Gastroenterology 2023;165:1016–1024

Surveillance for Presumed BD-IPMN of the Pancreas: Stability, Size, and Age Identify Targets for Discontinuation

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See editorial on page 827.

BACKGROUND & AIMS: Currently, most patients with branch duct intraductal papillary mucinous neoplasms (BD-IPMN) are offered indefinite surveillance, resulting in health care costs with questionable benefits regarding cancer prevention. This study sought to identify patients in whom the risk of cancer is equivalent to an age-matched population, thereby justifying discontinuation of surveillance. **METHODS:** International multicenter study involving presumed BD-IPMN without worrisome features (WFs) or high-risk stigmata (HRS) at diagnosis who underwent surveillance. Clusters of individuals at risk for cancer development were defined according to cyst size and stability for at least 5 years, and age-matched controls were used for comparison using standardized incidence ratios (SIRs) for pancreatic cancer. **RESULTS:** Of 3844 patients with presumed BD-IPMN, 775 (20.2%) developed WFs and 68 (1.8%) HRS after a median surveillance of 53 (interquartile range 53) months. Some 164 patients (4.3%) underwent surgery. Of the overall cohort, 1617 patients (42%) remained stable without developing WFs or HRS for at least 5 years. In patients 75 years or older, the SIR was 1.12 (95% CI, 0.23–3.39), and in patients 65 years or older with stable lesions smaller than 15 mm in diameter after 5 years, the SIR was 0.95 (95% CI, 0.11–3.42). The all-cause mortality for patients who did not develop WFs or HRS for at least 5 years was 4.9% (n = 79), and the disease-specific mortality was 0.3% (n = 5). **CONCLUSIONS:** The risk of developing pancreatic malignancy in presumed BD-IPMN without WFs or HRS after 5 years of surveillance is comparable to that of the general population depending on cyst size and patient age. Surveillance discontinuation could be justified after 5 years of stability in patients older than 75 years with cysts <30 mm, and in patients 65 years or older who have cysts ≤15 mm.

Keywords: Pancreas; Pancreatic Cyst; Surveillance Discontinuation; Pancreatic Cancer.

1

A worldwide increase of newly diagnosed pancreatic cysts (PCs) in the past 20 years has raised issues regarding the need for surveillance and subsequent intervention.[1] The greater part are small cysts found incidentally

Abbreviations used in this paper: **ACCI, age-adjusted Charlson comorbidity index; BD-IPMN, branch duct intraductal papillary mucinous neoplasm; CI, confidence interval; HGD, high-grade dysplasia; HR, hazard ratio; HRS, high-risk stigmata; IAP, International Association of Pancreatology; IQR, interquartile range; MPD, main pancreatic duct; PC, pancreatic cyst; PDAC, pancreatic ductal adenocarcinoma; SIR, standardized incidence ratio; WF, worrisome feature.**

Most current article

0016-5085/$36.00
https://doi.org/10.1053/j.gastro.2023.06.022

in asymptomatic individuals.[2–4] Intraductal papillary mucinous neoplasms of the branch ducts (BD-IPMNs) represent the vast majority of truly neoplastic PCs.[5] Understanding the natural history of these small lesions is important in promoting a surveillance system that balances health care costs with the likelihood of malignant transformation.

Although surgical management was originally widely adopted,[6] most case-series subsequently revealed that many PCs did not harbor either an associated invasive cancer or high-grade dysplasia (HGD).[7–10] Management has gradually shifted toward a "watch and wait" policy for most patients. The International Association of Pancreatology (IAP) guidelines currently recommends regular follow-up with clinical evaluation, imaging and/or endoscopy, and laboratory tests,[11] a strategy that places a significant burden on health care resources. Surveillance frequently lasts until the patient is deemed no longer fit for surgery with the potential for adverse physical and psychological effects on the patient's sense of well-being.[12,13] Unlike the original hypothesis that all BD-IPMNs will eventually progress to malignancy, even after many years of observation,[10,14] recent evidence has highlighted that most small and asymptomatic presumed BD-IPMNs remain basically unchanged, with minimal risk of evolving into invasive cancer.[15–18]

The present analysis was undertaken with the aim of identifying patient groups harboring presumed BD-IPMNs at very low risk of malignant progression, in which the likelihood of pancreatic cancer was no different from that of an age-matched general population.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Patients harboring presumed branch duct intraductal papillary mucinous neoplasm of the pancreas are offered indefinite surveillance. No data exist regarding possible surveillance discontinuation of those at minimal risk of developing pancreatic cancer.

NEW FINDINGS

Surveillance discontinuation is a feasible option in presumed branch duct intraductal papillary mucinous neoplasm stable for at least 5 years in patients older than 75 years with cysts $<$30 mm or older than 65 years with cysts $\leq$15 mm.

LIMITATIONS

The retrospective nature of the study, despite relying on prospectively maintained databases, and the relatively limited follow-up of surveilled patients.

CLINICAL RESEARCH RELEVANCE

Building on the evidence presented here, prospective clinical studies assessing the behavior of cysts candidate to surveillance discontinuation could be designed.

BASIC RESEARCH RELEVANCE

The integration of these parameters with biomarkers expression could improve risk stratification of pancreatic cystic neoplasms. The subset of cysts showing indolent behavior could allow us to uncover therapeutic options to treat intraductal papillary mucinous neoplasms with a malignant behavior.

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Methods

Study Design

This international study was approved by the institutional review board of each participating center and followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement.[19] Informed consent policy varied across centers. In most cases it was waived given the use of historic de-identified data.

