Intraductal Papillary Mucinous Adenocarcinoma of the Pancreas: Clinical Outcomes, Prognostic Factors, and the Role of Adjuvant Therapy

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Introduction

Intraductal papillary mucinous neoplasms (IPMNs) of the pancreas are mucin-producing cystic lesions involving the main pancreatic duct or its side branches that lack the ovarian stroma characteristic seen in mucinous cystic neoplasms. Likely a result of advances in cross-sectional imaging, these cystic lesions are being diagnosed and treated at an exponential rate over the past decade [1, 2]. Our understanding of the biology of IPMNs has evolved as pancreatic surgeons and gastroenterologists manage and follow these patients with increasing frequency. To date, IPMNs are regarded as a disease spectrum ranging from benign adenoma to in situ carcinoma and invasive carcinoma, and also possibly as a ‘field defect’. Most IPMNs are often diagnosed incidentally as benign cystic lesions with excellent survival outcomes, with most patients never succumbing to the disease [3]. The risk of malignant transformation hinges on the degree of main-duct involvement: main-duct IPMNs (MD-IPMN) harbor a malignancy risk of as high as 70%, whereas branch-duct IPMNs (BD-IPMN) have a malignancy risk which is about 25% in tumors that are resected [4–10], but in reality is much lower since the vast majority are managed non-operatively. Although the outcomes following resection of pancreatic ductal adenocarcinoma (PDAC) have been historically poor (5-year survival rates of 10–20%) [11, 12], the outcomes for IPMNs with associated invasive carcinoma, termed intraductal papillary mucinous adenocarcinoma (IPMC) for the purpose of this review, have been more favorable, with reported 5-year survival rates of about 40% [13–16]. It was not until recently that IPMCs were analyzed based on their histopathological subtypes (colloid, tubular) and epithelial phenotypes (gastric, intestinal, pancreaticobiliary, oncocytic). Within this article, we will review the clinical outcomes and prognostic factors of IPMC, specifically comparing it to the conventional PDAC, recurrence patterns, and the role of adjuvant therapy. It is important to note that PDACs arising from IPMNs are distinct entities from PDACs occurring concomitant to IPMNs.

Summary

Background: Intraductal papillary mucinous adenocarcinoma (IPMCs) occur more frequently in main-duct intraductal papillary mucinous neoplasms. Methods: Review of the literature. Results: The prognosis of IPMCs depends on its histopathological subtype: colloid IPMCs have superior survival rates mainly secondary to more favorable pathological features, whereas tubular IPMCs have survival outcomes similar to that of conventional pancreatic adenocarcinomas. The epithelial background plays an equally important role in defining the biology of IPMCs: gastric IPMC subtypes demonstrate an overall worse survival outcome when compared to intestinal, pancreaticobiliary, and oncocytic subtypes. Lymph node involvement is one of the strongest predictors of survival in IPMC, with a decreasing overall survival as the lymph node ratio increases. There is little evidence to support adjuvant chemoradiation in patients with IPMC. Conclusion: Our current understanding of IPMC biology based on histopathological and epithelial background subtypes as well as clinicopathological predictors should influence patient counseling and selection for adjuvant therapy.
Clinical Outcomes and Prognostic Factors

IPMCs are categorized by two distinctive histopathological subtypes with prognostic implications, i.e. colloid and tubular carcinoma. The tubular variant of IPMCs is characterized by neoplastic cells arranged in tubular glands with desmoplastic invasion, similar to that as seen in PDACs. They are generally associated with IPMNs of the pancreatobiliary subtype, expressing MUC1 glycoproteins that are also expressed in conventional PDACs on immunohistochemical examination. Colloid carcinomas are characterized stromal pools of acellular matrix containing neoplastic epithelial cells. As opposed to tubular IPMCs, colloid IPMCs typically are of the intestinal subtype, expressing MUC2 and CDX2 glycoproteins, markers of intestinal differentiation, and are biologically more indolent [17–19].

Besides the aforementioned molecular difference, these two entities are biologically distinct as well. Tubular and colloid IPMCs have significantly different survival outcomes. Tubular IPMCs are generally regarded to be a prognostically poorer subtype similar to that of PDACs, with 5-year survival rates ranging from 37 to 55% following surgical resection. In contrast, colloid IPMCs are often associated with excellent outcomes, with 5-year survival rates ranging from 61 to 87% post-resection [13, 15, 17–19] (fig. 1). This contrast in survival between both entities is largely attributed to the more aggressive oncobiology observed in tubular IPMCs, which often presented at advanced tumor (T) stages and have a higher likelihood of perineural invasion and lymph node metastases [15–17, 19]. In fact, lymph node involvement appears to be such a significant surrogate of invasive disease biology that patients with tubular IPMCs with negative regional lymph nodes have 5-year survival rates (73%) similar to that of colloid IPMCs, but similar to that of PDACs (27%) when there is regional lymph node involvement [16, 19].

In a collaboration study between our institution and the Verona’s group, lymph node ratio (LNR) was the strongest prognostic factor after resection for IPMCs (hazard ratio 6.15 when LNR > 0.2; p < 0.0001) (fig. 2) [20], supporting the notion that lymph node involvement is an important biological surrogate that could guide patient selection for adjuvant therapy.

It is also important to note that while IPMNs with a gastric epithelial background are more frequently associated with BD-IPMNs and are less frequently invasive, its prognosis, when invasive progression has occurred, is significantly worse when compared to non-gastric IPMNs. In a study of 61 patients with IPMCs, we previously reported that the overall survival for patients with gastric-type IPMCs were significantly worse than the non-gastric IPMCs (median survival 28 months for gastric type vs. 89 months for non-gastric type; p = 0.016) [17]. A recent Japanese study of 56 patients with IPMCs corroborated the findings (5-year survival rates of 52.7% and 89.7% in gastric- and intestinal-type IPMCs, respectively; p = 0.03) [21]. This suggests that the epithelial background plays an equal, if not, more important role than the histopathological subtype in defining the biology and prognosis of IPMCs.

