A Population-Based Study of Morbidity After Pancreatic Cancer Diagnosis

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ABSTRACT

Background: Pancreatic cancer is an aggressive disease characterized by early and relentless tumor spread, thus leading healthcare providers to consider it a "distant disease." However, local pancreatic tumor progression can lead to substantial morbidity. This study defines the long-term morbidity from local and nonlocal disease progression in a large population-based cohort. **Methods:** A total of 21,500 Medicare beneficiaries diagnosed with pancreatic cancer in 2000 through 2011 were identified. Hospitalizations were attributed to complications of either local disease (eg, biliary disorder, upper gastrointestinal ulcer/bleed, pain, pancreas-related, radiation toxicity) or nonlocal/distant disease (eg, thromboembolic events, cytopenia, dehydration, nausea/vomiting/motility problem, malnutrition and cachexia, ascites, pathologic fracture, and chemotherapy-related toxicity). Competing risk analyses were used to identify predictors of hospitalization. **Results:** Of the total cohort, 9,347 patients (43.5%) were hospitalized for a local complication and 13,101 patients (60.9%) for a nonlocal complication. After adjusting for the competing risk of death, the 12-month cumulative incidence of hospitalization from local complications was highest in patients with unresectable disease (53.1%), followed by resectable (39.5%) and metastatic disease (33.7%) at diagnosis. For nonlocal complications, the 12-month cumulative incidence was highest in patients with metastatic disease (57.0%), followed by unresectable (56.8%) and resectable disease (42.8%) at diagnosis. Multivariable analysis demonstrated several predictors of hospitalization for local and nonlocal complications, including age, race/ethnicity, location of residence, disease stage, tumor size, and diagnosis year. Radiation and chemotherapy had minimal impact on the risk of hospitalization. **Conclusions:** Despite the widely known predilection of nonlocal/distant disease spread in pancreatic cancer, local tumor progression also leads to substantial morbidity and frequent hospitalization.

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Background

Pancreatic cancer represents the fourth leading cause of cancer-related death, and the 5-year survival for all stages together ranges from 5% to 10%. Although "distant disease" spread represents the hallmark of pancreatic cancer, local tumor progression can lead to substantial patient morbidity. Recent data suggest that nearly 1 in 3 patients with pancreatic cancer will die of local disease progression.[1] In addition, cancer progression within the pancreas can cause intractable pain, gastrointestinal ulceration and bleeding, biliary obstruction, or pancreatitis.

Existing research documenting patterns of disease spread typically uses radiographic progression to define local or nonlocal/distant tumor progression.[2] However, radiographic progression—often defined as tumor diameter increasing by 30%—may not correlate with meaningful clinical outcomes, such as patient quality of life. Understanding the clinically meaningful patterns of disease spread will help inform providers and patients about patient-oriented consequences associated with pancreatic cancer. The purpose of this study was to characterize disease progression by evaluating patterns of hospitalization in a large cohort of patients with pancreatic cancer.

Methods

Data

A population-based retrospective cohort study was conducted using the SEER-Medicare linked database. The SEER database contains demographic and clinical data pooled from individual population-based cancer registries covering approximately 30% of the US population. Medicare provides federally funded health insurance, including inpatient and outpatient services, for individuals aged ≥65 years in the United States. The SEER-Medicare linkage includes Medicare claims data for patients within SEER, and claims extend from prior to diagnosis through death, which allows for assessment of patterns of care and hospitalizations over the entire course of a patient's disease.

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Study Population

A total of 32,475 patients aged ≥66 years diagnosed with histologically confirmed malignant adenocarcinoma of the pancreas in 2000 through 2011 were identified (supplemental eTable 1, available with this article at JNCCN.org). Our analysis was restricted to those aged ≥66 years at diagnosis to allow a full year of claims data from which to calculate a comorbidity score. We excluded 338 patients with prior malignancies or with pancreatic cancer diagnosed at autopsy or on the death certificate alone. Another 10,637 patients with incomplete data were excluded, including those without continuous Medicare coverage (Parts A and B) or with any Part C coverage (HMO enrollment) from 12 months prior to diagnosis through time of death or last follow-up. The final study cohort comprised 21,500 patients.

