PROGNOSTIC FACTORS FOR SURVIVAL IN PANCREATIC CANCER PATIENTS FROM UNIVERSITY MALAYA MEDICAL CENTRE, MALAYSIA

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Abstract

Objectives: Pancreatic cancer is an aggressive silent killer with a median survival of a few months. It is the fourth leading cause of cancer death in the United States. The aim of this study was to evaluate the prognostic factors affecting the survival of patients with adenocarcinoma of the pancreas in Malaysia.

Methods: This retrospective study examined 107 patients with adenocarcinoma of the pancreas from 2002 to 2012 at University Malaya Medical Centre. The factors evaluated were age, sex, race, smoking habits, performance status, the presence of jaundice, pre-treatment CA 19.9 serum level, the location of a primary tumour, tumour grade, tumour staging and intent of treatment.

Results: The median survival for the overall study population was 7.0 months (95% CI 5.1-8.8 months) with 1, 3, and 5-year survival rates of 30.8%, 8.4% and 3.7% respectively. The survival was 16.1 months (95% CI 7.7-24.4 months) for stage 1, 15.5 months (95% CI 8.1-22.8 months) for stage 2, 8.4 months (95% CI 6.1-10.8 months) for stage 3, and 3.8 months (95% CI 2.9-4.7 months) for stage 4. In multivariate analysis, independent and unfavourable prognostic factors which retained significance were performance status, tumour stage and treatment intent.

Conclusions: The biological characteristics are important as predictors of survival in patients with pancreatic cancer. Longer survival is possible if the disease is identified in its early stages with good performance status. Further development and evaluation of novel screening strategies need to be established to improve early detection of this disease.

Keywords: *Pancreatic, Cancer, Prognosis, Factors*

Introduction

Pancreatic cancer is an aggressive disease with a dismal outcome. It is the fourth leading cause of cancer death in the United States. It is a silent killer as it is difficult to detect with widespread metastasis at diagnosis. The 5-year survival rate is 7.2%[1]. Pancreatic cancer is uncommon in Malaysia. In 2011, the National Cancer Registry reported 1829 cases of pancreatic cancer and estimated the age-standardised rates as 2.0 per 100,000 for men and 1.5 per 100,000 for women. The sex ratio in Malaysia was 1.32:1 (M: F) and the Chinese had 50% higher incidence rate compared to the other ethnic groups[2]. A retrospective analysis of 56 patients at the Universiti Sains Malaysia Hospital (HUSM) reported a median survival of 3.4 months (95% CI 0.5- 6.3 months) as many presented at late stages of the disease[3]. Data on factors which may influence outcomes are essential to optimise the treatment options for pancreatic cancer patients. With the provision of

supportive care alone, adverse effects and complications of systemic therapy can be avoided in patients with poorer prognosis[4].

The aim of this study was therefore to identify prognostic factors affecting survival, to serve as a basis for a predictive model, for a more accurate and rational treatment selection for the Malaysian patient with cancer of the pancreas.

Materials and methods

This study was a retrospective investigation at a tertiary hospital and teaching centre, the University Malaya Medical Centre (UMMC). Following approval from the University of Malaya Medical Centre Ethics Committee (UMMC MEC Ref. No: 20156-1388), patient records from 2002 to 2012 were obtained from the new case registry in the Clinical Oncology Unit. Patients with histologically confirmed adenocarcinoma of the pancreas were enrolled. Exclusion criteria were a benign disease, the absence of histological proof and a histology of non-adenocarcinoma. The date and cause of death were retrieved from the National Registry Department.

Prognostic Variables

Data collection included patient demography of age, sex, race and smoking habits. Tumour characteristics based on tumour, lymph nodes and distant metastasis were restaged according to the 7th edition of the American Joint Committee on Cancer (AJCC) staging for pancreas cancer. Clinical characteristics evaluated were the Eastern Cooperative Oncology Group (ECOG) performance status, the presence of jaundice at first presentation, and the location of a primary tumour. Serum levels of pre-treatment Carbohydrate Antigen (CA) 19-9 were noted, where 37 U/ml was used as the upper limit of normal, based on UMMC laboratory standards. Histopathological data of tumour grade and post-resection margin, lymphovascular and perineural invasion, and positive lymph nodes were also recorded. The treatment given was recorded as types of surgery, adjuvant and palliative chemotherapy, concurrent chemoradiotherapy and best supportive care only.

