

Pancreatic cancer in an Asian population

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ABSTRACT

Background and Objectives: Most of the available data on pancreatic cancer are from Western countries. The aim was to characterize pancreatic cancer in Asian patients and to compare it with pancreatic cancer in Caucasians. **Materials and Methods:** Inpatients with histologically proven pancreatic cancer were retrospectively recruited at King Chulalongkorn Memorial Hospital from January 2005 to December 2011. **Results:** The study enrolled 100 patients (male:female = 55:45, mean age 62.7 ± 12.9 years). The amount of time between symptom onset and disease diagnosis was 59.89 ± 63.12 days. The common presenting symptoms included abdominal pain or discomfort (71%), weight loss (70%), and jaundice (60%). Fifty-three of the 100 patients had stage 4 pancreatic cancer. The most common metastatic organ was the liver ($n = 42, 79.25\%$). The survival rates after 1 and 3 years were 24 and 6%, respectively. The overall median time for survival was 5.1 months (range, 3 days to 62.4 months). According to the multivariate analysis, the staging at the time of diagnosis, serum albumin level, and tumor size were found to independently affect the survival rate. Twenty-two patients underwent endoscopic ultrasound-fine-needle aspiration with the sensitivity rate of 86.4% (19/22). **Conclusion:** Because pancreatic cancer in Asians may be clinically similar to the disease in Caucasians, the goals of future research of the disease may also be similar in the two populations.

Key words: Pancreas, pancreatic cancer, presentation, prognosis, survival, treatment

INTRODUCTION

Despite being a relatively rare type of cancer, pancreatic cancer is ranked as the 8th and 9th leading cause of death in men and women, respectively.^[1] This ranking is because pancreatic cancer has nonspecific symptoms in the early stages. Thus, this cancer is, usually, diagnosed when in the advanced stages; therefore, the curative treatment is ineffective. Commonly used noninvasive imaging modalities, including transabdominal ultrasounds

and computed tomography (CT) scans, have a relatively low diagnostic yield for early pancreatic cancers, which are generally small.

Little information is available concerning the prognosis of pancreatic cancer, particularly in Asia. Most available studies have been epidemiological, and only a few studies have been conducted with active follow-ups. As the nature of pancreatic cancer in Eastern and Western countries may differ in various aspects, different treatments may be required. Diagnostic and treatment approaches for pancreatic cancer are gradually being developed to improve the pancreatic cancer survival rate. For now, most of the treatments in Asian countries utilize a multidisciplinary approach. Therefore, it is interesting to examine the effects of these treatments in relation to those used by Western countries.

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Thus, this study was established in an attempt to demonstrate the clinical presentation and results of pancreatic cancer treatments in an Asian population using the survival rate as a key indicator. The study was set in a tertiary care hospital, King Chulalongkorn Memorial Hospital, in Bangkok, Thailand.

MATERIALS AND METHODS

From January 2005 to December 2011, the medical registration records of inpatients at the King Chulalongkorn Memorial Hospital were retrospectively searched for patients with an International Statistical Classification of Diseases and Related Health Problems, 10th Revision (ICD-10) code of pancreatic adenocarcinoma (ICD-10 code 25.0-25.9). Only the patients with histopathologically proven diagnoses were recruited into the study. The available relevant data, including age, gender, presenting symptoms, time frame, related blood tests, serum tumor markers, CT scan findings, tumor stage, and treatment mode, were collected and recorded in a data record form.

The survival time was recorded as the time elapsed from the initial diagnosis of pancreatic adenocarcinoma until the death of the patient. If the survival time could be reviewed and determined from the available medical records, it was used for the analysis. However, if no data were present, a researcher (Pichit Benjasupattananun, MD) directly contacted the patients' families by telephone to obtain the exact survival time. The protocol was approved by the Chulalongkorn University Institutional Review Board, Bangkok, Thailand.

All data were recorded and interpreted analytically to demonstrate the patients' characteristics, tumor stagings, treatment modes, and survival times.

