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Sani H. Kizilbash, *William Beaumont Hospital*
Kevin C. Ward, *Emory University*
Jackson J. Liang, *Mayo Clinic*
Ishmael Jaiyesimi, *William Beaumont Hospital*
Joseph Lipscomb, *Emory University*

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Survival outcomes in patients with early stage, resected pancreatic cancer – a comparison of gemcitabine and 5-fluorouracil based chemotherapy and chemoradiation regimens

Sani H. Kizilbash, MBBS, MPH[1], **Kevin C. Ward, PhD**[2], **Jackson J. Liang, DO**[3], **Ishmael Jaiyesimi, DO**[4], and **Joseph Lipscomb, PhD**[5]

[1]Department of Internal Medicine, William Beaumont Hospital, Royal Oak, MI

[2]Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA

[3]Department of Medicine, Mayo Clinic, Rochester, MN

[4]Division of Hematology/Oncology, Department of Internal Medicine, William Beaumont Hospital, Royal Oak, MI

[5]Department of Health Policy and Management, Rollins School of Public Health, Emory University, Atlanta, GA

Abstract

PURPOSE—We conducted a comparative survival analysis between patients with resected pancreatic cancer who received adjuvant treatment with either gemcitabine or 5-fluorouracil based chemotherapy and chemoradiation regimens.

PATIENTS AND METHODS—The Surveillance, Epidemiology and End Results (SEER)-Medicare database was used to identify patients with pancreatic cancer diagnosed from 1998 to 2005 who received curative surgery and adjuvant chemotherapy with either 5-fluorouracil or gemcitabine. These groups were subdivided by treatment with radiotherapy. Patients were followed until death, study endpoint or a maximum of five years after diagnosis.

RESULTS—359 patients received 5-fluorouracil and 346 received gemcitabine. Compared to chemoradiation with 5-fluorouracil, outcomes for patients who received chemoradiation with gemcitabine did not differ. Patients who received gemcitabine without radiation had increased hazards (poorly differentiated tumors: HR = 1.50, p = 0.01; moderately differentiated tumors, HR = 1.28, p = 0.11). However, outcomes of patients who received 5-fluorouracil without radiation varied with tumor grade. In moderately differentiated tumors, patients had better outcomes with 5-fluorouracil when compared with chemoradiation with 5-fluorouracil (HR = 0.42, p = 0.02). In poorly differentiated tumors, the opposite was true (HR 2.10, p = 0.09).

Correspondence: Sani Haider Kizilbash, MBBS, MPH. Division of Hematology/Oncology, Mayo Clinic. 200 First St SW, Rochester, MN 55905. kizilbash.sani@mayo.edu Ph: (507) 2842511; Fax (507) 2841803.

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CONCLUSION—Patients with low grade resected pancreatic cancer may have better outcomes with 5-fluorouracil based chemotherapy without radiation when compared to 5-fluorouracil with radiation.

Keywords

5-fluorouracil; gemcitabine; pancreatic cancer; radiotherapy; SEER-Medicare; tumor grade; survival

Background

Optimal management with chemotherapy and radiation for patients with resected pancreatic cancer remains controversial. Individually, both 5-fluorouracil [1] and gemcitabine [2] (without radiation) increase survival when compared to observation alone. The ESPAC-3 trial, the largest adjuvant trial for pancreatic cancer to date, randomized patients with resected pancreatic cancer to receive either 5-fluorouracil/folinic acid or gemcitabine [3] and showed no significant survival difference between the regimens. Although chemotherapy has beneficial outcomes, the use of radiotherapy in resected pancreatic cancer remains debatable. Initially the GITSG study [4] 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 much larger EORTC trial [5] which found no significant difference between chemoradiation and observation alone, although a trend towards the benefits of chemoradiation was noted. Later, the ESPAC 1 trial [6] found that patients who received chemoradiotherapy had worse outcomes than patients who did not receive chemoradiotherapy (i.e. either chemotherapy alone or observation). Consequently, clinical practice varies depending on the trial that is given most importance [7]. In the United States, chemoradiation has become the standard of care for resected pancreatic cancer.

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 resected pancreatic cancer.

Methodology

SEER-Medicare is a linked database that combines data from two large population based sources [8]. The Surveillance, Epidemiology and End Results (SEER) Program collects information on all patients diagnosed with cancer within 18 geographically defined areas in the USA [9], covering 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 claims. The Carrier (or National Claims History (NCH)) file includes all Part B non-institutional provider claims (e.g. physicians, nurse practitioners, etc.). The Outpatient file includes claims from institutional outpatient providers (e.g. hospital outpatient departments, rural health clinics, etc.)