Surgical Treatment

Radical surgical resection was carried out in the absence of haematogenous metastasis and gross retroperitoneal tumour infiltration, or with minimal invasion to the superior mesenteric or portal veins. The types of radical surgery in this study were pancreatectomy, pancreaticoduodenectomy and distal pancreatectomy. In patients with significant clinical and radiological signs of biliary obstruction, palliative stents were inserted endoscopically. Surgical bypass procedures were performed in patients with an unresectable tumour at laparotomy. Palliative bypass surgeries consisted of the biliary-enteric bypass, a Roux-en-Y hepaticojejunostomy or choledochojejunostomy, where the bile was rerouted from the common hepatic or common bile duct to the jejunum. Some patients had an additional gastroenterostomy with an anastomosis of the distal end of the stomach to the small intestine.

Chemotherapy Treatment

Intravenous monotherapy with Gemcitabine or Fluorouracil was used in the adjuvant setting. The dosages were administered according to the national chemotherapy protocol[5]. Gemcitabine (1 gm/m2) on day 1, 8 and 15 for six cycles, Fluorouracil using the QUASAR regime with weekly Fluorouracil (370 mg/m2) for 30 cycles, the Mayo regime with Fluorouracil (370-425 mg/m2) every 28 days for six cycles or oral Capecitabine (1250 mg/m2) for six cycles. There were slight modifications in chemotherapy palliation based on a clinical decision, with the addition of intravenous Carboplatin (area under the curve AUC 4-5) every three weeks for six cycles or intravenous Cisplatin (60-75 mg/m2) every three weeks for six cycles in some cases.

Concurrent Chemoradiotherapy Treatment

Patients received external beam radiotherapy (EBRT) to a total dose of 45-54 Gy in 1.8 Gy to 2 Gy per fraction delivered over five to six weeks. All patients who received radiotherapy had three different modified concurrent chemotherapy regimens; Gemcitabine (200-250 mg/m2) weekly; the Mayo regimen with Fluorouracil (350-375 mg/m2) for week 1 and week 5; and oral Capecitabine 800-1000 (mg/m2) daily[5].

Statistical Analysis

The SPSS software version 23 was used for statistical analysis. The significance level was specified at $p< 0.05$ with 95% confidence interval (CI) for a two-tailed analysis. The overall survival was determined as the time between the diagnosis with the first proven histopathological report to the date of death or censored at the time the study was closed. All deaths were considered as events, regardless of their cause. Patients who were alive at the time of the analysis were censored in the survival analysis. The Chi-squared test was used to compare the differences in the patient characteristics between groups. Time-dependent variables and overall survivals were estimated with the Kaplan Meier survival analysis, and their differences were evaluated by the log-rank test. Multivariate analysis with Cox proportional hazards model was used to determine the variables with an independent effect on survival.

Results

125 patients were identified with pancreatic cancer in the Clinical Oncology Unit registry in UMMC from 2002- 2012. Only 107 patients were included in the final analysis as six patients had no histopathological report and twelve patients had neuroendocrine tumours.

Demography

The mean age was 58.9 years (range 28-88 years), and male to female ratio was approximately 1.5:1 respectively. The

majority of our study population were of Chinese descent followed by patients of Malay and Indian origins. Many were non-smokers.

Tumour Characteristics

The details of the tumour characteristics were obtained from CT scans, MRI scans or PET scans, and histopathological findings from post-operative notes and reports. All were reviewed and staged according to AJCC 7th edition. Reporting was preferentially from histopathological reports, followed by surgical notes and lastly imaging modalities. The grading of a tumour was obtained from post-operative histopathological reports or biopsy reports. More than half of the population had moderately differentiated adenocarcinoma followed by poorly differentiated carcinoma and well-differentiated carcinoma. Many had a good performance status, no jaundice, increased in CA19.9 levels and tumours in the head of the pancreas. Post operatively, the majority had a negative margin, absence of lymphovascular and perineural invasion and negative lymph nodes. Table 1 summarises the demographic and tumour characteristics of pancreatic cancer patients in UMMC.

