ORIGINAL ARTICLE

Survival Effects of Adjuvant Chemoradiotherapy After Resection for Pancreatic Carcinoma

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Background: The survival benefit of adjuvant chemotherapy alone or chemoradiotherapy in patients with pancreatic cancer who have undergone surgical resection remains unclear.

Objective: To identify the additional benefit of adjuvant therapy by retrospectively examining a large population-based registry of patients who underwent definitive surgical resection for pancreatic adenocarcinoma.

Design and Setting: The Florida cancer registry and state inpatient and outpatient hospital data records were queried for pancreatic adenocarcinoma diagnosed between 1998 and 2002.

Patients: A total of 2877 patients who underwent surgical resection with curative intent for pancreatic adenocarcinoma were identified.

Main Outcome Measure: Overall survival time.

Results: Overall, 58.7% of patients were older than 65 years. Most patients were white (90.7%), were non-Hispanic (86.7%), and did not consume alcohol abusively (89.2%). Approximately half of the patients (51.9%) did not receive chemotherapy or chemoradiotherapy. Approximately 25.0% of the patients underwent chemoradiotherapy, and 10.0% received chemotherapy alone. Patients were more frequently treated at low-volume centers (57.6%) and nonteaching facilities (72.8%). Multivariate analysis correcting for patient comorbidities demonstrated that postoperative chemoradiotherapy (hazard ratio = 0.69, $P = .04$) and treatment at high-volume centers (hazard ratio = 0.85, $P < .001$) and teaching facilities (hazard ratio = 0.84, $P < .001$) were independent predictors of improved survival.

Conclusions: Adjuvant chemoradiotherapy was found to provide a significant additional survival benefit to surgical resection for patients with pancreatic adenocarcinoma. Furthermore, this benefit is independent of the additional survival advantage when patients are treated at teaching facilities or high-volume centers. Although selection bias may be contributing to the observed differences, these data nonetheless support the use of adjuvant chemoradiotherapy for pancreatic cancer.

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In the United States, pancreatic adenocarcinoma is the fourth leading cause of cancer-related deaths, accounting for an estimated 35 000 deaths in 2008. Surgical resection is the only curative modality for early-stage pancreatic cancer; however, few patients present with disease amendable to surgical extirpation (<25%).[1]

See Invited Critique at end of article

For this small percentage of patients, the role of adjuvant therapy remains somewhat controversial. Results of prospective studies investigating the effects of adjuvant chemoradiotherapy have been conflicting[2]; despite the current data, adjuvant chemoradiotherapy is a generally accepted treatment protocol in the United States for surgically resected pancreatic adenocarcinoma. Results of the randomized phase 3 study CONKO-001[3] showed a significant improvement in disease-free survival in patients with pancreatic cancer who received adjuvant gemcitabine after resection over patients who had R0 and R1 resections (13.4 vs 6.9 months, $P < .001$). Recent literature[4-16] also suggests a survival benefit for patients who receive care at high-volume centers (HVCs) and teaching facilities (TFs). Furthermore, concerns have been raised that improved outcomes with chemoradiotherapy reported in some series may be due, in part, to outcome differences associated with volume or teaching status.

Using a comprehensive population-based cancer registry, we sought to better understand the effects of neoadjuvant and adjuvant therapy on clinical outcomes in patients who underwent surgical resection for pancreatic adenocarcinoma. This analysis was strengthened with data modifiers inclusive of patient demographics, comorbidities, treatment, and facility data. Furthermore, by accounting for

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Table 1. Demographic and Social Characteristics of 2877 Patients With Pancreatic Cancer

	Patients, No. (%)	Survival, Median, mo	*P* Value
Sex			
Male	1455 (50.6)	14.7	.77
Female	1422 (49.4)	15.0	
Age, y			
<40	57 (2.0)	25.7	<.001
40-65	1130 (39.3)	16.6	
>65	1690 (58.7)	13.4	
Race			
White	2609 (90.7)	14.6	.72
Black	212 (7.4)	17.3	
Other	30 (1.0)	NA	
Unknown	26 (0.9)	NA	
Ethnicity			
Hispanic	361 (12.5)	15.1	.33
Non-Hispanic	2495 (86.7)	14.7	
Unknown	21 (0.7)	NA	
Abusive alcohol consumption			
Yes	177 (6.2)	14.3	.60
No	2565 (89.2)	14.7	
Unknown	135 (4.7)	NA	
Tobacco use			
Yes	1375 (47.8)	14.7	.72
No	1087 (37.8)	15.2	
Unknown	415 (14.4)	NA	
Community poverty level, %			
<5	825 (28.7)	17.6	<.001
5-10	825 (28.7)	14.0	
>10-15	474 (16.5)	13.5	
>15	554 (19.3)	12.4	
Unknown	199 (6.9)	NA	
Insurance			
Insured	1095 (38.1)	15.8	.02
No insurance	83 (2.9)	20.9	
Medicare	937 (32.6)	14.5	
Medicaid	92 (3.2)	18.8	
Medicare/Medicaid NOS	548 (19.0)	12.7	
Government	39 (1.4)	13.7	
Unknown	83 (2.9)	NA	

