

ORIGINAL ARTICLE

Carcinoma of the Body of Pancreas in Evolution: An Aggressive Disease Affecting Younger Patients?

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ABSTRACT

Context Pancreatic body carcinoma has a poor prognosis with advanced disease at presentation. Recent experience at multidisciplinary team (MDT) meetings suggests increasing prevalence.

Objective Our aim was to determine if introduction of MDT meetings has affected the natural history of this disease.

Design Retrospective diagnostic and survival data were collected from 1995 to 2006 at two large teaching hospitals, and divided into pre- and post 2003 groups (based on MDT introduction).

Participants Thirty-one patients with pancreatic body carcinoma (median age at diagnosis 72 years; range 43-87 years).

Results Commonest symptoms at presentation were abdominal pain and weight loss. Eight patients (25.8%) were diagnosed pre MDT (median age 71.5 years, range: 60-87 years) and 23 patients (74.2%) were diagnosed post MDT (median age 67 years, range: 43-85 years; $P=0.299$ vs. pre MDT). There was a significantly ($P=0.024$) greater prevalence of more advanced tumours post MDT (stage IV: 15/23, 65.2%) than pre MDT (stage IV: 2/8, 25.0%). Neither tumour

markers nor liver biochemistry differentiated tumour stage. Best supportive care was offered to 16 patients (51.6%) while 12 patients (38.7%) were suitable for chemotherapy: 2 out of 8 pre MDT (25.0%) and 10 out of 23 (43.5%) post MDT ($P=0.433$). For stage III tumours, post MDT patients tended to be younger (median 59 years vs. 74.5 years, $P=0.042$). Survival was not significantly increased after MDT introduction but chemotherapy offered significant survival benefit on multivariate analysis ($P=0.042$; hazard ratio: 0.39, 95% CI: 0.16-0.97).

Conclusion The trend is towards increased prevalence of pancreatic body cancer and more advanced disease at presentation. Chemotherapy was associated with a survival benefit, although the introduction of the MDT has not significantly altered disease management.

INTRODUCTION

Pancreatic cancer is the eighth most common cause of cancer in women and the tenth most common cancer in men [<http://www.cancerresearch.com>]. The incidence and mortality rates for pancreatic cancer are almost equal being 8.8 and 8.5/100,000 per year respectively [1, 2].

This represents 7,040 deaths per year and it is the fifth most common cause of cancer death in the UK [1]. It appears that age at diagnosis of pancreatic cancer is important in survival; the one- and five-year survival rates for those aged under 50 are reported to be 26% and 9% respectively, and 7% and 2% for those over 80 [3].

The prognosis of pancreatic carcinoma is poor as clinical signs and symptoms may be non-specific with patients presenting late in the disease. Generally it is perceived that the classic patient presenting with pancreatic cancer is elderly, thin and may have recently developed diabetes mellitus [4].

Tumours of the body and tail of the pancreas account for about 15% of cases of pancreatic cancer [5] and tumour site is important when considering presentation and survival rates [6]. Pancreatic body tumours can be defined as tumours involving the left border of the superior mesenteric vein and the left border of the aorta or the superior mesenteric/portal vein confluence and the aorta [7]. Localisation of the tumour in the pancreas correlates with stage; Watanabe *et al.* in 2004 demonstrated that 80% of pancreatic tumours in the pancreatic body and tail were stage IV in comparison to 33% of those in the pancreatic head [8]. These authors also found 60% of all asymptomatic patients with pancreatic cancer had pancreatic body tumours, which may explain increased stage of disease at diagnosis in these patients.

Considering the survival data for pancreatic tumours, prognosis is poorest for tumours of the tail of the pancreas, followed by those of the body and then those of the head (survival rates at 1,000 days were similar for carcinoma of the pancreatic head and body: around 5%, whilst no patients with carcinoma of the tail of the pancreas survived to 1,000 days) [8]. These studies have compared different sites of cancer however there are little published data on the epidemiology of pancreatic body carcinoma.

Given the poor prognosis associated with pancreatic cancer, the implementation of a

multidisciplinary team (MDT) approach to the management enables interdisciplinary management for effective care. This, along with subspecialisation within surgery has been shown by Stephens *et al.* in 2006 to have improved outcome after surgery for oesophageal cancer [9]. Our own perception is that there has been an increase in the number of patients being diagnosed with pancreatic body tumours discussed at our MDT meetings. The age at diagnosis also seemed to be decreasing which is at odds with the perception of the 'classic' patient group.