This investigation was organized as a multicenter observational study based on prospectively accrued institutional databases from international high-volume centers in Europe, the United States, and Asia under the auspices of the Verona Evidence-Based Meeting on IPMN Consortium (see author affiliations for details).[20]

Patient Eligibility

To include patients with presumed BD-IPMNs at low risk of degeneration, all patients with a radiologically presumed or cytologically/histologically confirmed BD-IPMN lacking any worrisome features (WFs) and/or high-risk stigmata (HRS) at the time of diagnosis and enrolled in a surveillance program for at least 12 months were considered. A presumptive diagnosis of BD-IPMN was based on the presence of 1 or more dilated branch duct(s) communicating with a nondilated main pancreatic duct (MPD) (5 mm or smaller) at high-resolution axial imaging and/or endoscopic ultrasonography.

To include only cysts properly enrolled in surveillance programs, lesions undergoing surgery within 12 months from diagnosis were excluded. The reason for this exclusion lies in the 6-month threshold that is considered for the baseline evaluation of these patients (accounting for referral from low-volume institutions and second-level examinations). Also considering the surgical waitlist of high-volume centers, a minimum of 12 months of surveillance was considered a safe threshold to retrospectively include BD-IPMN actually enrolled in a surveillance program. Similarly, those with a previous history of pancreatic ductal adenocarcinoma (PDAC) or who had undergone major pancreatic surgery were also excluded. Cysts highly suspicious for an alternative diagnosis (mucinous or serous cystic neoplasms, pseudocysts, solid pseudopapillary tumors, and cystic neuroendocrine tumors) were also excluded. Patients who did not comply with the inclusion criteria were excluded.

Data Collection

Clinicopathological data, including patient demographics and radiological and endoscopic characteristics of the cyst were collected. For those patients who underwent surgery after more than 12 months of surveillance, perioperative and histological data, recurrence, and survival, were recorded. Clinical reports focused on specific reported symptoms (jaundice, acute pancreatitis, new onset, or worsening diabetes), comorbidities status according to the age-adjusted Charlson comorbidity index (ACCI)[21] and IPMN-related features (CA19.9 elevation, cyst size, number and location, cyst wall, mural nodules, solid components, septa, MPD size). WFs and HRS were defined according to the latest update of the IAP guidelines,[11] with the exception of mural

nodules. Being a retrospective study, mural nodule size was not available, therefore the 2012 IAP guidelines[22] were used for the definition of nonenhancing mural nodules as a WF and enhancing mural nodules as an HRS. In patients with multiple lesions, the cyst with the largest size was considered for analysis. The greatest diameter was chosen to report cyst size. Duration of surveillance was the interval from diagnosis to the date of last follow-up, surgery, or death. Surveillance and postoperative follow-up visits were carried out on a regular basis according to international guidelines.[11,23] Pathological evaluation was performed by specialist pancreatic pathologists and reported as suggested in the Baltimore and Verona consensus meetings.[24,25]

Study Endpoints

The primary endpoint was the development of pancreatic cancer, defined as either IPMN with associated invasive carcinoma or IPMN with concomitant PDAC. Malignancy was confirmed by fine needle cytology/histology or following histological assessment of resected specimens. In patients without histopathologic confirmation of pancreatic cancer, evidence of malignancy, such as distant metastasis in the absence of any other primary neoplasm, was used as a surrogate for pathological diagnosis.

Secondary endpoints were development of WFs and HRS during follow-up, along with risk factors for developing pancreatic cancer with a specific focus on cyst size and growth rate, and survival.

A planned analysis on presumed BD-IPMN with a minimum of 5 years of surveillance that did not develop any WFs or HRS for the first 5 years of surveillance was undertaken. Cyst stability for at least 5 years was chosen as a parameter based on information suggested by the American Gastroenterological Association guidelines in 2015.[26] In addition, 2 cutoff levels for cyst size measured after the first 5 years of surveillance were chosen according to the IAP guidelines (30 mm)[11] and previous studies (15 mm).[15,27]

These 2 categories included Trivial BD-IPMN,[16] in which a cyst showed no development of WFs/HRS for at least 5 years and remained therefore $<$30 mm in size, and Trivial BD-IPMN $\leq$15 mm, in which a cyst showed no development of WFs/HRS developing for at least 5 years and remained $\leq$15 mm in size.

Statistical Analysis

Continuous variables were expressed as means with standard deviation or as medians with interquartile range (IQR) as appropriate. Categorical variables were expressed as frequencies with percentages. Chi-square tests with Yates correction in 2×2 contingency tables were used for categorical data, Mann-Whitney *U* test was used to compare medians. Right censored survival data were analyzed. Time from first observation to time of death or time of last follow-up was used for overall survival. Kaplan-Meyer curves were used to estimate survival. Log-rank test was used to compare survival between groups. Cox proportional hazard model with time-dependent covariates has been used to assess the association between WF/HRS development and overall survival.

To calculate the standardized incidence ratio (SIR) of pancreatic cancer between our cohort and the general population, sex-specific pancreatic cancer rates from Germany, Italy, Republic of Korea, The Netherlands, Spain, United Kingdom, England and Wales, and the United States were extracted from the IARC dataset (https://gco.iarc.fr/overtime/en/dataviz/tables?hide_tab_age_specific_numbers=1&mode=cancer&multiple_populations=1&populations=27600_38000_82610_41000_84000_52800_72400&group_populations=1&years=2010_2010&group_years=1&sexes=1). Data from Singapore were not available on the IARC dataset; therefore, it was extracted from the Singaporean national registry of disease (https://www.nrdo.gov.sg/publications/cancer). After assessment of the study cohort patient-time distribution, data from 2010 (or 2008–2012 for Singapore) were used. Age-standardized incidence of pancreatic cancer was assessed through the SIR, defined as the ratio of the observed to the expected number of patients developing pancreatic cancer. Therefore, a SIR of 2 means that, compared with the expected number, twice as many observed cancers are found in a defined population followed for a specific time interval. The expected number of cases of pancreatic cancer was calculated using age-standardized and sex-specific data on the incidence of cancer (see additional documentation provided on GitHub). The 95% confidence interval (CI) of the SIR was estimated using the Wilson and Hilferty approximation of the exact Poisson distribution. The R code used to calculate the number of expected cases and the SIR is available on GitHub (https://github.com/TomPoll/SIR-pancreatic-cancer-BDIPMN.git).

