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Impact of preoperative levels of hemoglobin and albumin on the survival of pancreatic carcinoma

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ABSTRACT

Introduction: Pancreatic cancer presents the worst survival rates of all neoplasms. Surgical resection is the only potentially curative treatment, but is associated with high complication rates and outcome is bad even in those resected cases. Therefore, candidates amenable for resection must be carefully selected. Identification of prognostic factors preoperatively may help to improve the treatment of these patients, focusing on individually management based on the expected response.

Patients and methods: We perform a retrospective study of 59 patients with histological diagnosis of pancreatic carcinoma between 1999 and 2003, looking for possible prognostic factors.

Results: We analyze 59 patients, 32 males and 27 females with a mean age of 63,8 years. All the patients were operated, performing palliative surgery in 32% and tumoral resection in 68%, including pancreaticoduodenectomies in 51% and distal pancreatectomy in 17%. Median global survival was 14 months (Range 1-110).

We observed that preoperative levels of hemoglobin under 12 g/dl (p = 0,0006) and serum albumina under 2,8 g/dl (p = 0,021) are associated with worse survival.

Conclusion: Preoperative levels of hemoglobin and serum albumina may be prognostic indicators in pancreatic cancer.

Key words: Pancreatic cancer. Prognostic factors. Hemoglobin. Albumina. Survival.

RESUMEN

Introducción: El cáncer de páncreas presenta la peor tasa de supervivencia de todas las neoplasias. La resección quirúrgica es el único tratamiento potencialmente curativo, pero está grabado con una alta tasa de complicaciones y el pronóstico continúa siendo malo en aquellos casos resecados, por lo que es necesario seleccionar bien a los candidatos. Por ello, la identificación de factores pronósticos de forma preoperatoria podría contribuir a mejorar el tratamiento de estos pacientes orientando hacia pautas más personalizadas en función de la respuesta esperable.

Material y métodos: Realizamos un estudio retrospectivo de 59 pacientes con diagnóstico histológico de carcinoma de páncreas entre 1999 y 2003, para identificar posibles factores pronósticos.

Resultados: De los 59 pacientes, 32 eran varones y 27 mujeres, con una edad media de 63,8 años. Todos los pacientes fueron operados, realizándose cirugía paliativa en el 32% y resección tumoral en el 68%, incluyendo duodenopancreatectomías cefálicas en el 51% y pancreatectomías distales en el 17%. La mediana de supervivencia global fue de 14 meses (intervalo 1-110).

Observamos que los niveles preoperatorios de hemoglobina inferiores a 12 g/dl (p = 0,0006) y de albúmina sérica por debajo de 2,8 g/dl (p = 0,021) se asocian a menor supervivencia global.

Conclusión: Los niveles preoperatorios de hemoglobina y albúmina pueden ser indicadores pronósticos en el cáncer de páncreas.

Palabras clave: Cáncer de páncreas. Factores pronósticos. Hemoglobina. Albúmina. Superviviencia.

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INTRODUCTION

Pancreatic cancer is a mortal pathology, representing a public health problem, more transcendental every day. In western countries, it represents the 4th leading cause of cancer-related death in males and the fifth in women, and, after colon cancer, it is the second cause of mortality related with digestive tumours (1,2).

This kind of neoplasm is associated with bad outcome, whose main cause is the delay in the diagnosis due to its anatomical location and the few symptomatic specificity, the great tendency to early dissemination to lymph nodes and liver, and the early affection of close regional structures, mainly vascular ones (3,4). Surgical resection is the only potentially curative treatment, but due to the presentation in advanced stages, only 15-20% is amenable for pancreatectomy. Surgical treatment is associated with a high morbidity rate and outcome is still bad even in those resected patients, thus it is necessary a selection of candidates, avoiding unnecessary surgeries in patients who will not get a benefit of them (5-7). Therefore, identification of prognostic factors preoperatively may contribute to a management improvement of these patients, focused on individualized treatments based on the expected response.

PATIENTS AND METHODS

We performed a retrospectie study of all the patients with pancreatic adenocarcinoma operated at University Hospitals la Princesa and Ramón y Cajal (Madrid – Spain) between 1998 and 2003. Inclusion criteria were histological diagnosis of pancreatic adenocarcinoma, a follow-up period of at least 4 years and complete clinical information. Those patients, whose complete clinical information or follow-up data were not available, were excluded.

