Published in final edited form as:

Pancreas. 2017 August ; 46(7): 904–912. doi:10.1097/MPA.0000000000000876.

Patterns of Care for Locally Advanced Pancreatic Adenocarcinoma Using the National Cancer Database

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Abstract

Objectives: The role of radiotherapy (RT) in locally advanced pancreatic cancer (LAPC) is uncertain. This study examines patterns of care and survival outcomes of LAPC undergoing chemotherapy alone vs. chemotherapy plus RT (C+RT).

Methods: The National Cancer Database (NCDB) was queried for non-metastatic LAPC who received chemotherapy alone or C+RT.

Results: Of the 13,695 patients included: 5,306 underwent chemotherapy alone, 4,971 C+RT. Use of C+RT declined from 2003 to 2011 (73% to 53%), while chemotherapy alone increased. Of those receiving RT, rates of intensity-modulated radiotherapy (IMRT) increased (27% to 72%) while 3D RT decreased (73% to 28%). Unadjusted 1-year OS was longer for C+RT vs. chemotherapy (45.6% vs. 38.7%), as was 2-year OS (12.9% vs. 11.9%) (**Hazard ratio** [HR], 0.88; 0.85–0.91; $p<0.001$). Under multivariate analysis, C+RT was associated with improved OS (HR, 0.84; 0.81–0.87; $p<0.001$). On subgroup analysis comparing C+IMRT, C+3D RT, and chemotherapy alone, 1-year OS was 49.1%, 45.1%, and 38.7%; 2-year OS was 13.1%, 11.6%, and 11.9% accordingly.

Conclusions: Utilization of RT in LAPC is decreasing while chemotherapy alone is increasing. Of patients undergoing RT, rates of IMRT are increasing. While C+IMRT appeared to be associated with improved OS compared to chemotherapy alone, 3D RT was not.

Keywords

pancreatic neoplasia; chemotherapy; radiotherapy

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Conflicts of Interest: The authors have no conflicts of interest to report.

Introduction

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in the United States.¹ At the time of diagnosis, approximately 30% present with locally advanced pancreatic cancer (LAPC).² For LAPC, current National Comprehensive Cancer Network (NCCN) guidelines suggest chemotherapy or chemotherapy with radiation (RT) in select patients without systemic disease and good performance scores.³ Median survival for these patients is poor, ranging from 6 to 11 months.⁴ Presently, the benefit of adding RT to chemotherapy (C+RT) to improve survival for LAPC is uncertain.^{4–6}

While current data demonstrating a survival benefit of RT is mixed, studies have shown improvements in local control with the addition of RT, especially with modern day RT techniques, translating into improved quality of life by reducing localized pain and symptoms related to tumor obstruction.^{7,8} Further, approximately 30% of patients with pancreatic cancer die with locally destructive disease as a component of their disease, contradicting the historical belief that all pancreatic cancer cases die from metastatic disease.⁹ RT may therefore play a major role for these patients who progress locally. In this population-based analysis, we queried the National Cancer Database (NCDB) to evaluate patterns of care and survival outcomes between C+RT compared to chemotherapy alone in order to assess whether there is a survival improvement with the addition of RT to chemotherapy in LAPC patients.

MATERIALS AND METHODS

Data Source and Patient Selection

The NCDB is a joint project of the Commission on Cancer of the American College of Surgeons and the American Cancer Society. It is a hospital-based registry that represents 70% of all cancer cases in the US, drawing data from more than 1,500 commission-accredited cancer programs.¹⁰ The data used in the study are derived from a de-identified NCDB file. The American College of Surgeons and the Commission on Cancer have not verified and are not responsible for the analytic or statistical methodology employed, or the conclusions drawn from these data.

