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**ORIGINAL ARTICLE**

# Clinical and pathologic prognostic factors for curative resection for pancreatic cancer

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**Abstract**

*Background.* Pancreatic cancer is the fifth leading cause of cancer-related deaths in the world. Operative resection is the only therapeutic option with curative potential for this disease. *Objective.* The aim of the present study was to correlate clinical and pathologic parameters with survival in patients submitted to pancreatic resection for pancreatic adenocarcinoma. *Methods.* Surgical resection with curative intent (R0 and R1 resections) was performed in 65 pancreatic cancer patients between 1990 and 2006. The overall results of surgical treatment were retrospectively analyzed and compared with the clinicopathologic features of these patients. *Results.* Pylorus-preserving pancreatoduodenectomy was performed in 37 patients (56.9%), classic resection in 35.4%, distal pancreatectomy in 4.6% and total pancreatectomy in 3.6%. The inhospital mortality was 5% (three patients). Postoperative complications occurred in 28 patients (43%). Mean survival and five-year survival rate after curative resection were 27 months and 9.0%, respectively. Sex, TNM stage, tumor differentiation, neural invasion, tumor size and involvement of resection margin were significant prognostic factors on univariate analysis. Multivariate analysis showed tumor differentiation and neural invasion as prognostic factors. *Conclusion.* Patients with pancreatic cancer, even those with poor prognostic factors should be given the opportunity of surgical resection with curative intent.

**Key Words:** adenocarcinoma; survival; prognosis; surgery; surgical pathology; pancreatoduodenectomy; pancreatectomy; pancreatic neoplasms

## Introduction

Pancreatic cancer is one of the most fatal malignant diseases and ranks fifth in cancer mortality worldwide. Survival after resection remains disappointing, with five-year survival rates ranging from 10 to 29% [1–3]. Advances in operative techniques and in perioperative care have increased the resecability of pancreatic cancer, and have decreased rates of operative morbidity and mortality [4–7]. Despite these improvements long-term outcomes still remain disappointing because early recurrence still represents the main challenge for surgeons dealing with pancreatic cancer patients. Although some reports show five-year survival rates of 25–30% [1,8–11] in the great majority of the reported series patient survival for more than five years is rare [12–16].

The incidence of pancreatic cancer in the USA approaches 32,000 cases each year [16,17]. And less than half of patients in the USA with Stage 1 disease are offered resection because of the persisting perception that resection is not worthwhile [18]. In Brazil, 4% of cancer-related deaths are due to pancreatic cancer and the incidence is about six cases per 100,000 habitants [19].

### *Objective*

The aim of the present study is to correlate clinical and pathologic findings with survival after

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attempted curative resection for pancreatic adenocarcinoma.

## Materials and methods

In the period between January of 1990 and December of 2006, 336 patients with pancreatic adenocarcinoma were admitted at the Pancreatobiliary Surgical Unit of the São Paulo University Medical School Hospital. From this patient population 65 were submitted to surgical treatment with curative intention. The retrospective review of the medical records of these patients consists the basis of the present report. Patients with neuroendocrine and cystic pancreatic neoplasms, and those undergoing R2 resections were excluded. Patient demographics, clinical presentation and findings, and pathologic factors were evaluated to determine the prognostic factors after resection. Variables studied included: sex, age, portal vein resection, blood transfusion, type of pancreatic resection (Whipple, pylorus-preserving pancreatoduodenectomy, distal pancreatectomy, DP and total pancreatectomy, TP), post-operative complications (bleeding, pancreatic fistula and infection) [20–22], tumor size, tumor differentiation, lymph node status, neural invasion, margin status and Tumor, Nodal status and Metastasis (TNM) staging (according to UICC-2002) [23].

Neoplasms were classified microscopically as well, moderate, or poorly differentiated tumors according to Kloppel [23].

### *Statistical analysis*

Continuos variables were compared using either the two-sample $t$ test or the Wilcox rank sum test depending on normally or non-normally distributed data, respectively. Nominal variables were compared using either the $\chi^2$ test or the Fisher's exact test. All calculated $p$ values were two-sided and $p$ value of less than or equal to 0.05 was considered statistically significant. Cumulative survival data were calculated using the Kaplan–Meier method. Cox regression model was used to calculate multivariate analysis and variables with significance at univariate model were included.

