Original Article

Concomitant or antecedent intraductal papillary mucinous neoplasm is not a prognostic factor in resected pancreatic cancer

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Background: Intraductal papillary mucinous neoplasm (IPMN)-associated pancreatic cancer is becoming a common subtype of pancreatic cancer found in resected specimens. The prognostic of this subtype is still under evaluation. The study aims to evaluate the prognosis of IPMN-associated pancreatic adenocarcinoma compared to the conventional pancreatic adenocarcinoma.

Methods: In this study, patients with resected pancreatic neoplasms and IPMN treated at Hospital Israelita Albert Einstein, from January 2016 to December 2020, were analyzed. Overall survival (OS) was estimated using the Kaplan-Meier method, and correlations between the variables of interest and the disease specific OS was assessed by multivariate analysis.

Results: Of 187 patients undergoing resection for pancreatic adenocarcinoma or IPMN, 125 (67%) had pancreatic adenocarcinoma, 33 (18%) had IPMN-associated pancreatic adenocarcinoma, and 29 (16%) had IPMN. Resected IPMN was associated with long-term OS for most of the patients. Similar OS was identified in this study in upfront resected pancreatic cancer associated or not with IPMN. No statistical differences in median OS were identified between resected pancreatic adenocarcinoma and IPMN-associated pancreatic adenocarcinoma (48 *vs.* 44 months, P=0.44). Size of the tumor [hazard ratio (HR), 1.33], resected stage III (HR, 1.31), perineural invasion (HR, 1.58), lymphovascular invasion (HR, 1.44), positive lymph nodes (HR, 1.34), and neoadjuvant treatment (HR, 1.70) were associated with worse outcomes.

Conclusions: Our findings confirm that resected pancreatic cancer has a poor prognosis and IPMN-associated pancreatic adenocarcinoma has the same prognosis as a conventional pancreatic adenocarcinoma. More than half of the cases of IPMN-associated adenocarcinoma already had positive lymph nodes. The impact of neoadjuvant treatment in this group of patients should be investigated in larger cohorts.

Keywords: Intraductal papillary mucinous neoplasm (IPMN); pancreatic cancer; pancreatic neoplasms

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Introduction

Pancreatic ductal adenocarcinoma is one of the most challenging cancers. In 2020, it was estimated 495,000 new cases of pancreatic cancer in the world and was the seventh leading cause of cancer mortality in the same period (1). In Brazil, it was estimated in 2023 around 11,000 new cases (2). Most patients are diagnosed with advanced stages, and the median overall survival (OS) is less than a year (3).

Localized pancreatic cancer is treated with surgery and perioperative chemotherapy (4). The impact of neoadjuvant treatment is being evaluated in multiple trials, and nowadays, is still under evaluation for resectable disease (5,6). For patients with resectable pancreatic cancer, in the SWOG 1505 trial, neoadjuvant chemotherapy with gemcitabine plus nab-paclitaxel or fluorouracil, leucovorin, irinotecan, and oxaliplatin (FOLFIRINOX) regimen followed by surgery resulted in a median OS of about 24 months for both arms (7). Considering the low rates of cure after surgery, better strategies are being developed to diagnose patients with earlier stages and disease burden. One strategy is to follow patients with higher risk of disease, such as germline carriers of pathogenic germline variants or preneoplastic lesions (8,9).