We identified 356,108 patients 18 years old with pancreatic cancer diagnosed between **2003** and 2011. This dataset was then limited to inoperable patients who had treatment with chemotherapy with or without RT, excluding those with unknown vital status, unknown T- and N-stage, M1 disease, and those undergoing surgery. The resulting 34,057 patients were then limited to adenocarcinoma histologic codes (International Classification of Disease for Oncology [third edition] histology code 8140–41, 8255, 8260–61, 8310, 8323, 8440). This left a total of 19,685 patients receiving chemotherapy alone or chemotherapy with RT (C+RT). Next to avoid selection bias, the start of RT was within 0–6 months of the chemotherapy start date; others outside this range were excluded (n=1,464). We then excluded palliative cases (n=4,526), an available category in the NCDB distinguishing treatment modality given for curative intent versus the same modality being used for palliation, based on prior NCDB analyses, leaving 13,695 cases for analysis.

Patient Demographics and Treatment Variables

Potentially relevant patient and treatment characteristics were included. Clinical tumor (T)-stage, nodal (N)-stage, and overall stage were based on the American Joint Committee on Cancer (AJCC) staging guidelines.¹¹ Distance to treatment facility was analyzed as a categorical variable, using the median as a cutoff. Chemotherapy was categorized in the NCDB as single-agent, multi-agent or not otherwise specified (NOS). CA19–9 was not included as this data was not recorded for the majority of cases. Three-dimensional (3D) and intensity-modulated radiotherapy (IMRT) are coded for a subset of patients in the NCDB. A minimum RT dose was not selected as an inclusion criteria as all cases included were coded as curative intent; however a subgroup analysis was performed for those who had received a complete course of RT. A complete course of RT was defined as 45–54 Gy based on NCCN guideline recommendations.¹²

Statistical Analysis

All statistical analyses were performed using SPSS V23.0 (SPSS Inc., Chicago, IL). Pearson chi-square tests were used to assess associations between categorical variables and treatment group. Similar to previous database analyses, survival analysis in this study excluded patients dying within the first 1 months of diagnosis in an effort to conservatively reduce the probability of type I error due to selection and immortal-time biases, where early-occurring deaths may be categorically attributed to the no-RT cohort,^{13,14} OS was first examined using the Kaplan Meier method. Univariate survival analysis (UVA) was performed with the log-rank test, with Cox proportional hazards regression used to estimate hazard ratios (HR). Multivariate Cox regression analysis (MVA) was performed using OS as outcomes; all tests were two sided with a 0.05 level of significance. Patient, clinical, and treatment variables were selected a priori. Multiple binary logistic regression models were used to assess the association between variables included and treatment modality. Hosmer-Lemeshow test was used to check for the goodness-of-fit of the regression models.

To further address confounding variables, propensity score matching (PSM) was performed for patients treated with C+RT or chemotherapy alone accounting for the following variables: age, gender, race, insurance status, residence, comorbidity score, facility type, distance to hospital (miles), year of diagnosis, T-stage, N-stage, and chemotherapy (single agent, multi-agent, NOS). The propensity score was calculated using logistic regression to estimate the probability of receiving C+RT vs. chemotherapy alone. One-to-one propensity matching without replacement was performed using caliper match algorithm described by Coca-Perraillon,¹⁵ with the caliper width set to 0.05 times the standard deviation of the logit of the propensity score.¹⁶ These outcomes were assessed using a log-rank test and the HR was determined by univariate Cox regression. The score calculation was blinded with respect to patient outcomes.

Subgroup analyses including the same variables used in the Cox regression model for the entire cohort was performed for the following: (1) patients starting RT 3–6 months after the chemotherapy start date in order to evaluate survival outcomes after a period of induction therapy, (2) patients receiving a complete course of RT (45–54 Gy), (3) those treated in more recent years (2008–2011), (4) T4 disease, and (5) patients coded as 3D (n=1,043), IMRT

(n=1,641) vs. chemotherapy alone (n=5,306) in order to assess for survival outcomes by RT modality.

Results

Patient Characteristics

A total of 13,695 patients were included: 5,306 (38.7%) underwent chemotherapy alone, 8389 (61.3%) received C+RT. Median follow up for all patients was 10.2 months (range, 1.0–120.3 months). Median follow up for the chemotherapy alone group was 9.2 months (range, 1.0–120.3 months); median follow up for the C+RT group was 10.8 months (range, 1.0–114.0 months). Patient and treatment characteristics are presented in Table 1.