Analyzed variables were age, gender, personal and familial history, clinical manifestation, exploratory findings, imaging tests, surgical treatment, adjuvant treatment, histopathological features, follow-up, recurrence, disease-free and global survival.

Data process and analysis were performed with the statistic software SPSS 12.0 for Windows. Quantitative variables following normal distribution were defined by mean, standard deviation and range; in those ones not following Gaussian distribution, median was used instead of mean as centralization measure. Qualitative variables were defined by number of cases and percentage. Comparison between quantitative variables was performed with t Student method for independent samples (comparison of 2 means) or ANOVA (comparison of more than 3 means), when quantitative variables followed normal distribution. When one or both variables did not follow Gaussian distribution, nonparametric tests were used (Mann-Whitney and Kruskal-Wallis). Comparison between 2 qualitative variables was performed with χ^2 – method. Association measurement was established by Odds Ratio. $p < 0,05$ was considered significative. Survival analysis was performed with Kaplan-Meier method and survivals were compared with long-rank, Breslow and Tarone-Ware test.

RESULTS

We analyzed 59 patients, 32 (55.2%) males and 27 (44.8%) females with a mean age of 63,76 ± 11,03 years. The most relevant personal history data are shown in table I. Most frequent clinical manifestations were jaundice (61%), abdominal pain (59.3%) and weight loss (52.5%). Physical examination revealed an abdominal mass in 5 patients (8.6%) and cachexia was observed in 1 (1.7%). Laboratory data are summarized in table II.

Table I. Personal history

Personal history	*N (%)*
Chronic pancreatitis	3 (5.1)
Diabetes mellitus type I	5 (8.5)
Diabetes mellitus type II	13 (22)
Neoplasms	8 (13.6)
Obesity (BMI>30)	2 (3.4)
Cholecystectomy	4 (6.8)
Gastrectomy	1 (1.7)
Helicobacter pylori +	8 (13.6)
Smoking	22 (37.3)
Alcohol	9 (15.3)

Table II. Laboratory data

	Min	*Max*	*Mean*	*Standar desviation*
Hemoglobine	6.5	16.5	13.05	2.25
WBC	3560	20600	8807.67	3636.97
Bilirrubin	0.3	22.1	6.52	5.76
GOT	7	1076	186.50	182.26
GPT	8	2231	343.46	363.35
GGT	19	3499	595.60	666.43
Alkaline phosphatase	13	2223	553.95	553.29
LDH	2	2027	333.59	364.56
Albumin	1.0	4.6	3.39	0.92
Creatinine	0.2	6.9	1.11	1.30
CA19.9	2.0	32809.0	1755.96*	5815.88
CEA	0.89	18.20	3.976	3.64

*Median CA 19-9: 145

The most frequently performed imaging tests were CT scan in 58 patients (98.2%) and ultrasonography in 44 patients (74.6%). Preoperative staging following imaging tests revealed that 41 cases (69.5%) were potentially resectable, 17 (28.8%) were locally advanced tumors and 1

case (1.7%) was a metastatic tumor. At surgical intervention, 40 tumors (67.8%) were resectable and in 19 (32,2%) criteria of non-resectability were observed (Table III).

Table III. Criteria of non-resectability

Criteria of non-resectability	*N (%)*
Peritoneal carcinomatosis	1 (17)
Liver metastases	2 (3.4)
Retroperitoneal infiltration	12 (20.3)
SMV* infiltration	12 (20.3)
SMA* infiltration	9 (15.3)
Lymph node metastases outside standard lymphadenectomy	4 (6.8)

* SMV: Superior mesenteric vein. **SMA: Superior mesenteric artery.

Most usually performed surgical techniques were pancreaticoduodenectomy, followed by distal pancreatectomy. Most frequent palliative technique was biliodigestive bypass. Referring to radicality, of 40 resected tumors, R0 (absence of tumoral rest) was achieved in 39 patients (97.5%) and R1 (microscopic tumor rest) in 1 case (2.5%).

Postoperative complications appeared in 20 patients (33.9%), being pancreatic leak the most frequent one (Table IV). Reoperation was necessary in 6 patients (10.2%), 3 because of postoperative bleeding, 2 due to multiple intrabdominal abscesses and 1 seocndary to a high-debit intestinal leak.

