Original Article

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Pancreatic adenocarcinoma: the impact of preneoplastic lesion pattern on survival

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Summary **Pancreatic adenocarcinoma is associated with a very poor prognosis, characterized with a 5-year survival rate of only 5%. Surgery is the only curative treatment for selected patients. Nevertheless, recurrence is very frequent. Identifying prognostic factors is thus warranted. Like numerous other tumors, adenocarcinomas are preceded by preneoplastic lesions. The role and the impact of these lesions remain unclear. This study aimed to assess the impact of the preneoplastic lesion pattern and histo-morphological features, on survival after pancreatic resection. Thirty-five patients who underwent pancreatic resection for pancreatic adenocarcinoma were identified from a prospective database of a single center, between 2003 and 2008. We considered demographics, tumor characteristics and type of treatment. The major outcome was survival. Analyzes were separated into two groups, according to the preneoplastic lesions: Pancreatic intraepithelial neoplasia (PanIN)-related carcinomas and intracanalar papillary mucinous neoplasia (IPMN)-related carcinomas. The former were more frequent, accounting for 63% (22/35). Moreover, they displayed more aggressive features, with a higher tumor stage ($p = 0.01$) and higher rate of positive lymph nodes ($p = 0.019$). Lymphatic ($p = 0.009$) and perinervous ($p = 0.019$) invasions were also more frequent. Survival was negatively influenced by PanIN preneoplastic lesions ($p = 0.015$), T3-4 tumor stage ($p = 0.038$), positive lymph nodes ($p = 0.044$), lymphatic ($p = 0.019$) and vascular ($p = 0.029$) invasions. Pancreatic adenocarcinoma displays different behavior according to its preneoplastic lesion. Indeed, PanIN-related adenocarcinoma showed more aggressive features and lower survival rate. Preneoplastic lesions may represent predictive factors for survival. Their role and predictive value should be investigated more thoroughly.**

Keywords: PanIN, IPMN, pancreatic resection

1. Introduction

Pancreatic adenocarcinoma represents the fourth leading cause of death by cancer, worldwide (*1*). Its aggressive pattern is partially due to the silent course of the disease, with symptoms like jaundice or weight loss occurring late (*1*). Although surgery may be curative for early stages (*2*), overall recurrence rate are high while 5-year survival rate only reaches 5% (*3*). Significant advances have been made in the understanding of the biology and mechanisms of pancreatic cancer, during the last decade. Adenocarcinoma of the pancreas seems to result from successive mutations. A continuum of lesions may be observed between normal parenchyma and adenocarcinoma (*4-7*). The most frequent preneoplastic lesions that usually precede pancreatic adenocarcinoma are subdivided into two types: pancreatic intraepithelial neoplasia (PanINs) and intracanalar papillary mucinous neoplasia (IPMN) (*8-11*). The former is a peripheral lesion affecting small pancreatic ducts (< 5mm in diameter), which is often described, in ductal adenocarcinoma. IPMN are less frequent lesions, usually occurring in the main pancreatic duct or its principle branches (*11*). Characterized by a size greater than 5 mm, they are more likely to be visible on imaging, compared to PanIN. As with PanIN, IPMN appear to follow an adenoma-carcinoma sequence with three continuous steps: low grade adenoma, borderline

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neoplasia, and carcinoma in situ (*12*).

Both preneoplastic lesions, PanIN and IPMN, follow a sequence of events leading to adenocarcinoma. Notwithstanding, tumor progression may be different depending on the preneoplastic lesion (*9*). Studies have described the trend for PanINs leading into ductal adenocarcinoma, and for IPMN evolving toward mucinous adenocarcinoma. Although ductal- and mucinous adenocarcinomas obviously display different outcomes, the impact of various tumor characteristics, like the pattern of preneoplastic lesions remains unclear. In this study, we aimed to analyze the impact of histo-morphological tumors' characteristics on survival, in the setting of pancreatic resection for adenocarcinoma.

