Trajectory of care and use of multimodality therapy in older patients with pancreatic adenocarcinoma

Abhishek D. Parmar, MD, MS,[a,b] **Gabriela M. Vargas, MD, MS,**[a] **Nina P. Tamirisa, MD,**[a,b] **Kristin M. Sheffield, PhD,**[a] *and* **Taylor S. Riall, MD, PhD,**[a] *Galveston, TX, and Oakland, CA*

Introduction. *Multimodality therapy with chemotherapy and operative resection is recommended for patients with locoregional pancreatic cancer but is not received by many patients.*
Objective. *To evaluate patterns in the use and timing of chemotherapy and resection and factors associated with receipt of multimodality therapy in older patients with locoregional pancreatic cancer.*
Methods. *We used Surveillance, Epidemiology, and End Results–linked Medicare data (1992–2007) to identify patients with locoregional pancreatic adenocarcinoma. Multimodality therapy was defined as receipt of both chemotherapy and pancreatic resection. Logistic regression was used to determine factors independently associated with receipt of multimodality therapy. Log-rank tests were used to identify differences in survival for patients stratified by type and timing of treatment.*
Results. *We identified 10,505 patients with pancreatic adenocarcinoma. 5,358 patients (51.0%) received either chemotherapy or surgery, with 1,166 patients (11.1%) receiving both modalities. Resection alone was performed in 1,138 patients (10.8%), and chemotherapy alone was given to 3,054 (29.1%) patients. In patients undergoing resection as the initial treatment modality, 49.4% never received chemotherapy; 97.4% of patients who underwent chemotherapy as the initial treatment modality never underwent resection. The use of multimodality therapy increased from 7.4% of patients in 1992–1995 to 13.8% of patients in 2004–2007 (*P *< .0001). The 2-year survival was 41.0% for patients receiving multimodality therapy, 25.1% with resection alone, and 12.5% with chemotherapy alone (*P *< .0001). Of the patients receiving multimodality therapy, chemotherapy was delivered in the adjuvant setting in 93.1% and in the neoadjuvant setting in 6.9%, with similar 2-year survival with either approach (neoadjuvant vs adjuvant, 46.9% vs 40.6%;* P *= .16). Year of diagnosis, white race, less comorbidity, and no vascular invasion were independently associated with receipt of multimodality therapy.*
Conclusion. *Only half of older patients with locoregional pancreatic cancer receive any treatment, and fewer than one quarter of treated patients receive multimodality therapy. Nearly all patients receiving chemotherapy as the initial treatment modality did not undergo resection, whereas half of those undergoing resection first received chemotherapy. When multimodality therapy is used, the vast majority of patients had chemotherapy in the adjuvant setting with a similar survival, regardless of approach. (Surgery 2014;156:280-9.)*

From the Department of Surgery,[a] *University of Texas Medical Branch, Galveston, TX; and Department of Surgery,*[b] *the University of California, San Francisco-East Bay, Oakland, CA*

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Reprint requests: Abhishek D. Parmar, MD, MS, Department of Surgery, University of Texas Medical Branch, 301 University Boulevard, Galveston, TX 77555-0541. E-mail: abparmar@utmb.edu.

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ONLY 20% OF PATIENTS with pancreatic cancer present with disease that is amenable to operative resection.[1] Although operative resection is the only potentially curative treatment option, most patients experience distant, extrapancreatic recurrence even after an R0 resection. This suggests that microscopic tumor spread may have occurred already at the time of presentation.[2-4]

Multiple prospective, randomized, controlled trials have documented improved disease-free survival when chemotherapy was administered in addition to pancreatic resection.[5-11] Based on these factors, the 2013 National Comprehensive

Cancer Network guidelines recommend systemic chemotherapy in conjunction with curative-intent surgery as the standard of care for resectable pancreatic adenocarcinoma.[12] Despite these recommendations, prior population-based studies have illustrated that multimodality therapy is administered rarely.[13,14]

Although previous studies have evaluated the receipt of resection in patients with locoregional pancreatic cancer,[15] the receipt of multimodality therapy in resected patients,[14] and trends in multimodality therapy use,[13] few studies have assessed population-based trends in the receipt and relative timing of chemotherapy and/or resection of the primary neoplasm. In addition, controversy exists regarding the optimal timing of chemotherapy (adjuvant versus neoadjuvant).[16] Most studies assessing the impact of neoadjuvant versus adjuvant therapy approaches on survival in patients with resectable pancreatic cancer have focused on only those patients who have undergone resection. As such, the number of patients who receive chemotherapy but never undergo resection owing to disease progression or declining performance status are often not reported and are not considered when comparing survival with the 2 approaches.

