

## RESEARCH ARTICLE

# Racial and Social Economic Factors Impact on the Cause Specific Survival of Pancreatic Cancer: A SEER Survey

Rex Cheung

### Abstract

**Background:** This study used Surveillance, Epidemiology and End Results (SEER) pancreatic cancer data to identify predictive models and potential socio-economic disparities in pancreatic cancer outcome. **Materials and Methods:** For risk modeling, Kaplan Meier method was used for cause specific survival analysis. The Kolmogorov-Smirnov's test was used to compare survival curves. The Cox proportional hazard method was applied for multivariate analysis. The area under the ROC curve was computed for predictors of absolute risk of death, optimized to improve efficiency. **Results:** This study included 58,747 patients. The mean follow up time (S.D.) was 7.6 (10.6) months. SEER stage and grade were strongly predictive univariates. Sex, race, and three socio-economic factors (county level family income, rural-urban residence status, and county level education attainment) were independent multivariate predictors. Racial and socio-economic factors were associated with about 2% difference in absolute cause specific survival. **Conclusions:** This study found significant effects of socio-economic factors on pancreas cancer outcome. These data may generate hypotheses for trials to eliminate these outcome disparities.

**Keywords:** Pancreatic cancer - radiotherapy - SEER - socio-economic disparity - cause specific survival

*Asian Pacific J Cancer Prev*, 14 (1), 159-163

### Introduction

Pancreatic cancer is an aggressive disease with an actuarial mortality rate is about 90% (Strimpakos et al., 2012). For operable pancreatic cancers, the patients are usually treated with adjuvant chemoradiotherapy (Regine et al., 2008) in the United States and with chemotherapy (Neoptolemos et al., 2012) in Europe. Systematic therapy is the mainstay for metastatic pancreatic cancer (Tokh et al., 2012). The results for current managements are disappointing, active investigations are under way to improve the outcome of pancreatic cancer (Strimpakos et al., 2012). There are scant data on the effects of socio-economic factors on the pancreatic cancer survival (van Loon et al., 1995; Gill and Martin, 2002). This study is a part of a larger effort to survey the Surveillance, Epidemiology and End Results (SEER) for socio-economic disparities in cancer treatment outcomes. In particular, this study investigated racial and socio-economic factors on the cause specific survival of pancreas cancer.

### Materials and Methods

SEER registers public use data. These data can be used for analysis with no internal review board approval needed. For risk modeling, Kaplan Meier method was used for cause specific survival analysis. Kolmogorov-Smirnov's test was used to compare survival curves. Cox

proportional hazard method was used for multivariate analysis. The variables were coded as below. SEER stage: 0=local/regional, 1=metastatic/un-staged; Grade: 0=grade 1-2, 1=grade 3-4, ungraded; Sex: 0=female, 1=male; Race: 0=non African American, 1=African American; Rural Urban residence status: 0=urban, 1= rural; County level % college graduate: 0>25%, 1≤25%; County level family income: 0=more than \$50k/year, 1=less or equal to \$50k/years. SEER Clinical Outcome Prediction Expert (SCOPE) (Cheung, 2012) was used to mine SEER data and construct accurate and efficient prediction models. The data were obtained from SEER 18 database. SEER\*Stat (<http://seer.cancer.gov/seerstat/>) was used for listing the cases. The filter used was: Site and Morphology. ICD-O-3 Hist/behav, malignant='8003/3: Malignant tumor, pancreatic type'. Patients diagnosed from 2004-2009 were included. The areas under the receiver operating characteristic (ROC) curve were computed for absolute cause specific deaths. These ROC models were optimized to improve efficiency. All of the statistics and programming of this study were performed in Matlab ([www.mathworks.com](http://www.mathworks.com)). The variable 'SEER cause-specific death classification' was used as the outcome variable.

