Prognostic factors in the operative and palliative treatment of pancreatic cancer*

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Received February 17, 2003

Recent studies have emphasized the importance of patient selection for the surgical resection of pancreatic adenocarcinoma based on reproducible prognostic factors. The aim of the study was to investigate the prognostic factors affecting long-term survival in patients with resectable and nonresectable pancreatic cancer and to evaluate their prognostic value.

Forty six patients (25 women, 21 men, aged 44–80) with ductal adenocarcinoma of the pancreas were reviewed. Primary tumor size and regional enlargement of lymph nodes was assesed with enhanced CT scan. 13 patients were treated conservatively, 9 with standard Whipple procedure (pancreatoduodenectomy) and 24 – with palliative surgery. Survival probabilities were computed using univariate Kaplan-Meier analysis. Log-rank test was used to compare survival between groups.

Overall median survival was 6 months with a 4 years survival of 2.2%. There was no difference in survival time (ST) between patients aged 65 years or younger and older ($p=0.71$). Mean ST in patients after Whipple procedure was 10.3, after palliative surgery – 9.4 and after conservative treatment – 4.4 months ($p<0.05$). Thirty-day surgical mortality was 9.4%. ST was significantly longer in patients with tumors 3 cm or less of diameter compared with larger ones ($p<0.05$). Presenting signs and symptoms, like jaundice, diabetes, alkaline phosphatase, aspartate and alanine aminotransferase elevation and history of cholecystectomy did not have any significant impact on survival.

The only significant independent factors improving survival were: operative treatment and tumor size smaller than 3 cm.

Key words: Pancreatic cancer, prognostic factors, palliative treatment.

Pancreatic cancer (PC) is fairly common malignancy, outnumbered only by colorectal and stomach cancer in the gastrointestinal tract. The incidence of pancreatic cancer has been documented rising in most countries with mortality rates in the range of about 6–10/100 000 per year. The death rate for PC is almost the same as its incidence, as the survival over-all is less than 5 percent [3, 27]. The role of prognostic parameters with regard to screening, diagnosis and therapy of PC is still controversial. The search for reliable prognostic factors is one of the main objectives of epidemiological research of many work groups [4, 5, 23].

Surgical resection offers the only potential cure for pancreatic cancer, but most patients show an advanced tumor at the time of diagnosis, due to either local progression or metastatic spread [24]. Some reports have confirmed the reduced perioperative mortality rates but not always improved survival benefit [11, 20]. Therefore, there is a strong need of adequate patient selection for pancreatic adenocarcinoma surgery based on reproducible prognostic factors. Until now, most studies analyze the prognostic factors related to long-time survival of patients after pancreatic cancer surgery [4, 17, 19, 26]. Only few authors had evaluated the parameters affecting survival time in nonresectable pancreatic cancer [6, 23].

The aim of the study was to investigate the prognostic factors affecting long-term survival in patients with resectable and nonresectable pancreatic cancer and to evaluate their prognostic value.

*Paper sponsored with Polish Committee for Scientific Research grant no. 3 P05B 121 23.

Patients and methods

Forty-six patients with pancreatic adenocarcinoma hospitalized in Medical University of Lodz Hospital between 1996–1999 were prospectively analyzed. There were 25 women and 21 men, mean age was 65 years (range 44–80). Primary tumor size and regional enlargement of lymph nodes was assesed based on ultrasound, computed tomography and, in some cases, also ERCP. The diagnosis has been confirmed with pathological examination of fine-needle aspiration biopsy noted in 13 cases, surgical biopsy in 24 cases or pathological examination of surgical specimen obtained at pancreatoduodenectomy in 9 cases. Only patients with confirmed histologic diagnosis of ductal adenocarcinoma of pancreatic origin have been included into the study.

In nine patients standard Whipple procedure have been performed, in 24 palliative surgery (biliary bypass surgery and/or gastrojejunostomy) and 13 patients were found not suitable for surgery. Whipple procedure includes removal of the head and neck of the pancreas, the duodenum, small part of proximal jejunum, gallbladder and loco-regional lymph nodes. Tumor-associated factors such as tumor size, histological grade, lymph node status and liver metastases have been analyzed. Histological grading of pancreatic ductal adenocarcinoma was based on the WHO system [13]. Type of intervention, patients demografics, medical history concerning mainly cholecystectomy or diabetes and pre-operative hematological and biochemical parameters (leukocytosis, aminotransferases, serum bilirubin and alkaline phosphatase levels) have been investigated (Tab. 1).

Median post-operative follow-up periods were 8 months (range, 7 days to 54 months). Perioperative mortality was defined as death within 30 days after surgery. Survival time (ST) was considered from the date of diagnosis to the date of death. Follow-up was recorded as date of death or date of last follow-up. Follow-up was obtained by office records and telephone contact with the primary care physicians.

