Underuse of surgical resection among elderly patients with early-stage pancreatic cancer

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Background. *Although surgery improves the health care quality and outcomes of patients with early-stage pancreatic cancer, these patients' operative resection rate has been historically low. We sought to identify factors that are associated with operative resection in this patient population.*

Methods. *In this retrospective population-based study, we used Texas Cancer Registry–linked and Surveillance and Epidemiology End Results Program–linked Medicare data to study factors potentially associated with operative resection in patients age ≥66 years who had been diagnosed with localized pancreatic cancer between January 1, 2001, and December 31, 2009. Variables were assessed using multivariate logistic regression and Cox proportional hazards regression models. We used Kaplan–Meier analysis to assess the effect of operative resection on survival rate.*

Results. *Of 1,501 patients with localized pancreatic cancer, only 340 (22.7%) underwent operation. Patients were more likely to undergo surgery if they were young, had small tumors, had low-grade tumors, and had nodal negativity (*$P < .05$*). Compared with patients who did not undergo surgery, patients who underwent surgery had a significantly higher 5-year overall survival rate (25.0 vs 2.3%;* $P < .0001$*) and had a higher median survival time (24.3 vs 5.8 months).*

Conclusion. *The rate of operative resection of early-stage pancreatic cancer did not increase significantly from 2001 to 2009. Although we identified several variables associated with operative resection, why the percentage of patients with localized pancreatic cancer who undergo definitive surgery is so low remains unclear. (Surgery 2015;■:■-■.)*

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Among the gastrointestinal cancers, pancreatic cancer has the most dismal prognosis owing to factors that include diagnosis at later stages, aggressive cancer biology, and lack of effective treatments.[1,2] According to the Surveillance, Epidemiology, and End Results (SEER) Program, the overall 5-year survival rate of pancreatic cancer patients is only 7%, the lowest among all cancer patients.[3] Unlike in other cancer types, chemotherapy and radiation are only modestly effective against pancreatic cancer, causing significant toxicity but only marginal improvements in survival. Although oncologists can offer a variety of treatments depending on disease stage, the only potentially curative treatment for patients with pancreatic cancer is operative resection.

Operative resection has been established by numerous studies and guidelines as a primary treatment option for localized pancreatic cancer. According to the 2000 National Comprehensive Cancer Network (NCCN)[4] guidelines, a patient with a localized pancreatic tumor and no distant metastases should be a candidate for operative resection. In its clinical practice guidelines, the European Society for Medical Oncology also indicates that radical pancreatic resection is the standard treatment option for patients with early-stage pancreatic cancer.[5] Despite these recommendations, numerous studies have reported substantial underuse of operative resection in pancreatic cancer patients.

According to SEER data, 67% of pancreatic cancers occur in patients age ≥65 years; the median age at diagnosis is 71 years.[6] However, few studies have evaluated the quality of care among patients in this age group who have

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early-stage pancreatic cancer. In the present study, we used cancer registry–linked Medicare claims data to assess the utilization of operative resection for early-stage pancreatic cancer among older patients. We also identified the patient and tumor characteristics associated with operative resection, and we assessed the effect of operative resection on these patients' survival.

MATERIALS AND METHODS

Data. We used Texas Cancer Registry (TCR)-linked and SEER registry–linked Medicare databases in this retrospective population-based study. The TCR is a statewide, population-based registry of patient and tumor data. The National Cancer Institute's SEER Program consists of 18 nationwide population-based registries of cancer cases among 28% of the US population.

The Institutional Review Board of The University of Texas MD Anderson Cancer Center approved this study by granting an exemption in the absence of informed consent. The study population was limited to patients age ≥66 years who had been diagnosed with pathologically confirmed localized pancreatic cancer between 2001 and 2009 (between 2001 and 2007 in the TCR-linked Medicare database). We used International Classification of Diseases (ICD)-Oncology-3 codes to limit our analysis to patients with pancreatic adenocarcinoma. Because the TCR does not include information about cancer staging (as per the American Joint Committee on Cancer) for all patients, we limited our analysis to patients who had localized disease. Patients who had been diagnosed at autopsy or by death certificate only were excluded. Patients were restricted to those who had continuous coverage under Medicare Parts A and B and who had not been covered by a health maintenance organization from 12 months before diagnosis and 12 months after diagnosis or until death.

