Original Article

Outcomes of adjuvant radiotherapy and lymph node resection in elderly patients with pancreatic cancer treated with surgery and chemotherapy

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Background: We sought to determine the effects of post-operative radiation therapy (PORT) and lymph node resection (LNR) on survival in patients ≥70 years with pancreatic cancer treated with surgery and chemotherapy.

Methods: An analysis of patients ≥70 years with surgically resected pancreatic cancer who received chemotherapy from the SEER database between 2004–2008 was performed to determine association of PORT and LNR on survival.

Results: We identified 961 patients who met inclusion criteria. There was a trend towards increased survival associated with PORT in all patients (P=0.052) and N1 patients (P=0.060) but no benefit in N0 patients (P=0.161). There was no difference in OS based on number of lymph nodes removed in all (P=0.741), N0 (P=0.588), and N1 (P=0.070) patients. MVA for all patients revealed that higher T stage, N1, and high grade tumors were prognostic for increased mortality, while there was decreased mortality with PORT and mild benefit with increased lymph nodes resected (P=0.084).

Conclusions: PORT demonstrated no benefit in survival of pancreatic cancer patients ≥70 who are resected and treated with adjuvant chemotherapy. Future investigation will need to address age as a stratification factor for pancreatic cancer in the adjuvant setting.

Keywords: Adjuvant radiation; pancreatic cancer; lymph node harvest; outcomes in the elderly population

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Introduction

Pancreatic cancer is a common disease in the United States with approximately 43,920 people diagnosed each year, and about 37,390 people will die from their disease (1). The median age at diagnosis of pancreatic cancer is 72, with approximately 43% of all patients being aged ≥75 in the United States (2). Outcomes continue to remain dismal with the only chance of cure being margin negative (R0) resection.

Chemotherapy remains a mainstay of treatment in the adjuvant setting however the addition of post-operative radiation therapy (PORT) continues to be a topic of controversy. Several studies have shown an overall survival (OS) benefit to PORT (3-5) compared to surgery alone while others have demonstrated no benefit and possible detriment (6-8). Some institutions recommend chemotherapy alone and

others recommend the addition of PORT.

Age is not a contraindication to surgical resection and has been extensively researched (9-12). Some studies have shown an increased in operative time and post-operative complications in the elderly population however no differences in post-operative mortality thus validating surgical resection in this aging population. Very few studies have looked at PORT and chemotherapy in the elderly population (13,14). The Surveillance Epidemiology End Result (SEER) database is one of the largest repositories of patient outcomes from cancer. Data on age, gender, survival, surgery, radiation, sequence of radiation with surgery, and pathologic variables like grade, lymph node involvement, number of lymph nodes removed, and tumor stage are available. A factor not routinely made available is the use of chemotherapy unless SEER grants special requests to provide data as a yes/no question. We present the first, largest, and most modern analysis of the SEER database on surgically resected pancreatic cancer patients who are age 70 or greater, who all received chemotherapy, to address to role of PORT and lymph node resection (LNR) on survival in this population.

Methods

Patients

After being granted a request to access chemotherapy data from the SEER database, a unique SEER 17-registries 1973–2008 dataset where a chemotherapy variable (yes/no) was now included was queried to identify patients ≥18 years old diagnosed from 2004–2008 with pancreatic adenocarcinoma who underwent curative resection (n=5,373). Included patients were 70 years or older, underwent Whipple, distal pancreatectomy, or total pancreatectomy for AJCC (6th ed) stage I–III cancer, received chemotherapy and either received PORT or no PORT (n=961). Patients were excluded from the analysis if they were 70 years old or younger (n=2,005), no chemotherapy was given (n=1,757), the type of surgery was local excision or unknown (n=129), no or unknown lymph node dissection (n=179), or had less than 3 months survival (n=342). Data not included in SEER include patient co-morbidities, nutritional status, performance status, surgical margin status, radiation dose and field design.