We used the Surveillance, Epidemiology and End Results (SEER)-linked Medicare database (1992–2007) to evaluate population-based patterns in the receipt of chemotherapy and/or operative resection. We identified the initial treatment modality used (chemotherapy or resection), and the proportion of treated patients who received the second modality. Among patients who received multimodality therapy (chemotherapy and resection), we evaluated the approach (neoadjuvant versus adjuvant therapy) and the association between neoadjuvant versus adjuvant therapy and long-term survival. Finally, we identified the factors independently associated with receipt of multimodality therapy for these patients.

METHODS

The institutional review board at the University of Texas Medical Branch determined this study to be exempt from review.

Data source. The SEER database is a prospectively collected database of incident cancer cases for patients in select regions designed to be representative of the U.S. population, accounting for approximately 28% of the population. Ninety-three percent of patients in the SEER database can be linked with patients who have Medicare claims files.[17] Medicare claims data used included the Denominator File, the Medicare Provider Analysis and Review file, the Carrier claims file, and the Outpatient Standard Analytic File.[18]

Cohort selection. We included patients diagnosed with pancreatic adenocarcinoma from 1992 to 2007. SEER data were used to identify the primary tumor site codes for pancreas and *International Classification of Diseases for Oncology, 3rd Edition,* histology codes consistent with adenocarcinoma (Fig 1). Only patients with pancreatic adenocarcinoma as their first primary diagnosis and those aged ≥66 years were included. Patients whose diagnosis was only confirmed at autopsy or death were excluded. Only patients with locoregional disease were included. Finally, patients without Medicare Parts A and B for 6 months before and after diagnosis, or until death, were excluded. All patients were followed for 2 years after diagnosis or until death.

Covariates. Patient baseline demographic and clinical characteristics included age, sex, marital status, race/ethnicity, education, income, area of residence (rural versus urban), SEER region, presence of vascular invasion, radiation, and year of diagnosis. Charlson comorbidity index[19] was used as a measure for patient comorbidity. Percent of residents with at least a 12th grade education and quartile of income were determined at the zip code level and categorized into quartiles. For education and income quartiles, quartile 1 is coded as the least educated/lowest income and quartile 4, the most educated/greatest income. SEER Extent of Disease Coding (1992–2003) and derived American Joint Committee on Cancer tumor T stage codes (2004–2007) were used to identify vascular invasion. Patients with codes 54 (pancreatic head, blood vessel[s] [major]: gastroduodenal artery, hepatic artery, pancreaticoduodenal artery, portal vein, superior mesenteric vein), 56 (body and tail, blood vessel[s]: Hepatic artery, portal vein, splenic artery/vein, superior mesenteric vein), and derived American Joint Committee on Cancer 6th edition tumor T stage code 40 (stage T4: tumor involves celiac axis or superior mesenteric artery) were classified as having vascular invasion.

Outcome variable: Multimodality therapy. Multimodality therapy was defined as receipt of both operative resection and any instance of chemotherapy before operative resection or within 6 months after surgery. Patients were considered not to have undergone multimodality therapy if they had resection only, received chemotherapy only, received chemotherapy >6 months after operative resection, or had no treatment. Codes

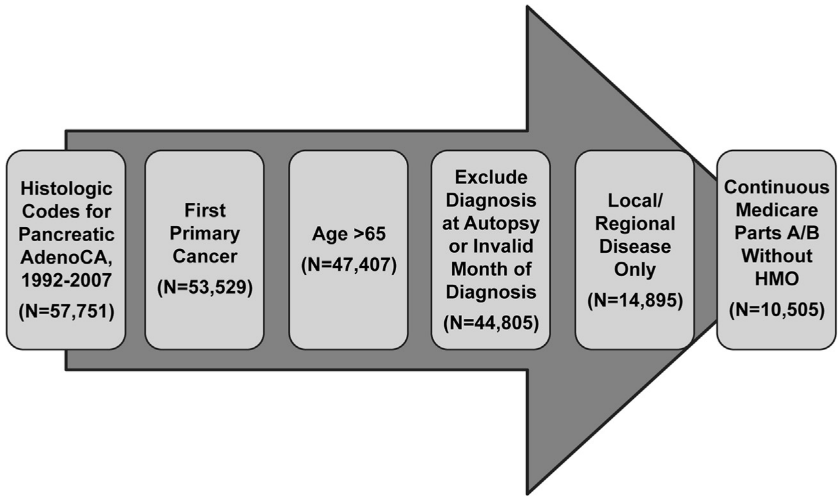

Fig 1. Cohort selection criteria. Only patients with histologically confirmed, locoregional pancreatic adenocarcinoma (AdenoCA) as their first primary cancer diagnosis were included. Patients without Medicare Parts A and B for 6 months before and after diagnosis, or until death, were excluded. All patients were followed for 2 years (n = 10,505).

used to identify chemotherapy, operative resection, and radiation are shown in Table I. Chemotherapy and radiation were identified from the Medicare claims (Medicare Provider Analysis and Review, Carrier, Outpatient Standard Analytical File) using Healthcare Common Procedure Coding System codes, *International Classification of Diseases, 9th Revision, Clinical Modification* (ICD-9-CM) procedure and diagnosis codes, J codes, and revenue center codes for administration of chemotherapy as defined by SEER-Medicare.[20] ICD-9-CM and Current Procedural Terminology codes used to identify pancreatic head resection are also listed in Table I. In patients receiving multimodality therapy, those receiving any chemotherapy (with or without radiation) before resection were considered to have undergone neoadjuvant therapy; if chemotherapy was within 6 months after resection, it was classified as adjuvant.