The study period for each patient ranged from one year prior to 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 [10, 11]. Furthermore, the five-year period was considered sufficient to follow the time course of the pancreatic cancer. As claims data were only available up to 2008, surviving patients who were diagnosed after the year 2003 were censored prior to the completion of a five-year follow-up.

All patients over the age of 65 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 and 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 unspecified 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. These groups were further subdivided into patients who received adjuvant radiotherapy and those who did not. Curative surgery needed to have been performed within six months after diagnosis in all subjects and acceptable adjuvant regimens needed to be initiated within six months after surgery for inclusion. Details of the codes used to identify surgical procedures, chemotherapy agents and radiotherapy regimens are described in table 1.

As information was being extrapolated from claims data without the benefit of actual clinician documentation, it was difficult to account for the great variability in actual treatment regimens that patients may have received. Furthermore, it was 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 initiated, regardless of whether the initial regimen was modified or completed.

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

receipt of neoadjuvant chemotherapy or radiation therapy or (m) 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 according to current American Joint Committee on Cancer (AJCC) staging guidelines using the specific size and extent of the tumor along with lymph node status [12]. ICD-9 diagnosis codes for comorbidities that were evident in claims data one to twelve months prior to diagnosis were used to calculate the Charlson comorbidity index [10, 11]. This index helped account for the severity of the patients' non-cancer illnesses. Both MEDPAR and NCH data were used to determine the index [13].

According to federal guidelines, census tracts with greater than 20 percent of the population living below the poverty level are defined as `poverty areas' [14]. 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 socioeconomic status. Other variables that were accounted for included the age at diagnosis, sex, race, metropolitan residence, cancer sequence, year of diagnosis, tumor site, tumor grade and type of surgery.

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

Statistical methods

Baseline demographic and clinical variables of the four permutations of the treatment regimen groups (gemcitabine or 5-fluorouracil, with and without radiation) were compared. 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 identify confounders and determine significant interactions.

Overall survival was primarily used to compare treatment regimens. Cause-specific survival was also calculated in accordance to the recommended SEER definitions [15]. Details of the codes used to identify patients considered to have died secondary to pancreatic cancer are described in table 2. Kaplan-Meier plots were constructed and multivariable survival analyses were 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. 9.3 (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 and the remaining 20 due to either date of death discrepancy between SEER and Medicare data, insufficient claims data to calculate the Charlson comorbidity index, absence of evidence of pancreatic cancer in the claims data or receipt of neoadjuvant radiation).

Of the remaining 712 patients, 359 received 5-fluorouracil and 346 received gemcitabine. Fewer than 11 patients received an unknown form of chemotherapy. As these only comprised <2% of the study sample, it was felt that this group would neither significantly impact nor bias the other groups. Hence, this group was not analyzed further. Study variables were categorized based on meaningful groups. On comparison of the groups, there were no differences in terms of tumor stage, grade and comorbidity index (see table 3). Significant differences included the age of diagnosis (elderly patients tended to receive adjuvant chemotherapy rather than adjuvant chemoradiation) and the tumor site (pancreatic head tumors were more likely treated with adjuvant chemoradiation as opposed to chemotherapy alone).

Survival analyses

The median survival for the entire sample was 17 months. The one- and five-year survivals 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). Patients who received chemoradiation demonstrated similar survivals, regardless of whether 5-fluorouracil or gemcitabine was used (median survival = 19 months and 17 months, respectively). Patients who received gemcitabine without radiation performed notably worse (median survival = 14 months) than those who received the abovementioned chemoradiation regimens. Interestingly, patients who received 5-fluorouracil without radiation had a longer median survival (22 months) than those who received chemoradiation. This difference becomes increasingly obvious with a comparison of the 3-year and 5-year survivals (table 4). Kaplan-Meier analyses of cause-specific survival revealed similar results and an even more impressive median survival for patients who receive 5-fluorouracil without radiation (27 months) when compared to the other groups.

Univariate analysis

In the univariate analyses, the most significant predictor of survival was the treatment regimen itself (table 5). A closer examination of the treatment regimens shows that 5-fluorouracil based chemoradiation and gemcitabine based chemoradiation were statistically similar in terms of outcomes. However, 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. In fact, the hazard ratio of the latter regimen trended towards an improvement in both overall and cause-specific survival.

Other significant predictors of overall survival included socioeconomic status, Charlson comorbidity index, age at diagnosis, tumor grade and stage. That being said, Charlson comorbidity index and socioeconomic status did not predict cause-specific survival. Otherwise, stage data had initially 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 correspond to lymph node involvement (Stage IIb vs. Stage Ia/Ib/IIa). Despite not being significant at conventional levels, race, gender and tumor site were included into the multivariable analyses based on a priori decisions.

