Distribution Agreement

In presenting this Thesis as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my Thesis in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this Thesis. I retain all ownership rights to the copyright of the Thesis. I also retain the right to use in future works (such as articles or books) all or part of this Thesis.

_____

Signature of Student Date

Survival outcomes in patients with early stage, resectable pancreatic cancer – a comparison of gemcitabine and 5-fluorouracil based treatment regimens.

BY

Sani Haider Kizilbash
M.P.H., Emory University, 2011
M.B.B.S., Aga Khan University, 2003

Joseph Lipscomb, PhD	(Committee Chair)	Date
Kevin Ward, PhD	(Field Advisor)	Date
Melissa Alperin, MPH, CHES Chair, Career MPH Program		Date

Survival outcomes in patients with early stage, resectable pancreatic cancer – a comparison of gemcitabine and 5-fluorouracil based treatment regimens.

BY

Sani Haider Kizilbash
M.P.H., Emory University, 2011
M.B.B.S., Aga Khan University, 2003

Thesis Committee Chair: Joseph Lipscomb, PhD

An abstract of
A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
In partial fulfillment of the requirements of the degree of
Master of Public Health in the Career MPH Program
2011

Abstract

Survival outcomes in patients with
early stage, resectable pancreatic cancer –
a comparison of gemcitabine and
5-fluorouracil based treatment regimens.

BY
Sani Haider Kizilbash

PURPOSE: Pancreatic cancer is the fourth leading cause of cancer mortality. Beyond curative surgery, the optimal treatment for early stage pancreatic cancer is still a matter of debate.
METHODS: We conducted a population based, retrospective cohort study using SEER-Medicare data to evaluate survival outcomes of patients with early stage pancreatic cancer. Patients diagnosed between the years 1998 and 2005 who had received curative surgery followed by adjuvant chemotherapy with either 5-fluorouracil or gemcitabine were examined. These groups were further divided based on the use of radiotherapy. Survival analyses and Cox proportional hazards modeling were conducted.
RESULTS: - 705 patients were studied of which 359 received 5-fluorouracil and 346 received gemcitabine. When compared to chemoradiation with 5-fluorouracil, survival outcomes for patients who received chemoradiation with gemcitabine did not differ (hazard ratio (HR) = 0.979 for high grade tumors (HGT), HR = 1.043 for low grade tumors (LGT)). Patients who received gemcitabine alone had worse survival (HR = 1.499 for HGT, 1.320 for LGT). However, survival outcomes of patients who received 5-fluorouracil alone varied with tumor grade. In low grade tumors, patients have increased survival with 5-fluorouracil when compared with chemoradiation with 5-fluorouracil (HR = 0.427). In high grade tumors, patient survival was worse (HR 2.099).
CONCLUSION: - Among patients who received chemoradiation, there was no difference in survival outcomes between patients receiving either 5-fluorouracil or gemcitabine. Patients with low grade resectable pancreatic cancer may have better outcomes with 5-fluorouracil based chemotherapy without radiation. Future clinical trials may need to be stratified or randomized based on tumor grade to resolve the debate on the role of chemoradiotherapy in resectable pancreatic cancer.

Survival outcomes in patients with early stage, resectable pancreatic cancer – a comparison of gemcitabine and 5-fluorouracil based treatment regimens.

BY

Sani Haider Kizilbash
M.P.H., Emory University, 2011
M.B.B.S., Aga Khan University, 2003

Thesis Committee Chair: Joseph Lipscomb, PhD

A Thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
In partial fulfillment of the requirements of the degree of
Master of Public Health in the Career MPH Program
2011

ACKNOWLEDGEMENTS

This thesis would not have been possible if it were not for my committee members,
Joseph Lipscomb and Kevin Ward.
For all the time that they took out of their busy schedules to mentor me and help me grow,
For all their attention to detail to help develop my work into a thesis,
For all the interest that they took in my small contribution to science,
Thank you for everything.

I also greatly appreciate the efforts of
The Applied Research Program, NCI;
The Office of Research, Development and Information, CMS;
Information Management Services (IMS), Inc.;
And the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries
In the creation of the SEER-Medicare database.
Without having a resource as well-structured as this,
I would never have been able to conduct a study of this nature on this scale.

Thank you Walter Burnett and Kevin Sullivan
For nudging me when I most needed direction.
Without your support,
I may still have been looking for a mentor and a project!

Thanks is also due to
Ishmael Jaiyesimi and Laura Nadeau,
My consultant oncologists,
Who always made sure they were available
At a moment's notice
To answer my questions.

And to
Paul Weiss and Judy Boura
Who helped me tame SAS
Whenever it became unruly.

My parents,
For everything that they have sacrificed to make me what I am today.

Finally,
My loving wife, Sarah and my precious son, Zain
After all, all the time that I spent on this thesis
Was time that I would have spent with them.
Without their love, encouragement and understanding,
I simply wouldn't have been able to come this far.

Survival outcomes in patients with early stage, resectable pancreatic cancer – a comparison of gemcitabine and 5-fluorouracil based treatment regimens.

Sani Haider Kizilbash [§¶], Kevin Ward [¶], Ishmael Jaiyesimi [§], Laura Nadeau [§], Joseph Lipscomb [¶].

From [§] William Beaumont Hospital (Royal Oak, MI) and [¶] Rollin's School of Public Health, Emory University (Atlanta, GA)

Research Support: This study was conducted with support from the Metropolitan Atlanta SEER Registry under NCI contract N01-PC-35135 with Emory University.

Corresponding Author: Sani Haider Kizilbash, MD. William Beaumont Hospital, 3601 W 13 Mile Rd, Royal Oak, MI 48073. Email: skizilbash@beaumont.edu.

Disclaimers: None

Contents:

Abstract:

PURPOSE: Pancreatic cancer is the fourth leading cause of cancer mortality. Beyond curative surgery, the optimal treatment for early stage pancreatic cancer is still a matter of debate.

METHODS: We conducted a population based, retrospective cohort study using SEER-Medicare data to evaluate survival outcomes of patients with early stage pancreatic cancer. Patients diagnosed between the years 1998 and 2005 who had received curative surgery followed by adjuvant chemotherapy with either 5-fluorouracil or gemcitabine were examined. These groups were further divided based on the use of radiotherapy. Survival analyses and Cox proportional hazards modeling were conducted.

