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

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Keywords
Intraductal papillary mucinous adenocarcinoma · Prognostic factors · Adjuvant therapy

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, pancreatobiliary, 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.

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 characteristically 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 IPMNs were analyzed based on their histopathological subtypes (colloid, tubular) and epithelial phenotypes (gastric, intestinal, pancreatobiliary, 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.
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
ever, are poorly described due to most studies being underpowered [25]. The recurrence rate and patterns for IPMCs specifically, how -

Table 1. Published series reporting 5-year survival outcomes for colloid and tubular IPMCs and PDACs

<table>
<thead>
<tr>
<th>First author, year [reference]</th>
<th>n</th>
<th>5-year survival, %</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>colloid</td>
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<tr>
<td>Maire, 2002 [34]</td>
<td>73</td>
<td>36</td>
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<tr>
<td>Sohn, 2004 [13]</td>
<td>52</td>
<td>43</td>
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<tr>
<td>Partelli, 2010 [20]</td>
<td>104</td>
<td>54.5</td>
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<tr>
<td>Sadakari, 2010 [35]</td>
<td>30</td>
<td>67</td>
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<tr>
<td>Yopp, 2011 [16]</td>
<td>59</td>
<td>87</td>
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<tr>
<td>Yamada, 2014 [21]</td>
<td>56</td>
<td>71</td>
</tr>
</tbody>
</table>

*Statistical significance at p < 0.05.

n = Sample size of IPMCs.

significantly worse than that of colloid IPMCs, more closely resembl -

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 IPMCs may dif -

Adjuvant Therapy

The retrospective and underpowered nature of these data does not allow definitive conclusions to be drawn about adjuvant ther -

Conclusion

IPMCs, more commonly occurring in MD-IPMNs, have a bet -

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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.

References


Disclosure Statement

The authors have no conflict of interest to disclose.

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