Intraductal papillary mucinous neoplasm (IPMN), is a type of neoplasia that can arise from the pancreatic ducts, it can produce mucus and mostly benign lesions however, it can progress and be a risk for pancreatic cancer (10). The overall risk of progression to carcinoma is between 3% and 15%, being higher among the years after diagnosis (10-14). International consensus has discussed exhaustively IPMN subtypes and proposed guidelines to follow and treat accordingly the risk of progression to cancer (11,12). Most guidelines recommend closely follow-up and further investigation or surgery in cases of worrisome features or higher risk for pancreatic cancer (11,12). Cases of higher risk of progression include main duct IPMN, presence of jaundice, dilatation of the main duct more than 10 mm, mass, or mural nodule above 5 mm or positive cytology (11,12). However, most of those cases could be already pancreatic cancer, and the OS would be already compromised (13,14). Three distinct clinical situations can be associated in the presence of an IPMN and a carcinoma: (I) IPMN-associated adenocarcinoma: this definition indicates a carcinoma resulting from an IPMN and can also be defined as a carcinoma derived from IPMN, which is sequential or probably related; (II) independent IPMN and invasive carcinoma: the two lesions are not related, and this situation is defined as concomitant or *de novo*; and (III) an IPMN and a carcinoma from branch-off pathway, where an invasive carcinoma and an adjacent IPMN develop divergently in a forked fashion from a common ancestral clone (15).

Data about OS of IPMN-associated pancreatic cancer is scarce, and surgical treatment before progression to cancer would probably be beneficial for selected groups of patients. This study aims to address OS of resected patients with IPMN, IPMN-associated cancer and pancreatic ductal adenocarcinoma, in a prospective cohort of patients treated and followed in a tertiary hospital in the same period. We present this article in accordance with the STROBE reporting checklist (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-157/rc).

Highlight box

Key findings

- Intraductal papillary mucinous neoplasm (IPMN) associated adenocarcinoma has a poor prognosis like a conventional adenocarcinoma without IPMN. Neoadjuvant chemotherapy was associated with worse outcomes however larger cohorts would be necessary to address this finding.

What is known and what is new?

- IPMN-associated pancreatic cancer is becoming a common subtype of pancreatic cancer found in resected specimens, whether this is related to better prognosis is unknown.
- In this study, we evaluated 187 cases of resected IPMN, adenocarcinoma and IPMN-adenocarcinoma, and we found no differences in overall survival between the two types of adenocarcinomas. Resected IPMN has excellent prognosis.

What is the implication, and what should change now?

- Based on these findings, it is neither possible nor adequate to affirm that all IPMN should be resected. However, based on the poor prognosis associated with the degeneration to cancer, further studies are necessary for better selection of patients, probably not based only on images but incorporating newer strategies like circulating tumor DNA. Even when most patients with IPMN are followed, more than half of the cases had already positive lymph nodes.

Methods

Patients

Patients with pancreatic resection due pancreatic adenocarcinoma or IPMN seen at Hospital Israelita Albert Einstein from January 2016 to December 2020, with prospective collected data, were evaluated. Data included

sex, age, pathological data and stage for adenocarcinomas [8th edition of American Joint Committee on Cancer (AJCC)/ Union for International Cancer Control (UICC)], adjuvant and neoadjuvant treatment. Median OS was calculated based on the period between diagnosis and date of death or last date of follow-up. The data is available upon request.

Statistic analysis

The OS was estimated using the Kaplan-Meier method. Chi-square regression Cox models were applied for the variables of interest. Statistical significance was set for a P<0.05, and the results were presented as hazard ratios (HRs). All analyses were performed using STATA 16.1 (Copyright 1985–2019 StataCorp LLC, College Station, TX, USA). Statistical significance was set at a threshold of P<0.05.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All experimental protocols were approved according to national standards. The study was approved by the ethics committee of Hospital Israelita Albert Einstein (CAAE: 81744017.6.0000.0071). Informed consent was waived due to the retrospective nature of study and low risk.

Results

Of 187 patients undergoing resection for pancreatic adenocarcinoma or IPMN, 125 (67%) had pancreatic adenocarcinoma, 33 (18%) had IPMN-associated pancreatic adenocarcinoma, and 29 (16%) had IPMN. Clinical and demographic data can be seen in *Table 1*. Median age for all groups ranged around 65–66 years, about half were male in the adenocarcinoma cohort. For both adenocarcinoma grade 2 was the most prevalent grade. About 40% of both adenocarcinoma groups had pancreatic intraepithelial neoplasia (PANIN) in the pathological report. With the majority of the PANINs being higher grades. Positive lymph nodes were observed in about half of patients with adenocarcinoma, with a median lymphadenectomy of 18 lymph nodes and a median overall positivity of one lymph node (*Table 1*).

