ORIGINAL ARTICLE

The Impact of Adjuvant Radiotherapy on Survival in Patients with Surgically Resected Pancreatic Adenocarcinoma - A SEER Study from 2004 To 2010

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ABSTRACT

Objectives The utility of adjuvant external beam radiation therapy after surgery for pancreatic adenocarcinoma remains controversial. Our aim was to identify subsets of patients who may benefit from adjuvant external beam radiation therapy. **Methods** 6114 patients with pancreatic adenocarcinoma treated with oncologic surgery between 2004 and 2010 were extracted from the SEER database. Demographic and treatment information was obtained for these patients, including whether or not patients received adjuvant external beam radiation therapy. A Cox multivariable analysis was performed to provide an adjusted hazard ratio of dying from pancreatic cancer. **Results** The adjusted hazard ratio of dying from pancreatic cancer favored the adjuvant external beam radiation therapy arm (HRDPC=0.75, 95% CI 0.70-0.79, p<0.0001). Unfortunately, it was not possible to elucidate subsets of patients who may or may not share the benefit of adjuvant external beam radiation therapy based on prognostic factors or treatment approaches. Interestingly, the hazard ratio of dying from pancreatic cancer for the overall population was statistically significantly improved in 2009 and 2010 as compared to 2004. The hazard ratio of dying from pancreatic cancer did not significantly improve in the adjuvant external beam radiation therapy population with time. **Discussion** For the overall population in the SEER database, patients receiving adjuvant EBRT after surgery are at decreased risk of dying from pancreatic cancer.

INTRODUCTION

Survival for patients with pancreatic adenocarcinoma remains poor. Five-year overall survival (OS) for resectable disease treated with surgery only was 5% at the time of the Gastrointestinal Tumor Study Group (GITSG) trial [1]. Since then, several key trials have sought to identify the optimal adjuvant therapy after curative resection of pancreatic cancer.

The GITSG trial was closed early due to poor accrual. Prior to closure, it randomized patients with pancreatic adenocarcinoma resected to negative margins to 40 Gy delivered with 2 Gy daily fractions with a split course (2 week break after the first 20 Gy were delivered) with concurrent 5-FU chemotherapy versus observation alone. Five-year OS was 15% *vs.* 5% and median disease-free survival (DFS) was 11 *vs.* 9 months, both favoring the adjuvant chemoradiotherapy arm [1]. After this trial, adjuvant chemoradiotherapy (CRT) became the standard of care in the United States.

The Radiation Therapy Oncology Group (RTOG) 97-04 sought to identify any role for gemcitabine as part of adjuvant treatment in resected disease. Patients with resected pancreatic adenocarcinoma were randomized to one of two adjuvant arms. Arm 1 consisted of pre- and post-CRT 5-FU, the concurrent segment of treatment being 5-FU based. Arm 2 consisted of pre-and post-CRT gemcitabine with the concurrent segment of treatment being 5-FU based. Radiation was delivered to 50.4 Gy using conventional fractionation without a pre-designed treatment break. Univariate analysis showed no difference in OS. Patients with tumors of the pancreatic head, however, had a 5-yr OS of 22% *vs.* 18% favoring the gemcitabine arm. On multivariable analysis, patients in the gemcitabine arm with pancreatic head tumors had an OS benefit which trended towards statistical significance (p=0.08) [2]. Thus, the location of tumor in pancreatic cancer seemed to have potential influence on outcome.

European trials have offered conflicting results when compared to American work. European Organisation for Research and Treatment of Cancer (EORTC) 40891 attempted to repeat the findings of GITSH. EORTC 40891 randomized resected patients to either adjuvant 5-FU based chemoradiation to 40 Gy using conventional

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fractionation or to observation. No statistically significant benefit was found for adjuvant therapy as measured by 2-yr OS or 5-yr OS [3]. The EORTC reported again with 10-years of follow-up; 10-yr OS was 17% for the adjuvant arm while 10-yr OS was 18% for the observation arm (not a statistically significant difference) [4].