Abbreviations: NA, not available; NOS, not otherwise specified.

the effects of clustering, we delineated the effects of treatment facilities on patient outcome. Thus, the relative contribution and relationship between volume and teaching status and chemoradiotherapy could be examined.

METHODS

The Florida Cancer Data System (FCDS) data set was used to identify all incident cases of pancreatic adenocarcinoma diagnosed in Florida between January 1, 1998, and December 31, 2002. Patients were identified as undergoing surgical resection with curative intent if they underwent partial pancreatectomy, total pancreatectomy, extended pancreatoduodenectomy, or surgery not otherwise specified. The FCDS data set was enhanced with data collected by the Florida Agency for Health Care Administration (AHCA), which maintains 2 databases: Hospital Patient Discharge Data and Ambulatory Outpatient Data. All hospitals and freestanding ambulatory centers in Florida have been required to report every discharge and outpatient encounter to the AHCA since 1987, including comorbid conditions, diagnoses, and procedures performed. The AHCA data from 1998 to 2002 were linked to cases in the FCDS data set on the basis of unique identifiers. Postal codes listed in the FCDS-AHCA database were then used to determine community poverty levels according to the US Census Bureau report.[17]

Medical facilities were defined as either TFs or nonteaching facilities (NTFs) on the basis of recognition as a teaching institution by the Association of American Medical Colleges (AAMC). At the time of this writing, there were 10 AAMC-recognized TFs in Florida. The data from the FCDS were tabulated to determine the number of surgical resections for pancreatic adenocarcinoma performed at each institution in Florida during the study period. Medical facilities were grouped into tertiles according to the number of curative-intent pancreatic resections performed during the study period. The upper one-third of the institutions were classified as HVCs and the lower two-thirds as low-volume centers (LVCs).

The staging criteria used by the FCDS are consistent with the Surveillance, Epidemiology, and End Results (National Cancer Institute) summary staging and are different from the TNM (tumor, node, and metastasis) staging guidelines; TNM staging was not available through this cancer registry.[18] Statistical analysis was performed using SPSS version 15 (SPSS Inc, Chicago, Illinois) and Stata version 8 (StataCorp, College Station, Texas). For group comparisons of categorical variables, χ^2 tests were used. Because the FCDS collects only the primary cause of death, we analyzed overall survival instead of disease-specific survival. Overall survival was calculated as the time from initial diagnosis until the date of death or last contact. Median survival rates were calculated using the Kaplan-Meier method. A multivariate Cox proportional hazards regression, which accounted for the fact that patients are clustered at the facility level, was used to determine the risk of death associated with pancreatic adenocarcinoma. Patient demographics, clinical characteristics, and comorbidities were included as categorical variables in the analysis.

In the univariate model, if data for a particular variable were available, the variable was included. To increase power for statistical analysis in the multivariate analysis, we did not want to exclude individuals who had missing data. Therefore, a dummy variable was created for variables for which there was a great deal of missing data. This category was labeled "unknown," and this value was assigned to patients in the database who did not have information on a given variable. However, because it is unclear how to interpret a hazard ratio (HR) for a category of missing data, these results are not included in the tables.