Study Variables

Demographic and tumor-related information, such as patient age and cancer stage at diagnosis, year of diagnosis, sex, race, marital status, histologic grade, tumor location, and tumor size were extracted from SEER. Patients were grouped into geographic region based on location of their SEER registry: West (San Francisco, San Jose, Los Angeles, and Greater California; Seattle, Washington; New Mexico; Utah; Hawaii), Midwest (Detroit, Michigan; Iowa), South (Atlanta, rural, and greater Georgia; Kentucky; Louisiana), and East (New Jersey; Connecticut). Socioeconomic status was assessed with median regional household income as measured from 2000 census tract data. Inpatient and outpatient Medicare claims from the year before diagnosis were used to assess preexisting comorbidity using the Deyo adaptation of the Charlson comorbidity index.[3] Care at a teaching hospital was defined as any indirect medical education payment noted during a hospitalization after the patient's cancer diagnosis.[4]

Treatment variables, including chemotherapy, surgery, and radiotherapy (RT), were identified from Medicare claims data. Administration of chemotherapy was determined through Medicare billing claims, including ICD-9 diagnosis and procedure codes and Healthcare Common Procedure Coding System (HCPCS) codes, using previously described methods (supplemental eTable 1).[5] RT was identified from claims related to its planning and delivery,[6] and a course of RT was defined as a cluster of radiation-related Medicare claims. Radiation is delivered in daily fractions, and for this study we assumed that each daily claim of a radiation treatment represented a single fraction. We further assumed that any break in RT of >30 days represented a separate course of treatment. In patients who received multiple courses of RT, we included only the first course in the analysis. Pancreatic surgery included partial, distal, or total pancreatectomy and a pancreaticoduodenectomy (Whipple procedure) (supplemental eTable 1).

Patient Groups

Compared with categorizing patients by classic AJCC staging, we categorized them into functional groups based on stage and operability: resectable, unresectable, or metastatic. This approach is consistent with both NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Pancreatic Adenocarcinoma[7] and other studies.[8] Patients who presented with stage IV disease at diagnosis composed the metastatic group; those with stage I–III disease at presentation who underwent cancer-directed surgery were included in the resectable group; and the remaining patients with stage I–III disease at presentation were placed into the unresectable group. The unresectable group likely included a mix of patients with technically unresectable disease and those with potentially resectable disease who did not undergo surgery due to medical comorbidity or patient choice. SEER does not include data to assess resectability and lacks information about patient preferences, so we were unable to further categorize this unresectable group.

Study End Points

The primary end point was hospitalization after pancreatic cancer diagnosis. All hospitalizations were identified from the inpatient Medicare Provider Analysis and Review (MedPAR) file and further categorized by the ICD-9 diagnosis codes during that hospitalization. We first categorized hospitalizations as either cancer-related or non–cancer-related. Among the cancer-related hospitalizations, these were further classified as due to either local disease progression or nonlocal/distant disease. Hospitalizations for local disease progression included those due to duodenal or gastric ulceration, upper gastrointestinal bleed, disorders of the biliary tree (eg, biliary obstruction, cholangitis), local pain (eg, postoperative, abdominal), problems of the pancreas itself (eg, pancreatitis), and radiation toxicity. Hospitalizations for nonlocal/distant disease included those due to thromboembolic events, cytopenia, dehydration, nausea or vomiting, malnutrition and cachexia, ascites, pathologic fracture, and chemotherapy toxicity. Complications were selected from the NCCN Guidelines for Pancreatic Adenocarcinoma.[7] Readmissions were included, but the initial hospitalization for pancreas-directed surgery was not.

Statistical Analysis

To describe the long-term rates of hospitalization, we used competing risk models to account for the competing risk of death,[9] which included unadjusted cumulative incidence analyses with differences between

groups assessed with Gray's test for inequality. Multivariable Fine-Gray regression models were used to identify independent predictors of hospitalization while controlling for potential confounding factors. Covariables included in the multivariable models were defined a priori and included age at diagnosis, marital status, race/ethnicity, residence in a metropolitan area, geographic region, treatment at a teaching hospital, median income, Charlson comorbidity index, disease group (resectable, unresectable, metastatic), tumor location and size, histologic grade, year of diagnosis, and sex. Because chemotherapy and RT are often delivered after diagnosis, to account for the immortal time bias we modeled receipt of these treatments as time-dependent covariables.[10,11] All statistical tests were 2-sided, and $P<.05$ was considered significant. Analyses were conducted using SAS 9.4 (SAS Institute Inc).