### Results

This study included 58747 patients (Table 1-2, Figure 1). The mean (S.D.) age was 70.2 (12.9) years. The mean

**Table 1. The Risk Models Include the Socio-demographic, Tumor and Treatment Factors for Pancreatic Cancer**

| Initial univariate risk models                       |                                                            | Number | %      | ROC Area | S.D. |
|------------------------------------------------------|------------------------------------------------------------|--------|--------|----------|------|
| Study population                                     |                                                            | 58747  |        |          |      |
| Age of diagnosis:                                    | Mean/S.D.                                                  | 70/13  |        |          |      |
|                                                      | <20 years                                                  | 32     | 0.054  | 0.5      | 0    |
|                                                      | ≥20 years old                                              | 58715  | 99.950 |          |      |
| Follow up (months):                                  |                                                            | 8/11   |        |          |      |
| Sex:                                                 | Female                                                     | 29590  | 50.370 | 0.51     | 0    |
|                                                      | Male                                                       | 29157  | 49.630 |          |      |
| SEER historic stage A:                               | Distant, level III*                                        | 29764  | 50.660 | 0.6      | 0.01 |
|                                                      | Regional, level II**                                       | 15813  | 26.920 |          |      |
|                                                      | Localized, level I***                                      | 5345   | 9.098  | 0.59     | 0    |
|                                                      | Unstaged, level IV                                         | 7825   | 13.320 |          |      |
| Grade:                                               | Poorly differentiated; Grade III                           | 7612   | 12.960 | 0.56     | 0    |
|                                                      | Moderately differentiated; Grade II                        | 7359   | 12.530 |          |      |
|                                                      | Unknown                                                    | 40629  | 69.160 |          |      |
|                                                      | Well differentiated; Grade I                               | 2594   | 4.416  |          |      |
|                                                      | Undifferentiated; anaplastic; Grade IV                     | 553    | 0.941  |          |      |
| Rural-Urban Continuum Code 2003                      | Counties in metropolitan areas ge 1 million pop            | 35380  | 60.220 | 0.5      | 0    |
|                                                      | Counties in metropolitan areas of 250,000-1 million pop    | 11082  | 18.860 |          |      |
|                                                      | Urban pop of ge 20,000 adjacent to a metropolitan area     | 1807   | 3.076  |          |      |
|                                                      | Unknown/missing/no match                                   | 8      | 0.014  |          |      |
|                                                      | Urban pop of ge 20,000 not adjacent to a metropolitan area | 884    | 1.505  |          |      |
|                                                      | Counties in metropolitan areas of lt 250 thousand pop      | 4919   | 8.373  |          |      |
|                                                      | Urban pop of 2,500-19,999, adjacent to a metro area        | 2310   | 3.932  |          |      |
|                                                      | Urban pop of 2,500-19,999, not adjacent to a metro area    | 1470   | 2.502  |          |      |
|                                                      | Comp rural lt 2,500 urban pop, adjacent to a metro area    | 440    | 0.749  |          |      |
|                                                      | Comp rural lt 2,500 urban pop, not adjacent to metro area  | 383    | 0.652  |          |      |
|                                                      | Unknown/missing/no match (Alaska - Entire State)           | 64     | 0.109  |          |      |
| County Family Income:                                | ≥\$50000                                                   | 32540  | 55.390 | 0.51     | 0.01 |
|                                                      | <\$50000                                                   | 26207  | 44.610 |          |      |
| County % college graduate:                           | ≥25%                                                       | 27224  | 46.340 | 0.52     | 0    |
|                                                      | <25%                                                       | 31523  | 53.660 |          |      |
| Race:                                                | White/others                                               | 51839  | 88.240 | 0.5      | 0    |
|                                                      | Black                                                      | 6908   | 11.760 |          |      |
| Radiation treatment given:                           | None                                                       | 46993  | 79.990 | 0.52     | 0    |
|                                                      | Refused                                                    | 640    | 1.089  |          |      |
|                                                      | Recommended, unknown if administered                       | 326    | 0.555  |          |      |
|                                                      | Unknown                                                    | 2339   | 3.981  |          |      |
|                                                      | Beam radiation                                             | 8219   | 13.990 |          |      |
|                                                      | Radiation, NOS method or source not specified              | 187    | 0.318  |          |      |
|                                                      | Radioisotopes                                              | 22     | 0.037  |          |      |
|                                                      | Combination of beam with implants or isotopes              | 8      | 0.014  |          |      |
|                                                      | Radioactive implants                                       | 13     | 0.022  |          |      |
|                                                      | Not recommended                                            | 39818  | 67.780 | 0.58     | 0    |
| Surgery:                                             | Surgery performed                                          | 9500   | 16.170 |          |      |
|                                                      | Recommended but not performed, unknown reason              | 2592   | 4.412  |          |      |
|                                                      | Recommended but not performed, patient refused             | 977    | 1.663  |          |      |
|                                                      | Unknown; death certificate or autopsy only case            | 2472   | 4.208  |          |      |
|                                                      | Not recommended, contraindicated due to other conditions   | 2944   | 5.011  |          |      |
|                                                      | Not performed, patient died prior to recommended surgery   | 175    | 0.298  |          |      |
|                                                      | Recommended, unknown if performed                          | 269    | 0.458  |          |      |
|                                                      | N/A not first tumor                                        | 10542  | 17.940 |          |      |
| SEER cause-specific death classification             | Dead                                                       | 37737  | 64.240 |          |      |
|                                                      | Alive or dead of other cause                               | 10468  | 17.820 |          |      |
|                                                      |                                                            |        |        |          |      |
| Derived AJCC Stage Group, 6 <sup>th</sup> ed (2004+) | IA, level I                                                | 845    | 1.438  | 0.57     | 0.01 |
|                                                      | IB, level II                                               | 2820   | 4.800  |          |      |
|                                                      | IIA, level III                                             | 5234   | 8.909  |          |      |
|                                                      | IIB, level IV                                              | 6256   | 10.650 |          |      |
|                                                      | IINOS, level V                                             | 450    | 0.766  |          |      |
|                                                      | III, level VI                                              | 4330   | 7.371  |          |      |
|                                                      | IV, level VII                                              | 27147  | 46.210 |          |      |
|                                                      | UNK Stage, level VIII                                      | 10965  | 18.660 |          |      |
|                                                      | NA, level IX                                               | 700    | 1.192  |          |      |

