

RESEARCH COMMUNICATION

Pancreatic Cancer in Universiti Sains Malaysia Hospital: A Retrospective Review of Years 2001-2008

Bachok Norsa'adah^{1*}, Azemi Nur-Zafira¹, Aishah Knight²

Abstract

Pancreatic cancer is usually detected late and has a high mortality rate. Since little is known about this cancer in Malaysia, a review of all cases admitted to Universiti Sains Malaysia Hospital was conducted to identify the epidemiological distribution and assess survival. A list of pancreatic cancer patients in 2001-2008 was obtained from the Hospital Record Department. Only cases confirmed by radio-imaging or histo-pathology examination were included. We excluded those with incomplete medical records. Kaplan-Meier and Cox proportional hazard approaches were used for data analysis. Only 56 cases were included with a mean (SD) age of 49.6 (16.0) years, with 60.7% males and 82.1% of Malay ethnicity. Previous history included cholelithiasis in 23.2%, diabetes mellitus in 16.1%, previous laparotomy in 10.7%, chronic pancreatitis in 7.1%, alcohol drinking in 5.4% and positive family history in 3.6%. The common presenting history included 67.9% loss of appetite, 66.1% loss of weight, 58.9% jaundice and 46.4% abdominal pain. Tumour staging was: 21.5% stage I, 17.8% stage II, 3.6% stage III and 57.1% stage IV. The median (95% CI) survival time was 3.4 (0.5, 6.3) months and significant prognostic factors were duration of symptoms (HR 0.97; 95% CI: 0.95, 0.99; p value 0.013), ascites (HR 2.64; 95% CI: 1.28, 5.44; p value 0.008) and Whipple surgery (HR 4.20; 95% CI: 2.27, 7.76; p value <0.001). The history of presenting complaints was short and the majority presented at late stages of the disease, thus the median survival time was very poor.

Keywords: Pancreas carcinoma - treatment - survival rate - Malaysia

Asian Pacific J Cancer Prev, 13, 2857-2860

Introduction

Pancreas cancer is not common in Malaysia, which probably reflects diagnostic capacity rather than the actual incidence. In 2006, the National Cancer Registry reported 253 cases of pancreas cancer and estimated the age-standardised rates as 2 per 100,000 men and 1.2 per 100,000 women. The sex ratio in Malaysia was 1.6:1 (M:F) and the Chinese had higher incidence rate compared to the other ethnic groups. It is also a disease of older people with the incidence increasing after 50 years of age (Zainal and Zainudin, 2006). In the United States, pancreas cancer was the fourth cause of cancer mortality (Lowenfels and Maisonneuve, 2002) and its incidence has been increasing (Barkin and Goldstein, 1999). The age and sex distribution was similar worldwide. The incidence of pancreas cancer increases with age and is more common among men (Ghadirian and Lynch, 2003; Luke et al., 2009). In general, the incidence of pancreatic cancer is higher in more developed countries than the less developed ones (Lowenfels and Maisonneuve, 2002).

Pancreas cancer is difficult to detect and in most cases, the cancer has already metastasized by the time of diagnosis; it is known as a silent killer as the symptoms and signs are vague and difficult to detect in the early stage

(Murr et al., 1994). This is one of the reasons for the high mortality rate of pancreas cancer which is nearly the same as the incidence rate (Lowenfels and Maisonneuve, 2002).

This study is a review of all cases of pancreas cancer admitted in Universiti Sains Malaysia hospital (HUSM) to describe the epidemiological distribution and assess survival. This study was conducted to fill in the gaps of knowledge about pancreas cancer as there has not been much research related to this cancer in Malaysia. By identifying the epidemiological distribution we can hopefully develop targeted strategies and activities for the early management of pancreas cancer in Malaysia.