2. Materials and Methods

Thirty-five patients who underwent pancreatic resection for adenocarcinoma of the pancreas were identified from prospective databases for pancreas surgery, in the Division of Visceral Surgery at University Hospital of Lausanne (CHUV), between 2003 and 2008. A complete preoperative workup was performed to determine whether the disease was completely resectable and each case had been previously discussed in a tumor board. Surgical procedures were performed by conventional pancreatic resection including pancreaticoduodenectomy and distal splenopancreatectomy. Distal splenopancreatectomy was performed through exclusive abdominal incision or laparoscopic procedure. The artery-first approach was not performed in pancreaticoduodenectomy and reconstruction was done by pancreaticogastrostomy or pancreaticojejunostomy according to pancreas texture (*13*). Patients' demographics, tumor characteristics, type of treatment and survival were analyzed. We considered: age, gender, type of surgery, histological type of tumor, preneoplastic lesion, TNM stage, tumor grade, lymphatic invasion, vascular invasion, neural invasion, margins status, adjuvant therapy and survival (DFS-disease free survival). Due to a limited number of patients, and in order to perform pertinent statistical analyzes, several classes of items were regrouped. Indeed, high grade tumors (G2 and G3) were grouped and compared to low grade tumors (G1). Tumor stages T1/2 were compared to T3/4 stages. The IPMN lesions were classified as low-grade (adenoma) and high grade (borderline neoplasia and carcinoma in situ). The margins status were separated into margins > 0.1cm and margins ≤ 0.1cm. Clinical follow-up was analyzed according to tumor-free survival, survival with disease, death without disease and death with disease.

The overall survival curves were determined using the Kaplan-Meier method and were compared using the log-rank test. A multivariate analysis was performed using a Cox proportional hazards model. A significant value of 0.05 was used in all tests. The statistical analysis was done using SPSS v20 statistical software, Chicago, IL.

3. Results

3.1. *Patients and tumors*

Patients' characteristics are summarized in Table 1. Median age was 69 years while men accounted for 57% (20/35). Tumors were separated in two groups, based on the preneoplastic lesion (Table 1). A majority of tumors were related to PanIN 63% (22/35) while 13 adenocarcinomas (37%) were related to IPMN. Although, the 2 groups were comparable in regard to several characteristics, they were significantly different for the following variables: tumor stage ($p = 0.01$), lymph node ($p = 0.019$), lymphatic invasion ($p = 0.009$) and perineural invasion ($p = 0.019$). Moreover, PanIN-related tumors more frequently required pancreaticoduodenectomy.

3.2. *PanIN-related adenocarcinomas*

They displayed aggressive features with 86% stage T3-4. Moreover, 73% had lymphatic metastasis. Distant metastasis accounted for 14% while a majority presented a high tumor grade G2-3 (86%). Vascular and perinervous invasion were highlighted in 46% and 91%, respectively. Treatment was mostly pancreaticoduodenectomy (91%) while pathological R0 resection was carried out in 46%. Furthermore, 64% of patients received adjuvant therapy.

3.3. *IPMN-related adenocarcinomas*

This subtype of tumors displayed less aggressive features than PanIN-related adenocarcinoma. However, we identified 39% as T3-4 stage, 31% with positive lymph nodes while distant metastasis concerned 15% (2/13). In term of invasion, tumors invaded vessels, lymphatics and nerves in 39%, 31% and 54%, respectively. Surgery was relatively well balanced between pancreaticoduodenectomy (61.5%) and distal splenopancreatectomy (38.5%). Pathological R0 resection was carried out in 54%, and half of the patients received an adjuvant treatment.

3.4. *Survival*

The impact on survival was analyzed for each variable and is described in Table 2. Demographics did not show a significant difference for survival rate. As mentioned above, PanIN-related adenocarcinomas displayed more aggressive features than IPMN-related ones. Indeed, these findings influenced survival with a significantly lower survival rate in the former group ($p = 0.015$, Figure 1). Lymph node metastasis was also identified