Two-tailed *P* values $<$ .05 were considered statistically significant. The analysis was performed using SPSS v.25 (SPSS; IBM, Chicago, IL) and R version 4.2.2 (2022–10–31 ucrt) (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria) with R studio.

Results

Twelve centers from 8 countries and 3 continents provided data. Indications for surgery varied across centers and with time. In general, they were more aggressive in the late 1990s and early 2000s. Since 2006, Sendai criteria were adopted,[28] and since 2012 the Fukuoka guidelines[22] and their revision in 2017[11] were used.

Overall BD-IPMN Population

The study cohort consisted of 4356 presumed BD-IPMNs, of those, 474 (10.8%) were excluded having less than 12 months of surveillance or presenting a WF/HRS at diagnosis and 38 (0.9%) for having a pathological diagnosis different from an IPMN (Supplementary Table 1 and Supplementary Figure 1). A total of 3844 patients were included in the final analysis. The median age was 66 (IQR 15) years and 60.2% were female (Table 1). The median diameter at the time of first observation was 12 (IQR 9) mm, with a median surveillance time of 53 (IQR 53) months. The 25th and 75th percentiles of the surveillance times were 29 and 82 months, respectively. The patients' distribution, accrual period, and median follow-up for each center are described in Supplementary Table 2. No cyst had either WFs or HRS at the time of first observation, but during surveillance 775 (20.2%) developed WFs and 68 (1.8%) HRS. Considering the 775 patients who developed a WF during surveillance, 121 (15.6%) developed an additional or more WFs. The development of 2 or more WFs was associated with overall survival with a hazard ratio (HR) of 2.38 (95% CI, 1.47–3.86; $P < .001$) compared with the development of only 1 WF that had an HR of 1.43 (95% CI, 1.02–2.02; $P =$

.036). Overall survival of the entire cohort is shown in Supplementary Figure 2.

There were 14 (0.4%) patients with radiological evidence of malignant progression during surveillance but who did not undergo surgery according to their will or because they were unfit for surgery. Considering all patients (both who underwent surgery or surveillance), malignancy was detected in 40 (1.0%) patients (Supplementary Table 3).

Predictors of Dysplasia in Resected Patients

A total of 202 patients were resected during surveillance, but 38 (18.8%) were found to have a lesion different from an IPMN and were therefore excluded from any subsequent analysis. A total of 164 (4.3%) patients underwent surgical resection for a pathologically proven IPMN after a median of 52 (IQR 58) months from first observation, of whom 52 (31.8%) had either HGD (n = 26, 15.9%) or an invasive carcinoma (n = 26, 15.9%) (Table 1). Of these 164 patients, 64 (39%) had a Trivial BD-IPMN (not developing any WFs or HRS for the first 5 years of surveillance). Major morbidity (Clavien-Dindo ≥ III) and 30-day mortality were 17.1% (n = 28) and 2.4% (n = 4), respectively.

Table 1. General Characteristics of the Study Population

Characteristics	N = 3844 (%)
Sex (female), n (%)	2313 (60.2)
Age, *y*, median (IQR)	66 (15)
Surveillance, *mo*, median (IQR)	53 (53)
Surveillance >60 mo, n (%)	1847 (44.6)
Initial diameter, *mm*, median (IQR)	12 (9)
Small cyst (initial diameter ≤15 mm), n (%)	2537 (66)
WFs during surveillance, n (%)	775 (20.2)
HRS during surveillance, n (%)	68 (1.8)
Cysts not developing WFs/HRS for first 5 y, n (%)	1617 (42.0)
Resected, n (%)	164 (4.3)
Final pathological diagnosis in resected patients, n (%)	
LGD	112 (68.2)
HGD	26 (15.9)
Invasive cancer	26 (15.9)
Malignancy during surveillance in patients who did not undergo surgery, n (%)	14 (0.4)
TNM stage of IPMN with an associated invasive adenocarcinoma according to the AJCC 8th edition staging, n (%)[a]	
Ia	8 (33.3)
Ib	5 (20.9)
IIa	—
IIb	7 (29.1)
III	3 (12.5)
IV	1 (4.2)

AJCC, American Joint Committee on Cancer; LGD, low-grade dysplasia.
[a]Data available on 24 of 26 patients.

Supplementary Table 4 outlines postoperative outcomes according to the grade of dysplasia at final pathology. The development of HRS during surveillance was associated with the diagnosis of an invasive cancer at final pathological examination (26.9% vs 10.1%, $P = .042$), whereas the development of a WF was not ($P > .05$). No individual WF or HRS was associated the diagnosis of HGD (Table 2). However, an abrupt change in the MPD caliber ($P = .021$), a Ca19.9 ≥ 37 U/L ($P = .001$) and the presence of jaundice ($P = .021$) were associated with the diagnosis of an invasive cancer.

Presumed BD-IPMN Not Developing WFs/HRS for the First 5 Years of Surveillance

Of the overall cohort, 1617 (42.0%) did not develop any WFs or HRS for the first 5 years of surveillance forming the Trivial BD-IPMN group.[16] Trivial BD-IPMN had a median surveillance time of 85 (IQR 37) months. Of these, after the first 5 years, 235 (14.5%) developed a WF, and 30 (1.9%) developed an HRS. Of 64 (4.0%) patients who were resected after 5 or more years of surveillance, 24 (38.1%) had either HGD (n = 14; 22.2%) or an associated or concomitant invasive cancer (n = 10; 15.9%) at final pathological examination. Four patients (0.2%) developed radiologic signs of pancreatic malignancy but did not undergo surgical resection (Table 3). The development of a WF or of an HRS was associated with the development of pancreatic cancer ($P < .001$).