Table 1. *Demographic & Tumour Characteristics of Pancreatic Cancer Patients in UMMC.*

Parameters	No. of patients (Total=107)	Percentage of patients (%)
Age (years)		
≤60	53	49.5
>60	54	50.5
Sex		
Male	64	59.8
Female	43	40.2
Race		
Malay	20	18.7
Chinese	75	70.1
Indian	11	10.3
Others	1	0.9
Smoker		
Yes	27	25.2
No	80	74.8
Tumour Stage		
T1	7	6.5
T2	27	25.2
T3	33	30.8
T4	40	37.5
Nodal Stage		
N0	52	48.6
N1	55	51.4
Metastasis		
M0	54	50.5
M1	53	49.5
Group Stage		
1	10	9.4
2	23	21.5
3	21	19.6
4	53	49.5
Performance Status (ECOG)		
0	20	18.7
1	45	42.1
2	14	13.1
3	12	11.1
4	16	15.0
Jaundice		
Present	46	43.0
Absent	61	57.0
Ca19.9 level		
≤37	14	13.1
>37	93	86.9
Location of tumour		
Head	78	72.9
Body	16	15.0
Tail	13	12.1
Tumour grade		
Well differentiated	19	17.8
Moderately differentiated	55	51.4
Poorly differentiated	30	28.0
Undifferentiated	3	2.8
Cohort who underwent radical surgery	**(n=30)**	
Margin		
Positive	7	23.3
Negative	23	76.7
Lymphovascular invasion		
Present	12	40.0
Absent	18	60.0
Perineural invasion		
Present	13	43.3
Absent	17	56.7
Lymph node		
Positive	9	30.0
Negative	21	70.0

Treatment

The study cohort was divided into three treatment groups; the radical (37.4%), the palliative (29.9%) and best supportive care only (32.7%). The radical group consisted of those who underwent radical surgery, radical concurrent chemoradiotherapy, radical surgery followed by concurrent adjuvant chemoradiotherapy or adjuvant chemotherapy. The palliative group consisted of those who had bypass surgery or palliative stenting, and palliative chemotherapy. The best supportive care only group consisted of patients who refused treatment or who were unfit for any form of treatment.

There were 67 patients who underwent surgery, 37 with palliative surgery, and 30 with radical surgery. Seventeen patients underwent bypass surgeries, and 27 patients underwent stenting. For the radical surgical group, two patients had total pancreatectomies, twenty-seven patients had pancreaticoduodenectomies, and one patient had a distal pancreatectomy.

43 patients received chemotherapy. In the adjuvant setting, 14 patients had the single agent Gemcitabine with a mean of 5.2 cycles (range 4-6 cycles). Of the four patients who received Fluorouracil in the adjuvant setting, one patient had the QUASAR regime, and the other three patients had the Mayo regime. They completed all their prescribed cycles. In the palliative setting, 24 patients were on the single agent Gemcitabine, with a mean of 4.8 cycles (range 1-6 cycles). Five patients had combination chemotherapy with Gemcitabine; three patients had Cisplatin with a mean of 4.7 cycles (range 4-6 cycles), and two patients had and completed Carboplatin. Oral Capecitabine for six cycles was used for one patient in the palliative setting.

14 patients underwent concurrent chemoradiotherapy. Five patients had Gemcitabine with a mean of 3.6 cycles (range 3-4 cycles), six patients had Mayo's regime with a mean of 1.8 cycles (range 1-2 cycles), and three patients had oral Capecitabine with a mean of 5.3 cycles (range 5-6 cycles). Table 2 depicts the treatment characteristics in the study populations.

Table 2. *Treatment Characteristics of Pancreatic Cancer Patients in UMMC.*

Types of surgery	No. of patients (Total=67)	Percentage of patients (%)
Radical Surgery		
Total pancreatectomy	2	3.0
Pancreaticoduodenectomy	27	40.3
Distal pancreatectomy	1	1.5
Palliative Surgery		
Bypass surgery	17	25.4
Stenting	20	29.9

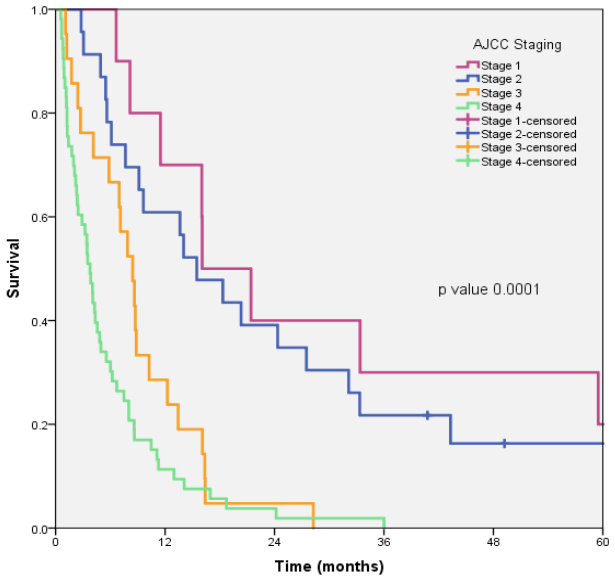
Chemotherapy Regimens.	No. of patients (Total=43)	Percentage of patients (%)
Adjuvant		
Gemcitabine	14	32.6
Fluorouracil	4	9.3
Palliative		
Gemcitabine	24	55.8
Fluorouracil	1	2.3
Concurrent chemotherapy and Radiotherapy	No. of patients (Total=14)	Percentage of patients (%)
Gemcitabine	5	35.7
Fluorouracil	9	64.3

