ORIGINAL ARTICLE

Unresectable pancreatic adenocarcinoma: do we know who survives?

Mohammad H. Jamal[1], Suhail A. Doi[2], Eve Simoneau[1], Jad Abou Khalil[1], Mazen Hassanain[1], Prosanto Chaudhury[1], Jean Tchervenkov[1], Peter Metrakos[1] & Jeffrey S. Barkun[1]

[1]Department of Surgery, McGill University Health Center, Montreal, QC, Canada and [2]School of Population Health, University of Queensland, Brisbane, QLD, Australia

Abstract

Background: This study attempts to define clinical predictors of survival in patients with unresectable pancreatic adenocarcinoma (UPA).

Methods: A retrospective study of 94 consecutive patients diagnosed with UPA from 2001 to 2006 was performed. Using data for these patients, a symptom score was devised through a forward stepwise Cox proportional hazards model based on four weighted criteria: weight loss of >10% of body weight; pain; jaundice, and smoking. The symptom score was subsequently validated in a distinct cohort of 32 patients diagnosed with UPA in 2007.

Results: In the original cohort, the overall median survival was 9.0 months (95% confidence interval [CI] 7.6–10.4). This altered to 10.3 months (95% CI 6.1–14.5) in patients with locally advanced disease, and 6.6 months (95% CI 4.2–9.0) in patients with distant metastasis. Median survival was 14.6 months (95% CI 13.1–16.1) in patients with a low symptom (LS) score and 6.3 months (95% CI 4.1–8.5) in patients with a high symptom (HS) score. A total of 73% of LS score patients survived beyond 9 months, compared with only 38% of HS score patients ($P < 0.001$). The discrimination of the LS score was greater than that of any conventional method, including imaging. The validation cohort confirmed the discriminative ability of the symptom score for survival.

Conclusions: A simple and clinically meaningful point-based symptom score can successfully predict survival in patients with UPA.

Correspondence

J. S. Barkun, Department of Surgery, McGill University Health Center, Montreal, QC H3A 1A1, Canada.
Tel: + 1 514-934 1934. Fax: + 1 514-843 1434. E-mail: jeffrey.barkun@muhc.mcgill.ca

Introduction

The vast majority of patients with pancreatic adenocarcinoma present with unresectable disease as a result of either local invasion or distant metastasis.[1] Although significant life-prolonging treatment remains evasive, the last decade has been associated with improved survival in this group, although care is still primarily aimed at palliative measures, including chemotherapy, the supportive management of pain, the relief of biliary and duodenal obstructive symptoms, cachexia and malnutrition.[2–4]

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The efficacious management of jaundice itself has been shown to significantly influence quality of life and even survival.[5–7] Whereas surgical bypass had long been the strategy of choice for the palliation of obstructive symptoms of the biliary tract, this dogma was successfully challenged in the early 1990s, often in the context of comparisons with endoscopic stenting.[8,9] These studies suggested that the surgical option of biliary decompression was less favourable than that of endoscopic decompression with plastic biliary stents with respect to early morbidity, although mortality remained unaffected. However, in the longer term, the surgical option was superior because of the absence of stent blockage and cholangitis in the surgical group. This finding appears to be true for patients who survive for ≥6 months. The advent of

metal stents[10] and, more recently, covered metal stents[11] has significantly prolonged their duration of patency. A more recent cohort study utilizing metal biliary stents[12] demonstrated a biliary patency of 6–7 months in patients with malignant biliary obstruction. With such improvements in non-operative palliation techniques, any possible benefit of bypass surgery can only occur if survival is longer than the duration of metal stent patency. In order to allow for optimal individualized patient care, it would thus appear essential to identify which patients with unresectable pancreatic adenocarcinoma (UPA) are likely to survive longer. To date there is a paucity of data in the literature regarding factors that predict the survival of patients with UPA prior to intervention. The aim of this study was to identify simple clinical factors that can help determine the prognosis in these patients.