Patient and tumor characteristics and treatment identification. We collected sociodemographic and tumor data from the SEER registries and TCR. Modified Charlson comorbidity scores were constructed with Klabunde's algorithm[7] using claims in the 12 months before the diagnosis of pancreatic cancer.[8,9] To identify the receipt of operative resection, chemotherapy, and radiotherapy in the Medicare claims data, we used a combination of ICD-9 diagnosis codes, Common Procedural Terminology codes, Healthcare Common Procedure Coding System codes, and revenue center codes (Supplemental Table). Because only the month and year of diagnosis are recorded in the SEER registries and TCR, we assigned the 15th of the month as the day of diagnosis for all patients.

Data analysis. Descriptive statistics (mean values and standard deviations of continuous variables and frequencies of discrete variables) of patients' sociodemographic and clinical characteristics were calculated. The Chi-square test (for discrete variables) or F test (for group means) were used to assess differences between patients' characteristics and treatments. Patients with claims for operative resection were assigned to the operative resection group, and patients with no claims for operative resection were assigned to the nonresection group. Using a binomial distribution, we computed the operative resection rate of the study population.

Multivariate logistic regression was used to identify patient characteristics associated with operative resection. Kaplan–Meier analysis was used to compare the overall survival rates of the operative resection group with that of the nonresection group. We evaluated the effect of surgery on survival by computing the hazard ratio (HR) for the operative resection group using the nonresection group as a reference. All analyses were conducted with the SAS statistical software program (version 9.3, SAS Institute, Cary, NC).

RESULTS

We identified 1,501 patients with localized pancreatic cancer, of whom 340 (23%) underwent operative resection (Table I). The resection rate increased from 23% in 2001 to 30% in 2009 (P = .4048) but the year-to-year changes in the rate were inconsistently positive or negative within this interval (Fig 1). Of the 1,161 patients who did not undergo operative resection, 576 (50%) received nonoperative treatment with chemotherapy and/or radiotherapy, and 585 (50%) received no anticancer treatment.

Univariate logistic regression analysis suggested that age at diagnosis, sex, comorbidity index, median income, education level, poverty level, tumor size, nodal status, and tumor grade were significantly associated with receipt of operative resection (Table II). Multivariate logistic regression model indicated that patient age, year of diagnosis, tumor size, tumor grade, and nodal status were correlated with operative resection. Patients age ≥81 years old were much less likely to undergo operative resection than patients age 66–70 years old (odds ratio, 0.27; 95% CI, 0.14–0.52). Patients who had tumors <25 mm and pathologically node-negative disease also were more likely to undergo resection. The univariate analysis indicated that

Table I. Sociodemographic and clinical characteristics of patients age ≥66 years with localized pancreatic cancer, by receipt of operative resection