Survival probabilities were computed using univariate Kaplan-Meier analysis. The significance of the difference between groups was ascertained using the log-rank test. Differences with p value less than 0.05 were considered significant.

Results

Overall median survival was 6 months with a 4 years survival of 2.2% (1 patient). Mean survival time (ST) in patients after Whipple procedure was 10.3, after palliative surgery – 9.4 and after conservative treatment – 4.4 months. ST was significantly longer ($p<0.05$) in patients operated than treated conservatively (Fig. 1). Survival probability of 6 months in patients after Whipple procedure was 0.47,

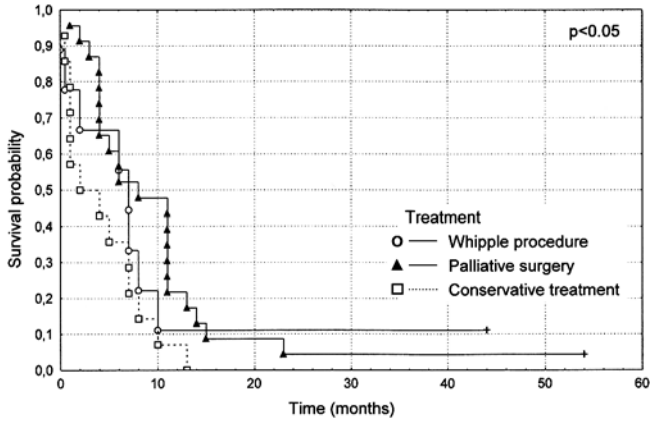

Figure 1. Survival in patiens with PC dependently on their treatment.

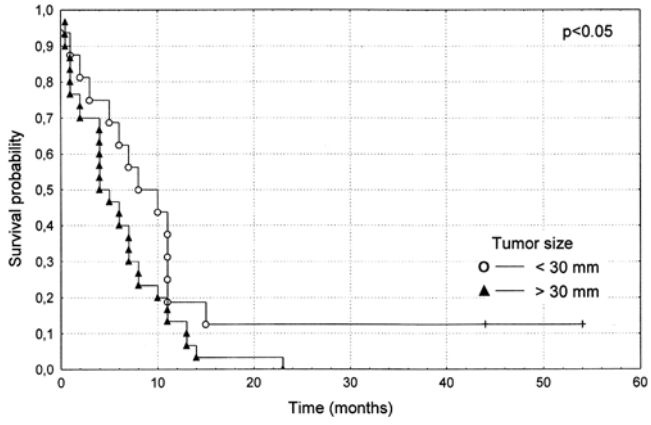

Figure 2. Survival in patients with PC dependently on tumor size.

after palliative surgery was 0.11 and after conservative treatment 0.08 ($p<0.01$). Overall thirty-day surgical mortality was 9.4% (3/32), including one patient after Whipple procedure and two after palliative surgery. The causes of death were intraoperative hemorrhage – in one – and post-operative infectious complications leading to multisystem failure in two patients.

The tumor was located in the head of the pancreas in 40 of 46 patients (87%) and was confined to the pancreas body or tail in the remaining patients. The tumor size ranged from 2 to 7.5 cm (mean 4.4 ± 1.1 cm). In 16 patients (35%) tumors smaller than 3 cm have been detected. ST was significantly longer in patients with tumors 3 cm or less of diameter compared with larger ones ($p<0.05$) (Fig. 2).

Table 2 includes the results of univariate analysis of the association of individual variables with PC patients survival. There was no difference in survival time between patients aged less than 65 years and older ($p=0.71$). Survival probability of 6 months in patients with local lymph node metastases was 0.33 and without them – 0.5, which was not significantly different ($p=0.25$). 6-month survival concerned 60% patients without hepatic metastases and only 21% with

Table 1. Patient demografics and characteristic

Variable	Patients
Full cohort	46
Age	65 (44–80)
Male sex	21 (45%)
Smoking habit	20 (43%)
Jaundice at admission	27 (57%)
Serum amylase (IU/L)	87 (54–215)
Bilirubin (mg/dl)	6.7 (0.4–14.1)
Alanine aminotransferase (IU/L)	68 (26–227)
Leukocyte count	8300 (4200–16 100)
Platelet count	234 t. (143–567 t.)
Prothrombin activity (%)	84 (56–99)
Alkaline phosphatase (IU/L)	98 (56–377)
γ-Glutamyl transpeptidase (IU/L)	356 (43–980)
Tumor location	
head	40 (87%)
body/tail	6 (13%)
Tumor size	
<3 cm	16 (35%)
>3 cm	30 (65%)
Tumor grade	
1 – well differentiated	11 (24%)
2 – moderatly differentiated	21 (46%)
3 – poorly differentiated	14 (30%)
Positives lymph nodes	15 (33%)
Liver metastases	13 (28%)
Diabetes	19 (41%)
Cholecystectomy	7 (15%)