Materials and methods
Patient characteristics
The McGill University Health Center (MUHC) is one of two accredited centres in the province of Quebec, Canada, for the treatment of complex hepatobiliary disease. Two cohorts were studied: the first ('original cohort') consisted of all patients presenting from January 2001 to December 2006 ($n = 94$) with pathological or radiological evidence of pancreatic adenocarcinoma and who were found on radiology or at laparotomy to have unresectable disease. This cohort was used to create the McGill–Brisbane Symptom Score (MBSS) presented below. A second cohort ('validation cohort') of patients diagnosed with UPA in 2007 and meeting similar criteria was used to validate the MBSS ($n = 32$). Imaging in all patients consisted of computed tomography scans with a triphasic pancreas protocol; patients who were found to have metastasis or local invasion on radiology were not offered bypass surgery and underwent endoscopic biliary stenting as appropriate. All patients selected for surgery therefore underwent a laparotomy with a curative intent. The findings of UPA at laparotomy, resulting either from local invasion of major arterial vessels (coeliac artery or superior mesenteric artery) or distant metastasis, confirmed the indication for palliation with a bypass (either choledochojejunostomy, gastrojejunostomy or both [i.e. a 'double bypass']). In most situations, a double bypass was performed. The surgical team consisted in all cases of an experienced hepatobiliary surgeon and a fellow or chief resident. Endoscopic stent insertion was performed by an endoscopist experienced in interventional endoscopic retrograde cholangiopancreatography. All patients received antibiotic prophylaxis 30 min before stent insertion. A plastic stent was inserted if the resectability of the patient had not yet been determined; otherwise a metal non-covered stent was inserted.

Preoperative data collection
Data on operative technique and findings, endoscopic procedures, preoperative symptoms and radiological investigations were collected using the MUHC prospective tumour registry database and by chart review. Admission notes, attending staff letters and nutrition consults were used to determine preoperative symptoms. These included jaundice (bilirubin more than five times the normal limit), self-reported weight loss of >10%, persistent abdominal or back pain, onset of diabetes mellitus within 1 year of diagnosis, and history of cigarette smoking within 5 years of diagnosis.

The actual date of death was confirmed in all patients ($n = 94$) in the original cohort by accessing the Government of Quebec Registry. In the validation cohort ($n = 32$), however, date of last contact was used to estimate survival as censored data via the Kaplan–Meier method. Survival was calculated from the date of diagnosis (the date with the first radiological evidence of pancreatic adenocarcinoma) to the date of death or last follow-up if the patient was still alive at the time of the study.

Statistical analyses
Original cohort
In the original cohort, univariate analysis was conducted to describe the distributions of baseline variables. Survival analysis was then performed with a view towards construction of a 'symptom score'.

(i) The McGill–Brisbane Symptom Score. Survival curves were plotted and survival times estimated using the Kaplan–Meier method with the Greenwood[13] procedure to estimate median survival and confidence intervals (CIs) in months. To avoid variable selection caused by spurious correlations, variables were excluded as potential predictors based on a visual examination of survival curves. Univariate tests of significance were not used to build the model because they lack power, but in the multivariable model we used a P-value of <0.1 in the realization that small datasets may not necessarily have sufficient power to detect the significance of small effects that cumulatively may affect prognosis. Only factors obtained early in diagnosis were used for the symptom score development, which was based on a forward stepwise Cox proportional hazards model. Results of this modelling were used to weigh each of these components and develop the MBSS. Two risk groups were created from the score – low intensity and high intensity MBSS – as we felt that more than two groups (e.g. tertiles or quartiles) would have less clinical relevance. Having created this clinical score, we evaluated the strength of its association with cancer-specific survival compared with that of conventional predictors.

(ii) Predictors of cancer-specific survival. Exploratory analyses were conducted using both binomial logistic regression and Cox regression analyses with cancer-specific survival as the outcome. Nine variables that impact on survival were identified: age; gender; tumour size; MBSS; presence of metastases; local invasion alone; use of surgical bypass; use of endoscopic bypass, and use of chemotherapy. Multivariable analysis was used to identify independent predictors of survival. The analysis was carried out by inserting one variable in the model

and then using forward stepwise regression to obtain a final model. Odds ratios (ORs) and 95% CIs for all individual variables in the final model were estimated. Significance statements refer to P-values of <0.05 in two-tailed tests, except for model building, in which P < 0.1 applied. We used SPSS for Windows (Version 13; SPSS, Inc., Chicago, IL, USA) for all statistical analyses.

Validation cohort

In the validation cohort, univariate analysis was conducted to describe the distributions of baseline variables. In order to validate the usefulness of the MBSS, we assessed its ability to discriminate survival using the Kaplan–Meier method with the Greenwood[13] procedure to estimate median survival (and 95% CI) in months.

