

Outcomes of resected pancreatic cancer in patients age ≥ 70

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Objective: To determine outcomes of patients ≥ 70 years with resected pancreatic cancer.

Methods: A study was conducted to identify pancreatic cancer patients ≥ 70 years who underwent surgery for pancreatic carcinoma from 2000 to 2012. Patients were excluded if they had neoadjuvant therapy. The primary endpoint was overall survival (OS).

Results: We identified 112 patients with a median follow-up of surviving patients of 36 months. The median patient age was 77 years. The median and 5 year OS was 20.5 months and 19%, respectively. Univariate analysis (UVA) showed a significant correlation for increased mortality with N1 ($P=0.03$) as well as post-op CA19-9 >90 ($P<0.001$), with a trend towards decreased mortality with adjuvant chemoradiation ($P=0.08$). Multivariate analysis (MVA) showed a statistically significant increased mortality associated with N1 ($P=0.008$), post-op CA19-9 >90 ($P=0.002$), while adjuvant chemoradiation ($P=0.04$) was associated with decreased mortality.

Conclusions: These data show that in patients ≥ 70 , nodal status, post-op CA19-9, and adjuvant chemoradiation, were associated with OS. The data suggests that outcomes of patients ≥ 70 years who undergo upfront surgical resection are not inferior to younger patients.

Keywords: Pancreatic cancer; surgery; elderly; adjuvant therapy; chemoradiation

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Introduction

Pancreatic cancer remains the fourth leading cause of cancer-associated deaths in the United States (1,2). Despite advancements in multi-modality therapy pancreatic cancer remains extraordinarily lethal with a 5-year overall survival (OS) of approximately 5% (1,3). Furthermore in the United States the incidence of pancreatic cancer has continued to increase since the 1930s (4). There are greater than 43,000 cases diagnosed annually in the United States, with a large proportion dying of their disease (5).

The current accepted standard of care for resectable

pancreatic cancer remains resection followed by adjuvant therapy consisting of chemotherapy. The use of post-operative radiotherapy (PORT) continues to be a topic of controversy (6). Several studies have shown an increase in OS compared to surgery alone (7-9), whereas others have shown no benefit (10-12).

In the United States the elderly population has continued to grow with a 30% increase from 2000 to 2010 (13). Additionally, the average life span has increased secondary to advancements in public health, nutrition, early detection of diseases, and continued medical progress. This increase in average life expectancy as well as advancements in cancer

screening has led to a growing number of cancer diagnoses in the elderly (14).

Pancreatic cancer tends to occur at an older age, with relatively rare occurrence before the age of 45 and a sharp increase in its incidence thereafter (4). Incidence of the disease increases with advancing age, with an incidence of 29 per 100,000 in patients aged 60-64 and 91 per 100,000 in patients aged 80-84 years (15). In the United States the median age for patients diagnosed with pancreatic cancer is 72 (16). Increasing age is a well-known risk factor for the development of pancreatic cancer (17,18). In fact, approximately two-thirds of cases are diagnosed in patients greater than 65 years old (4,15). As such, more elderly patients are being diagnosed with pancreatic cancer and being considered for multi-disciplinary treatment (19). However, elderly cancer patients remain underrepresented in many clinical studies, with age greater than 70 years as a frequent exclusion criterion (20,21). As such the question remains as to whether these data can be extrapolated to the elderly population. The aim of this study was to determine the outcomes of age ≥ 70 patients with resected pancreatic cancer at our institution.

Materials and methods

Patients

An analysis of pancreatic cancer patients ≥ 70 years who underwent upfront surgical resection for pancreatic carcinoma from 2000 to 2012 was conducted to determine outcomes. Patients were excluded if they had M1 disease, lack of surgical resection, use of neoadjuvant therapy, or age < 70 , and unusual histologies including lymphoma, cystadenoma, intraductal papillary mucinous neoplasm, signet ring cell carcinoma, neuroendocrine tumors, islet cell tumors such as gastrinoma, insulinoma, glucagonoma and VIPoma.