Statistics

All continuous variables were analyzed with a *t*-test, whereas the categorical variables were analyzed with the Chi-squared test. The survival times were plotted with the Kaplan–Meier curve. The confounding factors for survival time were compared using the log-rank test.

RESULTS

A total of 100 patients met the inclusion criteria and were recruited into the study. The study population included 55 males and 45 females; the mean patient age at the time of diagnosis was 62.7 ± 12.9 years.

Men and women were diagnosed at the mean ages of 61.76 ± 13.20 years and 63.78 ± 12.78 years, respectively. The number of patients diagnosed by age group is shown in Figure 1. The average length of time between the onset of symptoms and the diagnosis was 59.89 ± 63.12 days, ranging from 5 to 365 days as shown in Figure 2.

The patient's presenting symptoms included abdominal pain or discomfort (71%), weight loss (70%), jaundice (60%), itching (20%), palpable abdominal mass (14%), gut obstruction (4%), cholangitis (4%), incidental findings (3%), acute pancreatitis (2%), elevated serum tumor marker (2%), back pain (2%), fever (2%), steatorrhea (1%) and gastrointestinal hemorrhage (1%).

The initial blood chemistry values were serum total bilirubin (10.4 ± 11.8 mg/dL), alkaline phosphate (383.7 ± 364.7 U/L) and cancer antigen 19-9 (690.3 ± 1397.7 IU/mL). All tumor characteristics, including the cell differentiation, cancer location in the pancreas, and stage at the time of diagnosis are presented in Table 1. The mean tumor diameter was 4.2 ± 1.9 cm ($n = 83$). The diagnostic imaging included transabdominal ultrasound ($n = 43$), CT scan ($n = 96$), magnetic resonance imaging (MRI, $n = 11$), endoscopic ultrasound (EUS, $n = 13$), and laparoscopy ($n = 2$).

Organ involvement included the liver in 42 patients (79.25%), the peritoneum, mesentery, omentum, or mesocolon in 11 patients (20.75%), the lungs in 8 patients (15.09%), the supraclavicular lymph node in 4 patients (7.55%), the adrenal gland in 1 patient (1.89%), bone in 1 patient (1.89%), the appendix in 1 patient (1.89%), and bone marrow in 1 patient (1.89%).

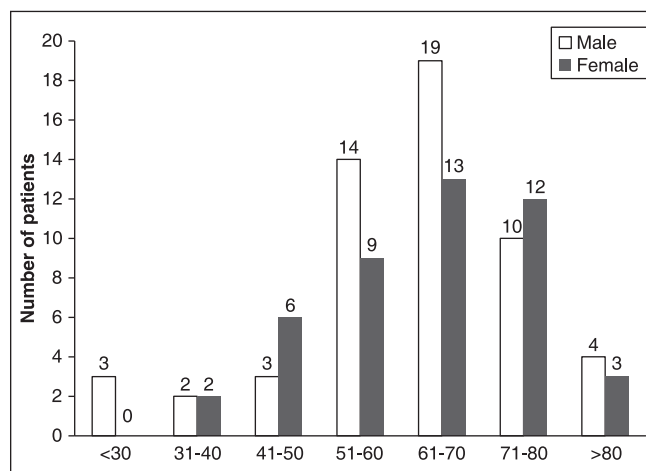


Figure 1. The age distribution patients at the time of the pancreatic cancer diagnosis

