

Survival of patients with pancreatic cancer treated with varied modalities: A single-centre study

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Abstract. The present retrospective chart review examined the overall survival (OS) of patients with pancreatic ductal adenocarcinoma based on the disease stage in a sample of 296 patients with pancreatic cancer. Secondary outcome measurements included OS in chemotherapy vs. supportive treatment groups among metastatic patients, OS based on response to chemotherapy among metastatic patients, and OS and disease free survival (DFS) in surgically resected disease with vs. without adjuvant therapy. Data were analyzed using Kaplan-Meier and multivariate cox-regression analyses based on a 95% confidence interval (CI) or an α -value of 0.05. OS was significantly different based on the disease stage, with 3.63 (95% CI, 2.84-4.43), 6.57 (95% CI, 4.06-9.08) and 15.57 (95% CI, 11.79-19.35) months in the advanced, locally advanced, and localized disease groups, respectively. OS was higher in metastatic-stage patients who received chemotherapy [6.07 months (95% CI, 4.75-7.39)] compared with those who received supportive therapy alone [2.50 months (95% CI, 2.16-2.84; $P<0.001$)]. Metastatic-stage patients with partial or stable response to chemotherapy had higher OS [10.53 months (95% CI, 6.35-14.72)] in comparison with those with progression [6.33 months (95% CI, 5.79-6.88)] or an undocumented response

[3.30 months (95% CI, 1.76-4.84; $P<0.001$)]. In patients who underwent surgical resection of localized disease, adjuvant therapy increased the adjusted OS and DFS as compared with surgical excision alone ($P=0.013$; 95% CI, 0.278-0.862). Positive margins reduced OS [hazard ratio (HR) 2.670; 95% CI, 1.467-4.860]. The present single-site study has demonstrated that OS may markedly differ on the basis of the disease status at the time of diagnosis. Metastatic-stage patients with stable or partial response to chemotherapy had an increased OS, as did surgical patients with localized disease who received adjuvant treatment, after adjusting for margin status.

Introduction

Pancreatic ductal adenocarcinoma is the fourth most common cancer-associated cause of death in the Western world (1). Surgical resection remains the only treatment modality with the potential for cure; however, only 15-20% of patients with pancreatic cancer are diagnosed with resectable disease (2). Given the high level of recurrences following surgery, both locally and systemically, adjuvant treatment using systemic chemotherapy, radiation and combined modalities has been used to improve the prospects of survival. However, the optimal treatment of choice remains controversial. Although findings of clinical trials have supported the use of adjuvant chemotherapy in patients with resected pancreatic cancer, reports are conflicting, particularly in the negative European Study Group for Pancreatic Cancer 1 (ESPAC-1) trial, concerning survival associated with the use of adjuvant chemoradiation therapy (CRT) (3).

Advanced pancreatic cancer is associated with an even worse prognosis; therefore, chemotherapies have been predominantly used to improve outcomes (4). Gemcitabine (Gem) has been the standard first-line chemotherapy since 1997 (5); however, two novel therapies, irinotecan-5-fluorouracil-leucovorin-oxaliplatin (FOLFIRINOX) and nab-paclitaxel plus Gem, have recently shown markedly improved overall survival (OS) rates in a certain subset of patients (6-9).

Given that the risk of pancreatic cancer increases with age, an aging population means that disease burden is expected to rise in the future. Thus, there is a clear need for further research on the diagnosis and treatment of pancreatic cancer (4).