Of the Trivial BD-IPMN group, 762 (47.1%) patients had a cyst ≤15 mm in diameter after 5 years of surveillance. They had a median age of 63 years (IQR 14), an initial cyst size of 10 mm (IQR 5) and a median surveillance time of 83 months (IQR 36). The cumulative incidence of WFs/HRS after the first 5 years was 6.1%. Table 3 details the development of the individual WFs and HRS within overall Trivial BD-IPMN, Trivial BD-IPMN older than 75 years, and subgroup ≤15 mm older than 65 years. Considering all Trivial BD-IPMN, data on comorbidity reported as ACCI was present in 1591 (98%) patients at diagnosis. Of these patients, 834 (52%) had an ACCI ≤3, 479 (30%) between 4 and 6, and the remaining 278 (18%) had an ACCI ≥7. After the first 5 years of surveillance, the ACCI was available for 1577 (97%) patients. Of these patients, 636 (40%) had an ACCI ≤3, 570 (36%) between 4 and 6, and the remaining 371 (24%) had an ACCI ≥7.

Role of WF/HRS Development in Trivial BD-IPMN

The all-cause mortality for patients with a Trivial BD-IPMN was 4.9% (n = 79). In patients with a Trivial BD-IPMN, the development of any WFs and/or HRS after the first 5 years of surveillance was associated with worse overall survival (HR, 3.49; 95% CI, 1.94–6.27; $P < .001$). In details, the development of a WF after the first 5 years of surveillance had an HR of 2.79 (95% CI, 1.46–5.32; $P = .002$), and the development of an HRS had an HR of 5.52 (95% CI, 1.94–15.69; $P = .001$). Five patients (n = 5, 0.3%) with a Trivial BD-IPMN died of disease-specific causes (ie, related to the IPMN) during surveillance. Only 1 of these patients underwent resection after 66 months from diagnosis and was found to harbor an IPMN with an associated PDAC (Supplementary Figure 3). The patient developed a

Table 2. Analysis of Predictors of Dysplasia in Resected IPMN

Characteristics	LGD n = 112 (%)	HGD n = 26 (%)	Invasive n = 26 (%)	*P* value[a]	*P* value[b]	*P* value[c]
Age at the time of surgery, *y*, median (IQR)	66 (15)	70 (11)	68 (9)	.098	.432	.068
Sex (female), n (%)	59 (57.2)	14 (53.8)	14 (53.8)	.790	.826	.625
Family history of pancreatic cancer, n (%)	9 (8.0)	1 (3.8)	1 (3.8)	.760	.808	.502
Growth rate >5 mm/2 y, n (%)	34 (30.4)	5 (19.2)	12 (46.2)	.372	.115	.905
Pancreatitis, n (%)	8 (7.1)	3 (11.5)	0 (0)	.731	.288	1
Size >30 mm, n (%)	28 (25.0)	7 (26.9)	7 (26.9)	1.000	1.000	.944
Nonenhancing mural nodules, n (%)	1 (0.9)	0 (0)	3 (11.5)	.084	.206	.024
Enhancing mural nodules, n (%)	6 (5.4)	5 (19.2)	3 (11.5)	.051	.830	.066
Thick walls, n (%)	8 (7.1)	4 (15.4)	2 (7.7)	.338	1.000	.524
MPD 5–9 mm, n (%)	20 (17.9)	8 (30.8)	7 (26.9)	.229	.620	.163
MPD ≥10 mm, n (%)	4 (3.6)	1 (3.8)	4 (15.4)	1.000	.052	.225
Abrupt change in MPD caliber, n (%)	0 (0)	0 (0)	2 (7.7)	NA	.021	.186
Lymphadenopathy, n (%)	0 (0)	1 (4.2)	0 (0)	.440	1.000	.667
Ca19.9 ≥ 37 U/L, n (%)	12 (10.7)	3 (11.5)	10 (38.5)	1.000	.001	.033
Jaundice, n (%)	0 (0)	0 (0)	2 (7.7)	NA	.021	.186

LGD, low-grade dysplasia; NA, not available.
[a]LGD vs HGD.
[b]LGD and HGD vs invasive.
[c]LGD vs HGD and invasive.

recurrence and died after 13 months of postoperative follow-up. The remaining 4 patients developed a pancreatic malignancy diagnosed radiologically or with endoscopic ultrasonography–fine needle aspiration.

SIR of Pancreatic Cancer Development

The crude rates of pancreatic cancer by sex, age, and country of origin are reported in Supplementary Table 5. The number of expected cases (number of expected cases of pancreatic cancer in this study cohort) was calculated using the R script that can be accessed through the GitHub link in the method section. The SIR of the overall cohort was 4.65 (95% CI, 3.32–6.33). A reduction of the SIR was observed for patient with a Trivial BD-IPMN with increasing age, from 7.02 (95% CI 2.26–16.38) in patients younger than 65 years of age to 1.12 (95% CI, 0.23–3.39) for patients 75 years or older, reflecting a higher incidence of pancreatic cancer in the older general population (Table 4). An inverse relationship was observed with size, where lesions smaller than 15 mm in diameter had an SIR of 0.93 (95% CI, 0.10–3.36) and lesions larger than 30 mm in diameter had an SIR of 10.29 (95% CI, 4.12–21.21). Patients older than 65 years with a Trivial BD-IPMN smaller than 15 mm in diameter had an SIR of 0.95 (0.11–3.42) (Table 4).

