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Management of Patients with Pancreatic Adenocarcinoma: National Trends in Patient Selection, Operative Management, and Use of Adjuvant Therapy

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Abstract

BACKGROUND—Surgical resection remains the only potentially curative option for patients with pancreatic adenocarcinoma (PAC). Advances in surgical technique and perioperative care have reduced perioperative mortality; however, temporal trends in perioperative morbidity and the use of adjuvant therapy on a population basis remain ill-defined.

STUDY DESIGN—Using Surveillance, Epidemiology, and End Results–Medicare data, 2,461 patients with resected PAC were identified from 1991 to 2005. We examined trends in preoperative comorbidity indices, adjuvant treatment, type of pancreatic resection, and changes in morbidity and mortality during 4 time intervals (ie, 1991–1996, 1997–2000, 2001–2003, and 2003–2005).

RESULTS—The majority of patients underwent pancreaticoduodenectomy (n = 1,945; 79%). There was a temporal increase in mean patient age (p < 0.05) and the number of patients with multiple preoperative comorbidities (Elixhauser comorbidities 3: 1991–1996, 10% vs 2003–2005, 26%; p < 0.001). Perioperative morbidity (53%) did not, however, change over time (p = 0.97) and 30-day mortality decreased by half (1991–1996: 6% vs 2003–2005: 3%; p = 0.04). Overall, 51% (n = 1,243) of patients received adjuvant therapy, with the majority receiving chemoradiation (n = 817; 33%). Among patients who received adjuvant therapy, factors associated with receipt of adjuvant chemotherapy alone relative to chemoradiation included older patient age (odds ratio = 1.75; p < 0.001) and 3 medical comorbidities (odds ratio = 1.57; p = 0.007). Receipt of adjuvant chemotherapy alone also increased over time (2003–2005 vs 1991–1996, odds ratio = 2.21; p < 0.001).

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Study conception and design: Mayo, Herman, Cameron, Nathan, Edil, Choti, Schulick, Pawlik

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CONCLUSIONS—Perioperative 30-day mortality associated with resection for PAC decreased by one-half from 1991 to 2005. Although patients undergoing resection for PAC were older and had more preoperative comorbidities, the incidence of perioperative complications remained stable. The relative use of adjuvant chemotherapy alone vs chemoradiation therapy for PAC has increased in the United States during the 15 years examined.

Pancreatic adenocarcinoma (PAC) remains one of the most challenging gastrointestinal malignancies, with little improvement in long-term survival during the past 20 years. In 2010, the American Cancer Society reported 43,140 new PAC cases with 36,800 associated deaths.¹ During the last several decades, advances in surgical techniques and perioperative care have substantially reduced perioperative mortality to <5% in high-volume centers.² Perioperative morbidity and complications, including pancreatic fistula, still remain between 15% and 50%, even in institutions with high volumes of pancreatic operations.^{2,3} Although data on long-term outcomes after PAC surgery have been described previously,² population-based data on temporal changes in patient selection, perioperative management, morbidity, and use of adjuvant therapy after surgery for PAC remain ill-defined.

Despite multiple randomized trials that have examined various adjuvant treatment regimens, there is still no consensus on what constitutes the most effective adjuvant treatment regimen—a fact that is reflected in the 2011 National Comprehensive Cancer Network guidelines.⁴ Recent reports from population-based analyses and from the most recent randomized controlled trials provide 5-year survival estimates ranging from 10% to 20% in patients resected with curative intent and treated with adjuvant chemoradiation (CRT).^{5–11} Results of recent adjuvant trials, including the European Study Group for Pancreatic Cancer-1,⁹ Radiation Therapy Oncology Group 97-04,¹¹ and Charité Onkologie-001¹⁰ have called into question the value of postoperative CRT compared with chemotherapy alone. Current trends in the relative use of adjuvant CRT vs chemotherapy only for patients undergoing resection with curative intent for PAC in the United States have not been examined using the Surveillance, Epidemiology, and End Results (SEER)–Medicare database since the reporting of major clinical trials.⁵ The objective of the current study was to evaluate trends in the type of adjuvant treatment (ie, CRT vs chemotherapy alone) that patients received after surgical resection of PAC among Medicare beneficiaries in the United States using SEER-Medicare data. Linkage of the SEER database with Medicare billing information allows for capture of population-based data on upwards of 26% of the US population.¹² Specifically, SEER-Medicare data have been evaluated for effectiveness in identifying persons receiving systemic chemotherapy¹³ and radiation treatment.¹⁴ In addition, use of SEER-Medicare data has been noted to be more effective at capturing perioperative comorbidities, types of procedures, and treatments, compared with the use of either database alone.¹⁵ As such, we also sought to define trends in patient comorbidities, as well as characterize the specific use of perioperative and operative procedures and treatments in patients with resected PAC on a population basis over time.