Statistical analysis. Summary statistics were calculated for the overall cohort. Demographic and tumor characteristics of patients who received multimodality therapy were compared with patients who did not receive multimodality therapy. We used χ^2 tests to test significance for categorical variables and t-tests for continuous variables.

Three logistic regression models were performed to determine factors independently associated with receipt of multimodality therapy. The first model included the overall cohort and included age, race, sex, marital status, education, income, Charlson comorbidity index, year of diagnosis, SEER region, area of residence (rural versus urban), vascular invasion, radiation, and biliary stent placement. The second model included only those patients without vascular invasion and included the same variables except for vascular invasion. Finally, a third logistic regression model was performed, including all variables only for those patients who received treatment with operation and/or chemotherapy.

Survival analysis. Unadjusted Kaplan-Meier estimates of overall survival were obtained for patients who (1) underwent operative resection and adjuvant chemotherapy, (2) underwent surgery alone, (3) underwent chemotherapy alone, and (4) received no treatment. For patients who received both modalities, Kaplan-Meier time-to-event analyses were performed for patients who underwent surgery and received neoadjuvant versus adjuvant chemotherapy. Log-rank tests were used to determine significant differences in survival between groups. A Cox proportional hazards model for survival at 2 years was developed only for those patients receiving multimodality therapy and included the variables age, sex, race, income, education, Charlson comorbidity, SEER region, radiation, endostent, vascular invasion, and timing of therapy (neoadjuvant versus adjuvant). Patients were censored when they were lost to follow-up or completed follow-up at 2 years.

RESULTS

We identified 10,505 patients who met our inclusion criteria. Table II illustrates baseline characteristics for these patients. The mean age was 77.1 ± 7.1 years, and the majority of patients were

Table I. International Classification of Diseases for Oncology, 3rd Edition codes, International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) codes, and Current Procedural Terminology (CPT) codes

Codes for	*ICD-9-CM codes*	*CPT codes*
Diagnosis		
Pancreatic adenocarcinoma	8000/3, 8010/3, 8020/3, 8021/3, 8022/3, 8140/3, 8141/3, 8211/3, 8230/3, 8500/3, 8521/3, 8050/3, 8260/3, 8441/3, 8450/3, 8453/3, 8470/3, 8471/3, 8472/3, 8473/3, 8480/3, 8481/3, 8503*	NA
Procedures/treatment		
Pancreatic head resection	52.6, 52.7, 52.51	48150, 48152, 48153, 48154, 48155
Biliary stent	51.86, 51.87, 51.99	43267, 43268, 43269
Chemotherapy	99.25	Q0083, Q0084, Q0085, J7150, J2353, J2354, J9000-J9999
Radiation	99.21–99.29	77520, 77523, G0256, G0261, 77401–77499

*International Classification of Diseases for Oncology, 3rd edition, codes.

female (58%), white (82%), married, and from a large metropolitan area. Only 5,358 (51.0%) received operative resection and/or chemotherapy at any time in their treatment course. Of these patients, 1,166 (11.1% of the overall cohort) received both chemotherapy and operative resection, 1,138 (10.8%) received operative resection alone, and 3,054 (29.0%) received chemotherapy alone. In the 1,166 patients receiving multimodality therapy, chemotherapy was delivered in the adjuvant setting in 93.1% and in the neoadjuvant setting in 6.9% (Fig 2, *A*). Of the patients classified as having received adjuvant chemotherapy, 78.4% received chemotherapy within 3 months after the date of operative resection (median, 62 days; interquartile range, 48–88).

In the 5,358 treated patients, chemotherapy was the initial treatment modality in 3,135 patients (58.5%), and operative resection was the initial treatment modality in 2,223 (41.5%). In patients undergoing operative resection as the initial treatment modality, 51.2% never received chemotherapy. Among patients undergoing chemotherapy as the initial treatment modality 97.4% never underwent operative resection (Fig 2, *A*). Among patients receiving chemotherapy as the initial treatment modality, 67.9% received radiation, compared with only 49.5% of those undergoing operative resection first. Among patients receiving multimodality therapy, 82.7% of patients who underwent neoadjuvant therapy underwent neoadjuvant radiation and 79.7% of patients who had adjuvant chemotherapy also received adjuvant radiation.