Discussion

The results of the present analysis suggest that surveillance of presumed BD-IPMN can be safely discontinued in selected patients once their risk of malignancy is no greater than the age-matched general population. Cyst stability for at least 5 years, cyst size at the end of such follow-up, and patient age are critical components (Figure 1).

The observation that small size is a crucial factor in identifying presumed BD-IPMN at minimal risk for malignant progression is not novel. Different groups worldwide have already published series showing that cysts remaining below thresholds of either 15 or 20 mm very seldom evolve into malignancy.[15,27] Furthermore, previous evidence already showed that cyst size at the time of surgery is not sufficient to identify a subgroup of BD-IPMNs at low risk of degeneration.[29–31] Indeed, Oyama et al[29] found that even in small cysts (<15 mm) the risk of evolving into malignancy was higher compared with the general population (SIR of pancreatic carcinoma 6.7; 95% CI, 3.9–9.5). Thus, both stability for at least 5 years and final cyst size were used in the present analysis to identify a population whose risk of developing pancreatic cancer is the same as in an age-matched general population.

A further issue that has been raised relates to the risk of pancreatic cancer developing in the entire pancreas, not simply arising from a recognized cyst.[16,32,33] The present analysis found that the incidence of pancreatic cancer in patients with stable cysts for at least 5 years and who were now at least 75 years old was not significantly higher than that of the general population. As previously suggested, the present results support the view that not all BD-IPMNs will

Table 3. Rate of WFs and HRS Development After 5 Years of Stability, n (%)

Characteristics	Trivial n = 1617 (%)	Trivial over 75 y/o n = 469 (%)	Subgroup ≤15 mm over 65 y/o n = 486 (%)
Jaundice	5 (0.3)	2 (0.4)	2 (0.4)
MPD ≥10 mm	12 (0.7)	3 (0.6)	2 (0.4)
Enhancing mural nodules	19 (1.2)	5 (1.1)	2 (0.4)
Pancreatitis	17 (1.1)	1 (0.6)	5 (1.0)
Cyst size ≥ 30 mm	116 (7.2)	37 (7.9)	1 (0.2)
Nonenhancing mural nodule	27 (1.7)	6 (1.3)	4 (0.8)
Thickened/Enhancing cyst walls	25 (1.5)	9 (1.9)	2 (0.4)
MPD 5–9 mm	67 (4.1)	21 (4.5)	14 (2.9)
Abrupt change in the caliber of the MPD	4 (0.2)	3 (0.6)	1 (0.2)
Lymphadenopathy	4 (0.2)	1 (0.2)	3 (0.6)
Ca19.9 ≥37 U/L	69 (4.3)	22 (4.7)	17 (3.5)
Growth rate ≥ 5 mm/2 y	73 (4.5)	28 (6.9)	0 (0)
WFs during surveillance	235 (14.5)	88 (18.8)	33 (6.8)
HRS during surveillance	30 (1.9)	9 (1.9)	3 (0.6)
Final pathological diagnosis in resected patients			
LGD	40 (2.5)	8 (1.7)	7 (1.4)
HGD	14 (0.9)	3 (0.6)	2 (0.4)
Invasive cancer	10 (0.6)	2 (0.4)	2 (0.4)
Malignancy during surveillance	4 (0.2)	1 (0.2)	0

LGD, low-grade dysplasia; y/o, years old.

eventually progress to HGD or invasive cancer through an adenoma to carcinoma sequence within the patient's lifetime.[34,35] Once BD-IPMNs remain stable for at least 5 years without WFs or HRS in individuals older than 75 years, it is justified to stop surveillance and reassure the patient about the likely harmless nature of such cysts. Notably, the SIR of pancreatic ductal adenocarcinoma for chronic pancreatitis has been reported to be 22.61 (95% CI, 14.42–32.720),

Table 4. SIR of Different BD-IPMN Subgroups

BD-IPMN subgroup	Patients (n)	Person-years	Observed (n)	Crude rate (per 100,000)	Expected (n)	SIR (95% CI)
All patients	3844	33251.76	40	120.29	8.61	4.65 (3.32–6.33)
Non-trivial	2227	10626.36	27	254.08	2.93	9.23 (6.08–13.42)
Trivial	1617	22625.40	13	57.45	5.68	2.29 (1.22–3.91)
Trivial ≤15 mm	678	8765.40	2	22.81	2.15	0.93 (0.10–3.36)
Trivial 16–29 mm	791	11277.80	4	35.46	2.81	1.42 (0.38–3.64)
Cysts >30 mm with no development of additional WFs/HRS for at least 5 y	148	2441.14	7	286.75	0.68	10.29 (4.12–21.21)
Trivial <65 y	523	7775.86	5	64.30	0.71	7.02 (2.26–16.38)
Trivial 65–74	619	8826.22	5	56.64	2.30	2.17 (0.70–5.07)
Trivial ≥75 y	475	6023.32	3	49.80	2.67	1.12 (0.23–3.39)
Trivial ≥65 y and cyst ≤15 mm	486	6265.9	2	31.91	2.11	0.95 (0.11–3.42)

NOTE. Size and age to identify the different subgroups were measured after the first 5 years of surveillance.