METHODS

Data source

This study was a retrospective analysis of prospectively collected data from the linked SEER-Medicare database from 1991–2005. The SEER-Medicare database represents the unique linkage of 2 large population-based sources of data that provide detailed information about Medicare beneficiaries with cancer. The SEER database is derived from 18 cancer registries representing approximately 26% of the US population and is maintained by the National Cancer Institute.¹⁶ The SEER dataset includes information on patient demographics, tumor and disease characteristics, cancer-associated treatments, use of cancer-directed surgery and medical therapy, and survival for individuals with cancer. The

linkage of SEER data to Medicare claims is performed by the National Cancer Institute and Center for Medicare and Medicaid Services. For Medicare-eligible individuals, the linked SEER-Medicare database also includes Medicare claims for covered health care services, including hospital, physician, outpatient, home health, and hospice bills, from the date of the individual's enrollment until the time of death.¹⁷ The linked SEER-Medicare database is available beginning in 1991 and has successfully matched 93% of individuals aged 65 years or older at the time of primary cancer diagnosis to their Medicare enrollment file.

Study population

All Medicare-enrolled patients aged 64 years or older diagnosed with incident malignant PAC between 1991 and 2005 in a SEER area were evaluated for inclusion. Although Medicare covers patients 65 years or older, we included patients 64 years or older from SEER to capture any patients that were diagnosed at age 64 but were then treated under Medicare coverage at age 65. Patients with PAC were identified by the *International Classification of Diseases for Oncology* (3rd ed) topography, behavior, and histology codes.¹⁸ Histology codes (Table 1) were selected to only identify patients with adenocarcinoma; other histology codes (eg, carcinoid, intraductal mucinous neoplasm, etc) were excluded. Identification of patients with resected PAC was accomplished using the ICD-9-CM diagnosis and procedure codes and CPT codes for various pancreatic operations (Table 2, under "Pancreas"). Patients who did not undergo operative management of their PAC were excluded from analysis (Fig. 1) as were patients undergoing an open pancreatic biopsy or other procedures done without curative intent. Finally, patients with metastatic or unstaged disease as indicated by the SEER dataset were excluded from analysis. The study cohort included only patients enrolled in both Medicare Parts A and B who were not enrolled in a managed care plan during the study period.

Outcomes and predictor variables

Data on perioperative procedures, treatments, and complications were selected a priori based on clinical relevance and then identified from the Medicare database using both ICD-9-CM diagnosis and procedure codes, as well as CPT codes (Table 2). Information on chemotherapy was designated as preoperative (within 3 months before) and adjuvant (within 6 months after) in relation to the pancreatic operation. Medicare billing codes to assess a wide range of outcomes have previously been demonstrated to be valid.¹⁹ Information on age, sex, race, marital status, and geographic region were obtained from the SEER portion of the database. Variables were transformed into categorical and indicator variables where appropriate. The Elixhauser comorbidity index, a comprehensive set of 30 comorbidity measures, was used to identify and adjust for comorbid conditions.^{20–24} Comorbid diagnoses related to the patient's admission diagnosis (eg, solid tumor), as well as any comorbid condition with a frequency <5, were excluded so that a total of 20 comorbidities remained for analysis.

Statistical analyses

Mean values were used to describe continuous data, with discrete variables displayed as totals and frequencies. Cells with <11 cases per variable cell were relabeled as "<11 (<%)” in compliance with the National Cancer Institute regulation for reporting of SEER-Medicare data. For purposes of analyses, the distribution of the total number of comorbid conditions per patient was divided into approximate quartiles: 0, 1, 2, and 3 comorbidities. When assessing temporal trends, data were similarly separated into calendar year quartiles (1991–1996, 1997–2000, 2001–2002, and 2003–2005) based on the year of operation. Trends in ordinal data were evaluated using the linear-by-linear association test²⁵ and the differences in mean values for continuous variables across time were assessed using ANOVA test. The linear-by-linear test of trend offers a measure of significance for ordinal variables (such as

calendar year quartiles ordered from lowest to highest) and is preferred when testing the significance of linear relationship between ordinal variables. Unless otherwise specified, the p values reported for an analysis of trend refers to all of the 4 calendar year quartiles.

Cumulative event rates were calculated using the method of Kaplan and Meier²⁶ and survival curves were compared using the log-rank test. The overall survival time was calculated from the date of the pancreatic operation to the date of last follow-up. Postoperative death was defined as patient survival <30 days after the pancreatic operation. Additionally, patient survival at 60 days was also assessed.²⁷ Univariable and multivariable logistic regression models were constructed to determine association with receipt of adjuvant therapy (ie, CRT or chemotherapy alone). To identify variables for inclusion in the multivariable model, variables were selected using a univariable significance of $p < 0.25$. Logistic regression models were built for patients who received adjuvant therapy to determine factors associated with receipt of CRT vs chemotherapy alone. Finally, a multivariable Cox regression model was constructed to examine the association of no adjuvant therapy, adjuvant CRT, and adjuvant chemotherapy only on survival. All reported p values were 2-tailed, and for all tests $p < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS Version 18.0 (SPSS, Inc).

RESULTS

Patient and primary tumor characteristics

Using the SEER-Medicare database, 56,820 patients diagnosed with PAC between 1991 and 2005 were identified. After selecting patients based on a combination of CPT and ICD-9 codes, and excluding patients younger than 64 years old and those who were not surgically managed, 6,676 patients remained (Fig. 1). Of the 6,676 patients with PAC, 3,146 patients (47.1%) who underwent an open pancreatic biopsy or other procedures done without curative intent were excluded. Patients who were unstaged, had metastatic disease, and those who did not have histology codes consistent with adenocarcinoma were then excluded, leaving 2,461 patients (4.3% overall) available for analysis.