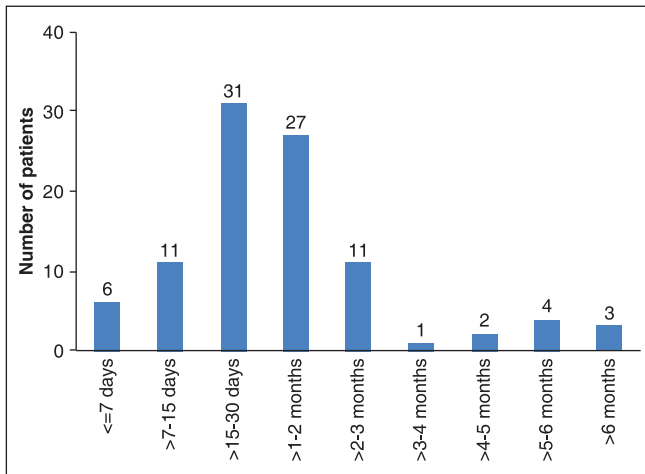


Figure 2. Distribution of the patients with regard to the length of time between onset of symptoms and establishment of diagnosis. The average time was 59.89 ± 63.12 days, ranging from 5 to 365 days (data were not available for 4 of the patients)

Table 1. The tumor characteristics of all patients recruited into the study

Tumor characteristics	Number of patients (%)
Pathology results	
Well-differentiated adenocarcinoma	26 (26)
Moderately differentiated adenocarcinoma	25 (25)
Poorly differentiated adenocarcinoma	11 (11)
Unknown	38 (38)
Location of pancreatic cancer	
Head or uncinate process of the pancreas	76 (76)
Body of the pancreas	6 (6)
Tail of the pancreas	8 (8)
Multiple location except head of the pancreas	10 (10)
Stage at the time of diagnosis	
Stage 1a	0 (0)
Stage 1b	5 (5)
Stage 2a	4 (4)
Stage 2b	20 (20)
Stage 3	18 (18)
Stage 4	53 (53)

Endoscopic ultrasound guided fine-needle aspiration (EUS-FNA) was performed in 22 patients. Malignant cells were identified in 19 patients. No malignant cell was seen in 2 patients. Atypical cells were identified in 1 patient. In summary, the sensitivity rate of EUS-FNA for diagnosing malignant pancreatic masses was 86.4%.

Treatments

The study treatment modalities included curative surgery in 29 patients (i.e., 20 cases of Whipple's operation, 6 cases of pancreatectomy, and 3 cases of pylorus-preserving pancreaticoduodenectomy). Of these

cases, 11 patients had undergone previous treatment modalities prior to the curative surgery, including endoscopic retrograde cholangiopancreatography (ERCP) with plastic stents in 9 patients and percutaneous transhepatic biliary drainage (PTBD) in 2 patients.

Among the 29 patients who underwent curative surgery, 21 also received adjuvant therapy (72.4%): Adjuvant chemotherapy alone in 4 patients (13.8%), adjuvant radiotherapy alone in 4 patients (13.8%), adjuvant concurrent chemoradiation in 5 patients (17.2%), and adjuvant chemotherapy and radiotherapy in 8 patients (27.6%).

Seventy-one patients underwent palliative operations. The first modality of choice was bypass surgery in 12 patients, noncurative surgery in 5 patients, PTBD in 9 patients, and ERCP with stent insertion in 19 patients (9 with metallic stents and 10 with plastic stents). Seventeen patients received chemotherapy or radiotherapy alone, and 9 patients received the best supportive care. Later, several patients underwent bypass operations, leading to a total of 22 bypass operations.

Of the 71 patients who received palliative treatment, 38 (43.5%) patients also received chemotherapy or radiotherapy. Of these patients, 19 patients (26.8%) underwent palliative chemotherapy; 5 patients (7%) underwent palliative radiotherapy; 7 patients (9.9%) underwent palliative concurrent chemoradiation, and 7 patients (9.9%) underwent both palliative chemotherapy and radiotherapy.

Of the 100 patients, 54 underwent concurrent chemotherapy and radiotherapy. There were 64 chemotherapy regimens. The two most common regimens were single-agent gemcitabine in 37 patients (57.8%) and gemcitabine + oxaliplatin in 6 patients (9.4%), the chemotherapy-related complications included thrombocytopenia in 2 patients, leukopenia in 1 patient, severe hepatitis in 1 patient, and catheter-related infection in 1 patient.