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Abbreviations: OS, overall survival; DFS, disease-free survival; CRT, chemoradiation therapy; Gem, gemcitabine; FOLFIRINOX, irinotecan-5-fluorouracil-leucovorin-oxaliplatin; 5FU, 5-fluorouracil; HR, hazard ratio; CI, confidence interval; ESPAC, European study group for pancreatic cancer; CT, computed tomography; ECOG, eastern cooperative oncology group; CA19-9, cancer antigen 19-9; RTOG, radiation therapy oncology group

Key words: pancreatic ductal adenocarcinoma, overall survival, disease free survival, chemotherapy, adjuvant therapy, prognosis, supportive therapy, surgical resection, margin, cancer

The primary aim of the present study was to explore the current OS of patients with pancreatic cancer treated at Windsor Regional Hospital Cancer Centre in southwestern Ontario, Canada, based on the stage of the disease. Secondary purposes of the study were to: (i) explore the OS of patients with metastatic pancreatic cancer treated with chemotherapy vs. supportive therapy alone; (ii) compare OS based on the response of these patients to chemotherapy, in order to determine whether patient response to therapy may help clinicians improve their predictions of patient prognosis; and (iii) to examine whether adjuvant therapy (chemotherapy, radiation or CRT) following the surgical resection of localized disease, as well as margin status, had any effect on disease-free survival (DFS) and OS.

Patients and methods

This study was a retrospective chart review of the medical records of 296 patients with pancreatic cancer treated at Windsor Regional Hospital Cancer Centre located in southwestern Ontario, Canada, between January 1, 2002 and May 9, 2013. The medical records of every pancreatic cancer patient treated at our regional cancer centre within the stated time-frame were reviewed via the online hospital database, and subsequently transferred to an Excel database after removing patient identifying information. All endocrine types, including intraductal papillary mucinous neoplasm, acinar cell carcinoma, cystadenocarcinoma, squamous cell carcinoma, and heptoid carcinoma of pancreatic origin, were excluded from the analysis due to the rarity of these tumors in the patient population under investigation. Histological pancreatic cancer diagnoses that were included in the present study consisted of adenocarcinoma, carcinoma only, carcinoma not otherwise specified (NOS) and signet ring cell carcinoma.

The date of diagnosis was defined as the date on which pathological evaluation of a tissue biopsy of either the primary tumour or metastasis confirmed malignancy. In cases where no tissue biopsy was performed (due to patient preference, patient health status and/or tumour location), but a clinical diagnosis of pancreatic cancer was noted in the chart, the date of diagnosis was instead defined as the date of the first computed tomography (CT) scan confirming the presence of a mass; these cases were specifically noted as having a 'radiological diagnosis only' during the later analysis. Cases where a tissue biopsy was performed, but a diagnosis could not be confirmed, were excluded.

Unless a date of mortality was recorded in the chart, the patient was listed as being alive at the date of last contact. Patients whose cause of death was unlikely to have been due to their diagnosis of pancreatic cancer were censored from the analysis, after the specific case had been reviewed by their respective oncologist.

The disease status (localized, locally advanced or metastatic/advanced) of the patient at the date of diagnosis was determined based on the documented clinician summary in the patient's chart; therefore, the patient's clinical presentation, radiological findings and histological evaluation were all taken into account.

Responsiveness to treatment was determined using the CT scan, with the date of recurrence or progression being defined as the date of the CT scan. Progression was defined as any

radiologically confirmed increase in tumour size (in cm) or further metastasis. In cases of multiple tumours in a patient, a decrease in the size of any tumour was defined as a partial response, regardless of growth of the remaining tumours. Recurrence was defined as radiological evidence of tumour growth either locally or distally; patients with evidence of both local and distant recurrence were noted as 'distant recurrence'. Complete responsiveness to treatment was defined as the elimination of the tumour, as determined by the CT scan; however, there were no such cases in the present study.

The metastatic group included all patients with stage 4 cancer. Patients receiving any form of chemotherapy/CRT that was intended to have treated the pancreatic cancer after the date of diagnosis, regardless of whether they completed the chemotherapy regime, were placed into the 'chemotherapy group', whereas the rest were placed into the 'supportive therapy only' group for analysis. Chemotherapy regimens included primarily Gem or 5-fluorouracil (5FU), as well as a minority (~11 cases) of FOLFIRINOX or alternate combinations (5FU/Gem plus leucovorin, Gem plus 5FU, Gem plus erlotinib, or erlotinib alone).

