Nontraditional criteria for prediction of patient survival following pancreaticoduodenectomy for malignancy

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Introduction
This study analyzed the histological features modifying the outcome after pancreaticoduodenectomy operation for periampullary tumors.
Patients and methods
This study is a prospective cohort. A total of 35 cases of pancreaticoduodenectomy operations were performed from March 2011 to February 2013. Of the procedures, 23 cases were diagnosed as pancreatic carcinoma, and the rest were ampullary carcinomas (7), cholangiocarcinomas (3), and duodenal carcinomas (2). Statistical analysis was completed by using log-rank and Cox regression multivariate analyses.
Results
The 5-year survival rate was 29% for all patients who went through pancreaticoduodenectomy. For periampullary carcinomas other than pancreatic carcinoma, the 1, 3, and 5-year survival rates were 100, 66.7, and 58.3%, respectively. The 1, 3, and 5-year survival rates for pancreatic carcinoma were 42.1, 10.5, and 10.5%, respectively (P=0.01). In the multivariate analysis, the existence of both perineural and lymphovascular invasions were the only independent factors influencing outcome. The 5-year survival rate was 88.9% in patients negative for both factors and 0% in patients positive for both (P=0.02).
Conclusion
Cases with both perineural and lymphovascular invasions on histopathological analysis have poor 5-year survival outcomes after Whipple's procedure for pancreatic and periampullary malignant tumors.

Keywords:
histopathological lymphovascular invasion, histopathological perineural infiltration, pancreatic tumors, pancreaticoduodenectomy, Whipple operation

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Introduction

Long-term survival of patients with cancer in the head of pancreas remains insufficient compared with other abdominal malignancies despite improvements in perioperative and hospital mortality. Traditional factors that affect long-term patient survival include tumor type, tumor size, lymph nodal status, resectability, patient age, and associated diseases. Perioperative mortality had decreased from 30% in the early 1980s [1] to up to 3% in the past decade [2], whereas the 5-year patient survival rates after curative resection remain poor. Most published large series demonstrate postresection survival rates of only 4–17% for pancreatic carcinoma [3,4]. The picture in periampullary carcinoma is better, where 5-year survival after resection is 60% [5].

The traditional criteria for determination of patient survival after pancreaticoduodenectomy operation include tumor type, size, margin, differentiation, and positive lymphatic infiltration. Two parameters that have not been fully studied are the lymphovascular and perineural infiltration. Groningen in his study reported that perineural involvement is a reliable factor in the prediction of patients' survival after pancreatic resection with high significance [6]. Two studies have reported that patients' survival decreases in pancreatic neuroendocrine tumors, when lymphovascular infiltration is present [7,8]. It is proposed that perineural infiltration may have a role in local failure because of tumor growth along nerves that innervate the pancreas and eventually form the periarterial nerves [9]. In a similar way, the lymphovascular infiltration is responsible for regional or distant metastasis in lymph nodes or other organs.

This study aimed to analyze the histopathological factors affecting long-term survival of patients after pancreaticoduodenectomy focusing on invasion of perineural and lymphovascular components as predictors of 5-years survival.

Patients and methods

Study design

This cohort is a prospective study. The work has been described in line with the STROCSS criteria [10].

Study participants and setting

All patients at Hepatobiliary Surgery Unit of Minia University Hospital and Surgical Department of Misr University for Science and Technology who underwent pancreaticoduodenectomy in the period between March 2011 and February 2013 were included in the study.

Data collection

The general data, including sex, age, clinical data, preoperative laboratory or imaging investigation, preoperative interventional and preoperative biopsy, any neoadjuvant chemotherapy or radiotherapy, of included cases were reviewed. Operative and postoperative data including postoperative morbidity based on Clavien–Dindo classification [11] were recorded.