Demographic and clinical characteristics of the 2,461 patients with resected PAC are outlined in Table 3. Mean patient age was 73.2 years (SEM 0.1 years). Most patients were women ($n = 1,321$; 53.7%), white ($n = 2,056$; 83.5%), and resided in an urban setting ($n = 2,304$; 93.6%). The mean age of patients undergoing surgery for PAC increased over time (for 1991–1996, mean age 72.1 years vs for 2003–2005, mean age 74.0 years; $p < 0.001$). In addition to being older, patients in the later time periods also had more medical comorbidities as indicated by the Elixhauser comorbidity index. Specifically, only 10.4% ($n = 59$) of patients undergoing surgical resection for PAC from 1991 to 1996 had 3 preoperative medical comorbidities, compared with 26.0% ($n = 222$) of patients undergoing surgery from 2003 to 2005 ($p < 0.001$). In contrast, there was a decrease in the number of patients with no medical comorbidities from the beginning to the end of the study period (1991–1996: $n = 281$ [49.5%] vs 2003–2005: $n = 210$ [24.6%]; $p < 0.001$). The most common preoperative comorbidities were hypertension ($n = 1,132$; 46.0%), diabetes ($n = 524$; 21.3%), and chronic pulmonary disease ($n = 322$; 13.1%).

The most prevalent histology code ($n = 1,661$; 67.5%) was 8140, corresponding to “adenocarcinoma not otherwise specified” (Table 1).¹⁸ The majority of patients had regional disease ($n = 2,015$; 81.9%) as classified by the SEER historic stage and this proportion increased over time ($P = 0.039$). Most patients ($n = 1,160$; 47.1%) had a tumor grade classified as moderately differentiated. Overall, 54.2% ($n = 1,333$) of patients had lymph node metastasis on final pathologic examination, with an increase in the number of patients

with nodal disease identified over time (1991–1996: $n = 287$ [50.5%] vs 2003–2005: $n = 515$ [60.3%]; $p < 0.001$).

Trends in preoperative diagnostic imaging

In the overwhelming majority of cases, CT was the imaging modality of choice ($n = 2,255$; 91.6%), and MRI ($n = 364$; 14.8%) and PET ($n = 44$; 1.8%) were used in only a minority of patients (Table 4). Overall use of cross-sectional imaging increased during the time periods examined ($p < 0.001$), with 94.3% and 24.7% of patients staged with CT and MRI, respectively, in 2003–2005. For MRI, this corresponded to a >10-fold increase from the beginning to the end of the study period (1991–1996: $n = 12$ [2.1%] vs 2003–2005: $n = 211$ [24.7%]; $p < 0.001$). Similarly, use of preoperative diagnostic laparoscopy increased by >5-fold with 15.5% ($n = 132$) of patients having a laparoscopic staging procedure before their pancreatic resection in 2003–2005 ($p < 0.001$). Of note, PET scan was used in only 4.4% of patients, even in the most recent time period examined.

Patients from a rural area ($n = 15$; 9.6%) were as likely to be staged with MRI as patients from an urban setting ($n = 349$; 15.1%) ($p = 0.06$). Use of PET ($p = 0.62$) and diagnostic laparoscopy ($p = 0.72$) was not statistically different in rural vs urban areas. In contrast, patients with ≥ 3 medical comorbidities were more likely to have undergone an MRI ($p < 0.001$) or staging laparoscopy ($p = 0.039$) before pancreatic resection, compared with patients who had fewer comorbidities. There was no statistical difference in the use of PET imaging based up the patient's comorbidity index ($p = 0.06$).

Trends in pancreatic operations and perioperative outcomes

Of the 2,461 patients who underwent pancreatic resection for PAC, 1,945 (79.0%) had a pancreaticoduodenectomy (PD), 333 (13.5%) had a distal pancreatectomy, 28 (1.1%) were managed with total pancreatectomy, and 155 (6.3%) had various other pancreatic resections, including partial and near total pancreatectomy (Table 4). There were several shifting trends noted in the type of pancreatic operations performed during the time periods examined (Table 4). Specifically, the proportion of patients managed with distal pancreatectomy increased over time (1991–1996: 13.2% vs 2003–2005: 15.9%; $p = 0.035$), but both PD and total pancreatectomy remained stable throughout the study period (both $p > 0.05$).

The overall proportion of patients who had any postoperative complication was 53.0% ($n = 1,304$) and did not change appreciably during the study periods examined (Table 4 and Fig. 2A). The most common complications were postoperative infection ($n = 302$; 12.3%), need for a percutaneous drain ($n = 246$; 10.0%), and postoperative hemorrhage ($n = 209$; 8.5%). Notably, use of percutaneous drains increased during the study period (1991–1996: $n = 43$; 7.6% vs 2003–2005: $n = 105$; 12.3%; $p = 0.005$). The risk of complication was associated with having ≥ 3 Elixhauser comorbidities (≥ 3 Elixhauser comorbidities: 59.8% vs < 3 comorbidities: 54.2%; $p = 0.025$).