The European Study Group for Pancreatic Cancer Trial 1 (ESPAC-1) further investigated the utility of adjuvant therapy in patients with this disease. Patients with both R0 (negative gross and negative microscopic margins) and R1 (negative gross but positive microscopic margins) were included; this is a criticism of this trial, as the previously described trials included patients with R0 resections only [5]. Patients were randomized in a 2x2 pattern. Following surgery patients were randomized to either 1) observation, 2) adjuvant chemotherapy x6 cycles, 3) adjuvant CRT, or 4) adjuvant CRT followed by outback chemotherapy x6 cycles. Median OS for adjuvant CRT *vs.* no adjuvant CRT was 16 months *vs.* 18 months (NS); 5-yr OS for adjuvant CRT *vs.* no adjuvant CRT was 10% *vs.* 20% favoring the no adjuvant CRT arm (p=0.05). Median OS for adjuvant chemotherapy *vs.* no adjuvant chemotherapy was 20 months *vs.* 15 months favoring the adjuvant chemotherapy arm, and this was statistically significant. Five-yr OS for adjuvant chemotherapy *vs.* no adjuvant chemotherapy was 21% *vs.* 8%, also favoring the adjuvant chemotherapy arm, and this was also statistically significant [6]. This trial suggests a survival detriment from CRT, probably due to treatment-related toxicity. However, criticisms of this trial have been described in the literature. For instance, many patients were treated with a split-course of RT to 40 Gy (20 Gy followed by a 2 week break followed by an additional 20 Gy), although doses of up to 60 Gy were allowed [5]. This of course differs from RTOG 97-04, where patients were treated to 50.4 Gy without a treatment break if possible.

Ghaneh *et al*. performed a meta-analysis of ESPAC-1 and a Japanese trial in order to further determine what are the most appropriate adjuvant treatments for resected pancreatic cancer and in which situations. Their work suggested that adjuvant chemotherapy provided a survival benefit over observation. Adjuvant CRT was not superior to adjuvant chemotherapy alone for the overall populations analyzed. However, adjuvant CRT might provide an advantage over adjuvant chemotherapy alone in R1 resections [7].

A meta-analysis by Stocken *et al*. included five randomized clinical trials of adjuvant treatment for resected pancreatic cancer. On original analysis, they found no benefit to adjuvant chemoradiation. However, on subgroup analysis, they found that chemoradiation was more effective than chemotherapy alone in patients with positive margins [8].

In this setting of conflicting evidence and controversy, the National Comprehensive Cancer Network (NCCN) recommends that either adjuvant CRT or adjuvant chemotherapy alone are appropriate, regardless of resection status.

Thus, the utility of adjuvant external beam radiotherapy (EBRT) in these patients remains controversial. Especially since survival for patients with pancreatic adenocarcinoma remains poor, determining the most appropriate adjuvant therapy is important.

Unanswered questions remain regarding what types of patients benefit from adjuvant EBRT. Are there other factors that might predict who benefits from adjuvant radiotherapy?

We utilized the SEER database to study the role of radiation therapy in disease-specific outcomes in pancreatic adenocarcinoma patients with various presentations of disease who underwent different oncologic surgeries [9]. Our aim was to elucidate subsets of patients who may or may not benefit from adjuvant radiotherapy.

METHODS

The SEER database collects cancer data from seventeen population-based cancer registries, and covers approximately 28% of US population [10]. We used the SEER (2004-2010) database to abstract patient demographics, tumor characteristics, and treatment modality for histologically confirmed pancreatic adenocarcinoma.

A sample size of 6708 patients with pancreatic adenocarcinoma treated with oncologic surgery between 2004 and 2010 were extracted from the SEER database. Additional information was obtained for each patient. This information included year of diagnosis, age (<60 or >=60), race (White, Black, or other), type of surgery (coded by the SEER database as either partial pancreatectomy NOS, local or partial pancreatectomy and duodenectomy, local or partial pancreatectomy and duodenectomy without distal/partial gastrectomy, local or partial pancreatectomy and duodenectomy with partial gastrectomy, total pancreatectomy, total pancreatectomy and subtotal gastrectomy or duodenectomy, extended pancreatoduodenectomy, or finally pancreatectomy NOS), T stage (1-4), N stage (0-2), Grade I-IV or unknown, type of lymph node (LN) dissection and number of nodes dissected (no LNs dissected, sentinel LN biopsy, 1-3 LNs dissected, or finally 4 or more LNs dissected). Also extracted was whether or not patients received adjuvant radiation. Finally, it was extracted at last follow-up if patients were dead from pancreatic cancer or if they were alive or dead from other causes.