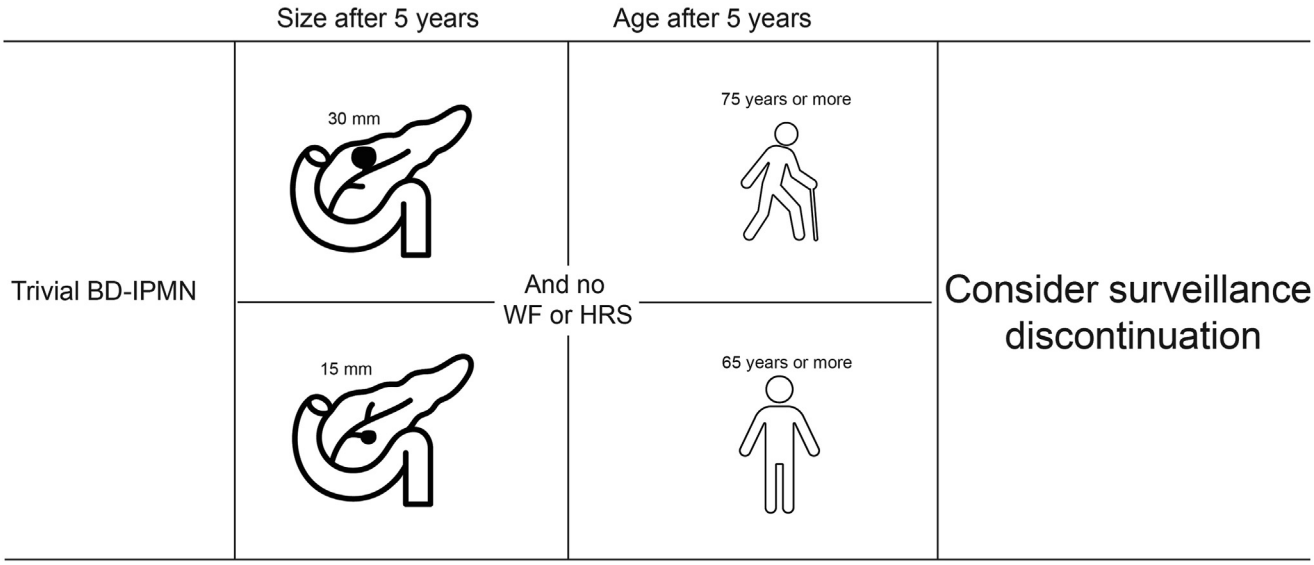

Figure 1. Summary of the recommendations on surveillance discontinuation derived from the present analysis according to clusters of individuals.

approximately 20 times higher that of Trivial BD-IPMN in those older than 75.[36] Furthermore, after the first 5 years of surveillance, 24% of patients with a Trivial BD-IPMN had an ACCI ≥7. One-year survival for patients with an ACCI ≥5 was 71.6%, as reported on more than 6 million patients discharged from a French hospital in 2010.[21] Therefore, especially in patients with multiple comorbidities, the presence of a Trivial BD-IPMN in those older than 75 might not significantly affect the life expectancy. Such data can be made evident to patients as they deliberate the best path forward for themselves in conjunction with their doctor's advisement.

Presumed BD-IPMNs ≤15 mm are of particular interest. They are common lesions representing more than two-thirds of the current study cohort. This subset of patients had no increased risk of developing pancreatic cancer compared with the general population in individuals older than 65 years. After 5 years of stability, the role of active surveillance must at least be questioned. Further validation is urgently needed to confirm these results, as the avoidance of continuing surveillance in this large cohort might significantly relieve the pressure on resource utilization by health care systems.[37] However, given that accurate diagnosis is particularly difficult in small cysts,[38,39] the utmost caution must be exercised before indicating follow-up discontinuation in this group.

Several limitations of the present analysis merit consideration. There are inevitable biases associated with the observational and retrospective nature of the study. Despite the prospective nature of the databases maintained at the high-volume institutions involved, the retrospective assessment of data collected over 30 years carries a certain amount of variability in features definition and patient management. Large patient numbers and long follow-up partly offset these deficiencies. It is also acknowledged that the current study was limited to high-volume centers. The extent to which these data are generalizable cannot be determined, but there seems to be logic in referring patients who are being followed up at low-volume centers to centers of expertise before suggesting follow-up discontinuation. Patients' data were extracted from each center's institutional database. In most cases, they have already been included in prior publication. No patients were enrolled in concomitant randomized clinical trials.

Presumed BD-IPMNs that remain stable at <30 mm in diameter without developing WFs or HRS for at least 5 years in patients older than 75 do not harbor a risk of malignancy that is significantly higher than age-matched controls. Discontinuation of follow-up appears to be a feasible option in these patients. The same applies to patients with cysts remaining ≤15 mm for the first 5 years of surveillance in patients older than 65 years, but they require additional caution given the high risk of incorrect diagnosis and a longer life expectancy. Such strategies could avoid needless and expensive examinations in individuals who are not at higher risk of developing pancreatic cancer than the general population. However, the indication to stop surveillance should be carefully balanced with a patient's will and expectations. Indeed, although indefinite surveillance can result in adverse physical and psychological effects on the patient's sense of well-being, the rationale behind surveillance discontinuation should be well understood by the patient.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Gastroenterology* at www.gastrojournal.org, and at https://doi.org/10.1053/j.gastro.2023.06.022.

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Received November 4, 2022. Accepted June 14, 2023.

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Acknowledgments
The authors acknowledge Patrick Maisonneuve for his supervision on the statistical analysis.