Localized patients were defined as having either stage IA or IB disease at the time of diagnosis, based on the American Joint Committee on Cancer (AJCC) staging guidelines. Patients undergoing any surgical procedure with a curative intent were placed in the 'surgery' group, regardless of margin status post-procedure. Adjuvant therapy was defined as any chemotherapy or CRT administered post-surgical resection, and prior to any documented evidence of recurrence. CRT was given at either a dose of 45 Gray (Gy) in 25 fractions or 50.4 Gy in 28 fractions with concurrent bolus or infusion of 5FU-based chemotherapy. Margin status was determined based on the post-procedure pathology report, and classified into one of three categories: Positive, ≤ 1 mm, and negative. The patient's response to treatment or recurrence status were listed as 'not documented' if the patient deteriorated rapidly, and no CT evaluation was performed to determine the response to treatment or recurrence prior to their date of mortality or the date of last contact.

Data analysis. Data were analyzed using the IBM SPSS version 22 (IBM SPSS, Armonk, NY, USA). Upon ensuring the accuracy of data entry and statistical assumptions, descriptive statistics were performed to describe the sample characteristics. Kaplan-Meier and multivariate Cox regression analyses were performed, as appropriate, to address the outlined study objectives.

Cox regression analysis of the metastatic population adjusted for general characteristics that were significantly different between groups. These included the patients' age, Eastern Cooperative Oncology Group (ECOG) status, and initial radiation treatment. Cox regression of the localized disease population also adjusted for margin status, as it was revealed to be significantly different between groups. All analyses were performed using a two-tailed α -value of 0.05, and either $P \leq 0.05$ or the 95% confidence interval (CI) was considered to indicate a statistically significant value.

Results

Upon completion of the chart review, 18 of a total of 296 patients were deemed ineligible, yielding a sample of 278 patients

Table I. Baseline characteristics divided into (A) the disease status and (B) the treatment type.

A, The disease status						
Characteristic	Disease status at diagnosis				χ^2/F	P-value
	Localized (n=93)	Locally advanced (n=46)	Metastatic (n=139)	Total (n=278)		
Age [mean (SD)]	66.08 (11.90)	67.04 (11.94)	66.45 (12.88)	66.42 (12.73)	0.09	0.91
Gender [n, (%)]					0.09	0.95
Male	51 (54.8)	26 (56.5)	79 (56.8)	156 (56.1)		
Female	42 (45.2)	20 (43.5)	60 (43.2)	122 (43.9)		
ECOG score at presentation [n, (%)]					3.66	0.45
0-2	58 (62.4)	25 (54.3)	86 (61.9)	169 (60.8)		
3-4	11 (11.8)	6 (13.0)	24 (17.3)	41 (14.7)		
Not documented	24 (25.8)	15 (32.6)	29 (20.9)	68 (24.5)		
B, The treatment type						
Characteristic	Group			Total (n=213)	χ^2/t	P-value
	Supportive (n=78)	Chemo (n=61)				
Age [mean (SD)]	69.47 (12.89)	62.59 (11.89)			3.32	<0.01
Gender [n, (%)]					1.23	0.25
Male	41 (52.6)	38 (62.3)		79 (56.8)		
Female	37 (47.4)	23 (37.7)		60 (43.2)		
ECOG score at presentation [n, (%)]					12.10	<0.01
0-2	41 (52.6)	45 (73.8)		86 (61.9)		
3-4	21 (26.9)	3 (4.9)		24 (17.3)		
Not documented	16 (20.5)	13 (21.3)		29 (20.9)		
Initial radiation treatment [n, (%)]					0.44	0.51
None	72 (92.3)	58 (95.1)		130 (93.5)		
Palliative	6 (7.7)	3 (4.9)		9 (605)		

ECOG, eastern cooperative oncology group.