Treatment

Surgery

Patients with pancreatic head tumors underwent pancreaticoduodenectomy with or without a pylorus-sparing procedure. A minority of patients with pancreatic body or tail tumors underwent pancreaticoduodenectomy, complete pancreatectomy, or partial pancreatectomy with or without splenectomy, and/or vein resection/repair depending on the size and location of the tumor with respect to regional

organs and vasculature.

Adjuvant therapy

Following surgery, patients received chemoradiation with or without neoadjuvant or adjuvant chemotherapy, chemotherapy alone, or no adjuvant therapy. Adjuvant therapy was initiated within 4 months from the time of surgery in all cases.

Patients treated with chemotherapy alone received single-agent gemcitabine. Patients treated with chemotherapy followed by radiation were treated in a similar fashion to the radiation therapy oncology group (RTOG) 9,704 protocol with 1 month of gemcitabine followed by concurrent chemoradiation with continuous infusion 5-FU or gemcitabine, followed by adjuvant gemcitabine. Patients treated with chemoradiation alone received concurrent radiation with 5-FU or gemcitabine. The median radiation dose was 50 Gy (range, 43.2-63 Gy) in 180 to 200 cGy daily fractions for a median of 28 fractions (range, 24-35 fractions) to the pancreatic tumor bed and regional lymphatics; a minority of patients received a boost to the tumor bed (median 0 Gy; range, 0-14.4 Gy).

Statistical analysis

The primary endpoint was OS, defined as the interval from surgery to date of death. Statistical analysis was performed using SPSS[®] version 21.0 (IBM[®], Chicago, IL, USA). Progression-free survival (PFS) was also analyzed and defined as the interval from surgery to first recurrence or death. Continuous variables were compared using both Wilcoxon rank sum test and the Kruskal Wallis test as appropriate. Pearson's Chi-square test was used to compare categorical variables. Actuarial rates of OS were calculated using the Kaplan-Meier method and the log-rank test. A Cox multivariate model was performed for OS, including all clinical, histopathologic, and treatment variables. Continuous variables for inclusion in the multivariate model were split at clinically meaningful cut-points; post-operative CA19-9 level was split at < 90 and ≥ 90 . All statistical tests were two-sided and an α (type I) error < 0.05 was considered statistically significant.

Results

Patient characteristics are shown in *Table 1*. A total of 112 patients age ≥ 70 who underwent upfront pancreatic resection were analyzed with a median follow-up of

Variable	Level	Age ≥ 70 y; N (%)
Gender	Male	59 (52.7)
	Female	53 (47.3)
Site	Head	87 (77.7)
	Body	7 (6.3)
	Tail	18 (16.1)
Days from diagnosis to surgery	≤ 30	83 (74.1)
	> 30	29 (25.9)
Median path tumor size (cm, range)		3.0 (0.5, 8.5)
Pathologic tumor stage	T1/2	24 (21.4)
	T3/4	88 (78.6)
Median nodes positive (range)		1 (0, 25)
Median nodes removed (range)		11 (0, 49)
Pathologic nodal stage	N0	49 (43.8)
	N1	63 (56.3)
Tumor grade	Well	12 (10.7)
	Moderate	75 (67.0)
	Poor	18 (16.1)
	Unknown	7 (6.3)
Surgical margins	Negative	94 (83.9)
	Positive	18 (16.1)
Post-op CA19-9 > 90	No	64 (57.1)
	Yes	19 (17.0)
	Unknown	29 (25.9)
Adjuvant treatment	None	34 (30.4)
	Chemoradiation	53 (47.3)
	Chemotherapy	25 (22.3)

surviving patients of 36 months. The median patient age was 77 years and the majority of patients presented with advanced disease and received adjuvant treatment.

Postoperative complications are presented in *Table 2*. The most common complications were pancreatic leak (14.3%) and wound infection (12.5%). Postoperative 30, 60, and 90 day mortality was 2.7%, 3.6%, and 4.5%.