Multivariable analysis

To conduct Cox proportional hazards modeling, interaction variables were created between each covariate and the treatment regimen. Due to the presence of a significant interaction between treatment regimen and tumor grade, analyses between regimens were further stratified by grade (table 6).

Among patients with poorly differentiated tumors, when 5-fluorouracil with radiation was compared to patients who received gemcitabine alone, the latter group had a significantly increased hazard (hazard ratio 1.50, $p = 0.01$). A trend towards significance was also demonstrated for patients who received 5-fluorouracil alone (hazard ratio 2.10, $p = 0.09$). On the other hand, in patients with moderately differentiated 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 demonstrated a trend towards a poorer outcome (hazard ratio 1.28, $p = 0.11$). However patients who received 5-fluorouracil alone had significantly better prognosis (hazard ratio 0.42, $p = 0.02$). This relationship was maintained in assessments of both overall survival and cause-specific survival.

Discussion

This study evaluated survival outcomes between various adjuvant regimens used to treat resected pancreatic cancer by assessing a retrospective, population-based cohort of patients. The split of patients between groups hence reflects the prevalent practice patterns in the community. 334 (47%) of the patients evaluated received 5-FU concurrent with radiation, while only 25 (3.5%) received 5-FU without radiation. The remaining patients were split evenly between patients who received gemcitabine with and without radiation.

The results of this study support the fact that patients who receive chemoradiation, regardless of whether it is 5-fluorouracil based or gemcitabine based have similar outcomes. In turn, patients who received either of the above chemoradiation regimens performed better than those who received gemcitabine alone. This relationship was especially prominent among poorly differentiated tumors. The CONKO-001 trial [2] has previously demonstrated that the use of adjuvant gemcitabine has a better prognosis than observation alone after curative resection of pancreatic cancer. However, despite chemoradiation having become the standard of care in the United States for resected pancreatic cancer, clinical trials comparing chemoradiotherapy with gemcitabine alone are lacking. An EORTC phase II study has already demonstrated the feasibility of adjuvant gemcitabine followed by chemoradiotherapy with gemcitabine versus gemcitabine alone in such patients [16]. The RTOG 9704 trial evaluated the addition of gemcitabine to adjuvant 5-fluorouracil based chemoradiation [17]. Although patients who received gemcitabine seemed to survive longer, this was not statistically significant. Later analyses revealed that lack of adherence to the specified radiation protocol may have contributed to this lack of significance [18]. Another RTOG study is currently underway to evaluate whether the addition of 5-fluorouracil based chemoradiation after adjuvant gemcitabine further enhances survival [19]

One unexpected finding in this study is the tumor grade based difference in survival among patients who received 5-fluorouracil based regimens. Patients with moderately differentiated tumors fared better without chemoradiation (HR = 0.42, p = 0.02) while those with poorly differentiated tumors showed a trend toward improvement with chemoradiation (HR = 2.10, p = 0.09) however statistical significance was not achieved. An assessment of cause-specific survival demonstrates consistent results. Although these results are interesting, some of the difference in the hazard ratios may be explained by selection bias as patients with tumors perceived to be more aggressive may have been more likely to receive concurrent radiation therapy. Furthermore, the low number of patients in the patient group that received 5-fluorouracil without radiation lead to concerns on result validity.

To explore this finding further, a second analysis was conducted which limited analyses to patients who had either received 5-fluorouracil based chemoradiation or 5-fluorouracil alone. By excluding patients who received gemcitabine based regimens, patients diagnosed in the pre-gemcitabine era (1991 –1997) could also be evaluated, hence expanding the sample size to 488 patients in the 5-fluorouracil based chemoradiation group and 45 patients in the 5-fluorouracil alone group. Again, similar results were noted (table 7). The tumor grade demonstrated interaction with the treatment regimen and hence the groups were stratified by tumor grade. Among poorly differentiated tumors, there was a trend towards an increased hazard in patients who do not receive radiation (hazard ratio 1.77, $p = 0.06$). On the other hand, among moderately differentiated tumors, patients who did not receive radiation had significantly better outcomes (HR 0.54, $p = 0.02$). The well-differentiated tumors also demonstrated a similar hazard ratio (HR = 0.52, p = 0.41), however the relationship was not statistically significant, likely secondary to the limited sample size.

