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Prognosis of invasive intraductal papillary mucinous neoplasm depends on histological and precursor epithelial subtypes

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Abstract

Objective—Invasive cancers arising from intraductal papillary mucinous neoplasm (IPMN) are recognised as a morphologically and biologically heterogeneous group of neoplasms. Less is known about the epithelial subtypes of the precursor IPMN from which these lesions arise. The authors investigate the clinicopathological characteristics and the impact on survival of both the invasive component and its background IPMN.

Design and patients—The study cohort comprised 61 patients with invasive IPMN (study group) and 570 patients with pancreatic ductal adenocarcinoma (PDAC, control group) resected at a single institution. Multivariate analyses were performed using a stage-matched Cox proportional hazard model.

Results—The histology of invasive components of the IPMN cohort was tubular in 38 (62%), colloid in 16 (26%), and oncocytic in seven (12%). Compared with PDAC, invasive IPMNs were associated with a lower incidence of adverse pathological features and improved mortality by multivariate analysis (HR 0.58; 95% CI 0.39 to 0.86). In subtype analysis, this favourable outcome remained only for colloid and oncocytic carcinomas, while tubular adenocarcinoma was

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associated with worse overall survival, not significantly different from that of PDAC (HR 0.85; 95% CI 0.53 to 1.36). Colloid and oncocytic carcinomas arose only from intestinal-and oncocytic-type IPMNs, respectively, and were mostly of the main-duct type, whereas tubular adenocarcinomas primarily originated in the gastric background, which was often associated with branch-duct IPMN. Overall survival of patients with invasive adenocarcinomas arising from gastric-type IPMN was significantly worse than that of patients with non-gastric-type IPMN (p=0.016).

Conclusions—Tubular, colloid and oncocytic invasive IPMNs have varying prognosis, and arise from different epithelial subtypes. Colloid and oncocytic types have markedly improved biology, whereas the tubular type has a course that resembles PDAC. Analysis of these subtypes indicates that the background epithelium plays an equally, if not more, important role in defining the biology and prognosis of invasive IPMNs.

INTRODUCTION

Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) are tumours characterised by intraductal proliferation of neoplastic mucinous cells with various degrees of atypia, which usually form papillae and lead to cystic dilatation of pancreatic ducts, forming clinically detectable masses.[1] In pancreatic surgery referral centres, IPMNs are being increasingly diagnosed, and currently account for approximately 8–20% of all resected pancreatectomy specimens.[2]

Histologically, IPMN encompasses variable grades of lesions ranging from low-grade dysplasia to invasive adenocarcinoma.[13] The prognosis of patients with non-invasive IPMN is excellent, and the 5-year survival rate is reported to be 77–100%.[4–10] Conversely, the 5-year survival rate for carcinoma arising in the background of IPMN (invasive IPMN) ranges from 34% to 62%.[6–911–16] The figures are significantly lower than those for non-invasive IPMN, but appear to be higher than those for pancreatic ductal adenocarcinoma (PDAC), which range from 9% to 21%.[5811–1316] It remains unclear, however, whether this difference in survival between invasive IPMN and PDAC represents distinct biology or simply a tendency for presentation at an early stage for invasive IPMN. To date, several studies have directly compared the clinicopathological features and long-term survival of invasive IPMN with those of PDAC, and there are conflicting results as to whether invasive IPMN has improved survival, even when matched by stage.[5811–131617] One factor contributing to the inability to come to a definite conclusion regarding better or worse outcome may be due to the analysis of heterogeneous lesions as a homogeneous group.

Morphological variations of IPMNs have been recently recognised, and criteria for distinguishing the four distinct subtypes, namely gastric, intestinal, pancreatobiliary and oncocytic, have been established.[18] The classification is based on the cyto-morphological features of the papillae supported by the immunohistochemical features of mucin glycoproteins. Likewise, invasive carcinoma arising in association with IPMN is cyto-morphologically heterogeneous, and can exhibit colloid (colloid carcinoma), tubular (tubular adenocarcinoma)[719] or oncocytic (oncocytic carcinoma) patterns.[20] It has been shown that intestinal-type IPMN often progresses to invasive IPMN with a colloid pattern.[21–24] However, the association, if any, between the other histological types of invasive carcinoma and those of underlying IPMN has not been well documented. In addition, while colloid carcinoma is felt to exhibit a particularly indolent behaviour[1419] and is associated with more favourable outcome than tubular adenocarcinoma,[14] there are no data on whether tubular adenocarcinoma has a better survival rate than PDAC.

The objectives of this study are twofold: (1) to determine whether there is an association between the histological subtypes of invasive carcinoma and those of underlying IPMN, and

what effects the differences in histology of invasive carcinoma and/or underlying IPMN have on the prognosis of invasive IPMN; (2) to identify histopathological and molecular characteristics that may account for differences in biological behaviour after resection of invasive IPMN compared with PDAC.

MATERIALS AND METHODS

Study population

The Massachusetts General Hospital institutional review board approved this study. A total of 271 patients with surgically resected, pathologically confirmed IPMN between January 1990 and December 2008 were identified from a prospectively collected database. Of these, 61 were found to have invasive carcinoma arising in the background of IPMN, including 12 with minimally invasive carcinoma (invasion <5 mm in size).[2526] This group formed our study cohort. The control group was 570 patients with conventional PDAC who underwent pancreatectomy with a curative intent. Clinical information, including demographics and the results of imaging procedures, was obtained. Survival time was defined from the date of surgery to the date of death. Follow-up time was assessed from the date of surgery to the last follow-up date, no later than 30 June 2009.

Pathological examination of IPMN

On gross and microscopic examinations of surgical specimens, special attention was paid to excluding the following from the invasive IPMN group: (1) invasive carcinoma coexisting with, but separate from, foci of IPMN; (2) degenerative cystic changes of PDAC.[27] Both intraductal and invasive components were histologically evaluated. Analysis of the background IPMN included histological grade,[1] type of duct involvement by IPMN, and epithelial subtype. The type of duct involvement by IPMN was determined by macroscopic and microscopic examinations as well as by clinical imaging studies, and was classified into main-duct, branch-duct and combined-type IPMNs.[28] Because the epidemiological and clinicopathological characteristics of main-duct and combined-type IPMNs have been found to be similar,[29] main-duct and combined types were grouped together into the main-duct type for statistical analysis.