Results

Original cohort

Baseline characteristics of the 94 original cohort patients are shown in Table 1. Of these, 71 had a lesion located in the head of the pancreas. The overall median survival in this cohort was 9.0 months. The actual survival associated with traditional predictors of survival in this cohort is illustrated in Table 2. Table 3 shows the results of the regression model that led to the creation of the

MBSS. Eventually, four factors were identified: weight loss of >10% of body weight; smoking; pain, and jaundice. The resulting continuous distribution of total risk scores across all patients in the model (range 0–21) was used for the exploratory analysis. It was then stratified into two equal categories (0–9 and 12–21) that grouped patients according to their MBSS values (Table 4). Results regarding the low and high intensity MBSS groups are shown in Table 2 and Fig. 1(A). Survival by MBSS category remained discriminatory even after patients were divided into local invasion and metastatic disease subgroups (Table 5), which suggests that the MBSS is a better discriminator than radiological staging.

Table 2 Overall survival data for the original cohort (Kaplan–Meier) (n = 94, 2001–2006)

Subgroups	Median survival, months	95% CI
Local invasion only	10.3	6.1–14.5
Distant metastasis	6.6	4.2–9.0
Surgical palliation	9.1	6.9–11.3
Endoscopic palliation	7.0	2.4–11.6
No palliative intervention	13.0	8.8–17.2
Low intensity symptoms	14.6	13.1–16.1
High intensity symptoms	6.3	4.1–8.5
Overall	9.0	7.6–10.4

Table 1 Patient characteristics (n = 126, 2001–2007)

Variable	Original cohort 2001–2006 (n = 94) n (%)	Validation cohort 2007 (n = 32) n (%)
Age, years		
Median	69.0	68.5
Range	40–96	41–87
Sex		
Men	53 (56)	15
Women	41 (44)	17
Tumour size, cm		
Median	3.80	3.95
Range	1–10.0	1–6.6
Missing data	n = 6	n = 8
Palliative intervention		
Stent	24 (26)	21 (66)
Bypass	42 (45)	8 (25)
Both	1 (1)	0
None	27 (29)	3 (9)
Presenting symptoms		
Weight loss (any)	71 (76)	22 (69)
Weight loss of >10%	55 (59)	22 (69)
Smoking	25 (27)	11 (34)
Pain	52 (55)	24 (75)
Jaundice	56 (60)	21 (66)

Table 3 Symptoms that independently predict survival (n = 94, 2001–2006) (odds that a patient with the symptom of interest reaches the endpoint [death] first)[a,b]

|	Odds ratio	P-value	Hazard ratio
Weight loss of >10%	0.811	<0.001	2.2
Pain	0.511	0.025	1.7
Jaundice	0.398	0.087	1.5
Smoker	0.393	0.092	1.5

[a]Any weight lost, use of narcotics, cholangitis and recent or new diabetes mellitus were not selected in the model
[b]Variables with P < 0.1 were included in the initial model in a stepwise manner, starting with the variable with the lowest P-value. A standard Cox regression was then run on the selected variables

Table 4 McGill–Brisbane Symptom Score (MBSS)

Symptom	Points
Weight loss of >10%	8
Pain	5
Jaundice	4
Smoking	4
Total possible	21
Low intensity	0–9 (median 5, IQR 4.0–8.0)
High intensity	12–21 (median 13, IQR 12.5–17.0)

IQR, interquartile range
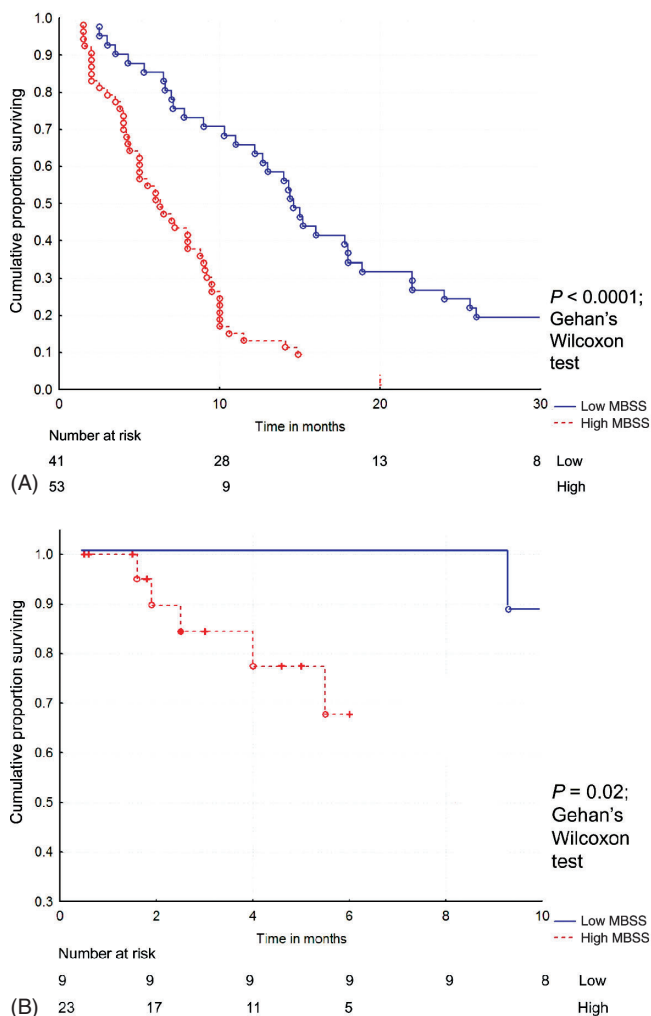
Figure 1 Cumulative proportion of patients surviving (Kaplan–Meier) in the (A) original cohort (n = 94) and (B) validation cohort (n = 32). ○, complete data; +, censored data; MBSS, McGill–Brisbane Symptom Score