Based on SEER extent of disease codes, 8,253 patients (78.6%) had no vascular invasion and were eligible potentially for neoadjuvant therapy plus resection or resection plus adjuvant therapy. Their trajectory is shown in Fig 2, *B*. Vascular invasion was more common in patients undergoing chemotherapy as the initial treatment modality compared with patients receiving resection initially (28.4% vs 5.3%; $P < .0001$). Finally, 4,058 patients (49.2%) received no treatment. Of the 4,195 who were treated, 2,117 received chemotherapy as the initial treatment modality, and 2,078 underwent resection as the initial treatment modality. Overall, 1,078 (13.1%) received multimodality therapy, 2,057 (24.9%) received chemotherapy alone, and 1,060 (12.8%) underwent resection alone.

Trends in the use of multimodality therapy are illustrated in Fig 3.Use of multimodality therapy increased over time from 7.4% in 1992–1995 to 13.8% in 2004–2007 ($P < .0001$). There was also an increase in the use of neoadjuvant therapy over time, from 2.5% of patients in 1992–1995 to 9.4% of patients in 2004–2007 ($P = .0095$). Among patients without vascular invasion ($n = 8{,}253$), use of multimodality therapy increased from 7.7% in 1992–1995 to 17.4% of patients in 2004–2007 ($P < .0001$); for these patients, neoadjuvant therapy use increased from 1.0% to 8.4% over the same time period ($P = .001$).

Patient demographics, and tumor and treatment characteristics differed significantly between the multimodality therapy and no multimodality therapy groups (Table II). Patients who received multimodality therapy were younger, and more likely to be female, white, married, have less comorbidity, live in higher socioeconomic areas, have received radiation therapy, and have no evidence for vascular invasion. The use of multimodality therapy was variable by SEER region.

Table II. Summary statistics for overall cohort and proportion of patients receiving multimodality therapy for each factor

Factor	Overall cohort, n (%)	Patients receiving multimodality therapy, n (%)	P value
n	10,505	1,166	
Age (mean ± SD)	77.2 ± 7.1	72.8 ± 4.8	<.0001
Female	6,129 (58.3)	633 (10.3)	.0029
Race			<.0001
White	8,631 (82.2)	1,032 (12.0)	
Black	979 (9.3)	53 (5.4)	
Other	895 (8.5)	81 (9.1)	
Marital status (*n* = 10,210)			<.0001
Single	1,457 (14.3)	149 (10.2)	
Married	5,369 (52.6)	769 (14.3)	
Widowed	3,384 (33.1)	226 (6.7)	
Stage			<.0001
Localized	2,782 (26.5)	139 (5.0)	
Regional	7,723 (73.5)	1,027 (13.3)	
SEER region			<.0001
Connecticut	922 (8.8)	124 (13.5)	
Louisiana	570 (5.4)	46 (8.1)	
New Jersey	1,142 (10.9)	192 (16.8)	
San Francisco	557 (5.3)	45 (8.1)	
San Jose	343 (3.3)	47 (13.7)	
Los Angeles	972 (9.3)	108 (11.1)	
Greater California	1,296 (12.3)	156 (12.0)	
Detroit	1,218 (11.6)	129 (10.6)	
Hawaii	243 (2.3)	32 (13.2)	
Iowa	839 (8.0)	81 (9.7)	
New Mexico	315 (3.0)	21 (6.7)	
Seattle	803 (7.6)	55 (6.9)	
Utah	325 (3.1)	28 (8.6)	
Atlanta	396 (3.8)	41 (10.4)	
Kentucky	564 (5.4)	61 (10.8)	
Charlson Comorbidity Index			<.0001
0	5,066 (48.2)	674 (13.3)	
1	3,032 (28.9)	332 (11.0)	
2	1,325 (12.6)	117 (8.8)	
≥3	1,082 (10.3)	43 (4.0)	
Education			<.0001
Quartile 1 (lowest)	2,607 (25.0)	211 (8.1)	
Quartile 2	2,607 (25.0)	252 (9.7)	
Quartile 3	2,607 (25.0)	321 (12.3)	
Quartile 4	2,605 (25.0)	374 (14.4)	
Income			<.0001
Quartile 1 (lowest)	2,606 (25.0)	178 (6.8)	
Quartile 2	2,607 (25.0)	259 (9.9)	
Quartile 3	2,606 (25.0)	307 (11.8)	
Quartile 4	2,607 (25.0)	414 (15.9)	
Diagnosis y			<.0001
1992–1995	1,596 (15.2)	118 (7.4)	
1996–1999	1,576 (15.0)	133 (8.4)	
2000–2003	3,471 (33.0)	382 (11.0)	
≥2004	3,862 (36.8)	533 (13.8)	
No vascular invasion (*n* = 10,013)	8,253 (78.6)	1,078 (13.1)	<.0001
Radiation	3,794 (36.1)	932 (24.6)	<.0001
Adjuvant	NA	844 (73.1)	
Neoadjuvant	NA	77 (24.8)	
Unknown	NA	11 (2.1)	
Biliary stent	4,031 (38.4)	560 (13.9)	<.0001
Therapy			<.0001
Both operative resection and chemotherapy	1,166 (11.1)	100%	
Operative resection only	1,138 (10.8)	NA	
Chemotherapy only	3,054 (29.1)	NA	
None	5,147 (49.0)	NA	
Initial treatment modality (*n* = 5,358)			<.0001
Operative resection	2,223 (41.5)	1,085 (48.8)	
Chemotherapy	3,135 (58.5)	81 (2.6)	

NA, Not applicable; *SEER*, Surveillance, Epidemiology, and End Results.