There were 104 deaths within 30 days of surgery (4.2%) and 271 deaths within 60 days (11.0%). Both 30-day (Fig. 2A) and 60-day mortality decreased during the study period (both $p < 0.05$). There was no association between perioperative mortality and rural residence, race, or ≥ 3 Elixhauser comorbidities (all $p > 0.05$). Patients undergoing a distal pancreatectomy did, however, have a lower risk of 30-day mortality compared with patients undergoing other types of pancreatic operations (odds ratio [OR] = 0.25; 95% CI, 0.07–0.69; $p = 0.003$). Specifically, patients undergoing a PD had a nearly 4-fold increase in the risk of death at 30 days vs patients undergoing distal pancreatectomy (OR = 3.90; 95% CI, 1.42–10.69; $p = 0.008$).

Trends in perioperative therapy: adjuvant chemotherapy vs chemoradiotherapy

Approximately one-half of patients (n = 1,243; 50.5%) received some form of adjuvant treatment with a temporal increase in the use of adjuvant therapy during the study period (1991–1996, 40.3%; 1997–2000, 51.8%; 2001–2002, 51.2%; 2003–2005, 56.1%; $p < 0.001$) (Table 4). Only a small number of patients (n = 26; 1.1%) received preoperative chemotherapy. Overall, 33.2% (n = 817) of patients received adjuvant CRT, and 10.2% (n = 251) received adjuvant chemotherapy only (Table 4). Of note, although use of adjuvant CRT decreased after 2000 (1991–1996, 26.9%; 1997–2000, 38.2%; 2001–2002, 34.4%; 2003–2005, 33.5%), use of adjuvant chemotherapy only increased during the time periods examined (1991–1996, 6.0%; 1997–2000, 5.8%; 2001–2002, 10.6%; 2003–2005, 15.6%) ($p < 0.001$) (Fig. 2B).

On univariable logistic regression analysis (Table 5), patient age, year of surgery, type of pancreatic operation, postoperative complications, and lymph node metastasis were each noted to be associated with receipt of adjuvant therapy (all $p < 0.05$). Specifically, age 72 years or younger (OR = 1.93; 95% CI, 1.65–2.27; $p < 0.001$), presence of lymph node metastasis (OR = 1.77; 95% CI, 1.51–2.08; $p < 0.001$), and those patients who had no postoperative complications (OR = 1.67; 95% CI, 1.41–1.96; $p < 0.001$) were the most likely to receive some type of adjuvant therapy. In addition, use of adjuvant therapy increased during the time periods examined (1991–1996, referent; 1997–2000, OR = 1.59; 2001–2002, OR = 1.55; 2003–2005, OR = 1.89; $p < 0.001$). On multivariable analysis, each of these factors remained independently associated with receipt of adjuvant CRT (Table 5).

Among those patients who received some type of adjuvant therapy (n = 1,243), factors associated with receipt of adjuvant chemotherapy alone relative to CRT included older patient age (OR = 1.75; $p < 0.001$), 3 medical comorbidities (OR = 1.57; $p = 0.007$), and time period 2003–2005 compared with 1991–1995 (OR = 2.21; $p < 0.001$). On multivariable logistic regression analysis, older patient age (OR = 1.60; 95% CI, 1.20–2.13; $p = 0.001$) and a later time period of pancreatic resection (2003–2005, OR = 2.0; 95% CI, 1.31–3.06; $p = 0.001$) remained independently associated with an increased likelihood to have received adjuvant chemotherapy alone vs CRT.

Long-term outcomes

Overall median survival of patients with PAC resected with curative intent was 14.0 months (95% CI, 13.2–14.8 months) with 1-, 3-, and 5-year survival of 53.2%, 19.7%, and 12.6%, respectively. There was a modest improvement in the median overall survival during the time periods examined, with an increase in the median survival from 12.0 to 16.0 months ($p = 0.005$) (Table 4). On multivariable Cox regression analysis with adjustment for patient clinicodemographics, including comorbidities and tumor characteristics, receipt of adjuvant therapy was associated with improved survival ($p < 0.001$). Specifically, receipt of adjuvant CRT relative to no adjuvant therapy (hazard ratio = 0.70; 95% CI, 0.63–0.77; $p < 0.001$) or chemotherapy only vs no adjuvant therapy (hazard ratio = 0.81; 95% CI, 0.69–0.97; $p = 0.018$) was associated with a decreased risk of death (Fig. 3).

DISCUSSION

Although surgery remains the only chance at cure, morbidity and mortality associated with pancreatic surgery have traditionally been high. In 1987, data from the Johns Hopkins Hospital noted a mortality for PD that decreased from 36% between 1969 and 1980 to 2% between 1981 and 1986.²⁸ During the same time periods, these authors noted a decrease in morbidity from 54% to 24%. Other data, mostly from single institutional series,^{2,3} have similarly noted a decrease in the perioperative mortality risk of pancreatic surgery. In the

current study, by using the SEER-Medicare dataset, we were able to assess the care of patients with surgically managed PAC on a population-based level. The SEER-Medicare dataset offers the ability to assess cancer surgery care in >25% of the US population and provide robust data concerning perioperative resource and procedure use.^{5,6} The current study is important because it examined population-based trends in perioperative management, surgical procedure use, and outcomes among patients undergoing surgical resection of PAC. We noted that over time, patients undergoing surgical resection of PAC were older and had more medical comorbidities. Despite this, the overall proportion of patients who had any postoperative complications did not change during the study periods examined and perioperative mortality actually decreased. We found that only approximately one-half of patients received any form of adjuvant treatment after surgery for PAC. In addition, although use of adjuvant CRT decreased after 2001, the use of adjuvant chemotherapy only increased during the time periods examined (Fig. 2B). These data can have important implications in helping to understand how population-level care of patients with resected PAC corresponds with recommendations (eg, National Comprehensive Cancer Network) for the treatment of PAC.