Complications of treatment

Whipple's operation and pylorus-preserving pancreaticoduodenectomy were performed for 23 patients, and postoperative complications were seen in 5 of the patients (21.7%), including an anastomosis leakage in 2 patients, wound infection in 2 patients, and a torn splenic hilum in 1 patient.

Bypass surgery was performed in 22 patients and resulted in complications in 5 of the patients (22.7%), consisting of acute cholangitis in 2 patients, anastomosis obstruction in 1 patient, surgical site bleeding in 1 patient, and wound infection in 1 patient.

Percutaneous transhepatic biliary drainage was completed in 11 patients and was found to have complications in 2 patients (18.2%), consisting of tumor bleeding in 1 patient and PTBD obstruction in 1 patient.

Endoscopic retrograde cholangiopancreatography was performed 31 times and resulted in complications in 8 patients (25.8%), including acute pancreatitis in 2 patients, acute cholangitis in 2 patients, acute pancreatitis and acute cholangitis in 1 patient, stent stenosis and acute cholangitis in 1 patient, upper gastrointestinal bleeding in 1 patient and duodenal perforation in 1 patient.

Survival rate and duration

The 1- and 3-year survival rates after pancreatic cancer diagnosis were 24% and 6%, respectively. The median survival times based on the staging, grading of adenocarcinoma, and first treatment are listed in Table 2. The overall median survival time was 5.1 months, with maximal survival duration of 62.37 months and a minimum of 3 days.

We considered factors that could have affected the survival rate using a Kaplan–Meier curve by comparing the differences in a log-rank test as shown in Figure 3. Three factors were found to be statistically significant, including the staging of the pancreatic cancer at the time of diagnosis ($P < 0.001$), the pathology of the cancer ($P < 0.001$), and the first treatment modality that the patient received ($P = 0.001$).

On univariate analysis, three factors were found to affect the survival rate: Serum albumin level (hazard ratio [HR]: 0.662; 95% confidence interval [CI]: 0.483-0.907; $P = 0.01$), the size of the tumor (HR: 1.166; 95% CI: 1.048-1.298; $P = 0.005$), and the staging at the time of diagnosis (HR: 1.818; 95% CI: 1.369-2.415; $P < 0.001$).

In the multivariate analysis of the 5 factors, i.e., the cancer staging at the time of diagnosis, pathology of the pancreatic cancer, first treatment modality, serum albumin level, and tumor size (based on 76 patients

because of missing data), [Table 3] that affected the survival rate (from the Kaplan–Meier curve and the univariate analysis), only three independent factors affected the survival rate: The staging at the time of diagnosis, serum albumin level, and tumor size at the time of diagnosis.

Table 2. This table shows the three significant factors determining the survival rate of patients with pancreatic cancer. These factors include the staging of pancreatic cancer at the time of diagnosis, the pathology of the cancer and the initial treatment modalities

Risk factors	Number of patients	Number of deaths	Median time of survival (months)	Log-rank P
Staging				
Stage 1a	0	0	—	<0.001
Stage 1b	5	4	5.73	
Stage 2a	4	4	5.43	
Stage 2b	20	18	10.57	
Stage 3	18	17	9.00	
Stage 4	53	53	3.33	
Grading of adenocarcinoma				
Well-differentiated	26	23	8.87	<0.001
Moderately differentiated	25	24	6.30	
Poorly differentiated	11	11	3.77	
Unknown	38	38	3.90	
First treatment				
Curative surgery [#]	18	17	5.73	0.001
Bypass surgery	12	12	7.87	
Other noncurative surgery	5	5	3.63	
PTBD [†] , ERCP [‡] with stent	39	36	5.77	
CMT/XRT [*]	17	17	3.57	
Best supportive care	9	9	1.70	

[#]Curative surgery consisted of Whipple's operation or total pancreatectomy, [†]PTBD: Percutaneous transhepatic biliary drainage, [‡]ERCP: Endoscopic retrograde cholangiopancreatography, ^{*}CMT/XRT: Chemotherapy with or without radiotherapy