Patterns of Care

From 2003 to 2011, the use of C+RT in LAPC steadily declined in contrast to the use of chemotherapy alone which gradually increased (Figure 1A). In 2003, 73% of patients underwent C+RT compared to 27% for chemotherapy alone; in 2011, C+RT was 53.3% compared to 46.7% for chemotherapy alone. For the subset of patients recorded as receiving 3D (n = 1043) or IMRT (n = 1641), use of IMRT increased from 2003 in contrast to 3D RT which declined (Figure 1B). In 2003, 27.1% were treated with IMRT compared to 72.9% with 3D; in 2011, 72.4% of cases were treated with IMRT compared to 27.6% with 3D.

Factors Associated with Treatment Selection

In a binary multiple logistic regression model that adjusted for patient and treatment demographics (Supplemental Table 1), patients treated with chemotherapy alone, compared to C+RT, were more commonly patients ≥ 65 years (odds ratio [OR], 0.78; 95% confidence interval [CI], 0.71–0.85; $P < 0.001$), female sex (OR, 0.93; 95% CI, 0.87–1.00; $P = 0.057$), uninsured (OR, 0.74; 95% CI, 0.60–0.91; $P = 0.005$), treated at comprehensive community (OR, 0.82; 95% CI, 0.72–0.95; $P = 0.008$) or academic/research hospitals (OR, 0.69; 95% CI, 0.60–0.80; $P < 0.001$), lived further than 12 miles from the hospital (OR, 0.89; 95% CI, 0.82–0.96; $P = 0.003$), had higher comorbidity scores (OR, 0.91; 95% CI, 0.84–0.98; $P = 0.017$), and more often presented with node positive disease (OR, 0.85; 95% CI, 0.79–0.92; $P < 0.001$). In contrast, patients treated with C+RT were more commonly in urban (OR, 1.39; 95% CI, 1.25–1.55; $P < 0.001$) or rural locations (OR, 1.83; 95% CI, 1.41–2.37; $P < 0.001$). There were statistically significantly lower odds of receiving RT in the more recent years from 2004 onward (ORs, 0.42–0.68; $P < 0.001$).

Predictors for Overall Survival

Unadjusted 1-year OS was longer for C+RT vs. chemotherapy alone (45.6% vs. 38.7%), as was 2-year OS (12.9% vs. 11.9%) (HR, 0.88; 95% CI 0.85–0.91; $P < 0.001$) (Figure 2A). Based on MVA, the C+RT was associated with an improved OS (HR, 0.84; 95% CI, 0.81–0.87; $P < 0.001$). Additional predictors correlating with longer OS under MVA included African-American race (HR, 0.93; 95% CI, 0.88–0.98; $P = 0.006$) and other race (HR, 0.87; 95% CI, 0.79–0.97; $P = 0.011$), primary treatment in an academic/research hospital (HR, 0.93; 95% CI, 0.86–1.00; $P = 0.038$), treatment in more recent years (2009–2011) (HR, 0.81–0.85; $P < 0.001$), and multi-agent chemotherapy (HR, 0.74; 95% CI, 0.72–0.77; $P < 0.001$).

0.001). On MVA, variables associated with worse OS included older age (HR, 1.09; 95% CI, 1.04–1.14; $P < 0.001$), urban (HR, 1.08; 95% CI, 1.03–1.14; $P = 0.004$) or rural residence (HR, 1.17; 95% CI, 1.04–1.32; $P = 0.011$), having government-type insurance (HR, 1.07; 95% CI, 1.02–1.12; $P = 0.010$) or no insurance (HR, 1.16; 95% CI, 1.04–1.30; $P = 0.008$), Charlson comorbidity score 1 (HR, 1.09; 95% CI, 1.05–1.14; $P < 0.001$), T2 (HR, 1.09; 95% CI, 1.02–1.29; $P = 0.018$) or T3 disease (HR, 1.12; 95% CI, 1.00–1.25; $P = 0.044$), and node positive disease (HR, 1.09; 95% CI, 1.06–1.14; $P < 0.001$) (Table 2).