Results

Cohort Characteristics

Of the 21,500 patients in the study cohort, 11,298 (52.5%) presented with metastatic disease, 3,092 (14.4%) were in the resectable group, and 7,110 (33.1%) were in the unresectable group. Complete demographic and clinical characteristics are presented in Table 1.

Incidence of Hospitalization

Overall, 43.5% of patients (n=9,347) required hospitalization for at least one local complication and 60.9% (n=13,101) required hospitalization for at least one nonlocal complication. Among patients who were hospitalized for a complication of local disease progression, 50.6% were hospitalized more than once and 13.6% were hospitalized >3 times. The median length of hospitalization was 6 days (interquartile range, 3–10 days).

Among all patients, the 2-month incidence of hospitalization was 32.8% for local and 35.7% for nonlocal complications (Figure 1), and the 12-month incidence of hospitalization was 40.9% for local and 54.9% for nonlocal complications. The most common causes of hospitalization from local progression were biliary disorders and pancreas-related (Table 2). The most common causes of hospitalization from nonlocal progression were cytopenia and malnutrition/cachexia (Table 2). Supplemental eTable 2 presents

Table 1. Patient Demographic and Clinical Characteristics

Characteristic	Total Cohort, %	Resectable, %	Unresectable, %	Metastatic, %	*P* Value
N	21,500	3,092 (14.4%)	7,110 (33.1%)	11,298 (52.5%)	
Age at diagnosis, y					<.001
66–69	18.3	23.9	14.0	19.5	
70–74	25.2	29.6	21.8	26.2	
75–79	25.6	28.0	24.3	25.7	
≥80	30.9	18.6	39.9	28.6	
Sex					<.001
Female	54.8	55.3	57.3	53.2	
Male	45.2	44.7	42.7	46.8	
Race					<.001
White	82.0	86.1	81.0	81.5	
Hispanic	2.0	1.4	2.3	2.0	
Black	10.1	6.5	10.2	11.1	
Other	5.9	6.0	6.5	5.5	
Marital status					<.001
Married	53.3	60.4	48.7	54.3	
Unmarried	46.7	39.6	51.3	45.7	
Geographic region					<.001
West	40.1	39.0	42.2	39.1	
Midwest	13.5	11.9	12.9	14.3	
South	22.9	23.9	22.5	22.9	
East	23.5	25.2	22.4	23.7	

(continued on next page)

Table 1. Patient Demographic and Clinical Characteristics (cont.)

Characteristic	Total Cohort, %	Resectable, %	Unresectable, %	Metastatic, %	*P* Value
Area of residence					.005
Metropolitan	84.6	85.6	83.5	85.0	
Other	15.4	14.4	16.5	15.0	
Median income					<.001
Bottom quartile	24.3	19.9	25.7	24.6	
2nd quartile	23.4	22.5	24.4	23.0	
3rd quartile	24.5	24.6	24.4	24.6	
Top quartile	27.8	33.1	25.6	27.8	
Teaching hospital					<.001
No	43.7	19.2	46.2	48.8	
Yes	56.3	80.8	53.8	51.2	
Pancreas site					<.001
Body/Tail	22.1	13.2	12.3	30.6	
Head	51.3	75.4	64.6	36.3	
Other	26.7	11.4	23.1	33.1	
Tumor size, cm					<.001
<2	7.3	17.3	6.7	4.9	
2–5	46.5	67.2	48.9	39.3	
>5	26.8	12.4	25.1	31.8	
Unknown	19.5	3.0	19.3	24.1	
Charlson comorbidity index					<.001
0	48.3	51.8	46.3	48.6	
1	28.1	30.0	27.8	27.8	
2	12.6	10.5	13.1	12.9	
≥3	10.9	7.6	12.8	10.7	
Radiotherapy, yes	17.7	40.9	25.0	6.8	<.001
Chemotherapy, yes	41.4	61.9	38.7	37.5	<.001

causes of hospitalization stratified by receipt of RT and chemotherapy.