In a logistic regression analysis, year of diagnosis was independently associated with receipt of multimodality therapy (odds ratio, 1.09; 95% CI, 1.06–1.11; Table III) reflecting evolving recommendations over this time period. Other factors independently associated with receipt of multimodality therapy included younger age, white race, higher education quartile, lesser Charlson comorbidity score, absence of vascular invasion, treatment with radiation, and biliary stent placement (Table III). The strongest effects were observed for no vascular invasion (odds ratio, 5.78; 95% CI, 4.5–7.4) and radiation treatment (odds ratio, 6.82; 95% CI, 5.8–8.0).

In the subset of patients without vascular invasion (*n* = 8,253), younger age, white race, lesser Charlson comorbidity score, treatment with radiation, and biliary stent placement continued to be

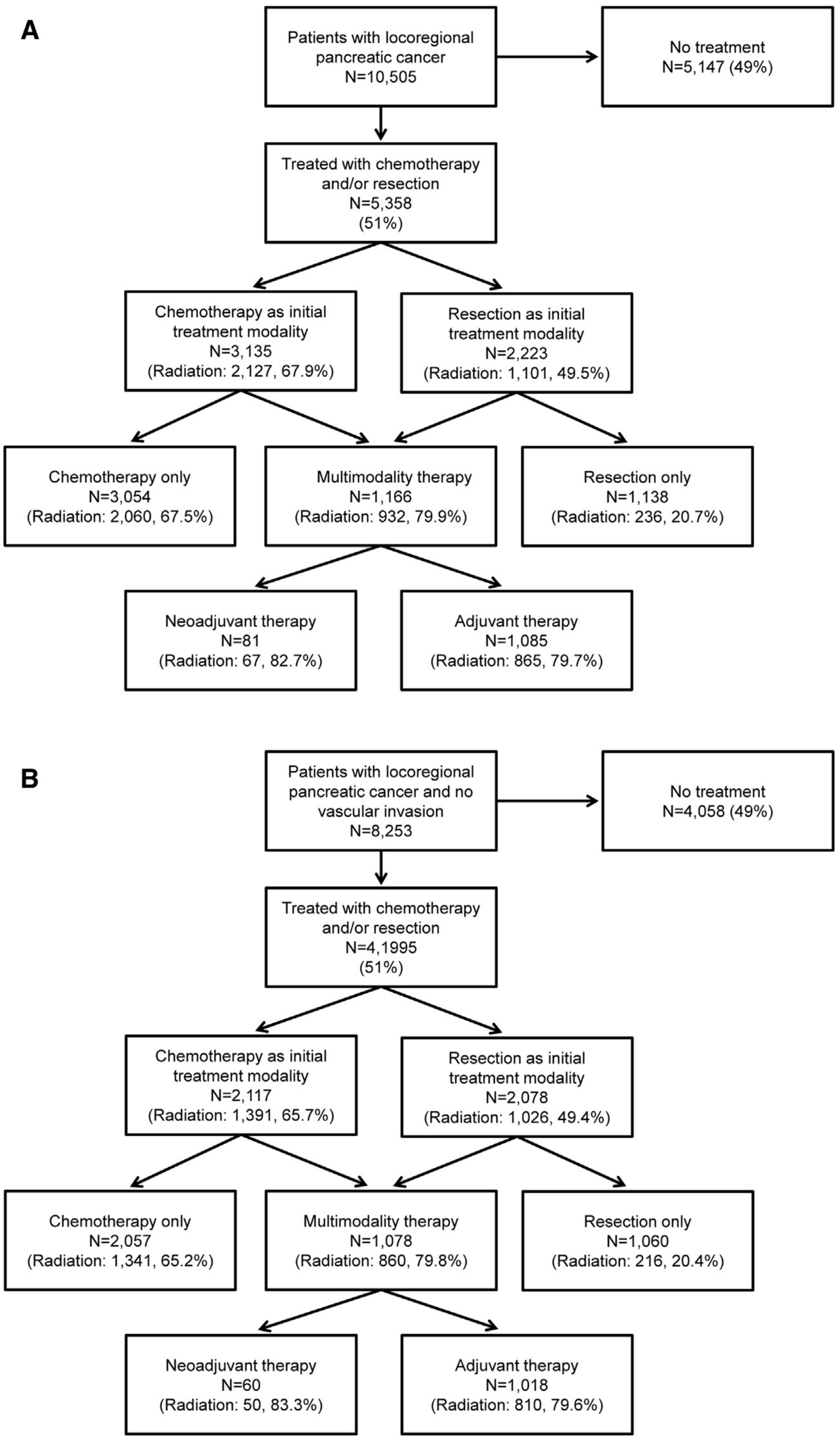

Fig 2. *A*, Management of older patients >65 years of age with locoregional pancreatic cancer. Nearly half of all patients received no treatment; 11.1% of the overall cohort received multimodality therapy. More than 97% of patients receiving chemotherapy as the initial treatment modality did not receive operative resection, whereas 51% of patients who received operative resection as the initial treatment modality did not receive chemotherapy. The proportion of patients receiving radiation therapy for each group is also listed. *B*, Management of older patients with locoregional pancreatic cancer and no vascular invasion. Of these patients with potentially treatable pancreatic cancer (n = 8,253), only 51% received any treatment, and only 13.1% received multimodality therapy. More than 97% of patients receiving chemotherapy as the initial treatment modality did not receive operative resection, whereas 51% of patients who received operative resection as the initial treatment modality did not receive chemotherapy. The proportion of patients receiving radiation therapy for each group is also listed.

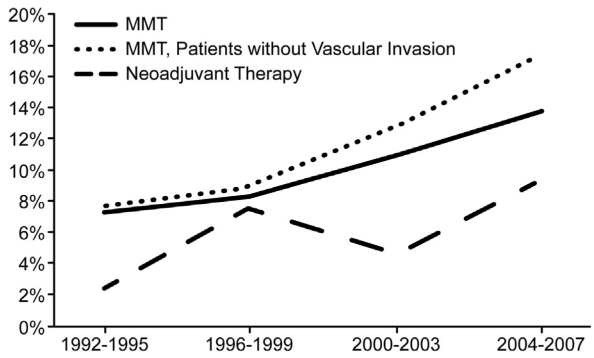

Fig 3. Trends in the use of multimodality therapy in older patients with locoregional pancreatic adenocarcinoma, 1992–2007. The use of multimodality therapy (MMT) increased over time from 7.4% of patients in 1992–1995 compared with 13.8% of patients in 2004–2007 ($P < .0001$); this increase was more pronounced for patients without vascular invasion (7.7% to 17.4%; $P < .0001$). Neoadjuvant therapy use in patients receiving MMT also increased over this same time period (2.5% vs 9.4%; $P = .0095$).

associated with receipt of multimodality therapy. Similar findings were observed for treated patients (Table III).