The intraductal components were classified into four distinct epithelial subtypes—gastric, intestinal, pancreatobiliary and oncocytic—on the basis of their epithelial morphology on routine (H&E) staining (figure 1) and, when available, immunoreactivity against mucin glycoproteins according to previously described criteria (online supplementary document).[1830] In cases exhibiting heterogeneous epithelium, the subtype was determined on the basis of the most prevalent epithelium of the highest grade.

Pathological assessment of invasive carcinoma

Invasive carcinomas arising in the background of IPMN were classified into three histological subtypes: tubular adenocarcinoma, colloid carcinoma and oncocytic carcinoma (figure 2).[12031] In cases containing more than one histological subtype, the predominant one was retained for the purpose of this study.

In both invasive IPMN and PDAC, the size of invasive carcinoma, tumour (pT) and nodal (pN) stages, the presence or absence of angiolymphatic invasion, perineural invasion and surgical margin status were evaluated. The size of invasive IPMN included only the invasive, and not the intraductal, component. The histological grade of tumour was categorised as low (well and moderately differentiated) or high (poorly differentiated and undifferentiated). The final stage of invasive carcinoma was diagnosed pathologically in

accordance with the TNM classification system of malignant tumours published by the American Joint Committee on Cancer (AJCC), 6th edition.

KRAS mutation analysis of invasive IPMN

Peptide nucleic acid clamp PCR assay[32] was performed to detect *KRAS* mutations in invasive IPMNs with available tissue blocks (online supplementary document).

Statistical analysis

For all statistical analyses, we used an SAS program (V.9.1). All p values were two-sided, and statistical significance was set at $p \leq 0.05$. For categorical data, the χ^2 test was performed.

For survival analysis, the Kaplan–Meier method was used to assess survival time distribution, and the log-rank test was applied. To assess independent effect of tumour type (PDAC vs invasive IPMN, including histological subtypes) on mortality, we constructed a multivariate, stage-matched (stratified) Cox proportional hazard model to compute a HR according to tumour type, initially containing sex, age (continuous), tumour location (proximal vs distal), tumour size (≤1.0 vs >1.0 cm), histological grade (low vs high), lymphatic invasion, vascular invasion, perineural invasion, and resection status. AJCC tumour stage (I, II, III+IV+unknown) was used as a stratifying (matching) variable in Cox models. A backward stepwise elimination with a threshold of p=0.10 was used to select variables in the final model. Variables in the final model were tumour type, histological grade, lymphatic invasion, vascular invasion and resection status. The proportionality of hazard assumption was satisfied by evaluating time-dependent variables, which were the cross product of tumour type variable and survival time (p=0.25). An interaction was assessed by including the cross product of tumour type variable and another variable of interest in a multivariate Cox model, and the Wald test was performed.

RESULTS

Preoperative clinical profiles of patients with invasive IPMN

In our cohort of 61 patients, the majority (n=44, 72%) presented with symptoms including abdominal pain (n=26, 43%), jaundice (n=17, 28%) and weight loss (n=23, 38%); however, 16 (26%) patients were asymptomatic and were diagnosed incidentally by CT or MRI performed for other reasons. Retrospective review of imaging was available in 32 patients and showed main-duct dilatation in 25 (78%) and a solid nodule/mass in 15 (47%, size 1.5 +0.9 cm). Furthermore, extrahepatic biliary dilatation was seen in eight (25%) patients, and lymphadenopathy in 11 (34%). A total of 23 patients had preoperative cytology: 22 by endoscopic ultrasound-fine needle aspiration (EUS-FNA) and one from bile duct brushing. Cytology was diagnostic of adenocarcinoma in 57% (13/23). An additional five cysts produced atypical epithelial cells consistent with at least moderate dysplasia, two cysts confirmed a neoplastic mucinous cyst, and three aspirates were non-diagnostic. Of note, all the patients carried high-risk stigmata (in accordance with the Sendai guidelines).

Clinicopathological features of invasive IPMN: comparison with PDAC (table 1)

Patients with invasive IPMN were more likely to be male (61% vs 47%, p=0.043) and present an average of 5 years later than those with PDAC (70.6±9.6 vs 65.8±10.4, p=0.0006). Although both were more likely to present in the head of the pancreas, invasive IPMNs were less likely to present with tumours located in the proximal pancreas (59% vs 85%, p<0.0001), and less likely to present at an advanced stage (T3 and T4) (63% vs 82%, p<0.0001). Pathologically invasive IPMNs were less likely to have nodal metastases (34% vs 64%, p<0.0001), high-grade histology (15% vs 41%, p<0.0001) or lymphatic (25% vs

55%, p<0.0001), vascular (18% vs 50%, p<0.0001) or perineural (44% vs 90%, p<0.0001) invasion.

Patient survival: invasive IPMN versus PDAC

Patients with invasive IPMN had a significantly better outcome than those with PDAC (figure 3A). Median survival was 58 months after resection among patients with invasive IPMN and 18 months among those with PDAC. Five- and 10-year overall survival for patients with invasive IPMN was 47% and 34%, respectively, and that for PDAC was 16% and 4%, respectively (log-rank p<0.0001).