Characteristic	*All patients* (n = *1,501*)	*Operative resection*		P *value*
		No (n = *1,161*)	*Yes* (n = *340*)	
Age at diagnosis (y)				<.0001*
66–70	259 (17.3)	164 (14.1)	95 (27.9)	
71–75	350 (23.3)	234 (20.2)	116 (34.1)	
76–80	398 (26.5)	311 (26.8)	87 (25.6)	
≥81	494 (32.9)	452 (38.9)	42 (12.4)	
Mean age at diagnosis, y (SD)	77.4 ± 6.7	78.4 ± 6.7	74.1 ± 5.2	<.0001†
Year of diagnosis				.3797*
2001	137 (9.1)	106 (9.1)	31 (9.1)	
2002	164 (10.9)	122 (10.5)	42 (12.4)	
2003	204 (13.6)	160 (13.8)	44 (12.9)	
2004	179 (11.9)	144 (12.4)	35 (10.3)	
2005	194 (12.9)	158 (13.6)	36 (10.6)	
2006	165 (11.0)	127 (10.9)	38 (11.2)	
2007	178 (11.9)	133 (11.5)	45 (13.2)	
2008	156 (10.4)	124 (10.7)	32 (9.4)	
2009	124 (8.3)	87 (7.5)	37 (10.9)	
Sex				.0272*
Male	624 (41.6)	465 (40.1)	159 (46.8)	
Female	877 (58.4)	696 (59.9)	181 (53.2)	
Race				.3170*
White (non-Hispanic)	1,192 (79.4)	915 (78.8)	277 (81.5)	
African American (non-Hispanic)	152 (10.1)	122 (10.5)	30 (8.8)	
Hispanic	108 (7.2)	89 (7.7)	19 (5.6)	
Other/unknown	49 (3.3)	35 (3.0)	14 (4.1)	
SEER-TCR registries				.2035*
Connecticut	79 (5.3)	56 (4.8)	23 (6.8)	
Detroit	76 (5.1)	54 (4.7)	22 (6.5)	
California/Hawaii	337 (22.5)	261 (22.5)	76 (22.4)	
Iowa	69 (4.6)	57 (4.9)	12 (3.5)	
New Mexico	44 (2.9)	‡	‡	
Seattle	37 (2.5)	‡	‡	
Utah	27 (1.8)	‡	‡	
Kentucky	109 (7.3)	89 (7.7)	20 (5.9)	
Louisiana	101 (6.7)	73 (6.3)	28 (8.2)	
New Jersey	171 (11.4)	124 (10.7)	47 (13.8)	
Texas	291 (19.4)	229 (19.7)	62 (18.2)	
Georgia	160 (10.7)	130 (11.2)	30 (8.8)	
Area of residence				.6263*
Large metropolitan	779 (51.9)	599 (51.6)	180 (52.9)	
Metropolitan	455 (30.3)	352 (30.3)	103 (30.3)	
Urban	81 (5.4)	59 (5.1)	22 (6.5)	
Less urban	150 (10.0)	‡	‡	
Rural	36 (2.4)	‡	‡	
Charlson comorbidity score				.0019*
0	690 (46.0)	516 (44.4)	174 (51.2)	
1	427 (28.4)	323 (27.8)	104 (30.6)	
≥2	384 (25.6)	322 (27.7)	62 (18.2)	
Census 2000 tract data, mean ± SD				
Percent living below poverty line	12.4 ± 10.4	12.7 ± 10.6	11.2 ± 9.7	.0151†
Median income in USD	48,032.7 ± 24,206.5	46,904.0 ± 23,498.9	51,947.8 ± 26,177.5	.0008†
Percent non–high school graduates	20.6 ± 14.0	21.2 ± 14.2	18.4 ± 13.2	.0010†

(*continued*)

Table I. (*continued*)

Characteristic	All patients (n = 1,501)	Operative resection		P value
		No (n = 1,161)	Yes (n = 340)	
Tumor size, mm				<.0001*
≤25	425 (28.3)	266 (22.9)	159 (46.8)	
26–50	561 (37.4)	451 (38.8)	110 (32.4)	
51–75	100 (6.7)	‡	‡	
≥76	27 (1.8)	‡	‡	
Unknown	388 (25.8)	345 (29.7)	43 (12.6)	
Mean tumor size, mm (SD)	33.5 ± 17.2	34.8 ± 16.2	30.0 ± 19.3	<.0001†
Location of primary tumor				.0656*
Head	996 (66.4)	778 (67.0)	218 (64.1)	
Body/tail	220 (14.7)	157 (13.5)	63 (18.5)	
Other	285 (19.0)	226 (19.5)	59 (17.4)	
Tumor grade				<.0001*
I	123 (8.2)	73 (6.3)	50 (14.7)	
II	313 (20.9)	181 (15.6)	132 (38.8)	
III/IV	282 (18.8)	195 (16.8)	87 (25.6)	
Unknown	783 (52.2)	712 (61.3)	71 (20.9)	
Nodal status				<.0001*
Pathologic N0	337 (22.5)	60 (5.2)	277 (81.5)	
Clinical N0	978 (65.2)	928 (79.9)	50 (14.7)	
Pathologic N+	‡	‡	‡	
Unknown	‡	‡	‡	
Radiotherapy				.0002*
None	995 (66.3)	798 (68.7)	197 (57.9)	
Any	506 (33.7)	363 (31.3)	143 (42.1)	
Chemotherapy				<.0001*
None	788 (52.5)	648 (55.8)	140 (41.2)	
Any	713 (47.5)	513 (44.2)	200 (58.8)	

