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The prognostic role of time to diagnosis and presenting symptoms in patients with pancreatic cancer

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ABSTRACT

Background: The aim of this study was to investigate the prognostic role of diagnostic delay and clinical presentation (regarding pain, jaundice, and weight loss) in pancreatic carcinoma. *Methods*: One hundred and seventy patients with pancreatic cancer were diagnosed and treated in the decade 2001–2010 (100 males and 70 females, with a mean age of 65.8 years [range, 36–91]). Patients were staged with spiral computed tomography and 75% were found to have advanced disease (28 stage III, 99 stage IV disease). Ductal adenocarcinoma was diagnosed in 147 cases, other subtypes of carcinoma in the remaining 23. Fifty patients were operated with radical intent, 19 had palliative surgery, 101 were considered inoperable because of advanced disease or heavy anesthesiologic risk; 31 of these inoperable patients underwent biliary decompression by insertion of an endoluminal or percutaneous stent. Gemcitabine-containing regimens were administered to 143 patients and radiotherapy was combined in 19. Overall and relative survival were the parameters studied. Multivariate analysis was performed by multiple regressions applied to proportional-hazards model. *Results*: From all the clinical, pathological and therapeutical factors evaluated the statistically significant ones were time to diagnosis and surgery. Among symptoms pain was related to the shortest mean time to diagnosis, weight loss to the longest, with corresponding differences in survival. These differences of observed survival were substantially confirmed in terms of relative survival. *Conclusions*: The poor prognosis of pancreatic carcinoma seems to depend, in part, on diagnostic delay and this, in turn, is influenced by the type of presenting symptoms.

1. Introduction

The prognosis of pancreatic carcinoma is variably related to a series of primary determinants such as clinical stage, involvement of lymph nodes and/or viscera, tumor size and differentiation, involvement of resection margins and serum CA19-9 level [1–4]. However, the variable presence of these factors can modulate survival within a limited time-frame and the prognosis of pancreatic carcinoma is very poor for the large majority of patients. Recently, attention has been focused on clinical symptoms which are present before diagnosis and/or during treatment, as additive prognostic indicators [5–7]. We, therefore, decided to include some of the most common early symptoms in our investigation of factors affecting the prognosis of our series of patients with pancreatic carcinoma. We intended to verify the prognostic role of each symptom, giving particular attention to diagnostic delays and to relationships with other known clinical and pathological factors.

2. Patients and methods

2.1. Patients

In the decade 2001–2010 we treated 170 patients with newly diagnosed pancreatic cancer. All signed informed consent to the analysis of their data, in accordance with the requirements of the Institute's Ethical Committee. Patients with neuroendocrine, ampullary or duodenal tumors were excluded from this series through re-evaluation of the histological or cytological specimens. The clinical investigation was retrospective and was possible because of the systematic, accurate registration in clinical records of symptoms at presentation, date of their onset, date of diagnosis and, moreover, of the availability of a series of data regarding comorbidity, laboratory findings, computed tomography staging

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information, date and type of surgical operation (or of biopsy in inoperable cases), time and type of chemotherapy (and of combined radiotherapy in a minority of patients) and date of last known vital status. The symptoms recorded were jaundice, abdominal pain and weight loss and they were analyzed only by time of first presentation, not by their severity or request of first medical observation. A component of subjectivity is unavoidable in this determination of time, but its approximation to ±1 month can be considered as tolerable related to the type of our study. The time from the date of onset of the first symptom(s) and the date of the pathologic diagnosis is indicated as diagnostic delay. The staging was assessed according to the Seventh Edition of the AJCC/TNM Classification [8] and pathological diagnosis was reviewed following the criteria of the last WHO Classification [9].

The majority of the patients was inoperable at diagnosis and a radical pancreatic resection was performed in 50 subjects; a gastric and biliary by-pass was constructed in 19 patients, while an endoluminal or percutaneous stent was inserted for biliary decompression in other 31. One hundred forty-three patients underwent gemcitabine-containing chemotherapy regimens, with or without fluorouracil or oxaliplatin. Eighty-nine of these were metastatic, 46 were treated with adjuvant therapy after resection, 8 with a neo-adjuvant intent. Nineteen patients received radiotherapy to the pancreas in combination with chemotherapy. Only 4/170 patients were still alive at the conclusion of the study.

2.2. Statistics

The diagnostic delay was calculated from the date of onset of the symptom (or the initial presenting symptom when there was more than one) to the date of diagnosis and the cumulative survival was computed from the date of diagnosis to that of the last known vital status. Curves of diagnostic delay and survival were drawn according to the Kaplan and Meyer techniques [10] and differences were tested for statistical significance with the log-rank test [11].