Figure 1 shows the OS and PFS Kaplan Meier curves for the patients included in this analysis. The median, 3 and 5 year OS was 20.5 months, 36%, and 19% respectively (*Figure 1A*). The median, 3 and 5 year PFS was 14.6 months, 24%, and 17% respectively (*Figure 1B*).

Post-op complications	N (%)
Pancreatic leak	16 (14.3)
Gastrojejunostomy leak	1 (0.9)
Atrial fibrillation	6 (5.4)
Pulmonary embolus	2 (1.8)
Abscess	2 (1.8)
Wound infection	14 (12.5)
Wound dehiscence	1 (0.9)
Anastomotic bleed	4 (3.6)
Stricture	1 (0.9)
Enterocutaneous fistula	0 (0)
SMA clot with bowel necrosis	1 (0.9)
Peritonitis	3 (2.7)
30 day mortality	3 (2.7)
60 day mortality	4 (3.6)
90 day mortality	5 (4.5)

SMA, superior mesenteric artery.

Table 3 illustrates the univariate analysis (UVA) and multivariate analysis (MVA) for OS. On UVA, increased mortality was associated with N1 status [hazard ratio (HR) 1.64: 1.05-2.56; $P=0.03$], post-operative CA19-9 > 90 (HR 2.78: 1.56-4.93; $P<0.001$). There was a trend towards decreased mortality associated with adjuvant treatment with chemoradiation (HR 0.64: 0.39-1.05; $P=0.08$). On MVA, increased mortality was associated with N1 status (HR 1.91: 1.19-3.07; $P=0.008$) and postop CA19-9 > 90 (HR 2.68: 1.45-4.94; $P=0.002$), while decreased mortality was significantly associated with adjuvant chemoradiation (HR 0.5: 0.26-0.95; $P=0.04$). Interestingly, there was no correlation associated with adjuvant chemotherapy alone. Age, tumor stage, interval from diagnosis to surgery, margin status, tumor site, and gender were not prognostic on UVA or MVA.

Discussion

This is one of the first studies to document outcomes and prognostic factors in patients ≥ 70 with pancreatic cancer treated with upfront resection with or without adjuvant therapy. Interestingly, adjuvant chemoradiation was associated with decreased mortality on MVA, whereas adjuvant chemotherapy was not prognostic. On both UVA and MVA, patients with N1 disease and post-operative

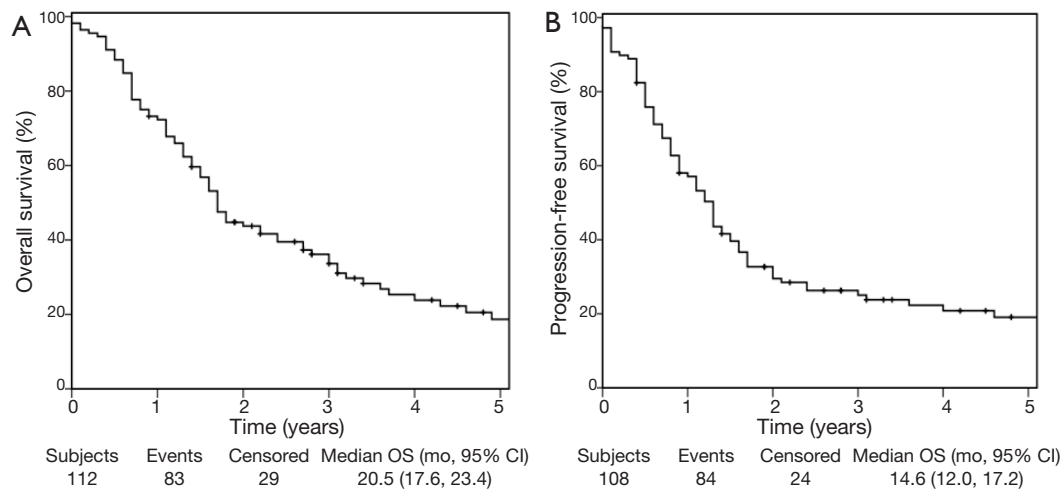


Figure 1 Kaplan-Meier survival curve of (A) overall survival (OS); (B) progression-free survival (PFS).