RESULTS

PATIENT DEMOGRAPHICS AND CLINICAL VARIABLES

During the 5-year period studied (1998-2002), 2877 patients identified as having a diagnosis of pancreatic cancer also underwent surgical resection with curative intent. The cohort was divided evenly among men (1455 patients [50.6%]) and women (1422 [49.4%]), and most patients were white (2609 [90.7%]) and non-Hispanic (2495 [86.7%]) (**Table 1**). According to Census 2000,[19] this racial and ethnic distribution differs slightly from that found in Florida: 78.0% white, 14.6% black, and 83.2% non-Hispanic.[19] The mean age at diagnosis was 67 years, and most patients were older than 65 years (1690 patients [58.7%]). Approximately half of the cohort (1375 patients [47.8%]) reported either current or past tobacco use, whereas a larger proportion (2565 [89.2%]) reported no abusive alcohol consumption. More than half of the study

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population (1650 patients [57.4%]) was defined as residing in a community block group in which 10% or less of the local population was below the federal poverty level according to the 2005 US Census Bureau report.[17]

The most common tumor stage was regional (792 patients [27.5%]), and the most common histologic grade was moderately differentiated (954 [33.2%]) (**Table 2**). A greater proportion of patients had either tumors larger than 5 cm (1251 patients [43.5%]) or positive lymph nodes (686 [23.8%]). Most patients underwent surgical extirpation alone (1494 patients [51.9%]). Approximately, one-quarter of the patients underwent postoperative adjuvant combined chemoradiotherapy (758 patients [26.3%]). A few patients underwent preoperative chemoradiotherapy (42 patients [1.5%]), and some underwent single-modality postoperative adjuvant therapy (299 [10.4%] for chemotherapy and 105 [3.6%] for radiotherapy). Most patients received all their therapy at LVCs (1656 patients [57.6%]) and NTFs (2094 [72.8%]).

SURVIVAL

The median overall survival time (MST) for the entire cohort was 15 months, and 90-day postsurgical survival was 88.8%. Patients younger than 40 years had the best MST (25.7 vs 13.4 months for patients >65 years old, $P<.001$) (Table 1). No differences were appreciated by race or ethnicity. Similarly, there was no significant survival benefit for patients who abstained from alcohol and tobacco use. As the poverty level increased, the MST shortened (17.6 months for patients <5% below the poverty level vs 12.4 months for patients >15% below the poverty level).

Patients with local disease (21.4 months vs 12.6 months for patients with distant disease, $P<.001$) and well-differentiated tumors (25.0 vs 11.3 months for poorly differentiated tumors, $P<.001$) had an improved MST, as did patients with smaller tumors (20.3 months for tumors <2.5 cm vs 13.4 months for tumors >5.0 cm, $P<.001$) (Table 2). Slight differences in MST were observed between patients who had positive vs negative lymph node involvement (12.4 vs 14.6 months, $P=.01$).

Patients who received any form of adjuvant therapy either preoperatively or postoperatively with chemotherapy or radiotherapy demonstrated a survival benefit compared with patients who received surgical extirpation alone (19.9 months for preoperative therapy and 17.0 months for postoperative chemoradiotherapy vs 12.6 months for surgery only, $P<.001$). Patients treated at HVCs demonstrated a longer MST than did those at LVCs (18.2 vs 13.1 months, $P<.001$). Similarly, patients receiving care at TFs had an improved MST over those treated at NTFs (19.8 vs 13.6 months, $P<.001$).

EFFECTS OF COMORBIDITIES

More than half of the study population had a diagnosis of hypertension (58.3%) and fluid and electrolyte disorder (57.5%) in addition to pancreatic cancer (data not shown). On multivariate analysis, valvular disease, hypertension, paralysis, neurologic disorders, chronic pulmonary disease, lymphoma, rheumatoid arthritis/collagen vascular disease, blood loss anemia, anemia, and drug abuse were associated with an improved prognosis in patients with pancreatic cancer. Conversely, the diagnoses of cardiac arrhythmia, peripheral vascular disease, renal failure, obesity, weight loss, and depression were associated with a decreased overall survival rate.

Table 2. Tumor and Treatment Characteristics of 2877 Patients With Pancreatic Cancer