The ESPAC 1 trial [6] indicated that the median overall survival was reduced by the use of 5-fluorouracil based chemoradiation (15.9 months) rather than 5-fluorouracil (21.6 months) alone (Table 7). For the 5-fluorouracil group in our study, the median survival corresponds to the survival noted in the ESPAC 3 trial (23.0 months) [3]. Similarly, the median overall survival in the 5-fluorouracil based chemoradiation group corresponds to the median overall survival of comparable groups in other studies (EORTC = 17.1 months [5], RTOG 16.9 months [17]).

On first glance it appears that patients receiving 5-fluorouracil alone have improved survival over those receiving 5-fluorouracil based chemoradiation. However, more detailed examination of these studies (table 8) reveals that all of them involved a minority of poorly differentiated tumors (14–27%). Given the results of our study's multivariable analysis, 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 in these trials as more differentiated 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. However, with that in mind, the multivariable 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 [6].

Beyond the impact of treatment regimens, this study also sheds light on pancreatic cancer among the elderly. The annual age-adjusted SEER incidence rate of pancreatic cancer is markedly higher among individuals over the age of 65 (67.6 per 100,000) as compared to individuals younger than that (4.0 per 100,000) [18]. However, clinical trials have historically focused on younger patient populations (median age = 59 – 63 years) [2, 3, 5, 6, 15], thus limiting their external validity in the elderly. In contrast, the median age was 72 years in this study of Medicare patients. As it better represents patients with advanced ages, it sheds light on nuances specific to the elderly, an area that is not well explored. In patients with more differentiated tumors, advancing age impacts survival above and beyond the effects of the treatment regimen used, however this is not the case in patients with poorly differentiated tumors.

This study has a number of limitations. 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. 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 [4] and underpowered studies [5]. To readily assess the outcomes of various treatment regimens in large numbers of patients, a population-based observational study was far more feasible. As data were readily available, this allowed procurement at a low cost and analysis with limited manpower in a short timeframe.

Other potential limitations include: (a) incompleteness of claims data and the need for extrapolation, (b) lack of precision for dates in the SEER data, (c) inability to account for temporal changes in treatment strategies, (d) inability to account for the heterogeneity of treatment regimens within each of the studied treatment groups, (e) imbalances in the variables in different patient groups, (f) the introduction of selection bias due to the assessment of treatment groups in retrospective data as random variables, and (g) the limited sample size of important variables ((i) well-differentiated tumors, (ii) patients receiving 5-FU without radiation).

Conclusions

In conclusion, among patients who receive chemoradiation, survival outcomes are similar between patients who receive either 5-fluorouracil or gemcitabine. Secondly, both of these regimens outperform the use of gemcitabine alone. Finally, poorly differentiated tumors have better outcomes when treated with 5-fluorouracil base chemoradiation while more differentiated tumors have better outcomes when treated with 5-fluorouracil alone. Given this grade-based difference in survival for patients receiving 5-fluorouracil, it would be interesting to see clinical trials which stratify based on tumor grade to account for possible differences in outcomes for various modalities of 5-fluorouracil based treatment.

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What's known

Adjuvant chemotherapy with 5-fluorouracil and gemcitabine based regimens increase survival in patients with resected pancreatic cancer after surgery. Controversy exists as to whether adjuvant radiotherapy should be added to chemotherapy in these patients.

What's New

Adjuvant radiotherapy improves outcomes when used in conjunction with gemcitabine-based chemotherapy regimens, regardless of tumor grade. For patients treated with 5-fluorouracil, the addition of radiotherapy improves outcomes in patients with poorly differentiated resected tumors, while it may be harmful in those with moderately differentiated resected tumors.

Table 1

Codes used to identify surqerv, 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

Codes used to define cause-specific survival

Other primary cancers other than pancreatic cancer during patient lifetime	ICD-8 codes	ICD-9 codes	ICD-10 codes
No	140–239, 444.2, 530–537, 560–562, 563.1, 569.9, 577, 784.5, 785.7, 990.9	042.2, 140–239, 530–537, 556–562, 577–578	B210–B219, C00–D489, K20–K31, K51–K57, K85, K86, K92
Yes	153.6, 157, 159, 199, 211.6, 230.3, 230.5, 230.7, 230.9, 444.2, 530–537, 560–562, 563.1, 569.9, 577, 784.5, 785.7, 990.9	157, 159, 199,211.6, 211.7, 230.9, 235.2–235.5, 530–537, 556–562, 577–578	C25–26, C798, C80, C97, D017, D136, D137, D371–D379, D489, K20–K31, K51–K57, K80–K83, K92