*Chi-square test for comparing differences between two treatment groups.
†*F* test for comparing means between two treatment groups.
‡Values are censored to maintain patient confidentiality ($n \leq 11$).
All data are no. of patients (%) unless otherwise specified.
SD, Standard deviation; *SEER*, Surveillance, Epidemiology, and End Results; *TCR*, Texas Cancer Registry.

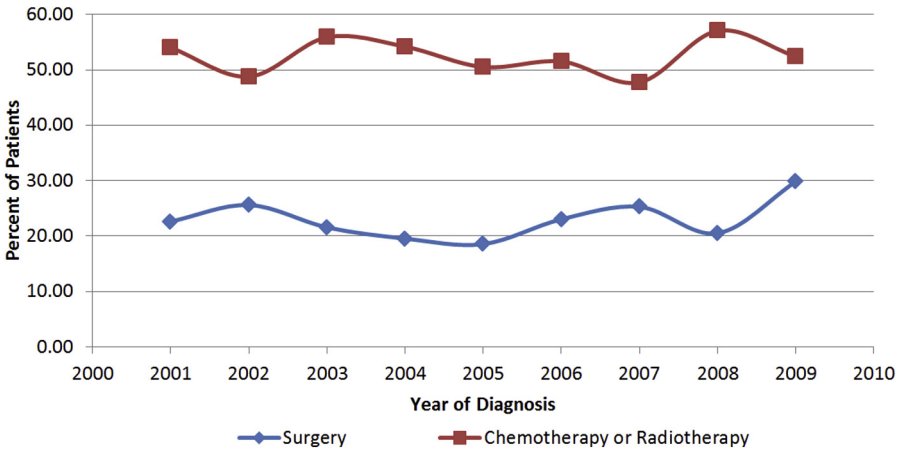

Fig 1. Treatment trends for patients with pancreatic adenocarcinoma, 2001–2009.

gender, comorbidity, census tract median income, and census tract education level influenced whether patients underwent operative resection; however, multivariate analysis indicated that none of these factors were associated with operative resection.