	Patients, No. (%)	Survival, Median, mo	*P* Value
Tumor stage			
Local	207 (7.2)	21.4	<.001
Regional	792 (27.5)	12.5	
Distant	277 (9.6)	12.6	
Unknown	1601 (55.6)	NA	
Tumor grade			
Well differentiated	246 (8.6)	25.0	<.001
Moderately differentiated	954 (33.2)	15.8	
Poorly differentiated	758 (26.3)	11.3	
Undifferentiated	42 (1.5)	8.4	
Unknown	877 (30.5)	NA	
Tumor size, cm			
<2.5	463 (16.1)	20.3	<.001
2.5-5.0	1076 (37.4)	13.8	
>5.0	1251 (43.5)	13.4	
Unknown	87 (3.0)	NA	
Lymph nodes			
Positive	686 (23.8)	12.4	.01
Negative	407 (14.1)	14.6	
Treatment			
Surgery alone	1494 (51.9)	12.6	<.001
Postoperative chemoradiotherapy	758 (26.3)	17.0	
Preoperative/combined chemoradiotherapy	42 (1.5)	19.9	
Postoperative chemotherapy	299 (10.4)	14.2	
Postoperative radiotherapy	105 (3.6)	16.0	
Unknown	179 (6.2)	NA	
Volume status			
High	1221 (42.4)	18.2	<.001
Low	1656 (57.6)	13.1	
Facility			
Teaching	783 (27.2)	19.8	<.001
Nonteaching	2094 (72.8)	13.6	

Abbreviation: NA, not available.

FACILITY CHARACTERISTICS

Two hundred one medical facilities performed at least 1 pancreatic resection during the 5-year study period. According to the AAMC, 10 of these facilities were TFs. Only 783 of the pancreatic resections (27.2%) were performed at these TFs. Most resections were performed at 191 individual NTFs. A total of 1221 of the surgical procedures (42.4%) were performed at 19 HVCs. The remaining 57.6% of the procedures were performed at 182 individual LVCs (Table 2). Facilities with a designated teaching status were not mutually exclusive of volume status. Of the 10 TFs identified, only 7 met the inclusion criteria identifying it as an HVC. More than half of the procedures were performed at NTFs and LVCs.

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Table 3. Multivariate Regression Analysis[a]

	HR (95% CI)	*P* Value
Age, y		
<40	1 [Reference]	
40-65	1.54 (1.35-1.75)	<.001
>65	2.12 (2.00-2.25)	<.001
Community poverty level, %		
<5	1 [Reference]	
5-10	1.16 (0.95-1.40)	.14
>10-15	1.36 (1.14-1.63)	.001
>15	1.37 (1.28-1.46)	.001
Tumor stage		
Local	1 [Reference]	
Regional	1.30 (1.13-1.50)	<.001
Distant	1.57 (1.21-2.03)	.001
Tumor grade		
Well differentiated	1 [Reference]	
Moderately differentiated	1.61 (1.41-1.84)	<.001
Poorly differentiated	2.35 (2.18-2.54)	<.001
Undifferentiated	3.47 (3.37-3.58)	<.001
Tumor size, cm		
<2.5	1 [Reference]	
2.5-5.0	1.28 (1.26-1.30)	<.001
>5.0	1.39 (1.32-1.46)	<.001
Lymph nodes		
Negative	1 [Reference]	
Positive	1.21 (1.07-1.38)	.003
Treatment		
Surgery alone	1 [Reference]	
Postoperative chemoradiotherapy	0.69 (0.48-0.99)	.04
Preoperative/combined chemoradiotherapy	0.97 (0.38-2.51)	.95
Postoperative chemotherapy	0.92 (0.61-1.41)	.71
Postoperative radiotherapy	0.74 (0.53-1.03)	.08
Volume status		
Low	1 [Reference]	
High	0.85 (0.79-0.91)	<.001
Facility		
Nonteaching	1 [Reference]	
Teaching	0.84 (0.76-0.92)	<.001

Abbreviations: CI, confidence interval; HR, hazard ratio.
[a] Multivariate analysis was also inclusive of sex, race, ethnicity, tobacco use, alcohol consumption, and insurance status. These characteristics were not significant in multivariate regression analysis.

MULTIVARIATE ANALYSIS

The results of the multivariate regression analysis are given in **Table 3**. Increasing age was a prognostic indicator of worse outcomes compared with patients younger than 40 years (HR=2.12 for patients >65 years and HR=1.54 for patients aged 40-65 years, $P<.001$ for both). Similarly, patients living in a community poverty level greater than 10% of the federal poverty line also had worse prognoses compared with patients living in community poverty levels less than 5% (HR=1.37 for patients >15% of the poverty level and HR=1.36 for patients with poverty levels of >10%-15%, $P=.001$ for both). Regarding tumor characteristics, more invasive stage (HR=1.57, $P=.001$ for distant disease), grade (HR=3.47, $P<.001$ for undifferentiated tumors), size (HR=1.39, $P<.001$ for tumors >5.0 cm), and lymph node involvement (HR=1.21, $P=.003$) were associated with worse outcomes.

