Prognostic factors following pancreaticoduodenectomy for pancreatic ductal adenocarcinoma

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ABSTRACT

Background: Pancreatic ductal adenocarcinoma (PDAC) had a poor prognosis and surgical resection remains the only potentially curative treatment. The aim of the study was to identify the outcome and risk factors affecting survival after pancreaticoduodenectomy (PD) for PDAC.

Methods: The patients who underwent PD for PDAC from 2007 to 2015 were retrospectively studied. Cox regression test for multivariate analysis was used for evaluation of prognostic factors for survival.

Results: Ninety-four patients underwent PD for PDAC, 20 patients (21.3%) had major postoperative complications. The perioperative mortality was 4.3%. The 1-, 3-, and 5-years survival rates were 74.5%, 38.7%, 23.4, respectively. In univariate analysis the risk factors for survival were; presence of co-morbidity (P=0.03), high preoperative carbohydrate antigen (CA)19-9 > 400U/ml (P=0.02), advanced tumor stage (P=0.03), large tumor diameter >3cm (P=0.01), poorly differentiated tumor (P= 0.02), involved resection margin (P=0.04), and positive lymph nodes in pathology after surgery (P=0.03). In multivariate analysis the independent risk factors for survival were; high preoperative CA 19-9 (P=0.042), tumor size >3cm (P=0.038), poorly differentiated tumor in histopathology (P=0.045).

Conclusions: High tumor marker CA19-9, tumor size, and grade are significant risk factors for poor survival after resection of PDAC and should be taken into account in the selection of patients for surgery to improve the outcome.

Keywords: Pancreatic duct adenocarcinoma, Pancreaticoduodenectomy, Postoperative complications, Pancreatic fistula, Survival

INTRODUCTION

Patients with pancreatic tumors still have a poor prognosis. Surgical resection of pancreatic ductal adenocarcinoma (PDAC) remains the only potential curative management to achieve long survival. At the time of diagnosis, only 30-40% of the patients can have a resectable tumor.
The 5-year survival after Pancreatoduodenectomy (PD) for cancer pancreas ranges from 10% to 25% at high volume centers.1-3

Early diagnosis, Meticulous selection of the patients who are liable for resection, and referral of these patients to specialized centers can improve the short and long-term outcome.

For a better selection of the patients that may have the benefits of the surgery and postoperative adjuvant therapy, we should assess the risk factors that can affect the outcome.

Most of the studies reported these prognostic factors for survival after resection of PDAC like; the age of the patients at the time of surgery, one or more co-morbidity, tumor size and stage, pathological grade of the tumor, the presence of positive lymph nodes (LNs), the surgical margin of resection.4-6

The aim of this study was to analyze the clinical outcome and the potential prognostic factors that may affect survival after PD for PDAC.

METHODS

Patients who underwent PD for PDAC from May 2007 to May 2015 at National Liver Institute (NLI), Menoufia University, Egypt were retrospectively conducted in this study.

The diagnosis of PDAC was done by the histopathological study of the specimen after surgery. Other types of pathology after PD or other periamillary adenocarcinoma were excluded from present study.

The collection of data was approved by the institutional review board of our NLI. Patients characteristics, preoperative clinical data, operative, and pathological data were collected and analyzed.

Patients underwent surgery due to the diagnosis of pancreatic head mass with suspicious of malignancy by multislice triphasic computed tomography or magnetic resonance image then confirmed by the postoperative pathological study.

Classic Whipple's operation or the pylorus-preserving PD (PPPD) was done according to the intraoperative decision of the surgeon.

Pancreatic stump anastomosis to the stomach or jejunal loop was done according to each surgeon experience.

Venous resection was done if there was partial involvement in the wall of the portal vein to have R0 resection.

Postoperative follow up to the patients was from the date of surgery to May 2018 with median 49 months follow up period. Clavien grades were used for assessment of postoperative complications.7

Grades I and II were considered as minor complications and any grade above this was recorded as a severe complication.

