

SHORT COMMUNICATION

Surveillance of Patients with IPMN

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INTRODUCTION

Modern medicine should be evidence-based. Clinical applicability of evidence that lacks appropriate context however, is difficult. The data for Intraductal Papillary Mucinous Neoplasia, or IPMN, is a good example of this. Good outcomes data exists, but there is paucity of consensus on how best it should be used and applied. Hence, despite high quality data, challenges remain in routine clinical practice for the surveillance and optimal management of IPMN [1].

IPMN History

In 1982, Ohhashi *et al.* described four cases of intraductal pancreatic neoplasms that accumulated large amounts of mucin within cystic dilated ducts. They termed this new entity "mucin-secreting pancreatic cancer" [2]. Prior to this, case reports had described instances of papillomatosis of the pancreatic duct [3, 4, 5, 6]. Within 6 years of the original paper by Ohhashi *et al.* 140 patients with mucin-producing pancreatic ductal neoplasms had been reported in Japan alone [7]. A review of pathology reports which included all pancreatic cancers diagnosed between 1960 and 1980 at the Mayo Clinic showed that IPMN as it is known today existed well before the original report by Ohhashi *et al.* only under other names [8].

Prevalence

Two ground-breaking studies provided us with an initial insight into the prevalence of IPMNs. In a study published in 2008 looking at contrast-enhanced CT scans of the abdomen from 2,832 consecutive examinations of patients without a history of pancreatic lesions or predisposing factors for pancreatic disease. A total of 73 patients had pancreatic cysts, representing a prevalence of 2.6 per 100 patients (95% confidence interval 2.0 to 3.2). Cysts

ranged in size from 2 to 38 mm (mean 9 mm) and were solitary in 85 percent of cases. Analysis of demographic information found a strong correlation between pancreatic cysts and patient age, with no cysts identified in patients below age 40. Individuals between 80 and 89 years of age had a prevalence of these cysts of 8.7 per 100 (95% confidence interval 4.6 to 12.9). After controlling for age, cysts were more common in Asians, with an odds ratio of 3.57 (95% confidence interval 1.05 to 12.13). Thus, in this outpatient population without known pancreatic disease, the prevalence of unsuspected pancreatic cysts identified on 16-MDCT was 2.6 percent [9]. With improvements in imaging techniques the rate of detection of even smaller pancreatic is likely to increase.

In another study, published in 2010, data from 2803 individuals who underwent abdominal MRI (mean age, 51 ± 11 years) at an institute of preventive medical care were reviewed for the presence of pancreatic cysts. Pancreatic cysts were detected in 66 persons (2.4%; 95% confidence interval 1.9 to 3.0). Again, the prevalence correlated with increasing age. No correlation was found between abdominal complaints and the presence of pancreatic cysts. Only a minority of cysts were larger than 2 cm [10].

More recently, a prospective study of a general population published in 2017 found the prevalence of IPMN to be even higher than previously described. A total of 1077 participants (mean age 56 ± 13 years) of 2333 participants from the population-based Study of Health in Pomerania underwent magnetic resonance cholangiopancreatography (MRCP) (2008-2012). The MRCP images were analysed for pancreatic cysts with a diameter ≥ 2 mm. 676 out of 1077 subjects were followed for a 5-year period (2014-2016). On initial imaging, pancreatic cysts had a weighted prevalence of 49 percent – making it from a semantical point of view almost normal to have a pancreatic cyst – with an average number of 3.9 cysts per subject in the subgroup harbouring cysts. Cyst size ranged from 2 to 29 mm. Prevalence, number, and maximum size increased significantly with age. The weighted incidence for newly diagnosed pancreatic cysts in the 5-year follow-up period was 12.9 percent none of the participants undergoing the MRCP surveillance died of pancreatic disease within the follow-up period. The authors concluded that only about 6 percent of cysts and 2.5 percent

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of the study group initially presented with cysts of more than 1 cm and thus might be clinically meaningful [11].

Although the actual prevalence of pancreatic cysts is difficult to accurately ascertain it appears that the number is large. As such there are inherent difficulties from a health care stand point for outlining guidelines on how these patients should be monitored and treated. The majority of these small pancreatic cysts are IPMNs [12, 13], which frequently are multifocal and can involve the entire pancreas [14, 15, 16, 17]. This multi-centric disease involving multiple, often non-contiguous, IPMNs of the pancreatic gland, presents a certain "surgical" dilemma, especially in the follow-up of patients with previously resected IPMNs [18].