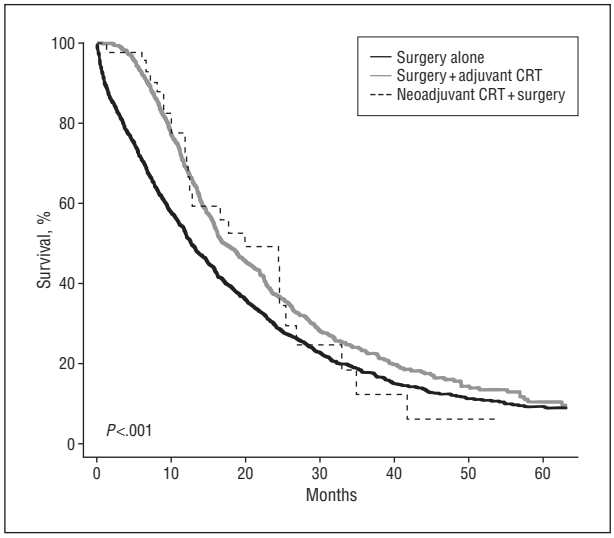

Figure 1. Kaplan-Meier survival curves illustrating outcomes according to treatment. CRT indicates chemoradiotherapy.

Regarding the treatment variables, patients who received postoperative chemoradiotherapy had a significant improvement in outcome compared with patients who underwent surgical extirpation alone (HR=0.69, $P=.04$). There was a trend toward significance for patients who underwent postoperative radiotherapy (HR=0.74, $P=.08$); however, no benefit was noted for either neoadjuvant therapy or postoperative chemotherapy. Patients treated at HVCs (HR=0.85) and TFs (HR=0.84) benefited from improved survival ($P<.001$ for both).

COMMENT

Pancreatic cancer is an aggressive and fatal disease. In contrast to other malignant neoplasms, there has been no significant improvement in 5-year overall survival rates in the past 20 years, and with overall 5-year survival of 5%, it is the deadliest solid tumor.[20] Nonetheless, outcomes for select patients who have successfully undergone surgical resection have seemed to improve, with series reporting 5-year survival rates approaching 20%.[21] Although surgical resection is considered the standard of care for localized pancreatic adenocarcinoma, there is no consensus on what should be the standard adjuvant therapy for pancreatic cancer after successful surgical resection.[22] For example, should it be chemotherapy alone or should chemotherapy be coadministered with radiotherapy (chemoradiotherapy)? In addition, compelling literature suggests a survival advantage for patients when specific complex surgical procedures, such as pancreatic resection, are performed at TFs and HVCs. These differences may be serving to confound studies related to chemotherapy, particularly when comparison groups represent published historical controls.[4-7]

Herein, we examined the effects of adjuvant treatment on outcomes in patients who received surgical resection for pancreatic adenocarcinoma using a large and relatively complete state cancer registry. Methodologically, this study represents a large retrospective,

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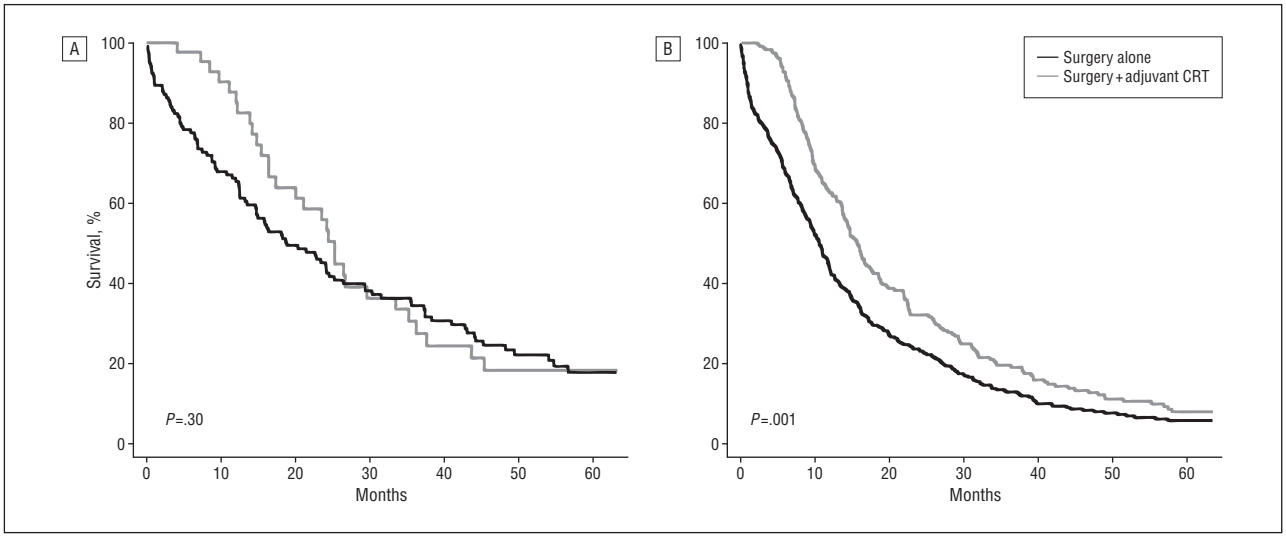