Comparison to Pancreatic Adenocarcinoma

Historically, IPMCs are regarded to have superior survival outcomes when compared to conventional PDACs (5-year survival rates of 36–54% observed in IPMCs vs. 12–21% in PDACs). However, most early reports lack dichotomization of IPMCs to its colloid and tubular variant when comparing survival outcomes. More recent contemporary analyses have revealed that the superior survival outcomes of IPMCs are largely attributed to the indolent nature of colloid carcinomas and the fact that a larger proportion of tubular carcinomas have negative lymph nodes when compared to conventional PDAC. The prognosis of tubular variant IPMCs is
The recurrence rates of resected IPMNs (including non-invasive lesions) have been reported in the literature to be 10–27% [22–25]. The recurrence rate and patterns for IPMCs specifically, however, are poorly described due to most studies being underpowered and lacking long-term follow-up. We most recently reviewed our institution’s data (Annals of Surgery, in press), analyzing 84 patients with IPMCs with a median follow-up of 38 months. We found that IPMCs occurred at a rate of 5% at a median of <2 years, significantly more common (9%), and earlier (>4 years) than non-invasive IPMNs. Of the IPMC lesions that recurred, only 14% of them required a reoperation. It is noteworthy that the recurrence rate of IPMCs was unaffected by adjuvant therapy. Independent predictors of recurrence include tubular invasive type, lymph node involvement, and high-grade dysplasia or cancer at the surgical margin during the index resection. While the recurrence of IPMCs occurred at a median of 19 months after surgery, it could also occur as far out as 11 years, which suggests that these patients will need lifelong postoperative surveillance.

**Recurrence Patterns**

The retrospective and underpowered nature of these data does not allow definitive conclusions to be drawn about adjuvant therapy in patients with invasive IPMNs. Given the biological heterogeneity of IPMNs and the need for accurate histopathological stratification before randomization (based on its prognostic implications), randomized controlled trials, although desirable, will be difficult to implement due to the rarity of the disease. At present, there are no formal evidence-based recommendations against or supporting adjuvant chemoradiation in invasive IPMNs. Our practice has been to offer such treatment in the right context, including all patients with positive nodes and node-negative patients with tubular carcinomas that have more than minimally invasive disease or have other bad features such as perineural invasion, but avoiding it in node-negative colloid carcinomas.

**Conclusion**

IPMCs, more commonly occurring in MD-IPMNs, have a better prognosis on the whole when compared to conventional PDAC. This is largely attributed to the superior survival outcomes seen in colloid carcinomas, with 5-year survival rates approaching 61–87%. Conversely, tubular carcinomas often demonstrate more unfavorable clinicopathological features, with a prognosis similar to that of PDACs. Patients with small, tubular carcinomas with no lymph node metastases are more likely to achieve long-term survival. Currently, there is no strong evidence to support adjuvant chemoradiation, and level I data may not be practical because of

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<td>Yamada, 2014 [21]</td>
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*Statistical significance at p < 0.05. n = Sample size of IPMCs.

significantly worse than that of colloid IPMNs, more closely resembling survival outcomes of PDACs (table 1). In a stage-matched control study comparing 61 patients with IPMCs with 570 patients with PDAC, we reported that this survival difference was attributed to more favorable clinicopathological features observed in IPMCs (especially colloid), specifically advanced T stage, nodal metastases, high-grade histology as well as lymphatic, vascular, and perineural invasion [17]. Similarly, in a separate study matching 59 patients with IPMCs with 59 patients with PDAC based on a prevalidated post-resection PDAC nomogram, the Memorial Sloan-Kettering Cancer Center group reported estimated 5-year survival rates of 87, 55, and 23% for colloid, tubular, and conventional PDAC, respectively, with the colloid variant demonstrating a more statistically significant favorable outcome than the tubular subtype and PDAC (p = 0.0001) [16].

**Adjuvant Therapy**

The role of adjuvant chemoradiation in invasive IPMNs is not well defined, with a scarcity of high-quality data in the literature. It is hypothesized that because the carcinogenesis of IPMNs may differ from conventional PDACs (DPC4 loss and p16 mutation are less common in IPMNs) [26–28], chemosensitivities may differ too. Many oncologists are hesitant in recommending adjuvant therapy to this cohort of patients because data demonstrating a benefit are lacking. In contrast, proponents extrapolate preexisting data available for the more common PDAC [29, 30]. In a retrospective review of our institution’s cohort (n = 200), patients with invasive IPMNs receiving chemoradiation had a similar overall and cancer-specific survival when compared to those that did not. However, the group that received chemoradiation presented at higher stages (p = 0.035) and had a higher frequency of positive nodes (p = 0.024) [31]. On the one hand, the Johns Hopkins group reported congruent outcomes, demonstrating that adjuvant chemoradiation conferred a decrease of 57% in confounders-adjusted relative risk of mortality, with patients with positive margins and lymph node involvement benefitting the most from it [32]. The Indiana group, on the other hand, reported differing outcomes. In their cohort of 98 patients, adjuvant chemoradiation did not affect overall survival in both node-positive (17 vs. 22 months; p = 0.67) and node-negative invasive IPMNs (63 vs. 48 months; p = 0.98) [33].
the biological heterogeneity of IPMCs. However, based on our understanding of the natural history of different variants of IPMCs, it is reasonable to recommend adjuvant therapy in patients with tubular IPMCs, IPMCs of gastric epithelial background, or those with regional lymph node involvement.

Disclosure Statement
The authors have no conflict of interest to disclose.

References