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Original Article

Chronic pancreatitis and resectable synchronous pancreatic carcinoma: A survival analysis

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ABSTRACT

Background/Objectives: : Chronic pancreatitis (CP) is a risk factor for pancreatic cancer (PDAC). CP and PDAC are characterized by an abundance of desmoplastic tissue. The effect of this pancreatic desmoplastic tissue on PDAC is poorly understood. In literature, negative and positive effects on the natural course of PDAC have been discussed. The present analysis aims to assess the impact of CP on patients with resectable synchronous PDAC regarding short- and long-term survival.

Methods: : All patients who underwent pancreatic resection at our institution from January 2005 to January 2014 were retrospectively evaluated. Definition of CP was based on clinical and radiological aspects and histological confirmation as used previously. We identified patients with CP, CP and PDAC, and PDAC without CP and compared perioperative course and survival. Statistical analysis was performed by chi-square, Kruskal-Wallis/Mann-Whitney-U and Breslow survival analysis. P-values <0.05 were defined as statistically significant.

Results: : 159 patients met our inclusion criteria for CP. 49 of them (30.8%) had synchronous PDAC. 145 patients had PDAC without a history of CP. There was a more advanced nodal involvement in PDAC patients with CP. Perioperative outcome and long-term survival of PDAC patients with and without CP did not differ significantly.

Conclusion: : In a large clinical series CP had no impact on survival of patients with PDAC after resection with curative intent.

Introduction

Chronic pancreatitis (CP) is a fibrotic reaction of the pancreatic connective tissue due to an ongoing inflammation with loss of exocrine and endocrine function [1]. The incidence of CP varies between 4 and 14/100.000 worldwide [2]. Patients with CP mostly suffer from pain, but can also develop mechanical complications [3]. Additionally, patients with CP carry a 13.3-fold higher risk for developing pancreatic ductal adenocarcinoma (PDAC) [4]. Therefore, clinicians will encounter patients with CP and synchronous PDAC [5]. Unfortunately, the diagnosis of early lesions of PDAC in patients with CP is still a clinical challenge [6]. Symptoms of cancer can mimic an acute episode of pancreatitis in patients with CP. This leaves the patient at risk to be underdiagnosed, especially as medical imaging still cannot accurately distinguish between inflammatory and malignant tumours [6–8]. Interestingly, the clinical impact of the interaction of CP with synchronous PDAC is still unclear. Both positive and negative effects of the desmoplastic reaction on the natural course of PDAC have been discussed. A recent retrospective analysis, for example, showed a prolonged survival in PDAC patients with acute or chronic pancreatitis at initial presentation [9]. One beneficial aspect of desmoplasia might be that the malignant process is encapsulated by the tumor host connective tissue and further local invasion is impeded [10]. Perineural invasion is one of the most important mechanisms for PDAC with regard to local infiltration and growth. In fact, it was shown that inflammatory cells in CP cause severe intrapancreatic neural damage [11,12]. Therefore, PDAC growth along the important neural structures is impeded. However, desmoplasia might also be of disadvantage for the patient. The desmoplastic reaction is thought to block an effective chemotherapy due to reduced intratumoral vessel density [13,14]. Furthermore, the abundance of inflammatory messengers within the microenvironment in CP leads to more aggressive growth of cancer cells [15,16].

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To our knowledge, there is currently no study addressing the influence of CP on the clinical course of PDAC. Therefore, the aim of our study was to evaluate whether there is a survival benefit or disadvantage for PDAC patients with underlying CP compared to PDAC patients without CP after resection with curative intent.

In order to clearly distinguish patients with pre-existing CP from patients with new onset pancreatitis as symptom of PDAC we used a definition for CP which combines well defined clinical, radiological, and histological aspects as described previously [6].

Methods

Patients

The institutional review board granted approval for this retrospective review of patient charts at the Department of Surgery, University Hospital Mannheim, University of Heidelberg. All patients who underwent pancreatic surgery at our department from January 2005 to July 2014 were included. In a first step, we identified individuals in our prospective pancreatic database who met our definition of CP ("CP") as described previously [6,17]. In brief, CP was defined as the combination of a typical history with two out of four additional criteria (clacifications at CT-scan, alcohol abuse, history lasting longer than 12 months, histologically confirmed CP). In a second step, we determined which of these patients had synchronous PDAC ("CP + PDAC"). Patients with PDAC without a history of CP served as control group ("PDAC"). Patients with significant missing clinicopathological data or tumours not clearly defined as PDAC were excluded (Fig. 1).