Figure 2. Kaplan-Meier survival curves illustrating differences in outcomes for regional (A) and local (B) disease when treated with surgery alone and surgery plus adjuvant chemoradiotherapy (CRT).

multi-institutional cohort that includes patients of all ages, comorbidities, race, ethnicity, and socioeconomic status, thus preventing potentially erroneous findings due to health differences or demographics. Furthermore, the multivariate analysis accounts for patients clustered at the facility level, thus controlling for the confounding issues of treating facility and volume.[23,24]

Therapy in the United States is frequently based on findings from initial studies by the Gastrointestinal Tumor Study Group, which demonstrated an improved survival rate for patients who received chemoradiotherapy after surgical resection[2]; these findings were further supported by Yeo et al[25] in a single-institution prospective series. Multi-institutional studies performed in Europe demonstrated less beneficial outcome differences for adjuvant chemoradiotherapy.[2,26,27] A meta-analysis[22] of adjuvant therapies has also suggested a benefit of adjuvant chemotherapy. To further complicate the role of adjuvant therapy, a significant survival advantage among patients receiving care at specialty centers has been demonstrated.[8-16] Thus, studies examining the benefits of adjuvant therapy based on historical controls or other series may have different outcomes owing to other confounders.

Although retrospective, this analysis represents an examination of an extremely large cohort, inclusive of demographics, tumor characteristics, treatment, and facility type. These data suggest that, after surgical extirpation for pancreatic adenocarcinoma, postoperative administration of chemoradiotherapy independently results in improved outcomes compared with surgical resection alone (**Figure 1**). Although not statistically significant, there was a trend toward improved survival in patients who received postoperative radiotherapy alone compared with surgical resection ($P = .07$). These results are consistent with those of a single-institution review[28] of clinical outcomes in 616 patients with resected pancreatic cancer that demonstrated a significant improvement in clinical outcome in patients who received adjuvant chemoradiotherapy. Furthermore, the receipt of

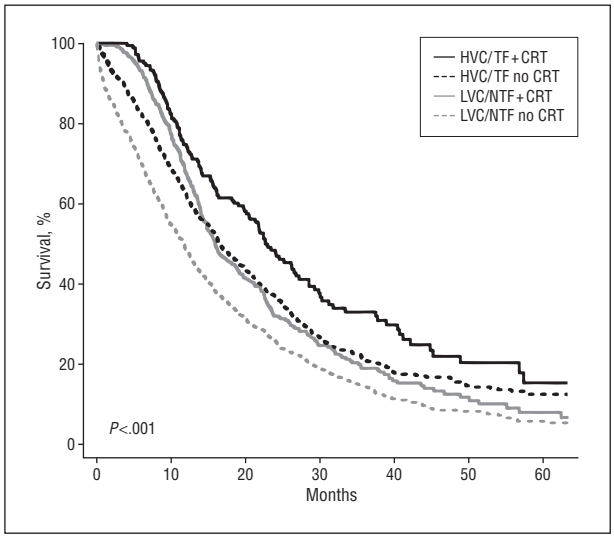

Figure 3. Kaplan-Meier survival curves illustrating the effects of treatment facility plus chemoradiotherapy (CRT). HVC indicates high-volume center; LVC, low-volume center; NTF, nonteaching facility; and TF, teaching facility.

adjuvant chemoradiotherapy demonstrates a marked improvement in survival in patients diagnosed as having regional disease (**Figure 2**A) compared with those with local disease (Figure 2B).