STATISTICAL ANALYSIS

Descriptive statistics (including mean, standard deviation, median, range, frequency, and percent) were calculated to characterize the study cohort in relation to demographic, prognostic, and treatment factors of interest. The primary endpoint was cause-specific survival (CSS). CSS was ascertained by selecting pancreatic cancer as the cause of death in the SEER database search. Deaths due to causes other than pancreatic cancer were censored when estimating CSS. CCS was defined as the time from

diagnosis until death from pancreatic cancer (or until date of last follow-up or death from other cause). Kaplan-Meier survival analysis was performed to evaluate CSS and the log-rank test was employed to compare CSS between treatment, demographic, and prognostic factors of interest (i.e., receipt of adjuvant EBRT [primary predictor], age, race, type of surgery, tumor site, stage, grade, year of diagnosis, etc.). Multivariable Cox proportional hazards regression analysis was performed to estimate the independent effect of adjuvant EBRT on CSS, controlling for age, race, type of surgery, tumor site, stage, grade, number of regional lymph nodes removed, and year of diagnosis. Kaplan-Meier analysis and multivariable cox regression were also performed among the subset of patients receiving adjuvant EBRT, to identify demographic and prognostics predictor of CSS in patients treated with adjuvant EBRT. Collinearity between predictors in the multivariable models was evaluated prior to the formation of the final multivariable models. Hazard ratios reflect the increased (or decreased) risk of pancreatic-specific death. All p-values are two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals (95% CI) for all hazard ratios were calculated to assess the precision of the obtained estimates. All analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC) and Stata Version 13.0 (StataCorp, College Station, TX).

RESULTS

Of the 6708 patients extracted from the SEER database, 2500 (37.2%) received adjuvant EBRT, while 4208 (62.7%) did not receive adjuvant EBRT. **Table 1** lists the demographic, tumor characteristics, and clinical characteristics for the overall study population, and then separately for the irradiated and non-irradiated patients. Approximately one-third of the study population was under the age of 60, while approximately two-thirds of the study population was age 60 or older. The most common race of the study population was white at 82.1%; 10.5% of the study population was black, while 7.4% of the study population was categorized as other. The different surgeries coded in SEER for the study population, from most to least common, were local or partial pancreatectomy with partial gastrectomy (53.83%), local pancreatectomy (13.2%), local or partial pancreatectomy without distal/partial gastrectomy (9.7%), total pancreatectomy and subtotal gastrectomy and duodenectomy (9.1%), local or partial pancreatectomy (5.5%), extended pancreatoduodenecomy (4.7%), total pancreactectomy (3.3%), and pancreactectomy NOS (0.8%). Most of the tumors were located in the head of the pancreas (79.9%), while 13.5% were located in the tail and 6.6% were located in the body. T-stages identified in the study population included T1 (6.6%), T2 (17.3%), T3 (71.0%), or T4 (5.1%). N-stages identified in the study population included N0 (35.8%) and N1 (64.2%). Disease grade varied in the study population; Grade I disease was found in 12.8% of the study population, while Grade II was found in 44.7%, Grade III in 32.2%, and Grade IV in 1.5%. In 8.9% of the study population, disease grade was unknown or not specified in the SEER database. The type of lymph node (LN) evaluation and the number of lymph nodes removed varied in the study population. In 89.8% of the study population, 4 or more LNs were removed; in 9.7%, 1-3 LNs were removed; in 0.3%, a sentinel LN biopsy was performed; in 0.2%, no LNs were removed. The absolute number of patients with pancreatic cancer increased with each year in the SEER database, with 11.2% of the study population being entered in 2004, 13.0% in 2005, 13.0% in 2006, 13.5% in 2007, 16.0% in 2008, 16.4% in 2009, and 16.9% in 2010. At last follow-up, 36.6% of the study population was either alive or dead from causes other than pancreatic cancer, while 63.5% of the study population was dead from pancreatic cancer.

A multivariable analysis was performed on the overall study population and on the portion of the study population that received adjuvant EBRT to determine prognostic factors for dying of pancreatic cancer. Patients for whom grade was not available were excluded from this portion of the analysis. Therefore, a total of 6114 patients were analyzed in the overall population, and 2309 patients were analyzed in the irradiated group. In the overall population, higher age, T stage, N stage, and grade were all independently found to significantly increase the hazard ratio of dying from pancreatic cancer (HRDPC). Race, type of surgery performed, location of the tumor, and extent of lymph node dissection did not significantly impact the HRDPC in this overall population. In the population receiving adjuvant EBRT, higher age, T stage, N stage, and grade were found to significantly increase the HRDPC. Race, type of surgery performed, location of the tumor, and extent of lymph node dissection did not significantly impact the HRDPC in the population receiving adjuvant EBRT.