Surveillance of Patients Who Have Not Undergone Surgery for IPMN

The natural course of IPMN – and especially the risk factors for progression to malignancy – have been extensively studied. The initial feature that needs to be ascertained as part of the decision making is the type of duct involvement in IPMN: branch-duct, mixed-duct and main duct.

Main Duct or Mixed IPMN

Imaging by magnetic resonance imaging (MRI) with MR Cholangiopancreatography (MRCP) and computed tomography (CT) scanning can almost always differentiate between branch-duct, main-duct IPMN and mixed IPMN. For the definition of MD-IPMN, a duct dilatation between 5-10 mm is required when following the current guidelines. However, more recent publications advocate for an even lower cut-off of ≥ 5 mm due to the risk of malignant progression [19].

Main-duct (MD) and mixed-type IPMNs harbour a high risk of malignant transformation. It is conceivable that most IPMNs with involvement of the main duct tend to progress to invasive carcinoma over time [20]. In a review of six "cornerstone papers" from 2008, malignancy (invasive or carcinoma in situ) was found in about 70 percent of resected main-duct IPMNs [21]. Another recent report from 2017 of 103 patients who had undergone resection for an MD or mixed IPMN found malignant disease in 62 percent [22]. According to a review of recent literature the risk of progression to malignant disease is significant, with rates between 36-87% in resected cases [22]. However, it must be underlined that while resection has been recommended for main-duct IPMNs for a long time, no population-based long term follow-up studies of main-duct IPMN exist. The majority of available data are from resected patients, and hence included very selected series

Based on a consensus symposium held during the meeting of the International Association of Pancreatology, in 2016, the working group revised earlier guidelines regarding prediction of invasive carcinoma and high-grade dysplasia, surveillance, and postoperative follow-up of IPMN. As the working group did not recognize the need for major revisions of the guidelines, only minor revisions were made. Resection remained the recommendation for patients with main or mixed duct IPMN [23].

Branch-Duct IPMN

Regarding symptomatic patients with branch duct intraductal papillary mucinous neoplasms (BD-IPMN) as well as patients with so-called high-risk stigmata resection is usually recommended. Asymptomatic patients with so-called worrisome features can either choose to undergo surveillance or surgical resection, with age and other comorbidities taken into consideration in the decision making process [24].

However, the majority of BD-IPMNs are frequently found incidentally in asymptomatic patients. For these patients – without high-risk stigmata and worrisome features and no symptoms – surveillance is recommended. The enormous importance of surveillance is underlined by [24]:

- high prevalence of BD-IPMN
- limitations in differential diagnostic possibilities
- an overestimation of the risk of malignancy due to an overrepresentation of symptomatic and suspected BD-IPMN in resected cohorts
- an overestimated role of BD-IPMN as precursor lesions for pancreatic carcinoma
- evidence of the safety of follow-up surveillance, underline

Meta-Analyses

A systematic search of the MEDLINE and Embase databases through November 30, 2016 for studies reporting the cumulative incidence of pancreatic cancer in patients with unresected IPMNs or studies that provided data in sufficient detail to calculate cumulative incidence values. They were categorized as studies on low-risk IPMNs (lesions without main pancreatic duct involvement or mural nodules) or non-low-risk IPMNs. Among 1514 articles included, 10 studies of low-risk IPMNs (n=2411) and 9 studies of non-low-risk IPMNs (n=825) were identified. In studies of low-risk IPMNs, the meta-analytic cumulative incidence values for pancreatic cancer were 0.02 percent at 1 year (95% confidence interval 0.0 to 0.23%), 1.40 percent at 3 years (0.58 to 2.48%), 3.12 percent at 5 years (1.12 to 5.90%), and 7.77 percent at 10 years (4.09 to 12.39%). These values were significantly higher in studies of non-low-risk IPMNs; cumulative incidence values for pancreatic cancer were 1.95 percent at 1 year (0.0 to 5.99%), 5.69 percent at 3 years (1.10 to 12.77%), 9.77 percent at 5 years (3.04 to 19.27%), and 24.68 percent at 10 years (14.87 to 35.90%). The pooled cumulative incidence increased linearly as the follow-up duration increased [25].