Using the Cox regression model, first looking at unadjusted overall mortality, we found that patients with invasive IPMN had a significant reduction in mortality (HR 0.38; 95% CI 0.26 to 0.54; table 2) compared with patients with PDAC. After adjustment for potential confounders, invasive IPMN remained significantly associated with improved overall mortality (HR 0.58; 95% CI 0.39 to 0.86). Next, we examined whether the favourable outcome after resection of invasive IPMN compared with PDAC was modified by other clinicopathological features. This was achieved by assessing the effect of the interaction between tumour type (invasive IPMN vs PDAC) and another variable such as lymph node status and tumour grade on mortality in a multivariate Cox model using the Wald test. Among node-negative tumours, multivariate HR for overall mortality in invasive IPMN compared with PDAC was 0.43 (95% CI 0.24 to 0.76); however, among node-positive tumours, it increased to 0.89 (95% CI 0.52 to 1.50). The results indicate that the favourable effect of invasive IPMN on mortality was diminished by the unfavourable effect of nodal disease (figure 3B), and that in fact there is no apparent difference in adjusted overall mortality between node-positive invasive IPMN and PDAC. Similarly, survival benefits of invasive IPMN were also seen only in low-grade tumours; multivariate HR for overall mortality in invasive IPMN compared with PDAC was 0.47 (95% CI 0.30 to 0.75), while it was 1.26 (95% CI 0.62 to 2.55) among high-grade tumours (figure 3C). There was no significant effect modification by any of the other variables, including AJCC tumour stage ($P_{\text{interaction}}$=0.96).

Histological subtypes of invasive IPMN and survival

The histology of invasive components was tubular adenocarcinoma in 38 patients (62%), colloid carcinoma in 16 (26%), and oncocytic carcinoma in seven (12%). No invasive IPMN was classified as anaplastic.

Among patients with invasive IPMN, a favourable behaviour was identified for the colloid and oncocytic types compared with the tubular one. Median survival was 35 months after resection among patients with tubular adenocarcinoma, 95 months for those with colloid carcinoma, and 132 months for those with oncocytic carcinoma. Five- and 10-year overall survival rates for patients with tubular adenocarcinoma (37% and 29%, respectively) were worse than for those with colloid carcinoma (61% and 41%, respectively; log-rank p=0.056) and those with oncocytic carcinoma (69% and 51%, respectively; log-rank p=0.196). Compared with patients with PDAC, those with tubular adenocarcinoma (HR 0.57; 95% CI 0.36 to 0.89), colloid carcinoma (HR 0.22; 95% CI 0.11 to 0.47) and oncocytic carcinoma (HR 0.25; 95% CI 0.091 to 0.67) all experienced a significant reduction in unadjusted overall mortality (table 2, figure 3D). After adjustment for potential confounders, colloid carcinoma combined with oncocytic carcinoma remained as a significant predictor of improved overall mortality (HR 0.36; 95% CI 0.20 to 0.68), while the tubular type showed no overall survival benefit (HR 0.85; 95% CI 0.53 to 1.36).

We then looked at the clinicopathological characteristics within subtypes of invasive IPMN (table 3), first comparing colloid carcinomas and tubular adenocarcinomas. Although the size of the invasive component and T stage distribution were similar between these two groups, tubular adenocarcinomas had higher rates of perineural invasion (68% vs 25%, p=0.038). There were also differences in the incidence of nodal metastasis (41% vs 27%), vascular invasion (26% vs 6.3%) and lymphatic invasion (29% vs 19%) between the two groups, but they did not reach statistical significance. Similarly, compared with oncocytic carcinomas, tubular adenocarcinomas had higher rates of advanced tumour stage (T3 and T4) (61% vs 43%), nodal involvement (41% vs 0%), AJCC Stage II–IV (66% vs 29%) and perineural invasion (68% vs 14%), although only the difference in the incidence of perineural invasion reached statistical significance (p=0.047). Histological indicators of poor prognosis, such as lymph node metastasis, high histological grade and vascular invasion, were not found in the oncocytic subtype, suggesting a more indolent biological behaviour.

Specific epithelial subtypes of precursor IPMN correlate with specific subtypes of invasive IPMN

IPMNs have been classified into four epithelial subtypes—gastric, intestinal, oncocytic and pancreatobiliary—and the histological subtypes of adenocarcinoma arising in the background of IPMN appear to correlate with a specific epithelial subtype. All the invasive IPMNs with colloid carcinoma originated in the background of intestinal-type IPMN, and those with oncocytic carcinoma were seen only in the background of oncocytic-type IPMN. The majority of tubular adenocarcinomas, 66%, originated in gastric-type IPMNs, although rare tubular adenocarcinomas were also found to arise in the background of pancreatobiliary-type (13%, n=5), intestinal-type (16%, n=6) and oncocytic-type (5%, n=2) IPMNs. These positive associations between (1) intestinal-type IPMNs and colloid carcinomas, (2) oncocytic-type IPMNs and oncocytic carcinomas, and (3) gastric-type IPMNs and tubular adenocarcinomas were all significant (p<0.0001).

Since the majority of tubular adenocarcinomas originated in gastric-type IPMNs, we compared the survival of patients with gastric-type IPMN-associated invasive adenocarcinoma and those associated with non-gastric-type IPMN, and found that invasive adenocarcinomas originating in gastric-type IPMNs had significantly worse survival rates than those originating in the other types of IPMN (median survival 28 months for gastric type vs 89 months for non-gastric type, p=0.016) (online supplementary table 1).

Historically, pancreatobiliary-type IPMNs have been reported to carry the worst prognosis. This finding is secondary to the fact that they are often associated with invasive cancers (50–60%).[33] In this cohort, the median survival of the patients with invasive carcinoma arising in pancreatobiliary-type IPMN was 89 months, not significantly different from 68 months for those with intestinal-type IPMN. Evaluating the prognostic determinants revealed that tumour stage and histological type were not significantly different between the gastric and pancreatobiliary types of IPMN. All gastric and pancreatobiliary-type IPMNs gave rise to tubular adenocarcinoma; however, high-grade histology of the invasive component, which is an independent predictor of poor prognosis, was found more often in the gastric-type IPMNs (table 4).

The histology of invasive components was also associated with the type of duct involvement by IPMN. It has been described that main-duct type IPMNs often exhibit intestinal-type epithelium, and branch-duct type IPMNs usually show gastric-type epithelium.[33] In our cohort, tubular adenocarcinoma comprised 85% of carcinomas that arose in the background of a branch-duct type, 63% of those that originated in a combined type, and 30% of carcinomas that arose in a main-duct IPMN, while colloid carcinoma comprised 60% of

carcinomas from the main-duct type and was only rarely identified in the branch-duct IPMNs (one of 13, 8%) (p=0.015) (online supplementary table 2).