## Results

### *Patient demographics, clinical factors*

Sixty-five patients with the diagnosis of pancreatic ductal adenocarcinoma underwent R0 or R1 resections. There were 37 females (57%) and 28 males (43%) with a mean age of 58 years (range 39–85 years). Weight loss was present in 79%, jaundice in 82.4% and nausea or vomiting in 25.4%. Thirty-eight percent of patients had new-onset diabetes mellitus.

Table I. Demographic and pre-operative data.

| Variable | *n* | Median survival (mo) | *P* |
|---|---|---|---|
| Race | | | 0.28 |
| White | 43 | 26.3 | |
| Black | 12 | 17.8 | |
| Oriental | 7 | 32.5 | |
| Age (years) | | | 0.55 |
| <60 | 36 | 24.5 | |
| >60 | 26 | 29.2 | |
| Sex | | | 0.008 |
| Male | 26 | 18.2 | |
| Female | 36 | 33.0 | |
| Weight loss | | | 0.46 |
| No | 13 | 28.9 | |
| Yes | 47 | 26.6 | |
| Upper GI obstruction symptoms | | | 0.19 |
| No | 46 | 28.2 | |
| Yes | 15 | 19.9 | |
| Diabetes | | | 0.67 |
| No | 36 | 25.5 | |
| Yes | 24 | 26.3 | |
| Jaundice (TB >3 mg/dl) | | | 0.56 |
| No | 21 | 30.5 | |
| Yes | 39 | 24.2 | |
| CEA (>5 ug/ml) | | | 0.25 |
| No | 20 | 24.8 | |
| Yes | 13 | 41.5 | |
| CA 19–9 (>200 ng/ml) | | | 0.09 |
| No | 22 | 33.2 | |
| Yes | 19 | 19.8 | |

Race, age, weight loss, symptoms of upper Gastrointestinal (GI) obstruction, diabetes, jaundice, Carcinoembryonic Antigen (CEA), Carbohydrate Antigen 19-9 (CA 19-9) levels were not identified as prognostic factors after resection for pancreatic cancer. Sex was the only parameter that showed statistical significance on univariate analysis ($p < 0.05$) (Table I).

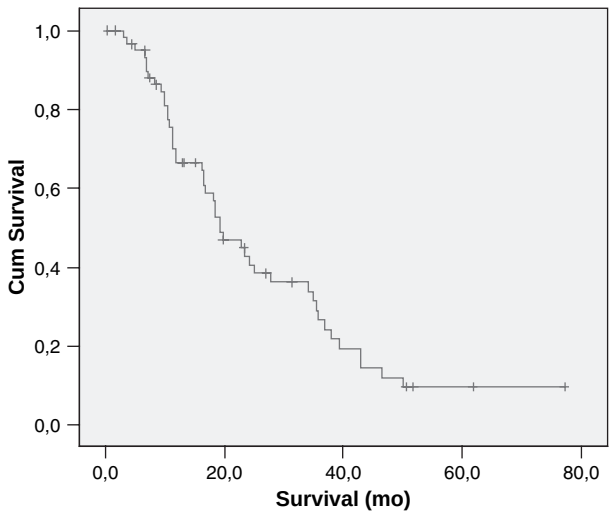


Figure 1. Overall cumulative survival of patients with pancreatic adenocarcinoma submitted to surgical resection.

*Operative procedures*

Types of pancreatic resection were: pylorus-preserving pancreatoduodenectomy (PPPD) 37 (57%), classic Whipple (PD) 23 (35%), DP 3 (5%) and TP 2 (3%). Portal vein (PV) resection was performed on 10 patients (15%) in order to obtain an R0 resection. Mean operative time was 600 minutes. Intra-operative blood transfusion was needed in 32 patients (49%), with a median of two units. Pancreatic and bilioenteric anastomosis were externally drained through two separate abdominal stab incisions.

*Morbidity and mortality*

Postoperative complications occurred in 28 patients (43%), delayed gastric emptying (DGE) (33%) (16 Grade A, five Grade B and one Grade C) being the most common, followed by, pancreatic fistula (all Grade A) (25%), bleeding (12%) and infection (11%) [21,22,24]. Four patients (6%) were re-operated because of bleeding (one Grade C and three Grade B) [21], three (one Grade C and two Grade B) of whom died because of systemic complications (in-hospital mortality of 5%). The median duration stay postoperatively was 15 days (range 7–46 days).