Although decreased mortality associated with pancreatic surgery has been reported,² heterogeneity in data reporting (eg, in-hospital, 30 days, 60 days), as well as the fact that data have largely come from large, single-center academic centers, making interpretation of the data difficult. In the current study, we report an overall population-based 30-day mortality of 4.2% after pancreatic surgery. As expected, mortality was associated with the type of surgical procedure, as PD had a 4-fold increased risk of 30-day mortality (OR = 3.90; $p = 0.008$) compared with distal pancreatectomy. Although the 30-day mortality we report was consistent with the mortality reported at most centers (eg, <5%),^{2,3} one important finding of the current study was the 11.0% incidence of postoperative death at the 60-day time period. Carroll and colleagues²⁹ had previously noted the importance of reporting mortality after pancreatic surgery beyond the traditional 30-day time period. The authors²⁹ noted a 60-day mortality of 11.9% similar to our report. We did, however, note a decrease in both 30- and 60-day perioperative mortality during the time periods examined (Fig. 2A). Importantly, this reduction in mortality was accompanied by an increase in patient age and the number of preoperative medical comorbidities (Fig. 2A). Although the morbidity associated with pancreatic surgery did not decrease over time, it did remain stable, albeit high at 53.0%. In aggregate, these data suggest that additional progress is needed to decrease the perioperative morbidity associated with pancreatic resection similar to the manner in which mortality has been reduced.

Another important finding of the current study was the overall and relative use of adjuvant therapy. We found that only one-half of patients (50.5%) received any form of adjuvant treatment. The reason for this is likely multifactorial, and might be related, in part, to the fact that the dataset included only patients aged 65 years or older. Several studies have reported that complications and prolonged recovery after PD for PAC can prevent delivery of postoperative therapy in at least 25% to 30% of patients.^{2,30–32} In the current study, we noted that PD and total pancreatectomy, as well as the occurrence of postoperative complications, were associated with a decreased likelihood of receiving adjuvant therapy (Table 5). Among those patients who did receive adjuvant therapy, we also noted some interesting trends with regard to the type of postoperative therapy delivered. Specifically, factors associated with receipt of adjuvant chemotherapy alone relative to CRT included older patient age, 3 medical comorbidities, and the time period treated. In fact, patients undergoing pancreatic resection from 2003–2005 had a 2-fold increased likelihood of receiving chemotherapy alone rather than CRT therapy. Conflicting results from several adjuvant studies have lead to differences in how patients with PAC are treated in the adjuvant setting. Although both the Gastrointestinal Tumor Study Group³³ and Radiation

Therapy Oncology Group 97-04¹¹ trials reported a benefit for CRT therapy, the European Study Group for Pancreatic Cancer-1 trial⁹ found a benefit for adjuvant chemotherapy alone and a deleterious effect for combined CRT. As such, although combined CRT remains the de facto treatment modality for resected PAC among many centers in the United States, adjuvant chemotherapy alone has become the standard of care in many European centers. Data from the current study suggest, however, that use of chemotherapy alone as adjuvant therapy in the United States has increased during the last decade.

Although the aim of the study was not to assess the survival benefit conferred by adjuvant therapy, we did note a survival benefit of adjuvant therapy for patients with resected PAC, even after controlling for competing risk factors using a multivariable Cox regression model (Fig. 3). Using a propensity-adjusted model, Simons and colleagues²⁷ similarly demonstrated a survival benefit for adjuvant therapy (chemotherapy and CRT) among a cohort of patients with resected PAC derived from SEER. Mayo and colleagues⁸ noted an improvement in survival associated with adjuvant therapy when using population-based data from the Oregon state cancer registry. In a large, single institutional database analysis of 908 patients, Herman and colleagues³² reported that adjuvant fluorouracil-based CRT therapy improved survival compared with patients not receiving CRT. Although assessing the therapeutic effect of any treatment modality using retrospective data can be problematic, data from the current study as well as others^{5,6} suggest a beneficial role of adjuvant therapy after surgical resection of PAC.

The current study had several limitations. Although the data derived from the linked SEER-Medicare dataset offer a perspective that is generalizable to many practice patterns, the data do not include detailed data on the characteristics of the adjuvant treatment regimen. As such, although the dataset allowed for accurate identification with regard to whether a patient received no adjuvant therapy, chemotherapy alone, or CRT therapy, it did not contain data on the type of chemotherapy or dose of radiation delivered. Data from the SEER-Medicare dataset are also limited to Medicare beneficiaries (aged 65 years and older) and might not be appropriate to extrapolate to younger populations. Finally, data in the current study include patient data only through 2005 and do not include the time period in which 2 of the most recent randomized clinical trials for adjuvant treatment for PAC (ie, Charité Onkologie-01 and Radiation Therapy Oncology Group 97-04) were reported.