Table II. Factors associated with receipt of operative resection

	Univariate model		*Multivariate Model*	
Variable	*OR (95% CI)*	P *value**	*OR (95% CI)*	P *value**
Age at diagnosis, y		<.0001		<.0001
66–70	1.00 (Referent)		1.00 (Referent)	
71–75	0.86 (0.61–1.20)		0.95 (0.53–1.70)	
76–80	0.48 (0.34–0.68)		0.78 (0.43–1.41)	
≥81	0.16 (0.11–0.24)		0.27 (0.14–0.52)	
Year of diagnosis		.3863		.0071
2001	1.00 (Referent)		1.00 (Referent)	
2002	1.18 (0.69–2.00)		1.37 (0.55–3.47)	
2003	0.94 (0.56–1.58)		0.93 (0.39–2.23)	
2004	0.83 (0.48–1.43)		0.72 (0.29–1.84)	
2005	0.78 (0.45–1.34)		0.59 (0.24–1.46)	
2006	1.02 (0.60–1.76)		1.85 (0.75–4.57)	
2007	1.16 (0.69–1.95)		1.42 (0.57–3.50)	
2008	0.88 (0.51–1.54)		1.13 (0.43–2.95)	
2009	1.46 (0.84–2.53)		3.61 (1.40–9.28)	
Sex		.0274		.2563
Male	1.00 (Referent)		1.00 (Referent)	
Female	0.76 (0.60–0.97)		0.79 (0.52–1.19)	
Race		.3207		.6020
White (non-Hispanic)	1.00 (Referent)		1.00 (Referent)	
African American (non-Hispanic)	0.81 (0.53–1.24)		0.67 (0.32–1.39)	
Hispanic	0.71 (0.42–1.18)		1.14 (0.49–2.69)	
Other/unknown	1.32 (0.70–2.49)		1.37 (0.53–3.54)	
Charlson comorbidity score		.0021		.1518
0	1.00 (Referent)		1.00 (Referent)	
1	0.96 (0.72–1.26)		1.04 (0.65–1.68)	
≥2	0.57 (0.41–0.79)		0.63 (0.37–1.06)	
Census tract median income†		.0257		.4147
1st Quartile	1.00 (Referent)		1.00 (Referent)	
2nd Quartile	1.13 (0.79–1.62)		0.72 (0.36–1.40)	
3rd Quartile	1.24 (0.87–1.77)		1.01 (0.48–2.16)	
4th Quartile	1.65 (1.17–2.33)		1.30 (0.55–3.07)	
Census tract percentage of non–high school graduates†		.0206		.4679
1st Quartile	1.00 (Referent)		1.00 (Referent)	
2nd Quartile	0.78 (0.56–1.09)		1.30 (0.69–2.44)	
3rd Quartile	0.71 (0.51–1.00)		1.09 (0.53–2.26)	
4th Quartile	0.58 (0.41–0.82)		0.73 (0.30–1.75)	
Tumor size, mm		<.0001		.0048
≤25	1.00 (Referent)		1.00 (Referent)	
26–50	0.41 (0.31–0.54)		0.44 (0.27–0.72)	
51–75	0.37 (0.21–0.63)		0.40 (0.17–0.96)	
≥76	0.98 (0.44–2.20)		1.00 (0.29–3.48)	
Unknown	0.21 (0.14–0.30)		0.43 (0.24–0.78)	
Nodal status		<.0001		<.0001
Pathologic N0	1.00 (Referent)		1.00 (Referent)	
Clinical N0	0.01 (0.01–0.02)		0.02 (0.01–0.03)	
Pathologic N+	‡		‡	
Unknown	0.01 (0.01–0.03)		0.02 (0.01–0.04)	

(*continued*)

Table II. (*continued*)

Variable	Univariate model		Multivariate Model	
	OR (95% CI)	P *value**	*OR (95% CI)*	P *value**
Tumor grade		<.0001		<.0001
I	1.00 (Referent)		1.00 (Referent)	
II	1.07 (0.70–1.63)		1.21 (0.59–2.49)	
III/IV	0.65 (0.42–1.01)		1.13 (0.53–2.38)	
Unknown	0.15 (0.09–0.23)		0.33 (0.16–0.68)	

*Pearson Chi-square test.
†Based on 2000 census data.
‡Not enough cases to estimate the OR.
OR, Odds ratio.