\*Model: I,II,III,IV; \*\*Model: optimized; \*\*\*Model: (I,II),III,IV

**Table 2. Absolute Cause Specific Mortality (%) Associated with Different Models**

| Variables: Risk models                                                                                                                                                         | No. at risk | expected risk of death |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------|------------------------|
| Age of diagnosis:                                                                                                                                                              |             |                        |
| <20 years                                                                                                                                                                      | 32          | 0.16                   |
| ≥20 years old                                                                                                                                                                  | 58715       | 0.64                   |
| Sex: Female                                                                                                                                                                    | 29590       | 0.65                   |
| Male                                                                                                                                                                           | 29157       | 0.63                   |
| Grade: Well differentiated; Grade I                                                                                                                                            | 2594        | 0.42                   |
| Moderately differentiated; Grade II                                                                                                                                            | 7359        | 0.54                   |
| Poorly differentiated; Grade III                                                                                                                                               | 7612        | 0.63                   |
| Undifferentiated; anaplastic; Grade IV                                                                                                                                         | 553         | 0.62                   |
| Unknown                                                                                                                                                                        | 40629       | 0.68                   |
| Rural-Urban Continuum Code 2003:                                                                                                                                               |             |                        |
| Counties in metropolitan areas ge 1 million pop/ Counties in metropolitan areas of 250,000-1 million pop/ Urban pop of ge 20,000 adjacent to a metropolitan area versus Others | 48269       | 0.64                   |
|                                                                                                                                                                                | 10478       | 0.66                   |
| County Family Income:                                                                                                                                                          |             |                        |
| ≥\$50000                                                                                                                                                                       | 32540       | 0.63                   |
| <\$50000                                                                                                                                                                       | 26207       | 0.66                   |
| County % college graduate:                                                                                                                                                     |             |                        |
| ≥25                                                                                                                                                                            | 27224       | 0.63                   |
| <25                                                                                                                                                                            | 31523       | 0.65                   |
| Race: White/others                                                                                                                                                             | 51839       | 0.64                   |
| Black                                                                                                                                                                          | 6908        | 0.65                   |
| Radiation treatment given:                                                                                                                                                     |             |                        |
| Beam Radiation                                                                                                                                                                 | 8219        | 0.58                   |
| Others                                                                                                                                                                         | 50528       | 0.65                   |
| Reason no cancer-directed surgery:                                                                                                                                             |             |                        |
| Surgery performed                                                                                                                                                              | 9500        | 0.41                   |
| Others                                                                                                                                                                         | 49247       | 0.69                   |
| SEER Staging:                                                                                                                                                                  |             |                        |
| Localized                                                                                                                                                                      | 5345        | 0.45                   |
| Regional                                                                                                                                                                       | 15813       | 0.55                   |
| Distant                                                                                                                                                                        | 29764       | 0.71                   |
| Un-staged/others                                                                                                                                                               | 7825        | 0.71                   |
| Derived AJCC Stage Group, 6 <sup>th</sup> ed (2004+):                                                                                                                          |             |                        |
| IA                                                                                                                                                                             | 845         | 0.32                   |
| IB                                                                                                                                                                             | 2820        | 0.46                   |
| IIA                                                                                                                                                                            | 5234        | 0.54                   |
| IIB                                                                                                                                                                            | 6256        | 0.52                   |
| IINOS                                                                                                                                                                          | 450         | 0.63                   |
| III                                                                                                                                                                            | 4330        | 0.64                   |
| IV                                                                                                                                                                             | 27147       | 0.71                   |
| UNK Stage                                                                                                                                                                      | 10965       | 0.69                   |
| NA                                                                                                                                                                             | 700         | 0.25                   |