We used the International Study Group of Pancreatic Surgery (ISGPS) definitions and grading for postoperative pancreatic fistula (POPF), delayed gastric emptying (DGE), and post pancreatectomy hemorrhage (PPH).8-10 The hospital mortality was considered as a perioperative mortality.

Statistical analysis

The statistical analysis of the data was performed by version 23.0 of SPSS (Chicago, IL, USA, SPSS, Inc). The Fisher’s exact test or a χ²-test was used in the univariate analysis of risk factors for survival.

A Cox regression test with likelihood ratios was employed in the multivariate analysis for the independent risk factors of survival. Patients survival was calculated and plotted using Kaplan-Meier method. A P-value was considered significant if less than 0.05.

RESULTS

Ninety-four patients underwent PD for PDAC. Table 1 shows the patients’ characteristics, preoperative clinical data, operative, and pathological data.

The main preoperative complaints were jaundice in 60.6% and anorexia or nausea in 47.9% of the patients.

A preoperative biliary stent was done in 51 patients (54.3%) by endoscopic retrograde cholangiopancreatography (ERCP) or percutaneous transhepatic biliary drainage (PTD).

Classic Whipple's operation was done in 57 patients (60.6%) and pancreatojejunoanastomosis was the main type of pancreatic anastomosis in 69 patients (73.4%) by duct to mucosa in 55.1% of these patients.

Twenty-eight patients (29.8%) had no postoperative complications and 20 patients (21.3%) had major complications mainly grade III (Table 2).

Seven patients (7.4%) underwent reoperation due to postoperative bleeding, and pancreatic, biliary or gastric leak.

The perioperative mortality was 4.3%. The 1, 3, and 5 years survival rates were 74.5%, 38.7%, 23.4% respectively (Figure 1).
**Table 1: Patients characteristics, preoperative, operative and pathological data.**

| Variables                        | Patients with PDAC (n=94) |
|----------------------------------|---------------------------|
| Age (y)                          | Mean±SD (range)           |
| Male gender                      | 5861.7%                   |
| Body mass index (kg/m²)          | ≤25 43 (45.7%)             |
| ≥25                              | 51 (54.3%)                |
| Co-morbidities (yes)             | 58 (61.7%)                |
| DM                               | 30 (31.9%)                |
| HTN                              | 35 (37.2%)                |
| Main symptoms                    |                           |
| Abdominal pain                   | 36 (38.3%)                |
| Jaundice                         | 57 (60.6%)                |
| Loss of weight                   | 42 (44.7%)                |
| Anorexia, nausea, vomiting       | 45 (47.9%)                |
| Preoperative total bilirubin (mg/dl) | 4.4±5.5 (0.7-21)   |
| ALT (U/L)                        | Mean±SD (range)           |
| Albumin (g/dl)                   | 3.5±0.6 (2.9-4.1)         |
| CA 19-9 (U/mL)                   | Mean±SD (range)           |
| Normal                           | 31 (33%)                  |
| High                             | 63 (67%)                  |
| Preoperative biliary stent       | 51 (54.3%)                |
| Type of operation                | Whipple 57 (60.6%)        |
| PPPD                             | 37 (39.4%)                |
| Pancreatic texture               | Firm 56 (59.6%)           |
| soft                             | 38 (40.4%)                |
| Type of pancreatic reconstruction| Pancreaticogastrostomy 25 (26.6%) |
| Pancreatecojejunostomy           | 69 (73.4%)                |
| -invagination                    | 31 (44.9%)                |
| -duct to mucosa                  | 38 (55.1%)                |
| Vascular reconstruction          | yes 15 (16%)              |
| Operative time (min)             | Mean±SD (range) 432±90 (240-760) |
| Operative blood loss             | Mean±SD (range) 530±150 (200-3000) |
| Blood transfusion (unit)         | Mean±SD (range) 1±2 (0-8)  |
| Maximum tumor diameter           | Mean±SD (Range) 3.2±1.1 (1.4-6) |
| Tumor stage                      | T1 8 (8.5%)               |
| T2                               | 32 (34.1%)                |
| T3                               | 52 (55.3%)                |
| T4                               | 2 (2.1%)                  |
| Tumor differentiation            | Well 15 (16%)             |
|       Moderate                   | 50 (53.2%)                |
|       Poor                       | 29 (30.8%)                |
| Positive LNs                     | Mean±SD (Range) 1±2 (0-10) |

