolent, slowly growing entities, that seldom develop features related to malignancy and proper pancreatic cancer. Consequently, only a small subset of them requires surgical resection.

While the advances in cross-sectional imaging technology has led to an increase of in the incidence of newly discovered asymptomatic small BD-IPMNs worldwide[10], yet it is extremely difficult to detect substantial changes in cyst size during surveillance. In this regard, we found that the median growth rate of presumed IPMNs is approximately 1mm/year. What should be learned from the present analysis is that most IPMNs will never significantly grow during follow-up and remain stable throughout the years. Conversely, the growth rate increases in presence of HRS, larger cysts at baseline, and in younger patients. The relevance of growth rate in the natural history of IPMNs reinforces the role of repeated observations during time. Together with the changing in cyst size, specific clinical and radiological signs defined as WF and HRS call for a

careful assessment. According to the present series, the cumulative risk of developing a WF within 5 years from diagnosis is relatively low, accounting for the 6% of cases. However, since one out of four patients will show signs of progression to malignancy even after 5 years from the first observation, follow-up might not be discontinued after this tier as contrariwise suggested by AGA guidelines[14].

Although PC may also originate from a trivial BD-IPMN and it is not possible to predict which patients are actually at higher risk, most of events happen very slowly. For this reason, it is possible to count on a "safety window", a sufficiently long period of time during which the risk for PC can be better stratified through repeated observations. Moreover, whenever surgical resection would become the treatment of choice, it could be scheduled in the best moment in terms of surgical risk for the patient. During this "safety window", in fact, the risk of developing PC is actually minimal, but always present.

As the goal of IPMN surveillance remains the prediction of cancer development, we reinforce that PC may arise even from benign-looking BD-IPMNs. Unfortunately, there is not a specific time interval after which the risk of PC terminates, as cancer can be detected either immediately after diagnosis and even after more than 10 years of follow-up. However, referring to the non-operated individuals of the present series, it is impossible to assess whether PC arises within the cyst or if it is a concomitant entity. The main predictors of PC development during follow-up are the presence of HRS and the cyst growth rate. Of note, patients undergoing upfront surgery were excluded for the analysis of PC development, and most of those developing HRS during surveillance did not undergo resection as they refused or were not fit for surgery. Considering only trivial BD-IPMNs, the incidence of PC during follow-up is 1.1%, equaling or even being lower the rate of post-operative mortality and long-term sequelae of major pancreatic resections at high-volume centers[27]. This stresses the fact that systematic surgery is not the right answer, and over treating the disease still remains a major criticism for GI specialists. Our age-adjusted analysis for PC development is aimed to enrich the debate on IPMN management. We found that trivial BD-IPMNs are indeed at increased risk of developing cancer with a SIR of 21 (95% CI 10 – 38) as the age standardized incidence of PC in Italy accounts for 10.1/100.000 individuals/year. However, considering the age-specific IR (incidence ratio) for patients over 65 y/o, namely the median age of patients with IPMNs, we did not find a significant difference (IR 1.8, 95% CI 0.5 – 4.7) as the incidence of PC for patients of the same age in Italy is about 79/100.000 individuals/year. This data need further confirmation, as they might show that the presence of a BD-IPMN without WF/HRS in a 65y/o individual would not confer a higher risk of developing PC than the general population.

The "risk" for surgical resection during follow-up was analyzed as its directly depends on the type of management applied through the years. Surgeons were more concerned in presence of well-known predictors of cancer, suggesting surgical resection in presence of WF, symptoms or cyst size >30mm, but always after and adequate follow-up interval. In particular, in presence of a faster growth rate, surgery was more frequently proposed, but only after 5 years of surveillance.

As expected, the IPMN-specific mortality was equal to the incidence of PC, therefore comparable to the post-operative mortality of a major pancreatic resection in high volume Institutions. When considering trivial BD-IPMNs, the 5 years DSS rate almost reaches 100% and the overall risk of dying of PC is almost nil, reinforcing that surveillance is the best choice for this type of disease. Moreover, survival can be predicted by well-known factor like cyst size, cyst growth rate, symptoms

and development of WF or HRS. Once again, these features can be promptly detected during follow-up, indicate further investigation for risk assessment and, eventually, surgical resection.

