Acute Pancreatitis as the Initial Presentation of Pancreatic Adenocarcinoma does not Impact Short- and Long-term Outcomes of Curative Intent Surgery: A Study of the French Surgical Association

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Acute pancreatitis as the initial presentation of pancreatic adenocarcinoma does not impact short- and long-term outcomes of curative intent surgery. A study of the French Surgical Association

short title : acute pancreatitis before pancreatic resection

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Abstract (words 250)

Background**:** Acute pancreatitis (AP) can be one of the earliest clinical presentation of pancreatic ductal adenocarcinoma (PDAC). Information about the impact of AP on postoperative outcomes as well as its influences on PDAC survival is scarce. This study aimed to determine whether AP as initial clinical presentation of PDAC impact the short- and long-term outcomes of curative intent pancreatic resection.

Patients and Methods: From 2004 to 2009, 1449 patients with PDAC underwent pancreatic resection in 37 institutions (France, Belgium and Switzerland). We used univariate and multivariate analysis to identify factors associated with severe complications and pancreatic fistula as well as overall and disease-free survivals.

Results: There were 764 males (52,7%) and the median age was 64 years. 781 patients (53.9%) developed at least one complication, among whom 317 (21.8%) were classified as Clavien-Dindo ≥ 3. 114 (8.5%) patients had AP as the initial clinical manifestation of PDAC. This situation was not associated with any increase in the rates of postoperative fistula (21.2% vs 16.4%, p=0.19), postoperative complications (57% vs 54.2%, p=0.56), and 30-day mortality (2,6% vs 3,4%, p=1). In multivariate analysis, AP did not correlate with postoperative complications or pancreatic fistula. The median length of follow-up was 22.4 months. The median overall survival after surgery was 29.9 months in the AP group and 30.5 months in the control group. Overall recurrence rate and local recurrence rate did not differ between groups.

Conclusion: AP before PDAC resection did not impact postoperative morbidity and mortality, as well as recurrence rate and survival.

Key words: Acute pancreatitis; pancreatic ductal adenocarcinoma; complications; pancreatic fistula; survival; recurrence

Introduction

In 2018, a total of 458,918 new cases of pancreatic cancer and 432,242 related deaths were reported throughout the world[1] and pancreatic ductal adenocarcinoma (PDAC) is the most frequent type of pancreatic cancer[2]. The global age-standardized rates (ASR) of incidence is estimated to be 4.8 per 100,000, with the highest incidence rates observed in Western Europe, North America, and Central and Eastern Europe[1]. Actual 5-year survival for PDAC is still below 5% with the highest mortality rates observed in Europe and North America[1,3] .

There are many clinical features associated with PDAC such as weight loss, abdominal pain and jaundice. Acute pancreatitis (AP) is an uncommon initial presentation of PDAC[4,5]. In most patients, the acute inflammatory response and pancreas damage ultimately resolve[6]. Nevertheless the need to wait for the resolution of AP related inflammation before surgery may be associated with pre-hospital, but also hospital delays in diagnosing and treating patients[7]. Since PDAC is a rapidly progressing disease, an adverse correlation between the delay of treatment initiation and prognosis seems likely[8,9]. Furthermore, although the stimulation of PDAC progression and metastases by the inflammation associated with AP[6,10] remains speculative in humans, animal studies have identified that AP could markedly accelerate pancreatic cancer development[11].

It is unclear if AP is a potential means for earlier diagnosis of PDAC[12] or, on the contrary, might delay it[4]. Herein, Kimura et al. showed that only the detection of a pancreatic mass enabled the early diagnosis of pancreatic cancer at the onset of acute pancreatitis[13].

Indeed, up to date, the question whether PDAC patients with an inaugural AP have different outcomes from those without, remains unsolved. Thus, the primary aim of our study was to determine whether AP as the main clinical presentation of resected PDAC affects early-outcomes and influences survival.

Patients and Methods

Patient selection and data collection

In 2009, the French Surgical Society (*Association Française de Chirurgie*) asked its members to collect data of all consecutive patients who underwent resection for pancreatic cancer. Medical records from patients consecutively diagnosed between 2004 and 2008 were entered retrospectively, whereas data from patients operated during 2009 were collected prospectively. A total of 1887 patients underwent pancreatic resection for PDAC in 37 institutions (France, 34; Belgium, 1; Monaco, 1; Switzerland, 1). All patients from each participating center were collected in the study period. A standardized form was created to retrieve information on preoperative, intraoperative and postoperative data. Three experienced pancreatic surgeons (FP, PB, JRD,) reviewed all data sheets before their transfer into the database in order to get a uniform interpretation of the retrospective data[14–16].