RESULTS: - 705 patients were studied of which 359 received 5-fluorouracil and 346 received gemcitabine. When compared to chemoradiation with 5-fluorouracil, survival outcomes for patients who received chemoradiation with gemcitabine did not differ (hazard ratio (HR) = 0.979 for high grade tumors (HGT), HR = 1.043 for low grade tumors (LGT)). Patients who received gemcitabine alone had worse survival (HR = 1.499 for HGT, 1.320 for LGT). However, survival outcomes of patients who received 5-fluorouracil alone varied with tumor grade. In low grade tumors, patients have increased survival with 5-fluorouracil when compared with chemoradiation with 5-fluorouracil (HR = 0.427). In high grade tumors, patient survival was worse (HR 2.099).

CONCLUSION: - Among patients who received chemoradiation, there was no difference in survival outcomes between patients receiving either 5-fluorouracil or gemcitabine. Patients with low grade resectable pancreatic cancer may have better outcomes with 5-fluorouracil based chemotherapy without radiation. Future clinical trials may need to be stratified or randomized

based on tumor grade to resolve the debate on the role of chemoradiotherapy in resectable pancreatic cancer.

Background:

Despite decades of effort, pancreatic cancer still carries a very poor prognosis. Annually, 42,470 individuals are diagnosed with pancreatic cancer in the USA and 35,420 individuals die from this disease making it the fourth leading cause of cancer mortality [1]. Beyond the well-established need for surgical resection, optimal management with chemotherapy and radiation for patients with resectable pancreatic cancer remains controversial. Individually, both 5-fluorouracil [2] and gemcitabine [3] have clearly been shown to increase survival when compared to observation alone. Recently, the ESPAC-3 trial randomized patients with resected pancreatic cancer to receive either 5-fluorouracil/folinic acid or gemcitabine [4]. This was the largest adjuvant trial for pancreatic cancer to date and it showed no significant difference in survival between the regimens. Although chemotherapy has been shown to have beneficial outcomes, the use of radiotherapy in resectable pancreatic cancer is debatable. Initially the GITSG study [5] demonstrated improved survival outcomes in patients who received chemoradiotherapy followed by maintenance chemotherapy versus patients who received no adjuvant treatment. This was followed by the EORTC trial [6] which involved a larger number of patients. This trial found no statistically significant difference between chemoradiation and observation alone, although a trend towards the benefits of chemoradiation was noted. Later, the ESPAC 1 trial [7] revealed that patients who received chemoradiotherapy have a significantly poorer outcome than patients

who did not receive chemoradiotherapy. Consequently, clinical practice varies from country to country depending on the trial that is given most importance [8].

Although the use of gemcitabine and 5-fluorouracil, with and without radiotherapy, in pancreatic cancer has been compared in clinical trial settings, we are not aware of any non-experimental population based comparisons between the two regimens. Hence, we conducted a population-based retrospective cohort study using the SEER-Medicare database to compare survival outcomes between adjuvant regimens based on either gemcitabine or 5-fluorouracil in patients with resectable pancreatic cancer.

Methodology:

SEER-Medicare is a linked database that combines data from two large population based sources [9]. The Surveillance, Epidemiology and End Results (SEER) Program collects information on all patients diagnosed with cancer within 18 geographically defined areas in the USA [10]. Altogether, the SEER Program covers approximately 28% of the US population. Information collected includes patient demographics, tumor characteristics, stage, first course treatment and follow-up. On the other hand, Medicare is a federal health insurance program for the elderly, some disabled individuals and those with end-stage renal disease. Medicare claims data account for all services provided by Medicare from a person's program eligibility to their death. The claims data are divided into multiple files of which three were used for data acquisition. The Medicare Provider Analysis and Review (MEDPAR) file includes all Part A short stay, long stay and skilled nursing facility bills. The Carrier Claims (or National Claims History (NCH)) file includes all Part B non-institutional provider claims (e.g. physicians, nurse practitioners,

ambulance providers, etc.). The Outpatient file includes claims from institutional outpatient providers (e.g. hospital outpatient departments, rural health clinics, etc.)

All patients who were older than 65 years of age and enrolled in fee for service Medicare for the study period of interest were eligible for inclusion. Patients with pathologically confirmed pancreatic adenocarcinoma diagnosed between 1/1/1998 to 12/31/2005 who received curative surgery were identified. Of this group, patients who received adjuvant chemotherapy with either gemcitabine or 5-fluorouracil were isolated for evaluation. Patients who received an unknown form of chemotherapy were also initially included for the purpose of comparison with the gemcitabine and 5-fluorouracil groups and to establish a measure of the degree to which bias might exist in the data. In turn, these groups were further divided into patients who received adjuvant radiotherapy and those who didn't. With regards to timeframe, curative surgery must have been performed within six months after diagnosis and acceptable adjuvant regimens must have been initiated within six months after surgery.

Table 1 details the codes used to identify the patients' surgical procedures, chemotherapy agents and radiotherapy regimens. A full discourse on treatment identification and consequent inclusion/exclusion is described in the appendix.

As information is being extrapolated from claims data without the benefit of actual clinician documentation, it is difficult to account for the great variability in actual treatment regimens that patients may have received. Furthermore, it is almost impossible to determine the clinical rationale behind any adjustments in the chemotherapy regimen (e.g. patient intolerance, failure of treatment, patient preference, etc). While one could certainly utilize claims data to explore regimen modification and completion, this would be a complex process and would require a

number of assumptions to be made. Hence, patients were categorized based on the chemotherapy and radiotherapy that the patients started, regardless of whether the initial regimen was modified or completed.

The study period for each patient ranged from one year prior patient cancer diagnosis up to either death or a maximum of five years after diagnosis. Information for the year prior to cancer diagnosis was necessary to calculate the patient's comorbidity [11, 12]. Furthermore, the five-year period was considered sufficient to follow the time course of the pancreatic cancer. Of note, claims data was only available up to 2008. So, surviving patients who were diagnosed after the year 2003 were censored prior to the completion of a five-year follow-up.