Statistical analysis

Survival was evaluated on the basis of time from date of diagnosis to date of death or censoring. Unadjusted survival analyses were performed using the Kaplan-Meier method comparing survival curves with the log-rank test. Multivariate analysis (MVA) of prognostic factors related to survival was performed by the Cox Proportional Hazard Regression modeling. Data were analyzed using STATA IC (Stata Statistical Software, Release 10.0; Strata Corp., College Station, TX, USA). All statistical tests were two-sided and α (type I) error <0.05 was considered statistically significant.

Results

We identified 961 patients who met inclusion criteria (555 PORT, 406 No RT). Patient characteristics are presented in *Table 1*. The only statistically significant difference between the groups was age. Patients receiving PORT had a median age of 75 (range 70–88) *vs.* 76 (range 70–91) years in patients not treated with PORT (P=0.007). The majority of patients were moderately differentiated, node positive (N1) tumors of the pancreatic head.

Figure 1 illustrates the OS curves for all patients and according to nodal status stratified by PORT *vs.* no PORT. Median OS for all patients with PORT was 19 *vs.* 18 months without PORT (P=0.0642). There was no difference in survival in node negative (N0) patients receiving PORT (P=0.8036), however there was a trend towards improved survival favoring PORT in N1 patients (P=0.0501).

We performed univariate analyses to determine the optimal number of lymph nodes resected both categorically and as a continuous variable (*Table 2*). In all, N0, and N1 patients there was no associated survival benefit for increasing number of lymph nodes removed.

MVA for OS is presented in *Tables 3-5*. MVA for all patients is presented in *Table 3* and revealed that increasing T stage, tumor grade, and N1 status were prognostic for increased mortality, while there was a trend for decreased mortality in the patients receiving PORT (P=0.052). Age, number of lymph nodes removed, tumor location, and gender demonstrated no prognostic significance. MVA for N0 patients showed that increasing T stage and grade were associated with increased mortality (*Table 4*). Age, gender, tumor location, PORT, and number of lymph nodes removed were not prognostic in N0 patients. MVA for N1 patients indicated that increasing T stage was prognostic for increased mortality and number of lymph nodes removed was prognostic for decreased mortality (*Table 5*). PORT showed a trend towards decreased mortality (P=0.060)

Table 1 Patient characteristics

Demographic or characteristic	No RT		PORT		P
	No. of patients	%	No. of patients	%	
No. of patients	406	42.2	555	57.8	–
Median age at diagnosis* [range]	76 [70–91] years		75 [70–88] years		0.007
Median LN removed* [range]	12 [1–52]		12 [1–70]		0.630
Gender					
Female	222	54.7	272	49.0	0.087
Male	184	45.3	283	51.0	
AJCC T-stage					
T1	23	5.7	24	4.3	0.340
T2	52	12.8	84	15.1	
T3	316	77.8	423	76.2	
T4	12	3.0	23	4.1	
TX	3	0.7	1	0.2	
AJCC N-stage					
N0	131	32.3	191	34.4	0.489
N1	275	67.7	364	65.6	
AJCC stage					
IA	15	3.7	13	2.3	0.395
IB	24	6.0	45	8.1	
IIA	88	21.8	122	22.0	
IIB	264	65.5	351	63.4	
III	12	3.0	23	4.2	
Location					
Body	17	4.4	38	7.2	0.367
Head	305	79.4	401	76.2	
Overlap	18	4.7	26	4.9	
Tail	44	11.5	61	11.6	
Grade					
Poorly or undifferentiated (grade III or IV)	156	40.9	201	38.6	0.772
Moderately differentiated (grade II)	188	49.2	270	51.8	
Well differentiated (grade I)	38	9.9	50	9.6	

*, continuous variable. LN, lymph node; PORT, post-operative radiation therapy.