Validation cohort

Descriptive analyses of baseline variables in patients in the validation cohort were similar to those for the original cohort (Table 1) except with respect to the method of palliation from jaundice: the use of biliary stents was more common in the 2007 group. In assessing survival in this validation cohort, the MBSS was again seen to be an excellent discriminator of survival (Fig. 1B).

Subsequent analyses were performed on both cohorts pooled together using actual survival for the original cohort and censored survival for the validation cohort. Exploratory analyses on the total cohort revealed that factors predicting survival to or beyond median survival via logistic regression analysis were MBSS, tumour size, age and chemotherapy in decreasing order of importance. Chemotherapy was associated with an increased chance of

survival, whereas the others were associated with decreased survival. Local invasion, involvement of more than one site and use of either method of palliation of jaundice were not independently associated with survival in this model. On Cox regression analysis, however, survival was not only significantly worse in patients with a higher MBSS (hazard ratio [HR] 2.9, 95% CI 1.8–4.5), but also in endoscopically palliated patients (HR 2.1, 95% CI 1.2–3.8). The discrepancy between the findings of the logistic and Cox regression models is related to the survival difference between stented and other patients. This difference in survival became prominent only 9 months after diagnosis, whereas chemotherapy, tumour size and age made their maximum impact on survival before that time.

Finally, we looked at the distribution of individual variables in the two MBSS groups. In the low symptom (LS) MBSS group, the most common variables in decreasing order were jaundice (25/50), pain (22/50), smoking (7/50) and weight loss of >10% (4/50). In the high symptom (HS) MBSS group, the most common variables in decreasing order were weight loss of >10% (73/76), pain (54/76), jaundice (52/76) and smoking (29/76).

Discussion

Few reports in the literature have attempted to identify factors associated with survival in patients with UPA.[14,15] The paucity of such studies is partly related to difficulties in obtaining complete follow-up in this cohort of seriously debilitated patients. In this study, we therefore used the validated Quebec-wide population database to confirm follow-up data for the original cohort patients until death. The median survival was 10.3 months in patients with locally invasive disease and 6.6 months in patients with metastasis, for an overall median survival of 9.0 months (Table 2). This is longer than in prior historical cohorts and is in keeping with recent reports showing an increase in survival in UPA.[16,17] The cause of this increase in survival is not clearly identified and is probably multifactorial. Gemcitabine therapy has been shown in retrospective studies and randomized control trials to increase survival.[18,19] It is currently the standard chemotherapeutic agent for treatment of UPA with distant metastases. Refinements in surgical and endoscopic techniques have also improved the palliation of patients with jaundice and duodenal obstruction and may well affect survival. Jaundice affects quality of life and survival through its associations with pruritis, anorexia, impaired renal function and immunosuppression.[20–22] Another factor promoting survival may be the increased interest among oncology specialists in cancer palliation, which leads to better supportive care of patients with UPA.[22] Whatever the cause of this increase in survival may be, this newly observed longevity provides a unique opportunity to study subgroups of UPA patients who previously had universally dismal survival.[23]

Several factors that predict prolonged survival in patients with UPA have been previously described. In a study at the MD Anderson Cancer Centre (Houston, TX, USA),[24] which looked at

Table 5 Symptom score[a] by disease group and survival

Group	Criteria	Median survival, months
Original cohort, locally invasive group (*n* = 51, 2001–2006)		
A (lower intensity symptoms)	Score 0–9	15.0
B (higher intensity symptoms)	Score 12–21	8.0
Original cohort, metastatic cancer group (*n* = 43, 2001–2006)		
A (lower intensity symptoms)	Score 0–9	12.2
B (higher intensity symptoms)	Score 12–21	4.2