Survival after resection of invasive IPMN correlated with the type of ductal involvement. The median overall survival of the patients with invasive adenocarcinoma arising in the background of branch-duct IPMN was shorter than those with main-duct IPMN (18 vs 58 months). There is an 85% probability that the invasive carcinoma arising within a branch-duct IPMN will be tubular adenocarcinoma, which, in this cohort, correlates with a poorer outcome. In order to remove the effect of histology of the invasive component on prognosis, analysis was limited to tubular adenocarcinomas. There was a trend towards the invasive carcinoma arising in a branch-duct IPMN having a shorter survival (median, branch-duct 18 months vs main-duct 35 months). On multivariate analysis, although there was a trend of gastric epithelial subtype and the branch type of duct involvement carrying a poorer outcome, statistical significance was not reached, probably secondary to the small size of each subtype (online supplementary table 1).

KRAS mutations are common in both tubular and colloid carcinomas, but not in oncocytic carcinoma

KRAS mutations, which are seen in >90%[34] of PDAC, were also found in ~80% of both tubular and colloid carcinomas; however, *KRAS* mutations were rare in oncocytic carcinomas (20%). Similarly, when looking at the prevalence of *KRAS* mutations within the invasive component when stratified by the epithelial subtypes of the background IPMN, we found that the prevalence of *KRAS* mutations was not different except for those arising in the background of oncocytic-type IPMN (online supplementary table 3).

DISCUSSION

Much remains to be determined about adenocarcinomas arising in the background of IPMN and their relationship to standard PDAC. The picture now evolving is that invasive IPMN is a heterogeneous group of histologically distinct cancers each with a unique biology. Similarly to previously published findings,[14,16] we also find that the histology of the invasive component of IPMN affects prognosis: patients with colloid or oncocytic carcinoma experience significantly better outcomes than those with PDAC, while the prognosis of patients with tubular adenocarcinoma is equivalent to that of patients with PDAC. Our study goes on to further show that distinct epithelial subtypes of IPMN give rise to different histological types of invasive carcinomas: intestinal-type IPMNs correlated with colloid carcinomas, and the gastric epithelial subtype correlated with tubular adenocarcinomas. Furthermore, the epithelial subtype of IPMN, as well as the type of duct involved, also affected the survival of patients with invasive IPMN.

There is no question that patients with IPMN-associated adenocarcinoma have a better prognosis than patients with PDAC, but the reasons for this advantage remain controversial. Two recent studies, one from the Mayo Clinic, and another from Johns Hopkins, suggest that this improved survival is merely a function of earlier stage—that is, smaller size of the invasive component coupled with lesser incidence of nodal metastases.[16,17] In the present study, the survival advantage of invasive IPMN as a whole compared with PDAC remained significant in multivariate analysis, stage by stage. The difference in results between the studies may be attributed to the difference in statistical methods applied and/or the proportion of histological subtypes. For example, our study had a larger proportion of the oncocytic type, which has a very good prognosis, and no anaplastic subtypes. Finally, the difference in the definition of IPMN-associated invasive adenocarcinoma may also have contributed. In our study, adenocarcinomas were included only if they arose in an IPMN, while the Johns Hopkins' study included any invasive carcinoma that arose in a pancreas

that had an IPMN even if the invasive component was located separate from an area involved by IPMN.

Studies have also shown that the type of duct involvement—branch versus main duct—is associated with the risk of invasive cancer.[2435] However, the type of duct involvement may also identify the likely histological subtype of cancer, given that the type of duct involvement correlates with epithelial subtypes of IPMN. Colloid carcinomas and oncocytic carcinomas developed only in the background of intestinal- and oncocytic-type IPMNs, respectively, the vast majority of which were of the main-duct type, whereas side-branch IPMNs were often associated with the gastric epithelial type, which gives rise to predominantly tubular adenocarcinomas. The association between branch-duct type and tubular adenocarcinoma seems paradoxical, since branch-duct IPMNs harbouring gastric-type epithelium are most often associated with low-grade dysplasia, absence of invasion, and fair survival,[2435] to the point that many are managed with observation. However, in our cohort, 15.6% of surgically resected gastric-type IPMNs gave rise to tubular adenocarcinoma (data not shown). The figure is similar to previously published results.[22]

The heterogeneity seen in these histological subtypes of pancreatic adenocarcinoma and their different prognosis probably reflects unique molecular features and genetic drivers. The overall survival of patients with tubular adenocarcinoma was significantly worse than those with colloid or oncocytic carcinoma, but little is known about the difference in the molecular events between histological subtypes of invasive adenocarcinoma and PDAC. In this study, we found that *KRAS* mutations, which had been reported in >90% of PDAC,[34] were rare in oncocytic carcinomas, but were equally prevalent in tubular and colloid carcinomas. Thus, *KRAS* mutations that usually occur in the early stage of neoplastic progression in PDAC[36] do not appear to indicate the aggressiveness of pancreatic adenocarcinoma. It has been reported that colloid carcinomas uniformly express intestinal differentiation markers, MUC2 and CDX-2, which are rarely seen in tubular adenocarcinomas and PDAC[3738]; perhaps this difference in molecular alterations in addition to uniquely different biology is an indicator that they are different cancers. Many previous studies have reported differences in molecular alterations between IPMN and PDAC. However, the vast majority of these studies failed to specify histological subtypes of intraductal and/or invasive components of IPMN and the difficulties that have surrounded finding signature mutations for these cancers may be in part the result of mixing of histologically and genetically distinct tumours into one large group.

Although certain types of invasive IPMN may be uniquely different from PDAC, tubular adenocarcinomas appear to be similar. Notably, the prognosis of the patients with tubular adenocarcinoma was not significantly different from that of PDAC, suggesting biological, molecular and perhaps genetic similarities. In support of this view, it has been shown that PanIN, a known precursor to PDAC, exhibits a gastric phenotype.[39–41] It has also been reported that both PanIN and IPMN aberrantly express sonic hedgehog.[42] Most recently a novel compartment in the pancreas has been identified and termed pancreatic duct glands, which are gland-like outpouches from the proximal ductal system.[43] These glands, which exhibit a gastric phenotype, express sonic hedgehog, and are physically located in buds off the main-duct lumen, morphologically resemble low-grade PanINs (PanIN-1A), and can also undergo hyperplasia in the setting of inflammation, resulting in an upregulation of gastric mucins, morphologically taking on a side-branch IPMN-like appearance. It is reasonable to speculate that these pancreatic duct glands may be a precursor to both PanIN and side-branch IPMNs.