(93 localized, 46 locally advanced and 139 metastatic). The baseline characteristics of age, gender, and ECOG status were not significantly different between the groups, as shown in Table I. The mean age at diagnosis was 66 years [standard deviation (SD)±12.73]. The majority of patients presented with metastatic disease (50%) and an ECOG between 0-2 (61%). A total of 80 patients (29%) presented with localized disease that was treated with surgical resection.

Table IB shows that the chemotherapy and supportive therapy groups for patients with metastatic cancer were significantly different in their age and ECOG score ($P<0.01$). The median OS was identified to be statistically significant ($P<0.001$) among groups, with 3.63 (95% CI, 2.84-4.43) months in the metastatic group, 6.57 (95% CI, 4.06-9.08) months in the locally advanced group, and 15.57 (95% CI, 11.79-19.35) months in the localized disease group (Table II). The results of the Kaplan-Meier analysis indicated that the median OS was significantly longer in metastatic patients who received

chemotherapy [6.07 months (95% CI, 4.75-7.39)] compared with those who received supportive therapy alone [2.50 months (95% CI, 2.16-2.84; $P<0.001$)] (Table II). This result held true in the multivariate cox regression analysis, after adjusting for age, ECOG status and initial radiation treatment (Table III).

The results pertaining to the subgroup of metastatic patients receiving chemotherapy (Table II) indicated that those with a partial or stable response to treatment had a significantly higher median OS [10.53 months (95% CI, 6.35-14.72)] compared with those with progression [6.33 months (95% CI, 5.79-6.88)] or an undocumented response [3.30 months (95% CI, 1.76-4.84); $P<0.001$]. Within the subgroup of patients who underwent surgical resection (Tables IV and V), adjuvant treatment was not associated with an increase in the median OS ($P=0.09$), DFS ($P=0.60$) or recurrence location ($P=0.14$). However, adjuvant treatment significantly increased the median OS after adjusting for the margin and nodal status ($P=0.013$; 95% CI, 0.278-0.862). Once the margin status had been adjusted, patients with

Table II. Kaplan-Meier survival comparisons.

Group	Sample size (n)	Median survival in month (95% CI)	P-value
Overall	278		<0.001
Localized disease	93	15.57 (11.79-19.35)	
Metastatic	139	3.63 (2.84-4.43)	
Locally advanced	46	6.57 (4.06-9.08)	
Metastatic group	139		<0.001
Chemotherapy treatment	61	6.07 (4.75-7.39)	
Supportive treatment	78	2.50 (2.16-2.84)	
Response to chemotherapy in metastatic group	61		<0.001
Partial or stable response	10	10.53 (6.35-14.72)	
Progression	23	6.33 (5.79-6.88)	
Not documented	28	3.30 (1.76-4.84)	
Surgical resection patients	80		0.090
Adjuvant treatment	52	18.80 (15.54-22.15)	
No adjuvant	28	10.53 (3.83-17.23)	

CI, confidence interval.

Table III. Cox regression comparing overall survival based on type of treatment among metastatic disease patients.

Variable	β -value	SE	P-value	Hazard ratio	95% CI
Age (years)	0.01	0.01	0.56	1.01	0.99-1.02
Gender (male)	0.48	0.20	0.02	1.16	1.10-2.38
Treatment (chemo)	-0.75	0.21	<0.01	0.47	0.32-0.70
Supportive (reference group)	-	-	-	-	-
ECOG 3-4	0.14	0.27	0.61	1.15	0.68-1.94
ECOG not documented	0.11	0.26	0.67	1.12	0.67-1.85
ECOG 0-2 (Reference)	-	-	-	-	-
Initial radiation treatment	-0.24	0.40	0.55	0.79	0.36-1.71

ECOG, Eastern cooperative oncology group; SE, standard error.

positive margins were revealed to have significantly shorter OS [hazard ratio (HR)=2.670; 95% CI, 1.467-4.860]. Intermediate margins had no significant effect on OS (HR=1.429; 95% CI, 0.566-3.605). Positive lymph node status was not associated with decreased survival in the 1-2 positive node group (P=0.097), or in the 3+ positive node group (P=0.106). Table V shows that 18 of 80 patients (22%) with surgical resection did not have any documented recurrence of disease.