The present study is consistent with others exploring the natural history of pancreatic cystic neoplasm and published in the last three years by the leading high-volume Institutions worldwide. The study from the MSKCC[22] reports similar rate of disease specific mortality, PC occurrence and cross-over to resection rate during follow-up. Despite the median growth rate was also similar, more than double the IPMN of the American series showed an increase in size during follow-up compared to the present. Of note, the MSKCC study includes all type of pancreatic cystic neoplasms with a median follow-up of 2.2 years, potentially short if considering the indolent natural history of the disease.

In contrast, the topic of IPMN growth rate has seldom been rigorously assessed in the available literature. In line with our results, the recent study from Seoul National University Hospital[21] has underlined the role of cyst growth rate and its association with the development of WF and HRS. Moreover, the Korean colleagues have confirmed how the majority of cysts are indolent and do not require surgical resection. Of note, the above-mentioned study focuses on BD-IPMNs with more than 5 years of follow-up only. Moreover, the present examination has the strength of being originated from a linear-mixed model and not just a descriptive analysis.

With regards to survival outcomes, the study from Karolinska University Hospital[20] has reported a 5 years DSS rate for BD-IPMNs of approximately 100% as well, but a higher median cyst growth rate and risk for surgery. Again, the authors acknowledge the possibility of a safe surveillance for BD-IPMN without WF or HRS is remarked. Though, the analysis on PC occurrence is limited to patients undergoing surgery after follow-up and median follow-up was about 2.5 years. Similar evidences have been already reported by a multi-centric series of Crippa et al[18], showing excellent 5 years DSS for BD-IPMNs under surveillance with almost 5 years of follow-up is actually excellent, and by the Mayo Clinic group[28] reporting a less than 1% PC developing rate in BD-IPMN without WF under surveillance. A recent study by the Harvard Medical School[19], strengthened by one of the longest median follow-up reported in the literature (more than 80 months), showed a rate of PC occurrence for BD-IPMNs of 4.4%. However, considering only those without WF and <1.5cm in size, the rate dropped down to 0.9%. Despite presenting a shorter median follow-up of 33.5 months, also a mid-term analysis of the NSPINAL study group[23] showed how the 3-years risk of developing PC was 1.2% in BD-IPMNs, being radiological progression and symptoms the main predictors of PC occurrence.

As a matter of fact, most of these recent studies have been actually triggered by the release of the AGA guidelines for the management of asymptomatic BD-IPMN. For the first time, the AGA guidelines suggested to discontinue follow-up after 5 years from diagnosis in case of indolent cysts without radiological or clinical signs of progression. The AGA should be commended for the efforts in reducing the impact of IPMN on Health systems worldwide. Since their publication in 2015[14], several groups[19,21,22] attempted to identify a subpopulation of IPMNs in which follow-up could be discontinued after 5 years due to the lack of a fundamental principle that must be accomplished in all screening campaigns: namely that tests should be cost-effective demonstrating a reduction in disease-specific mortality of the screened population. However, none of those studies had sufficient power to demonstrate that follow-up can be discontinued in selected cases. We reinforce this

concept, as in our experience the surveillance of IPMNs without indication for surgery should never be ceased. Several clinical and radiological features may help in predicting the risk of malignant progression, and repeated observation in time should be individualized according to that risk. Due to the evidence about age-specific incidence ratio of PC, the population of patients aged more than 65 years with a trivial BD-IPMN that do not develop WF and HRS within 5 years from diagnosis, seems to be the most adequate to assess the cost-effectiveness of surveillance discontinuation. As the incidence of PF radically increase with age, the presence of a trivial BD-IPMN appears to not affect the risk.