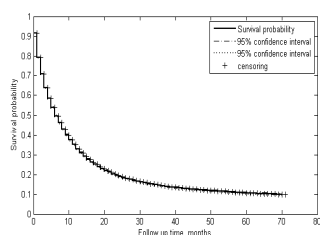
follow up time (S.D.) was 7.6 (10.6) months. SEER stage (Figure 2a) and grade (Figure 2b) were strongly predictive univariates. Sex, race, and three socio-economic factors (SEER county level family income, rural-urban residence status, and county level education attainment) were independent multivariate predictors (Table 3). Racial and socio-economic factors were associated with about 2% difference in absolute cause specific survival (Table 2). The absolute risk of death from pancreatic cancer was 64.2% for the entire study population. Only 32 SEER patents younger than 20 years old were diagnosed with pancreatic cancer from 2004-2009. They had a 15.6% risk of cause specific death compared with 64.3% for the older patients (Table 2). There was slightly higher risk of cause specific death for female and male patients (Table 2). Pancreatic adenocarcinomas accounted for about 1/3 of all cases. Pancreatic adenocarcinomas had a similar risk of cause specific death compared with other histological types (Table 2). The risk of cause specific death was 42% for grade I, 54% for grade II, 63% for grade III and 62% for grade IV. Being un-graded had a 68% risk of cause specific death.

SEER staging was more accurate in terms of measured ROC areas (Table 1). Using SEER stage, there was a 45% and 55% risk of death respectively for localized and regional disease respectively. This risk increased to more than 71% for distant metastasis. When the staging was not complete, it was associated with 71% risk of death (Table 2) that is same as that of the metastatic disease. The three socio-economic factors, lower county family income, rural residence, and lower county education attainment were associated with about 2% disadvantage in cause specific survival. Radiotherapy had a 7.6% cause specific survival advantage. Surgery was associated with 40.9% risk of pancreatic cancer death while 68.7% risk of death was associated with no surgery performed. For the SEER stage model, the staging was defined as localized, regional, distant or incompletely staged/others. The stage status was highly predictive of cause specific survival (ROC area or 0.60). This 4-tiered staging model was optimized to a 3-tiered model consisted of localized/regional versus distant versus un-staged/others with a ROC area of 0.59

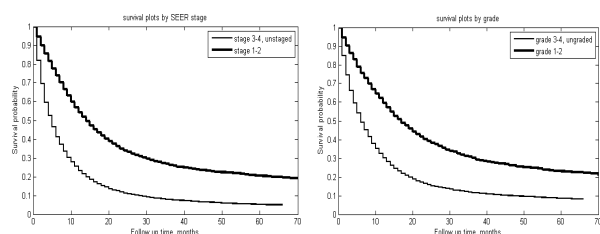
**Table 3. Univariate Kolmogorov-Smirnov's 2-sample Tests and Multivariate Cox Proportional Hazard Models**