Only patients with non-metastatic PDAC were included. Thus, distal bile duct cancers, duodenal and ampullary tumors, benign cystic lesions as well as cystadenocarcinomas and neuroendocrine tumors were excluded. Finally, to ascertain coherence of the population study, we also excluded patients with confirmed history of chronic pancreatitis (N=83). The remaining 1449 patients were included in this study. Thus, we compared patients with acute pancreatitis (AP group) as the first sign of PDAC with those without acute pancreatitis (control group). A subgroup analysis including only pancreatoduodenectomies (PD) (N=1140) was also performed.

Owing to the multicentric and retrospective design, pancreatic resection and pathological analyses were not standardized among centers and therefore could not be described precisely[17].

Patient's characteristics included demographic data (age, gender, ASA score, body mass index [BMI], presence of preoperative jaundice and biliary stenting, acute pancreatitis as initial manifestation of PDAC). Intraoperative data included type of pancreatic resection,

vascular resection, intraoperative transfusion, and prophylatic use of somatostatin analogue. Postoperative data included in-hospital mortality (in-hospital mortality or death within the first month after patient discharge), complications graded according to Clavien-Dindo classification system[18]. A severe complication was defined as grade III or IV. Grade V was considered as in-hospital mortality and excluded from the study of long-term survival. For patients with multiple complications, the highest grade was considered. Postoperative pancreatic fistula (POPF) was defined in accordance with the guidelines of the international study group of pancreatic surgery (ISGPS)[19]. A clinically relevant POPF (CR-POPF) was defined as grade B or C. Postpancreatectomy hemorrhage and delayed gastric emptying (DGE) were defined according to ISGPS classification[20,21]. Reoperation, length of hospital stay, and adjuvant treatment were also recorded.

Tumors were graded according to the 7th edition of the American Joint Committee on Cancer staging manual[22]. Tumor size was categorized as ≤2 cm, >2 cm but ≤4 cm, and >4 cm in maximal diameter. At the time of this study, a positive margin was defined as tumor present at the resection margin (R1=0 mm).

End points

We compared patients with acute pancreatitis (AP group) as the first sign of PDAC with those without acute pancreatitis (control group) in both the whole population and the subgroup of patients who underwent PD. Primary end point was the presence of severe postoperative complication (defined as Clavien-Dindo ≥IIIA). Secondary end points included intraoperative complications (rate of extended resection and volume of blood transfusion); short-term postoperative results (occurrence of any complication, rate of pancreatic fistula); pathological findings (size of the tumor, number of harvested lymph nodes, and rate of incomplete resection); and long-term results (recurrence rate, disease free survival and overall survival).

In order to adjust the impact of AP for potential confounders, we performed multivariate analysis.

Statistical analysis

Two biostatistician (MF and AB) performed statistical analysis. Quantitative data were expressed as mean ± standard deviation and median, qualitative data as frequency and percentages (if applicable, missing data were not included in the denominator). Comparisons of means were performed using the Student's t-test. Comparisons of frequencies were performed using the Chi square test and the Fisher's exact test as appropriate. Comparison of median was performed using the Mood's Median test. Kaplan-Meier's method was used to calculate PFS and OS estimates. Comparison of OS and PFS were tested with the log-rank test. A p value <0.05 was considered significant. The multivariable analysis was done with a Cox Proportional Hazard model for time to event endpoints (OS, DFS), and binary logistic regression for dichotomous ones (severe postoperative complications, postoperative pancreatic fistula). No variable selection method was used for the variables included in the multivariate analysis. Multivariate analysis included the presence of acute pancreatitis as the initial symptom and clinically pertinent variables with a p-value < 0.3 in univariate analysis. It was performed to identify factors related to severe postoperative complications, grade B/C postoperative pancreatic fistula, disease-free survival and overall survival. Statistical analyses were performed using R software version 3.2.3 (http://www.r-project.org).