Causes of Hospitalization by Patient Group

Risk of hospitalization varied by disease stage at presentation (Figure 2). Patients from the resectable and unresectable groups tended to be hospitalized because of local complications early in their clinical course, although over time the risk of hospitalization from nonlocal complications surpassed that from local complications. The 12-month cumulative incidence of local complications was highest for patients from the unresectable group (53.1%), followed by the resectable group (39.5%), and lowest for the metastatic group (33.7%). The 12-month cumulative incidence of nonlocal complications was highest for patients from the metastatic group (57.0%), followed by those from the unresectable (56.8%) and resectable groups (42.8%) (Table 2).

Predictors of Complications Requiring Hospitalization

On multivariable analysis identifying predictors of hospitalization, compared with patients with metastatic

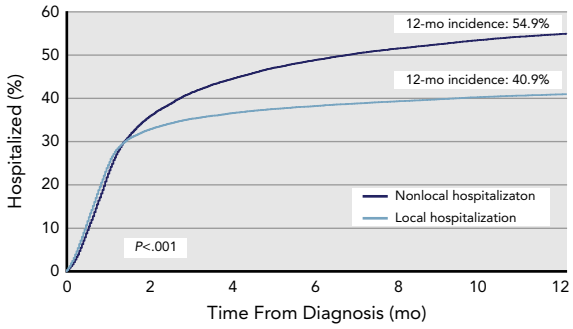

Figure 1. Cumulative incidence of hospitalization after diagnosis caused by local complication (light blue line) and nonlocal complication (dark blue line).

Table 2. Twelve-Month Cumulative Incidence of Local and Nonlocal Complications Requiring Hospitalization[a]

Complication	12-Month Cumulative Incidence, %			
	All Patients (N=21,500)	Resectable (N=3,092)	Unresectable (N=7,110)	Metastatic (N=11,298)
Local				
Biliary disorder	30.4	29.4	43.2	22.6
Upper gastrointestinal ulcer/bleed	5.7	4.3	7.8	4.7
Pain	6.0	5.7	5.6	6.2
Pancreas-related	11.3	14.2	15.1	8.2
Radiation toxicity	0.2	0.5	0.4	0.1
Local composite	40.9	39.5	53.1	33.7
Nonlocal/Distant				
DVT/PE	6.6	5.3	4.7	8.1
Cytopenia	30.1	25.9	32.8	29.6
Dehydration	13.5	13.4	14.0	13.2
Nausea/Vomiting/Motility problem	20.8	20.8	23.0	19.4
Malnutrition and cachexia	23.0	20.5	24.7	22.7
Ascites	5.9	4.0	4.4	7.4
Pathologic fracture	0.8	0.6	0.5	1.0
Chemotherapy-related toxicity	0.7	0.7	0.9	0.7
Nonlocal composite	54.9	42.8	56.8	57.0

Abbreviation: DVT/PE, deep vein thrombosis/pulmonary embolism.
[a]Each patient may have presented with >1 symptom.

disease, those with unresectable disease were at a 49% increased risk of hospitalization for local complications (subdistribution hazard ratio [SDHR], 1.49; 95% CI, 1.43–1.57), whereas those with resectable disease were at a 13% decreased risk (SDHR, 0.87; 95% CI, 0.81–0.94) (Figure 3). Other factors that increased risk of hospitalization for local complications included younger age, Hispanic ethnicity, living in the Midwest, care at a teaching hospital, higher comorbidity, smaller tumor size, and tumor in the head of the pancreas. Neither chemotherapy nor RT were associated with a significant decrease in the risk of local complications.

When considering predictors of hospitalization for nonlocal disease, we found that patients with resectable disease had a 32% decreased risk of hospitalization compared with those with metastatic disease (SDHR, 0.68; 95% CI, 0.65–0.72). There was no difference in the risk of hospitalization for a nonlocal complication between the unresectable and metastatic groups (SDHR, 0.96; 95% CI, 0.92–1.00) (Figure 3). Other factors that increased the risk of hospitalization for complications of nonlocal disease included younger age, black race, living in a metropolitan area, living in the Midwest, care at a teaching hospital, lower income (bottom quartile), higher comorbidity, larger tumor size, and tumor in the head of the pancreas (Figure 3). Neither chemotherapy nor RT were associated with a significant decrease in the risk of nonlocal complications (Figure 3).