The aim of this study was to identify changes in the pattern of presentation, (including demography and stage of tumour), and subsequent management of patients presenting with these cancers based on the introduction of the loco-regional MDT.

METHODS

We retrospectively reviewed all patients diagnosed with pancreatic body carcinoma managed at Leeds Teaching Hospitals, UK, and the Bradford Teaching Hospitals NHS Trust, UK, between 1995 and July 2005. Prospective data were collected between August 2005 and July 2006, inclusive. Patients notes were identified either by the use of the hospital database or by searching the histology reports and the radiology reports for those patients with pancreatic body carcinomas. Prospective cases were also identified by discussion at the Hepatic-Pancreatobiliary (HPB) multidisciplinary team meetings. A standardised proforma for each patient detailing patient demographics, clinical presentation and past medical history, biochemical investigations, imaging, treatment decisions and patient survival was completed. All available computerised tomography (CT) images were reviewed by one consultant radiologist (A.L.). Analysis of the results was divided into pre- and post-2003; the date of introduction of the Loco-Regional Cancer Network MDT for pancreatic cancer.

Table 1. Tumour markers at presentation.

Tumour marker	Abnormal results	Median (range)
CA 19.9 (n=15/31, 48.4%) Reference range: 0-33 kU/L	15 (100%)	1,308 kU/L (54-6,1264)
CEA (n=14/31, 45.2%) Reference range: 0-5 µg/L	5 (35.7%)	64 µg/L (10.0-464.4)

STATISTICS

Data are reported as medians, ranges and frequencies. All statistical analyses were performed using the SPSS for Windows™ version 14.0 (SPSS Inc, Chicago, Illinois, USA). Continuous data were analysed using the Mann-Whitney U test and contingency data using the Fisher's exact and the linear-by-linear chi-squared association tests, where appropriate. Survival times were calculated using the Kaplan Meier curves and analysed by log-rank test. A multivariate analysis was performed by Cox regression (stepwise forward model) for variables significant on univariate analysis. Significance was taken at two-tailed P less than 0.05.

RESULTS

A total of 31 patients were included with a median age at diagnosis of 72 years (range: 43-87 years), and an almost equal male to female ratio (16 males, 15 females). Eight patients (25.8%) were diagnosed pre MDT and 23 patients (74.2%) were diagnosed post MDT. There was no significant (P=0.299) difference between median age at diagnosis in the two groups (pre-MDT: median age: 71.5 years; range: 60-87 years) and post-MDT (median age: 67 years; range: 43-85 years). However, we demonstrated a trend towards decreased age at diagnosis in stage III patients post introduction of the MDT with a median age of 59 years (range: 43-84 years) in comparison to 74.5 years (range: 57-85 years) before the introduction of the MDT (P=0.042).

Before the introduction of the MDT (1995-2002 inclusive), 613 patients were diagnosed with pancreatic cancer in our region, with 8 (1.3%) of these having carcinoma of the body of the pancreas. Between 2003 to July 2006

inclusive, 281 patients were diagnosed with pancreatic cancer and 23 (8.2%) of these involved the pancreatic body (equivalent to 9 new cases per year post 2003 MDT compared with one new case per year pre 2003 MDT). On average, 76.6 patients were diagnosed with pancreatic cancer per year pre-MDT with 80.3 per year after MDT introduction.

Clinical Presentation

Twenty eight (90.3%) patients presented with abdominal pain and a further 28 (90.3%) presented with weight loss. Six patients (19.4%) presented with jaundice and seven patients (22.6%) had diabetes (four new onset diabetes and one experienced deterioration in their glucose control). One patient (3.2%) presented with pancreatitis, and in one patient (3.2%) the diagnosis was incidental.

In the six patients that presented with obstructive jaundice two had extrinsic compression by tumour, three had liver metastases, and one had a stone in the common bile duct. Jaundiced patients had significantly (P<0.001) higher bilirubin (median 108 µmol/L, range 85-240 µmol/L vs. median 15 µmol/L, range 7-24 µmol/L), and alanine-L-transpeptidase (ALT) (median 110 IU/L, range 37-354 IU/L vs. median 26 IU/L, range 10-80 IU/L) values than non-jaundiced patients. No significant differences were observed for alkaline phosphatase (median 640, IU/L range 125-2,485 vs. median 229 IU/L, range 66-1,434 IU/L; P=0.095).