[a]Symptom score is the sum of the following: weight loss of >10% = 8, otherwise 0; pain = 5, otherwise 0; jaundice = 4, otherwise 0; smoking = 4, otherwise 0

patients with UPA without metastasis who received chemoradiation therapy, Karnofsky performance scale (KPS) values and weight loss of <5% of body weight were found to be associated with overall survival on univariate analysis. The only independent prognostic factor on multivariate analysis, however, was KPS score.[24] It correlated with both disease-free and overall survival. The KPS is a functional impairment scale on which scores range from 0 (dead) to 100 (normal, no complaints). A median survival of 3.9 months was observed in patients with a KPS score of <80, as opposed to 4.9 months in those with a KPS score of >80. This discrimination is, however, obviously not very good, possibly because the KPS is not specifically tailored towards pancreatic cancer. Cubiella *et al*. investigated factors predictive of survival in 134 patients with UPA.[25] Eight of 34 factors on univariate analysis correlated with survival; these were: jaundice; toxic syndrome at admission; serum cholesterol, iron and alanine aminotransferase concentrations; leukocyte count; baseline Eastern Cooperative Oncology Group (ECOG) performance status (measured on a scale of 0–5, where 0 denotes perfect health and 5 denotes death), and the presence of distant metastases. Cox regression analysis identified the absence of metastasis and a preserved baseline ECOG performance status as the only factors associated with improved overall survival. These authors did not consider weight loss in their model. Finally, a recent study by Muller *et al*.[26] found that ASA (American Society of Anesthesiologists) score, presence of liver metastasis, pain, CA 19-9, and carcinoembryonic antigen (CEA) levels were independent predictors of poor survival on multivariate analysis. The presence of four or five of these risk factors was associated with a median survival of 3.5 months, whereas patients with none or only one of these risk factors had a median survival of 13.5 months. Of note, the patients in this study had all been candidates for the Whipple procedure and none had undergone stenting as initial definitive palliation, indicating a positive survival selection bias.

In the present study, the aim was to create a simple clinical score that could discriminate survival in patients presenting with UPA, based on preoperative data, in order to help tailor palliation. In the original UPA cohort, patients in the LS score group (scores of 0–9) were likely to survive on average more than twice as long as patients in the HS score group (scores of 12–21) (Table 2). The

median actual survival of patients in the HS group was 6.3 months, whereas the median survival of patients in the LS group was 14.6 months (Table 2). Indeed, the MBSS provided a better discrimination of survival than even the radiological documentation of distant metastasis (Table 5). When both these predictors were combined in a multivariable Cox regression model, the MBSS had an HR of 2.7 (*P* < 0.001) compared with an HR of 1.3 (*P* = 0.22) for the radiological presence of distant metastases. This does not mean that the presence of distant metastases does not impact on survival, but, rather, that its impact is much smaller than that of the MBSS. These findings were corroborated in a separate population: the validation cohort of UPA patients from 2007 (Fig. 1B). A comparison of the MBSS with other conventional predictors of survival in a logistic regression using both UPA cohorts together showed the symptom score to have the strongest association with survival (beyond 9 months), followed by the use of chemotherapy and age.

The strength of the association between the MBSS and survival is greater than that of conventional predictors and is intriguing because it is not measurable through findings on imaging (Table 5). We believe that it may reflect an expression of disease burden by measuring its clinical rather than its radiological or biochemical expression. It could thus act as a very useful tool early in the clinical encounter of a UPA patient for the purposes of directing and tailoring palliation on an individual basis. Currently, nearly all UPA patients are indiscriminately offered palliation through endoscopic stenting because this modality is believed to be associated with lesser morbidity and mortality. However, it is well documented that metal stents appear to have a median patency of about 7 months.[12] Upon blockage, the patient will develop cholangitis, which is associated with morbidity and decreased quality of life.[5] This 7-month period is in fact much shorter than the anticipated survival of a patient with an LS MBBS value (14.6 months). Patients presenting with jaundice or obstructive symptoms and lower MBBS values might thus be better served by initial surgical palliation because of their increased anticipated survival.

In conclusion, the McGill–Brisbane Symptom Score appears to be useful and to have validity in predicting the survival of UPA patients on clinical grounds. This ability could lead to a better

selection of palliative methods in these patients. Although the system was validated in a separate cohort from the same institution, a broader validation across multiple centres is desirable.

Conflicts of interest
None declared.

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