27 patients (45.8%) underwent chemotherapy and 18 (30.5%) radiotherapy.

Referring to location, 13 tumors (22.1%) were located in body-tail of the pancreas, while 46 (77.9%) were located in the head. In 23 cases (39%) the tumor presented good differentiation, 17 (28.8%) moderately differentiated, 16 (27.1%) bad differentiated and 3 (5.1%) undifferentiated. Vascular infiltration was present in 8 patients (13.6%) and perineural one in 29 (49.2%). Mean tumoral size was 3.59 ± 2.26 cm. The mean number of isolated lymph nodes was 10,09 + 5,82 (range 2-28), of whom 1.54 ± 2,44 (range 0-12) were positive.

Table IV. Postoperative complications

	N	%
Pancreatic leak	9	15.3
Intestinal leak	2	3.4
Biliary leak	1	1.7
Bleeding	3	5.1
Intrabdominal abscess	3	5.1
Pneumonia	1	1.7
Central catheter infection	1	1.7

Recurrence was estimated among those patients without residual tumor after surgery (radicality R0 = 39 patients). Recurrence was considered the appearance of tumor at least 3 months after surgery. Only 7 patients (17.9%) did not present any recurrence, 15 (38.5%) presented local recurrence, 3 (7.7%) developed liver metastases, in 7 cases (17.9%) recurrence was local combined with liver metastases, in 5 (12.8%) it was disseminated and in 2 (5.1%) appeared as peritoneal carcinomatosis.

After a minimum follow-up period of 4 years, 50 patients (84.7%) deceased, 2 (3.4%) remain alive but with tumor recurrence and 7 (11.9%) are alive and disease-free. Mean disease-free period after surgery was 19.29 ± 33.31 months; (median 3.5 [0-110] months) and mean survival 25.08 ± 28.91 months (median 14 [1-110] months). 1-year survival rate was 44%, 2-years 30%, 3-years 17.5%, 4-years 14% and 5-years one 12% (Fig. 1).

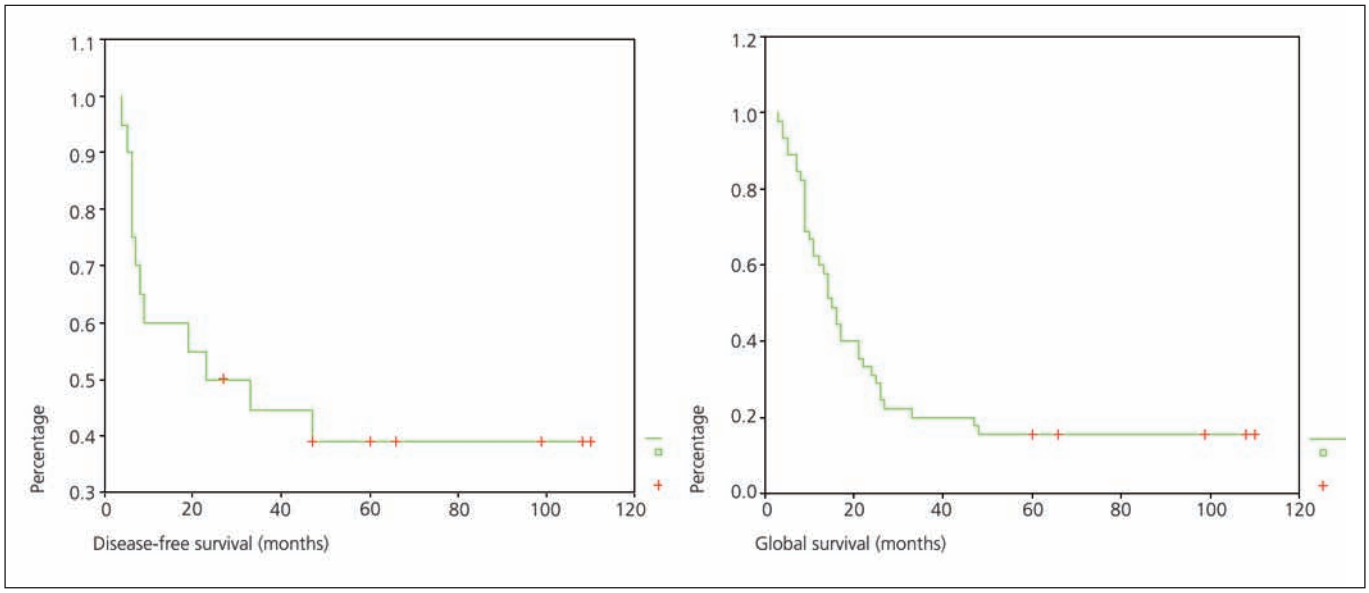

Fig. 1. Disease-free and global survival curves.