PDAC (pancreatic ductal adenocarcinoma), DM (diabetes mellitus) HTN (hypertension), SD (standard deviation), ALT (alanine aminotransferase), CA (Carbohydrate antigen), LNs (lymph nodes).

**Table 2: Postoperative data and complications.**

| Variables                        | Patients with PDAC (n=94) |
|----------------------------------|---------------------------|
| Post-operative complications     |                           |
| Postoperative pancreatic fistula| 10 (10.6%)                |
| A                                | 5                         |
| B                                | 3                         |
| C                                | 2                         |
| Postpancreatectomy hemorrhage    | 5 (5.3%)                  |
| A                                | 1                         |
| B                                | 1                         |
| C                                | 3                         |
| Delayed gastric emptying         | 12 (12.8%)                |
| A                                | 9                         |
| B                                | 2                         |
| C                                | 1                         |
| -Biliary fistula                 | 5 (5.3%)                  |
| -Gastric fistula                 | 3 (3.1%)                  |
| -Wound infection                 | 12 (12.8%)                |
| Clavien grades of complication   |                           |
| 0                                | 28 (29.8%)                |
| I                                | 20 (21.3%)                |
| II                               | 26 (27.7%)                |
| IIIa                             | 8 (8.5%)                  |
| IIIb                             | 5 (5.3%)                  |
| IVa                              | 2 (2.1%)                  |
| IVb                              | 1 (1%)                    |
| V                                | 4 (4.3%)                  |
| Reoperation                      | 7 (7.4%)                  |
| ICU stay (days)                  | mean±SD (range) 4±5 (1-28) |
| Hospital stay (days)             | mean±SD (range) 16±12 (7-56) |
| Hospital mortality              | 4 (4.3%)                  |
| Recurrence of tumor              | 31/90 (34.4%)             |

PDAC (pancreatic ductal adenocarcinoma), ICU (intensive care unit), SD (standard deviation).

![Figure 1: Overall survival in patients with PDAC.](image)
Table 3: Potential risk factors for 3-year survival.