Survival analysis. Survival for the overall cohort was 13.8% at 2 years (median, 7.2). Fig 4, *A* shows 2-year survival in patients who received multimodality therapy (41.0%), resection only (25.1%), chemotherapy only (12.5%), or no therapy (5.1%; $P < .0001$). For patients who received multimodality therapy, there was no difference in survival when chemotherapy was administered in the neoadjuvant versus adjuvant setting (Fig 4, *B*; 46.9% vs 40.6%; $P = .16$). In a Cox proportional hazards model controlling for age, sex, race, income, education, Charlson comorbidity, SEER region, radiation, endostent, and vascular invasion, neoadjuvant therapy was not independently associated with improved survival relative to adjuvant therapy in patients receiving multimodality therapy (hazard ratio, 0.76; 95% CI, 0.55–1.06). The absence of vascular invasion was most strongly associated with improved survival for these patients (hazard ratio, 0.54; 95% CI, 0.40–0.72).

DISCUSSION

We observed that only 11% of older patients with locoregional pancreatic cancer in SEER regions received multimodality therapy. In addition, over half of these older patients (usually >65 years old) with potentially treatable pancreatic cancer did not receive any treatment at all. When treatment was instituted, over half of patients received chemotherapy as the initial treatment modality, but very few of these patients ultimately underwent operative resection. Finally, we observed that when patients received multimodality therapy, there were no differences in survival between patients who received chemotherapy in the neoadjuvant versus adjuvant setting.

Our study illustrates general trends in the management of an older population with locoregional pancreatic cancer. Although previous studies have focused on the timing of chemotherapy in only those patients undergoing resection,[14,21,22] we identified trends in the treatment in all patients with potentially treatable pancreatic cancer. Although the majority of patients who received treatment were treated with chemotherapy as the initial treatment modality, only 2% of these patients ultimately underwent resection. There may be several reasons for this observation. Patients may have developed progressive metastatic disease during neoadjuvant therapy and would not have benefited from resection. Proponents of neoadjuvant therapy would argue that these patients would have been spared the morbidity of a noncurative, invasive operation.[16,23] Some patients may, however, have experienced local disease progression without distant metastatic disease and missed their window for curative resection.[24] It is also possible that patients may have developed toxicity related to neoadjuvant therapy with an associated decline in performance status and were no longer operative candidates. Finally, it is possible that patients were treated with chemotherapy with palliative intent for locally unresectable disease and were never considered for resection; however, even in the group without vascular invasion, nearly all patients receiving chemotherapy first did not undergo resection.