The gross specimens were examined by a pathologist who was blind to any prior knowledge about the clinical data. Histopathological data were entered into a prospective database maintained since 2011 by the departments of surgery. The histopathological factors analyzed were tumor type, tumor size, tumor grade, regional lymph node status, lymph node capsular invasion, resection margin, and the presence of perineural and lymphovascular invasion. If there was incomplete information about the required histopathological parameters, the histopathological slides (n=4 patients) were re-evaluated.

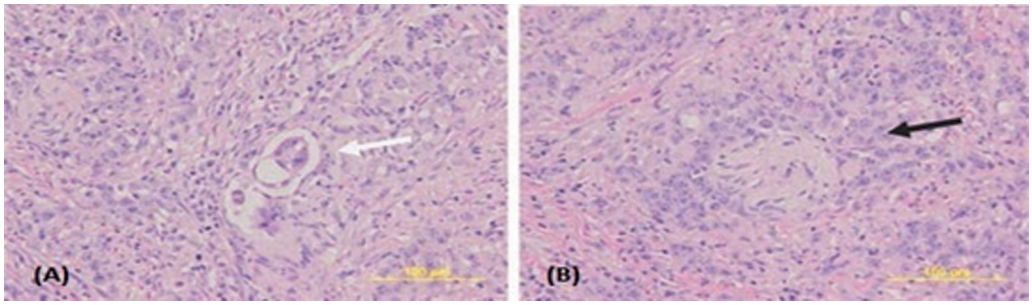
There were two groups of tumors according to the analysis of gross specimens: pancreatic and periampullary carcinoma. The latter group includes ampullary carcinoma, duodenal carcinoma, and cholangiocarcinoma. Tumors were classified according to size as less than 2 cm and more than 2 cm. Tumor differentiation was classified as well, moderate, or poor. The resection-free margins were analyzed as positive up to 2 mm or negative more than 2 mm. Typically, specimens were inked and then fixed before sectioning for margin analysis. Nodal status was categorized into negative or positive according to the presence or absence of malignant infiltration.

If malignant cells were identified inside the lymphovascular channels, lymphovascular invasion was considered as positive (Fig. 1a). Perineural infiltration was considered to be present if tumor cells were identified within the perineural space and/or nerve fibers (Fig. 1b). For statistical analysis purposes, hematoxylin and eosin stained slides in which lymphovascular invasion were not detected on histopathological examination while lymph nodes examination was positive were considered as negative for lymphovascular invasion.

Follow-up

Follow-up visits were obtained by patient interview or personal contact with the attending physician once every 3 months during the first year, re-examined once every 6 months during the second and third years, and re-examined once a year later. Patients were examined during the follow-up visits by routine laboratory investigations, tumor markers, chest radiography, abdominal ultrasound, and computed tomography/MRI. The follow-up deadline was June 2017.

Figure 1



Hematoxylin and eosin sections showing (a) invasion of the tumor in lymphovascular channel(white arrow) away from the main tumor and (b) perineural infiltration (black arrow) by tumor along nerve fibers in the pancreas.

Ethical approval

The protocol of the study was discussed and approved regarding ethics of research in general surgical department. The study had been approved by the ethical committee for human studies in our institution. The study has a registry number (research registry 3064). Full written, informed consent was signed from all participants.

Data analysis

Univariate analysis was applied using the log-rank test with differences in patients' survival as the outcome measured. Continuous variable, such as tumor size, was converted into categorical variables. Variables that were significant on univariate analysis were then subjected to multivariate analysis using Cox's multiregression analysis. All statistical analyses were carried out using SPSS, version 23 (SPSS Inc., Chicago, Illinois, USA). Overall survival at 1, 3, and 5 years was determined and analyzed by the Kaplan–Meier method, and differences in survival were compared using the log-rank test.

Results

A total of 35 pancreaticoduodenectomy cases were performed in our institutions and were included in the study over the 2-years period. Of the 35 patients, 33 went through a pylorus-preserving pancreaticoduodenectomy, whereas two patients underwent a total pancreatectomy. In five patients, parts of the portal vein or superior mesenteric vein were removed with the specimen, and the venous structure was reconstructed. No patient underwent resection with arterial involvement during this time period (Table 1).