The median age for patients with IPMN with no adenocarcinoma was 66.3 (43.7–87.3) years, 55% were male, size ranged between 0.6 and 3.5 cm, 58% had PANIN in their pathological report. For those cases with IPMN and associated PANIN, 88% were grade I, and 12% grade 2, no higher grades were identified.

Almost all patients with adenocarcinoma were treated with perioperative chemotherapy. Overall, gemcitabine-based regimens were the most used regimens in adjuvant treatment. About a third of patients were treated with neoadjuvant treatment, mostly modified FOLFIRINOX (mFOLFIRINOX). Resected IPMN was associated with long-term OS for most of the patients, with a median OS not reached (*Figure 1*). No statistical differences in median OS were identified between resected pancreatic adenocarcinoma and IPMN-associated pancreatic adenocarcinoma (48 *vs.* 44 months, P=0.44) (*Figure 1*).

In multivariate analysis, size of the tumor (HR, 1.33), resected stage III (HR, 1.31), perineural invasion (HR, 1.58), lymphovascular invasion (HR, 1.44), positive lymph nodes (HR, 1.34), and neoadjuvant treatment (HR, 1.70) were associated with worse outcomes, however without reaching statistical significance (*Figure 2*). The median OS of resected stage I adenocarcinoma was 54 months; stage II adenocarcinoma was 45 months, and stage III adenocarcinoma was 27 months. The median OS of resected stage I IPMN-associated adenocarcinoma was 30 months, stage II adenocarcinoma was 68 months, and stage III adenocarcinoma were 22 months. No statistical significance was reached between the groups.

Discussion

In this analysis of patients with resected pancreatic cancer and IPMN, the median OS of IPMN-associated adenocarcinoma was like an adenocarcinoma without IPMN.

Recently, multiple guidelines and studies evaluated when and how IPMN should be treated and followed (9-11). However, data about IPMN-associated adenocarcinoma compared to pancreatic ductal adenocarcinoma is scarce. In a series of around 600 patients that undergone pancreatic surgery for IPMN, the median OS of IPMN with low/ intermediate grade dysplasia was like high-grade dysplasia, 118 months, and 92 months, respectively (13). However, in the same study, patients that had invasive carcinoma in the pathological report had markedly worse median OS, of about 29 months (13).

A more conservative approach of IPMN is being a subject of some studies and specialized centers. Nowadays, surgery is formally indicated for IPMN with the defined high-risk stigmata (9-12). The definition of higher risk can change between expert opinions but mostly includes

Table 1 Patients characteristics

Characteristics	Adenocarcinoma (n=125)	IPMN-associated adenocarcinoma (n=33)	P value[†]
Age (years), median [range]	65.4 [34.6–91.3]	65.8 [51.2–90.9]	–
Sex, n [%]			0.18
Male	64 [51]	12 [36]	
Female	61 [49]	21 [64]	
Size (cm), range	0.4–10	1.2–5.7	–
Grade, n [%]			0.05
1	13 [10]	1 [3]	
2	76 [61]	24 [73]	
3	15 [12]	7 [21]	
Indeterminate	21 [17]	1 [3]	
PANIN, n [%]	51 [41]	14 [42]	0.53
Grade, n [%]	51 [41]	14 [42]	–
I	16 [31]	7 [50]	
II	11 [22]	2 [14]	
III	24 [47]	5 [36]	
Staging, n [%]			0.72
I	19 [15]	4 [12]	
II	93 [74]	24 [73]	
III	13 [10]	5 [15]	
Lymph nodes positivity, n [%]	65 [52]	22 [67]	0.19
Resected lymph nodes, median [range]	18 [3–86]	18 [1–81]	–
Positive lymph nodes, median [range]	1 [1–13]	1 [1–28]	–
Adjuvant chemotherapy, n [%]	98 [78]	21 [64]	0.09
mFOLFIRINOX	29 [30]	2 [10]	
Gemcitabine-based and other regimens	69 [70]	19 [90]	
Neoadjuvant chemotherapy, n [%]	29 [23]	11 [33]	0.22
mFOLFIRINOX	24 [83]	7 [64]	
Gemcitabine-based and other regimens	5 [17]	4 [36]	
Deaths, n [%]	61 [49]	20 [61]	–
OS (months), median [range]	48 [30–66]	44 [22–78]	0.44