Patients were excluded if any of the following applied: (a) metastatic disease at diagnosis (surgery would be non-curative), (b) stage III disease or evidence of major blood vessel involvement (surgery would be non-curative), (c) unstaged disease, (d) Medicare entitlement due to end- stage renal disease or a disability, (e) diagnosis from death certificate or autopsy, (f) diagnosis from non-microscopic, clinical only or unknown methods, (g) pancreatic cancer involving the islets of Langerhans, (h) unavailable month of diagnosis, (i) HMO enrollment at any point during the study period, (j) lack of either continuous Medicare Part A or B enrollment during the study period, (k) death within 30 days after surgery (to eliminate the effects of post-operative mortality), (l) discrepancy in date of death between the SEER and the Medicare databases, (m) receipt of neoadjuvant chemotherapy or radiation therapy or (n) possibility of simultaneous use of gemcitabine and 5-fluorouracil as part of the same regimen.

The stage of the tumor was determined for each patient using the specific size and extent of the tumor along with lymph node status according to current American Joint Committee on Cancer (AJCC) staging guidelines[13].

ICD-9 diagnosis codes for comorbidities that were evident in claims data ranging from 12 months prior to diagnosis to 1 month prior to diagnosis were used to calculate the Charlson comorbidity index [11, 12] for each patient. This index helps account for the severity of the patients' non-cancer illnesses. Both MEDPAR and NCH data were used to determine the index [14].

Socioeconomic status (SES) was extrapolated from the degree of poverty that existed within the census tract where the patient resided. The SEER variable for the percentage of the census tract population living below the poverty level was used to define this area based measure of SES. If the percentage of this variable was greater than 20%, the patient was considered to reside in an area of lower socioeconomic status. Census tracts with greater than 20 percent of the population living below the poverty level are defined as 'poverty areas' according to federal guidelines[15].

Other variables that were accounted for included the age of diagnosis, sex, race, metro residence, cancer sequence, year of diagnosis, tumor site, tumor grade and the type of surgery conducted.

This study was approved by the Emory University Institutional Review Board.

Statistical methods:

Initial analyses revealed that significant interaction existed between the chemotherapy regimen and the use of radiotherapy. Hence, four groups were created to account for the various

combinations of the two drug regimens (5-fluorouracil and gemcitabine) with and without radiation. These four groups were compared with regards to demographic and clinical variables to assess whether there were statistically significant differences in the baseline characteristics of the groups. Categorical variables were presented as counts and frequencies and were examined by Pearson's chi-square testing. Both univariate and multivariable analyses were then conducted to examine associations between variables and to determine significant confounders and interactions.

In order to compare survival between the treatment regimens, Kaplan-Meier plots were constructed and multivariable survival analyses was conducted by Cox proportional hazards modeling. The fit of the proportional hazards model was tested and satisfied.

All analyses were conducted using SAS statistical software v. 9.2 (SAS Institute Inc., Cary, NC).

Results:

The initial study sample consisted of 901 patients with pathologically confirmed pancreatic adenocarcinoma who received curative surgery and underwent adjuvant chemotherapy with the study regimens. Of these patients, 189 patients were excluded (169 patients due to Medicare enrollment criteria, 1 due to date of death discrepancy between SEER and Medicare data, 15 due to insufficient claims data to calculate the Charlson comorbidity index, 1 due to absence of evidence of pancreatic cancer in the claims data, 3 due to receipt of neoadjuvant radiation).

Of the remaining 712 patients, 359 received 5-fluorouracil and 346 received gemcitabine. Only 7 patients received an unknown form of chemotherapy. As these only comprised 1% of the study

sample, it was felt that this group would neither have any significant impact on the other groups nor would it lead to any substantial bias. Hence, this group was not analyzed any further.

Study variables were categorized based on meaningful groups. A comparison of the groups is presented in table 2.

Overall Survival:

The median overall survival for the entire sample was 17.0 months. The one and five year survival for the entire sample were 64.7% and 11.0% respectively. A total of 601 patients died during the study period. Kaplan-Meier analyses revealed that the median follow up in the surviving patients was 49 months (range 24 – 60 months). Unadjusted 1-, 3- and 5-year-survival among the four treatment groups and the entire sample are described in table 3.

Univariate analysis:

In the univariate analyses, the most significant predictor of survival was the treatment regimen itself (table 4). Other significant predictors included socioeconomic status, Charlson comorbidity index, age at diagnosis, tumor grade, and stage. Despite not being significant at conventional levels, race, gender and tumor site were included into the multivariable analyses based on a priori decisions.

Initially, stage data had been categorized into stage I, stage IIa and stage IIb tumors. However, categorization of the variable in this manner violated the proportional hazards assumption. For

the purpose of multivariable analysis, stage data was collapsed to coordinate with lymph node involvement (Stage IIb vs. Stage Ia/Ib/IIa).

Multivariable analysis:

All above-mentioned variables were included in the multivariable analyses. To conduct Cox proportional hazards modeling, interaction variables were created between each variable and the treatment regimen. Due to the presence of interaction between treatment regimen and tumor grade, analyses between regimens were further stratified by grade (table 5).

Discussion:

With the univariate analyses alone, 5-fluorouracil based chemoradiation and gemcitabine based chemoradiation seem to be statistically similar in terms of outcomes. When compared to 5-fluorouracil based chemoradiation, gemcitabine without the use of radiation had a significantly poorer outcome while 5-fluorouracil alone was not significantly different. However, multivariate analyses demonstrate that the relationship between chemoradiotherapy and chemotherapy alone actually varies significantly with the grade of the tumor.

Among patients with high grade tumors, when 5-fluorouracil with radiation is compared to patients who received gemcitabine alone, the latter group has a significantly poorer survival (hazard ratio 1.499). A trend towards significance was also demonstrated for patients who received 5-fluorouracil alone (hazard ratio 2.099). Statistical significance was probably not achieved due to the low number of patients in the 5-fluorouracil alone group.

On the other hand, in patients with low-grade tumors who received chemotherapy alone, the effects of gemcitabine and 5-fluorouracil were quite different. When compared to patients who received 5-fluorouracil based chemoradiation, patients who received gemcitabine alone seemed to have a trend towards a poorer outcome (hazard ratio 1.320). However patients who received 5-fluorouracil alone seemed to have a much better prognosis (hazard ratio 0.427). One may wonder whether the results may have been accidental due to the low number of patients who received this particular regimen. Furthermore, it is possible that some selection bias may have existed in that patients with a more aggressive disease process may have been more likely to receive concurrent radiation therapy. However, those caveats being made, this difference is highly statistically significant despite the small number of patients who actually received this regimen ($p = 0.0102$). Unadjusted survivals in this group demonstrate this relationship too (median survival 22 months vs. 19 months).