|                                |                                              | Kolmogorov-Smirnov 2-sample test |          |        | Cox proportional hazard model |        |        |
|--------------------------------|----------------------------------------------|----------------------------------|----------|--------|-------------------------------|--------|--------|
|                                |                                              | l                                | p        | k      | beta                          | s.e.   | p      |
| SEER stage                     | 0=local/regional<br>1=metastatic/unstaged    | 1                                | 1.32E-17 | 0.7619 | 0.7741                        | 0.0118 | 0      |
| Grade                          | 0=grade 1-2<br>1=grade 3-4, ungraded         | 1                                | 4.97E-16 | 0.7231 | 0.5541                        | 0.0156 | 0      |
| Sex                            | 0=female<br>1=male                           | 0                                | 0.1692   | 0.1896 | -0.0391                       | 0.0105 | 0.0001 |
| Race                           | 0=non African American<br>1=African American | 0                                | 1        | 0.0565 | 0.0811                        | 0.016  | 0      |
| Rural Urban residence          | 0=urban<br>1=rural                           | 0                                | 0.9503   | 0.0908 | 0.0543                        | 0.0143 | 0.0001 |
| County level %college graduate | 0>25%<br>1≤25%                               | 0                                | 0.3948   | 0.1538 | 0.0311                        | 0.0144 | 0.0311 |
| County level family income     | 0≥\$50k/year<br>1≤\$50k/year                 | 0                                | 0.2026   | 0.1818 | 0.0614                        | 0.0148 | 0      |

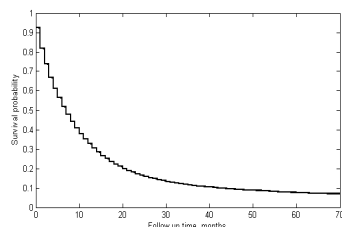
\*The l is equal to 1 for positive pair-wise comparison of the survival curves as measured by statistics k. Cox proportional hazard coefficients and their standard errors are respectively beta and s.e



**Figure 1. Kaplan-Meier Plot of Pancreatic Cancer Cause Specific Survival of SEER Patients.** The 95% confidence intervals and censoring markers '+' were shown but were very close to each others



**Figure 2. The Kaplan-Meier Survival Plots by Risk Stratification Based on a) SEER Stage and b) Grade.** The results of their respective 2-sample Kolmogorov-Smirnov's tests were shown in Table 3



**Figure 3. The Cox Proportional Hazard Fit Based on the Parameters**

(Table 1).

Figure 2 shows the survival curves separated by univariates including a) SEER stage and b) grade. Table 3 shows the results of the univariate analysis. SEER stage and grade were very strong predictors and were very statistically significant. Sex, race and socio-economic predictors were not significant in univariate analysis (Table 3). When all the pretreatment and socio-economic factors were analyzed in a multivariate analysis, all of the predictors became statistically significant (Table 3). Female sex was shown to have a higher cause specific mortality (Table 2) and under Cox multivariate analysis (Table 3). The Cox proportional hazard fit for the model is shown in Figure 3.

## Discussion

The effects of socio-economic factors on the treatment outcome of pancreas cancer have been controversial. Some studies have linked low socio-economic status with poor pancreas outcome (Brown et al., 1998). This link has been attributed to an increased distance to major medical centers (Gill and Martin, 2002), and a lack of specialization (van Oost et al., 2006). Other studies have shown a lack of effects from socio-economic factors on pancreas cancer treatment outcome (Kuhn et al., 2010). The Surveillance Epidemiology and End Results (SEER) cancer registry

data have been to build prognostic models for pancreatic cancer (Baine et al., 2011; Singal et al., 2012). SEER data have been a particularly important source for identifying disparities in cancer treatment. However, the nature of the socio-economic barriers in good outcome for pancreatic cancer has not been well characterized. This study also examined socioeconomic factors that were predictors of treatment outcome. Receiver operating characteristic (ROC) curve was used to construct and measure the accuracy of models from (Cheung, 2012) SEER outcome data. In addition to constructing the best predictors of absolute cause specific survival for pancreas cancer (Figure 1 and Table 1-2), this study also aimed to identify barriers to good treatment outcome that might be discernable only from a large national database.

In order to be consistent over decades, SEER historical stage abstracts the staging into simple but important stages for cancer progression: localized, regional and distant. SEER stage was highly predictive of patient outcome (Table 1, 2). The model has a ROC area of 0.60. Thus complete staging is important in this disease since it will aid patient selection and council. Regional pancreatic cancer was an aggressive disease; there was a 55% risk of cause specific (Table 2). These are patients most likely to benefit from radiotherapy (Franko et al., 2012; Worni et al., 2012). Thus radiation oncologist should be more attentive in recommending RT for these patients. After optimization the 4-tiered stage model was reduced to a 3-tiered model based on ROC area calculations (Table 1) with essentially the same ROC area but with the improved simplicity.