Note: The first strata for each variable acted as the reference group with a hazard ratio of 1.0 for which other groups were compared against, * p-value < 0.05

Survival

The median survival in our study was 7.0 months (95% CI 5.1-8.8 months). There was a total of 98 (91.6%) cancer-related deaths, one (0.9%) death due to cardiac causes and two (1.9%) deaths due to natural cause. A total of six (5.6%) patients were still alive and under follow up after this study. The survival based on AJCC staging 7th edition was 16.1 months (95% CI 7.7-24.4 months) for stage 1, 15.5months (95% CI 8.1-22.8 months) for stage 2, 8.4 months (95% CI 6.1-10.8 months) for stage 3, and 3.8 months (95% CI 2.9-4.7 months) for stage 4. Figure 1 depicts the Kaplan Meier curves for survival based on the stage of pancreatic cancer in patients in UMMC.

Figure 1. *Kaplan Meier curve for survival based on stage for pancreatic cancer patients in UMMC.*



In univariate analysis, performance status (ECOG), the location of a primary tumour, grading of a tumour, tumour staging (AJCC 7th edition) and treatment intent were significant prognostic factors for overall survival. Parameters which retained independent prognostic significance on Cox's multivariate analysis were performance status, tumour staging (AJCC 7th edition), and treatment intent. Table 3 depicts the multivariate analysis of prognostic factors for overall survival.

Table 3. Multivariate Analysis of Prognostic Factors for Overall Survival.

	HR	95% CI	p value
Performance Status ECOG			
0	1.0	-	-
1	1.4	0.8-2.6	0.25
2	2.6	1.2-5.5	0.017*
3	3.3	1.4-7.8	0.006*
4	8.5	3.1-22.8	0.0001*
Location of Tumour			
Body & Tail	1.0	-	-
Head	0.7	0.4-1.1	0.163
Tumour Grade			
1	1.0	-	-
2	1.2	0.6-2.2	0.579
3	1.3	0.6-2.6	0.504
4	1.1	0.3-4.6	0.891
AJCC Staging			
1	1.0	-	-
2	1.7	0.7-4.4	0.246
3	3.8	1.4-9.8	0.007*
4	5.7	2.2-14.4	0.0001*
Treatment Intent			
Radical	1.0	-	-
Palliative	1.2	0.6-2.4	0.698
Best Supportive Care	3.2	1.5-6.9	0.003*

Note: The first strata for each variable acted as the reference group with a hazard ratio of 1.0 for which other groups were compared against, * p-value < 0.05

Adverse events

Toxicity due to chemotherapy was evaluated according to the various National Cancer Institute - Common Toxicity Criteria (NCI-CTC). The majority of the adverse events were grade 1 and 2. Thirty-two percent of patients required admission for various reasons such as blood transfusions requirements, infections and grade 3/4 toxicities. There was no treatment-related death. Table 4 shows the adverse effects of chemotherapy in the study.

Discussion

The median overall survival in this study was 7.0 months. It is comparable with data published in SEER from 2001-2010 which had a median survival of 7.0 months[7]. A few other studies reported shorter median survivals, ranging from 4.7 months[8], 5.9 months[9], 5.1 months to 6.8 months[10,11] with similar prognostic factors.