The ESPAC 1 trial [7] indicated that the median overall survival is reduced by the use of 5-fluorouracil based chemoradiation (15.9 months) over 5-fluorouracil (21.6 months) alone (Table 7). For the 5-fluorouracil group here, the median survival corresponds to the survival noted in the ESPAC 3 trial (23.0 months) [4]. Similarly, the median overall survival in the 5-fluorouracil based chemoradiation group is lower than the median overall survival of comparable groups in other studies (EORTC = 17.1 months [6], RTOG 16.9 months [16]).

Hence, on first glance it seems that patients who receive 5-fluorouracil alone have improved survival over those who receive 5-fluorouracil based chemoradiation. However, a more detailed examination of these studies reveals that all of them involved an approximate 3:1 ratio of low grade to high grade tumors. With the results of our study's multivariable analysis in mind, this may account for the above-described improved survival. That is, one could speculate that 5-

fluorouracil would be expected to perform better than 5-fluorouracil based chemoradiation as low-grade tumors dominated these groups.

One cannot make a direct comparison to the ESPAC 1 trial's chemoradiotherapy vs. no chemoradiotherapy arms, as the control group is a mixture of patients receiving chemotherapy alone and no adjuvant therapy. However, with that in mind, the multivariate analyses in the ESPAC 1 trial also demonstrate findings that are consistent with our results. Although not statistically significant, the Forrest plots reveal that chemoradiotherapy seems to favor tumors that are poorly differentiated while 'no chemoradiotherapy' tends to favor tumors that are well- or moderately-well differentiated [7].

Limitations:

A number of issues limit the findings of this study.

First, the study was designed as a quasi-experimental population-based retrospective cohort study. This design was chosen as it is fairly simple to implement and it adequately permits an assessment of survival outcomes between various treatment regimens. Certainly, the optimal design to compare the outcomes of treatment regimens among newly diagnosed patients is the randomized controlled trial. This would ensure comparable baseline variables between groups along with similar sample sizes. However, as experience with prior trials has demonstrated, patient accrual for studies on early-stage pancreatic cancer is very slow. This has led to early study termination [5] and underpowered studies [6]. In order to readily assess the outcomes of various treatment regimens in large numbers of patients, a population-based observational study

is far more feasible. As data was readily available, this allowed procurement at a low cost and analysis with limited manpower in a short timeframe.

Next, as this study deals with the Medicare population, the median age (72 years) is higher than in other studies (59 – 63 years) [3, 4, 6, 7, 16, 17]. This by itself may have led to a worsened survival, especially in patients with low grade tumors. Furthermore, this limits extrapolation to younger populations.

As claims data are not collected for the purpose of research, data are not always complete and extrapolations need to be made on occasion. Many potentially significant prognostic factors cannot be accounted for such as resection status, performance status, etc. Otherwise, the claims data does not always report accurately or clearly the diagnosis for which adjuvant therapy was administered. A general assumption was made that if these treatments were administered after a diagnosis of pancreatic cancer and within six months of curative pancreatic surgery, the treatments were likely related to the pancreatic cancer. However, if discrepancies were noted between the data in the SEER registry and the Medicare claims, the claims data was rigorously examined by manual assessment. As another example, for patients who lacked claims data on their pancreatic surgery, the date of surgery was assumed to be the date of the first course of therapy per the SEER registry (as specific dates for surgery are not available in the SEER data). However, because the latter date could also correspond to neoadjuvant chemotherapy or radiation, patients were excluded if evidence of neoadjuvant treatment was found.

Furthermore, SEER data does not document exact dates for events such as diagnosis or first course of therapy. Rather information is only presented in terms of the month and year. As a general rule, all dates extracted from SEER data were assumed to be the 15^{th} of that month for consistency. On the other hand, claims data would frequently present a range of possible dates

for a therapy. In these cases, the midpoint of this range was assumed to be the date of therapy. These assumptions can certainly lead to imprecision in determining whether treatments were truly adjuvant, etc. Data was manually assessed in such circumstances to try to determine the likely course of events.

Another point to note is that strategies for treatment have changed over time. For example, the definition of a complete resection has been adjusted to include a negative retroperitoneal margin. Split course radiotherapy is no longer used. Furthermore, chemotherapy and radiotherapy doses and regimens have also evolved over time. None of these have been accounted for in this study.

With that in mind, the study also doesn't account for the multitude of different drug combinations, chemotherapy cycles and radiotherapy regimens that may have been adopted within each of these groups. For example, patients in the category of '5-fluorouracil with radiation' may have received 5-fluorouracil based chemoradiotherapy followed by gemcitabine, 5-fluorouracil or no maintenance chemotherapy at all.

Finally, the particular chemotherapy and radiotherapy regimen selected for a particular patient is expected to be based on a complex clinical scenario which cannot be adequately assessed by databases of this nature. By studying the treatment groups as random variables, selection bias is inevitably introduced. Beyond this, the retrospective nature of the data may lead to a variety of other biases. For example, Medicare claims data identified 72 patients who had received adjuvant radiotherapy, yet the SEER registry showed that no radiotherapy had been administered. It certainly remains possible that patients had received chemotherapy alone as their initial modality of treatment and were switched to radiation or chemoradiation within 6 months

after surgery due to a change in patient status. Such discrepancies would be difficult to examine without a detailed manual examination of the data.

Conclusions:

Given the abovementioned tumor grade based difference in survival for patients receiving 5-fluorouracil, it would be interesting to see clinical trials which stratify, or even randomize, based on tumor grade to account for possible differences in outcomes for various modalities of 5-fluorouracil based treatment.

As noted, a second important finding from this study is that patients who receive chemoradiation, regardless of whether it is 5-fluorouracil based or gemcitabine based, perform better than patients who receive gemcitabine alone. The CONKO-001 trial [3] has already clearly demonstrated that the use of adjuvant gemcitabine has a better prognosis than observation alone after curative resection of pancreatic cancer. However, despite the fact that chemoradiation has become the standard of care in the USA for resectable pancreatic cancer, there are still no large trials that compare chemoradiotherapy with gemcitabine alone. Such trials are needed to resolve the debate on the role of chemoradiotherapy in resectable pancreatic cancer.