Subgroup analysis was then performed for patients treated with 3 months of induction chemotherapy, who either continued on chemotherapy alone or treated with RT. The addition of RT for these patients demonstrated a modest survival improvement under MVA (HR, 0.65; 95% CI, 0.60–0.72; $P < 0.001$). **Under multivariate logistic regression, there were also statistically significantly lower odds of receiving RT in the more recent years from 2004 onward (ORs, 0.44–0.86; $P < 0.001$).** On further subgroup analysis of patients receiving a definitive dose of RT (45–54 Gy), C+RT was again associated with a longer OS under MVA, compared to chemotherapy alone (HR, 0.80; 95% CI, 0.77–0.84; $P < 0.001$). For patients with T4, any N disease, C+RT was also associated with longer OS under MVA (HR, 0.85; 95% CI, 0.80–0.89; $P < 0.001$); 1- and 2-year OS was longer for C+RT compared to chemotherapy alone, 46.9% vs. 40.2% and 13.6% vs. 12.8% respectively. Lastly, subgroup analysis of patients treated in more recent years (2008–2011), demonstrated C+RT was associated with a longer OS under MVA (HR, 0.82; 95% CI, 0.78–0.86; $P < 0.001$).

We next compared survival outcomes by RT modality (**3D RT vs. IMRT**). **Median follow up for 3D RT vs IMRT is 10.58 and 11.47 months respectively.** On subgroup analysis comparing chemotherapy + IMRT, chemotherapy + 3D RT, and chemotherapy alone, unadjusted 1-year OS was 49.1%, 45.1%, and 38.7% respectively; 2-year OS was 13.1%, 11.6%, and 11.9% accordingly (Figure 2B). Under MVA, chemotherapy + 3D RT (HR, 0.86; 95% CI, 0.80–0.92; $P < 0.001$) and chemotherapy + IMRT (HR, 0.81; 95% CI, 0.77–0.86; $P < 0.001$) were associated with a statistically significant improvement in OS (Supplemental Table 2).

Propensity Score Matching

PSM for all patients combined resulted in well-matched comparison groups between chemotherapy alone, chemotherapy + 3D RT, and chemotherapy + IMRT. Consistent with the results from MVA, patients receiving CRT had longer 1-year (47.2% vs. 38.4%) and 2-year OS (13.0% vs. 11.9%) (HR, 0.86; 95% CI, 0.82–0.89; $P < 0.001$). Further analysis demonstrated patients receiving IMRT vs. chemotherapy alone had longer 1-year (49.0% vs. 37.8%) and 2-year OS (13.1% vs. 10.8%) (HR, 0.80; 95% CI, 0.75–0.86; $P < 0.001$) (Figure 3A). Inconsistent with MVA, patients receiving 3D RT did not have a statistically significant longer 1-year (45.2% vs. 39.5%) or 2-year OS (11.6% vs. 12.4%) (HR, 0.92; 95% CI, 0.84–1.03; $P = 0.060$) when compared to chemotherapy alone (Figure 3B). When comparing survival outcomes between IMRT and 3D RT, IMRT was associated with improved 1-year (50.6% vs. 44.7%) and 2-year OS (13.9% vs. 11.6%) (HR, 0.86; 95% CI, 0.78–0.95; $P = 0.002$) (Figure 3C).

DISCUSSION

Utilization of RT in LAPC appears to be decreasing while the rate of chemotherapy alone is increasing in this population-based analysis. Specifically, the use of C+RT declined from 2003 to 2011 (73% to 53%), while the rate of chemotherapy alone increased. Of those receiving RT, rates of IMRT increased (27% to 72%), while 3D RT decreased (73% to 28%). Use of C+RT also correlated with patients' age, gender, insurance status, treatment facility, distance to the hospital, residence, and having node positive disease, consistent with other study findings.¹⁷ Lastly, the addition of RT appeared to be associated with a modest improvement in survival, in particular for those receiving IMRT.