CA 19-9 was measured in 15 patients and CEA in 14 patients (Table 1). CA 19-9 measurements were abnormal in all patients (reference range: 0-33 kU/L) and 35.7% of CEA measurements were abnormal (reference range: 0-5 µg/L). Only one patient with a raised CEA presented with jaundice.

Thirteen patients (41.9%) had pancreatic adenocarcinoma confirmed histologically; in the remainder either tissue diagnosis was not appropriate or was refused by the patient.

Multi-slice CT (pancreatic protocol) was the principal imaging modality in all cases. Tumour stage ranged from stage IIb to stage IV at presentation. The post-2003 group had a

Table 2. Tumour stage at presentation.

Tumour stage	Pre 2003 MDT (n=8)	Post 2003 MDT (n=23)
IIb	1 (12.5%)	0
III	5 (62.5%)	8 (34.8%)
IV	2 (25.0%)*	15 (65.2%) ^a
P value^a	P=0.024	

^a Liner-by-linear association chi-squared test

significantly (P=0.024) increased prevalence of stage IV tumours (Table 2).

Correlation

There was no significant relationship between presenting symptoms and stage of disease (data not shown). Neither tumour markers (CEA and CA 19.9) nor liver biochemistry could differentiate tumour stage (data not shown). For the 16 patients (51.6%) in whom CT images were available for assessment by the radiologist (A.L.), there was no significant correlation between tumour size (maximal tumour dimension) and stage of the disease (stage III, n=3: median 4.8 cm, range 2.8-5.7 cm; stage IV, n=13: median 5.3 cm, range 3.7-10.8 cm; P=0.201).

Management

Among the six patients presenting with jaundice, stent insertion was performed in three patients (50.0%); in two of these patients, the pancreatic body tumour was

causing the obstruction. Median survival in these six jaundiced patients was 1.5 months (range 0.75-14 months).

Best supportive care was offered to 16 of 31 cases (51.6%). Two patients underwent an exploratory laparotomy for their tumours (6.6%); one had a pancreatectomy planned as stage Ib disease was diagnosed on CT but the tumour was irresectable with no obstruction (and then it was re-staged accordingly). The second underwent a gastrojejunostomy for gastric outflow obstruction.

Twelve patients (38.7%) were suitable for chemotherapy (one of whom underwent exploratory laparotomy); eight (66.7%) of these 12 patients received gemcitabine based chemotherapy and the remaining four (33.3%) received a 5-fluorouracil combination chemotherapy. One of these 12 patients died on admission. The other 19 patients were considered unsuitable for chemotherapy due to advancing age, poor quality of life and presence of significant co-morbidity. Patients in the chemotherapy group were significantly younger (median 62 years, range 43-78 years) than those in the non-chemotherapy group (median 74 years, range: 51-87 years) (P=0.026). There was no significant difference in the stage of the disease between the chemotherapy and non-chemotherapy groups (P=0.602).

Based on the introduction of the MDT, 2 (25.0%) out of 8 patients in the pre MDT

Table 3. Demographics for patients with chemotherapy.

Demographic	Chemotherapy		No chemotherapy	
	Pre 2003 MDT (n=2)	Post 2003 MDT (n=10)	Pre 2003 MDT (n=6)	Post 2003 MDT (n=13)
Age: median (range); years	64.5 (61-68)	60 (43-78)	76.5 (60-87)	74 (51-85)
	P=0.182 ^a		P=0.077 ^a	
Gender				
- Males	1 (50.0%)	5 (50.0%)	3 (50.0%)	8 (61.5%)
- Females	1 (50.0%)	5 (50.0%)	3 (50.0%)	5 (38.5%)
	P=1.000 ^b		P=1.000 ^b	
Stage of disease				
- IIb	0	0	1 (16.7%)	0
- III	1 (50.0%)	4 (40.0%)	4 (66.7%)	4 (30.8%)
- IV	1 (50.0%)	6 (60.0%)	1 (16.7%)	9 (69.2%)
	P=1.000 ^b		P=0.022 ^c	