Variable	Level	Median OS (m)	UV HR (95% CI)	P value	MV HR (95% CI)	P value
Age*			1.02 (0.98, 1.07)	0.37	1.01 (0.96, 1.06)	0.76
Gender	Male	20.5	Ref			
	Female	19.9	0.92 (0.60-1.41)	0.70	0.86 (0.55, 1.36)	0.53
Diagnosis to surgery (days)	≤30	19.8	Ref			
	>30	21.9	0.93 (0.57-1.51)	0.76	0.85 (0.48, 1.49)	0.57
Tumor site	Head	20.8	Ref			
	Body	65.9	0.54 (0.20, 1.50)	0.24	1.03 (0.32, 3.35)	0.96
	Tail	15.6	1.26 (0.70, 2.24)	0.44	1.62 (0.84, 3.13)	0.15
Tumor grade	Well	28.9	Ref			
	Moderate	18.7	1.24 (0.63, 2.45)	0.53	1.13 (0.52, 2.47)	0.75
	Poor	19.1	1.17 (0.51, 2.69)	0.71	1.04 (0.42, 2.62)	0.93
	Unknown	48.2	0.66 (0.23, 1.94)	0.45	0.52 (0.14, 2.01)	0.35
Pathologic tumor stage	T1/2	19.8	Ref			
	T3/4	20.8	1.19 (0.70-2.02)	0.53	1.27 (0.67, 2.41)	0.47
Pathologic nodal status	N0	28.8	Ref			
	N1	18.2	1.64 (1.05-2.56)	0.03	1.91 (1.19, 3.07)	0.008
Surgical margins	Negative	19.9	Ref			
	Positive	21.1	0.75 (0.40-1.42)	0.38	0.94 (0.46, 1.93)	0.87
Post-op CA19-9	≤90	26.4	Ref			
	>90	10.1	2.78 (1.56-4.93)	<0.001	2.68 (1.45, 4.94)	0.002
	Unknown	20.5	1.31 (0.79-2.17)	0.29	1.13 (0.64, 1.98)	0.68
Adjuvant treatment	None	15.6	Ref			
	Chemoradiation	21.1	0.64 (0.39-1.05)	0.08	0.50 (0.26, 0.95)	0.04
	Chemotherapy	20.5	1.05 (0.58-1.90)	0.87	0.67 (0.33, 1.33)	0.25

*, continuous variable; OS, overall survival; m, months; HR, hazard ratio; CI, confidence interval; UV, univariate; MV, multivariate; Ref, reference (HR 1.00).

CA19-9 >90 were prognostic for increased mortality.

The elderly population continues to remain underrepresented in clinical literature, representing only 25-30% of study participants (20). Secondary to this dearth of data there has been recent interest in defining the roles of different therapies in the elderly with pancreatic cancer. A retrospective study by Sehgal *et al.* (n=16,694) reported the rates of chemotherapy delivered and associated survival in different age groups in all patients with pancreatic cancer from the Cancer Information Resource files registry (4). They found that elderly patients with pancreatic cancer receive treatment less frequently than younger patients. Additionally, median OS was significantly less in the age >70 group (4.21 *vs.* 7.07 months and 7.89 months for age >70 , 51-70, and ≤ 50 years respectively), however these patients were shown to have a comparable or better survival benefit from chemotherapy. In their UVA, age >70 was not prognostic for OS. This study also showed an OS benefit in all patients treated with radiotherapy (HR 0.47, $P < 0.001$). Our results are in general agreement with this study, suggesting that elderly patients with pancreatic cancer do derive a benefit from treatment, specifically chemoradiotherapy (CRT).