Acknowledgements:

This study used the linked SEER-Medicare database. The interpretation and reporting of these data are the sole responsibility of the authors. The authors acknowledge the efforts of the Applied Research Program, NCI; the Office of Research, Development and Information, CMS;

Information Management Services (IMS), Inc.; and the Surveillance, Epidemiology, and End Results (SEER) Program tumor registries in the creation of the SEER-Medicare database.

Tables:

Table 1 – Codes used to identify surgery, chemotherapy and radiotherapy

Surgery	ICD – 9	525, 5251, 5252, 5253, 5259, 526, 527
	CPT procedure codes	48140, 48145, 48146, 48150, 48152, 48153, 48154, 48155
	Surgery of primary site (SEER)	30, 35, 36, 37, 40, 60, 70, 80
Chemotherapy	CPT procedure codes	J9190, J9201, J9999
Radiotherapy	ICD-9 diagnosis codes	V58.0, V66.1, V67.1
	ICD-9 procedure codes	92.21 – 92.29
	CPT procedure codes	77400-77499, 77750-77799
	Revenue center codes	0330, 0333

Table 2 – Frequency table

N = 705 (unless otherwise specified)	5-Fluorouracil with Radiation		Gemcitabine with Radiation		Gemcitabine without Radiation		5-Fluorouracil without Radiation		P value
	N	%	N	%	N	%	N	%	
Age of diagnosis									
65-69	91	27.3%	55	31.1%	38	22.5%	4	16.0%	
70-74	122	36.5%	75	42.4%	50	29.6%	7	28.0%	
75-79	91	27.3%	31	17.5%	49	29.0%	10	40.0%	
80+	30	9.0%	16	9.0%	32	18.9%	4	16.0%	0.0015
Sex									
Female	177	53.0%	89	50.3%	88	52.1%	17	68.0%	
Male	157	47.0%	88	49.7%	81	47.9%	8	32.0%	0.4237
Race									
White	292	87.4%	161	91.0%	151	89.3%	23	92.0%	
Non-white	42	12.6%	16	9.0%	18	10.7%	2	8.0%	0.6193
Residence in metro area									
Yes	289	86.5%	158	89.3%	154	91.1%	23	92.0%	
No	45	13.5%	19	10.7%	15	8.9%	2	8.0%	0.4192
Percent of census tract below the poverty level (n = 699)									
≤ 20%	302	91.5%	154	88.0%	145	85.8%	21	84.0%	0.1941
> 20%	28	8.5%	21	12.0%	24	14.2%	4	16.0%	

Charlson comorbidity index									
0	203	60.8%	118	66.7%	97	57.4%	14	56.0%	0.3121
1+	132	39.2%	59	33.3%	72	42.6%	11	44.0%	
Cancer sequence									
1st or only cancer	294	88.0%	163	92.1%	160	94.7%	22	88.0%	
Other	40	12.0%	14	7.9%	9	5.3%	3	12.0%	0.0866
Year of diagnosis									
1998	27	8.1%	3	1.7%	5	3.0%	0	0.0%	
1999	21	6.3%	2	1.1%	4	2.4%	1	4.0%	
2000	63	18.9%	21	11.9%	9	5.3%	4	16.0%	
2001	45	13.5%	14	7.9%	20	11.8%	4	16.0%	
2002	51	15.3%	27	15.3%	17	10.1%	3	12.0%	
2003	55	16.5%	25	14.1%	29	17.2%	5	20.0%	
2004	46	13.8%	40	22.6%	34	20.1%	2	8.0%	
2005	26	7.8%	45	25.4%	51	30.2%	6	24.0%	<0.0001
Tumor site									
Head	258	77.2%	144	81.4%	121	71.6%	15	60.0%	
Other	76	22.8%	33	18.6%	48	28.4%	10	40.0%	0.0383
Stage (n = 702)									
Ia / Ib	47	14.1%	22	12.5%	25	15.0%	8	32.0%	
IIa	84	25.2%	38	21.6%	35	21.0%	4	16.0%	
IIb	203	60.8%	116	65.9%	107	64.1%	13	52.0%	0.2053
Grade (n = 659)									
Low (1-2)	191	61.2%	99	58.9%	84	53.9%	17	73.9%	
High (3-4)	121	38.8%	69	41.1%	72	46.1%	6	26.1%	0.2174
Surgery (n = 704)									
Radical	259	77.5%	141	79.7%	125	74.4%	19	76.0%	
Total	12	3.6%	9	5.1%	7	4.2%	0	0.0%	
Partial	63	18.9%	27	15.3%	36	21.4%	6	24.0%	0.6546

Table 3 – Kaplan Meier analysis based survivals

	5-Fluorouracil with Radiation	Gemcitabine with Radiation	Gemcitabine without Radiation	5-Fluorouracil without Radiation	Total sample
Median survival	19.0 months	17.0 months	14.0 months	22.0 months	17.0 months
1 year survival	69.2%	68.9%	52.1%	60.0%	64.7%
3 year survival	19.4%	22.6%	13.5%	43.6%	19.6%
5 year survival	11.8%	12.8%	4.8%	26.6%	11.0%

Table 4 – Univariate analysis

	Hazard Ratio	95% CI interval	p value
Chemotherapy			
5-Fluorouracil	1		
Gemcitabine	1.202	1.024 – 1.411	0.0248
Radiotherapy (RT)			
No	1		
Yes	0.771	0.645 – 0.922	0.0043
Treatment regimen			
5-Fluorouracil + RT	1		
Gemcitabine + RT	0.990	0.811 – 1.209	0.9228
Gemcitabine, No RT	1.431	1.174 – 1.744	0.0004
5-Fluorouracil, No RT	0.701	0.430 – 1.144	0.1554
Overall			0.0005
Age of diagnosis			
65-69	1		
70-74	1.197	0.973 – 1.472	0.0896
75-79	1.317	1.054 – 1.646	0.0155
80+	1.429	1.079 – 1.892	0.0128
Overall			0.0357
Sex			
Female	1		
Male	1.161	0.989 – 1.362	0.0677
Race			
White	1		
Non-white	1.093	0.852 – 1.403	0.4838
Residence in metro area			
Yes	1		
No	0.955	0.743 – 1.228	0.7198
Percent of census tract below the poverty level			
$\leq$ 20%	1		
> 20%	1.293	1.007 – 1.660	0.0437
Charlson comorbidity index			
0	1		
1+	1.220	1.036 – 1.436	0.0172
Cancer sequence			
1st or only cancer	1		
Other	1.017	0.776 – 1.334	0.9014

