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TOPIC HIGHLIGHT

Natural history of intraductal papillary mucinous neoplasia: How much do we really know?

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Abstract

Information on the natural history of intraductal papillary mucinous neoplasia (IPMN) is currently inadequate due to a lack of carefully orchestrated long-term follow-up on a large cohort of patients with asymptomatic disease. Based on the available data, one can draw the conclusions that main duct IPMN is commonly associated with malignancy and an aggressive operative stance should be taken with resection being offered to most patients who are suitable operative candidates. In contrast, the majority of branch type IPMN with a diameter of less than 3 cm can be safely followed with routine surveillance imaging provided they lack the high-risk covariates of age, symptomatology, nodularity or wall thickness.

Key words: Intraductal papillary mucinous neoplasia; Cystic pancreatic neoplasm; Pancreas

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Natural history is defined as the "study of the natural development of a disease over a period of time"[1]. While this task for intraductal papillary mucinous neoplasm (IPMN) of the pancreas may seem straightforward, the recent recognition of IPMN as a distinct pathological entity coupled with its histopathological complexity makes this assignment exceedingly difficult. The initial description of IPMN was published in 1982[2]. However, it was not until 1996 (further clarified in 2000) that the World Health Organization formally differentiated it from other mucin-producing cystic lesions of the pancreas through a uniform classification scheme[3,4]. With this consensus nomenclature came the realization that IPMN consists of a spectrum of neoplasms (subtypes include: gastric, intestinal, pancreatobiliary and oncocytic) which show both morphological and immunohistochemical variation[5]. It is currently unknown whether these four subtypes represent distinct pathological entities (with different biological potentials) or simply histological variations along a single progressive neoplastic lineage[6]. Confounding these distinctions is the ambiguity over the exact sequence of events and the precise time frame of histopathological lesion progression from noninvasive (adenoma, borderline tumor, carcinoma-in-situ) to invasive adenocarcinoma. Even with recent data supporting the concept of clonal progression in IPMN[7], evidence substantiating a stepwise and orderly evolution by way of the adenoma to dysplasia

to carcinoma sequence remains circumstantial at best[8-16]. In fact, while genetic evidence for the progression of pancreatic ductal adenocarcinoma is believed to be orderly and sequential (adenoma-carcinoma sequence), alternative theories of tumor development and progression do exist[17,18]. These differences may be explained by the recognition that not all IPMNs possess an equal potential for malignancy[19,20]. While there is broad consensus that the overall prognosis of patients with IPMN depends on the presence of invasive carcinoma, two distinct types of cancer (invasive ductal adenocarcinoma or invasive colloid carcinoma) associated with IPMN, each exhibit vastly different biological behaviors[6]. The five year survival rate in resected patients with IPMN was found to be significantly shorter ($P < 0.01$) in patients with invasive ductal adenocarcinoma (19%) than in patients with invasive colloid carcinoma (62%)[8]. These observations had been previously established by an independent group showing remarkably consistent findings of a five year survival rate of 12% for resected IPMN with invasive ductal adenocarcinoma *vs* a 57% five year survival for patients with colloid carcinoma[6,10]. These authors also found that colloid carcinoma was a favorable prognostic factor independent of patient age, tumor diameter or disease stage. Lastly, debate around the concepts of a local field defect versus disease multicentricity further clouds our understanding of the exact biology of these lesions[13,14,21-26].

As an epidemiological exercise, the ideal study to define natural history (prospective, longitudinal) would consist of a disease-free cohort undergoing continuous surveillance until they develop stage 1 disease (asymptomatic)[27]. In this idealized world, screening tests to detect disease have a sensitivity and specificity of 1.0. This cohort is then followed with periodic surveillance but without treatment until they develop stage 2 disease (symptomatic). Unfortunately, the majority of published literature on IPMN is either cohort or case-controlled studies that contain patients who have been treated (partial pancreatectomy). The overall level of evidence is poor[21]. It has been estimated, based on autopsy findings that up to 50% of all cadavers possess cystic pancreatic lesions[28]. This, coupled with the ubiquitous use of high resolution cross-sectional imaging, implies that identification of occult IPMN lesions seems likely to increase[29]. The paradox is that without properly constructed prospective observational trials at a time when the identification of IPMNs is becoming endemic, our understanding of its natural history is based solely on the extrapolation of indirect observations.