Several events may be contributing to the decrease in RT use. For example, the notable decline of RT between the year 2004 and 2005 (Figure 1A) may be due to results from the European Study Group for Pancreatic Cancer 1 Trial (ESPAC-1), published in 2004, which demonstrated a detriment in OS with the addition of CRT in the adjuvant setting.¹⁸ Further, the decline in RT use between 2007 and 2009 may be related to the negative results from the French trial (FFCD-SFRO) comparing chemotherapy alone versus C+RT in LAPC.¹⁹ Improved chemotherapy regimens including FOLFIRINOX and gemcitabine/nab-paclitaxel may also contribute to the downtrend in RT use as these regimens have demonstrated significantly better response rates when compared to gemcitabine alone.²⁰

While the majority of pancreatic cancer patients die of systemic disease, a substantial portion progress and die of local disease, suggesting the importance of local treatment modalities including RT.⁹ Further, local progression can cause pain and obstruction, translating into worse quality of life outcomes. Early studies published in the 1980s comparing chemotherapy to C+RT, using split course RT with older techniques, demonstrated mixed results.^{21,22} More recent studies including the French trial (FFCD-SFRO), which randomized LAPC to gemcitabine alone vs. high-dose RT (60 Gy) with concurrent 5-FU and cisplatin followed by gemcitabine, found increased toxicity in the C+RT arm and worse survival outcomes when compared to the gemcitabine alone arm (median survival 8.6 vs 13.0 months; $p=0.03$).¹⁹ In contrast, the subsequent European Cooperative Oncology Group (ECOG) study, comparing gemcitabine alone versus gemcitabine plus RT (50.4 Gy) in LAPC, found C+RT improved OS (9.2 vs. 11.0 months; $p=0.017$).⁴ Both trials lacked RT quality assurance measures. This brings us to the phase III LAP 07 trial, which evaluated the use of gemcitabine alone versus gemcitabine followed by RT.⁶ RT quality assurance was available. At a median follow-up of 36 months, OS was not significantly different between chemotherapy alone and C+RT.

Many of these prior trials applied older RT techniques without significant quality measures in place. Even the LAP 07 trial, which had quality measures in place, used conventional RT techniques that may have reduced the impact of the local therapy in these patients given dose constraints of surrounding organs at risk.⁶ Data presented in this NCDB analysis suggests that patients who undergo RT may benefit more from advanced RT techniques such as IMRT, particularly when abdominal RT can be associated with significant toxicity. While the results in our study demonstrate only a modest improvement in OS with C+RT, the OS improvement is only appreciated in patients undergoing IMRT, suggesting reasonable

candidates for RT should be offered IMRT over 3D planning. The slight absolute survival benefit with the addition of RT must be weighed with the risk of additional RT toxicity, especially with 3D modality treatment. Decision for additional RT in this setting ought to be personalized to each patient based on their performance status, comorbidities, disease status, and goals of care.

Lack of RT central quality control is a major criticism in prior pancreatic cancer trials that have demonstrated deleterious effects of RT, including the ESPAC-1 trial, which compared adjuvant chemotherapy to CRT in resected pancreatic cancer.^{18,23} A meta-analysis of 8 cooperative group clinical trials (including Radiation Therapy Oncology Group [RTOG] 9704: adjuvant CRT+5-fluorouracil vs. CRT+gemcitabine) demonstrated a significant association between RT quality deviation and detriment in OS (HR, 1.74), further emphasizing the importance of quality control and RT technique.^{24,25} This has led to stricter RT contouring guidelines and centralized review in the current protocols including RTOG 0848 and 1201.^{26,27} The RTOG 0848 study is evaluating the benefit of adjuvant CRT in resectable pancreatic cancer. The RTOG 1201 is a phase II randomized trial comparing standard (50.4 Gy) or high-dose (63.0 Gy) RT with gemcitabine and nab-paclitaxel to gemcitabine and nab-paclitaxel alone for unresectable pancreatic cancer. Both cooperative group trials incorporate the requirement for strict adherence (via rapid central review) to contouring guidelines and treatment planning. IMRT is allowed in both trials and mandated in the high-dose arm of RTOG 1201.