Results

Patients' characteristics

Overall, 1449 patients underwent pancreatic resections. There were 764 males (52.7%) and the median age was 64 years. The ASA score was graded ≥ 3 in 210 patients. Jaundice was present in 876 (60%) patients at time of surgery and a biliary stent was inserted preoperatively in 389 (27%) patients. Obesity (BMI > 30 kg/m²) was present in 9% of patients. One hundred fourteen patients (8.5%) developed an inaugural AP before the diagnosis of PDAC. Patients were significantly younger in the AP group (61 ± 10.2 years vs 64.8 ± 11 years; p <0.001), and this difference persisted in the PD subgroup analysis (60.5 ± 10.7 vs 64.8 ± 11.1 years; p<0.001). Jaundiced patients were more frequent in the control group (62% vs 42%, P<0.0001) whereas the proportion of patients who had a biliary stent inserted preoperatively did not differ between groups (27% vs 26%, P=0.78). These results did not vary for the PD subgroup analysis. Patients' demographics are summarized in **table 1**.

Surgical procedure

1140 patients (78.7%) underwent PD, 228 (15.7%) underwent distal pancreatectomy (DP) and 73 (5%) underwent total pancreatectomy (TP). Venous resection was performed in 395 (27.2%) patients and 33 (2.3%) patients had arterial resection. Associated multi-visceral resection was performed in 133 (9.2%) patients. There were no statistically significant differences between the type of surgical procedure, the rate of extended (vascular and/or visceral) resection and the volume of blood transfusion between groups. Surgical procedures are detailed in **table 1**.

Primary end-point

Overall, 781 patients (53.9%) developed at least one complication, among whom 317 (21,8%) were classified as Clavien-Dindo ≥ IIIA (severe). In multivariate analysis, only age, male sex, obesity, and the absence of neoadjuvant therapy were associated with severe postoperative

complications. Indeed, AP as the initial clinical presentation of PDAC was not related to the occurrence of severe postoperative complications in neither univariate nor multivariate analysis (OR 1.07 [95% CI 0.60 – 1.83], p=0.8). **Table 2** and **table 3**.

Early outcomes (secondary end points)

Forty-seven (3.2%) died during the first 30 days after surgery. No significant differences were observed between the two groups regarding postoperative fistula rate and location (pancreatic, biliary or digestive), complication rate (overall or severe), reoperation rate, readmission and mortality. Distribution of complications is given in **table 2**. Multivariate analysis of factors related to postoperative grade B/C pancreatic fistula can be found in the **supplementary table 1**.

Pathological findings

Tumor size was ≤ 4 cm in 796 (59%) patients. Patients with inaugural acute pancreatitis had tumors ≤ 4 cm more frequently than the control group (43.4% vs 35.6%) although it did not reach statistical significance (p=0.07). The number of harvested lymph nodes (LN) was significantly greater in the AP group (21.4 vs 19.6; P=0.02) and it was confirmed in the PD subgroup analysis. Number of positive lymph nodes, presence of tumor emboli and surgical margins were not different between groups. Pathological findings are described in detail in **table 4**.

Adjuvant treatment and long-term survival

Table 5 summarizes survival analysis. The median length of follow-up was 22.4 months. Patients who died in hospital or after discharge on any day within the first 30 days after surgery were excluded from the long-term survival analysis. The median overall survival after surgery was 29.9 months (95% CI 27 – NA) in the AP group and 30.5 months (95% CI 27 – 34.4) in the control group (p=0.54). Overall recurrence rate (42% vs 47%, P=0.39) and local recurrence rate (25% vs 29%, P=0.1) did not differ between groups. Multivariate analysis

revealed venous resection, N+ patients and no adjuvant treatment to be associated with worst overall survival, as shown on **table 6**. Indeed, inaugural AP was not associated with survival in multivariate analysis. **Figure 1** illustrates overall and disease-free survivals.

Discussion

In this retroprospective study of 1,449 resected PDAC, patients with an initial history of AP before the diagnosis of PDAC were younger. Localization of the tumor inside the pancreas, and the corresponding type of surgery did not differ between AP and control group. The need for multivisceral and/or vascular resection and the volume of intraoperative transfusions were not different. Postoperative morbidity and mortality were comparable. At last, AP before pancreatectomy did not affect disease-free and overall survivals.

AP is reported to be an early and rare symptom of PDAC[23]. In our series, AP represented 8.5% of resected PDAC patients, in accordance with the reported incidence of 1.2% and 13.8%[12,13,24–26]. AP due to PDAC has been reported to be more frequent in females[27], smokers[28], and patients with more comorbidities[25,28]. Also, AP patients have been reported to undergo more frequently surgical resection[12] and to be younger[25,27,28] as observed in our series (median age of 61 years vs 65 years).