Discussion

This population-based study is likely the first to define the specific patterns and causes of hospitalization for a large real-life cohort of elderly patients with pancreatic cancer. The key finding of this study is the high observed rates of hospitalization for both local and nonlocal disease progression. Pancreatic cancer represents an aggressive lethal cancer characterized by early and aggressive tumor spread. Most patients have overt metastatic or micrometastatic disease on presentation, which leads researchers and clinicians to often consider pancreatic cancer a problem of "distant" metastatic disease. Improving outcomes among this challenging disease will certainly require novel advances in systemic therapy; however, the findings of our study highlight the clinical importance of considering both the local pancreatic tumor and nonlocal/distant metastatic disease in optimizing patient care.

Our findings complement other research that demonstrates the clinical importance of local pancreatic tumor progression. A group from Johns Hopkins performed autopsies on 76 patients with pancreatic cancer and

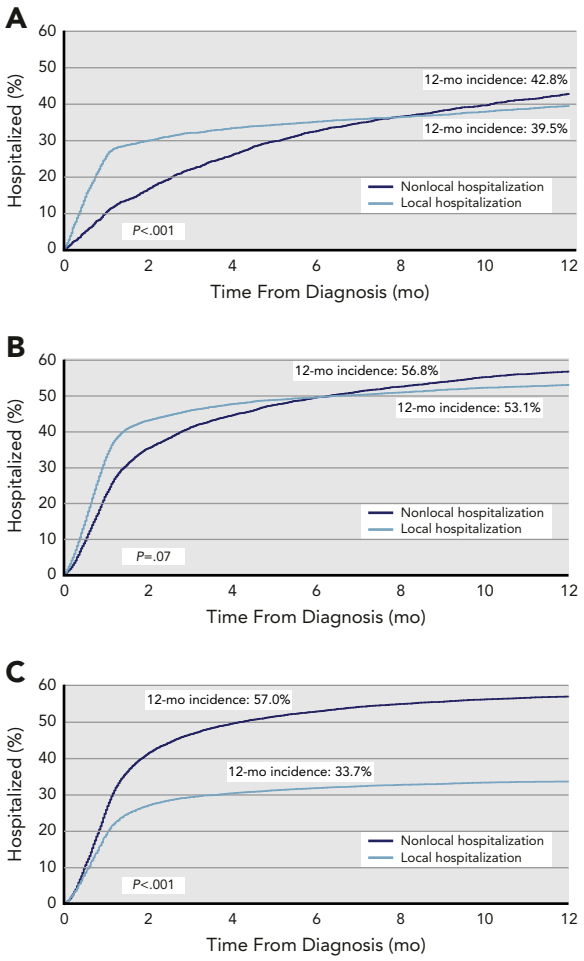

Figure 2. Cumulative incidence of hospitalization after diagnosis by patients with (A) resectable, (B) unresectable, and (C) metastatic disease.

found that 30% died of local tumor destruction.[1] Furthermore, a single-center study from our institution found that the risk of hospitalization from complications of the local tumor was 45%.[12] Local tumor progression can lead to pain, biliary obstruction, and gastric ulcers and bleeding, all of which reduce patient quality of life. Although RT has the capacity to improve local tumor control and reduce complications from local tumor progression, randomized clinical trials have produced mixed survival results for patients with pancreatic cancer treated with RT.[13,14] Furthermore, the absolute local control benefit of using conventionally fractionated radiation seems to be small. The randomized LAP07 trial[13] found that chemoradiotherapy among patients with locally advanced pancreatic cancer decreased the risk of local tumor progression by 14%. Similarly, our study found that RT did not significantly reduce the risk of hospitalization from local tumor progression. Although alternative radiation strategies such as stereotactic body RT[15] and dose-escalated RT[16] hold promise, researchers lack randomized evidence supporting widespread use. Optimizing patient quality of life requires improved strategies to mitigate the complications from local tumor progression. These strategies could include ablative local therapies, such as cryotherapy[17]; irreversible electroporation[18]; or palliative measures, such as biliary stenting/bypass[19] and celiac plexus block.[20] Another possible intervention includes monitoring patient-reported outcomes, which in select populations of patients with cancer may reduce the risk of hospitalization[21] and improve survival.[22] Finally, an option that should be explored is early integration of palliative care, which has been shown to relieve symptoms, reduce hospitalizations, and improve survival in metastatic non–small cell lung cancer.[23] Given the high cost of hospitalizations,[24] improvements in locally directed palliative interventions may reduce the overall economic impact of pancreatic cancer. In general, research efforts in pancreatic cancer most often strive to improve survival, although the impact of treatment on long-term quality of life and cost of care must also be considered.