While C+RT has been a component of therapy for LAPC since the early studies in the 1980s, there have been many recent advances including improvements in chemotherapy agents, newer RT techniques such as IMRT, and better knowledge of the underlying molecular biology. **There have been several recent advances for example, including use of multi-agent chemotherapy regimens for LAPC.²⁸ In a phase III trial comparing FOLFIRINOX to gemcitabine alone, FOLFIRINOX had an improved median OS of 11.1 vs. 6.8 months (HR, 0.57; $p<0.001$).²⁹ While the majority of patients in this NCDB analysis were treated with single-agent chemotherapy and before the published phase III trials, results demonstrating OS improvement with multi-agent chemotherapy was consistent with the phase III data. Improvements in distant disease control may make the role of local therapy even more important in LAPC patients who do not progress on systemic induction therapy.**

The NCDB confers several benefits over other population databases, including a large sample size and the availability of treatment details including receipt of chemotherapy. However, the NCDB is limited by its retrospective nature and the potential for miscoding. **There is also inherent selection bias by treatment modality, which we attempt to account for in MVA and PSM analyses.** CA19-9 was not available for the majority of patients. Proper staging during the study time period is also an issue, as staging workup including the use of endoscopic ultrasound, varied by institution. **A large proportion of patients in this study were considered unresectable with T1–3 stage; we attempted to address this by performing a subgroup analysis of only T4 tumors.** Information on chemotherapy agent, dose, and number of cycles administered were unknown. Restaging is not recorded in the NCDB; as such, patients in the chemotherapy alone arm may have had

progressive disease preventing them from receiving RT, which would not have been recorded. To account for this, we performed a subset analysis including patients alive after 3 months of induction chemotherapy, who were subsequently treated with RT or additional chemotherapy. Additionally, RT modality including 3D RT and IMRT is not coded for all patients and therefore could only be analyzed for a subset of individuals. Data on RT modality in the NCDB is reported broadly, with a large proportion of patients coded as receiving a particular photon energy, but not specifying planning modality (3D vs. IMRT), which contributed to those excluded from subgroup analyses. It may be that patterns of coding between photon energies and modality could contribute somewhat to the increased utilization of IMRT found in our study. However, our findings are consistent with other studies showing increased use of IMRT in gastrointestinal malignancies including pancreatic cancer.³⁰ Lastly, outcome measurements are limited to OS as the NCDB does not record data on locoregional control, distant disease, cancer-specific survival, or symptom control which would have been a valuable endpoint in this study.

Published randomized data on the efficacy of RT with chemotherapy in LAPC continues to remain inconclusive. This may be due to insufficient RT doses and older techniques used in the past, suboptimal chemotherapy regimens to control systemic disease or increase radiosensitization, or inherent radioresistance of pancreatic cancer. Based on data presented in this study, use of RT for LAPC continues to decline in the United States. For patients who are good candidates for C+RT, consideration should be given to the use of IMRT over 3D given results from this population-based analysis. Randomized controlled trials including IMRT planning, stringent RT quality control measures, use of improved systemic agents, and incorporation of molecular markers, will provide further insight into the value of RT in LAPC.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Percent rate of chemotherapy alone vs. chemotherapy + radiotherapy (RT) for locally advanced pancreatic cancer (LAPC) treated from 2003–2011 (A); percent rate of intensity-modulated radiotherapy (IMRT) and three-dimensional (3D) in subpopulation analysis of LAPC undergoing RT from 2003–2011 (B).

Figure 2. Unadjusted Kaplan Meier curves comparing overall survival outcomes between chemotherapy + radiotherapy (RT) and chemotherapy alone (A) and subpopulation analysis comparing chemotherapy + intensity modulated radiotherapy (IMRT), chemotherapy + three-dimensional (3D) RT and chemotherapy alone (B).

Figure 3.

Kaplan Meier curves of overall survival adjusted by propensity score matching between chemotherapy + intensity modulated radiotherapy (IMRT) and chemotherapy alone (A), chemotherapy + three-dimensional (3D) RT and chemotherapy alone (B), and chemotherapy + IMRT and chemotherapy + 3D (C).

TABLE 1.