Table II. Surgical and peri-operative data.

| Variable | *n* | Mean survival ±SEM (mo) | *P* |
|---|---|---|---|
| Type of pancreatectomy | | | 0.89 |
| PD | 22 | 28.9 (3.9) | |
| PPPD | 35 | 24.2 (3.2) | |
| Distal | 3 | | |
| Total | 2 | | |
| Intra-operative blood transfusion | | | 0.81 |
| No | 28 | 26.5 (3.9) | |
| Yes | 32 | 26.8 (3.7) | |
| Portal vein resection | | | 0.004 |
| No | 52 | 29.4 (3.2) | |
| Yes | 10 | 13.8 (3.8) | |
| PO complication[a] | | | 0.11 |
| No | 35 | 23.4 (4.0) | |
| Yes | 25 | 29.5 (3.2) | |
| Pancreatic fistula[a] | | | 0.96 |
| No | 45 | 27.6 (3.3) | |
| Yes | 14 | 24.7 (4.5) | |
| Delayed gastric emptying[a] | | | 0.29 |
| No | 47 | 25.7 (3.3) | |
| Yes | 12 | 29.6 (4.6) | |
| Infection | | | 0.49 |
| No | 53 | 26.3 (3.2) | |
| Yes | 7 | 34.4 (6.6) | |
| Bleeding | | | 0.61 |
| No | 55 | 28.1 (3.3) | |
| Yes | 5 | 23.2 (7.3) | |

[a]Data not available for all patients.

Table III. Pathological data.

| Variable | *n* | Median survival ±SEM (mo) | *P* |
|---|---|---|---|
| Tumor size (>3 cm) | | | 0.04 |
| No | 34 | 29.9 (3.0) | |
| Yes | 28 | 21.0 (4.3) | |
| *N* stage | | | 0.09 |
| 0 | 27 | 30.0 (4.1) | |
| 1 | 35 | 22.9 (3.0) | |
| TNM | | | 0.05 |
| 1a | 58 | 31.3 (10.3) | |
| 1b | 13 | 37.6 (6.2) | |
| 2a | 34 | 23.0 (4.4) | |
| 2b | 2 | 23.3 (3.1) | |
| 3 | | 10.5 (00) | |
| Tumor differentiation | | | 0.001 |
| Well | 16 | 25.6 (4.2) | |
| Moderate | 44 | 27.8 (3.4) | |
| Poor | 2 | 6.8 (3.0) | |
| Neural invasion | | | 0.026 |
| No | 10 | 39.6 (5.5) | |
| Yes | 52 | 23.7 (2.8) | |
| Vascular invasion | | | 0.15 |
| No | 37 | 28.7 (3.3) | |
| Yes | 25 | 22.2 (3.7) | |
| Peri-pancreatic invasion | | | 0.023 |
| No | 51 | 26.6 (3.3) | |
| Yes | 11 | 15.2 (2.6) | |
| Tumor margin status | | | 0.006 |
| R0 | 43 | 31.6 (3.8) | |
| R1 | 19 | 17.1 (2.5) | |

*Prognostic factors*

Overall cumulative survival is shown in Figure 1 and the five years survival rate was 9%. The type of pancreatic resection, amount of intra-operative bleeding, need for blood transfusion, DGE and the occurrence of postoperative complications did not correlate with the long-term survival. Patients

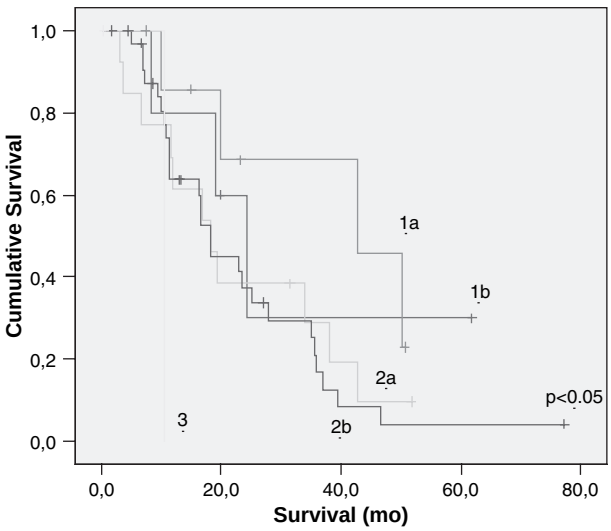


Figure 2. Cumulative survival according to TNM stages on univariate analysis.