[†], chi-square. IPMN, intraductal papillary mucinous neoplasm; PANIN, pancreatic intraepithelial neoplasia; mFOLFIRINOX, modified FOLFIRINOX; FOLFIRINOX, fluorouracil, leucovorin, irinotecan, and oxaliplatin; OS, overall survival.

presence of mural nodules or solid masses, presence of jaundice, main pancreatic duct diameter ≥10 mm or positive cytology obtained by aspiration (11,12). However, based on our results and the current data, those findings could be associated with adenocarcinoma already, and the OS of the patient would be already compromised (14). Worrisome features are features related to caution, indicating further investigation or closer look (11,12). These would include

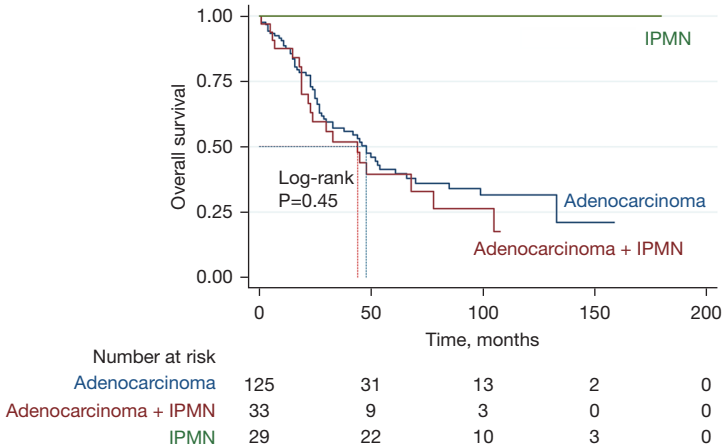

Figure 1 OS of resected patients based on primary diagnosis. IPMN, intraductal papillary mucinous neoplasm; OS, overall survival.