Discussion

Clinical trials have supported the use of adjuvant chemotherapy in patients with resected pancreatic cancer (10,11). However, the use of CRT in adjuvant treatment remains a hotly debated topic, and currently no studies have been published demonstrating the superiority of the addition of radiotherapy with modern delivery techniques to adjuvant chemotherapy alone (2,12,13). Furthermore, efforts are now focused on

increasing the resectability of locoregional disease by incorporating neoadjuvant treatment prior to surgery. Adjuvant CRT is, however, generally agreed upon to improve local control in surgically resected patients with adverse risk factors for locoregional disease recurrence that include an older age, large tumour size, advanced tumour stage, high histological grade, an elevated cancer antigen 19-9 (CA19-9) level, positive lymph nodes and positive surgical margins (13).

In this single-centre chart review, a higher percentage of patients (29%) were diagnosed with localized disease, and were subsequently treated with surgical resection, compared with the previously cited value of 15-20% (2). Furthermore, patients treated with adjuvant therapy (chemotherapy or CRT) had a median OS that was comparable with previous studies, which ranged from 17.1-23.2 months (10,11,14,15). It is important to note, however, that these published studies excluded certain patients based on various negative prognostic factors [i.e., the CONKO-001 trial excluded patients

Table IV. Cox regression comparing survival based on adjuvant treatment among localized pancreatic cancer patients undergoing resection.

Variable	β -value	SE	P-value	Hazard ratio	95% CI
Adjuvant treatment	-0.715	0.289	0.013	0.489	0.278-0.862
Margin status					
Positive	0.982	0.306	0.001	2.670	1.467-4.860
≤ 1 mm	0.357	0.472	0.450	1.429	0.566-3.605
Negative (reference)	-	-	-	-	-
Node status					
3 or more positive nodes	0.563	0.348	0.106	1.755	0.888-3.470
1-2 positive nodes	0.606	0.365	0.097	1.833	0.897-3.745
Negative nodes (reference)	-	-	-	-	-

CI, confidence interval.

Table V. Disease-free survival and recurrence status of localized disease patients undergoing surgical resection.

Variable	Group		Total (n=80)	χ^2/t	P-value
	Adjuvant (n=52)	No adjuvant (n=28)			
Recurrence time in months [mean, (SD)]	13.39 (13.43)	11.47 (11.42)	12.73 (12.70)	-0.53	0.60
Recurrence status [n, (%)]					
None	14 (26.9)	4 (14.3)	18 (22.5)	5.42	0.14
Local/regional only	5 (9.6)	3 (10.7)	8 (10.0)		
Distant	31 (59.6)	16 (57.1)	47 (58.7)		
Not documented	2 (3.9)	5 (17.9)	7 (8.8)		

with CA19-9 levels >2.5 times the upper limit of normal, the ESPAC-1 and ESPAC-3 trials excluded patients with macroscopically remaining tumour post-resection, and the Radiation Therapy Oncology Group (RTOG) trial excluded patients with lower performance scores, which limits the comparison]. Furthermore, in the subgroup of patients who were treated with surgical resection alone, the fact that patients were not excluded based on negative prognostic criteria in the present study provides a possible explanation for why the median OS was comparatively shorter than the range of 11-20.2 months that was reported by Sen *et al* (2).

In contrast with previous studies, which reported that positive nodal status is a negative prognostic indicator, the present study identified no significant effect of nodal status on prognosis (13). A possible explanation of this discrepancy could be attributed to the lack of standardization among patients with regard to the number of lymph nodes that were sent to pathology for evaluation (ranging from 0 to >3) in the present study, whereas, by contrast, the RTOG trial by Regine *et al* (15) did standardize for the number of lymph nodes, and had that as part of their eligibility criteria. It is important to note, however, that standardization in the present study was not possible, given its retrospective nature.