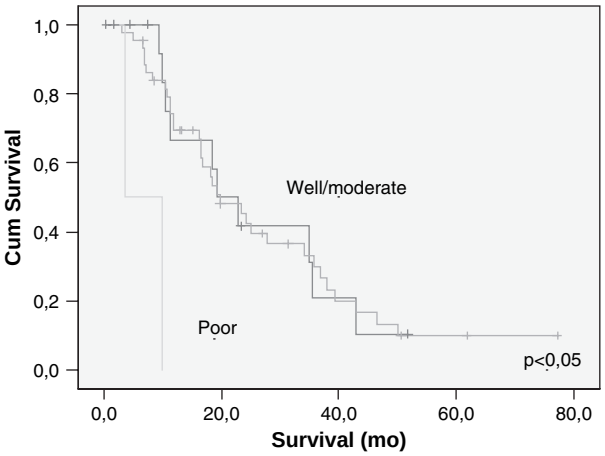


Figure 3. Cumulative survival related to tumoral differentiation – univariate analysis.

submitted to PV resection had lesser survival than patients whose PV was not resected (14 vs. 29 months) ($p < 0.025$) (Table II). Mean tumor size was 3.3 cm and most of them had moderate differentiation (68%). Vascular and neural invasion were present in 38 and 85%, respectively. A positive histologic margin (R1) was present in 20 patients (31%). Five (8%) patients were Stage IA, nine (14%) Stage IB, 13 (20%) Stage IIA, 36 (55%) Stage IIB and three (3%) Stage III. Mean follow-up and survival times were 21 and 27 months, respectively. Poorly differentiated tumors or those with neural invasion or a positive margin status also had lower survival rates ($p < 0.03$ each).

Lymph node metastasis and vascular invasion did not correlate with prolonged survival. In contrast, TNM stage, neural invasion, tumor differentiation, peri-pancreatic invasion, tumor size (>3 cm) and

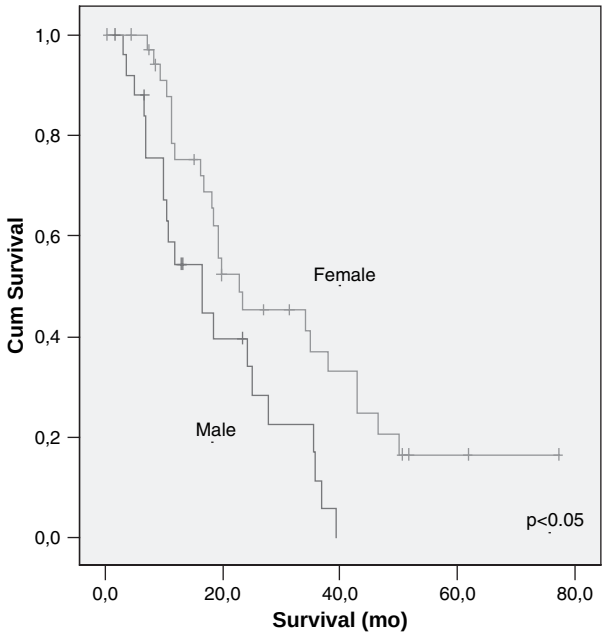


Figure 4. Cumulative survival related to gender – univariate analysis.

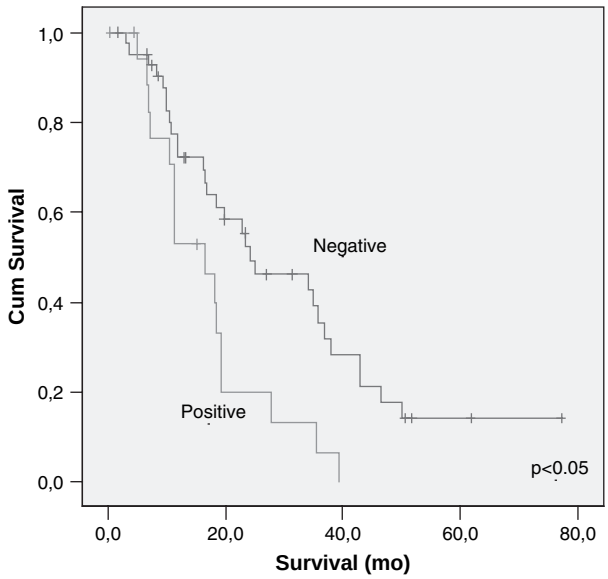


Figure 5. Cumulative survival related to margin status – univariate analysis.

resection margin involvement all correlated with survival ($p < 0.05$) (Table III) (Figures 2–9). On multivariate analysis, neural invasion and tumoral differentiation were significant ($p < 0.05$) (Table IV).