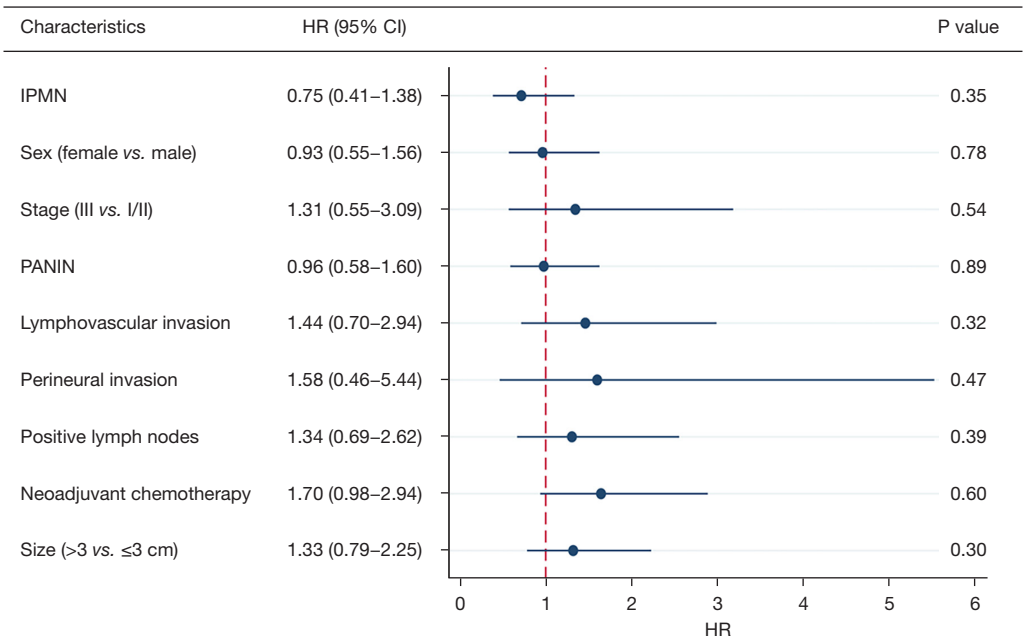

Figure 2 Forest plot analysis. IPMN, intraductal papillary mucinous neoplasm; HR, hazard ratio; CI, confidence interval; PANIN, pancreatic intraepithelial neoplasia.

history of pancreatitis, new onset diabetes, rapid increasing of the cysts or elevated carbohydrate antigen 19-9 (CA19-9). But again, those parameters could be already pancreatic cancer (11,12).

In our data, clinical factors including stage or size of the tumor were not associated with different outcomes when compared both types of adenocarcinomas. It is important to note that all IPMN-associated cancers in this study were adenocarcinomas, colloid tumors are an entity with better prognosis and was not included in our set (14). We also evaluated the presence of PANIN. PANIN are the most common precursors of pancreatic ductal adenocarcinoma (16). PANIN are also divided by grade, from low- to high-grade according to tissue deterioration into invasive neoplasia (16). It is also shown that PANIN shares genomic alterations similar to pancreatic cancer including *KRAS* and *TP53* mutations (16). In this cohort, the presence of PANIN was not related to outcomes in both cohorts of adenocarcinoma.

Interestingly, about half of the resected IPMN presented with combined PANIN, but only low and intermediate grades, a high-grade PANIN were identified in 46% and 36% of the adenocarcinoma and IPMN-associated adenocarcinoma groups, respectively, suggesting that an association with a higher grade PANIN would be related to invasive disease. To confirm these findings further studies would be necessary considering that only 29 patients with IPMN with no adenocarcinoma were evaluated in this study.

During the 4 years of follow-up of the patients, no patient died from IPMN, and about half of patients diagnosed with adenocarcinoma with or without IPMN died from the disease in the same period. Based on these findings, it is neither possible nor adequate to affirm that all IPMN should be resected; because the indication of the procedure would include considerations of the risks associated with the surgery, the overall low risk of degeneration to carcinoma and comorbidities associated with pancreatectomies. However, based on the poor prognosis associated with the degeneration to cancer, further studies are necessary for better selection of patients, probably not based only on images but incorporating newer strategies like circulating tumor DNA (ctDNA). Although patients with worrisome features could be followed with active surveillance, IPMN-associated adenocarcinoma has poor prognosis, this finding is consistent with data from other groups and is a strong rationale for better ways to follow and intervene in those patients (13,14).

This study has some limitations, first, data about response to chemotherapy regimens and time to tumor progression was not assessable, second, although data about somatic and germline testing is important in pancreatic adenocarcinoma, in our center, the recommendation was included in the institutional pathway in the year 2021, so data about pathogenic genomic variants in those cases are not present. And it is a study conducted in a single center. Some strengths of our study include a fair number of pancreatic resections including adenocarcinoma, IPMN-associated adenocarcinoma and IPMN, considering that these entities are somewhat rare. Also, clinical characteristics were evaluated bringing a strong rationale to the findings.

Conclusions

IPMN-associated adenocarcinoma has a poor prognosis akin to pancreatic ductal adenocarcinoma without IPMN. Further studies evaluating the incorporation of molecular biomarkers or ctDNA with the aim of earlier diagnosis could be associated with earlier stages and better outcomes.

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Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-157/rc

Data Sharing Statement: Available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-157/dss

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Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jgo.amegroups.com/article/view/10.21037/jgo-24-157/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). All experimental protocols were approved according to national standards. The study was approved by the ethics committee of Hospital Israelita Albert Einstein (CAAE: 81744017.6.0000.0071). Informed consent was waived due to the retrospective nature of study and low risk.

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