Table 4. *Side Effects of Chemotherapy.*

	No of patients (%)	
	(n=38)	(n=5)
	Gemcitabine	**5 Fluorouracil**
Grade 3 & 4		
Nausea	2 (5.3)	0 (0)
Vomiting	6 (15.8)	1 (20.0)
Neutropenia	6 (15.8)	1 (20.0)
Diarrhoea	6 (15.8)	2 (40.0)
Hand Foot Syndrome	4 (10.5)	2 (40.0)
Mucositis	3 (7.9)	1 (20.0)

The ECOG performance status had been shown to be an independent predictor of survival in pancreatic cancer patients[12]. In this study, the ECOG performance status was found to be strongly significant as an independent prognostic factor on multivariate analysis in predicting overall survival. ECOG performance status 2 was associated with a hazard ratio of 2.6 (p-value 0.017), ECOG performance status 3 was associated with a hazard ratio of 3.3 (p-value 0.006) and ECOG performance status 4 was associated with a hazard ratio of 8.5 (p-value 0.0001) when compared to performance status 0 as the reference group. It was found that patients with metastatic disease with tumours of more than 3 cm had shorter overall survivals when associated with a weight loss of more than 10% and a poor performance status[9]. A meta-analysis of five trials of 4465 metastatic pancreatic cancer patients, indicated that combination chemotherapy consisting of Gemcitabine with platinum analogue or Fluoropyrimidine had the greatest benefit in patients with a good performance status (ECOG 0-1). However, patients with a poor performance status had no survival advantage from more intensive combination chemotherapy[13]. Another significant prognostic factor on

multivariate analysis was a tumour staging Stage 3 disease had a hazard ratio of 3.8 (p-value 0.007), and Stage 4 disease had a hazard ratio of 5.7 (p-value 0.0001) when compared to stage 1. Many of the patients in the study were in an advanced stage of disease, stage 3 (19.6%) and stage 4 (49.5%). Patients with pancreatic cancer present with vague abdominal symptoms of gastritis, and may miss a vital thorough investigation at the primary care level. Many Malaysian patients only seek medical treatment after the failure of traditional treatment as illness is attributed to supernatural causes. Traditional medicine is seen to be supportive, personal and holistic in contrast with modern scientific medicine which is viewed to be mechanistic, impersonal, organ-oriented and individualistic. There is a general belief that cancer-related treatment is filled with complications, especially in elderly patients.

The last factor which was of poor prognostic significance in the study was the treatment intent. The hazard ratio was 1.2 (p-value 0.698, 95% CI 0.6-2.4) for palliative therapy, and 3.2 (p-value 0.003, 95% CI 1.5-6.9) for the best supportive care only therapy when compared to radical therapy as the reference standard of care. This indicated that palliative therapy improved survival compared to best supportive care only. Glimelius et al. reported that patients who underwent palliative chemotherapy had an improved or prolonged high quality of life for a minimum period of 4 months compared to those in the best supportive care group (p-value < 0.01). Overall survival was significantly longer in the chemotherapy group compared to the best supportive care group, 6.0 months and 2.5 months respectively (p-value < 0.01). The results showed that chemotherapy could add to both quantity and quality of life in advanced pancreatic cancer[14]. Berger AK et al. in a retrospective review at Heidelberg University Hospital, surveyed 53 patients and noted that survival after disease progression was significantly longer for second-line treatment compared to best supportive care (p-value 0.019)[15].

Supportive care is an important part of cancer care. Supportive care helps people meet the physical, practical, emotional and spiritual challenges of pancreatic cancer. Over the past few decades, numerous other terms have been used to describe this ever-evolving entity. More recently "supportive care" and "best supportive care" have gained popularity[16]. There is yet no single universal definition of best supportive care, and this lack of a standardised, detailed definition of best supportive care in oncology diminishes the value clinical trials and hampers the translation of investigational results to the usual care setting.

Patients with advanced cancer who are expected to live less than six months may want to consider hospice care. Hospice care is designed to provide the best possible quality of life for people who have a terminal illness. However, many patients are not keen on hospice care as they refuse to accept a non-curative, non-aggressive approach. It was reported that 53% of cancer patients were willing to accept intensive chemotherapy and endure toxicity for a 1% cure rate. More than 40% would do the same to extend their lives by three months.

Some patients distrust all conventional medical care including hospice and choose an alternative or complimentary medicine approach[17]. An early approach towards palliative care has been shown to minimise physical and emotional symptom and improve quality of life and patient satisfaction while minimizing costs and caregivers burden[18].