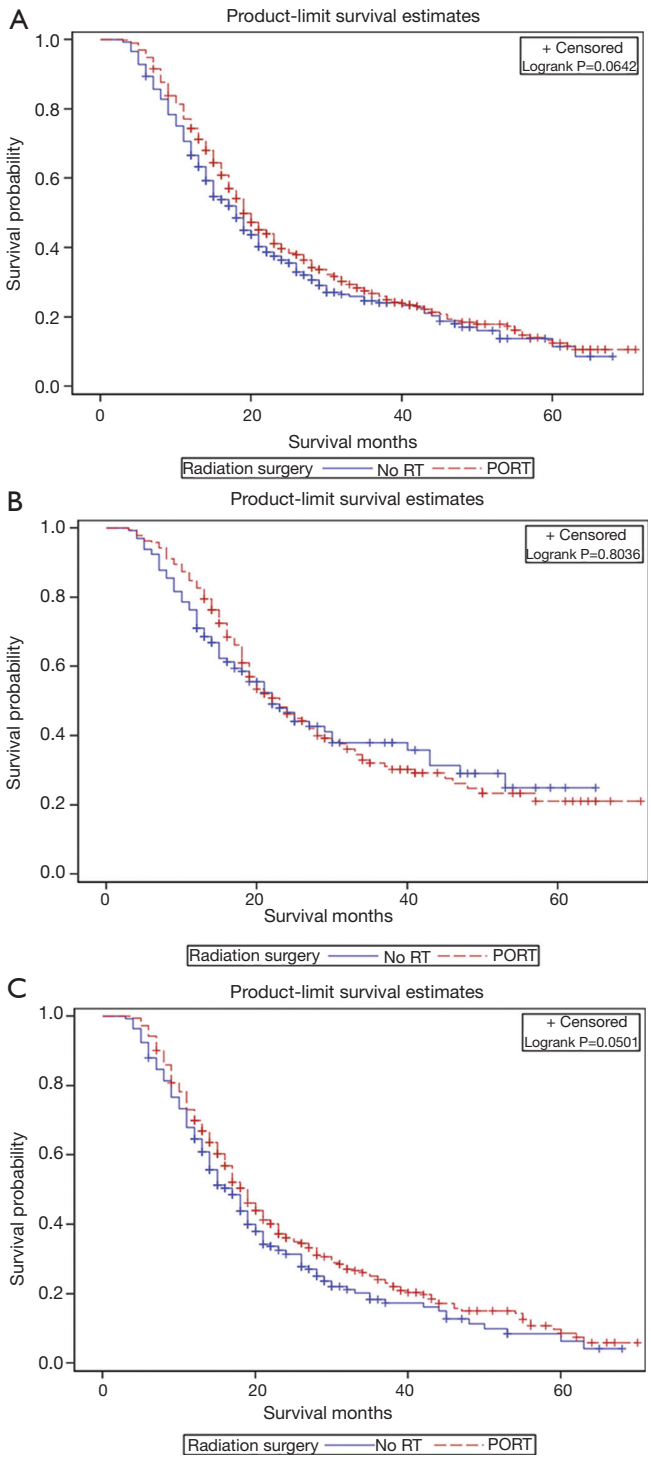

Figure 1 Illustrates the OS curves for all patients and according to nodal status stratified by PORT *vs.* no RT. (A) Kaplan-Meier survival curves of all patients treated with or without PORT; (B) Kaplan-Meier survival curves of N0 patients treated with or without PORT; (C) Kaplan-Meier survival curves of N1 patients treated with or without PORT. Significance was determined by log-rank analysis. OS, overall survival; PORT, post-operative radiation therapy.

Table 2 Hazard ratio for mortality based on LNS

	No. of patients	Hazard ratio	95% CI	P
All patients				
LN removed*	961	0.998	0.989–1.008	0.741
N0 patients				
LN removed*	322	1.005	0.987–1.023	0.588
N1 patients				
LN removed*	639	0.990	0.978–1.001	0.070

*, continuous variable. LN, lymph node.

Table 3 Multivariate analysis of overall survival for all patients

All patients	Hazard ratio	95% CI	P
Age*	1.016	0.996–1.036	0.123
Female (*vs.* male)	0.927	0.786–1.093	0.366
LN removed*	0.991	0.981–1.001	0.084
AJCC N1 (*vs.* N0)	1.397	1.152–1.695	<0.001
PORT (*vs.* no radiation)	0.847	0.717–1.001	0.052
AJCC T-stage (*vs.* T1)			
T2	1.222	0.755–1.977	0.414
T3	1.716	1.111–2.651	0.015
T4	3.664	2.052–6.541	<0.001
Location (*vs.* head)			
Body	1.354	0.968–1.896	0.077
Overlap	0.948	0.641–1.404	0.791
Tail	1.086	0.840–1.404	0.527
Grade (*vs.* well)			
Moderately	1.204	0.901–1.610	0.210
Poor/undifferentiated	1.567	1.165–2.107	0.003

*, continuous variable. CI, confidence interval; LN, lymph node.

and poorly differentiated tumors showed a trend towards increased mortality (P=0.057). Age, gender, and tumor location, were not prognostic in N1 patients.