Table 3

Demographic and clinical characteristics of patients, by treatment regimen

***N* = 705 (unless otherwise specified)**	**5-Fluorouracil with Radiation (*N* = 334)**	**Gemcitabine with Radiation (*N* = 177)**	**Gemcitabine without Radiation (*N* = 169)**	**5-Fluorouracil without Radiation (*N* = 25)**	***P* value**
Age of Diagnosis					0.002
65–69	91 (27.3%)	55 (31.1%)	38 (22.5%)	*	
70–74	122 (36.5%)	75 (42.4%)	50 (29.6%)	*	
75–79	91 (27.3%)	31 (17.5%)	49 (29.0%)	*	
80+	30 (9.0%)	16(9.0%)	32(18.9%)	*	
Sex					0.42
Female	177 (53.0%)	89 (50.3%)	88 (52.1%)	*	
Male	157 (47.0%)	88 (49.7%)	81 (47.9%)	*	
Race					0.62
White	292 (87.4%)	161 (91.0%)	151 (89.3%)	*	
Non-white	42 (12.6%)	16 (9.0%)	18 (10.7%)	*	
Residence in metro area					0.42
Yes	289 (86.5%)	158 (89.3%)	154 (91.1%)	*	
No	45 (13.5%)	19 (10.7%)	15 (8.9%)	*	
Percent of census tract below the poverty level (*n*=699)					0.19
≤ 20%	302 (91.5%)	154 (88.0%)	145 (85.8%)	*	
>20%	28 (8.5%)	21 (12.0%)	24 (14.2%)	*	
Charlson comorbidity index					0.31
0	203 (60.8%)	118 (66.7%)	97 (57.4%)	14 (56.0%)	
1+	132 (39.2%)	59 (33.3%)	72 (42.6%)	11 (44.0%)	
Cancer sequence					0.09
1st or only cancer	294 (88.0%)	163 (92.1%)	*	*	
Other	40 (12.0%)	14 (7.9%)	*	*	
Year of diagnosis					<0.001
1998	27 (8.1%)	*	*	*	
1999	21 (6.3%)	*	*	*	
2000	63 (18.9%)	21 (11.9%)	*	*	
2001	45 (13.5%)	14 (7.9%)	20 (11.8%)	*	
2002	51 (15.3%)	27 (15.3%)	17 (10.1%)	*	
2003	55 (16.5%)	25 (14.1%)	29 (17.2%)	*	
2004	46 (13.8%)	40 (22.6%)	34 (20.1%)	*	
2005	26 (7.8%)	45 (25.4%)	51 (30.2%)	*	
Tumor site					0.04
Head	258 (77.2%)	144 (81.4%)	121 (71.6%)	*	
Other	76 (22.8%)	33 (18.6%)	48 (28.4%)	*	

***N* = 705 (unless otherwise specified)**	**5-Fluorouracil with Radiation (*N* = 334)**	**Gemcitabine with Radiation (*N* = 177)**	**Gemcitabine without Radiation (*N* = 169)**	**5-Fluorouracil without Radiation (*N* = 25)**	***P* value**
Stage (*n*=702)					0.21
Ia / Ib	47 (14.1%)	22 (12.5%)	25 (15.0%)	*	
IIa	84 (25.2%)	38 (21.6%)	35 (21.0%)	*	
IIb	203 (60.8%)	116 (65.9%)	107 (64.1%)	13 (52.0%)	
Grade (*n* = 659)					0.44
Well differentiated	23 (7.4%)	14(8.3%)	*	*	
Moderately differentiated	168 (53.9%)	85 (50.6%)	76 (48.7%)	14 (60.9%)	
Poorly differentiated	121 (38.8%)	69 (41.1%)	72 (46.1%)	*	
Surgery (*n* = 704)					0.65
Radical	259 (77.5%)	141 (79.7%)	125 (74.4%)	19 (76.0%)	
Total	12 (3.6%)	*	*	*	
Partial	63 (18.9%)	27 (15.3%)	36 (21.4%)		

* Omitted as number of cases in cell less than eleven

Table 4

Kaplan Meier analyses based patient survival, by treatment reqimen

	5-Fluorouracil with Radiation	Gemcitabine with Radiation	Gemcitabine without Radiation	5-Fluorouracil without Radiation	Total sample
Overall survival					
Median survival	19 months	17 months	14 months	22 months	17 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%
Cause-specific survival					
Median survival	20 months	18 months	14 months	27 months	18 months
1 year survival	70.3%	71.2%	54.1%	63.5%	66.4%
3 year survival	22.2%	24.8%	14.8%	46.2%	21.9%
5 year survival	14.5%	16.4%	6.2%	35.2%	13.8%