We observe a statistically significant association (p = 0,039) between hemoglobin levels at diagnosis and global survival, with a Spearman coefficient of 0,336. Cut point was established in 12 g/dl, revealing that survival was significantly worse among patients with preoperative hemoglobin values under 12 g/dl (p = 0.0006) (Fig. 2). Initially, this observation was considered to be associated with postoperative mortality, but excluding the cases presenting postoperative mortality, results were not altered. We analyzed a possible association between hemoglobin values and other already known prognostic factors, such as lymph node metastases, tumor stage or respectability, without reaching statistical signification.

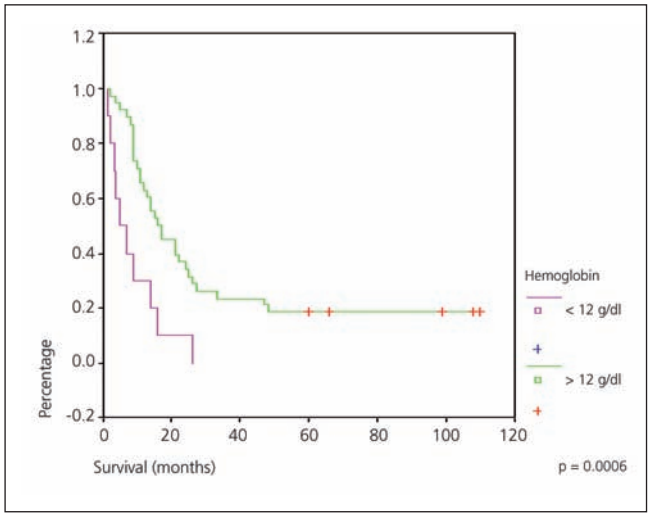

Fig. 2. Survival curve depending on hemoglobin level.

Similar to this, we observed that preoperative low serum albumin levels tend to be associated with a shorter survival (p = 0.069) with Spearman coefficient of 0.452. Cut point was established in 2.8 g/dl, revealing that global survival is significantly worse among those patients with albumin levels under 2.8 g/dl (p = 0.021) (Fig. 3). As occurred with hemoglobin, albumin levels were not associated with other prognostic variables for pancreatic cancer.

DISCUSSION

Investigation on oncologic pathology must be focused on the search for new therapeutic targets, such as chemotherapy, radiotherapy, biological or molecular agents, completing the surgical treatment, in order to improve survival rates of these patients. Moreover, preoperative prognostic factors should also be studied, to predict the course of the disease that may help the clinician to choose the appropriate therapy individually for each patient, aiming an increase in survival and an improvement in the quality of life.

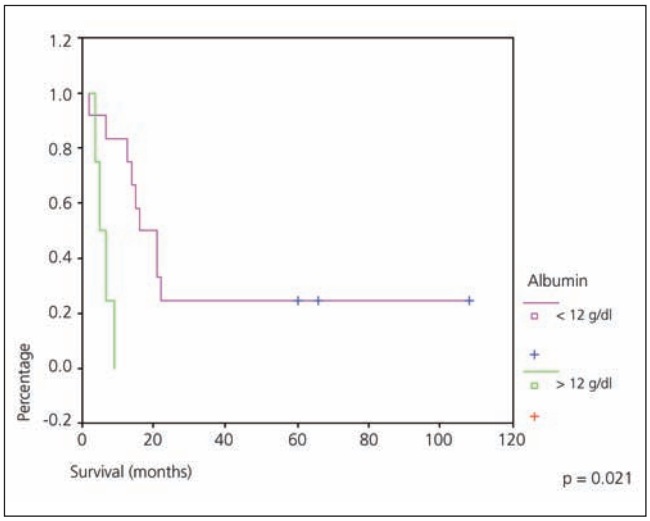

Fig. 3. Survival curve depending on albumin levels.