Discussion

SEER database analyses are usually criticized for the lack of chemotherapy data. However, we were able to obtain data on chemotherapy from SEER. This is the first, largest, and

Table 4 Multivariate analysis of overall survival for N0 patients

N0 patients	Hazard ratio	95% CI	P
Age*	1.016	0.978–1.056	0.413
Female (*vs.* male)	0.837	0.609–1.151	0.275
LN removed*	1.009	0.987–1.031	0.436
PORT (*vs.* no radiation)	0.789	0.567–1.099	0.161
AJCC T-stage (*vs.* T1)			
T2	1.135	0.542–2.380	0.737
T3	2.199	1.128–4.288	0.021
T4	7.975	3.144–20.22	<0.001
Location (*vs.* head)			
Body	1.431	0.812–2.521	0.215
Overlap	0.590	0.295–1.183	0.137
Tail	1.006	0.612–1.655	0.980
Grade (*vs.* well)			
Moderately	1.559	0.912–2.665	0.105
Poor/undifferentiated	2.038	1.183–3.512	0.010

*, continuous variable. CI, confidence interval; LN, lymph node; PORT, post-operative radiation therapy.

Table 5 multivariate analysis of overall survival for N1 patients

N1 patients	Hazard ratio	95% CI	P
Age*	1.016	0.992–1.040	0.196
Female (*vs.* male)	0.980	0.805–1.193	0.841
LN removed*	0.988	0.976–0.999	0.041
PORT (*vs.* no radiation)	0.827	0.678–1.008	0.060
AJCC T-stage (*vs.* T1)			
T2	1.268	0.661–2.434	0.475
T3	1.333	0.739–2.401	0.339
T4	2.346	1.069–5.148	0.034
Location (*vs.* head)			
Body	1.378	0.892–2.129	0.149
Overlap	1.254	0.774–2.032	0.359
Tail	1.194	0.881–1.617	0.252
Grade (*vs.* well)			
Moderately	1.108	0.782–1.569	0.564
Poor/undifferentiated	1.415	0.991–2.021	0.057

*, continuous variable. CI, confidence interval; LN, lymph node; PORT, post-operative radiation therapy.

most modern SEER database analysis on elderly pancreatic cancer patients treated with surgical resection and chemotherapy analyzing the relationship between PORT and LND. We found no statistically significant benefit to the addition of PORT. There was also no difference in OS based on number of lymph nodes removed. MVA for all patients revealed that increasing tumor stage, N1 patients, and higher grade tumors were prognostic for increased mortality. While PORT showed a trend towards decreased mortality, it wasn't statistically significant. In N0 patients, increasing tumor stage and grade were prognostic for increased mortality, while PORT and number of lymph nodes removed showed no significant prognostic importance. In N1 patients, higher tumor stage and grade were prognostic for worse OS, while increasing number of lymph nodes removed was associated with increased OS. While PORT showed a trend to increased OS in N1 patients, it wasn't statistically significant.