There continues to be controversy regarding the role of PORT in resected pancreatic cancer patients (6). Several trials have shown benefit from the use of PORT in pancreatic cancer. In Gastrointestinal Tumor Study Group (GITSG) 9,173 (n=43) patients who had undergone curative resection were randomized to observation or CRT with 40 Gy split course radiation and concurrent 5-fluorouracil (5-FU) chemotherapy (9). The median survival in the CRT arm was significantly improved compared to the observation arm (20 *vs.* 11 months, $P = 0.035$). Additionally, the 2-year survival rates were significantly improved with CRT *vs.* the observation group (42% *vs.* 15%; $P = 0.035$). This initial study has led to adjuvant CRT being adopted in the United States. The European Organisation for Research and Treatment of Cancer (EORTC)-40,891 (n=218) phase III study sought to confirm these results and as such randomized patients with resected pancreatic cancer or periampullary cancer to observation or 5-FU based CRT (12). The initial data showed no difference in median survival between the two groups, (19 *vs.* 24.5 months; $P = 0.208$). However, further subgroup analysis of just pancreatic tumor showed use of adjuvant CRT improved 2-year OS (23% *vs.* 37%; $P = 0.049$) (22).

While these studies support the use of PORT in the treatment of pancreatic cancer there are additional data

that do not support its use. The European Organisation for Research and Treatment of Cancer (ESPAC)-1 trial (n=541) compared observation, chemotherapy alone or CRT (11). They reported that adjuvant CRT worsened the median survival compared to those who did not receive CRT (16 *vs.* 18 months) as well as reported an inferior 2-year survival (29% *vs.* 49%; $P = 0.05$). However, this study has been widely criticized for lack of quality assurance and the split-course treatment techniques. The study allowed radiation oncologists to choose their dose with a range of 40-60 Gy. Moreover, only 53% of patients enrolled in the study were included in the final analysis. Lastly the physician was able to choose how the patient was randomized and prescribe chemotherapy or “background” CRT.

While the previously mentioned trials included elderly patients, but did not specifically analyze this population, there have been two other trials that have specifically examined the elderly population. Miyamoto *et al.* examined pancreatic cancer patients age ≥ 75 (n=42) treated with CRT as adjuvant or definitive therapy (23). Median OS for the patients that received surgery followed by CRT was 20.6 months *vs.* 8.6 months for CRT as definitive therapy. Importantly, they showed that in this elderly population outcomes after CRT were similar to historic controls, although many patients experienced substantial treatment-related toxicity. Another study, Horowitz *et al.* from Johns Hopkins analyzed 655 patients from their prospectively collected database of patients who underwent resection and 5-FU based CRT (n=313) or no adjuvant treatment (n=342) (24). They showed that the 2-year survival for elderly patients receiving adjuvant CRT was significantly greater than those who received surgery alone (49% *vs.* 31.6%; $P = 0.013$); however, the 5-year survival in both groups was similar (11.7% *vs.* 19.8% respectively; $P = 0.310$). Upon MVA adjuvant CRT had protective effect with respect to 2-year survival [relative risk (RR) 0.59; $P = 0.44$].

Our study differs from the aforementioned studies in the fact that we examined patients who underwent upfront surgical resection followed by no treatment, chemotherapy, and CRT. The study by Horowitz *et al.* compared surgery alone to CRT, and the Miyamoto *et al.* study compared only CRT as an adjuvant therapy to CRT as definitive therapy. While these differences do exist it appears that our data is in general agreement that elderly patients with pancreatic cancer benefit from treatment, specifically chemoradiation in the adjuvant setting.

Our study does present several inherent limitations based on the fact that this is a retrospective analysis, a time

period spanning 12 years, including that fact that patient selection may influence survival. Overall, our study suggests that elderly patients with resected pancreatic cancer benefit from therapy and specifically that adjuvant CRT, however, conclusion drawn from this analysis are hypothesis generating and not definitive.

Conclusions

Our study begins to define prognostic variables associated with OS in elderly patients, a group that continues to be underrepresented in clinical research. Our data shows an increase in OS in patients that were treated with adjuvant CRT but not chemotherapy alone.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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