Several previous studies[4,29] of different cancers have demonstrated a correlation between facility volume and outcomes. Other studies[5-7] suggest survival benefits when treatment is provided at TFs. Herein, this analysis is consistent with the current literature in that treatment at either a TF or an HVC was an independent predictor of improved clinical outcomes. Patients with the greatest overall survival benefit were those who had undergone surgery at an HVC or a TF and who had received adjuvant chemoradiotherapy (MST = 20 months, $P = .01$ at HVCs and MST = 22 months, $P < .001$ at TFs). Patients with the worst overall survival were those who did not receive care at an HVC or a TF and further did not receive adjuvant

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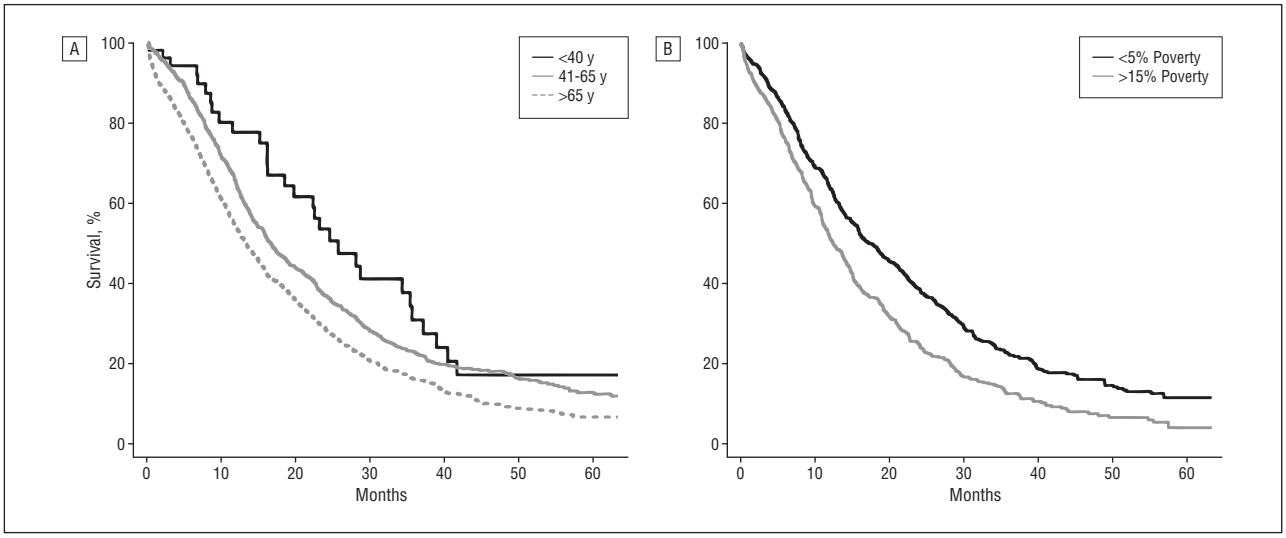

Figure 4. Kaplan-Meier survival curves for patients undergoing surgical resection for pancreatic adenocarcinoma according to age (A) and community poverty level (B).

chemoradiotherapy (MST = 16 months, $P = .01$ at LVCs and MST = 16 months, $P < .001$ at NTFs) (**Figure 3**). The effect of adjuvant chemoradiotherapy in patients who had surgery at LVCs or NTFs was observed to be initially more beneficial in the first 15 months postoperatively compared with patients who received surgery at HVCs or TFs without adjuvant chemoradiotherapy. Therefore, in this cohort, patients having treatment in a TF or an HVC and adjuvant chemoradiotherapy were the 2 most important treatment factors that significantly improved overall survival.

The multivariate analysis in this study confirms several findings previously noted in the literature. Increasing age (**Figure 4**A) and low socioeconomic status (Figure 4B) were independent adverse prognostic factors in patients who underwent surgical resection for pancreatic adenocarcinoma. Tumor size, histologic differentiation, and lymph node status have been extensively identified in the literature[2,30-38] as significant prognostic indicators of survival in pancreatic adenocarcinoma. As demonstrated and supported by the present analysis, increased tumor size, poorly differentiated tumors, and positive lymph node status were all independent poor prognostic factors. It has also been reported previously that low socioeconomic status is a determinant of poor outcomes,[34] and, in the present cohort, low socioeconomic status was also an adverse prognostic factor.