Most importantly for this analysis, the adjusted hazard ratio of dying from pancreatic cancer favored the adjuvant EBRT arm (HRDPC=0.75, 95% CI 0.70-0.79, p<0.0001).

Interestingly, the HRDPC for the overall population was statistically significantly improved in 2009 and 2010 as compared to 2004, with p=0.005 and p=0.0005, respectively. The HRDPC did not significantly improve in the adjuvant EBRT population with time.

Kaplan-Meier Cause-Specific Survival Curves were generated and median Cause-Specific Survival (CSS) times were calculated **(Figure 1)**. Median CSS was 22.0 months in the irradiated group, with a 95% confidence interval of 21.0-24.0 months. Median CSS was 20.0 months in the non-irradiated group, with a 95% confidence interval of 19.0-21.0 months. P=0.003 by log-rank test between the two groups.

DISCUSSION

In the SEER database, patients receiving adjuvant EBRT after oncologic surgery are at decreased risk of dying from pancreatic cancer. Unfortunately, it was not possible to elucidate subsets of patients who may or may not share this benefit with the overall group based on prognostic factors or treatment approaches.

Table 1. Demographic, tumor characteristics, and clinical characteristics of the study population.

	Overall		Irradiated Patients		Non-Irradiated Patients	
Total	**6708**		**2500**		**4208**	
	number	**%**	**number**	**%**	**number**	**%**
Age						
<60	2170	32.35	902	36.08	1268	30.13
>=60	4538	67.65	1598	63.92	2940	69.87
Race						
White	5510	82.14	2068	82.72	3442	81.8
Black	705	10.51	268	10.72	437	10.38
Other	493	7.35	164	6.56	329	7.82
Surgery						
Local pancreatectomy NOS	888	13.24	253	10.12	635	15.09
Local or partial pancreatectomy	367	5.47	118	4.72	249	5.92
Local or partial pancreatectomy without distal/ partial gastrectomy	651	9.7	223	8.92	428	10.17
Local or partial pancreatectomy with partial gastrectomy	3611	53.83	1480	59.2	2131	50.64
Total pancreactectomy	218	3.25	63	2.52	155	3.68
Total pancreactectomy and subtotal gastrectomy and duodenectomy	609	9.08	231	9.24	378	8.98
Extended pancreatoduodenectomy	312	4.65	118	4.72	194	4.61
Pancreatectomy NOS	52	0.78	14	0.56	38	0.9
Tumor Site						
head	5358	79.87	2106	84.24	3252	77.28
body	445	6.63	153	6.12	292	6.94
tail	905	13.49	241	9.64	664	15.78
T Stage						
1	444	6.62	102	4.08	342	8.13
2	1157	17.25	369	14.76	788	18.73
3	4765	71.03	1875	75	2890	68.68
4	342	5.1	154	6.16	188	4.47
N Stage						
N0	2403	35.82	794	31.76	1609	38.24
N1	4305	64.18	1706	68.24	2599	61.76
Grade						
I	858	12.79	234	9.36	624	14.83
II	2999	44.71	1218	48.72	1781	42.32
III	2157	32.16	825	33	1332	31.65
IV	100	1.49	32	1.28	68	1.62
Unknown/Not Specified	594	8.86	191	7.64	403	9.58
Pancreatic Regional Lymph Nodes (LNs) Removed						
None	14	0.21	3	0.12	11	0.26
Sentinel LN	20	0.3	7	0.28	13	0.31
1-3 LNS	651	9.7	213	8.52	438	10.41
4 or more LNs	6023	89.79	2277	91.08	3746	89.02
Year of Diagnosis						
2004	748	11.15	333	13.32	415	9.86
2005	869	12.95	358	14.32	511	12.14
2006	875	13.04	333	13.32	542	12.88
2007	905	13.49	348	13.92	557	13.24
2008	1075	16.03	387	15.48	688	16.35
2009	1101	16.41	379	15.16	722	17.16
2010	1135	16.92	362	14.48	773	18.37
Cause of Death						
alive or dead from other causes	2452	36.55	832	33.28	1620	38.5
pancreatic cancer deaths	4256	63.45	1668	66.72	2588	61.5