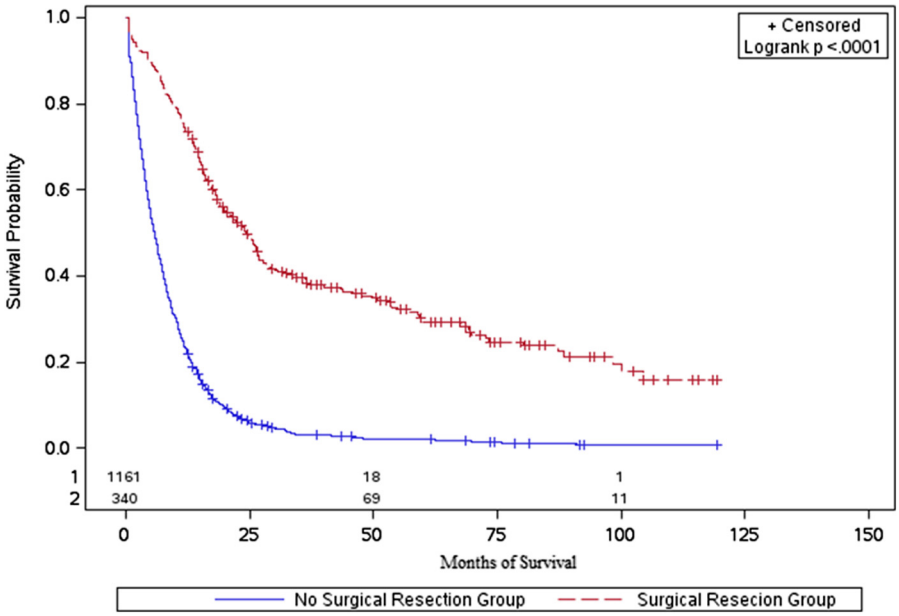

Fig 2. Estimated product limit survival rates of pancreatic adenocarcinoma patients who underwent operative resection and those who did not undergo operative resection. The numbers of patients in both groups at risk of death at 0, 50, and 100 months is shown.

We compared the overall survival of the patients who underwent operative resection with that of patients who did not (Fig 2; Table III). The median survival time of the patients who underwent operative resection (24.3 months) was substantially greater than that of patients who did not undergo operative resection (5.8 months). The 5-year overall survival rate of patients who underwent operation (25%; 95% CI, 18.8–31.1%) was significantly greater than that of patients who did not (2%; 95% CI, 1.2–3.4%).

After we controlled for patient sociodemographic factors and tumor characteristics, both the univariate and multivariate analyses revealed that the operative resection group had a 3-fold higher likelihood of survival (univariate analysis HR, 3.84 [95% CI, 3.31–4.46]; multivariate analysis HR, 2.98 [95% CI, 2.39–3.71]) compared with the nonresection group. In the multivariable model, other factors associated with survival were age at diagnosis, sex, SEER registries, Charlson comorbidity score, household income, tumor size, nodal status, tumor grade, chemotherapy, and radiotherapy.

DISCUSSION

Operative resection is widely considered the only curative treatment for patients with early-stage pancreatic cancer and therefore has been recommended by the NCCN and European Society for Medical Oncology as a primary treatment option for these patients.[4,5] Nevertheless, multiple studies have shown that the surgery is grossly underused. Bilimoria et al,[10] using the National

Table III. Survival analysis comparing patients who underwent operative resection with those who did not undergo operative resection

Variable	*Operative resection group*	*Nonresection group*
Unadjusted HR (95% CI)	1.00 (Referent)	3.84 (3.31–4.46)*
Adjusted HR (95% CI)†	1.00 (Referent)	2.98 (2.39–3.71)*
Median survival duration (mo)	24.3	5.8
1-Year survival rate, % (95% CI)	73.8 (69.1–78.5)	23.3 (20.9–25.8)
5-Year survival rate, % (95% CI)	25.0 (18.8–31.1)	2.3 (1.2–3.4)

*Significantly different from the referent values.
†Adjusted for age, gender, Surveillance, Epidemiology, and End Results registries, census tract median income, comorbidity, tumor size, tumor grade, nodal status, receipt of chemotherapy, and receipt of radiotherapy.
HR, Hazard ratio.

Cancer Data Base, demonstrated the underuse of pancreatectomy among patients with early-stage disease between 1995 and 2004: Of the 9,559 patients with potentially operable tumors the authors identified, only 2,736 (29%) underwent operation. Of the nearly 7,000 patients who did not undergo operation, more than one-half did not have any identifiable constraints, such as advanced age or severe comorbidities, that would have precluded surgery. Other studies using SEER data have also reported the underuse of operative resection for localized pancreatic cancer, noting resection rates of only 21.0–26.2% from 1988 through 2002.[11-13] Lucas et al,[14] who also used the National Cancer Data Base to study patients with stage I pancreatic cancer, found a similar underuse of surgery, reporting an overall resection rate of 22% from 1985 through 1995.