Table 2. Univariate analysis of prognostic factors

Variable	Group	Mean survival (months)	Log-rank p-value
Kind of treatment	Operative	9.8	<0.05
	Conservative	4.4	
Tumor size	<3 cm	12.4	<0.05
	>3 cm	6.1	
Lymph node metastases	Negative	8.9	0.15
	Positive	3.9	
Liver metastases	Negative	9.5	0.22
	Positive	5.3	
Gender	Males	9.7	0.29
	Females	7.2	

those changes. Among 13 patients with hepatic metastases, in 4 (30.8%) the tumor size in CT scan was less than 3 cm. There was no difference in the survival time between patients of different sex. In 11 patients pathologic examination has revealed tumor grade 1, in 21 – grade 2, and in 14 – grade 3. There was no correlation between tumor grading and survival time (p=0.42). Presenting signs and symptoms, like jaundice (p=0.23), diabetes (p=0.74), alkaline phosphatase (p=0.68), aspartate and alanine aminotransferase elevation (p=0.47) and history of cholecystectomy (p=0.52) did not have any significant impact on survival.

Discussion

The results of our study confirm that patients with pancreatic cancer have overall a very poor prognosis. Surgical resection is probably the first step toward the opportunity for long term survival in patients with PC. Our study does not show a difference in survival between patients after palliative surgery and operated by Whipple procedure. Similar results have been also reported by Harris et al [11], with average survival 6 months, independently of type of surgical intervention. Nakao et al [18] concluded that the role of extensive pancreatic surgery is to obtain a carcinoma-free surgical margin. If it can be obtained, there is better prognosis and a chance for long-term survival.

In resected patients, several prognostic parameters have been analyzed (tumor size, blood vessel invasion, lymph node status or blood transfusion requirements) [2, 4, 19]. We confirmed that tumor size could be used both preoperatively as a prognostic tool to preclude potentially curative resection and postoperatively as the factors influenting survival time. Ashmad et al [1] similarly reported that tumor size >2 cm was associated with poor survival. Other authors also demonstrated a significant correlation between tumor diameter and survival of patients who have undergone surgery for pancreatic cancer [8, 21]. According to Pantalone et al [22] 5-year survival rate for patients with small lesion confined to the pancreas was up to 31%.

The relationship between involved lymph nodes and prognosis is no longer a matter of discussion [2, 6, 15, 17, 25]. In retrospective study of Sperti et al [25] lymph node status was independent reliable predictor of long-term survival. Our study also confirm an impact on survival of lymph node metastases presence however not of statistical significance.

In contrast, the value of tumor grade as a prognostic factor is controversial [9, 14]. Luttges et al [14] found histological grade as an independent prognostic factor, however it is often criticized as being subjective and difficult to reproduce. In our study there was no correlation between tumor grading and survival time.

As with the other digestive tract tumors the risk of pancreatic cancer increases rapidly with age, but the correlation between survival of patients with PC and their age is controversial [3, 12, 26]. Takeuchi et al [26] found that in group of patient older than 62 years perioperative mortality was higher than in younger. In the present series there was no differences in survival time and in perioperative mortality between the different age groups (p=0.71). Most studies, including ours did not show the difference in survival time between patients of different sex [12, 22–24].

Little is known about factors influencing the survival in the cases of patients with more advanced tumor stage not suitable for surgical resection. In our study a group of 33 patients (72%) was not qualified for radical surgery. In 28% cases even palliative surgery was not possible due to metastatic spread and severe physical condition at the time of diagnosis. In our series presenting signs and symptoms, like jaundice, diabetes, alkaline phosphatase, aspartate and alanine aminotransferase elevation as well as history of cholecystectomy did not have any significant impact on survival. In contrast CUBIELLA et al [6] using univariate analysis demonstrated that leukocyte count, serum bilirubin, alanine aminotransterase, cholesterol and iron concentration have significant influence on patients survival. They also found physical condition and distant metastases as independent prognostic factors in patients with nonresectable pancreatic cancer [6]. Those discrepancies may be explained by differences in cancer staging and small number of patients studied.

An improvement of poor prognosis for patient with pancreatic cancer consists on diagnosing the disease at an earlier and hopefully more curable stage. Molecular tumor analysis might be helpful in establishing a diagnosis in patients for whom typical procedures provide only inconclusive results. The expression of several growth factors (EGF and TGF-α) and oncogene mutations (K-ras) has been found to be associated with poorly differentiated tumors of an advanced stage and decreased survival. These molecular markers may prove to be important in the diagnosis and choice of future therapies for pancreatic cancer [10, 16].

In conclusion, the present investigation identified operative treatment and tumor size smaller than 3 cm as independent prognostic factors in patients with pancreatic cancer. Our results demonstrate that patients having tumors of small size with no metastases and with possibility for operative treatment have better prognosis than the others. Those parameters may represent the additional tools helpful for the optimal management choice.

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