Baine and Lin conducted a retrospective review of patients treated at their institution and of national data from the SEER database. Five hundred sixty-one patients from their own institution were included, as were 60,587 patients from the SEER database. They analyzed patients diagnosed with pancreatic adenocarcinoma over a period of 16 years from 1995 and 2011. They adjusted for age, race, gender, stage, year of diagnosis, having surgery, and having chemotherapy (in the

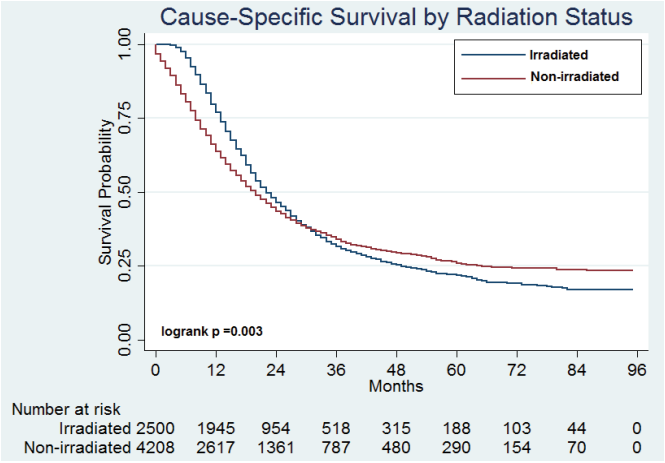

Figure 1. Kaplan-Meier Cause-Specific Survival Curves. Median Survival 22.0 months in irradiation group, 95% Confidence Interval 21.0-24.0 months. Median Survival 20.0 months in the non-irradiated group, 95% Confidence Interval 19.0-21.0 months. P=0.003 by log-rank test.

institutional data only, as SEER did not contain relevant data on chemotherapy). On Cox analysis, they found that receiving EBRT was an independent prognostic factor for an improved hazard ratio of dying from pancreatic cancer (HR=0.65, p<0.0001) [11].

Sugawara and Kunieda analyzed 2,532 patients from the SEER database treated with surgery plus/minus adjuvant radiotherapy from 2004 to 2009. They also found a survival advantage in the radiotherapy group. Overall survival (OS) was 20 months *vs.* 16 months in the adjuvant radiotherapy and observation groups, respectively (p<0.0001). Disease-specific survival was 22 months *vs.* 18 months in the adjuvant radiotherapy and observation arms, respectively (p<0.0001) [12].

Opfermann *et al*. analyzed 3,314 patients from the SEER database treated with surgery plus/minus adjuvant radiotherapy from 1998 to 2006. They also found a survival advantage in the radiotherapy group. OS was 19 months *vs.* 14 months favoring the radiotherapy arm (p<0.001) [13].

Our analysis adds to this previous work in suggesting that the type of surgery performed and the location of the tumor do not influence the benefit of adjuvant radiation. Alternatively, the relatively short lifespan of these patients could mean that survival differences potentially attributable to the type of surgery performed and the location of the tumor do not appear within the available follow-up period even in our relatively large sample size of irradiated patients.

Interestingly, the HRDPC decreased in 2009 and 2010 as compared to 2004 for the overall population – this is worthy of further investigation. It may be due to an improvement in efficacy of the systemic agents utilized over the intervening years. If that is the case, these presumably matched agents did not make the same impact in the irradiated population. Unfortunately, SEER does not give us more information as to which systemic agents were used in these patients. RTOG 9704 was published in 2008. It was one of the important trials investigating the utility of gemcitabine as part of adjuvant treatment for pancreatic cancer. Perhaps gemcitabine was used more often after the publication of this trial, and could thus explain why patients in 2009 and 2010 did better in our analysis. However, this would still not explain why this advantage was seen in the overall population but not in the radiotherapy group.

It is important to note some important disadvantages of using the SEER database. This database does not report chemotherapy data and does not report the dose or duration of radiotherapy. In addition, margin status was not available in the SEER database for this group of patients. However, previous meta-analyses conducted have suggested that the benefit of adjuvant radiotherapy may be limited to patients with positive margins, so perhaps these patients were more likely to have gotten this adjuvant treatment in the SEER database, and thus would be over represented in the irradiation arm [7, 8]. Therefore, using databases which do include more information on chemotherapy, radiotherapy, and margin status would be useful in investigating the effects of these factors on survival in pancreatic cancer patients. Data from randomized clinical trials would be even better at investigating the impact of various treatment approaches.

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Conflict of Interest

The authors have no other conflicts of interest to report.

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