There are clinically important messages that can be extrapolated from our results that may assist in the surveillance and postoperative management of these patients. First, although the

majority of branch-duct IPMNs are reportedly benign, their prognosis can be dismal once they develop invasive carcinoma. The recent study by Sawai *et al* reported that 20% of patients with side-branch IPMN who are followed will develop cancer in 10-years.[44] Therefore, regular and continued clinical and imaging follow-up may be essential even in patients with clinically benign branch-duct IPMN in order to capture neoplastic progression before they develop invasive carcinoma. The other message from this study may assist in postoperative clinical management. Although further studies are needed to reach a definitive conclusion, the finding that colloid and oncocytic carcinomas have 5-year survival rates of 61–69% whereas patients with tubular adenocarcinoma (especially those with nodal disease) have a survival rate similar to standard PDAC may allow stratification of those patients that would most likely benefit from adjuvant therapy.

In summary, this study shows that patients with invasive IPMN have a threefold better 5-year survival than patients with conventional PDAC. While indicators of favourable prognosis, such as smaller size and negative lymph node status, are indeed more common in invasive IPMN, the disease itself has independent prognostic significance. Furthermore, our analysis shows that this advantage is due to the markedly improved biology of the indolent colloid and oncocytic types of invasive IPMN, whereas the more common tubular type has a course that resembles that of PDAC. We have also shown that the various epithelial subtypes of precursor IPMN (gastric, intestinal, pancreatobiliary and oncocytic) correlate with the type of duct involvement, with the histological subtype of invasive carcinoma, and ultimately with prognosis. Further molecular characterisation of IPMNs needs to acknowledge the differences within these histological subtypes in order to better understand the biology of this unique disease and its relationship with pancreatic cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Significance of this study

What is already known about this subject?

- Intraductal papillary mucinous neoplasms of the pancreas (IPMNs) comprise distinct morphological subtypes—gastric, intestinal, pancreatobiliary and oncocytic. Similarly, invasive carcinomas arising in IPMN (invasive IPMN) consist of three histological subtypes—tubular, colloid and oncocytic.
- An association between the histological subtypes of invasive carcinoma and those of underlying IPMN, and differences in outcome between subtypes of invasive carcinoma and/or underlying IPMN have not been thoroughly documented.
- Invasive IPMN, as a whole, appears to have improved survival compared with pancreatic ductal adenocarcinoma (PDAC), but there are conflicting results as to whether the improved survival of invasive IPMN remains when matched by stage.

What are the new findings?

- Overall, patients with invasive IPMN have significantly better outcomes than those with PDAC in a multivariate analysis using a stage-matched Cox proportional hazard model.
- In subtype analysis of invasive carcinoma, the favourable outcome remained only for colloid and oncocytic carcinomas, while tubular adenocarcinoma was associated with worse overall survival, not significantly different from that of PDAC.
- The various subtypes of underlying IPMN correlate with the type of duct involvement, with the histological subtype of invasive carcinoma, and ultimately with prognosis.

How might it impact on clinical practice in the foreseeable future?

- Assessing the subtypes of invasive carcinoma as well as underlying IPMN may provide useful information for clinical management of patients with IPMN.
- The results may facilitate molecular characterisation and biomarker development for the distinct subtypes of IPMN in order to better understand the biology of IPMN and its relationship with pancreatic cancer.

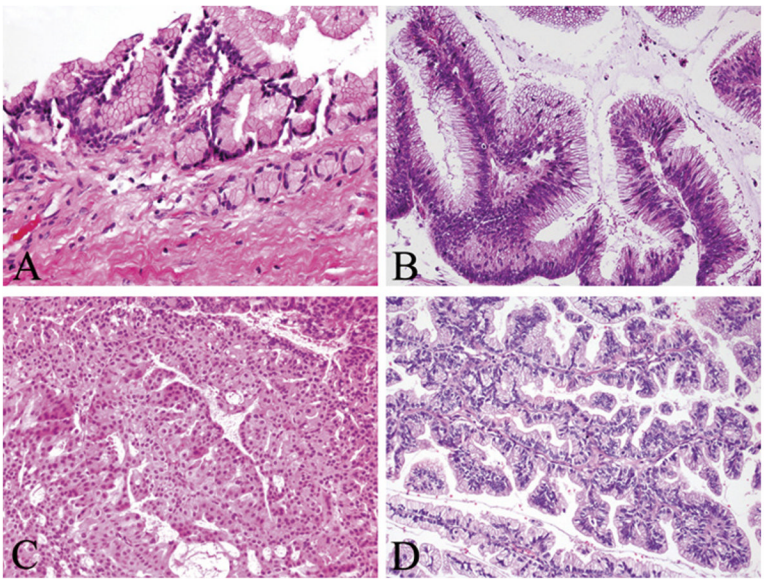

Figure 1.
Epithelial subtypes of intraductal papillary mucinous neoplasm: (A) gastric; (B) intestinal; (C) oncocytic; (D) pancreatobiliary.