This study builds on a prior study by Reddy et al[25] of 1,730 Medicare beneficiaries with resectable pancreatic cancer who underwent pancreatectomy. In this study, which resulted in a readmission rate of 53% at 1 year, 25% of readmissions likely arose from operative complications and 48% were potentially associated with recurrence. Our study sought to define risk factors for hospitalization to help better risk-stratify patients (Figure 3). With hospitalization due to local tumor progression, we found the highest risk among patients with unresectable disease, and for hospitalization from nonlocal disease spread, the highest risk was among those with metastatic disease. We also found that younger patients had a higher risk of hospitalization. Recent studies have shown that younger patients have longer overall survival,[26,27] raising the question of whether disease biology may differ by patient age.

In addition, we found that the risk of hospitalization was higher in nonwhite patients, which could reflect known health disparities that influence patterns of care,[28,29] and that the risk of hospitalization varied by geography. Other research has documented variability in hospitalization rates by geographic region, which may reflect regional differences in patient behavior, referral patterns, or treatment options offered to patients.[24,30]

In this study, receiving care at a teaching hospital was associated with a significantly increased risk of both local and nonlocal hospitalization. These data lack the granularity to determine the etiology of the link between academic teaching hospitals and hospitalizations. However, this observation could arise due to underlying

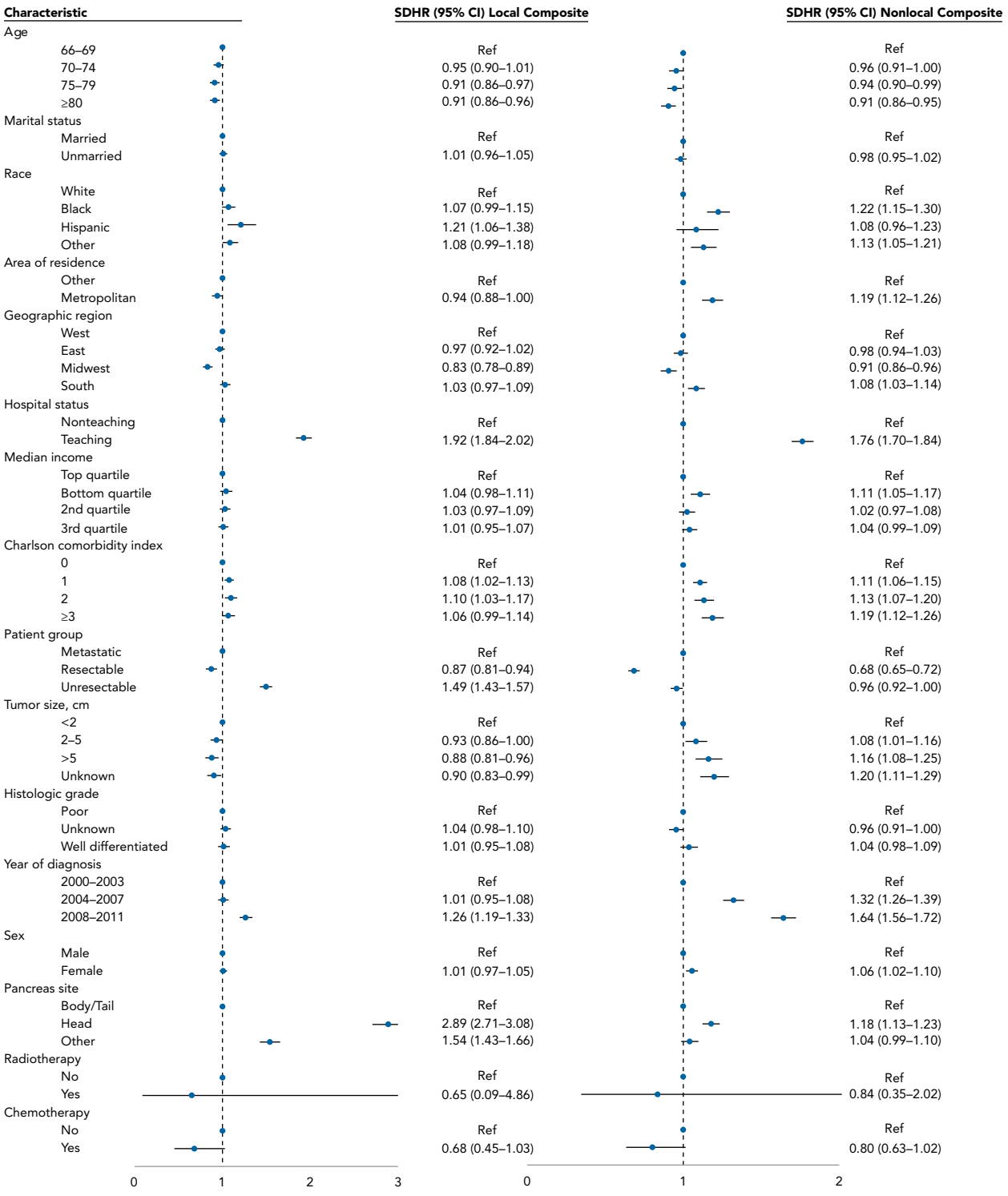

Figure 3. Results of multivariable Fine-Gray regression model. This forest plot depicts results of the multivariable competing risk analysis used to identify predictors of hospitalization caused by local and nonlocal causes. SDHRs >1 reflect increased risk of hospitalization and SDHRs <1 reflect decreased risk of hospitalization. An SDHR of 1.0 means that there was no increased risk of hospitalization.
Abbreviation: SDHR, subdistribution hazard ratio.

differences in patient complexity or difference in institutional treatment patterns.[31,32]