Prior studies have suggested that neoadjuvant therapy may be associated with improved survival.[21,25] In our population-based cohort, however, we observed no difference between neoadjuvant and adjuvant approaches in patients who received multimodality therapy. Furthermore, like the other studies, our survival comparison does not account for the patients who received chemotherapy with the intent to eventually undergo resection, but whose disease progressed in the interim. As a result, we have likely overestimated the survival benefit with a neoadjuvant approach. All of these survival comparisons, including our own, are limited by their retrospective nature but represent the best available evidence until large-scale, prospective data are accumulated. Two previous, recent, single-center reviews compared retrospectively patterns in care for patients with pancreatic

Table III. Logistic regression models, factors associated with receipt of multimodality therapy* for overall cohort, for patients without vascular invasion, and for treated patients

	Multimodality therapy†					
	Overall cohort (n = *10,505*)		*Patients without vascular invasion* (n = *8,253*)		*Patients treated with surgery or chemotherapy* (n = *5,358*)	
Factor (reference)	*OR*	*95% CI*	*OR*	*95% CI*	*OR*	*95% CI*
Year of diagnosis	1.09	1.06–1.11	1.10	1.08–1.12	1.08	1.05–1.09
Age (y)	0.90	0.89–0.91	0.90	0.88–0.91	0.92	0.91–0.94
Married (single)	1.22	0.99–1.5	1.31	1.04–1.65	1.0	0.81–1.26
Widowed (single)	1.00	0.78–1.29	1.07	0.82–1.40	0.94	0.72–1.22
Male (female)	1.00	0.78–1.29	1.01	0.86–1.18	0.98	0.85–1.15
White (black)	1.90	1.36–2.65	1.91	1.34–2.71	1.67	1.19–2.35
Other (black)	1.16	0.75–1.80	1.16	0.73–1.84	1.01	0.65–1.59
Education Q2 (Q1)	1.15	0.90–1.46	1.11	0.86–1.44	1.14	0.88–1.46
Education Q3 (Q1)	1.33	1.02–1.74	1.18	0.89–1.57	1.31	0.99–1.72
Education Q4 (Q1)	1.39	1.03–1.88	1.26	0.92–1.74	1.32	0.97–1.81
Charlson comorbidity 0 (3)	3.18	2.26–4.49	3.51	2.43–5.07	2.48	1.74–3.53
Charlson comorbidity 1 (3)	2.58	1.81–3.68	2.85	1.96–4.16	2.02	1.40–2.90
Charlson comorbidity 2 (3)	2.17	1.47–3.21	2.34	1.54–3.54	1.84	1.23–2.76
Vascular invasion (yes)	5.78	4.49–7.44	NA	NA	5.63	4.37–7.26
Radiation (no)	6.82	5.79–8.02	7.10	6.00–8.41	3.55	3.00–4.21
Stent (no)	1.38	1.19–1.59	1.34	1.15–1.56	1.37	1.18–1.59

*Defined as any course of chemotherapy and surgery (n = 1,166).
†SEER region, quartile of income, and location of residence were also controlled for in the model and were not significant.
OR, Odds ratio; *NA*, not applicable; *SEER*, Surveillance, Epidemiology, and End Results.

adenocarcinoma who underwent a neoadjuvant-intent approach versus a surgery-first approach. Of the 167 patients in their study, Tzeng et al[26] identified improved receipt of multimodality therapy in those patients receiving a neoadjuvant-intent approach compared with patients undergoing surgery first (95/155 [83%] vs 29/50 [50%], respectively; $P < .001$), and no difference in survival between the 2 approaches.[26] Another study by Papalezova et al[27] similarly identified no difference in median overall survival between the 2 approaches (15 vs 13 months; P = NS). Although these studies provide insight into specific reasons for failure of therapy and survival outcomes, their single institution nature limits their generalizability. These studies are biased by institutional practices that may favor aggressive neoadjuvant approaches first in patients who are surgical candidates and do not represent population-based practices; as a result, the external validity of these studies is limited.

Our study expands on previous findings[13,15] that treatment for pancreatic cancer is underutilized. In this specific population of patients >65 years old, this disparity in pancreatic cancer care is even more pronounced. As has been suggested previously,[15] this disparity may be owing to nihilistic attitudes regarding pancreatic cancer care, particularly for older patients who may have limited life expectancy.