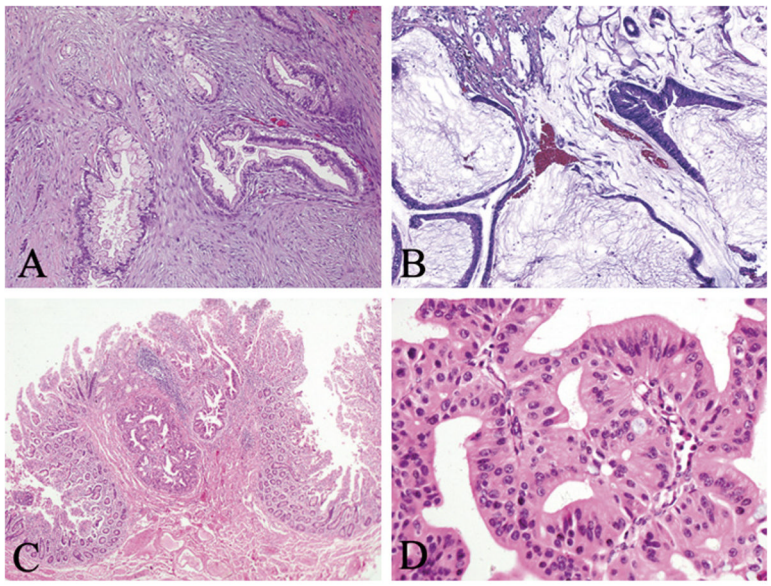

Figure 2.
Histological subtypes of intraductal papillary mucinous neoplasm-associated invasive adenocarcinoma: (A) tubular adenocarcinoma which resembles pancreatic ductal adenocarcinoma and consists predominantly of infiltrating tubular neoplastic glands associated with a desmoplastic stroma devoid of significant stromal mucin; (B) colloid carcinoma characterised by extensive (>80%) stromal mucin pools, containing relatively scant neoplastic cells; (C) low-power and (D) high-power magnifications of oncocytic carcinoma, showing infiltrating tubules and/or nests composed of oncocytic cells (invading into the duodenal mucosa in this case).

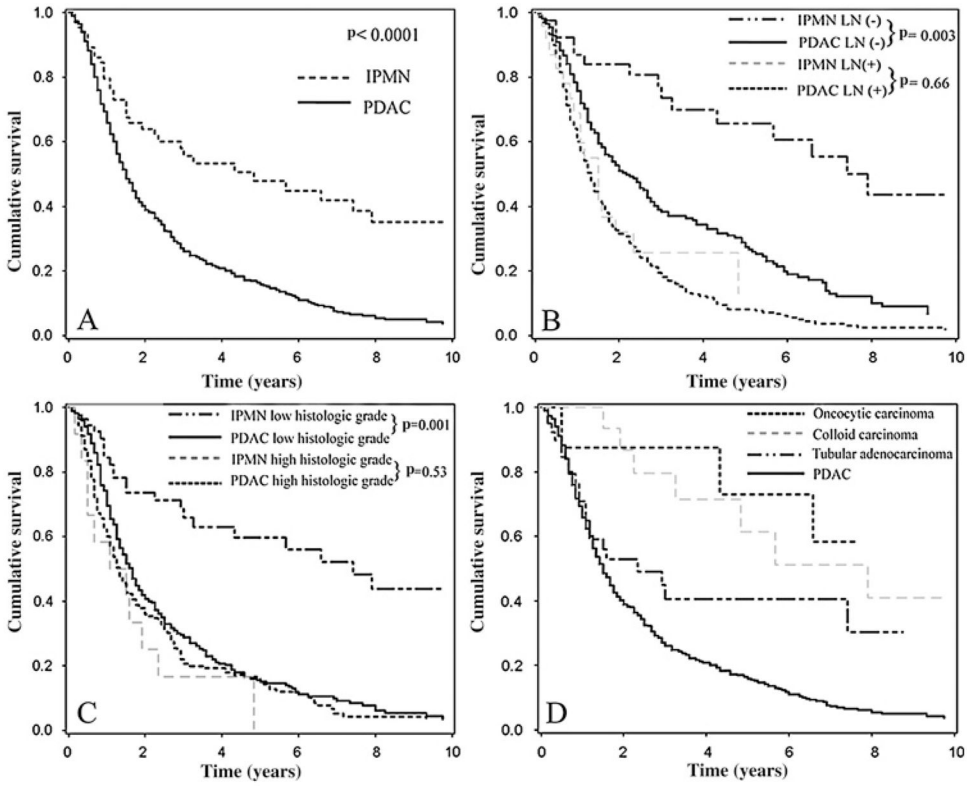

Figure 3.

(A) Overall survival after resection of intraductal papillary mucinous neoplasm (IPMN)-associated invasive adenocarcinoma (IPMN) was significantly better than conventional pancreatic adenocarcinoma (PDAC) (median survival, 58 vs 18 months). (B) Overall survival curves after resection of IPMN-associated invasive adenocarcinoma (IPMN) and conventional ductal adenocarcinoma (PDAC) stratified by nodal status. The favourable survival of invasive IPMN compared with PDAC was noted in patients with node-negative disease (LN (−): median survival, 89 vs 26 months), but not in those with node-positive disease (LN (+): median survival, 18 vs 16 months). (C) Overall survival curves after resection of IPMN-associated invasive adenocarcinoma (IPMN) and conventional ductal adenocarcinoma (PDAC) stratified by histological grade of tumour. The favourable survival of invasive IPMN compared with PDAC was seen in patients with low histological grade (median survival, 89 vs 20 months), but not in those with high histological grade (median survival, 16 vs 16 months). (D) Overall survival curves after resection of IPMN-associated invasive adenocarcinoma based on histological subtype and conventional ductal adenocarcinoma (PDAC). Compared with patients with PDAC, those with oncocytic carcinoma and colloid carcinoma experienced significantly improved outcomes ($p<0.0001$, median survival, 18 vs 95 and 132 months, respectively), but those with tubular adenocarcinoma did not, upon multivariate analysis ($p=0.76$, median survival, 18 vs 35 months).