Table 1. Characteristics of patients, tumors and treatments

Characteristics	*n* (%) PanIN-related adenocarcinoma (*n* = 22)	*n* (%) IPMN-related adenocarcinoma (*n* = 13)	*p* value
Patients			
Age			0.552
< 70 years	11 (50)	7 (53.8)	
> 70 years	11 (50)	6 (46.2)	
Gender			0.482
Men	12 (54.5)	8 (61.5)	
Women	10 (45.5)	5 (38.5)	
Tumors			
Subtypes			0.004*
Ductal	0	8 (61.5)	
Mucinous	22 (100)	5 (38.5)	
Preneoplastic lesion			
PanIN 1a-b	16 (72.7)	0	
PanIN 2-3	6 (27.3)	0	
IPMN Adenoma	0	4 (30.8)	
IPMN borderline-CiS	0	9 (69.2)	
Stage			0.01*
T1-2	3 (13.6)	8 (61.5)	
T3-4	19 (86.4)	5 (38.5)	
Lymph node metastasis			0.019*
N+	16 (72.7)	4 (30.8)	
N−	6 (27.3)	9 (69.2)	
Metastases			0.626
M+	3 (13.6)	2 (15.4)	
M−	19 (86.4)	11 (84.6)	
Tumor grade			0.103
G1	3 (13.6)	5 (38.5)	
G2-3	19 (86.4)	8 (61.5)	
Lymphatic invasion			0.009*
Yes	17 (77.3)	4 (30.8)	
No	5 (22.7)	9 (69.2)	
Vascular invasion			0.482
Yes	10 (45.5)	5 (38.5)	
No	12 (54.5)	8 (61.5)	
Perineural invasion			0.019*
Yes	20 (90.9)	7 (53.8)	
No	2 (9.1)	6 (46.2)	
Treatment			
Type of surgery			0.05*
Pancreaticoduodenectommy	20 (90.9)	8 (61.5)	
Distal splenopancreatectomy	2 (9.1)	5 (38.5)	
Margins			0.621
≤ 1 mm	12 (54.5)	7 (53.8)	
> 1 mm	10 (45.5)	6 (46.2)	
Adjuvant therapy			0.340
Yes	14 (63.6)	6 (50)	
No	8 (36.4)	6 (50)	

as a prognostic factor and was associated with lower survival ($p = 0.038$, Figure 2).

The invasion of adjacent tissues by the tumor appeared to influence survival, via three mechanisms: direct invasion ($p = 0.038$), vascular invasion ($p = 0.029$) and lymphatic invasion ($p = 0.019$), while perinervous invasion was not associated with poorer outcomes ($p = 0.119$). None of the therapeutic variables influenced survival in our study. Multivariate analysis did not detect any significant impact on survival for the studied variables.

4. Discussion

This study assessed the impact of preneoplastic lesion pattern and histo-morphological features of pancreatic adenocarcinoma, on survival after pancreatic resection. Although, pancreatic adenocarcinoma may be classified according to their subtype: ductal *vs*. mucinous, the preneoplastic lesion pattern appeared to play an important role (*9*). Indeed, PanIN-related tumors displayed more aggressive characteristics than IPMN-related ones. These findings were translated into survival with poorer prognosis in the PanIN-related group. The survival rate at 1-, 3- and 5-years were 69%, 58% and 58% for IPMN-related tumors while it only reached 45%, 19% and 9% for PanIN-related adenocarcinomas.

Tremendous effort has permitted a significant improvement in understanding tumorigenesis of pancreatic adenocarcinoma and precancerous lesions, during the last decade (*14-16*). The pathological

Table 2. Predictive factors of survival

Items	Survival (month) 95% CI	*p* value
Demographics		
Age		0.074
< 70 years	21.7-43	
> 70 years	8.2-11.1	
Gender		0.805
Men	16.8-32.5	
Women	17.1-53	
Tumors		
Subtypes		0.293
Ductal	18.4-43.4	
Mucinous	18-40.1	
Preneoplastic lesion		0.015*
PanIn-related adenocarcinoma	10-32.1	
IPMN-related adenocarcinoma	27-51.6	
PanIN		0.233
PanIN 1a-b	22.7-65.9	
PanIN 2-3	13.7-28	
IPMN		0.029*
IPMN Adenoma	12-35.3	
IPMN borderline-CiS	27.9-55.9	
Stage		0.038*
T1-2	26.2-52.6	
T3-4	13.1-38.1	
Lymph node metastasis		0.044*
N+	11.7-25.3	
N−	33.5-72.3	
Metastases		0.555
M+	11-32.6	
M−	22.3-50	
Tumor grade		0.471
G1	13.9-40.2	
G2-3	16.9-42.4	
Lymphatic invasion		0.019*
Yes	11.4-24.5	
No	36.8-76	
Vascular invasion		0.029*
Yes	9.4-21.4	
No	27-61.3	
Perineural invasion		0.119
Yes	16.5-40.2	
No	20.1-43.7	
Treatment		
Type of surgery		0.291
Pancreaticoduodenectommy	16.5-43.5	
Distal splenopancreatectomy	19.1-41.1	
Margins		0.934
≤ 1 mm	16.1-31.5	
> 1 mm	18.2-55.7	
Adjuvant therapy		0.854
Yes	17.8-32.2	
No	17.5-58.2	