Materials and Methods

This study was conducted at Universiti Sains Malaysia Hospital (HUSM), which is located in Kota Bharu, Kelantan, a north-eastern state in Peninsular Malaysia. It is a tertiary referral centre and the main provider of cancer care services in the area. A list of pancreatic cancer patients admitted to HUSM in 2001-2008 was obtained from the Department of Records. We included only confirmed cases of pancreas cancer by radio-imaging or histo-pathology examination. We excluded those with incomplete medical record. A standardised check list was

¹Unit of Biostatistics & Research Methodology, School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, ²Advanced Medical & Dental Institute, Universiti Sains Malaysia, Bandar Putra Bertam, Penang, Malaysia *For correspondence: norsaadah@kb.usm.my

used to collect data from the records. The data that were extracted were socio-demographic factors such as age, race, occupation and marital status; clinical characteristics such as family history of pancreatic cancer, presenting symptoms, smoking status, alcohol intake, other factor risks; method of diagnosis and the treatment received. We also collected dates of when first symptoms related to pancreatic cancer were noted, when diagnosis was made, when patient was last seen and death. Status of death was confirmed by the National Department of Registration. This study was granted an ethical clearance for Research Ethics (Human) Committee Universiti Sains Malaysia.

Data entry and analysis was conducted using the Statistical Package for the Social Science (SPSS) version 16.0. Data distributions and frequencies (%) were examined. All continuous variables were expressed as mean and standard deviation (SD) or as median and interquartile range (IQR), while categorical variables as frequency and percentage. Kaplan Meier and Cox Proportional Hazard were used to determine the survival rate and prognostic factors. Results are presented as hazard ratio (HR), 95% confidence interval (CI) and p value. The level of significance was set at < 0.05.

Results

There were 85 cases of pancreatic cancer in the list from the Records Department, HUSM. However, 12 case notes were not found, 10 had incomplete records and four were not confirmed pancreas cancers, thus only a total number of 56 patients were included in the final analysis.

Table 1 shows that there were 60.7% male and 39.3% female. The median (IQR) age of pancreas cancer patients was 60.5 years (19.0) and the mean (SD) was 49.6 years (16.0). The majority of pancreas cancer patients (82.1%) were Malay ethnic, 42.9% unemployed and 96.4% married.

Table 2 shows the clinical feature of pancreas cancer cases in HUSM. Regarding the risk factors; 53.6% had ever smoked, 23.2% had cholelithiasis, 17.9% had pernicious anaemia, 16.1% had diabetes, 10.7% had previous laparotomy, 7.1% had chronic pancreatitis, 5.4% had been taking alcohol and only 1.8% had family history of pancreas cancer. There were 42.9% patients who defaulted their appointments. The duration of presenting symptoms ranged from 0-48 months. The mean (SD)

Table 1. Socio-Demography Background of Pancreas Cancer in HUSM

	Frequency (%)	Mean (SD)
Age (years)		49.6 (16.0)
	<50	11 (19.6)
	≥50	45 (80.4)
Sex:	Male	34 (60.7)
	Female	22 (39.3)
Race:	Malay	46 (82.1)
	Others	10 (17.9)
Occupation:	Employed	32 (57.1)
	Unemployed	24 (42.9)
Marital status:	Married	54 (96.4)
	Not married	2 (3.6)

Table 2. Clinical and Pathologic Characteristics

	Frequency (%)	Mean (SD)	Median (IQR)
Risk factors*:			
Ever smoke	30 (53.6)		
Cholelithiasis	13 (23.2)		
Pernicious anaemia	10 (17.9)		
Diabetes mellitus	9 (16.1)		
Previous laparotomy	6 (10.7)		
Chronic pancreatitis	4 (7.1)		
Alcohol drinker	3 (5.4)		
Family history	2 (3.6)		
Defaulted appointment	24 (42.9)		
Traditional treatment	3 (5.4)		
Duration of symptom (months)		10.5 (28.3)	3.5 (7.0)
Presenting symptoms*:			
Loss of appetite	38 (67.9)		
Loss of weight	37 (66.1)		
Jaundice	33 (58.9)		
Tea colour urine	28 (50.0)		
Abdominal pain	26 (46.4)		
Pale stool	22 (39.3)		
Hepatomegaly	19 (33.9)		
Lethargy	15 (26.8)		
Fever	12 (21.4)		
Ascites	11 (19.6)		
Abdominal discomfort	10 (17.9)		
Vomiting	9 (16.1)		
Nausea	8 (14.3)		
Location of tumour:			
Head only	42 (75.0)		
Tail only	6 (10.7)		
Others	8 (14.3)		
Tumour size (largest diameter cm)		5.9 (1.8)	5.7 (2.6)
Type of carcinoma			
Adenocarcinoma	54 (96.4)		
Mucin	2 (3.6)		
Staging:		I	14(21.5)
II	10 (17.8)		
III	2 (3.6)		
IV	32 (57.1)		
Diagnostic tests*:			
CT scan	52 (92.9)		
Ultrasound	41 (73.2)		
Endoscopic retrograde cholangiopancreatography	24 (42.9)		
Endoscopy	10 (17.9)		
Treatment*			
Whipple	29 (51.8)		
Stenting	9 (16.1)		
Chemotherapy	9 (16.1)		
Radiotherapy	1 (1.8)		