Table 5

Predictors of Survival on Univariate analysis

	Overall survival		*Cause-specific survival*	
	Hazard Ratio (95% CI)	***P*-value**	**Hazard Ratio (95% CI)**	***P*-value**
Chemotherapy				
5-Fluorouracil	1		1	
Gemcitabine	1.20 (1.02 – 1.41)	0.02	1.21 (1.02 – 1.43)	0.03
Radiotherapy (RT)				
No	1		1	
Yes	0.77 (0.65 – 0.92)	0.004	0.76 (0.63 – 0.91)	0.004
Treatment regimen				
5-Fluorouracil + RT	1		1	
Gemcitabine + RT	0.99 (0.81 – 1.21)	0.92	0.98 (0.79 – 1.20)	0.83
Gemcitabine, No RT	1.43 (1.17 – 1.74)	<0.001	1.45 (1.19 – 1.78)	<0.001
5-Fluorouracil, No RT	0.70 (0.43 – 1.14)	0.16	0.67 (0.40 – 1.13)	0.13
Overall		<0.001		<0.001
Age of diagnosis				
65–69	1		1	
70–74	1.20 (0.97 – 1.47)	0.09	1.14 (0.92 – 1.42)	0.23
75–79	1.32 (1.05 – 1.65)	0.02	1.30 (1.03 – 1.63)	0.03
80+	1.43 (1.08 – 1.89)	0.01	1.42 (1.06 – 1.89)	0.02
Overall		0.04		0.05
Sex				
Female	1		1	
Male	1.16 (0.99 – 1.36)	0.07	1.13 (0.96 – 1.33)	0.15
Race				
White	1		1	
Non-white	1.09 (0.85 – 1.40)	0.48	1.04 (0.80 – 1.35)	0.07
Residence in metro area				
Yes	1		1	
No	0.96 (0.74 – 1.23)	0.72	0.89 (0.68 – 1.16)	0.39
Percent of census tract below the poverty level				
≤ 20%	1		1	
>20%	1.29 (1.01 – 1.66)	0.04	1.22 (0.94 – 1.59)	0.14
Charlson comorbidity index				
0	1		1	
1+	1.22 (1.04 – 1.44)	0.02	1.12 (0.94 – 1.32)	0.22
Cancer sequence				
1st or only cancer	1		1	
Other	1.02 (0.78 – 1.33)	0.90	0.93 (0.70 – 1.25)	0.64

	Overall survival		*Cause-specific survival*	
	Hazard Ratio (95% CI)	***P*-value**	**Hazard Ratio (95% CI)**	***P*-value**
Year of diagnosis				
1998	1		1	
1999	1.30 (0.76 – 2.20)	0.33	1.18 (0.68 – 2.05)	0.56
2000	0.98 (0.64 – 1.50)	0.93	0.95 (0.61 – 1.45)	0.80
2001	1.20 (0.78 – 1.84)	0.41	1.17 (0.75 – 1.81)	0.49
2002	1.12 (0.74 – 1.71)	0.59	1.00 (0.65 – 1.54)	0.99
2003	1.11 (0.74 – 1.68)	0.62	1.10 (0.72 – 1.67)	0.66
2004	1.03 (0.68 – 1.56)	0.88	0.97 (0.63 – 1.48)	0.88
2005	1.27 (0.84 – 1.92)	0.26	1.23 (0.80 – 1.87)	0.35
Overall		0.68		0.65
Tumor site				
Head	1		1	
Other	1.13 (0.94 – 1.37)	0.19	1.10 (0.90 – 1.34)	0.36
Stage				
Ia/Ib	1		1	
IIa	0.95 (0.72 – 1.26)	0.71	0.94 (0.70 – 1.26)	0.67
IIb	1.28 (1.01 – 1.63)	0.05	1.29 (1.00 – 1.65)	0.05
Overall		0.005		0.005
Lymph node status				
Involved (Stage IIb)	1		1	
Not involved (Stagela/Ib/IIa)	0.77 (0.65 – 0.91)	0.002	0.76 (0.64 – 0.90)	0.002
Grade				
Well differentiated	1		1	
Moderately differentiated	1.28 (0.91 – 1.81)	0.15	1.34 (0.93 – 1.92)	0.12
Poorly differentiated	1.61 (1.14 – 2.28)	0.007	1.70 (1.18 – 2.45)	0.005
Overall		0.004		0.003
Surgery				
Radical	1		1	
Total	1.30 (0.87 – 1.93)	0.20	1.34 (0.89 – 2.01)	0.16
Partial	1.13 (0.91 – 1.39)	0.27	1.13 (0.91 – 1.41)	0.25
Overall		0.27		0.22

Table 6

Predictors of Survival on Cox multivariable regression analysis, stratified by grade