| Variables                        | Number of Deaths in (PDAC) per cases observed | % Deaths | P-value |
|----------------------------------|-----------------------------------------------|----------|---------|
| Age >60                          | 27/58                                         | 71.1%    | 0.08    |
| <60                              | 31/56                                         | 55.4%    |         |
| Gender                           |                                               |          |         |
| Male                             | 38/58                                         | 65.5%    | 0.65    |
| Female                           | 20/36                                         | 55.5%    |         |
| Body mass index (kg/m2)          |                                               |          |         |
| >25                              | 28/51                                         | 54.9%    | 0.09    |
| <25                              | 30/43                                         | 69.8%    |         |
| Co-morbidities                   |                                               |          |         |
| yes                              | 42/58                                         | 72.4%    | 0.03    |
| no                               | 16/36                                         | 44.4%    |         |
| -DM                              |                                               |          |         |
| yes                              | 21/30                                         | 70%      | 0.57    |
| no                               | 37/64                                         | 57.8%    |         |
| -HTN                             |                                               |          |         |
| Yes                              | 25/35                                         | 71.4%    | 0.29    |
| no                               | 13/59                                         | 55.9%    |         |
| Total bilirubin                  |                                               |          |         |
| >10mg/dl                         | 9/15                                          | 60%      | 0.76    |
| ≤10mg/dl                         | 32/49                                         | 63.5%    |         |
| Preoperative biliary drainage    |                                               |          |         |
| yes                              | 21/32                                         | 65.6%    | 1.0     |
| no                               | 20/32                                         | 62.5%    |         |
| Carbohydrate antigen 19-9 (U/ml)|                                               |          |         |
| >400                             | 39/54                                         | 72.2%    | 0.02    |
| ≤400                             | 19/40                                         | 47.5%    |         |
| Pancreatic texture               |                                               |          |         |
| soft                             | 28/58                                         | 73.7%    | 0.08    |
| firm                             | 14/49                                         | 55.4%    |         |
| Type of pancreatic reconstruction|                                               |          |         |
| Pancreatocogastrostomy           | 15/25                                         | 60%      | 0.89    |
| Pancracicojejunostomy            | 43/69                                         | 62.3%    |         |
| Vascular reconstruction          |                                               |          |         |
| yes                              | 11/15                                         | 73.3%    | 0.09    |
| no                               | 5/51                                          | 59.5%    |         |
| Operative time (min)             |                                               |          |         |
| >480                             | 25/37                                         | 67.6%    | 0.48    |
| ≤480                             | 33/57                                         | 57.9%    |         |
| Operative blood loss (ml)        |                                               |          |         |
| >1000                            | 19/26                                         | 73.1%    | 0.19    |
| <1000                            | 39/68                                         | 57.4%    |         |
| Blood transfusion (≥5 unit)      |                                               |          |         |
| Yes                              | 10/14                                         | 71.4%    | 0.36    |
| no                               | 48/80                                         | 60%      |         |
| Postoperative pancreatic fistula |                                               |          |         |
| yes                              | 5/7                                           | 71.4%    | 0.45    |
| no                               | 36/57                                         | 63.1%    |         |
| Tumor stage                      |                                               |          |         |
| T1                               | 3/8                                           | 37.5%    |         |
| T2                               | 16/32                                         | 50%      | 0.03    |
| T3                               | 27/52                                         | 71.2%    |         |
| T4                               | 2/2                                           | 100%     |         |
| Maximum tumor diameter (cm)      |                                               |          |         |
| ≥3                               | 39/52                                         | 75%      | 0.01    |
| <3                               | 19/42                                         | 45.2%    |         |
| Tumor differentiation            |                                               |          |         |
| Well                              | 7/15                                          | 46.7%    |         |
| Moderate                         | 28/50                                         | 56%      | 0.02    |
| Poor                             | 23/29                                         | 79.3%    |         |
| Resection margin                 |                                               |          |         |
| R0                               | 44/76                                         | 57.9%    | 0.04    |
| R1 or R2                         | 14/18                                         | 77%      |         |
| Positive lymph nodes             |                                               |          |         |
| yes                              | 29/38                                         | 76.3%    | 0.03    |
| no                               | 29/56                                         | 51.8%    |         |
| Lymph node-ratio                 |                                               |          |         |
| ≥0.2 (n = 134)                   | 36/64                                         | 56.3%    | 0.08    |
| ≤0.2 (n = 60)                    | 22/30                                         | 73.3%    |         |

The statistical test used was Fisher’s exact test, SD (standard deviation).

In univariate analysis (Table 3) the risk factors for 3-years survival were; presence of one or more comorbidities (P=0.03), high preoperative serum level of carbohydrate antigen (CA19-9) >400U/ml (P=0.02), large tumor diameter >3cm (P=0.01), tumor stage T3 and T4 (P=0.03), poorly differentiated tumor (P= 0.02), involved resection margin in histopathology (P=0.04), and positive lymph nodes (LNs) in pathology after surgery (P=0.03). High preoperative bilirubin level, preoperative biliary stent, type of pancreatic anastomosis, vascular reconstruction during surgery, long operative time and perioperative blood transfusion were not risk factors for survival.

In multivariate analysis the independent risk factors for 3-years survival were; high preoperative CA 19-9 (P=0.042), Tumor size >3cm (P=0.038), poorly differentiated tumor in histopathology (P=0.045).