The median patient age was 58 years (range: 25–65 years). There were 23 men among the patients. The time required for the operative procedure ranged from 5.0 to 10.0 h, with a median of 7.0 h. Estimated blood or fluid loss ranged from 100 to 3000 ml, with a median of 1000 ml. Requirements of blood transfusion ranged from 0 to 6.0 U, with a median of 2.0 U (Table 2).

Postoperative morbidity was based on Clavien–Dindo classification: grade 4 was seen in 11.4% of cases, grade 3 in 11.4%, grade 2 in 31.4%, and grade 1 occurring in 37.1%. The most common complications were intra-abdominal abscess; pancreatic fistula and biliary fistula were less frequently seen. There were four (11.4%) in-hospital/30-day deaths, being Clavien–Dindo grade 5.

There was no difference in 5-year survival in term of sex (Table 3). The overall 5-year actuarial survival for all patients with malignant tumors was 29% (Fig. 2).

Tumor characteristics and patient survival

Most tumors were pancreatic in origin 65.7 versus 20% ampullary, 5.7% duodenum, and 8.6% distal common bile duct. Similar results were obtained in a cohort of patients from the SEER cancer registry who went through pancreaticoduodenectomy between 1993 and 2003: 62.5% pancreatic, 18.9% ampullary, 7% duodenal, and 11.6% distal bile duct [12]. Patients who went through resection for pancreatic adenocarcinoma had poorer survival (10.5% at 5 years) than patients with periampullary malignancies (58.3% at 5 years; P=0.01) (Fig. 3).

The patient survival was significantly better in smaller and well-differentiated tumors (P<0.0001). The survival was reduced when lymph nodes were positive (P<0.0001). Well-differentiated tumors were related significantly to better survival compared with moderately and poorly differentiated tumors (P<0.0001) (Table 3). Long-term survival was poor with positive margin up to 2 mm.

Perineural infiltration and lymphovascular invasion

The absence of any of these factors, malignant perineural infiltration or lymphovascular invasion, was related with high significance to better survival (Figs 3 and 4).

Table 1 Malignancies treated by pancreaticoduodenectomy (n=31)

Types of tumor	n (%)
Pancreatic adenocarcinoma	23 (65.7)
Periampullary malignancies	12 (34.3)
Distal CBD	3 (8.6)
Duodenum	2 (5.7)
Ampulla	7 (20)

CBD, common bile duct.

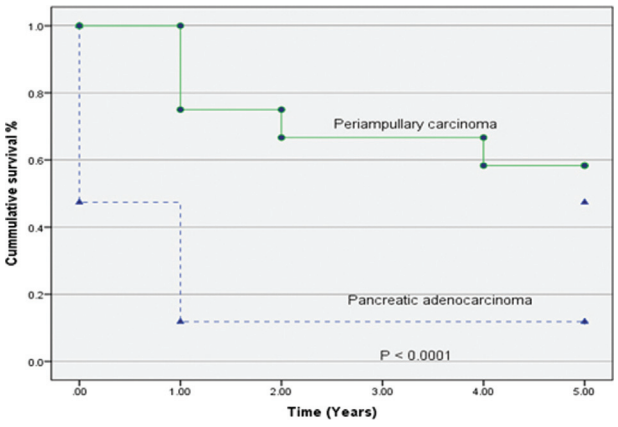
Table 2 Preoperative and operative data of patients