CONCLUSIONS

Mortality associated with pancreatic resection for PAC has decreased by one-half during the 15 years examined in the study. Surgical resection for PAC is being offered to older patients with more preoperative comorbidities without an increase in perioperative mortality or morbidity. Although perioperative mortality has decreased, the incidence of perioperative complications has remained unchanged. Only about 50% of patients received adjuvant therapy after resection of PAC and failure to receive adjuvant therapy was associated with advanced age and a history of postoperative complications. In addition, the specific use of adjuvant chemotherapy alone vs CRT therapy has increased in the United States during the 15 years examined. These data should help to inform our collective understanding of how patients with PAC are being managed at the population-based level and serve as a reference point when trying to interpret and extrapolate published data from high-volume tertiary academic centers.

Abbreviations and Acronyms

CRT chemoradiation/chemoradiotherapy

OR	odds ratio
PAC	pancreatic adenocarcinoma
PD	pancreaticoduodenectomy
SEER	Surveillance, Epidemiology, and End Results

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Figure 1. Flow diagram of patient selection out of the total 56,820 patients identified with pancreatic adenocarcinoma to arrive at those patients who had their cancer resected with curative intent within the Surveillance, Epidemiology, and End Results–Medicare database 1991–2005.

A

B

Figure 2.

(A) Trends in Elixhauser medical comorbidities, postoperative complications, and 30-day postoperative mortality for patients with pancreatic adenocarcinoma (PAC) undergoing pancreatic resection. Star (★) indicates the overall test for trend across the 4 calendar-year quartiles. (B) Temporal trends in use of adjuvant therapy among patients with PAC. Star (★) indicates the overall test for trend across the 4 calendar-year quartiles.

Figure 3.

Multivariable Cox overall survival from the time of the pancreatic resection stratified by receipt of adjuvant therapy. Patients who received any adjuvant therapy (chemoradiation or chemotherapy only) had a lower risk of death than patients who did not receive adjuvant treatment (both $p < 0.05$).

Table 1

International Classification of Diseases for Oncology (3rd ed) Histology Codes Specific to Pancreatic Adenocarcinoma

Histology code	Patients (n = 2,461)	
	n	%
8140	1,661	67.5
8500	660	26.8
8010	52	2.1
8560	25	1.0
8490	20	0.8
8000	15	0.6
8260	11	0.4
Other (8255, 8261, 8263, 8020, 8050, 8141, 8144, 8210, 8211, 8262)	17	0.7

Table 2**CPT/ICD-9-CM Codes Used In Identification of Medicare Claims**

	CPT codes	ICD-9-CM codes
Procedure		
Endoscopy	43234, 43235, 43239, 43241, 43242, 43245, 43250, 43251, 43256, 43258	42.24, 44.14, 45.13, 45.14, 45.16
ERCP without stent	43260, 43261, 43262, 43263, 43264, 43265	
ERCP with stent	43268, 43269	51.87, 52.93, 97.05
Cholangiogram	74320	87.52, 87.54
Abdominal ultrasound	76700, 76705	88.74, 88.76, 88.79
Percutaneous transhepatic cholangiography	47500, 47505, 47510, 74363, 75980	51.98, 87.51
MRI abdomen (with and without contrast)	74181, 74182, 74183, 74185	88.97
CT abdomen (with and without contrast)	74150, 74160, 74170	87.41, 87.42, 87.72, 88.01, 88.02
PET	78811, 78812, 78813, 78814, 78815, 78816, G0235, S8085	88.90, 92.04, 92.18
Diagnostic laparoscopy	49320, 49321, 49329	54.21
Lymphadenectomy	38747, 38780	40.29, 40.50
Unlisted laparoscopy procedure, intestine (except rectum)	44238	
Pancreas		
Open biopsy	48100	52.12
Excision of lesion	48120	52.22, 52.59
Unlisted pancreatic procedure	48999	
Distal pancreatectomy without PJ	48140	52.52
Distal pancreatectomy with PJ	48145	
Near total pancreatectomy	48146	52.53
Total pancreatectomy	48155	52.6
Total pancreatectomy with islet cell transplant	48160	
Pancreaticoduodenectomy (classic)	48150, 48152	52.51, 52.7
Pancreaticoduodenectomy (pylorus-preserving)	48153, 48154	
Pancreaticojejunostomy, side to side anastomosis (Puestow-type operation)	48548	52.96
Resection or debridement of pancreas tissue for acute necrotizing pancreatitis	48105	
Perioperative treatment (within 3 mo before to 6 mo after)		
Intravenous chemotherapy	36260, 36640, 36823, 96400, 96401, 96402, 96405, 96406, 96408, 96409, 96410, 96411, 96412, 96413, 96414, 96415, 96416, 96417, 96420, 96422, 96423, 96425, 96445, 96520, 96530, 96542, 96545, 96549, 99555, C8953, C8954, C8955, G0355, G0356, G0357, G0358, G0359, G0360, G0361, G0362, G0363, J8999, Q0083, Q0084, S9329, S9330, S9331	99.25, 99.28

	CPT codes	ICD-9-CM codes
Radiation therapy	0082T, 0083T, 4165F, 4181F, 77263, 77290, 77301, 77334, 77373, 77401, 77402, 77403, 77404, 77406, 77407, 77408, 77409, 77411, 77412, 77413, 77414, 77416, 77418, 77419, 77422, 77423, 77427, 77430, 77431, 77470, 77761, 77762, 77763, 77776, 77777, 77778, 77789	99.2, 92.20–92.29,
Complication		
Surgical re-exploration	49000, 49002	54.11, 54.12
Percutaneous drain	47000, 49021, 49041, 49061, 75989	54.91
Accidental laceration		998.2, E8700
Postoperative hemorrhage		998.1–998.19
Posthemorrhagic anemia		285.1
Anesthetic reaction		995.4, E938, E9452
Wound dehiscence		998.3, 998.6, 998.83
Peritonitis		567.2
Gastrointestinal hemorrhage		578, 578.0, 578.1, 578.9
Gastrointestinal complications		997.4
Biliary fistula		576.4
Intestinal fistula		569.81
Stomach or duodenal fistula		537.4
Postoperative infection		998.5–998.59
Paralytic ileus		560.1

PJ, pancreaticojejunostomy.