Table 3. The factors affecting the survival rate of patients with pancreatic cancer, as determined by multivariate analysis

Factor	HR (95% CI)	P
Staging at the time of diagnosis		
Stage 2a*	1.386 (0.337-5.702)	0.651
Stage 2b*	1.447 (0.467-4.484)	0.552
Stage 3*	1.397 (0.393-4.965)	0.695
Stage 4*	3.893 (1.275-11.889)	0.017
Serum albumin	0.517 (0.356-0.751)	0.001
Size of the tumor	1.20 (1.044-1.379)	0.01

*When compared with stage 1b, CI: Confidence interval, HR: Hazard ration

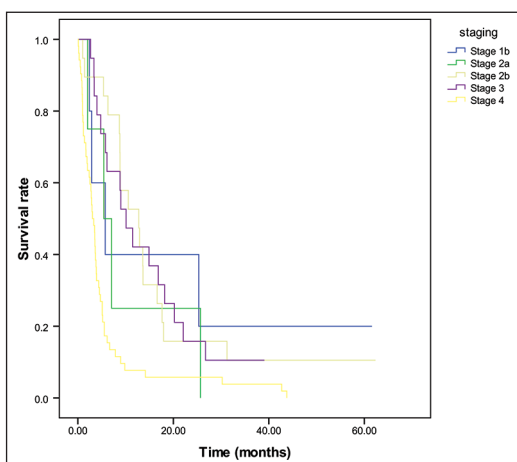


Figure 3. Survival duration versus the pancreatic cancer stage in the form of a Kaplan – Meier curve

DISCUSSION

All patients in this study were Asian and lived in Thailand. Little is known about the demographic data, prognosis, and survival of pancreatic cancer in this part of the world, which makes this population an interesting population to explore. The demographic data of pancreatic cancer patients in our study are similar to those in many reports from Western nations. For example, the age and gender of the various populations are similar.^[2,3] The data from this study indicated that this cancer was mostly found in patients between 60 and 70 years old. Few patients younger than 45 years were identified, and men were more prone to pancreatic cancer than women. This finding is comparable with the Caucasian data from the Surveillance Epidemiology and End Results (SEER) registries, which demonstrate that advancing age is the main risk factor for pancreatic cancer. (*SEER Fact Sheets: Pancreas*: <http://seer.cancer.gov/>). However, in this present study, number of patients in age group between 61 and 70 years old was highest. This might be due to the average age of Thai population is younger than that in Caucasian and elderly patients in Thailand probably did not come to our tertiary care hospital for treatment as they might prefer palliative treatment after discussion with primary physicians.

The three most common presenting symptoms in our series were pain, jaundice, and weight loss. This result is comparable with the results from a multi-institutional series of 185 patients from Spain.^[4] Only 3% of the pancreatic cancers in our series were incidentally found. This result is similar to a study from the United States.^[5] Therefore, based on the results of this study

and others, the presentation of patients between 60 and 70 years old with unexplained abdominal pain, weight loss, and jaundice should raise a suspicion of pancreatic cancer, particularly when a solid pancreatic mass is present. However, it is impossible for clinicians to reliably diagnose pancreatic cancer based on symptoms and signs alone, as demonstrated in a classic prospective study.^[6] An awareness of pancreatic cancer in patients with high-risks for pancreatic cancer and who present with suggestive symptoms is the only method of diagnosing early-stage pancreatic cancer.

The poor prognosis of pancreatic cancer appears to depend on the diagnostic delay. In our study, we found that the time interval from the presentation of symptoms to the delivery of a diagnosis was between 2 and 4 weeks. An Italian study that focused on the prognostic role of a diagnostic delay found that the majority of patients had advanced disease. The symptoms of pain and weight loss were related to the shortest and longest mean times to diagnosis, respectively.^[3] In our study, we did not analyze the effect of the time intervals between the presentation of symptoms and diagnosis on the survival rate. However, most of the patients in our study had symptoms and were in advanced stages of the disease at the time of diagnosis. This result suggests that diagnosing pancreatic cancer in the symptomatic stages is most likely too late. Therefore, detecting the cancer in the presymptomatic stages is a key factor to increasing the patient survival time.