DISCUSSION

PDAC was considered one of the tumors that had a poor prognosis with late diagnosis. Optimal patient selection and meticulous surgical maneuver can improve the postoperative outcome and long-term patient survival. To achieve this, we should know the most common prognostic factors that may affect the outcome of these patients with PDAC and liable for curative resection.2,11,12

Our overall postoperative complications were 70.2%, but it was mainly minor complications 49%, like wound infection and grade A DGE, which were within range as demonstrated in different studies.13,14

Some studies identified that tumor-associated biological properties like tumor diameter, LNs status, and histopathological grading are the most important prognostic factors in PDAC as most of the other tumors.13,15 Other series reported that advanced age, comorbidity, body mass index (BMI), tumor markers, resection margin, and adjuvant therapy are also predictors of outcome in PDAC.15,17

Tumor markers like CA19-9 may be elevated in more than 80% of the patients with PDAC, it is usually used as a predictor marker of tumor recurrence after resection and very high levels can be used for diagnosis especially if it was used with elevated carcinoembryonic antigen (CEA). Hartwig et al. showed that elevated CA19-9 >400U/ml is a strong predictor of low survival, as seen in our study, but cholestasis can affect the level of CA19-9 and CEA as it is excreted in bile.4,5,18 In contrast to our study, other studies identified that CA19-9 has no prognostic effect on survival in the multivariate analysis.2,19

Regarding the perioperative blood transfusion, there is a controversy between different series, some reported the negative prognostic effect of perioperative blood transfusion on survival, and others showed no effect of perioperative blood transfusion as seen in this study.13,15,19,20
Hazem et al, in their study of venous resection (VR) with PD at high volume pancreatic center reported that VR and reconstruction were safe to achieve complete tumor removal and had no risk on survival in the multivariate analysis. This was shown also in our study and other studies. In contrast to these studies, other surgical series reported unfavorable outcome with VR with malignant pancreatic tumors. 

Most of the available studies reported that tumor size is one of the most biological tumor characters to predict the outcome after tumor resection. Dumont et al, and others showed that tumor size >3cm was an independent risk factor for poor survival after resection of PDAC as demonstrated in present study.

The incidence of LN positive tumors ranges from 28% to 88.6% in large series. The majority of studies reported that positive LNs have its negative impact on the outcome of pancreatic tumor resection in the univariate or multivariate analysis, as shown in our univariate analysis. The Lymph nodes ration (LNR) is more accurate in prediction of the outcome than the status of LNs alone, so more LNs removal by extended lymphadenectomy can improve the outcome and survival.

Surgical resection margin involvement is considered as an indicator of biological tumor aggressiveness than an independent risk factor for survival, with reported lower survival rates in R1 resection than R0. With the improvement of histopathological assessment, the incidence of R1 resection has been increased up to 80%. In our data, the poorly differentiated tumor was a strong predictor of poor outcome as reported in many series. This may be explained by the aggressive infiltration and behavior of poorly differentiated pancreatic tumors and presence occult microvascular metastasis.

In our center, the postoperative adjuvant therapy was not routinely used in early years of our study, so our data about the regimen and dose of adjuvant chemotherapy (CTx) and radiotherapy was unspecified. One series reported median survival of 21 months in patients with adjuvant Tx versus 16.4 months in patients without CTx, with no statistical significance between the two groups. Others reported that a combination of CTx and radiotherapy was the most significant positive prognostic factor for survival.

In this study, we had 4.3% perioperative mortality which is nearly similar to what was reported in other studies. Seppänen et al, reported perioperative mortality 2.1%, and 5-year survival 22% after PD for PDAC. Lim et al, reported 1- and 3-year survival rates of, 60.1%, and 34.3%, respectively. Distler et al, had survival rates of 31.5% and 11.86% at 3- and 5-year respectively.

**CONCLUSION**

In conclusion, preoperative serum level of CA19-9 >400 U/ml, preoperative tumor diameter >3cm in cross-sectional image, and poorly differentiated tumors in histopathological assessment are significant predictors of poor survival after resection of PDAC, and it should be taken in account with the other common risk factors during preparation and selection of the patients for surgery to improve the outcome of PD in the future.

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