It another meta-analysis, published in 2017, systematically searched MEDLINE for studies with a cohort of patients with presumed branch-duct IPMN who initially were managed non-surgically. Twenty-four studies with 3440 patients and 13,097 patient-years of follow-up were included. Rates of morphologic progression, surgery,

malignancy, and death were 3.79, 2.50, 0.98, and 0.43 percent per patient-year, respectively. Thus, the risk of malignancy calculated in this study was low and in line with recent systematic reviews [26].

These data give good indication for the actual risk for the individual patient, and it is unlikely that further research will change these findings significantly.

Can Surveillance Ever Be Stopped?

The management of patients with pancreatic cysts, especially presumed branch duct intraductal papillary mucinous neoplasms (BD-IPMNs), remains a challenge. BD-IPMNs carry a very low risk of malignancy and occur in predominantly older individuals who often die from causes other than their pancreatic disease. The specific decision to stop surveillance of presumed low risk BD-IPMNs (those without either worrisome features or high risk stigmata) is controversial, and needs to balance the real risk of harboring a or developing a malignancy as well as IPMN-related mortality, with the patient's life expectancy, quality of life expectations, and mortality from non-pancreatic-related causes. With improved life expectancy, improved survival from non-pancreatic malignancies, rising health costs, and growing detection of ever smaller presumed BD-IPMNs, this issue is becoming ever more critical [21].

Current Recommendations

The optimal management of BD-IPMN is still the subject of discussions. Numerous studies have shown that an individualized therapeutic strategy with a follow-up observation of most BD-IPMNs is feasible and safe, considering age, comorbidities and patient preference. An accurate evaluation of BD-IPMN with a detailed history and physical examination, high-resolution imaging techniques and endoscopic ultrasound is, however, necessary [15].

The 2012 International Consensus Guidelines of Fukuoka have been widely accepted for the management of IPMN. They recommend surgical resection for branch duct IPMN with "high risk stigmata", while branch duct IPMN with "worrisome features" should undergo observation without immediate resection. Consequently, patients with asymptomatic branch duct IPMN and a presumed low malignant potential mostly undergo primary surveillance to avoid surgery-related morbidity and mortality following pancreatic resection. However, over time, surgical resection might also be indicated for patients with branch duct IPMN with "worrisome features" [17].

Conflict of Interest

The authors declare that they have no conflicts of interest.

References

1. Ohhashi K, Murakami Y, Takekoshi T. Four cases of mucin producing cancer of the pancreas on specific findings of the papilla of Vater (Japanese). *Prog Dig Endosc* 1982; 20:348-51.