Table 1

Clinicopathological features of pancreatic adenocarcinoma according to tumour type

		Tumour type		
Clinical or pathological feature	**Total (N)**	**PDAC**	**Invasive IPMN**	**p Value**
All cases	631	570	61	
Gender				
Male	305	268 (47%)	37 (61%)	0.043
Female	326	302 (53%)	24 (39%)	
Age (years)				
Mean	66.3	65.8	70.6	0.0006
SD	10.4	10.4	9.6	
Age (years)				
<65	266	248 (44%)	18 (30%)	0.035
≥65	365	322 (56%)	43 (70%)	
Tumour location *				
Proximal	523	487 (85%)	36 (59%)	<0.0001
Distal	101	80 (14%)	21 (34%)	
Other	7	3 (0.5%)	4 (6.6%)	
Tumour size				
≤1.0	36	21 (3.9%)	18 (30%)	<0.0001
>1.0	558	522 (96%)	43 (70%)	
Tumour stage				
pT1	44	26 (4.6%)	18 (30%)	<0.0001
pT2	83	78 (14%)	5 (8.2%)	
pT3	481	444 (78%)	37 (61%)	
pT4	23	22 (3.9%)	1 (1.6%)	
Nodal stage				
pN0	241	203 (36%)	38 (67%)	<0.0001
pN1	385	366 (64%)	19 (33%)	
Stage				
IA	33	20 (3.5%)	13 (21%)	<0.0001
IB	48	43 (7.5%)	5 (8.2%)	
IIA	148	129 (23%)	19 (31%)	
IIB	371	351 (62%)	20 (33%)	
III	21	20 (3.5%)	1 (1.6%)	
IV	6	6 (1.1%)	0 (0%)	
Unknown	4	1 (0.2%)	3 (4.9%)	
Histological grade †				
Low	379	327 (59%)	52 (85%)	<0.0001
High	235	226 (41%)	9 (15%)	
Lymphatic invasion				
(−)	211	165 (45%)	46 (75%)	<0.0001

		Tumour type		
Clinical or pathological feature	**Total (N)**	**PDAC**	**Invasive IPMN**	**p Value**
(+)	219	204 (55%)	15 (25%)	
Vascular invasion				
(−)	246	196 (50%)	50 (82%)	<0.0001
(+)	208	197 (50%)	11 (18%)	
Perineural invasion				
(−)	78	44 (9.8%)	34 (56%)	<0.0001
(+)	432	405 (90%)	27 (44%)	
Resection status				
0	405	360 (63%)	45 (74%)	0.104
1	225	209 (37%)	16 (26%)	

*Proximal: head and/or uncinate and/or neck; Distal: body and/or tail; Other: diffuse or head and tail.

†Low: grade 1 or 2; High: grade 3 and 4.

PDAC, pancreatic ductal adenocarcinoma; Invasive IPMN, invasive carcinoma arising in the background of intraductal papillary mucinous neoplasm.

Table 2

Tumour type and patient survival in pancreatic adenocarcinoma

		Overall mortality			
	Total N	**Deaths/person-years**	**Univariate HR (95% CI)**	**Stage-matched HR (95% CI)**	**Multivariate HR (95% CI)**
PDAC	558 (90%)	449/1150	1 (referent)	1 (referent)	1 (referent)
Invasive IPMN					
All	60 (9.7%)	31/223	0.38 (0.26 to 0.54)†	0.43 (0.30 to 0.62)†	0.58 (0.39 to 0.86)**
Tubular type	37	20/91	0.57 (0.36 to 0.89)*	0.66 (0.42 to 1.05)	0.85 (0.53 to 1.36)
Colloid type	16	7/85	0.22 (0.11 to 0.47)†	0.25 (0.12 to 0.53)‡	0.34 (0.16 to 0.73)**
Oncocytic type	7	4/48	0.25 (0.091 to 0.67)**	0.28 (0.10 to 0.76)*	0.41 (0.15 to 1.15)

*p<0.05;

**p<0.01.

†p<0.0001.

‡p<0.0005.

PDAC, pancreatic ductal adenocarcinoma; Invasive IPMN, invasive carcinoma arising in the background of intraductal papillary mucinous neoplasm. Survival analysis excluded six patients who died in the 30-day postoperative period (0.9%) and seven who lost to follow-up.

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Table 3

Clinicopathological features of IPMN-associated adenocarcinoma according to histological subtypes

	Invasive IPMN		
Clinical or pathological feature	**Tubular**	**Colloid**	**Oncocytic**
All cases	38	16	7
Gender			
Male	19 (50%)*	14 (87%)*	4 (57%)
Female	19 (40%)	2 (13%)	3 (43%)
Age (years)			
Mean	72.2	68.3	67.1
SD	9.4	9.2	11.0
Age (years)			
<65	9 (24%)	7 (44%)	2 (29%)
≥65	29 (76%)	9 (56%)	5 (71%)
Tumour location†			
Proximal	19 (50%)	13 (81%)	4 (57%)
Distal	16 (41%)	2 (13%)	2 (29%)
Other	3 (7.9%)	1 (6.3%)	1 (14%)
Tumour size			
≤1.0	10 (26%)	5 (31%)	3 (43%)
>1.0	28 (74%)	11 (69%)	4 (57%)
Tumour stage			
pT1	12 (32%)	3 (19%)	3 (43%)
pT2	3 (7.9%)	1 (6.3%)	1 (14%)
pT3	22 (58%)	12 (75%)	3 (43%)
pT4	1 (2.6%)	0 (0%)	0 (0%)
Nodal stage‡			
pN0	22 (59%)	11 (73%)	5 (100%)
pN1	15 (41%)	4 (27%)	0 (0%)
Stage			
IA	9 (24%)	2 (13%)	2 (29%)
IB	3 (7.9%)	1 (6.3%)	1 (13%)
IIA	9 (24%)	8 (50%)	2 (29%)
IIB	15 (39%)	4 (25%)	0 (0%)
III	1 (2.6%)	0 (0%)	0 (0%)
IV	0 (0%)	0 (0%)	0 (0%)
Unknown	1 (2.6%)	1 (6.3%)	2 (29%)
Histological grade§			
Low	32 (84%)	13 (81%)	7 (100%)
High	6 (16%)	3 (19%)	0 (0%)
Lymphatic invasion			
(−)	27 (71%)	13 (81%)	6 (86%)

	Invasive IPMN		
Clinical or pathological feature	**Tubular**	**Colloid**	**Oncocytic**
(+)	11 (29%)	3 (19%)	1 (14%)
Vascular invasion			
(−)	28 (74%)	15 (94%)	7 (100%)
(+)	10 (26%)	1 (6.3%)	0 (0%)
Perineural invasion			
(−)	16 (42%) *	12 (75%) *	6 (86%) *
(+)	22 (68%)	4 (25%)	1 (14%)
Resection status			
0	28 (74%)	11 (69%)	6 (86%)
1	10 (26%)	5 (31%)	1 (14%)
Underlying IPMN			
Epithelial subtype			
Gastric ¶	25 (66%)	0 (0%)	0 (0%)
Intestinal **	6 (16%)	16 (100%)	0 (0%)
Oncocytic ††	2 (5.3%)	0 (0%)	7 (100%)
Pancreatobiliary	5 (13%)	0 (0%)	0 (0%)
Type of duct involvement			
Main only	3 (7.9%)	6 (38%)	1 (14%)
Combined	24 (63%)	9 (56%)	5 (72%)
Branch	11 (29%)	1 (6.3%)	1 (14%)

* $p<0.05$.