Given the limitations discussed above, a body of developing literature specifically devoted to IPMN was used as the foundation for this review. Based on these data, the natural history of IPMN lesions can be divided into two morphological subtypes: IPMN arising from the branch pancreatic ducts and IPMN arising from the main pancreatic duct. Main-duct IPMN involves and produces dilation of the duct of Wirsung. These lesions are associated with malignancy and invasive carcinoma in 43% to 70% of reported cases[21,30]. In contrast, branch-duct type IPMN lesions originate from side duct branches, do not involve the main pancreatic duct and are associated with invasive malignancy in only 15% to 25% of reported cases[13,14,31-36]. Despite the strong association between main duct IPMN and invasive adenocarcinoma, this connection does not prove causality or support any specific theory of carcinogenesis. Nevertheless, because of this strong association with malignancy, clinical exigency has resulted in consensus groups recommending operative excision of all main duct IPMNs[21,30]. These recommendations were broadened to include all "good-risk" patients with mixed-type IPMN (hybrid lesions involving both branch and main pancreatic duct)[30]. On a purely scientific note, the consequence of these proposals for aggressive resection will undoubtedly alter the landscape such that the "true" natural history of main duct IPMN may remain unknown.

In contrast to main duct IPMN, branch duct variants have significantly more published literature from which to make indirect inferences regarding their natural history. Approximately 90% of all lesions presumed to be IPMN (lacking definitive pathological analysis) which have undergone a period of surveillance without treatment have been branch duct variants[21]. Due to this wealth of surveillance data, a greater number of covariates have been identified in branch duct type IPMN that are associated with malignancy when compared to main duct IPMN. Tumor factors such as the size of a branch duct lesion (> 3 cm in cross-sectional diameter)[8,30,32,37-39], radiological characteristics (wall thickness or mural nodules)[37,40-43] or the presence of symptoms (jaundice, steatorrhea, new onset diabetes)[15,40,44] have all correlated with a higher incidence of associated invasive carcinoma. While lesions greater than 3 cm and the presence of mural nodules are associated with concurrent malignancy rates in resected patients of up to 82%, there is continued debate as to the utility of this measure to reliably predict tumor behavior[40,42,45]. In those series where invasive malignancy in branch duct IPMNs were not correlated with size, all had a high percentage of symptomatic patients, a known confounding variable, in their cohort[40,42,45]. Alternatively, the invasive malignancies identified in these patients might be synchronous malignancy at a site distant from the IPMN[46]. Broadly, it appears that the incidence of malignancy increases proportionately to the number of patients in the series with symptoms[8,13,38,39]. In point of fact, there are no known biological systems with sharp size "cutoffs". In this context, 3 cm likely constitutes an arbitrary threshold within a large continuum. Given these data, the natural history of branch duct IPMN is more aggressive in patients who present with symptoms, display mural nodules and/or solid components on imaging or possess lesions greater than 3 cm in cross-sectional diameter.

Patient age at the time of diagnosis represents another covariate in the natural history of IPMN. Resected patients with malignant IPMN are older than resected patients with benign IPMN[8,13-15]. On average, patients with malignant (invasive) IPMN are approximately 5 years older than pa-

tients with benign (adenoma or borderline) IPMN[8,14,15]. Of interest in this observation is the finding of an increased incidence of dysplastic changes in the lesions of older patients with IPMN[13]. Both observations lend weak indirect support to the theory of sequential genetic alterations consistent with clonal progression[7]. While age at the time of diagnosis is indirect evidence, non-operative surveillance of IPMN is the gold standard for defining natural history. The cumulative published experience of surveilling 450 patients with presumed branch duct IPMN using serial imaging and clinical examination indicates that very few asymptomatic, small (< 3 cm), branch duct lesions either enlarge (6% to 12%) or progress to invasive malignancy[16,19,21,35,36,39,47-51]. In these observations, the frequent lack of a firm histopathological tissue diagnosis also obscures the generalizability of these data. In addition, all have relatively short mean follow-up periods (maximum 40 mo) further complicating the interpretation of a neoplasm with a known indolent course. Following operation, the risk of recurrence in either the remnant pancreas or distant sites is high (up to 65%) in patients with invasive IPMN[13,14,21-23]. This rate is substantially lower (< 8%) in patients with noninvasive IPMN (adenoma, dysplasia, carcinoma in situ)[13,14,21-23].

In summary, the current literature regarding the natural history of IPMN is limited by selection bias (mostly resected patients), unclear definitions, varying inclusion criteria, heterogeneous patient groups, small nonoperative surveillance cohorts and relatively short follow-up periods[52,53]. Although these issues challenge our ability to accurately define the natural history of IPMN, it is clear that main duct IPMN at the time of its diagnosis commonly coexists with malignancy. These lesions should be resected when identified in patients who are suitable operative candidates since their risk of occult malignancy far outweighs their operative risk, even for pancreaticoduodenectomy. The clinical decision making for branch duct IPMN is more complex. To fully evaluate risk/benefit ratios in these patients, one must consider patient age, symptoms, lesion size, radiological findings, type of operation and the ability of a patient to potentially engage in a lengthy surveillance program. Most branch duct IPMN are currently being identified with a diameter of less than 3 cm, a size which, given the lack of other high risk covariates (age, symptoms, nodularity, thick wall), can be safely surveilled[54]. Only with the combination of long periods of observation and direct evidence of true malignant transformation (or lack thereof) will we be able to better define the natural history of IPMN.

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