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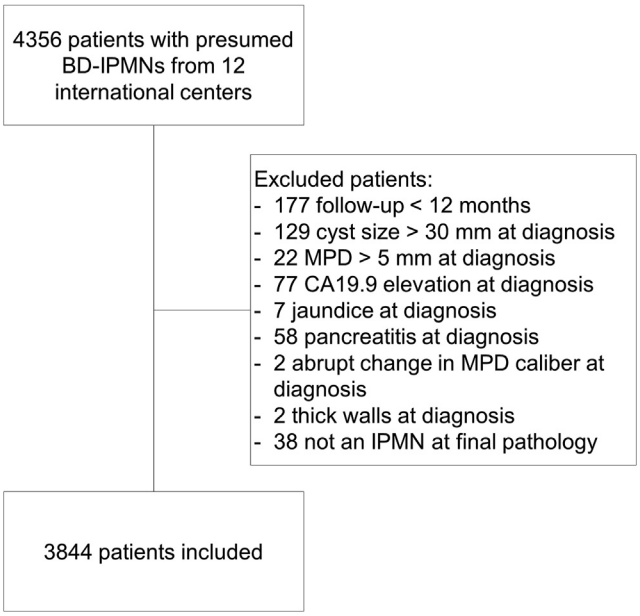
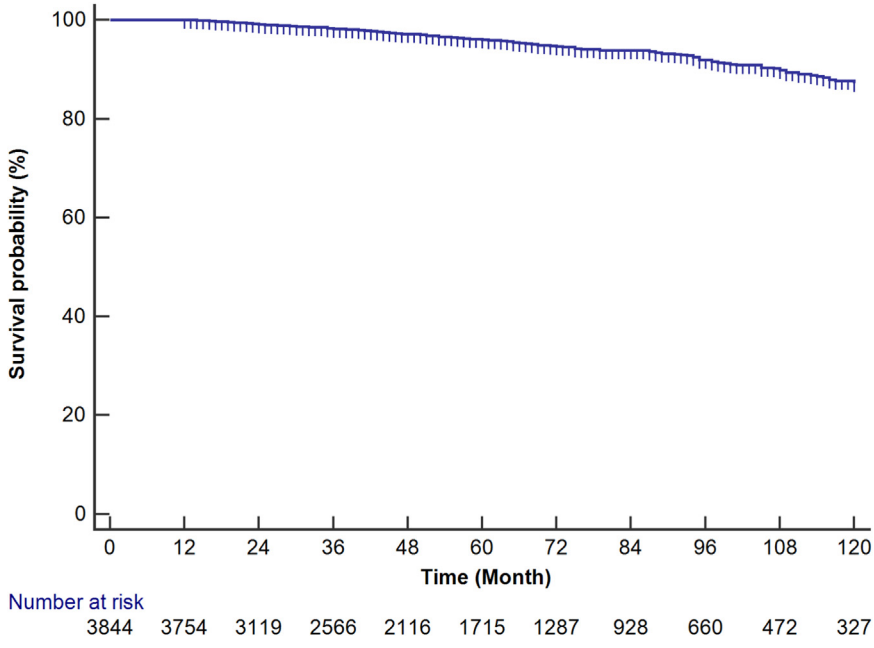
Conflicts of interest
The authors disclose no conflicts.

Funding
The Department of General and Pancreatic Surgery at the University of Verona received funding from the Italian Ministry of Health (Grant FIMP-CUP J38D19000690001).

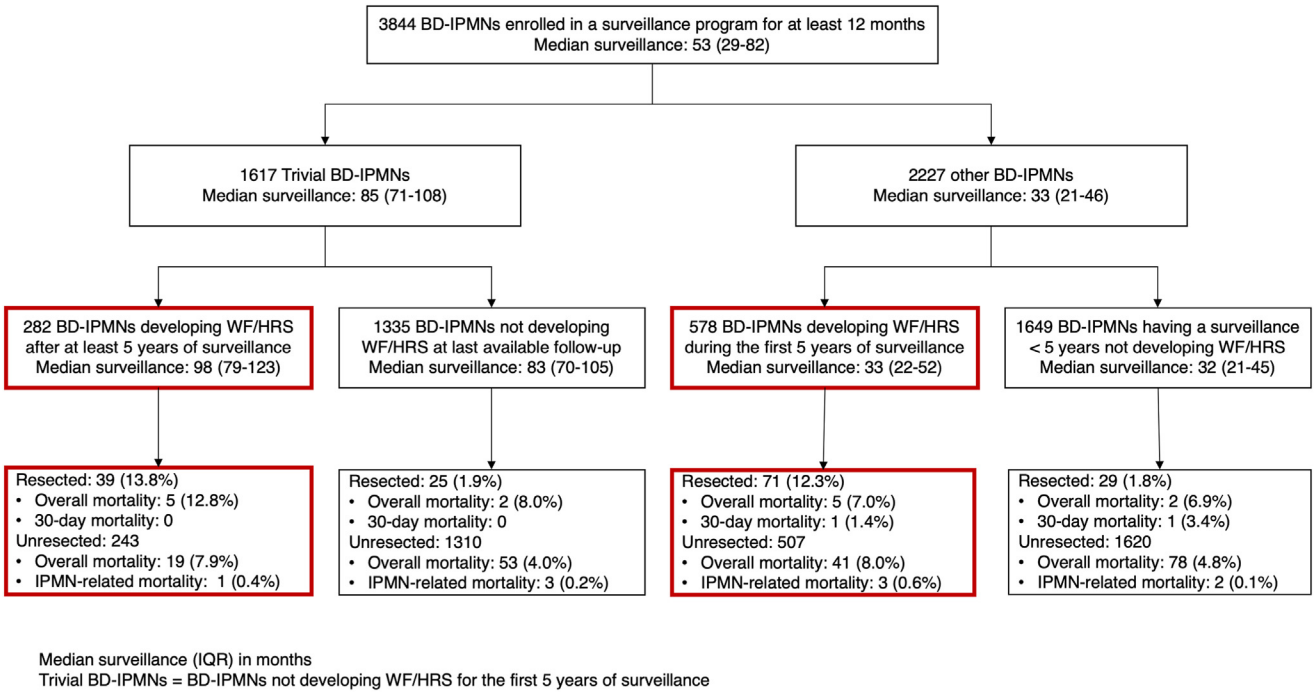
Data Availability
Study data not presented within this article are available on request.



Supplementary Figure 1. Flow diagram detailing the exclusion of the 512 patients from the original dataset including 4356 presumed BD-IPMN.