Some authors consider AP to be an early marker of pancreatic cancer[12,26]. As AP is a painful condition, patients are likely to seek medical care, which could lead to a cancer diagnosis at an earlier stage, particularly for distal pancreatic cancers. We observed a tendency towards a smaller size of the tumors in the AP group in accordance with this assumption and it is supported by previous studies [12,25,28,29]. Why most tumors, although obstructive, do not trigger AP but only upstream dilatation of the pancreatic ducts and parenchymal atrophy remains unknown. AP is probably more likely related to the anatomy of the ducts in which the tumor arises. The pancreatic site of the obstructive tumor was not correlated with the risk of acute pancreatitis, since it was comparable in AP and control group.

The natural history of PDAC is overwhelming: i) the progression time from stage T1 to T4 is estimated to be 1 year[8]; ii) tumors >2 cm develop CT-detectable metastases in a mean period of 3.5 months (range 1.2–8.4 months)[30], and iii) assuming exponential tumor growth, the

speed of tumor cell replication is highest just before treatment initiation[31]. Thus, earlier diagnosis and treatment could contribute to better patient survival[27]. Contrary to others [12,23,25,28,29], however, we did not find any improvement of DFS or OS in the AP group compared to controls. This comparable survival despite younger age and the tendency towards smaller tumors could result from the inflammation associated with AP. Inflammation might indeed promote PDAC progression and metastasis[6,10] as in animal experimental studies reporting that AP markedly accelerates pancreatic cancer development[11]. On the opposite, it must be emphasized that our survival analysis did not take account the waiting delay frequently induced by the AP prior to surgical resection. Thus, survival from the very first symptom might be improved in the AP group compared to controls, but this remains hypothetical.

Comparison with the published literature is challenging. The studied periods between the onset of an AP episode and the diagnosis of PDAC varies widely, ranging from ten days to two years[5,12,24,25,28]. Information on tumor stage from administrative databases is often missing, and clinical staging of PDAC is particularly difficult when inflammation co-exists[32]. Finally, tumor stage may be inaccurately determined in patients not undergoing surgery.

To our knowledge, there is no guideline concerning the timing of surgical intervention in patients with PDAC associated pancreatitis. Pancreatic edema and peripancreatic inflammation can render pancreas resection and pancreatic anastomosis hazardous. Li and Tian.[5] suggested that 24 days was the most apposite cutoff for surgery, and showed a significant difference in postoperative morbidity (7.1% vs 44%) and equivalent postoperative survival. In a large Danish study, Kirkegård et al. grouped patients into three groups according to waiting time between AP and pancreatic resection (<4 weeks ; 4-8 weeks ; and ≥8 weeks) and found that waiting time to surgery did not affect survival in patients

undergoing surgery for pancreatic cancer[25]. Herein, the wait time paradox and its association of longer delays with better outcomes has already been described[33–35].

The main strengths of our study are the large sample size collected in a short period of time and the histological confirmation of the PDAC obtained in all patients. The multicentric design reflects the common reality in comparison with the experience of highly specialized tertiary centers. The major limitations of this study are its retrospective nature, lack of available data about the severity of AP and the delay between AP and pancreatectomy. Determine the optimal timing of pancreatic surgery after AP was not the aim of our study but it is clinically relevant and deserves further research.

Also, we can not be completely sure that some patients' pancreatitis were not related to biliary stent insertion. The data collection sheet used for this study specifically argued investigators about acute pancreatitis as the initial clinical presentation of PDAC. Therefore, acute pancreatitis following ERCP should not be included. It seems to be the case because both groups have the same frequency of biliary stenting (26.6% vs 27.9%) although jaundice was significantly more frequent in the control group (62.1% vs 42.1%, $p<0.001$).

Conclusion

In conclusion, in this retrospective multicenter series of 1449 patients with resected PDAC, inaugural AP was a rare event occurring in younger patients. AP as the initial presentation of PDAC was not associated to worst short-term results nor a less favorable survival after curative intent pancreatic resection.

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Figure's legend

Figure 1. Disease-free and overall survival curves. A, DFS for the whole series; B, DFS for the PD subgroup; C, OS for the whole series; D, OS for the PD subgroup