*Non mutually exclusive

duration of symptoms was 10.5 (28.3) months and the median (IQR) was 3.5 (7.0) months. The majority of patients (67.9%) presented with complain of loss of appetite, 66.1% had loss of weight, 58.9% presented with jaundice, 50.0% had tea colour urine, 46.4% presented with abdominal pain.

The majority of patients (96.4%) had adenocarcinoma of pancreas and only 3.6% had mucin type of pancreas cancer. Most tumours located at 75.0% head only, 10.7% tail only and 14.3% others. The median (IQR) largest

Table 3. Prognostic Factors of Pancreatic Cancer in HUSM

	Crude HR (95% CI)	β (SE)	Adjusted HR (95% CI)	P value
Duration of symptom	0.98 (0.95, 0.99)	-0.03 (0.01)	0.97 (0.95, 0.99)	0.013
Ascites	2.16 (1.08, 4.34)	0.97 (0.37)	2.64 (1.28, 5.44)	0.008
Operation	3.29 (1.84, 5.88)	1.43 (0.31)	4.20 (2.27, 7.76)	<0.001

tumour diameter was 5.7 (2.6) cm. The majority of cancers were moderately differentiated grade and in stage IV.

Most of cases (92.9%) were diagnosed pancreas cancer by computerized tomography (CT scan) and 73.2% by ultrasound (US), 42.9% by endoscopic retrograde cholangiopancreatography (ERCP). The majority of pancreas cancer patients (57.1%) were in stage IV. More than half of patient underwent Whipple operation, while 48.2% did not have operation because of tumour were unresectable or presented late.

The mean (95% CI) overall survival rate was 14.4 (7.3, 21.5) months and the median (95% CI) was 3.4 (0.5, 6.3) months. The 6-month, one-year and two-year survival rates were 37.3%, 21.4% and 16.1% respectively. Table 3 shows the prognostic factors of pancreas cancer in HUSM. The prognostic factors for pancreas cancer were duration of symptoms (HR 0.97; 95% CI: 0.95, 0.99; p value 0.013), ascites (HR 2.64; 95% CI: 1.28, 5.44; p value 0.008) and having Whipple operation (HR 4.20; 95% CI: 2.27, 7.76; p value <0.001).

Discussion

Our present study showed that there were more males having pancreas cancer compared to females. Throughout the world, pancreas cancer is more common among males, with a male-to-female ratio of between 1.3 and 2 (Bramhall et al., 1995; Barkin and Goldstein, 1999; Luke et al., 2009). This male preponderance is probably related to the fact that there is a higher prevalence of smoking and some other risk factors among males.

The incidence of pancreatic cancer increases steadily with age; approximately 80% of cases are diagnosed between 60-80 years of age (Barkin and Goldstein, 1999). The disease is rare before the age of 45 years. The median age for pancreas cancer patients in HUSM was 59.2 years. As the population of developed countries ages, there will be an increasing number of patients with pancreas cancer.