In this study, we evaluated the use of curative operative intervention and characterized its underuse among Medicare beneficiaries with localized pancreatic cancer in a more recent time frame using TCR– and SEER registry–linked Medicare data. As in the studies discussed, the operative resection rate in our study population was low, ranging from 23% to 30% between 2001 and 2009. In fact, the overall operative resection rate in the present study was only 23%, which is even lower than the 29% reported by Bilimoria et al.[10] However, this difference may have been owing in part to our older study population; the mean patient age in our study (77.4 years) was higher than that in the study by Bilimoria et al (72.4 years).[10]

We identified several characteristics associated with not undergoing operative resection, including age, tumor size, tumor grade, and nodal status. Although some studies have described racial disparities in the care of pancreatic cancer patients,[15,16] we did not find race to be associated with a decreased use of recommended surgery. Elderly patients with localized pancreatic cancer do benefit from surgery,[17,18] and age alone is not a selection criterion for surgical treatment. In our analysis, patients aged 66–70 years were more likely to have undergone operative resection than were patients age ≥81 years. Given the significant morbidity of and low overall cure rates associated with operative resection, some older patients may decide to forgo pancreatectomy. Although the univariate analysis showed that patients were more likely to undergo surgery if their Charlson comorbidity index score was 0 or 1, the multivariate analysis did not identify comorbidity as being associated with receipt of operative resection. We also found that patients were less likely to undergo surgery if they had a tumor >25 mm, unknown nodal status, or unknown tumor grade.

In our study, year of diagnosis was associated with operative resection. Patients diagnosed in 2009 were more likely than patients diagnosed in 2001 to undergo operative intervention. However, we found no trend for patients' operative resection rates increasing over the study period. Since 2001, the NCCN's guidelines have evolved to account for the introduction of neoadjuvant therapy to improve surgical resectability and/or outcomes. In our study, however, the rates of chemotherapy and radiotherapy did not increase over the same period (Fig 1).

Operative intervention is the primary treatment option for early-stage pancreatic cancer. It offers a better survival rate than does chemotherapy or radiotherapy alone.[2,19] For pancreatic cancer patients who undergo operative resection for localized, nonmetastatic disease, the 5-year survival rate is 15–30%,[11,20–23] and the median survival time is 12–22 months.[11,22,24] In our study, the median survival time of patients who underwent operative resection was 24.3 months, which is slightly greater than those previously reported, and the 5-year survival rate was 25%, which is in line with previous studies' findings.

Our study has several limitations. This retrospective population-based study was restricted to patients aged ≥66 years and thus may not reflect the experience of all pancreatic cancer patients in the United States. Medicare data provide excellent information on treatment, including all aspects of clinical practice, such as inpatient hospitalization, outpatient clinical visits, physician office visits, medical equipment usage, hospice stay, and so on, but the use of claims data to identify treatment and comorbidity status could introduce some misclassification in these areas. Moreover, because they do not capture patients covered by private insurance, Medicare claims data may lead to the underestimation of operative resection rates. In addition, information on some potentially important confounding factors, such as smoking status, body mass index, and performance status, were not available in the registries we used. Finally, information about whether patients were appropriate candidates for surgery, whether they were offered surgery, and whether they were willing to undergo surgery was lacking.

In conclusion, our analysis offers additional evidence that operative resection is underutilized in patients with localized pancreatic cancer. Despite the demonstrated survival benefit that resection offers, >70% of patients with resectable cancer in our study population failed to receive this curative treatment. Patients who underwent operative resection clearly had better survival than those who did not. The only opportunity for cure that patients with early-stage pancreatic cancer have is surgery, but multiple factors may contribute to the striking underuse of curative resection. Even so, to improve the quality of the care of pancreatic cancer patients in the United States, all patients with resectable disease should be offered surgery as appropriate. The findings of the present study are useful for patients, physicians, and other health care providers who make treatment decisions. In addition, hospitals should develop appropriate health care policies and interventions to improve pancreatic cancer patients' outcomes after surgery.

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SUPPLEMENTAL DATA

Supplementary data related to this article can be found online at http://dx.doi.org/10.1016/j.surg.2015.04.031.

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