Patient and Treatment Characteristics

Variable	All Patients		Chemotherapy Alone		Chemotherapy + RT		P
	n (%)		n (%)		n (%)		
Age (years)							< 0.001
< 65	6055 (44.2)		2139 (40.3)		3916 (46.7)		
65	7640 (55.8)		3167 (59.7)		4473 (53.3)		
Sex							0.039
Male	6852 (50.0)		2596 (48.9)		4256 (50.7)		
Female	6843 (50.0)		2710 (51.1)		4133 (49.3)		
Race							0.390
White	11,323 (82.7)		4353 (82.0)		6970 (83.1)		
Black	1806 (13.2)		721 (13.6)		1085 (12.9)		
Other	415 (3.0)		173 (3.3)		242 (2.9)		
Missing	151 (1.1)		59 (1.1)		92 (1.1)		
Residence							< 0.001
Metropolitan	10,475 (76.5)		4212 (79.4)		6263 (74.7)		
Urban	2160 (15.8)		725 (13.7)		1435 (17.1)		
Rural	313 (2.3)		88 (1.7)		225 (2.7)		
Missing	747 (5.5)		281 (5.3)		466 (5.6)		
Insurance Status							< 0.001
Private	5286 (38.6)		1889 (35.6)		3397 (40.5)		
Government	7782 (56.8)		3168 (59.7)		4614 (55.0)		
Uninsured	392 (2.9)		165 (3.1)		227 (2.7)		
Missing	235 (1.7)		84 (1.6)		151 (1.8)		
Facility Type							< 0.001
Community Cancer Program	1056 (7.7)		337 (6.4)		719 (8.6)		
Comprehensive Community Cancer Program	6191 (45.2)		2312 (43.6)		6191 (45.2)		
Academic/Research (includes NCI)	6440 (47.0)		2653 (50.0)		3787 (45.1)		
Not Specified	8 (0.1)		4 (0.1)		4 (0.0)		
Distance to Hospital (miles)							0.556

Variable	All Patients		Chemotherapy Alone		Chemotherapy + RT		P
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	
12	6889 (50.3)	2640 (49.8)	4249 (50.6)				
> 12	6288 (45.9)	2467 (46.5)	3821 (45.5)				
Missing	518 (3.8)	199 (3.8)	319 (3.8)				
Charlson-Deyo Comorbidity Score							
0	9936 (72.6)	3755 (70.8)	6181 (73.7)				< 0.001
1	3759 (27.4)	1551 (29.2)	2208 (26.3)				
Diagnosis Year							
2003	992 (7.2)	268 (5.1)	724 (8.6)				< 0.001
2004	1039 (7.6)	314 (5.9)	725 (8.6)				
2005	1154 (8.4)	406 (7.7)	748 (8.9)				
2006	1365 (10.0)	514 (9.7)	851 (10.1)				
2007	1507 (11.0)	556 (10.5)	951 (11.3)				
2008	1767 (12.9)	696 (13.1)	1071 (12.8)				
2009	1901 (13.9)	792 (14.9)	1109 (13.2)				
2010	1905 (13.9)	796 (15.0)	1109 (13.2)				
2011	2065 (15.1)	964 (18.2)	1101 (13.1)				
Tumor Stage							
T1	388 (2.8)	152 (2.9)	236 (2.8)				< 0.001
T2	1966 (14.4)	853 (16.1)	1113 (13.3)				
T3	4510 (32.9)	1854 (34.9)	2656 (31.7)				
T4	6831 (49.9)	2447 (46.1)	4384 (52.3)				
Nodal Stage							
N0	8614 (62.9)	3236 (61.0)	5378 (64.1)				
N1	5081 (37.1)	2070 (39.0)	3011 (35.9)				< 0.001
Chemotherapy							
Single Agent	7788 (56.9)	2663 (50.2)	5125 (61.1)				
Multi-agent	4801 (35.1)	2134 (40.2)	2667 (31.8)				
NOS	1106 (8.1)	509 (9.6)	597 (7.1)				

Abbreviations: RT, radiation therapy; NCI, National Cancer Institute; NOS, not otherwise specified

TABLE 2.