There continues to be a controversy on the role of PORT in the adjuvant setting in resected pancreatic cancer patients over all ages. There have been several prospective trials which have shown a benefit to the addition of PORT with chemotherapy; which included the elderly patient population. In GITSG 9173 (n=43), patients were randomized to observation or CRT with 40 Gy split-course and concurrent 5-FU after R0 resection (3). Although this study had poor accrual it was closed early when interim analysis showed improvement in median survival in the trimodality group compared to observation (20 *vs.* 11 months, P=0.035). The EORTC-40891 (n=218) phase III study randomized resected pancreatic cancer or periampullary cancer patients to observation *vs.* 5-FU based chemoradiotherapy similar to the GITSG trial (15,16). There was no difference in survival in pancreatic cancer patients receiving adjuvant chemoradiotherapy. The EORTC-40013/FFCD-9203/GERCOR phase II study randomized pancreatic cancer patients after R0 resection to gemcitabine alone *vs.* gemcitabine followed by CRT (50.4 Gy with weekly gemcitabine) (8). Median OS was 24 months in both groups; however CRT reduced the likelihood of first local recurrence (11% *vs.* 24%) and was well tolerated. The analysis of the ESPAC-1 trial reported that there was no benefit to adjuvant CRT with possible detriment (7). Despite the criticisms of a complicated trial design and poorer outcomes of chemoradiation patients compared to other trials, adjuvant chemotherapy was adopted as the standard of care in Europe.

Lymphadenectomy in pancreatic cancer is also a controversial topic, however several randomized trials have shown no benefit to extended lymphadenectomy compared to standard lymphadenectomy (17). However, a recent report from RTOG 9704 (18) concluded that removing >12 and >15 lymph nodes was associated with increased survival in node positive patients but not node negative patients on univariate and MVA. In RTOG 9704, all patients were treated with adjuvant chemoradiation therapy. In our analysis, only 58% received adjuvant radiation therapy, however, our findings in regards to lymphadenectomy are similar to RTOG 9704, where we find the benefit of lymphadenectomy is restricted to node positive patients.

Surgery has been shown to be well tolerated in the elderly (9-12). However, there have been few studies addressing the tolerability and outcomes of adjuvant chemoradiation. A study from Harvard analyzed 42 pancreatic cancer patients age 75 years and older treated with chemoradiation therapy either as definitive therapy (n=24) in the locally advanced setting or as adjuvant therapy (n=18) (14). Median OS in the patients that received surgery and adjuvant chemoradiotherapy was 20.6 and 8.6 months in the patients treated with definitive chemoradiotherapy. While outcomes were similar to historical controls, there was substantial treatment-related toxicity necessitating a treatment break and hospitalizations. A study conducted at Johns Hopkins Hospital analyzed the outcomes of patients >75 years with pancreatic cancer who underwent pancreaticoduodenectomy (13). They identified 166 patients treated between 1993 and 2005 of which 49 (29.5%) received adjuvant chemoradiotherapy. For elderly patients, N1 disease (P=0.008), poorly differentiated tumors (P=0.012), and undergoing a total pancreatectomy (P=0.010) predicted poor survival. Adjuvant chemoradiotherapy was associated with a 2-year survival benefit compared with surgery alone (49.0% *vs.* 31.6%, P=0.013); however, this benefit was lost at 5 years (11.7% *vs.* 19.8%, respectively, P=0.310). Our analysis of patients age 70 years or older addressing the role of adjuvant radiation in chemotherapy treated patients shows similar results with a median survival of 19 months in radiated patients with no apparent survival benefit on univariate and MVA.

There are several limitations to the use of the SEER retrospective database, most importantly lack of chemotherapy data. Fortunately, chemotherapy data was made available for this analysis after special requests were made. Other information that is missing includes no data on nutritional status and performance status which play an important role in the elderly. However, given that

we restricted our analysis to patients who underwent radical resection (Whipple, distal pancreatectomy, and total pancreatectomy), lived at least 3 months, and all were treated with chemotherapy, we feel that this dataset represents a very healthy population that would be able to tolerate surgery and chemotherapy.

Conclusions

This is the first, largest, and most modern analysis of the SEER database which demonstrates in radically resected pancreatic cancer patients, age ≥70 years, who received chemotherapy, that there is marginal survival benefit for the addition of adjuvant radiation therapy or aggressive lymph node dissection. The survival benefit of LNR is limited to node positive patients on MVA, consistent with data from RTOG 9704.

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None.

Footnote

Conflicts of Interest: Presented at American College of Surgeons Clinical Congress in October 2016, Washington DC.

Ethical Statement: The study was IRB approved at Moffitt Cancer Center (NO. #105286Z). The study was IRB approved for waiver of informed consent.

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