An important and thought provoking recent 10-15 years long term study has shown that moving patients from low income neighborhoods to high income ones improve their obesity and diabetes (Ludwig et al., 2011). It is conceivable that similar effects may be observed for cancer patients including pancreatic cancer patients. In this study, SEER stage (Figure 2a) and grade (Figure 2b) were significant predictors of actuarial cause specific survival of pancreas cancer (Table 3). The socio-economic factors were not significant as univariate predictors, this were probably due the masking effects of the very strong SEER stage and grade predictors. When these factors were accounted for in a multivariate Cox (Figure 3) analysis, rural residence, living in low income and low education attainment neighborhoods decreased cause specific survival of pancreatic cancer (Table 3).

In conclusion, this study has found significant effects of socio-economic factors on pancreas cancer outcome. These data may generate hypotheses for trials to eliminate these outcome disparities.

## References

- Baine M, Sahak F, Lin C, et al (2011). Marital status and survival in pancreatic cancer patients: a SEER based analysis. *PLoS One*, **6**, 21052.
- Brown J, Harding S, Bethune A, Rosato M (1998). Longitudinal study of socio-economic differences in the incidence of stomach, colorectal and pancreatic cancers. *Popul Trends*, **94**, 35-41.

- Cheung R (2012). Poor treatment outcome of neuroblastoma and other peripheral nerve cell tumors may be related to under usage of radiotherapy and socio-economic disparity: a us SEER data analysis. *Asian Pac J Cancer Prev*, **13**, 4587-91.
- Franko J, Puri DR, Goldman CD (2012). Impact of radiation therapy sequence on survival among patients with resected pancreatic head ductal carcinoma. *Ann Surg Oncol*, **19**, 26-30.
- Gill AJ, Martin IG (2002). Survival from upper gastrointestinal cancer in New Zealand: the effect of distance from a major hospital, socio-economic status, ethnicity, age and gender. *ANZ J Surg*, **72**, 643-6.
- Kuhn Y, Koscielny A, Glowka T, et al (2010). Postresection survival outcomes of pancreatic cancer according to demographic factors and socio-economic status. *Eur J Surg Oncol*, **36**, 496-500.
- Ludwig J, Sanbonmatsu L, Gennetian L, et al (2011). Neighborhoods, obesity, and diabetes--a randomized social experiment. *N Engl J Med*, **365**, 1509-19.
- Neoptolemos JP, Moore MJ, Cox TF, et al (2012). Effect of adjuvant chemotherapy with fluorouracil plus folinic acid or gemcitabine vs observation on survival in patients with resected periampullary adenocarcinoma: the ESPAC-3 periampullary cancer randomized trial. *JAMA*, **308**, 147-56.
- Regine WF, Winter KA, Abrams RA, et al (2008). Fluorouracil vs gemcitabine chemotherapy before and after fluorouracil-based chemoradiation following resection of pancreatic adenocarcinoma: a randomized controlled trial. *JAMA*, **299**, 1019-26.
- Singal V, Singal AK, Kuo YF (2012). Racial disparities in treatment for pancreatic cancer and impact on survival: a population-based analysis. *J Cancer Res Clin Oncol*, **138**, 715-22.
- Strimpakos AS, Syeasigos KN, Saif MW (2012). Translational research. New findings and potential future applications in pancreatic adenocarcinoma. *JOP*, **13**, 177-9.
- Tokh M, Bathini V, Saif MW (2012). First-line treatment of metastatic pancreatic cancer. *JOP*, **13**, 159-62.
- van Loon AJ, Brug J, Goldbohm RA, et al (1995). Differences in cancer incidence and mortality among socio-economic groups. *Scand J Soc Med*, **23**, 110-20.
- van Oost FJ, Luiten EJ, van de Poll-Franse LV, et al (2006). Outcome of surgical treatment of pancreatic, peri-ampullary and ampullary cancer diagnosed in the south of The Netherlands: a cancer registry based study. *Eur J Surg Oncol*, **32**, 548-52.
- Worni M, Akushevich I, Gloor B, et al (2012). Adjuvant radiotherapy in the treatment of invasive intraductal papillary mucinous neoplasm of the pancreas: an analysis of the surveillance, epidemiology, and end results registry. *Ann Surg Oncol*, **19**, 1316-23.