Year of diagnosis			
1998	1		
1999	1.298	0.764 – 2.204	0.3349
2000	0.981	0.644 – 1.496	0.9306
2001	1.196	0.779 – 1.838	0.4135
2002	1.124	1.737 – 1.713	0.5881
2003	1.111	0.735 – 1.679	0.6183
2004	1.033	0.682 – 1.564	0.8786
2005	1.267	0.836 – 1.920	0.2640
Overall			0.6786
Tumor site			
Head	1		
Other	1.133	0.939 – 1.368	0.1923
Stage			
Ia / Ib	1		
IIa	0.949	0.717 – 1.255	0.7126
IIb	1.279	1.005 – 1.627	0.0452
Overall			0.0051
Lymph node status			
Involved (Stage IIb)	1		
Not involved (Stage Ia/Ib/IIa)	0.766	0.647 – 0.906	0.0019
Grade			
Low (1-2)	1		
High (3-4)	1.297	1.097 – 1.534	0.0025
Surgery			
Radical	1		
Total	1.297	0.873 – 1.926	0.1979
Partial	1.125	0.913 – 1.385	0.2684
Overall			0.2704

Table 5 – Multivariable analysis (stratified by grade)

	High Grade			Low Grade		
	Hazard Ratio	95% CI	p-value	Hazard Ratio	95% CI	p-value
Treatment regimen						
5-FU with radiation	1			1		
Gemcitabine with radiation	0.979	0.706 – 1.356	0.8975	1.043	0.791 – 1.376	0.7636
Gemcitabine without radiation	1.499	1.090 – 2.062	0.0128	1.320	0.996 – 1.749	0.0531
5-FU without radiation	2.099	0.899 – 4.903	0.0866	0.427	0.223 – 0.817	0.0102
Overall			0.0239			0.0076
Age at diagnosis						
65-69 years	1			1		
70-74 years	0.947	0.672 – 1.334	0.7537	1.387	1.045 – 1.840	0.0233
75-79 years	1.094	0.751 – 1.595	0.6393	1.490	1.086 – 2.045	0.0136
80+ years	1.309	0.840 – 2.039	0.2339	1.522	1.007 – 2.301	0.0462
Overall			0.4901			0.0459
Sex						
Female	1			1		
Male	1.072	0.819 – 1.403	0.6149	1.140	0.913 – 1.422	0.2466
Race						
White	1			1		
Non-white	1.301	0.818 – 2.070	0.2666	0.946	0.664 – 1.349	0.7606
Percent of census tract below the poverty level						
$\leq$ 20%	1			1		
> 20%	1.453	0.912 – 2.315	0.1159	1.327	0.950 – 1.853	0.0968
Charlson comborbidity index						
0	1			1		
1+	1.239	0.943 – 1.628	0.1239	1.239	0.986 – 1.558	0.0664
Tumor site						
Head of pancreas	1			1		
Other	0.961	0.701 – 1.317	0.8047	1.307	0.999 – 1.709	0.0507
Lymph node status						
Involved (Stage IIb)	1			1		
Not involved (Stage Ia/Ib/IIa)	0.730	0.540 – 0.985	0.0398	0.796	0.630 – 1.006	0.0561

Table 6 – Survival and grade distribution in clinical trials involving 5-fluorouracil based treatment

	Regimen	No. of patients	Comments	Low grade / High grade	Median survival
EORTC (1999)	5-FU with Radiotherapy	60	Limited to pancreatic head tumors	73% / 23% *	17.1 months
ESPAC 1 (2004)	5-FU with Radiotherapy	145		75% / 14%	15.9 months
RTOG (2008)	5-FU with Radiotherapy	201	Limited to pancreatic head tumors	71% / 23% **	16.9 months
ESPAC 1 (2004)	5-FU without radiotherapy	75		70% / 22% ***	**21.6 months**
ESPAC 3 (2010)	5-FU without radiotherapy	551		75% / 25%	**23.0 months**

* For pancreatic head tumors, differences in grade were not described. For the entire sample (including periampullary tumors), 73% of the patients had low grade tumors while 23% had high grade tumors.

** For pancreatic head tumors, differences in grade were not described. For the entire sample, 71% of the patients had low grade tumors while 23% had high grade tumors.

*** For the group which combined 5-fluorouracil alone with observation alone, 70% of patients had low grade tumors while 22% had high grade tumors. No statistics were separately given for patients who received 5-fluorouracil alone.

APPENDICES

Research Objective:

To conduct a population based retrospective cohort study comparing survival between patients with resectable pancreatic cancer who received adjuvant chemotherapy with gemcitabine versus such patients who received 5-fluorouracil and to assess the impact of radiotherapy on these regimens.

Research Questions:

1) Is there a statistically significant difference between the survivals of patients with resectable pancreatic cancer who received adjuvant chemotherapy with gemcitabine versus such patients who received 5-fluorouracil?
2) Does the use of radiation therapy in conjunction with adjuvant chemotherapy significantly impact the survival of such patients?
3) What other contributing variables are important to help better understand the survival experience of such patients?

Detailed Literature Review:

Although surgical resection for Stage I and II pancreatic tumors has been well established, the role of adjuvant therapy is far less defined.

Initially, the Gastrointestinal Tumor Study Group (GITSG) evaluated patients with resected pancreatic cancer by randomizing them to either treatment with external beam split-course radiation and 5-fluorouracil followed by maintenance chemotherapy (intervention) or no adjuvant treatment (control) [5]. Despite the low sample size of only 43 patients, the intervention group demonstrated improvements in median survival (20 vs. 11 months). The same group later registered additional patients to the intervention arm which also demonstrated similar results (median survival of 18 months) [17].

This trial was followed by the EORTC (European Organization for Research and Treatment of Cancer) study [6]. Although the actual study enrolled patients with either cancer of the pancreas or of the periampullary region, subgroup analyses allowed the investigation of patients with pancreatic head tumors. A larger number of patients (114 patients) were enrolled and randomized to undergo either 5-fluorouracil with external beam radiation versus observation alone. In this study, intervention did not lead to any significant benefit, although a trend towards this was noted (median overall survival 17.1 vs. 12.6 months, $p = 0.099$).