	Median	Range (minimum–maximum)
Age (years)	58	40 (25–65)
Duration of symptoms before surgery (weeks)	10	24 (1–25)
Total bilirubin (mg/dl)	5	19.1 (0.9–20)
Direct bilirubin (mg/dl)	4.1	17.7 (0.4–18.1)
Albumin (g/dl)	3.7	2 (3–5)
ALT	45	50 (40–90)
AST	44	47 (33–80)
Prothrombin concentration (%)	80	40 (60–100)
Alkaline phosphatase (U/l)	750	1400 (200–1600)
CA19–9 (U/l)	400	1494 (6–1500)
Operative time (h)	7	5 (5–10)
Operative blood loss (ml)	1000	2900 (100–3000)
Operative blood transfusion (U)	2	6 (0–6)
Hospital stay (days)	12	53 (7–60)

Table 3 Five-year survival rates by tumor characteristics (*n*=31)

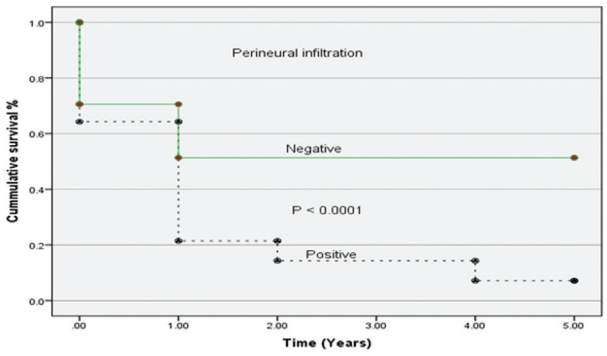
	N	1-year survival (*n*=20) (64.5%) [*n* (%)]	3-years survival (*n*=10) (33.3%) [*n* (%)]	5-year survival (*n*=9) (29%) [*n* (%)]	*P* value
Sex					
Male	21	15 (71.4)	7 (33.3)	6 (28.6)	0.4
Female	10	5 (50)	3 (30)	3 (30)	
Type of tumor					
Pancreatic head adenocarcinoma	19	8 (42.1)	2 (10.5)	2 (10.5)	0.01
Periampullary carcinoma	12	12 (100)	8 (66.7)	7 (58.3)	
Size (cm)					
<2	11	10 (90.9)	9 (81.8)	9 (81.8)	<0.0001
>2	20	10 (50)	1 (5)	0 (0)	
Regional LN status (N1)					
Positive	14	7 (50)	0 (0)	0 (0)	<0.0001
Negative	17	13 (76.5)	10 (58.8)	9 (52.9)	
LN capsular invasion					
Yes	6	4 (66.7)	1 (16.7)	1 (16.7)	0.02
No	25	16 (64)	9 (36)	8 (32)	
Tumor differentiation					
Good	6	6 (100)	6 (100)	6 (100)	<0.0001
Moderate	18	13 (72.2)	4 (22.2)	3 (16.7)	
Poor	7	1 (14.3)	0 (0)	0 (0)	
Vascular encasement					
Yes	8	1 (12.5)	0 (0)	0 (0)	0.002
No	23	19 (82.6)	10 (43.5)	9 (39.1)	
Lymphovascular invasion					
Yes	7	5 (71.4)	0 (0)	0 (0)	<0.0001
No	24	15 (62.5)	10 (41.7)	9 (37.5)	
Perineural infiltration					
Yes	14	9 (64.3)	2 (14.3)	1 (7.1)	<0.0001
No	17	11 (64.7)	8 (47.1)	8 (47.1)	
Postoperative radiotherapy					
Yes	11	10 (90.9)	3 (27.3)	3 (27.3)	<0.0001
No	20	10 (50)	7 (35)	6 (30)	
Postoperative chemotherapy					
Yes	21	15 (71.4)	7 (33.3)	7 (33.3)	0.5
No	10	5 (50)	3 (30)	2 (20)	