^a Mann-Whitney U test

^b Fisher's exact test

^c Liner-by-linear association chi-squared test

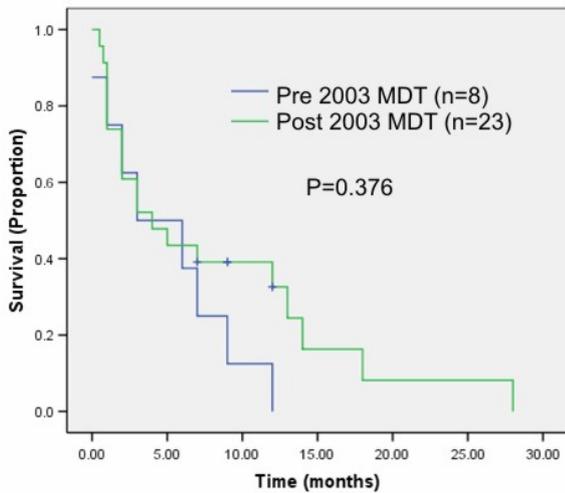


Figure 1. Survival curves in relation to the introduction of the multidisciplinary team (MDT) in 2003.

group were suitable for chemotherapy compared to 10 out of 23 (43.5%) of the post MDT group (P=0.433). Patient demographics in the chemotherapy group did not significantly change with the introduction of the MDT (Table 3). However, for patients who did not receive chemotherapy, the post-MDT group had significantly higher stage of disease in comparison to the pre-MDT group (P=0.022).

Survival

Median survival for all patients was 4 months (95% CI: 0.4-7.6 months, range: 0-28 months). Four patients were still alive at the time of the study; all of them were diagnosed after 2005. The presence of jaundice at presentation had no significant effect on survival (jaundiced patients: median 1.5 months, 95% CI: 0.0-4.6 months, range 0.75-14 months; non-jaundiced patients: median 5 months, 95% CI: 2.8-11.2 months, range 0-28 months; P=0.210). There was no significant difference in survival based on the introduction of the MDT (P=0.376; Table 4, Figure 1) both in stage III (P=0.076) and in stage IV (P=0.349) patients. Age at diagnosis of less than 60 years (P=0.033) and chemotherapy (P=0.012; Figure 2) were associated with significantly longer survival on univariate analysis. On multivariate analysis, chemotherapy alone was a significant predictor of longer survival, irrespective of age at diagnosis (P=0.042;

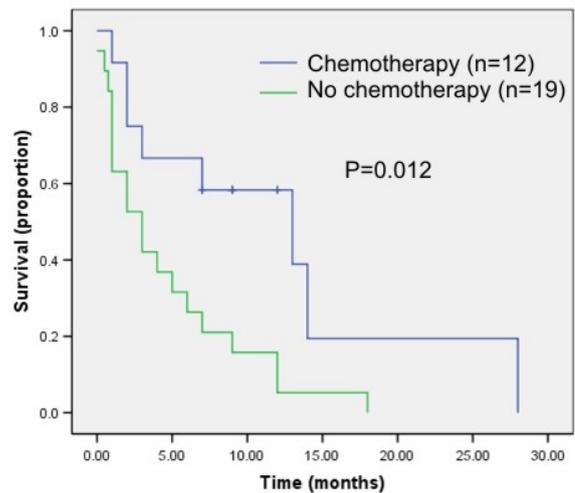


Figure 2. Survival curves comparing chemotherapy and non-chemotherapy.

hazard ratio: 0.39; 95% CI: 0.16-0.97). Median survival of patients receiving chemotherapy was 9 months (95% CI: 0-18.4 months, range: 1-28 months) compared to 3 months (95% CI: 1.6-4.4 months, range: 0-18 months) in those not receiving chemotherapy.

DISCUSSION

This study was prompted by the perception that the patient group with pancreatic body tumours is changing, with increased number of patients presenting and at a younger age. Multidisciplinary Team meetings are now established practice in the management of cancer and have been shown to improve

Table 4. Survival (months) in relation to stage and year of presentation. Median, 95% CI, and range values are reported. 95% CI values of the median survival are reported within parentheses.

Stage	Pre 2003 MDT	Post 2003 MDT	P value ^a
Stage III	3 (0.0-4.6) Range: 0-12 n=5	12 (0.0-26.3) Range: 1-28 n=8	0.076
Stage IV	4 (NA) Range: 2-6 n=2	3 (0.5-5.5) Range: 0.5-13 n=15	1.000
Overall ^b	3 (0.4-5.6) Range: 0-12 n=7	4 (0.5-7.5) Range: 0.5-28 n=23	0.185

^a Log-rank test

^b The patient with stage IIb disease was not included in this table

NA: not available

outcome [9]. These meetings also enable us to observe any changes in patient demographics which may be associated with change in the pattern of disease.