Moreover, the multivariate analyses demonstrated that a diagnosis of valvular disease, hypertension, paralysis, neurologic disorders, chronic pulmonary disease, lymphoma, rheumatoid arthritis/collagen vascular disease, blood loss anemia, anemia, or drug abuse improved survival in patients diagnosed as having pancreatic adenocarcinoma. Although this may speak to the intensity of treatment with patients who received the most intense therapy—the ones with anemia—the reason for these findings remains unclear.

Data from such a large population-based cancer registry provide insight into tumor behavior and allow examination of outcomes based on current treatment strategies.[39-42] A database of this size, however, is not without its limitations. The status of the surgical resection margins (negative vs positive) is not included in the database and, thus, was not included in the analysis. Furthermore, although data on radiotherapy and chemotherapy were examined, information on whether the patient received palliative vs curative-intent treatment, including the specific regimen and dosage, was also unavailable. Inherent to the data set is the possibility of selection bias. A selection bias may have occurred in that patients selected to receive adjuvant therapy after surgery were healthier than those who did not receive adjuvant therapy. Although the correction for comorbidities makes this less likely, we did not have performance status information to better correct for patient health status.

Pancreatic adenocarcinoma remains an aggressive and highly fatal disease, and only a small percentage of patients with localized disease are amenable to surgical resection. This analysis supports continued efforts directing the care of pancreatic adenocarcinoma toward specialty centers. In patients completing surgical resection for pancreatic adenocarcinoma, there are conflicting reports of the benefit of adjuvant chemoradiotherapy in the literature. However, this analysis provides strong evidence in a real-world setting that postoperative chemoradiotherapy and possibly adjuvant radiotherapy alone improve clinical outcome in patients with pancreatic cancer. We further substantiate that this benefit is independent of the improved clinical outcomes obtained at HVCs and TFs. Nonetheless, this benefit remains modest, underscoring that further investigation is needed to establish a better adjuvant regimen after complete resection of pancreatic cancer. Research is needed to examine the quality of life experienced by patients who undergo surgical resection with and without postoperative chemoradiotherapy. In addition, future multi-institutional randomized prospective trials should examine whether incorporation of new

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biologic agents into standard adjuvant therapy for pancreatic cancer can begin to significantly move 5-year overall survival rates in a positive direction during the next decade.

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INVITED CRITIQUE

Is the Debate Finally Over?

In this study, Yang et al use data from a large population-based registry to show a significant survival advantage with adjuvant chemoradiotherapy after pancreatic cancer resection. Moreover, they explore the effects of variables such as HVCs and teaching status that have been previously shown to affect outcomes in pancreatic cancer survival. The authors nicely confirm that patients treated at HVCs and TFs indeed have improved survival but also show that all patients benefit from adjuvant chemoradiotherapy after resection. However, like most studies generated using these large databases, there are several weaknesses to this study. There is missing information on cancer stage in more than 50% of the patients, the margin status is not known (R0 or R1), and there is no information on the type or duration of chemoradiotherapy, all of which limit the potential utility of such studies. Nevertheless, such studies can be hypothesis generating and can also point to large societal trends. The present study shows that pancreatic cancer surgery still happens at LVCs despite the large volume of data showing better outcomes at HVCs. Importantly, the majority of patients receive no adjuvant therapy, likely reflecting the morbidity of the operation and that most patients do not recover their performance status to receive adjuvant therapy. In this context, the finding on univariate analysis by the authors of a potential survival benefit of neoadjuvant therapy is intriguing and warrants further investigation.

At the end of the day, however, the present study will do little to quell the debate over the relative benefits of adjuvant chemoradiotherapy compared with chemotherapy alone after surgical resection of pancreatic cancer. In North America, the bias has been that adjuvant chemoradiotherapy improves survival in patients with pancreatic cancer after surgical resection, and this study lends further credence to this notion. This has been based primarily on data from the small randomized study by the Gastrointestinal Tumor Study Group[1] and retrospective studies[2,3] showing a survival benefit of chemoradiotherapy compared with no further treatment after curative resection. In contrast, our colleagues across the Atlantic continue to favor adjuvant chemotherapy alone after pancreatic cancer resection based on the recent favorable data on the use of gemcitabine-based adjuvant chemotherapy alone in the CONKO-001[4] trial and the negative data on the use of adjuvant chemoradiotherapy in the European Study Group for Pancreatic Cancer 1[5] and European Organisation for Research and Treatment of Cancer[6] trials. The present study will do little to change the minds of either camp.

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