† Proximal: head and/or uncinate and/or neck; Distal: body and/or tail; Other: diffuse or head and tail.

‡ No lymph node was found in four cases.

§ Low: grade 1 or 2; High: grade 3 and 4.

¶ Association of gastric type IPMN and tubular adenocarcinoma, $p<0.0001$.

** Association of intestinal type IPMN and colloid carcinoma, $p<0.0001$.

†† Association of oncocytic IPMN and oncocytic carcinoma, $p<0.0001$.

Invasive IPMN, invasive carcinoma arising in the background of intraductal papillary mucinous neoplasm; tubular, tubular adenocarcinoma; colloid, colloid carcinoma; oncocytic, oncocytic carcinoma.

Table 4

Clinicopathological features of IPMN-associated adenocarcinoma according to epithelial subtypes of IPMN

	Epithelial subtype of IPMN			
Clinical or pathological feature	**Gastric**	**Intestinal**	**Oncocytic**	**Pancreatobiliary**
All cases	25	22	9	5
Gender				
Male	11 (44%)	17 (77%)	6 (67%)	3 (60%)
Female	14 (56%)	5 (23%)	3 (33%)	2 (40%)
Age (years)				
Mean	73.1	70.2	65.0	69.6
SD	9.3	9.2	10.8	8.7
Age (years)				
<65	5 (20%)	8 (36%)	4 (44%)	1 (20%)
≥65	20 (80%)	14 (64%)	5 (66%)	4 (80%)
Tumour location *				
Proximal	12 (48%)	16 (73%)	4 (44%)	4 (80%)
Distal	11 (44%)	4 (18%)	4 (44%)	1 (20%)
Other	2 (8.0%)	2 (9.1%)	1 (11%)	0 (0%)
Tumour size				
≤1.0	4 (16%)	7 (32%)	5 (44%)	2 (40%)
>1.0	21 (84%)	15 (68%)	4 (66%)	3 (60%)
Tumour stage				
pT1	5 (20%)	6 (27%)	5 (56%)	2 (40%)
pT2	3 (12%)	1 (4.6%)	1 (11%)	0 (0%)
pT3	16 (64%)	15 (68%)	3 (33%)	3 (60%)
pT4	1 (4.0%)	0 (0%)	0 (0%)	0 (0%)
Nodal stage †				
pN0	15 (63%)	14 (67%)	6 (86%)	3 (60%)
pN1	9 (37%)	7 (33%)	1 (14%)	2 (40%)
Stage				
IA	4 (16%)	4 (18%)	3 (33%)	2 (40%)
IB	3 (12%)	1 (4.6%)	1 (11%)	0 (0%)
IIA	7 (28%)	9 (41%)	2 (22%)	1 (20%)
IIB	9 (36%)	7 (32%)	1 (11%)	2 (40%)
III	1 (4.0%)	0 (0%)	0 (0%)	0 (0%)
IV	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Unknown	1 (4.0%)	1 (4.6%)	2 (22%)	0 (0%)
Histological grade ‡				
Low	19 (76%)	19 (83%)	9 (100%)	5 (100%)
High	6 (24%)	3 (14%)	0 (0%)	0 (0%)
Lymphatic invasion				
(−)	16 (64%)	17 (77%)	8 (89%)	5 (100%)

	Epithelial subtype of IPMN			
Clinical or pathological feature	**Gastric**	**Intestinal**	**Oncocytic**	**Pancreatobiliary**
(+)	9 (36%)	5 (23%)	1 (11%)	0 (0%)
Vascular invasion				
(−)	17 (68%)	19 (86%)	9 (100%)	5 (100%)
(+)	8 (32%)	3 (14%)	0 (0%)	0 (0%)
Perineural invasion				
(−)	7 (28%)	16 (73%)	8 (89%)	3 (60%)
(+)	18 (72%)	6 (27%)	1 (11%)	2 (40%)
Resection status				
0	17 (68%)	16 (73%)	7 (78%)	5 (100%)
1	8 (32%)	6 (27%)	2 (22%)	0 (0%)
Histological type of invasive carcinoma[§]				
Tubular[¶]	25 (100%)	6 (27%)	2 (22%)	5 (100%)
Colloid[**]	0 (0%)	16 (73%)	0 (0%)	0 (0%)
Oncocytic[††]	0 (0%)	0 (0%)	7 (78%)	0 (0%)
Type of duct involvement				
Main only[‡‡]	0 (0%)	8 (36%)	1 (11%)	1 (20%)
Combined	15 (60%)	13 (59%)	7 (78%)	3 (60%)
Branch[***]	10 (40%)	1 (4.6%)	1 (11%)	1 (20%)

[*] Proximal: head and/or uncinate and/or neck; Distal: body and/or tail; Other: diffuse or head and tail.

[†] No lymph node was found in four cases.

[‡] Low: grade 1 or 2; High: grade 3 and 4.

[§] Tubular: tubular adenocarcinoma; Colloid: colloid carcinoma; Oncocytic: oncocytic carcinoma.

[¶] Gastric-type IPMN versus the other types, p<0.0001.

[**] Intestinal-type IPMN versus the other types, p<0.0001.

[††] Oncocytic-type IPMN versus the other types, p<0.0001.

[‡‡] Intestinal-type IPMN versus the other types, p<0.005.

[***] Gastric-type IPMN versus the other types, p<0.005.

IPMN, intraductal papillary mucinous neoplasm.