There are many factors that can increase the risk of pancreas cancer. The important risk factors are diabetes mellitus, pancreatitis, pernicious anaemia, cholecystectomy, alcohol, smoking, family history of pancreas cancer, and previous laparotomy (Lin et al., 2001; Lowenfels and Maisonneuve, 2002; Ghadirian and Lynch, 2003). A study conducted in Taiwan reported that pancreatic cancer was significantly associated with diabetes mellitus with more than three times of risk compared to the non diabetics (Chiou et al., 2011). The increased risk of pancreatic cancer seems related to the duration of diabetes mellitus (Lin et al., 2001). There was a significant association between all types of pancreatitis and the occurrence of pancreas cancer (Bansal and

Sonnenberg, 1995). Patients with chronic pancreatitis were associated with a significant increased risk of pancreas cancer with odds ratio 2.23 (CI, 1.43-3.49). In our study, many of the patients were discovered having cholelithiasis at presentation of pancreas cancer. The prevalence of cholelithiasis was 23.2% in the present study which was the second highest risk factor after smoking. More than half of our patients were smokers which is not surprising as nearly 50% of male population in Malaysia were smokers (Institute for Public Health, 2008).

The clinical presentation of pancreas cancer patients in our study was almost similar to other studies. The majority of our patients presented to the hospital with complaints of loss of appetite and loss of weight. In addition, patients also presented with abdominal pain, abdominal discomfort, fever, lethargy and abdominal mass. On examination, half of the pancreas cancer patients presented with jaundice, followed by hepatomegaly. Currently, there is no screening program for the early detection of pancreatic cancer. The diagnosis of pancreas cancer is challenging as the pancreas is located in a relatively inaccessible site within the abdominal cavity, thus this cancer is usually diagnosed in the advanced stage. In the early stage of disease, most patients have very few symptoms, which are usually non specific (Barkin and Goldstein, 1999). The non-specific symptoms include generalized dyspepsia, early satiety and nausea which are unlikely to be acted on seriously by the patient or general practitioner. The mean duration of presenting symptoms of our patients was 10.5 months and the mean of the largest tumour diameter was 5.9 cm. Studies have showed that tumour with size greater than 1 cm had a significantly lower 5-year survival rate (Barkin and Goldstein, 1999).

Most of our patients were diagnosed pancreas cancer by computerized tomography scan (CT scan). Very few had biopsy done preoperatively because many refused it due to the invasiveness of the procedure. CT scan is an accurate method of detecting small lesions in the pancreas but the facility is not available in many hospitals in Malaysia. Many of our patients did have abdominal ultrasonography but this modality lacks sensitivity.

Ductal adenocarcinoma was the most common type of pancreas cancer and this is similar as elsewhere (Bramhall et al., 1995; Barkin and Goldstein, 1999; Ghadirian and Lynch, 2003). The majority of our patients were in stage IV and most of them had liver and lungs metastases. This is probably related to the delay of presentation of symptoms and the difficulty of diagnosing pancreas cancer.

Surgical resection is the best choice of treatment for pancreas cancer. However, many patients were not candidates for surgery because of local spread and disease metastases. Only 51.8% of our patients had the Whipple procedure because of advanced disease and other complications. In addition, nine patients had some palliative treatments such as chemotherapy.

Survival of pancreatic cancer is poor especially in untreated patients. Our study reported that the mean overall survival rate was 14.4 months and the median was 3.4 months. The 1-year survival rate was 21.4%. This figure is higher than reported in the United States, a 1-year survival rate of 19% (Greenlee and Hill-Harmon, 2001).

An Australian study reported a lower 1-year survival rate of 18% (Luke et al., 2009). The survival rate was higher in cases diagnosed in year 2001-2006 (23.9%) than cases diagnosed in year 1977-1988 (14.3%). Meanwhile our cases were diagnosed in year 2001-2008. In another study, the 3-year overall survival was 6% for the married group, compared with 4% for the unmarried group (Baine et al., 2011).

The significant prognostic factors for pancreatic cancer in our study were duration of symptom, ascites and having operation. Baine et al. (2011) reported that marital status was a significant positive factor for survival of pancreas cancer patients. Patients who were married at the time of diagnosis had a significantly decreased risk of death at both 2 months (15% risk reduction) and 3 years (13% risk reduction) post diagnosis. An Australian study of cases diagnosed in year 1977-2006 reported that older age was a poor prognostic factor while, neuroendocrine type, high socio-economic status and later year diagnosis were good prognostic factors (Luke et al., 2009).