Data collection and definitions

Patient characteristics included age, gender, body mass index (BMI), comorbidity profile and risk factors. Comorbidities were listed for cardiac history (coronary artery disease, congestive heart failure, history of myocardial infarction, artificial valves), pulmonary diseases (chronic obstructive pulmonary disease, pulmonary hypertension, bronchial asthma), hypertension (HTN) and diabetes mellitus (DM). We further assessed risk factors such as history of smoking and alcohol abuse. Aetiology for chronic pancreatitis was determined as „alcoholic", „idiopathic" and „hereditary" causes. Specific pancreatic morbidity was recorded according to the criteria of the international study group of pancreatic surgery (ISGPS) as postoperative pancreatic hemorrhage (PPH) [18], postoperative pancreatic fistula (POPF) [19] and postoperative delayed gastric emptying (DGE) [20]. To determine the long-term survival, all patients were followed up by telephone in January 2015 and the survival period or the time of death was recorded. Patients with loss to follow up were censored.

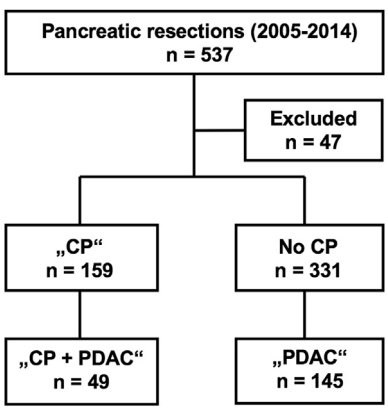

Fig. 1. Flow chart of study.

Statistics

All clinical and pathological characteristics were grouped to build categorical or nominal variables. The cut-off points used for categorizations were based on previously described cut-off points in the literature and/or recursive partitioning as previously described [6]. The Kruskal-Wallis-Test with a post hoc Mann-Whitney-U-Test was performed for continuous parameters (nonparametric data). Continuous data are presented as 95% confidence intervals (95% CI) and SD. Categorical variables were compared using the chi-square-test or Fisher-exact test. Univariate examination of the relationship between assessed criteria and the different patient cohorts was performed with χ^2-test. Survival analysis was done by using the Kaplan-Meier method with the Breslow-Test (generalized Wilcoxon). *P*-values <0.05 were defined as statistically significant. Results were reported as median (IQR, interquartile range) and proportions (%) as applicable. SPSS version 21.0 (IBM Corporation, Armonk NY) was used for all statistical analyses.

Results

Patient cohort

Of 490 patients who met our inclusion criteria 159 patients were identified with CP and 331 patients without a history of CP (Fig. 1). We further divided the patients in cohorts of CP and synchronous PDAC ("CP + PDAC", n = 49), PDAC only ("PDAC", n = 145), and CP only ("CP", n = 110). All 49 specimens of patients in the "CP + PDAC" group had signs of CP confirmed by histology. The characteristics of our patient cohort are summarized in Table 1. The median age of patients with PDAC only (68 years, IQR 60-74) and CP with synchronous PDAC (66 years, IQR 59-75) was significantly older compared to patients with CP only (55 years, IQR 48-66, p = 0.001). The CP only group showed a decreased median BMI level of 24 (IQR 21-27) in comparison to "PDAC" (p = 0.006) and "PDAC + CP" (p = 0.07) with a median BMI level of 25 (IQR 23-28), respectively. The frequency of smoking was significantly higher in the "CP" group (n = 66, 60.0%) and "CP + PDAC" group (n = 22, 44.9%) compared to "PDAC" group (n = 28, 19.3%, p < 0.001). Similarly, the prevalence of alcohol abuse was significantly higher in patients with CP only (n = 63, 57.3%) and in the "CP + PDAC" group (n = 19, 38.8%) compared to patients with PDAC only (n = 14, 9,7%,

Table 1
Characteristics of our patient cohort.

	PDAC (n = 145)	CP + PDAC (n = 49)	*p-value*
Age (years, IQR)	68 (60–74)	66 (59–75)	0.278
Sex	145	49	0.512
male	78 (53.8%)	29 (59.2%)	
female	67 (46.2%)	20 (40.8%)	
BMI (IQR)	25 (23–28)	25 (23–28)	0.964
Cardiac history	43 (29.7%)	12 (24.5%)	0.488
Pulmonary history	21 (14.5%)	9 (18.4%)	0.528
HTN	84 (57.9%)	29 (59.2%)	0.226
Diabetes	43 (29.7%)	19 (38.8%)	0.261
Smoking	28 (19.3%)	22 (44.9%)	0.001[a]
Alcohol abuse	14 (9.7%)	19 (38.8%)	0.001[a]

PDAC pancreatic ductal adenocarcinoma, CP + PDAC patients with chronic pancreatitis and synchronous pancreatic ductal adenocarcinoma, IQR interquartile range, BMI body mass index, HTN arterial hypertension.
[a] p < 0.05.

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