Advancement in medical care has increased the life expectancy of a country's population. The elderly patients form the majority of the population affected by cancer and yet only constitute 30-40% of the cancer patients in many trials[19]. The treatment of an elderly patient with pancreatic cancer poses a significant challenge, with underlying comorbidities and limited benefit/ toxicities ratio with long-term chemotherapy, their underrepresentation[20]. Chemotherapy can be conveniently given and is as well tolerated in the elderly as in the younger pancreatic cancer patients[19,20,21]. However in a study of 154 metastatic pancreatic cancer patients, reported a poorer median survival time in elderly patients compared the younger patients, 148 days versus 198 days respectively (p-value 0.039). The one-year survival rate was 3% in the elderly and 10% in the younger patients [22].

In this study, age did not have any effect on survival. The two age groups of ages more than 60 and of less than or equal to 60 years old, were almost similar in size. The older patients had a better median survival with a higher percentage who underwent radical treatment than the younger group, 57.5% and 42.5% respectively. However, the small population number in this study would have impaired the prognostic significance.

CA 19-9 levels have a sensitivity and specificity of 79-81% and 82-90% respectively for the diagnosis of pancreatic cancer in symptomatic patients. The low positive predictive value of 0.5-0.9% .precludes its role as an early biomarker (23). A retrospective review from UMMC showed that CA19-9 was a tumour-associated antigen, but not a tumour -specific antigen. Elevated levels of Ca 19.9 were present in various malignancies of lung, ovarian and hepatobiliary cancer, with higher levels in advanced cases of colorectal and pancreatic cancer[24]. An elevated level of Ca 19.9 at onset has 5.7 times predictive risk for reduced survival compared to a normal level at onset. Raised Ca 19.9 levels are found in benign conditions of inflammation of the biliary tract, chronic pancreatitis, and obstruction of the biliary tract. Galli et al. found that Ca 19.9 at 37 U/mL was the threshold value that appeared to discriminate between benign and malignant diseases. In post-surgical patients, levels between 90 and 200 U/mL or higher are associated with reduced survival. It is recommended that levels of Ca 19.9 be monitored in patients with pancreatic cancer after surgical resection or in patients treated with systemic chemotherapy, in association with diagnostic imaging[25].

In this study cohort, 86.9% had an elevated level from the baseline, but the levels were not correlated significantly with survival. Those trials that identified elevated levels of Ca 19.9 as a poor prognostic marker were examining only patients who had radical resections. Those in the palliative or best supportive care setting were excluded. The numbers of patients in the radical resection cohort were too small to be analysed separately in this study. Some of the patients had CA 19-9 serum levels from referring medical centres with laboratories with which have standards of reference differing from the UMMC laboratory. This might have affected the outcome.

The grading of a tumour measures the degree of differentiation in the morphology and functional status of a tumour cell from the normal tissue. For pancreatic adenocarcinoma, histologic grade is based on the glandular differentiation and are classed as well differentiated, moderately differentiated, poorly differentiated and undifferentiated carcinoma. Tumour grade is an important prognostic variable of survival in pancreatic cancer[26]. Winter JM et al. 1423 pancreatic cancer patients who underwent pancreaticoduodenectomy, and reported that histologic grade was an independent predictor of survival on multivariate analysis, with a hazard ratio of 1.6[27]. This finding was validated by a SEER series of 8082 pancreatic cancer patients where poorly differentiated and undifferentiated tumours had a poorer prognosis with a hazard ratio of 1.4[26].

In this study, tumour grading was not a significant prognostic factor with the small number of patients where 30.8% had poorly differentiated and undifferentiated tumours, and 69.2% well and moderately differentiated tumours. The histopathological reporting was not standardised, and the reporting was less stringent in the earlier years. The significance is further diluted due to the divergence of histopathology interpretation and reporting from various referring medical centres.

There were several limitations to the study. This study was retrospective in design with a small cohort of patients, and it was a single centre study based on the review of clinical notes in the medical records with some difficulties in accurate and complete data collection. The factors of resection margins, perineural and vascular invasion, and lymph node positivity could not be analysed as the number who underwent radical surgery was small and any difference noted could be by chance. A multicentre study would be required to prove their prognostic significance. Lastly, there might be overlap between pancreatic cancer, duodenal cancer and cholangiocarcinoma which could lead to a classification bias.

Conclusion

The biological characteristics are important as predictors of survival in patients with pancreatic cancer. Longer survival is possible if the disease is identified in its early stages with good performance status. Further development and evaluation of novel screening strategies need to be established to improve early detection of this disease.

Conflict of interests

The authors declare no conflict of interests.

Acknowledgement

The authors thank the University of Malaya Medical Centre, for providing necessary facilities for this research.

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