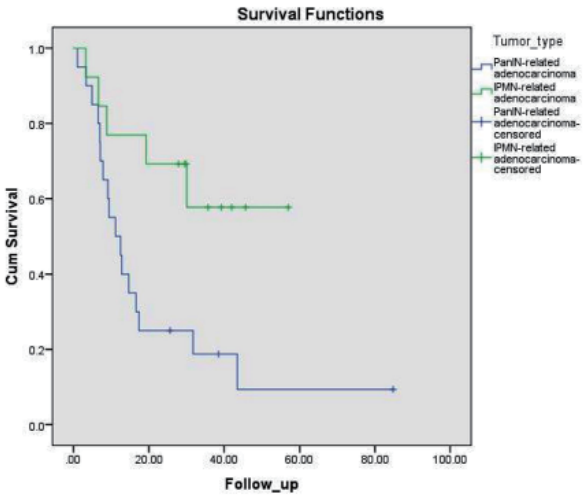

Figure 1. Survival and preneoplastic lesion pattern.

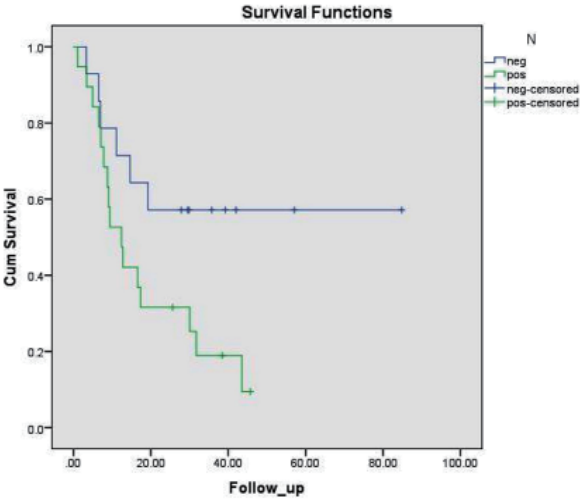

Figure 2. Survival and lymph nodes stage.

characteristics and molecular mechanisms have rapidly evolved, leading to new classification of preneoplastic lesions (*8*). Notwithstanding, the relationship between these findings and the clinical setting is not obvious yet.

This study displays some limitations. The retrospective design leads to missing data and missing variables. Moreover, the number of included patients is relatively low. Based on these potential biases, results should be interpreted with caution.

In a landmark article, Andea *et al*. showed the association between PanIN and ductal adenocarcinomas (*9*). Therefore, the need to address and treat these progressive lesions at an early stage is crucial. Of note, the influence of preneoplastic lesion pattern on survival after resection has rarely or not been addressed, to our knowledge. Based on our results, preneoplastic lesions may play an important role. At least, they may reflect different oncogenic pathways, according to their respective type. Pancreatic adenocarcinomas are heterogeneous tumors with poor prognosis while prognostic tools as biomarkers are somewhat lacking. Identifying subclasses is thus a critical step for the future.

The relatively small number of cases (n = 35) was a limitation of our study. This may be the reason why well-known risk factors, such as perinervous invasion, were not associated with poorer outcomes. This result should be confirmed in a future study carried out in a larger cohort of patients.

In summary, this study supports the influence of preneoplastic lesions on survival, after pancreatic resection for adenocarcinoma. PanIN-related lesions displayed more aggressive features than IPMN-related ones, leading to a lower survival rate. Further studies are needed in order to explore the role of precancerous lesions of the pancreas, in more depth.

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