The incidence of pancreatic cancer is somewhat low; therefore, screening for this cancer in an average-risk patient is not cost-effective. In fact, the surveillance of only high-risk patients is the suggested approach to increasing the survival rate of patients with pancreatic cancer.^[7] EUS and MRI seem to be the best tools for the surveillance of early pancreatic cancer.^[8,9] In our study, EUS and MRI were used in <20% of patients, whereas CT was the most commonly used imaging modality. This type of imaging is mainly used in patients who already have symptoms and are in the advanced stages, not for screening or surveillance purposes. For the staging of pancreatic cancer, CT is suggested as the optimal imaging modality to evaluate liver metastases, even in patients with small pancreatic cancers.^[10] In conclusion, we determined that pancreatic cancer in our population has a poor prognosis, partly because of its delayed diagnosis and the lack of a surveillance protocol in our country.

Over the last decade, a multimodality approach has been used to improve the prognosis of pancreatic cancer, particularly for those patients who are not candidates for curative surgery. On the basis of our data, different primary modes of treatment provide significantly different survival results. However, based upon the disease stages and patient conditions, it is difficult to note which method affected the selection of treatment procedures. To directly compare the results of each treatment, the study must be well-controlled, and fair randomization should be applied to prevent selection bias. In our series, approximately 30% of our patients underwent curative surgery, which is similar to other large series.^[11] Gemcitabine was the most commonly used chemotherapy in our series. Using gemcitabine alone for pancreatic cancer seems to provide a greater benefit over other chemotherapy modalities, as shown in other series.^[12] Our study results indicate that the treatment plan for pancreatic cancer in this part of the world does not differ from those plans in other parts of the world.

Regarding the treatment complications in each modality in our series, PTBD appeared to have the lowest complication rate. However, PTBD is not a permanent treatment and is inconvenient for long-term patient care. In patients who are candidates for curative surgeries, such as Whipple's operation, the complication rate is approximately 20%, which is similar to that of other studies.^[13] For patients who require bypass procedures (e.g., ERCP and palliative bypass surgery), the complication rates were quite similar, approximately 20%. In comparison with the reported complication rates of ERCP from a series of ERCPs with stent placement in patients with malignant distal biliary strictures, the complication rates aligned with ours.^[14]

In our study, the 1-year survival rate was studied using the active follow-up method. Few studies have reported the survival rate using this method,^[15-18] whereas a majority of studies have calculated the survival rate using population-based data.^[16,19-29] Some studies have used a combination of these methods to calculate the survival rate.^[30] Despite the often limited availability of certain advanced, sophisticated, diagnostic, and therapeutic measures that are used in the Western world, the survival rate in our patients is similar to the survival rates in these countries. This similarity may reflect the inherent biological behavior of the cancer around the world and the worldwide inability to diagnose the disease early in its course.

According to our study results, a prognostic factor that may impact patient survival is the degree of differentiation of the malignant cells. Poorly differentiated cells had worse prognoses, whereas the patients with well-differentiated cancer cells tended to survive longer. This result is similar to the results from Gray *et al.*, who showed that 1 of the 4 main factors for early mortality following bypass surgery is the poor differentiation of cancer cells.^[31] Nonetheless, after a multivariate analysis, the degree of cell differentiation did not seem to be a significant prognostic factor. However, as this study was not designed to directly answer this question, no final conclusions can be made based on the results of this study.

CONCLUSION

The data on pancreatic cancer in Asians from this series are comparable to the demographic data of Caucasians. With current multimodality treatments, the regimens and prognoses seem to be similar to those in Western countries. Pancreatic cancer remains a challenging disease to diagnose and treat. Future directions for pancreatic cancer diagnosis and treatment in Asians should, therefore, adhere to the same regimen followed in Western countries. It is possible that the data obtained for each country can be applied to others.

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