Figure 2



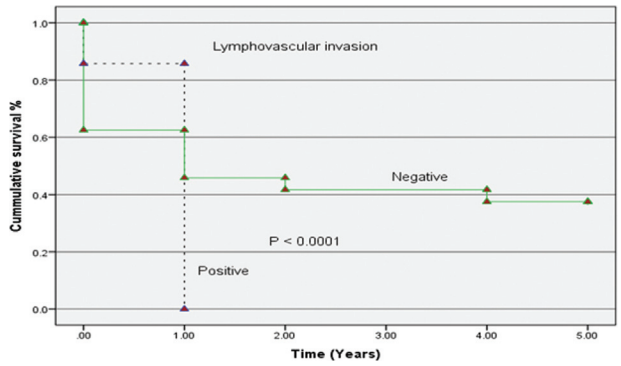
Cumulative survival in patients with pancreatic adenocarcinoma, and patients with periampullary malignancies. At 5-year survival, the periampullary group had achieved a significantly better 5-year actuarial survival of 58.3%.

Figure 3



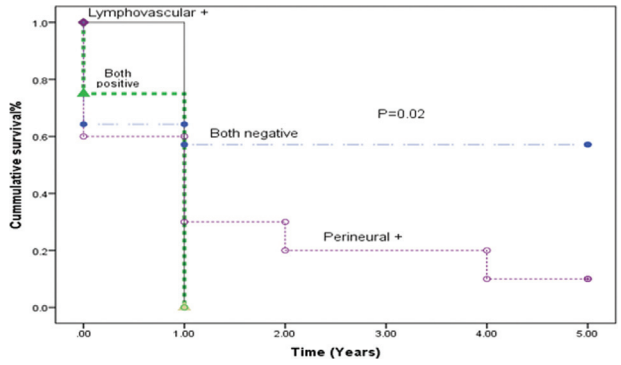
Cumulative patient survival in the presence of perineural infiltration. A significantly poorer survival outcome was noted in the presence of perineural infiltration.

Figure 4



Cumulative patient survival in the presence of tumor invasion in lymphovascular channels. A worse survival outcome was marked in the presence of lymphovascular invasion.

Figure 5



Cumulative patient survival in the presence or absence of perineural infiltration and lymphovascular invasion after resection. Significant improvement was noted if both features are absent on microscopic examination.

When all the significant histopathological variables on univariate analysis were assessed using a multivariate regression model, perineural infiltration ($P<0.0001$) and lymphovascular invasion ($P<0.0001$) were independently significant factors for prediction of long-term survival.

Prognostic modeling using perineural infiltration and lymphovascular invasion

As these two factors were independently significant in multivariate analysis, the effects of combining them in terms of predicting long-term survival were analyzed. The 31 patients with malignancies were divided into four categories consisting of those who were positive for both factors, those who were positive for either one of the factors, and those who were negative for both. Figure 5 illustrates that significantly better survival result was obtained in patients who were negative for both parameters rather than other groups ($P=0.02$). The 5-year actuarial survival is tabulated in Table 4.

Table 4 Five-year survival rates after resection of pancreatic malignancies in patients positive and negative for perineural infiltration and lymphovascular invasion ($n=31$)

	Perineural negative [*n* (%)]	Perineural positive [*n* (%)]
Lymphovascular negative	14 (82.4)	10 (71.4)
Lymphovascular positive	3 (17.6)	4. (28.6)

Discussion

During the 1980s and 1990s, the morbidity and mortality for Whipple procedure were so high, that many thought the operative procedure should be abandoned for tumors of head of pancreas. During the 2000s, however, results improved, and now many centers are reporting hospital mortality rates of less than 5% [13]. Many factors are definitely responsible. Better intensive care and nutritional support in caring for postoperative complications have almost certainly contributed. During the 1990s, general surgeons specialized so that now a significantly high proportion of pancreaticoduodenectomies are being operated by hepatobiliary surgeons experienced in pancreatic surgery. This specialization has resulted in less time, with intraoperative less blood loss and with better results.