The present study has several important limitations. First, its retrospective nature and the related issue of data availability. Enormous efforts have been made to retrieve additional information regarding followed-up patients. Despite the experience of the leading dedicated outpatient clinic in Italy for pancreatic cystic lesions harvested a large population, the lack of complete data for all patients made it necessary to perform several focused analyses on smaller subpopulations, partially reducing the power of the study. Second, the study period of about thirty years was rather long to obtain a large study population and one of the longer median follow-up reported in the literature. However, during these three decades the management of IPMNs has radically changed, resulting in a noticeable bias for the analysis. Third, the study included also resected cyst with a final pathological diagnosis different form IPMN. However, they were included in the final analysis to balance the counterpart of cysts under surveillance that probably were not IPMN. This approach reflected the actual decision-making process when facing a presumed IPMN.

CONCLUSION

IPMN of the pancreas is an indolent precursor of PDAC requiring life-long surveillance in surgically fit patients. Half of those entered into a surveillance program will not show any detectable growth at all, while around the 10% will rapidly increase their size. A rapid cyst growth rate (>2.50 mm/year) is an independent predictor of pancreatic cancer development, together with the development of HRS. Those individuals developing PC will soon progress through WF and HRS within 1 year in most of the cases, highlighting the importance of a closer follow-up after initial diagnosis. Patients with BD-IPMN without HRS or WF at diagnosis have an increased incidence of PC than the general population. However, after 65 years of age, the presence of such cyst might not confer a higher risk of developing malignancy.

TABLES

Table 1 – Characteristic of the cohort (n= 2189)		
		N (%)
Sex	Male	891 (40.7)
	Female	1298 (59.3)
Age (mean ± SD, years)		64.6 ± 11.1
History of other malignancy		492 (22.5)
History of pancreatic malignancy		107 (6.3)
Symptoms		646 (29.5)
Abdominal Pain		465 (21.2)
Follow-up (median, range, months)		43 (0-281)
Acute Pancreatitis		195 (8.9)
Cyst Size (median-range, mm)		17 (1-190)
Presumptive Diagnosis	BD-IPMN	1718 (78.4)
	MD-IPMN	200 (9.1)
	Mixed-IPMN	271 (12.4)

Table 2 – Linear Mixed Model		
Test of Fixed Effects		
	F	P Value
HRS	167.173	<0.001
Test of Random Effect		
	Wald Z	P value
Age	6.542	<0.001
Baseline tumor diameter	13.739	<0.001

Table 3 - Development of WF during follow-up for BD-IPMN without WF o HRS at diagnosis (n= 1076)	
	During follow-up (n, %)
Diameter > 30mm	35 (3.2)
Pancreatitis	19 (1.7)
MPD 5-9mm	13 (1.2)
Mural Nodules	14 (1.3)
Thickened cyst walls	4 (0.3)

Table 4 - Univariate analysis of predictors of PC for trivial BD-IPMN (n= 1002)				
		PC		P
		No (n=991)	Yes (n=11)	
Age (median, years)		66.0 (17-94)	60.5 (36-73)	0.272
Sex	M	300 (30.3)	3 (27.3)	1.000
	F	691 (69.7)	8 (72.7)	
Diameter (median, mm)		14.0 (2-29)	18.5 (10-25)	0.103
Growth rate > 2.5mm/y		67 (8.3)	4 (40.0)	**0.007**
Presence of Symptoms		122 (12.3)	2 (18.2)	0.635

Table 5 - Clinical and radiological features of best* vs. worst** IPMN case							
		Univariate			Multivariable		
		Best (n= 365)	Worst (n= 24)	P	OR	95%CI	P
Sex	Male	96 (26.3)	9 (37.5)	0.240			
	Female	269 (73.7)	15 (62.5)				
Any Symptoms at diagnosis°		28 (7.7)	7 (29.2)	**0.003**			
Age at diagnosis (mean ± SD, year)		64.2 ± 10.7	64.9 ± 10.7	0.180			
Diameter at diagnosis (mean ± SD, mm)		14.8 ± 6.2	18.1 ± 9.1	0.053			
Growth rate (median, range, mm/y)		0.0 (-3.6 – 5.3)	2.5 (0.0 – 20.5)	**<0.001**	1.988	1.469-2.691	<0.001