One unexpected finding was the observed association between larger primary tumor size on presentation and paradoxically lower rates of hospitalization caused by local complications. The underlying explanation of this association is unknown; however, it could reflect differences in presentation. Perhaps patients who present with larger primaries have tumors anatomically located in regions that elicit fewer symptoms and have a decreased likelihood of leading to hospitalization. Overall, understanding these associations could help clinicians better identify patients at a higher risk of hospitalization from pancreatic cancer.

Limitations of this study largely arise from those surrounding the data within the SEER-Medicare linked database, which lack specific details of patient characteristics, performance status, metastatic disease burden, and treatment, all of which very likely influence a patient's risk of hospitalization. Another limitation is an inability to account for complications managed on an outpatient basis or in an emergency department, including pain, lethargy, nausea, and dysphagia, all of which contribute substantially to pancreatic cancer morbidity but may not be severe enough to warrant an inpatient admission.[33] Along these lines, we suspect that the number of emergency department visits is higher than the number of hospitalizations. In addition, we determined the cause of hospitalization through billing codes, which raises the possibility of misclassification of this study's primary outcome. Unmeasured confounding factors, such as patient anatomy and performance status, could also impact these study results. Furthermore, distinguishing whether complications arise from local or nonlocal disease can pose a challenge in retrospectively collected data, particularly when using billing claim data as a proxy for patient complications. For example, biliary obstruction could arise from the primary tumor obstructing bile flow (local) or from a metastatic tumor in the hilum of the liver causing bile obstruction. Although one would expect most biliary obstruction cases in this study to arise from local tumor progression, misclassification remains a possibility. Despite these limitations, this study offers useful insight into the morbidity that patients experience with pancreatic cancer.

Conclusions

Combating metastatic disease represents a key therapeutic goal in the overall management of pancreatic cancer, although this study demonstrates the clinical importance of considering the local tumor and nonlocal disease in the overall management of patients with pancreatic cancer.

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