Next, a trial was conducted by the European Study Group for Pancreatic Cancer (ESPAC-1) to assess various adjuvant treatments involving 5-fluorouracil with and without radiotherapy [18]. The study compared patients who received chemoradiotherapy with those who received no chemoradiotherapy (that is, either chemotherapy alone or no adjuvant therapy). Another arm compared those who received chemotherapy (either with or without initial chemoradiotherapy)

with those who received no chemotherapy. Yet another arm used a 2x2 factorial design with four separate groups (observation, chemotherapy, chemoradiotherapy and both chemoradiotherapy with maintenance chemotherapy). The results from these were combined to demonstrate a survival advantage among patients who received chemotherapy vs. no chemotherapy (median overall survival 19.7 vs. 14.0 months, $p = 0.0005$). No significant difference was found between patients who received chemoradiotherapy vs. no chemoradiotherapy (median overall survival 15.5 vs. 16.1 months, $p = 0.24$). This trial was later reported with a limited but extended analysis of the patients in the 2x2 factorial design alone [7]. Here, chemoradiotherapy seemed to have a significantly poorer outcome than no chemoradiotherapy (median overall survival 15.9 vs. 17.9 months, $p = 0.05$) while chemotherapy continued to demonstrate a better outcome compared to no chemotherapy (median overall survival 20.1 vs. 15.5 months, $p = 0.009$).

The beneficial effects of gemcitabine were demonstrated in the CONKO-001 (Charité Onkologie) trial which compared patients who received gemcitabine vs. observation after curative resection for pancreatic cancer [3]. The primary end-point of disease free survival was significantly higher in patients who received gemcitabine (median disease free survival 13.4 vs. 6.9 months, $p < 0.001$). Although overall survival did not differ, a trend towards improved survival was noted (median overall survival 22.1 vs. 20.2 months, $p = 0.06$).

The effects of gemcitabine were further assessed in the Radiation Therapy Oncology Group (RTOG) 97-04 trial, which randomized patients to receive adjuvant chemoradiation along with either adjuvant chemotherapy with 5-fluorouracil or gemcitabine [16]. More specifically, the regimens involved chemotherapy for 3 weeks prior and 12 weeks after 5-fluorouracil based chemoradiotherapy. Among pancreatic head tumors, gemcitabine had a univariate trend towards improved median overall survival when compared to 5-fluorouracil (20.5 vs. 16.9 months, p =

0.09). After multivariate analysis, this relationship was demonstrated to be statistically significant (p=0.05).

The most recent comparison between 5-fluorouracil and gemcitabine was the ESPAC-3 trial. This trial compared patients who received 5-fluorouracil vs. gemcitabine [4]. No radiotherapy was administered. Median overall survival did not differ (23.0 vs. 23.6 months, p = 0.39).

Although no SEER-Medicare analyses have been conducted comparing gemcitabine and 5-fluorouracil, a couple of descriptive studies have assessed adjuvant therapy in patients with pancreatic cancer who underwent curative resections. Lim et al. evaluated 396 patients to assess prognostic factors that influence survival [19]. The study reported a significant improvement in median overall survival between patients who received adjuvant chemoradiation therapy vs. those who did not receive any adjuvant treatment (25.1 vs. 11.5 months, p = 0.0003). In another study, Davila et al. also demonstrated improvements in two year survival between patients who received chemoradiation therapy vs. no adjuvant therapy (adjusted hazard ratio 0.76, p = 0.001) [20].

Details on treatment regimen identification

Curative Surgery

Patients were considered to have received curative surgery if the SEER registry documented that cancer-directed surgery had been performed and if any of the following were present in either the SEER registry or Medicare claims:

ICD – 9	525, 5251, 5252, 5253, 5259, 526, 527
CPT procedure codes	48140, 48145, 48146, 48150, 48152, 48153, 48154, 48155
Surgery of primary site (SEER)*	30, 35, 36, 37, 40, 60, 70, 80

* As Medicare data on surgery was lacking in these patients, these patients were further assessed to check for evidence of pancreatic cancer in any of the claims files. Patients without any indication of pancreatic cancer at any point were excluded.

The date of surgery was also identified to assess if chemotherapy and radiotherapy were adjuvant. If data was extracted from the MEDPAR database, exact dates of surgery were available and were used for further analyses. If the National Claims History (NCH) file data was

used, the midpoints between the start and end claim dates were used. If Medicare data was lacking, the SEER data was used to identify the date of surgery. In SEER data, there isn't a specific variable for the date of surgery in SEER. Furthermore, data on the timing of such events is documented in terms of the month and year only. Hence, information on the date of surgery was extrapolated from the month and year of the data of first course of treatment. As the exact date of surgery was not available, the 15th of the month was used for analyses. As surgery is usually done prior to chemotherapy or radiation, this variable would be accurate in most cases. However, as the first course of treatment in SEER is non-specific and doesn't necessarily refer to surgery, patients were excluded from this population if there was any evidence of neoadjuvant radiation or chemotherapy.

Likewise, the date of diagnosis was considered to be the 15th of the month for the given month/year of diagnosis according to the SEER registry. If the date of surgery was more than 6 months after diagnosis, patients were excluded because the surgery would be unlikely to be relevant and curative. On the other hand, because the dates of surgery were not precise, only if the surgery date was more than one month prior to the date of diagnosis were patients excluded. If a patient had more than one pancreatic surgery (3 cases), a manual review was conducted to identify the likely curative surgery.

For the purpose of analysis, the type of surgery conducted was divided into three categories: radical pancreatectomy, total pancreatectomy and partial pancreatectomy.

Chemotherapy:

Initially, all claims involving any chemotherapy (J9000 – J9999) were identified from the Medicare outpatient and NCH files. The midpoints between the start and end claim dates were used to establish the date of chemotherapy.

Claims for chemotherapy prior to the earliest date of diagnosis (the 1st of the given SEER month/year of diagnosis) were excluded. Claims for chemotherapy prior to surgery (neoadjuvant) or more than 6 months after surgery (unlikely to be adjuvant) were also excluded. If the surgical data was acquired from the SEER registry alone, patients were also excluded if the month and year for chemotherapy and the first course of treatment were equal (7 patients), as it is impossible to rule out neoadjuvant chemotherapy in these cases.