A multivariate analysis was performed by means of multiple regression applied to survival according to the Cox proportional hazards model [12]. The following clinical covariates were analyzed, after reduction of the multilevel categorical variables to binary ones: sex, age (years), time to diagnosis (weeks), pancreatic site of the tumor (pancreatic head or otherwise), histological type (ductal adenocarcinoma or otherwise), tumor size (cm), stage [(I + II) vs. (III + IV)], surgical resection (radical resection vs. partial resection or no operation), and administration of chemotherapy (yes or no). The proportional hazard assumption was tested by the procedure proposed by Therneau and Grambsch [13], based on the Schoenfeld residuals. Only chemotherapy turned out to have a changing effect in time and, therefore, was used as a stratifying factor in the model.

Finally, the role of individual symptoms was checked through an evaluation of the relative survival, which was calculated as the ratio of the overall survival rate observed in the patients' series to the expected survival rate drawn from the general reference population for subjects similar to the patients with respect to age, sex, calendar year of initial observation and duration of observation. The age-, gender-, and calendar year-specific death rates available from national Italian mortality tables (ISTAT, Istituto Nazionale di Statistica) were used to calculate the expected deaths – and, thus, the expected survival, as exemplified elsewhere [14].

The analyses were performed using the Stat View 5.0 software (Abacus Concepts, Berkeley, California, 1995) for Macintosh.

Table 1
Clinical characteristics of the patients.

Total number: 170	Male/female: 100/70 (58.8/41.2%)
Age, years (mean ± SD): 65.8 ± 10.2	Site
Age range, years: 36.4–91.5	Head: 91 (53.6%)
Stage	Body: 17 (10.0%)
I: 6 (3.5%)	Tail: 20 (11.8%)
II: 37 (21.8%)	Diffuse: 42 (24.6%)
III: 28 (16.5%)	Histology
IV: 99 (58.2%)	Ductal adenocarcinoma: 147 (86.5%)
Surgery	Intraductal papillary carcinoma[a]: 6 (3.5%)
Not operated: 101 (59.4%)	Acinar carcinoma: 5 (2.9%)
With palliative intent: 19 (11.2%)	Adenosquamous carcinoma: 4 (2.4%)
With radical intent: 50 (29.4%)	Signet-ring-cell carcinoma: 3 (1.8%)
Median diagnostic delay (weeks): 8.4 (range: 0.4–44.7)	Undifferentiated carcinoma: 5 (2.9%)
Treatments	
Gemcitabine-containing chemotherapy regimens: 143 (84.1%)	
Radiotherapy: 19 (11.2%)	
No oncological therapies: 27 (15.9%)	

[a] The full definition according the WHO Classification is "intraductal papillary mucinous neoplasm with an associated invasive carcinoma".

3. Results

The main clinical characteristics of the patients are illustrated in Table 1 and their comorbidities are reported in Table 2. The general features of our study population are concordant with those of many other series in the literature, with three-quarters of all patients having advanced clinical stage (III or IV). The prevalence and type of comorbidities do not exceed what can be expected from a population with a mean age at diagnosis of 65 years, as confirmed by other comparable cohorts of patients admitted to the center. The median survival of the whole population was 8.6 months (95% confidence interval: 7.1–10.2). Table 3 presents the results of the multivariate analysis of the clinical factors considered. By the evaluation of the Shoenfeld residuals chemotherapy showed a clear but decreasing effect on mortality in time; for this reason it was used as stratifying factor and no hazard ratio related to chemotherapy is given. The clinical factors with significant and independent prognostic value were diagnostic delay from the onset of signs and symptoms (in weeks) and surgery (radical resection vs. partial or no resection), whereas clinical stage [(I + II) vs. (III + IV)] did not reach the conventional limits of statistical significance. The analysis excluded sex, age, site and size of the tumor, and histology from the variables important for survival. The surprising result was the prognostic weight of the

Table 2
Comorbidities variably associated with pancreatic cancer in the 170 patients of the study.

Hypertension	59 (34.7%)	Diabetes mellitus	51 (30.0%)
Chronic hepatitis/cirrhosis	26 (15.3%)	Ischemic heart diseases	18 (10.6%)
Cerebrovascular diseases	14 (8.2%)	Cholelithiasis	14 (8.2%)
Gastritis/gastric ulcers	11 (6.5%)	Chronic obstructive pulmonary disease	10 (5.9%)
Previous/concomitant neoplasms	10 (5.9%)	Cardiac arrhythmias	8 (4.7%)
Peripheral arterial diseases	7 (4.1%)	Thyroid diseases	5 (2.9%)
Chronic renal insufficiency	5 (2.9%)	Psycological/psychiatric disorders	4 (2.4%)
Thromboembolic disease	4 (2.4%)	Autoimmune disorders	3 (1.8%)
HIV positivity	1 (0.6%)	Monoclonal gammopathy	1 (0.6%)
Von Willebrand disease	1 (0.6%)		