	Overall survival						*Cause-specific survival*					
	Poorly differentiated		**Moderately differentiated**		**Well differentiated**		**Poorly differentiated**		**Moderately differentiated**		**Well differentiated**	
	Hazard Ratio (95% CI)	***p***	**Hazard Ratio (95% CI)**	***p***	**Hazard Ratio (95% CI)**	***p***	**Hazard Ratio (95% CI)**	***p***	**Hazard Ratio (95% CI)**	***p***	**Hazard Ratio (95% CI)**	***p***
Treatment regimen												
5-Fluorouracil + RT	1		1		1		1		1		1	
Gemcitabine + RT	0.98 (0.71 – 1.36)	0.90	1.02 (0.76 – 1.38)	0.89	1.22 (0.54 – 2.78)	0.63	1.04 (0.75 – 1.46)	0.80	0.94 (0.69 – 1.29)	0.70	0.93 (0.38 – 2.27)	0.87
Gemcitabine, No RT	1.50 (1.09 – 2.06)	0.01	1.28 (0.94 – 1.73)	0.11	1.07 (0.36 – 3.22)	0.90	1.54 (1.11 – 2.15)	0.01	1.26 (0.92 – 1.72)	0.14	1.56 (0.54 – 4.47)	0.41
5-Fluorouracil, No RT	2.10 (0.90 – 4.90)	0.09	0.42 (0.20 – 0.85)	0.02	0.87 (0.13 – 5.66)	0.88	2.29 (0.98 – 5.36)	0.06	0.39 (0.18 – 0.84)	0.02	0.53 (0.05 – 5.76)	0.60
Overall		0.02		0.03		0.96		0.02		0.03		0.76
Age of diagnosis												
65–69	1		1		1		1		1		1	
70–74	0.95 (0.67 – 1.33)	0.75	1.30 (0.96 – 1.76)	0.09	3.71 (1.28 – 10.7)	0.02	0.85 (0.60 – 1.22)	0.38	1.24 (0.91 – 1.71)	0.18	3.46 (1.11 – 10.77)	0.03
75–79	1.09	0.64	1.54	0.01	0.83	0.78	1.03	0.87	1.46	0.03	0.93	0.92
	(0.75 – 1.60)		(1.10 – 2.14)		(0.21 – 3.23)		(0.70 – 1.52)		(1.03 – 2.05)		(0.23 – 3.79)	
80+	1.31 (0.84 – 2.04)	0.23	1.85 (1.18 – 2.90)	0.007	0.70 (0.17 – 2.82)	0.61	1.30 (0.83 – 2.04)	0.25	1.84 (1.16 – 2.91)	0.009	0.74 (0.17 – 3.28)	0.69
Overall		0.49		0.02		0.02		0.29		0.04		0.06
Sex												
Female	1		1		1		1		1		1	
Male	1.07 (0.82 – 1.40)	0.61	1.25 (0.99 – 1.58)	0.07	0.66 (0.30 – 1.48)	0.32	1.08 (0.81 – 1.42)	0.61	1.18 (0.92 – 1.50)	0.19	0.57 (0.24 – 1.36)	0.20
Race												
White	1		1		1		1		1		1	
Non-white	1.30 (0.82 – 2.07)	0.27	1.02 (0.70 – 1.48)	0.93	1.11 (0.26 – 4.71)	0.88	1.25 (0.77 – 2.02)	0.37	0.98 (0.66 – 1.45)	0.92	0.34 (0.05 – 2.11)	0.25

	Overall survival						*Cause-specific survival*					
	Poorly differentiated		**Moderately differentiated**		**Well differentiated**		**Poorly differentiated**		**Moderately differentiated**		**Well differentiated**	
	Hazard Ratio (95% CI)	***p***	**Hazard Ratio (95% CI)**	***p***	**Hazard Ratio (95% CI)**	***p***	**Hazard Ratio (95% CI)**	***p***	**Hazard Ratio (95% CI)**	***p***	**Hazard Ratio (95% CI)**	***p***
Percent of census tract below the poverty level												
≤ 20%	1		1		1		1		1		1	
>20%	1.45 (0.91 – 2.32)	0.12	1.44 (1.02 – 2.03)	0.04	0.65 (0.14 – 3.04)	0.59	1.45 (0.89 – 2.36)	0.14	1.32 (0.92 – 1.91)	0.14	1.95 (0.35 – 10.78)	0.45
Charlson comorbidity index												
0	1		1		1		1		1		1	
1+	1.24 (0.94 – 1.63)	0.12	1.13 (0.88 – 1.44)	0.34	3.50 (1.42 – 8.65)	0.007	1.06 (0.79 – 1.41)	0.70	1.11 (0.86 – 1.44)	0.41	3.28 (1.26 – 8.55)	0.02
Tumor site												
Head	1		1		1		1		1		1	
Other	0.96 (0.70 – 1.32)	0.80	1.39 (1.04 – 1.86)	0.02	1.47 (0.51 – 4.23)	0.48	0.95 (0.69 – 1.32)	0.77	1.39 (1.03 – 1.88)	0.03	1.36 (0.44 – 4.21)	0.60
Lymph node status												
Involved (Stage IIb)	1		1		1		1		1		1	
Not involved (StageIa/Ib/IIa)	0.73 (0.54 – 0.99)	0.04	0.81 (0.63 – 1.03)	0.09	0.94 (0.42 – 2.10)	0.87	0.76 (0.55 – 1.03)	0.08	0.82 (0.64 – 1.07)	0.14	0.59 (0.24 – 1.47)	0.26