In our series, a significant correlation between hemoglobin levels at diagnosis and global survival (p = 0,039) was observed, with a Spearman coefficient of 0,336. Patients presenting postoperative mortality were excluded from the analysis, to eliminate postoperative mortality as a confusion factor, but the results remain unaltered. In literature, there is only one study reporting an association between hemoglobin levels at diagnosis and global and disease-free survival in pancreatic cancer8. In this study, only patients with unresectable tumors undergoing radiochemotherapy were analyzed, but up to date there are no studies reported in literature analyzing the influence of hemoglobin levels in operated patients, undergoing respective or palliative surgery. In head and neck tumors the effect of hemoglobin levels at diagnosis was determined in patients undergoing respective surgery (9) or radiotherapy (10), revealing both studies a better survival and local disease control in those patients with hemoglobin levels in normal range. The same results have been obtained in other neoplasms, such as epidermoid esophageal carcinomas (10), cervix (11) or transitional tumors of the bladder (12), associating higher hemoglobin levels with longer survival in tumors surgically resected or treated with radio or chemotherapy. Probably, anemia could be a prognostic factor of many neoplasms, thus it is associated with other conditions related with survival, such as nutritional status. On the other hand, it is already known that tumor hypoxia increases the DNA damage produced by free radicals. It

has been suggested that in anemic patients, the reduced oxygen tension in the tumor reduces the neoplastic growth control (13). Some authors have observed that pancreatic tumors present a high grade of hypoxia in intraoperative tissular oxygenation measures, postulating that the fatal outcome of this neoplasm could be partially caused by the cellular hypoxia (14). Considering that anemia may be correlated with the tissular hypoxia grade, this is the way how it influences in survival (15). Some studies have demonstrated that neoplastic cells develop resistance to radiochemotherapy in hypoxia conditions, as happens in situations of anemia (9). Anemia reduces the tumoral oxygenation and angiogenesis starts, increasing by this way the metastatic potential of the tumor. This affirmation has been confirmed, observing that low hemoglobin levels are associated with increased ones of VEGF (16), and low tumoral oxygenation levels are associated with a higher incidence of distant metastases (17). To evaluate the different response depending on the hemoglobin values at diagnosis, different cut points have been established between 11.5-13 g/dl (9-11). In our study we established 12 g/dl as cut point, observing a shorter survival among patients with hemoglobin levels under 12 g/dl ($p = 0.0006$). Given these results, some authors have even postulated the possibility of transfusion or recombinant erythropoietin administration to any anemic patient before treatment, aiming to achieve better survival rates (11,18), but there are no studies demonstrating this hypothesis.

We have also observed a tendency to association between serum albumin levels at diagnosis and global survival ($p = 0.069$) with a correlation coefficient of 0,452. Establishing a cut point in 2.8 g/dl, we observed a shorter survival among patients with albumin levels under 2.8 g/dl ($p = 0.021$). Serum albumin is considered a marker of the nutritional status and in patients undergoing major surgery it has been demonstrated to be a prognostic indicator (19). On the other hand, serum albumin levels have been associated to survival in oncologic patients, in tumors such as melanoma (20) or in other locally advanced or metastatic neoplasms (21). In pancreatic carcinoma, low albumin levels have been associated with early mortality before 6 months5. It has been suggested that low albumin levels in oncologic patients may be secondary to the intense systemic inflammatory response against the tumor. Inflammation requires an important synthesis of acute phase proteins, implying a reduction in albumin production. When this process is prolonged, it leads to a depletion of the protein reservations and therefore a decrease in the body strength, contributing to early death (20,22,23). Given this, it seems to be logical, that when the patient already presents a protein lack at diagnosis, the catabolic mechanisms of the tumor are in advanced stages and the worsening of the patient will take place in a short period of time.

CONCLUSION

Identification of prognostic factor in pancreatic cancer, mainly those that can be determined preoperatively, will give information about the probable course of the disease and may help the clinician to choose the most accurate therapy individually for each patient. This is of great importance in a neoplasm like this, whose outcome is bad despite performing a respective surgery with curative aims that on the other hand presents high complication and mortality rates. We have identified hemoglobin levels under 12 g/dl and serum albumin ones under 2.8 g/dl as bad prognostic factors in pancreatic cancer.

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