Multivariate Cox Regression Model of Overall Survival for All Patients

Variable	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Treatment Group				
Chemotherapy Alone	1		1	
Chemotherapy + Radiation	0.88 (0.85-0.91)	< 0.001	0.84 (0.81-0.87)	< 0.001
Age (years)				
< 65	1		1	
65	1.18 (1.14-1.22)	< 0.001	1.09 (1.04-1.14)	< 0.001
Sex				
Male	1		1	
Female	1.01 (0.98-1.05)	0.429	0.99 (0.96-1.03)	0.590
Race				
White	1		1	
Black	0.93 (0.88-0.98)	0.004	0.93 (0.88-0.98)	0.006
Other	0.85 (0.77-0.95)	0.003	0.87 (0.79-0.97)	0.011
Missing	0.80 (0.67-0.95)	0.010	0.81 (0.68-0.97)	0.020
Residence				
Metropolitan	1		1	
Urban	1.10 (1.05-1.15)	< 0.001	1.08 (1.03-1.14)	0.004
Rural	1.19 (1.06-1.34)	0.004	1.17 (1.04-1.32)	0.011
Missing	1.19 (1.10-1.28)	< 0.001	1.20 (1.05-1.37)	0.006
Insurance Status				
Private	1		1	
Government	1.18 (1.14-1.23)	< 0.001	1.07 (1.02-1.12)	0.010
Uninsured	1.19 (1.07-1.33)	0.002	1.16 (1.04-1.30)	0.008
Missing	1.24 (1.08-1.42)	0.002	1.20 (1.05-1.38)	0.010
Facility Type				
Community Cancer Program	1		1	
Comprehensive Community Cancer Program	0.99 (0.92-1.06)	0.720	1.00 (0.94-1.08)	0.925

Variable	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
Academic/Research (includes NCI)	0.89 (0.83-0.95)	0.001	0.93 (0.86-1.00)	0.038
Not Specified	1.08 (0.52-2.28)	0.833	1.03 (0.49-2.17)	0.934
Distance to Hospital (miles)				
12	1		1	
> 12	0.99 (0.96-1.03)	0.558	0.99 (0.95-1.03)	0.628
Missing	1.15 (1.05-1.06)	0.003	0.97 (0.83-1.13)	0.660
Charlson-Deyo Comorbidity Score				
0	1		1	
1	1.12 (1.08-1.17)	<0.001	1.09 (1.05-1.14)	<0.001
Diagnosis Year				
2003	1		1	
2004	0.96 (0.88-1.05)	0.358	0.94 (0.86-1.03)	0.187
2005	1.00 (0.92-1.09)	0.956	1.01 (0.93-1.11)	0.750
2006	0.98 (0.90-1.07)	0.679	1.00 (0.92-1.08)	0.954
2007	0.98 (0.90-1.06)	0.634	0.98 (0.90-1.06)	0.627
2008	0.97 (0.90-1.05)	0.464	0.96 (0.88-1.03)	0.253
2009	0.96 (0.89-1.04)	0.309	0.94 (0.87-1.02)	0.112
2010	0.86 (0.79-0.93)	<0.001	0.85 (0.79-0.92)	<0.001
2011	0.81 (0.74-0.87)	<0.001	0.81 (0.75-0.88)	<0.001
Tumor Stage				
T1	1		1	
T2	1.13 (1.01-1.27)	0.034	1.15 (1.02-1.29)	0.018
T3	1.07 (0.96-1.19)	0.213	1.12 (1.00-1.25)	0.044
T4	1.01 (0.91-1.12)	0.869	1.08 (0.97-1.20)	0.180
Nodal Stage				
N0	1		1	
N1	1.09 (1.05-1.13)	<0.001	1.09 (1.06-1.14)	<0.001
Chemotherapy				
Single Agent	1		1	
Multi-agent	0.73 (0.70-0.76)	<0.001	0.74 (0.72-0.77)	<0.001

Variable	Univariate		Multivariate	
	HR (95% CI)	P	HR (95% CI)	P
NOS	0.92 (0.86-0.98)	0.010	0.90 (0.84-0.96)	0.001

Abbreviations: HR, hazard ratio; 3D, three-dimensional; IMRT, intensity modulated radiotherapy; NCI, National Cancer Institute; NOS, not otherwise specified