## Discussion

In the early 1970s, pancreatoduodenectomy was not consistently performed for the management of pancreatic cancer, because according to some studies its results were similar to or even worse than bypass procedures [25,26]. Nowadays, however, pancreatoduodenectomy can be performed in specialized centers for the surgical treatment of periampullary malignancies with a low operative mortality and morbidity [7,15,27,28]. Many studies have demonstrated that this improvement was related to the concentration of this operation in high volume

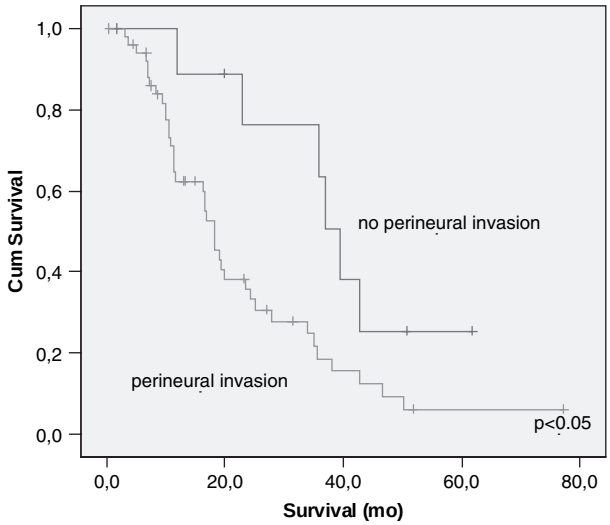


Figure 6. Cumulative survival related to perineural invasion on univariate analysis.

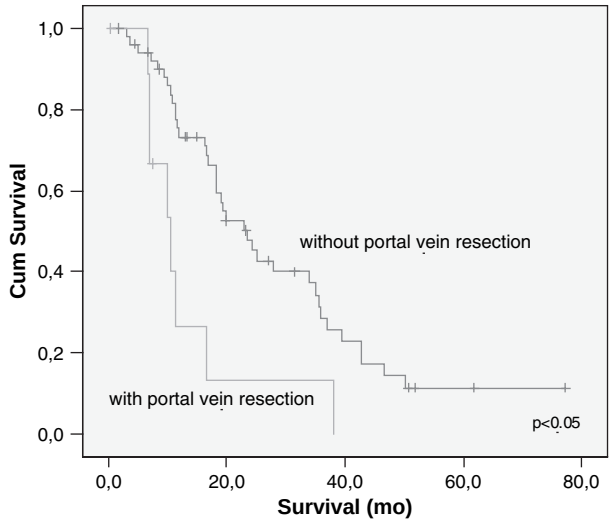


Figure 7. Cumulative survival related to portal vein resection on univariate analysis.

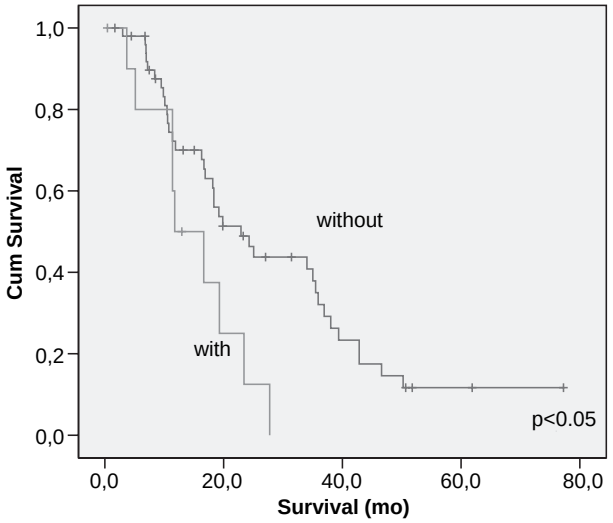


Figure 9. Cumulative survival related to peri-pancreatic tissue invasion on univariate analysis.