Finally, our data support previous observations[13] that, although patient and tumor characteristics largely determine the receipt of multimodality therapy, administration of therapy can be improved. In an analysis of 301,033 patients with pancreatic adenocarcinoma from the National Cancer Data Base, Bilimoria et al[13] determined that patients at high-volume centers, patients at NCCN/National Cancer Institute hospitals, and patients in metropolitan areas were more likely to receive multimodality therapy. We observed that patients who received multimodality therapy were selected to do so based on favorable patient characteristics (younger age, less comorbidity) or favorable tumor biology (no vascular invasion). Multimodality therapy did, however, increase over time and was also associated with higher education/income quartile, biliary stenting, and radiation use, factors that should not typically in theory drive multimodality therapy use. In addition, the use of multimodality therapy varied widely by SEER region, from 6% to almost 17% of patients for each region. This variation may reflect treatment practices of physicians

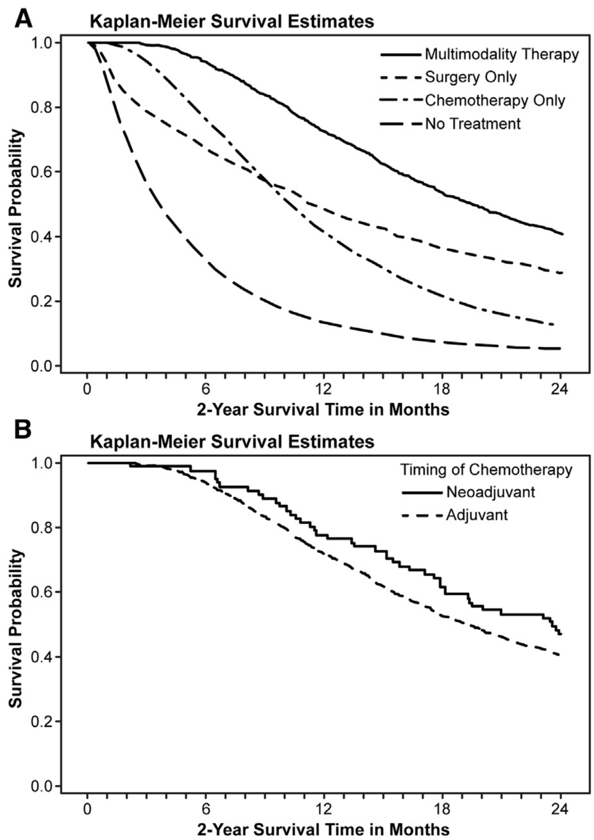

Fig 4. *A*, Kaplan-Meier 2-year survival curves in patients with locoregional pancreatic adenocarcinoma (n = 10,505) by treatment group: Multimodality therapy, surgery (operative resection) alone, chemotherapy alone, and no treatment. Survival improved with multimodality therapy compared with the other groups (41.0% vs 29.0% vs 12.5% vs 5.1%, respectively; $P < .0001$). Patients were censored at loss of follow-up and at 2 years. *B*, Kaplan-Meier estimate of 2-year survival for patients who received multimodality therapy (n = 1,166). There were no differences in survival between a neoadjuvant and adjuvant approach to chemotherapy (46.9% vs 40.6%; P = .16). Patients were censored at loss of follow-up and at 2 years.

in these states, patient preferences regarding aggressiveness of care, or variable access to resources, but we cannot identify the precise reasons behind these observations with these data.

Our study has limitations. Confounding by treatment indication is a very real possibility when using administrative data. We attempted to control for locally advanced/unresectable disease using Extent of Disease Coding, but resectability may not have been captured accurately with our methodology, because 74% of patients without vascular invasion did not undergo resection. In addition, we do not know the intent of therapy, so it would have been inappropriate to compare survival on an "intent-to-treat" basis in those patients who received chemotherapy as an initial treatment modality to those who received operative resection as an initial treatment. We limited this bias by only comparing survival between neoadjuvant and adjuvant therapy in those patients who received ultimately both resection and chemotherapy. We also do not know whether patients who received chemotherapy in the 6 months after resection did so with adjuvant intent or for treatment of recurrent or advancing disease. As a result, we may have overestimated the use of multimodality therapy; however, nearly 80% of patients received chemotherapy within 3 months after resection, making treatment for recurrent or advanced disease less likely. Previous population-based studies have also used similar methodology to identify adjuvant treatment.[14] Finally, the sample size for patients receiving neoadjuvant and adjuvant therapies is still relatively small; as a result, our study may be underpowered to detect significant survival differences between these groups. As a result, our survival analysis is limited, and only a multicenter, prospective, randomized collaboration can determine definitively the efficacy of a neoadjuvant-intent approach versus an adjuvant-intent approach.

We observed that for older patients undergoing treatment for pancreatic cancer, a chemotherapy-first approach is likely associated with a lesser likelihood for receipt of multimodality therapy. Multimodality therapy seems to be underutilized in patients >65 years of age with pancreatic cancer. Although patient and tumor characteristics are being used to guide treatment decisions, the variability in the administration of multimodality therapy and the increased use over time imply that improvements in the delivery of care can be made. Finally, our data suggest that there are no differences in survival between a neoadjuvant versus adjuvant approach when multimodality therapy is administered.

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