There were some limitations in this study. This was a review of medical records and has some inherent weaknesses such as missing variables, in particular, socio-economic details and blood investigations. Not many patients had Carcinoembryonic Antigen (CEA) and CA 19-9 levels done. Both of these tumour markers have been reported to be useful in patients with suspected pancreatic cancer (Barkin and Goldstein, 1999). These tumour markers are not routinely done in HUSM. Because of our retrospective design, we could not also examine the effects of diet and obesity on the occurrence of pancreatic cancer. This was also a single-centre study, thus the results may not be generalized; however, we believe that this is the first review of pancreas cancer in Malaysia.

In conclusion, this retrospective study was conducted in HUSM and included 56 patients with pancreas cancer. This disease affected older people and there was a male preponderance. The majority of pancreas cancer patients was Malay, unemployed and married. The commonest risk factors were smoking, cholelithiasis, pernicious anaemia, diabetes mellitus, previous laparotomy and chronic pancreatitis. The majority of patients presented with loss of appetite, loss of weight, jaundice, tea colour urine, abdominal pain and discomfort. Most of patients presented late with metastatic disease, thus some were not treated or given only palliative care. Only 53.6% had Whipple operation. The survival rate of our study was almost similar with other studies abroad, which was very poor. The significant prognostic factors were duration of presenting symptom, the presence of ascites and had an operation. We are advocating early detection of pancreatic cancer by using an imaging modality or molecular markers especially in a high risk population. Our institution also needs to improve surgical intervention for pancreatic cancer.

The awareness about pancreas cancer should be raised among the Malaysian population especially with regards common presenting symptoms and risk factors. Pancreas cancer represents a considerable challenge to the clinician. Surgical advancement is needed that can be performed safely in patients who are fit for surgery in a specialist

centre. In view of the poor survival rate of this disease, special attention must also be given to the advancement of palliative care and the training of specialized hospice care personnel. Advances in symptom palliation and novel treatments may improve the survival and quality of life for those patients who cannot undergo surgery.

References

- Baine M, Sahak F, Lin C, et al (2011). Marital status and survival in pancreatic cancer patients: A SEER based analysis. *PLoS One*, **6**, 21052.
- Bansal P, Sonnenberg A (1995). Pancreatitis is a risk factor for pancreatic cancer. *Gastroenterol*, **109**, 247-51.
- Barkin JJ, Goldstein JA (1999). Diagnostic approach to pancreatic cancer. *Gastroenterol Clin N Am*, **28**, 709-19.
- Bramhall SR, Allum WH, Jones AG, et al (1995). Treatment and survival in 13,560 patients with pancreatic cancer and incidence of the disease in the West Midlands: an epidemiological study. *Br J Surg*, **82**, 111-5.
- Chiou W-K, Huang B-Y, Chou W-Y, Weng HF, Lin J-D (2011). Incidences of cancers in diabetic and non-diabetic hospitalized adults patients in Taiwan. *Asian Pac J Cancer Prev*, **12**, 1577-81.
- Ghadirian P, Lynch HT, Krewski D (2003). Epidemiology of pancreatic cancer: an overview. *Cancer Detection Prev*, **27**, 87-93.
- Greenlee R, Hill-Harmon MB, Murray T (2001). Cancer statistics, 2001. *CA Cancer J Clin*, **51**, 15-36.
- Institute for Public Health (2008). The third national health and morbidity survey 2006, Executive summary, Ministry of Health, Kuala Lumpur, pg45.
- Lin Y, Tamakoshi A, Kawamura T, Inaba Y, et al (2001). An epidemiological overview of environmental and genetic factors of pancreatic cancer. *Asian Pac J Cancer Prev*, **2**, 271-80.
- Lowenfels AB, Maisonneuve P (2002). Epidemiology and etiological factors of pancreatic cancer. *Hematol Oncol Clin N Am*, **16**, 1-16.
- Luke C, Price T, Karapetis C, Singhal N, Roder D (2009). Pancreatic cancer epidemiology and survival in an Australian population. *Asian Pac J Cancer Prev*, **10**, 369-74.
- Murr MM, Sarr MG, Oishi AJ, et al (1994). Pancreatic cancer. *Ca Cancer J Clin*, **44**, 304-18.
- Zainal AO, Zainudin MA, Nor Saleha IT (2006). Malaysian cancer statistics- data and figure. Peninsular Malaysia 2006, National Cancer Registry, Ministry of Health, Malaysia, Kuala Lumpur.