Trends in Baseline Demographic and Clinical Characteristics of Patients with Surgically Managed Pancreatic Adenocarcinoma, Surveillance, Epidemiology, and End Results–Medicare, 1991–2005

Table 3

	Total (n = 2,461)	1991–1996 (n = 568)	1997–2000 (n = 539)	2001–2002 (n = 500)	2003–2005 (n = 854)
Demographics					
Age at PAC diagnosis, y, mean ± SEM *	73.2 ± 0.1	72.1 ± 0.2	72.9 ± 0.2	73.5 ± 0.3	74.0 ± 0.2
Women, * n (%)	1321 (53.7)	290 (51.1)	276 (51.2)	275 (55.0)	480 (56.2)
White, n (%)	2056 (83.5)	464 (81.7)	443 (82.2)	431 (86.2)	718 (84.1)
Married, n (%)	1516 (61.6)	344 (60.6)	344 (63.8)	289 (57.8)	539 (63.1)
Urban, n (%)	2304 (93.6)	523 (92.1)	505 (93.7)	477 (95.4)	799 (93.6)
Elixhauser comorbidities, * n (%)					
No comorbidities	839 (34.1)	281 (49.5)	206 (38.2)	142 (28.4)	210 (24.6)
1 comorbidity	662 (26.9)	151 (26.6)	140 (26.0)	132 (26.4)	239 (28.0)
2 comorbidities	460 (18.7)	77 (13.6)	100 (18.6)	100 (20.0)	183 (21.4)
3 comorbidities	500 (20.3)	59 (10.4)	93 (17.3)	126 (25.2)	222 (26.0)
Time from diagnosis of PAC to operation, d, mean ± SEM *	13.8 ± 0.4	9.1 ± 0.7	12.3 ± 0.8	13.7 ± 0.9	18.0 ± 0.8
Pathology, n (%)					
SEER historic stage *					
Localized	446 (18.1)	111 (19.5)	108 (20.0)	92 (18.4)	135 (15.8)
Regional	2015 (81.9)	457 (80.5)	431 (80.0)	408 (81.6)	719 (84.2)
Grade					
Well-differentiated	252 (10.2)	65 (11.4)	50 (9.3)	54 (10.8)	83 (9.7)
Moderately differentiated	1160 (47.1)	271 (47.7)	228 (42.3)	239 (47.8)	422 (49.4)
Poorly differentiated	788 (32.0)	157 (27.6)	197 (36.5)	168 (33.6)	266 (31.1)
Undifferentiated	30 (1.2)	<11 (<1.9)	<11 (<2.0)	<11 (<2.2)	<11 (<1.3)
Unknown	231 (9.4)	<11 (<1.9)	<11 (<2.0)	<11 (<2.2)	<11 (<1.3)
Lymph node metastasis, * n (%)	1333 (54.2)	287 (50.5)	268 (49.7)	263 (52.6)	515 (60.3)

* Significant at p < 0.05 by either ANOVA test or the linear-by-linear association test of trend.

Preoperative Staging, Operative Details, and Postoperative Outcomes of Patients with Resected Pancreatic Adenocarcinoma, Surveillance, Epidemiology, and End Results–Medicare, 1991–2005