Supplementary Figure 2. Kaplan-Meyer curve of the overall survival for the entire study cohort of 3844 patients.



Supplementary Figure 3. Flow diagram of all-cause and disease-specific mortality for patients developing or not WF/HRS within or after 5 years of surveillance and according to resection status.

Supplementary Table 1. Excluded Patients' Distribution by Country

Country	Patients N = 4356	Excluded patients n = 512 (%)
Italy	1937	286 (14.8)
United States	588	54 (9.1)
Singapore	847	80 (9.4)
Korea	503	49 (9.7)
Spain	176	21 (11.9)
The Netherlands	113	5 (4.4)
Germany	98	3 (3.0)
United Kingdom	94	14 (14.9)

Supplementary Table 2. Patients' Distribution by Center

Center	Country	Accrual period	Patients, n	Women, n (%)	Age median (IQR), *y*	Surgery, n (%)	Median surveillance (IQR), *mo*
Department of General and Pancreatic Surgery, The Pancreas Institute, Verona University Hospital	Italy	1993–2020	1054	730 (69.3)	64 (56–71)	45 (4.3)	44 (24–78)
Department of Hepatopancreatobiliary and Transplant Surgery, Singapore General Hospital and National Cancer Centre Singapore	Singapore	2010–2020	767	455 (59.3)	67 (60–75)	1 (0.1)	42 (26–65)
Department of Surgery, Harvard Medical School, Massachusetts General Hospital, Boston, MA	USA	1988–2020	500	200 (40.0)	67 (58–74)	58 (11.6)	77 (44–111)
Department of Surgery and Cancer Research Institute, Seoul National University Hospital	Korea	2006–2020	454	219 (48.2)	63 (56–69)	27 (5.9)	76 (65–89)
Pancreato-Biliary Endoscopy and Endoscopic Ultrasound, San Raffaele Scientific Institute, Milan	Italy	2003–2020	325	225 (69.2)	66 (58–72)	10 (3.1)	48 (29–83)
Division of Pancreatic Surgery, San Raffaele Scientific Institute, Milan	Italy	2001–2020	272	179 (65.8)	65 (54–71)	9 (3.3)	39 (22–67)
Endoscopy and Pancreatic Unit, University Hospital of Santiago de Compostela	Spain	2008–2020	155	107 (69.0)	66 (58–72)	4 (2.6)	36 (22–63)
Department of Surgery, Amsterdam UMC	The Netherlands	2006–2020	108	68 (63.0)	65 (59–70)	3 (2.8)	47 (30–65)
Royal Liverpool University Hospital, Liverpool	United Kingdom	2012–2020	80	50 (62.5)	67 (60–75)	0	32 (21–49)
Department of Surgery, Klinikum rechts der Isar School of Medicine, Technical University Munich, Munich, Germany	Germany	1999–2020	67	41 (61.2)	70 (65–74)	0	60 (38–92)
Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA	USA	2006–2020	34	21 (61.8)	63 (54–67)	5 (14.7)	92 (55–124)
Department of General, Visceral and Transplantation Surgery, Heidelberg University Hospital	Germany	2009–2020	28	18 (64.3)	68 (58–77)	2 (7.1)	63 (48–79)
Total	8 countries	1988–2020	3844	2313 (60.2)	66 (58–72)	164 (4.3)	53 (29–82)

Supplementary Table 3. Malignancy Rate in the Overall Cohort

	Surgery, n = 164 (%)	No surgery, n = 3680 (%)
Malignancy	26 (15.8)	14 (0.3) - 9 histologically proven - 5 liver metastases with pancreatic mass

Supplementary Table 4. Postoperative Morbidity and Mortality of Resected Patients According to the Grade of Dysplasia Found at Final Pathology

	Overall N = 164 (%)	LGD n = 112 (%)	HGD n = 26 (%)	Invasive cancer n = 26 (%)
POPF	47 (28.7)	32 (28.6)	8 (30.7)	7 (26.9)
PPH	8 (4.9)	4 (3.6)	2 (7.7)	2 (7.7)
DGE	11 (6.7)	8 (7.1)	3 (11.5)	—
Overall morbidity	82 (50.0)	57 (50.9)	16 (61.5)	9 (34.6)
Major morbidity (CD ≥III)	28 (17.1)	17 (15.2)	7 (26.9)	4 (15.3)
30-d mortality	4 (2.4)	1 (0.9)	2 (7.7)	1 (3.8)

CD, Clavien-Dindo; DGE, delayed gastric emptying; LGD, low-grade dysplasia; POPF, postoperative pancreatic fistula; PPH, postpancreatectomy hemorrhage.

Supplementary Table 5. Crude Rate (per 100,000 People) of Pancreatic Cancer

	List A countries (data from 2010)		Singapore (data from 2008–2012)	
Age (*y*)	Male	Female	Male	Female
0–4	0.02	0.02	0	0
5–9	0.02	0	0	0
10–14	0.04	0.02	0	0
15–19	0.02	0.09	0.2	0.2
20–24	0.12	0.17	0	0
25–29	0.19	0.27	0.3	0.1
30–34	0.43	0.38	0.3	0.3
35–39	1	0.83	1.6	0.6
40–44	2.7	1.8	3	2
45–49	5.7	3.8	3.1	4.4
50–54	11.5	7.5	7.9	4.7
55–59	20.1	13.2	17.7	10.4
60–64	33.3	22.5	21	16.4
65–69	48.1	35.7	45.1	26.6
70–74	62	52.4	50.8	38.2
75–79	82.4	67.4	61	63.6
80–85	98.2	79.4	72.5	52.5
85+	106.9	93.2	71.8	83.7

NOTE. List A countries: Germany, Italy, Republic of Korea, The Netherlands, Spain, United Kingdom, England and Wales, and the United States.