Symptoms and Signs of Patients with Pancreatic Body Tumours

The symptoms at presentation of patients with pancreatic body tumours has not significantly changed over the last decade. Most of the patients (90%) we identified presented with abdominal pain and weight loss. No patients were suitable for a resection of their tumour (97% patients had stage III or IV disease at diagnosis) which fits with previous observations that pain at presentation is associated with advanced stage of the disease [6].

Recent onset of diabetes, especially in those over 70 years has been suggested to be an important 'red flag' for the diagnosis of pancreatic cancer. Permert *et al.* in 1993 found that 56% of patients had diabetes diagnosed at the same time as their pancreatic tumour with 16% being diagnosed in the two years prior to cancer diagnosis [10]. It has also been suggested that more patients with a resectable tumour have diabetes (58%) than those with unresectable tumours (37%), however these groups included all pancreatic tumours and not just those confined to the body. All seven patients with diabetes in our study had essentially unresectable cancer.

It is of interest to note that two patients presented with jaundice due to mass effect of their body tumours instead of any liver metastases. Generally pancreatic head tumours are thought to have a better prognosis in part due to their earlier presentation with jaundice. Even though these patients with pancreatic body tumours presented with jaundice, their prognosis was still poor as the local disease was advanced enough to cause biliary obstruction.

Effect of the MDT Meeting on the Management of Patients with Pancreatic Body Tumours

Although 86% of the patients under the age of 60 at diagnosis were diagnosed after 2003, we

found no significant difference in median age at diagnosis before and after the MDT introduction. However, those patients with stage III disease were significantly younger.

Fifty-eight percent of all patients with pancreatic body tumours within the last ten years were given their diagnosis in 2005 or 2006. The fact that the proportion of pancreatic body tumours expressed as a percentage of pancreatic tumours as a whole has increased from 1.3 to 8.2% after the introduction of the MDT suggests a trend towards increased incidence of these tumours, although a more likely explanation is one of increased referrals to a dedicated MDT. We also demonstrated a trend towards increased stage of disease at presentation in younger patients (63% of patients were stage III at diagnosis pre 2003 in comparison to 65% of stage IV disease post 2003). It is possible that more pancreatic body tumours are diagnosed due to better imaging techniques and more aggressive management of these patients. Previously these patients may not have been referred to a MDT and instead offered a palliative option without discussion. The Loco-regional Cancer Network MDT for pancreatic cancer may have contributed to this change in referral pattern.

It appears that eventual outcome in terms of survival was no better after the introduction of the MDT. It is therefore unlikely that current management protocols could in any way alter the outcome of this disease. Best supportive care remains the most common strategy and chemotherapy usage has not been affected by the introduction of the MDT. Current literature agrees that those patients suitable for chemotherapy are in the minority [11, 12, 13].

Median survival was 3 months from diagnosis, reflecting the inoperability of these tumours at presentation. Pancreatic body and tail tumours are less resectable than those of the pancreatic head due to the often earlier presentation of head tumours with obstructive jaundice [14]. Brennan *et al.* reported that only 10% of patients with tumours of the body and tail of the pancreas are suitable for pancreatic resection [14]. This is much higher

than our experience, however tumours in the tail of the pancreas were included and the authors admit that figure is likely to be an exaggeration as patients with metastatic disease were not included. Fifty-eight percent of our patients had metastatic disease at presentation.

When survival data are considered, chemotherapy in our relatively small series showed a significant survival benefit ($P=0.042$; hazard ratio: 0.391, 95% CI: 0.158-0.966). A systematic review of chemotherapy and radiotherapy in inoperable advanced pancreatic cancer found survival benefit with chemotherapy (one year mortality odds ratio: 0.37, 95% CI: 0.25-0.57; $P<0.001$) [15]. Clinical benefit was demonstrated in the gemcitabine group when compared with 5-fluorouracil, however this did not translate into better survival. This trial involved all patients with pancreatic cancer with no separate analysis of patients with pancreatic body tumours.

Gemcitabine based chemotherapy was used in the majority of our patients, in keeping with the recommendations of Burris *et al.* in 1997 [16]. Our observations based on a small number of patients need to be interpreted with some degree of caution. However, in view of the grave prognosis associated with ductal adenocarcinoma of the body of pancreas, gemcitabine based chemotherapy may be of benefit to all suitably fit patients. Currently there are no published randomised controlled trials of chemotherapy *versus* best supportive care in these patients, and this would be challenging due to the rarity of the disease.

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Keywords Carcinoma; Drug Therapy; Interdisciplinary Communication; Pancreas; Survival

Abbreviations MDT: multidisciplinary team

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