Table 4

	Total (n = 2,461)	1991–1996 (n = 568)	1997–2000 (n = 539)	2001–2002 (n = 500)	2003–2005 (n = 854)
Preoperative staging within 3 mo, n (%)					
ERCP *	1,443 (58.6)	282 (49.6)	329 (61.0)	324 (64.8)	508 (59.5)
MRI abdomen *	364 (14.8)	12 (2.1)	45 (8.3)	96 (19.2)	211 (24.7)
CT abdomen *	2,255 (91.6)	499 (87.9)	481 (89.2)	470 (94.0)	805 (94.3)
PET *	44 (1.8)	<11 [†] (<1.9)	<11 [†] (<2.0)	<11 [†] (<2.2)	38 (4.4)
Diagnostic laparoscopy *	240 (9.8)	15 (2.6)	41 (7.6)	52 (10.4)	132 (15.5)
Type of operation, n (%)					
Pancreaticoduodenectomy	1,945 (79.0)	433 (76.2)	441 (81.8)	405 (81.0)	666 (78.0)
Distal pancreatectomy *	333 (13.5)	75 (13.2)	55 (10.2)	67 (13.4)	136 (15.9)
Total pancreatectomy	28 (1.1)	12 (2.1)	<11 [†] (<2.0)	<11 [†] (<2.2)	<11 [†] (<1.3)
Other pancreatic resection * [‡]	155 (6.3)	48 (8.5)	<11 [†] (<2.0)	<11 [†] (<2.2)	<11 [†] (<1.3)
Perioperative treatment, n (%)					
Any adjuvant therapy *	1,243 (50.5)	229 (40.3)	279 (51.8)	256 (51.2)	479 (56.1)
Preoperative chemotherapy [§]	26 (1.1)	<11 [†] (<1.9)	<11 [†] (<2.0)	<11 [†] (<2.2)	15 (1.8)
Adjuvant chemotherapy only [¶]	251 (10.2)	34 (6.0)	31 (5.8)	53 (10.6)	133 (15.6)
Adjuvant radiotherapy only	175 (7.1)	42 (7.4)	42 (7.8)	31 (6.2)	60 (7.0)
Adjuvant chemoradiation *	817 (33.2)	153 (26.9)	206 (38.2)	172 (34.4)	286 (33.5)
Time from operation to receipt of radiation or chemotherapy, mo, mean ± SEM *	3.9 ± 0.4	3.5 ± 0.1	3.7 ± 0.1	3.8 ± 0.1	4.2 ± 0.1
Postoperative morbidity, n (%)					
Any complication	1,304 (53.0)	310 (54.6)	268 (49.7)	274 (54.8)	452 (52.9)
Re-exploration after operation *	148 (6.0)	48 (8.5)	38 (7.1)	28 (5.6)	34 (4.0)
Postoperative hemorrhage *	209 (8.5)	61 (10.7)	45 (8.3)	43 (8.6)	60 (7.0)
Postoperative infection *	302 (12.3)	67 (11.8)	52 (9.6)	55 (11.0)	128 (15.0)

	Total (n = 2,461)	1991–1996 (n = 568)	1997–2000 (n = 539)	2001–2002 (n = 500)	2003–2005 (n = 854)
Percutaneous drain *	246 (10.0)	43 (7.6)	52 (9.6)	46 (9.2)	105 (12.3)
Survival after pancreatic operation					
Median, mo *	14.0	12.0	15.0	12.0	16.0
3-year, %	19.7	16.7	22.0	18.2	NR
30-day mortality, % [†] n (%)	104 (4.2)	31 (5.5)	22 (4.1)	25 (5.0)	26 (3.0)
60-day mortality, % [‡] n (%)	271 (11.0)	78 (13.7)	55 (10.2)	56 (11.2)	82 (9.6)

* Significant at $p < 0.05$ by either ANOVA test or linear-by-linear association test of trend.

[†] Cell totals were <11 patients and could not be reported per National Cancer Institute data usage agreement.

[‡] Other pancreatic resection includes partial pancreatectomy and near total pancreatectomy.

[§] Preoperative chemotherapy within 3 months before pancreatic resection.

^{||} Postoperative chemotherapy given within 6 months after pancreatic resection.

[¶] Death within 30 days of pancreatic resection.

[#] Death within 60 days of pancreatic resection.

NR, not reached; PAC, pancreatic adenocarcinoma; SEER, Surveillance, Epidemiology, and End Results cancer registry.

Table 5

Logistic Regression Analyses of Variables Associated with Receipt of Adjuvant Therapy in Patients with Resected Pancreatic Adenocarcinoma in Surveillance, Epidemiology, and End Results–Medicare 1991–2005

Prognostic factor	Univariable			Multivariable		
	Odds ratio	95% CI	p Value	Odds ratio	95% CI	p Value
Year of pancreatic resection						
1991–1996						
			Reference			
1997–2000	1.59	1.25–2.02	<0.001	1.72	1.34–2.20	<0.001
2001–2002	1.55	1.22–1.98	<0.001	1.74	1.35–2.24	<0.001
2003–2005	1.89	1.53–2.35	<0.001	2.10	1.67–2.65	<0.001
Age 72 y or younger vs older than 72 y	1.93	1.65–2.27	<0.001	2.13	1.80–2.52	<0.001
Male vs female sex	1.00	0.85–1.17	0.95	—	—	—
White race vs nonwhite *	1.23	0.99–1.52	0.06	1.24	0.99–1.55	0.06
Urban vs rural residence	0.98	0.71–1.36	0.91	—	—	—
3 Elixhauser comorbidities vs <3	0.90	0.74–1.10	0.29	0.89	0.72–1.09	0.25
Type of operation						
Pancreaticoduodenectomy			Reference			
Distal pancreatectomy	1.20	0.95–1.52	0.12	1.29	1.01–1.65	0.043
Total pancreatectomy	0.40	0.18–0.92	0.031	0.45	0.19–1.06	0.07
Other pancreatic resection †	1.26	0.91–1.75	0.17	1.45	1.03–2.05	0.034
No postoperative complications vs postoperative complications	1.67	1.41–1.96	<0.001	1.66	1.41–1.96	<0.001
Lymph node metastasis vs no metastasis	1.77	1.51–2.08	<0.001	1.76	1.4–2.08	<0.001

Bold type indicates variables that were significant at $p < 0.05$ in the multivariable analysis.

* Nonwhite refers to race designations in Surveillance, Epidemiology, and End Results that include black, Native American, and all other designations of race and/or ethnicity.

[†] Other pancreatic resection includes partial pancreatectomy and near total pancreatectomy.