The present study is the first, to the best of our knowledge, that has explored intermediate margin status, and the findings

in this study indicated no difference in the median OS between patients with intermediate margins and those with negative margins. This lack of difference in the median OS suggests that these patients may not be at an increased risk, and thus will not benefit from CRT as long as they do not have any other adverse risk factors for locoregional disease recurrence. Consistent with several published reports (10,11,13,16,17), the findings of the present study suggest that positive margin status is a negative prognostic indicator, further demonstrating that margin status is independently associated with OS. However, two previously published studies (10,11) suggested that margin status is of significantly less prognostic value than primary tumour characteristics, which tend to dominate the outcome.

The findings of the present study have shown that patients with metastatic pancreatic cancer who received chemotherapy had a significantly longer median OS. This finding was consistent with the findings of past studies that reported on patients with advanced stage pancreatic cancer who were treated with single-agent Gem, as well as Gem plus other cytotoxic and targeted agents (1). Furthermore, a previous study (8) suggested that OS is also influenced by a number of independent, adverse prognostic factors, including age and gender. In contrast with the present study, Moore *et al* (18) and Conroy *et al* (8) reported that age was negatively associated with OS. The reasons for this discrepancy are not entirely clear, although it is possible that

it may be a result of differences in the patient sample size, i.e., in our study there were 139 patients with metastatic disease, compared with 569 and 342 in the above-mentioned articles respectively. Therefore, it is advisable that a further study should investigate the association between age and OS with a larger sample size, to reduce the possibility of type II error. The present study has suggested that response to therapy, in patients with metastatic disease who are treated with chemotherapy, is potentially a beneficial prognostic factor.

Di Marco *et al* (1) argued that Gem remains a mainstay of treatment for advanced pancreatic cancer, and that the combination of Gem with a variety of cytotoxic and targeted agents has generally revealed no significant survival advantage as compared with Gem alone, aside from the recent metastatic adenocarcinoma of the pancreas (MPACT) study by Tabernero *et al* (9). The present study examined the OS of patients treated with chemotherapy, and did not compare specific treatment regimes, since, in this study, the majority of patients were treated with Gem alone. In recent years, FOLFIRINOX has emerged as the most effective chemotherapy regime in a select subset of patients with pancreatic cancer (8). Given that Windsor Regional Hospital Cancer Centre has recently begun to treat more patients with FOLFIRINOX, further research is warranted to determine whether patients' OS improves in response to the introduction of FOLFIRINOX.

It is important to note that the findings in the present study need to be interpreted with caution due to the retrospective chart review nature of our study, which increases the potential for confounding, selection and measurement bias. The relatively small sample size that was obtained from a single community-based cancer centre presents an additional limitation to this study that ought to be taken in consideration prior to making generalizations based on the findings. As the centre's patient sample increases in size, further studies evaluating adjuvant CRT against adjuvant chemotherapy alone may provide useful information to add to the current debate.

In conclusion, in the present study OS was revealed to significantly differ on the basis of the disease status at diagnosis, with patients diagnosed with localized disease having the longest OS. Furthermore, in metastatic patients receiving chemotherapy, a partial or stable response to chemotherapy appeared to significantly increase OS in comparison with those with progression. Adjuvant therapy significantly increased OS in comparison with patients treated with surgical excision alone, once margin and nodal status had been adjusted for. Positive margins were a negative prognostic indicator. Localized patients undergoing surgical resection treated with adjuvant therapy were identified to have significantly longer OS after adjusting for margin status, with positive margins significantly reducing survival; however, intermediate margins were not associated with a significant difference in OS when compared with negative margins.

This study has added to the burgeoning body of evidence that will aid clinicians in terms of determining prognostic estimates during the treatment of pancreatic ductal adenocarcinoma.

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