2. Haban G. Papillomatose und Carcinom des Gangsystems der Bauchspeicheldrüse. *Virchows Arch* 1936; 297:207-20 (in German).
3. Caroli J, Hadchouel P, Mercadier M. Papillome benin du canal de Wirsung. *Med Chir Dig* 1975; 4:163-6.
4. Gourevitch A, Whitfield AGW. Total pancreatectomy. *Br J Surg* 1952; 40:104-7. [PMID: 12987638]
5. Hendry WG. Radical duodenopancreatectomy for papilloma of pancreatic duct. *Br Med J* 1952; 2:815-6. [PMID: 12978340]
6. Obara T, Saitoh Y, Maguchi H, Ura H, Yokota K, Okamura K, et al. Papillary adenoma of the pancreas with excessive mucin secretion. *Pancreas* 1992; 7:114-7. [PMID: 1557339]
7. Tollefson MK, Libsch KD, Sarr MG, Chari ST, DiMagno EP, Urrutia R, et al. Intraductal papillary mucinous neoplasm: did it exist prior to 1980? *Pancreas* 2003; 26:e55-8. [PMID: 12657965]
8. Laffan TA, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, et al. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008; 191:802-7. [PMID: 18716113]
9. de Jong K, Nio CY, Hermans JJ, Dijkgraaf MG, Gouma DJ, van Eijck CH, et al. High prevalence of pancreatic cysts detected by screening magnetic resonance imaging examinations. *Clin Gastroenterol Hepatol* 2010; 8:806-11. [PMID: 20621679]
10. Kromrey ML, Bülow R, Hübner J, Paperlein C, Lerch MM, Ittermann T, et al. Prospective study on the incidence, prevalence and 5-year pancreatic-related mortality of pancreatic cysts in a population-based study. *Gut* 2018; 67:138-145. [PMID: 28877981]
11. Scheiman JM. Pancreatic cysts – Part 1: using the American Gastroenterological Association guidelines for the management of pancreatic cysts-a practical approach. *Pancreas* 2017; 46:742-4. [PMID: 28609360]
12. Farrell JJ. Pancreatic cysts and guidelines. *Dig Dis Sci* 2017; 62:1827-39. [PMID: 28528374]
13. Han Y, Lee H, Kang JS, Kim JR, Kim HS, Lee JM, et al. Progression of pancreatic branch duct intraductal papillary mucinous neoplasm associates with cyst size. *Gastroenterology* 2018; 154:576-584. [PMID: 29074452]
14. Lensing RJ, Bipat S. Incidences of pancreatic malignancy and mortality in patients with untreated branch-duct intraductal papillary mucinous neoplasms undergoing surveillance: a systematic review. *Pancreas* 2017; 46: 1098-110. [PMID: 28902778]
15. Brunner M, Weber GF, Kersting S, Grützmann R. Branch duct intraductal papillary mucinous neoplasm – contra resection. *Chirurg* 2017; 88:918-26 (in German). [PMID: 28871376]
16. Ceyhan GO, Scheufele F, Friess H. Resection of main duct and mixed type IPMN ≥ 5 mm. *Chirurg* 2017; 88:913-7 (in German). [PMID: 28842734]
17. Kaiser J, Büchler MW, Hackert T. Branch duct intraductal papillary mucinous neoplasm – surgical approach. *Chirurg* 2017; 88:927-33 (in German). [PMID: 28801818]
18. Imbe K, Nagata N, Hisada Y, Takasaki Y, Sekine K, Mishima S, et al. Validation of the American Gastroenterological Association guidelines on management of intraductal papillary mucinous neoplasms: more than 5 years of follow-up. *Eur Radiol* 2018; 28:170-178. [PMID: 28770404]
19. Pergolini I, Sahora K, Ferrone CR, Morales-Oyarvide V, Wolpin BM, Mucci LA, et al. Long-term risk of pancreatic malignancy in patients with branch duct intraductal papillary mucinous neoplasm in a referral center. *Gastroenterology* 2017; 153:1284-94. [PMID: 28739282]
20. Tanaka M, Fernández-Del Castillo C, Kamisawa T, Jang JY, Levy P, Ohtsuka T, et al. Revisions of international consensus Fukuoka guidelines for the management of IPMN of the pancreas. *Pancreatol* 2017; 17: 738-53. [PMID: 28735806]
21. Farrell JJ. Editorial: stopping pancreatic cyst surveillance? *Am J Gastroenterol* 2017; 112:1162-4. [PMID: 28725064]
22. Crippa S, Pezzilli R, Bissolati M, Capurso G, Romano L, Brunori MP, et al. Active surveillance beyond 5 years is required for presumed branch-duct intraductal papillary mucinous neoplasms undergoing non-operative management. *Am J Gastroenterol* 2017; 112:1153-61. [PMID: 28244498]

23. Ooka K, Rustagi T, Evans A, Farrell JJ. Surveillance and outcomes of nonresected presumed branch-duct intraductal papillary mucinous neoplasms: a meta-analysis. *Pancreas* 2017; 46:927-35. [PMID: 28697134]

24. Blackham AU, Doepker MP, Centeno BA, Springett G, Pimiento JM, Malafa M, et al. Patterns of recurrence and long-term outcomes in patients who underwent pancreatectomy for intraductal papillary mucinous neoplasms with high grade dysplasia: implications for surveillance and future management guidelines. *HBP* 2017; 19:603-10. [PMID: 28495434]

25. Aronsson L, Andersson R, Ansari D. Intraductal papillary mucinous neoplasm of the pancreas - epidemiology, risk factors, diagnosis, and management. *Scand J Gastroenterol* 2017; 52:803-15. [PMID: 28446039]

26. Rong Y, Wang D, Xu C, Ji Y, Jin D, Wu W, et al. Prognostic value of histological subtype in intraductal papillary mucinous neoplasm of the pancreas: A retrospective analysis of outcome from one single center. *Medicine* 2017; 96:e6599. [PMID: 28403101]