* best: trivial BD-IPMN with at least 5 years of follow-up that did not developed PC

**worst: BD-IPMN developing PC during follow-up

°abdominal pain, weight loss, pancreatitis, bowel movement pattern change, dyspepsia

Table 6 - Univariate and Multivariable analysis of predictors of disease specific survival for 1529 IPMNs					
		Univariate	Multivariable		
		P value	HR	95%CI	P value
Age	>75y	0.003			
	<75y				
Size	>30mm	<0.001	2.40	1.17 – 4.96	0.017
	<30mm				
Growth-rate	>2.75mm/year	<0.001			
	<2.75mm/year				
Symptoms at diagnosis		<0.001	2.72	1.24 - 5.97	0.013
HRS at diagnosis		<0.001	5.96	2.70 – 13.18	<0.001
WF at diagnosis		<0.001			
Presumed diagnosis of BD-IPMN		<0.001	0.37	0.16 – 0.88	0.024

FIGURES

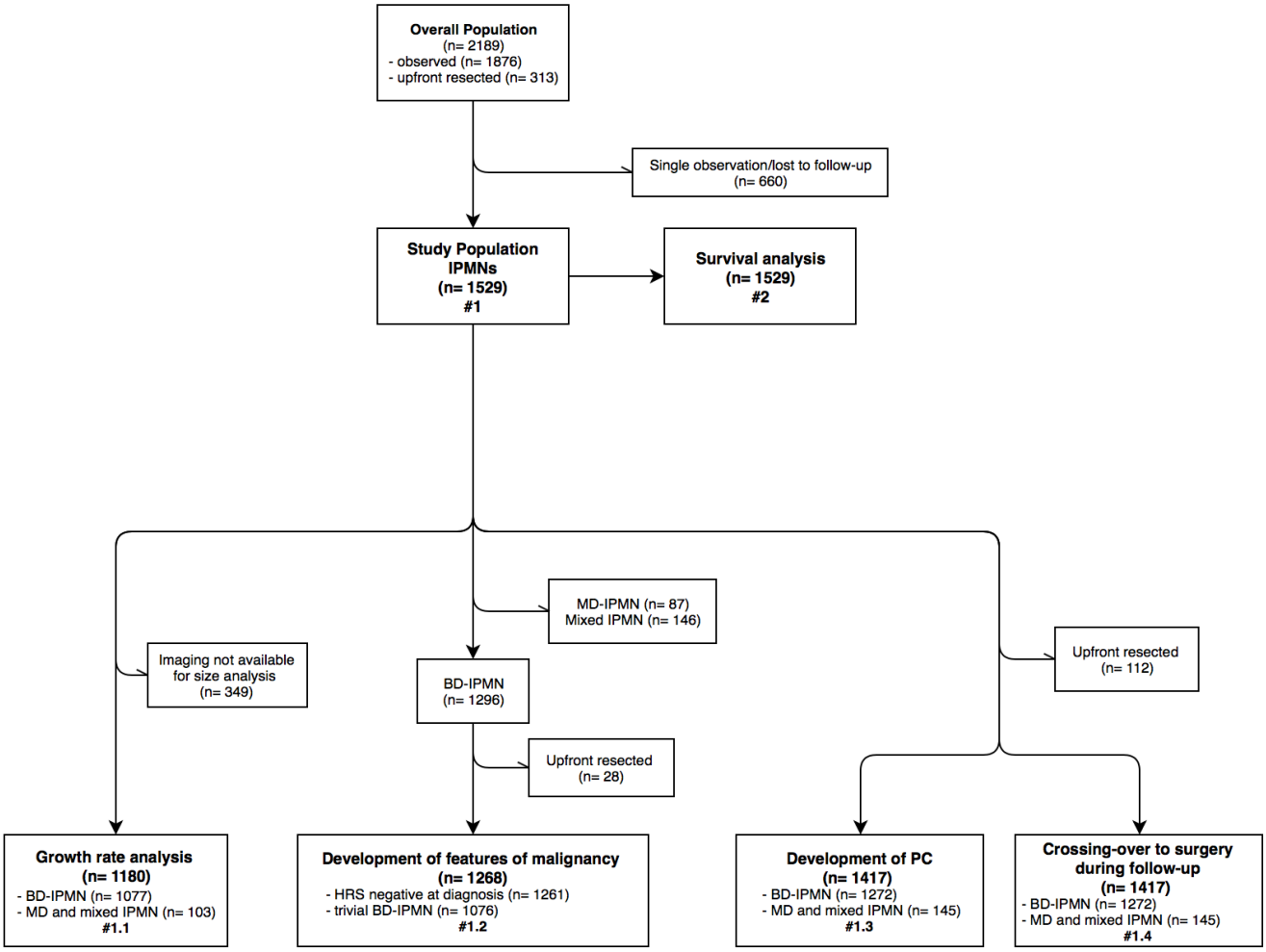

Figure 1 - STROBE compliant study flow-chart

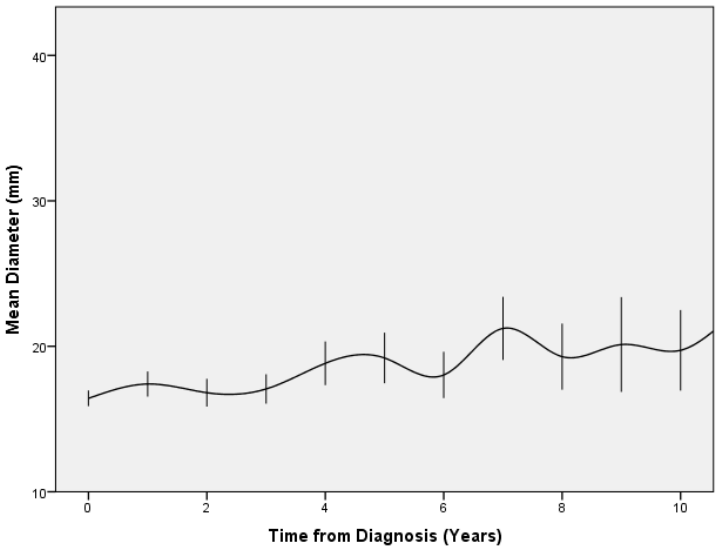

Figure 2 – Curve showing BD-IPMN growth over time

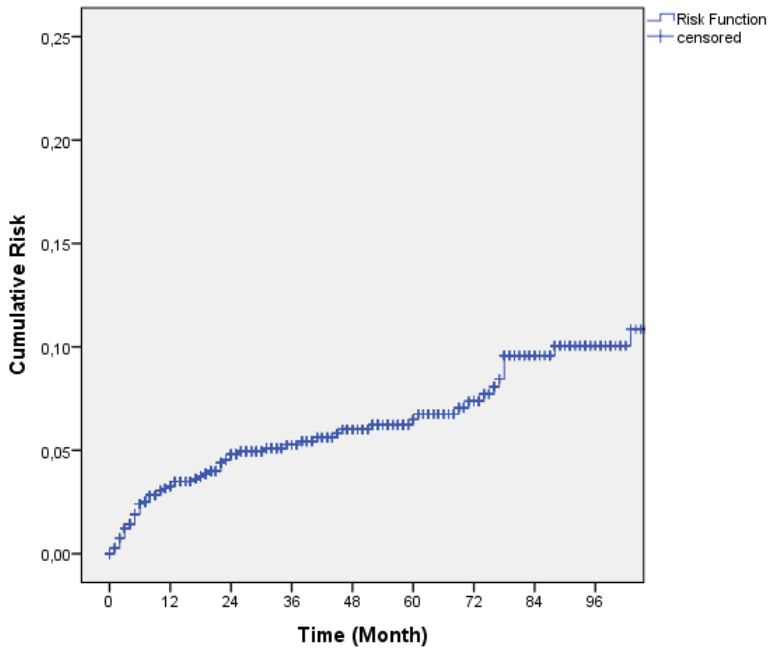

Figure 3 – Kaplan-Maier curve depicting the cumulative risk of developing WF during follow-up for trivial BD-IPMN

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