centers, specialized in pancreatic surgery [7,29]. Furthermore, technical advances in operative technique and alternative methods for reconstruction of the alimentary tract after pancreatoduodenectomy [30–34] also contributed for these achievements and appear to be responsible for the good early results obtained in the present study. However, these improvements do not necessarily correlate with long-term postoperative survival [15,35], probably due to the heterogeneity of the clinicopathologic characteristics of pancreatic cancer [36,37]. This diversity was also found in the present study and possibly counted for the poorer prognosis observed in male patients as there were more women than men with Stage I disease.

Although PV resection was undertaken in this series as an attempt to achieve an R0 resection, 31% of patients still had a positive surgical margin (R1 resection) despite the presumption of a "curative resection". The finding of a worse prognosis in patients submitted to PV resection may be also attributed to the fact that these patients also presented with larger tumor sizes ($p < 0.05$).

The present study demonstrated similar rates of R0 resection, lymph node involvement and status of surgical margin for both PPPD and PD procedures, in accordance with published randomized, controlled trials [38–41].

Although lymph node metastasis, poorly differentiated tumors and positive margins have been associated with a worse prognosis in some studies, [8,42,43], a few patients presenting some of these poor prognostic factors may live longer than expected [15,35], whereas other patients without bad prognostic factors will die early. In the present series, poorly differentiated tumors, neural invasion and the presence of positive resection margins were associated with a poor long-term outcome. In contrast, absence of lymph node metastasis was not a significant predictor of long-term survival. Schwarz and Smith demonstrated that an adequate assessment of lymph node involvement in pancreatic cancer depends on the number of nodes evaluated, what sometimes can occur when the surgeon dealing with this disease is not used to perform a reasonable amount of pancreaticoduodenectomies per year [44]. The small number of retrieved lymph nodes and the variability of sampling in the present series may account for the lack of correlation observed between lymph node involvement and survival. Furthermore, occult tumor cells may be found in apparently tumor-free lymph nodes of pancreatic cancer patients and often overlooked in conventional histopathology [45]. These

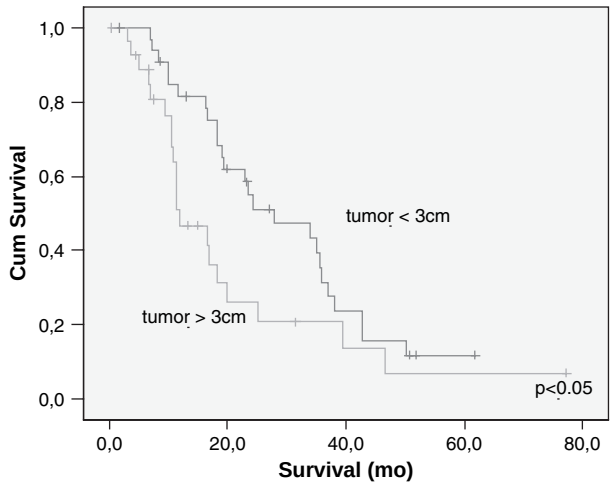


Figure 8. Cumulative survival related to tumor size on univariate analysis.

Table IV. Significant variables – multivariate analysis.

| Variable | *P* |
|---|---|
| Neural invasion | 0.03 |
| Tumor differentiation | 0.04 |

micrometastases can, thus, impair prognosis, making it comparable to that of patients with true lymphatic metastases [46]. Better methods such as molecular classification may improve patient selection and though stratifying the risk of occult metastatic disease. Current studies of our service are underway to evaluate the pathological specimen of this patients population looking for molecular markers (VEGF receptors, COX2, D2-40).

Long-term survival after pancreatoduodenectomy for pancreatic carcinoma is far from excellent. The five-year survival rate nears 10% and patients surviving more than five years are exceptional [15,35,47]. The actual five-year survival rate of 9% reported herein is in accordance of other reports that could not show an improvement in long-term survival after operative resection of pancreatic cancer [3,35,47].

The results of the present study corroborates with the findings of other reports which point to the fact that surgical resection is the only hope for cure of patients with pancreatic cancer and, thus, this modality of treatment, followed by an effective adjuvant therapy, should always be offered to these patients.

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