Table 7

Predictors of Overall Survival on Cox multivariable regression analysis (stratified by grade) for the expanded 5-FU population only

	Poorly differentiated		Moderately differentiated		Well differentiated	
	Hazard Ratio (95% CI)	***P*-value**	**Hazard Ratio (95% CI)**	***P*-value**	**Hazard Ratio (95% CI)**	***P*-value**
Treatment regimen						
5-Fluorouracil + Radiotherapy	1		1		1	
5-Fluorouracil, No Radiotherapy	1.77 (0.97 – 3.23)	0.06	0.54 (0.32 – 0.92)	0.02	0.52(0.11 – 2.43)	0.41
Age of diagnosis						
65–69	1		1		1	
70–74	1.12 (0.75 – 1.66)	0.58	1.13 (0.80 – 1.60)	0.49	3.17 (1.42 – 7.06)	0.005
75–79	1.09 (0.72 – 1.66)	0.69	1.20 (0.82 – 1.75)	0.35	1.06 (0.37 – 3.00)	0.92
80+	1.07 (0.61 – 1.87)	0.83	1.40 (0.73 – 2.71)	0.31	0.51 (0.09 – 2.73)	0.43
Overall		0.96		0.68		0.01
Sex						
Female	1		1		1	
Male	1.07 (0.77 – 1.48)	0.70	1.03 (0.77 – 1.37)	0.85	1.40 (0.60 – 3.30)	0.44
Race						
White	1		1		1	
Non-white	1.17 (0.71 – 1.92)	0.54	1.36 (0.89 – 2.06)	0.16	1.92 (0.33 – 11.24)	0.47
Percent of census tract below the poverty level						
≤ 20%	1		1		1	
>20%	1.08 (0.59 – 1.99)	0.80	1.52 (0.93 – 2.47)	0.09	0.27 (0.02 – 3.19)	0.30
Charlson comorbidity index						
0	1		1		1	
1+	1.33 (0.96 – 1.85)	0.09	0.95 (0.71 – 1.29)	0.76	1.66 (0.69 – 3.98)	0.26
Tumor site						
Head	1		1		1	
Other	1.07 (0.72 – 1.60)	0.73	1.41 (1.01 – 1.95)	0.04	1.78 (0.75 – 4.22)	0.19
Lymph node status						
Involved (Stage IIb)	1		1		1	
Not involved (StageIa/Ib/IIa)	0.90 (0.65 – 1.25)	0.53	0.76 (0.57 – 1.01)	0.06	0.55 (0.27 – 1.15)	0.11

Table 8

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

	Regimen	No. of patients	Comments	Well differentiated	Moderately differentiated	Poorly differentiated	Median survival
EORTC (1999)[a]	5-FU with Radiotherapy	60	Limited to pancreatic head tumors	33%	40%	27%	17.1 months
ESPAC 1 (2004)	5-FU with Radiotherapy	145		20%	55%	14%	15.9 months
RTOG (2008)[b]	5-FU with Radiotherapy	201	Limited to pancreatic head tumors	17%	54%	23%	16.9 months
ESPAC 1 (2004)[c]	5-FU without radiotherapy	75		23%	47%	22%	21.6 months
ESPAC 3 (2010)	5-FU without radiotherapy	551		15%	60%	25%	23.0 months

[a]The described data on tumor grading was for the entire group (periampullary and pancreatic head tumors). Differences in grade were not separately described for pancreatic head tumors.

[b]The described data on tumor grading was for the entire group (all pancreatic tumors). Differences in grade were not separately described for pancreatic head tumors.

[c]The group described is a combination of patients who either received 5-fluorouracil alone or underwent observation alone. No statistics were separately available for patients who received 5-fluorouracil alone.