There were four hospital deaths among the 35 patients in our series who underwent a pancreaticoduodenectomy for malignancy of the pancreas. When the 31 hospital survivors are compared with the four patients who died after their surgery, they are demographically similar. The differences were that those patients who died after their procedure had more advanced stage of tumor with positive margin and poor degree of differentiation, lost more blood, required more transfusions, and had a longer duration of operative procedure than those who survived.

There was marked decrease in hospital morbidity and mortality in addition to the improvement in long-term survival of these patients. Most of this improvement is not owing to the drop-in hospital mortality but owing to other factors. Some have attributed the recent improvements to the better advanced radiological diagnosis that allows surgeons to operate on patients with pancreatic carcinoma at earlier stages. However, most patients with cancer of head of pancreas still do not seek for medical advice until the development of jaundice. Moreover, there is similar outcome when tumor size and stage are taken into account in patients going through pancreaticoduodenectomy for pancreatic carcinoma today compared with those patients treated a decade or more ago [14].

Five-year survival rates following Whipple procedure for pancreatic malignancy remain low (<20%) even in large volume institutions. In this study, the actuarial survival was 29% for the 5-year follow-up. This is comparable with the recently published MD Anderson series [14]. The 5-year survival for patients who went through pancreaticoduodenectomy for periampullary malignancies other than pancreatic adenocarcinoma was 58.3%. This result is also similar to previously published results for. periampullary malignancies, including a recently published series from Birmingham which reported an actuarial 5-year survival of 60% for ampullary carcinoma following resection [5].

The patient outcome is poor when the pancreatic resection margin is positive, that is, the surgical margin up to 2 mm [15]. The European Study Group for Pancreatic Cancer defines an R0 resection as having a margin of 1 mm. In our series, a surgical margin of less than 2 mm was considered negative and was associated with better patient survival. A recent study reported a margin of 1.5 mm to be associated with better outcome [16]. If this is borne out by other investigators, a re-evaluation of the R0 margin will be required. The TNM classification and its modifications have been the standard prognostic parameters used for most malignancies, including those of pancreatic origin [17].

Multivariate analysis in this cohort identified that perineural and lymphovascular invasions were independent significant factors for long-term survival, and they are not included as a part of the TNM system. Perineural infiltration as a significant prognostic factor after pancreatic head resection has been reported previously and has been proven to be related to local failure by various authors [13]. As the tumor grows along nerves in the pancreas, it infiltrates distally to follow an arterial channels, reducing the chances of complete microscopic clearance [6,9].

Lymphovascular infiltration would provide a channel for metastasis as indicated by poorer outcome despite aggressive vein resection, as reported in more patients [9]. Lymphovascular invasion has been noted as a poor prognostic factor following resection of pancreatic neuroendocrine tumors [7]. In cases with no lymphovascular or perineural infiltration, the 5-year survival was 82.4% in our patients who had pancreatic malignancy (n=31). It is apparent that these two parameters, which are easily identified on hematoxylin and eosin sections, are highly suggestive pathological prognostic criteria for prediction of patient survival following pancreatic resection for malignancies.

Currently, perineural and lymphovascular invasions are not included among the traditional prognostic factors after resection of pancreatic or other periampullary cancers. These results would strongly recommend the inclusion of these parameters in the postoperative staging system as standard criteria. We propose that a new staging system specific for periampullary tumors is required for both research and clinical purposes.

Conclusion

The presence of perineural infiltration and lymphovascular invasion on histopathology is highly significant in predicting 5-year outcomes after Whipple's procedure for periampullary and pancreatic malignancies.

Strengths of the study

(1) This is a prospective cohort study which is one of the strong studies in research.
(2) We operated on cases with pancreatic cancer, which is an invasive cancer in a hidden area in the body.
(3) We focused on perineural infiltration and lymphovascular invasion as predictors of long-term survival.

Limitation of the study

The sample size needed to be increased, but the cases analyzed were the only patients who attended our institutes during the study duration. More studies with a bigger sample size needed to be performed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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