Next, cases that received the study drugs (5-fluorouracil (J9190), gemcitabine (J9201), or an unclassified chemotherapy (J9999)) were identified. If both gemcitabine and 5-fluorouracil were received within 30 days of each other (34 patients), these patients were excluded as the two drugs may have been part of the same treatment regimen. Otherwise, the first chemotherapy drug received between these was considered to be the 'study drug'. Of course, some of these excluded patients can be explained by regimens such as 5-fluorouracil based chemoradiation followed by gemcitabine, etc. However, precise regimen details are beyond the scope of this study. Hence, in order to facilitate analysis, such patients were excluded.

Then, all patients who had received the study drug were further assessed for any chemotherapy received after diagnosis but prior to the study drug. Of the patients who had received the study drug, 27 patients were identified who had received some form of chemotherapy prior to the study drug yet within the abovementioned period. These patients underwent further manual evaluation

and twenty subjects were considered to be includable. Some of these had received unrelated drugs such as goserelin (4 patients) or leuprolide (3 patients). In the remaining thirteen patients, chemotherapy with agents other than the study drugs had been initiated less than one month prior to the study drug. Hence, the other chemotherapy agents were considered to be part of the same regimen.

Radiation:

Patients were considered to have received radiation if any of the following codes were present in the Medicare claims:

ICD-9 diagnosis codes	V58.0, V66.1, V67.1
ICD-9 procedure codes	92.21 – 92.29
CPT procedure codes	77400-77499, 77750-77799
Revenue center codes	0330, 0333

For radiation identified by the ICD-9 procedure codes, the exact date of radiation was available. Otherwise the midpoints between the start and end claim dates were used. Claims involving radiation prior to the earliest diagnosis date were excluded. Also, claims involving radiation beyond six months after surgery were also excluded. (If surgical data was derived from the SEER registry only, the latest date of surgery was used, that is, the last date of the month).

Information on the receipt of radiation was compared between the SEER data and the Medicare claims. Among patients who had claims data for radiation (n = 517), 61 patients had no SEER documentation regarding this. Of these, 60 patients were coded to have received radiation for pancreatic cancer. The remaining patient had received radiation to the prostate and was hence counted among the chemotherapy only groups. On the other hand, 12 patients were documented to have received radiation per the SEER registry. Nine of these had received radiation outside of the abovementioned time window. The remaining 3 patients were treated as if they had received radiation.

Finally, the SEER registry also reported that 6 patients received neoadjuvant radiation. On review of the claims files, only three of these had evidence of neoadjuvant radiation and these were excluded from the database.

References:

1. Jemal, A., et al., *Cancer statistics, 2009.* CA Cancer J Clin, 2009. **59**(4): p. 225-49.
2. Neoptolemos, J.P., et al., *Adjuvant 5-fluorouracil and folinic acid vs observation for pancreatic cancer: composite data from the ESPAC-1 and -3(v1) trials.* Br J Cancer, 2009. **100**(2): p. 246-50.
3. Oettle, H., et al., *Adjuvant chemotherapy with gemcitabine vs observation in patients undergoing curative-intent resection of pancreatic cancer: a randomized controlled trial.* JAMA, 2007. **297**(3): p. 267-77.
4. Neoptolemos, J.P., et al., *Adjuvant chemotherapy with fluorouracil plus folinic acid vs gemcitabine following pancreatic cancer resection: a randomized controlled trial.* JAMA, 2010. **304**(10): p. 1073-81.
5. Kalser, M.H. and S.S. Ellenberg, *Pancreatic cancer. Adjuvant combined radiation and chemotherapy following curative resection.* Arch Surg, 1985. **120**(8): p. 899-903.
6. Klinkenbijl, J.H., et al., *Adjuvant radiotherapy and 5-fluorouracil after curative resection of cancer of the pancreas and periampullary region: phase III trial of the EORTC gastrointestinal tract cancer cooperative group.* Ann Surg, 1999. **230**(6): p. 776-82; discussion 782-4.
7. Neoptolemos, J.P., et al., *A randomized trial of chemoradiotherapy and chemotherapy after resection of pancreatic cancer.* N Engl J Med, 2004. **350**(12): p. 1200-10.
8. Tempero, M.A., et al., *Pancreatic cancer treatment and research: an international expert panel discussion.* Ann Oncol, 2011.
9. *SEER-Medicare Linked Database*. [cited April 8th 2011]; National Cancer Institute website]. Available from: http://healthservices.cancer.gov/seermedicare/.
10. *Overview of the SEER Program*. [cited April 8th 2011]; National Cancer Institute website]. Available from: http://seer.cancer.gov/about/overview.html.
11. Charlson, M.E., et al., *A new method of classifying prognostic comorbidity in longitudinal studies: development and validation.* J Chronic Dis, 1987. **40**(5): p. 373-83.
12. Deyo, R.A., D.C. Cherkin, and M.A. Ciol, *Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases.* J Clin Epidemiol, 1992. **45**(6): p. 613-9.
13. Edge, S.B., Byrd, D.R., Compton, C.C., Fritz, A.G., Greene, F.L., Trotti, A. (editors), *AJCC Cancer Staging Manual*. 7th ed. 2010, New York, NY: Springer.
14. Klabunde, C.N., et al., *Development of a comorbidity index using physician claims data.* J Clin Epidemiol, 2000. **53**(12): p. 1258-67.
15. *Poverty*. [cited April 20th 2011]; U.S. Census Bureau website]. Available from: http://www.census.gov/hhes/www/poverty/methods/definitions.html.
16. Regine, W.F., et al., *Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial.* JAMA, 2008. **299**(9): p. 1019-26.
17. *Further evidence of effective adjuvant combined radiation and chemotherapy following curative resection of pancreatic cancer. Gastrointestinal Tumor Study Group.* Cancer, 1987. **59**(12): p. 2006-10.
18. Neoptolemos, J.P., et al., *Adjuvant chemoradiotherapy and chemotherapy in resectable pancreatic cancer: a randomised controlled trial.* Lancet, 2001. **358**(9293): p. 1576-85.
19. Lim, J.E., M.W. Chien, and C.C. Earle, *Prognostic factors following curative resection for pancreatic adenocarcinoma: a population-based, linked database analysis of 396 patients.* Ann Surg, 2003. **237**(1): p. 74-85.
20. Davila, J.A., et al., *Utilization and determinants of adjuvant therapy among older patients who receive curative surgery for pancreatic cancer.* Pancreas, 2009. **38**(1): p. e18-25.