Published in final edited form as:

J Surg Oncol. 2016 May ; 113(6): 599–604. doi:10.1002/jso.24217.

Multimodal Cancer Care in Poor Prognosis Cancers: Resection Drives Long-Term Outcomes

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Abstract

Background and Objectives—Hospitals with high complex oncologic surgical volume have improved short-term outcomes. However, for long-term outcomes, the influence of other therapies must be considered. We compared effects of resection with other therapies on long-term outcomes across U.S. hospitals.

Methods—We examined claims in the Surveillance, Epidemiology, and End Results (SEER)-Medicare dataset for patients with esophageal (EC) and pancreatic (PC) cancers between 2005–2009, with follow-up through 2011, performing multivariable Cox proportional hazards analyses. We stratified hospitals by volume and compared rates of treatments in the context of survival.

Results—We studied 905 EC and 3,293 PC patients at 138 and 375 hospitals, respectively. For EC, resection rates were significantly higher (32.9% vs. 9.5%, $P < 0.001$) in the highest versus lowest volume hospitals. Adjusted survival was also statistically significantly better (48.5% vs. 43.1%, $P < 0.001$). For PC, resection rates were also statistically significantly higher (30.1% vs. 12.0%, $P < 0.001$) with higher adjusted survival (21.5% vs. 19.9%, $P = 0.01$). We did not find variation in rates of other cancer treatments across hospitals.

Conclusions—A significant association exists between long-term survival and rates of cancer-directed surgery across hospitals, without variation in rates of other therapies. Access to resection appears to be key to reducing variation in long-term survival.

Keywords

esophageal; pancreatic; neoplasms; clinical oncology; radiation oncology; surgery

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Disclosures: None.

Previous presentation: Part of this work was presented at the 68th Society of Surgical Oncology Annual Cancer Symposium, Houston, TX, USA, March 25–28, 2015.

INTRODUCTION

Hospitals are characterized by different cancer treatment patterns and differences in cancer mortality rates [1–5]. Patients who undergo certain cancer operations at hospitals with high surgical volume have lower inpatient and 30-day mortality than similar patients at low-volume hospitals [6–7]. But, the extent to which this volume-outcomes relationship extends to other facets of cancer care is unclear. The impact of these patterns in utilization on long-term survival is also unknown.

These factors are highly relevant in modern cancer care, as questions remain regarding the receipt of different treatments at different hospitals and to what extent the role of coordinated cancer care influences outcomes. However, it is unclear whether broad differences in multimodal cancer care utilization contribute to a more sustained volume-outcome relationship. To that extent, we first examined the relationship between volume of patients (both surgical and non-surgical) treated in hospitals and survival. Second, we sought to identify whether high-volume hospitals were associated with greater use of multimodal cancer care and other high intensity hospital services. We hypothesized that the volume-outcomes relationship would be similar for surgery as for other modalities of cancer treatment.

MATERIALS AND METHODS

Data Source and Study Population

We identified incident cases of esophageal (EC) and pancreatic cancer (PC) using national Surveillance Epidemiology and End Results (SEER)-Medicare linked data, which includes population-based cancer socio-demographic and tumor characteristic data for cancer patients, encompassing approximately 28% of the U.S. population over a wide geographic distribution [8]. We chose to study EC and PC as they are two relatively poor prognosis cancers that likely would not be treated by the same surgeons. This allows for a broader understanding of trends in practice patterns across hospitals that is not limited to a single diagnosis or surgeon-level variable. The subset of Medicare beneficiaries in the SEER registry is linked with claims data, which allows for examination of the details of diagnostic and therapeutic interventions of inpatient and outpatient medical care. Using this data, we identified incident cases of primary EC and PC in the period from 2005–2009, with follow-up through 2011, using relevant International Classification of Diseases, 9th Revision (ICD-9) diagnosis codes (esophageal: 150×, pancreatic: 157×) for primary malignancies. Our exclusion criteria included patients with other primary tumors, patients first diagnosed prior to 2005 or with an unknown diagnosis date, patients diagnosed on autopsy, patients aged less than 65 years old or greater than 99 years old at diagnosis, patients with HMO or incomplete Medicare part A & B coverage 12 months prior to and after diagnosis, and patients at hospitals treating less than 10 patients with the given diagnosis in the study time period. To better identify patients who could undergo therapeutic intervention with potentially curative intent in these poor prognosis cancers, we only chose to include patients with AJCC 6th edition Stage I or II disease.

We used a previously designed algorithm to attribute all patients with an index diagnosis of esophageal or pancreatic cancer to the hospitals at which they received the plurality of their care based on magnitude of Medicare payments. We excluded patients for which such a hospital could not be assigned. Medicare claims for cancer-directed surgery, chemotherapy, and radiation therapy were identified using both relevant Current Procedural Terminology (CPT) and International Classification of Diseases, 9th Edition (ICD-9) codes (Appendix). ICU admissions were identified using ICU location codes via the Medicare Provider and Review File (MedPAR). Our goal in including ICU rates was to capture, in a broad way, if there were any differences in “intensity” of treatment for patients across hospitals. Use of this data for these purposes was approved by the University of Michigan Institutional Review Board.

Statistical Analysis

For our survival analysis, hospital volume was defined by the number of incident cases attributed to an individual hospital. This includes all patients with each diagnosis, including those who did not undergo surgical resection. In preparation for risk-adjustment and to compare case mix by hospital volume, patient tumor and sociodemographic characteristics were then analyzed using multivariable Cox proportional hazards regression modeling. Examined factors included AJCC stage, comorbidities, age, sex, race, marital status, and urban/rural location [9]. We then used multivariable logistic regression, controlling for patient and tumor characteristics, to calculate risk-adjusted 2-year overall survival.

In our utilization analysis, we assessed the receipt of chemotherapy, radiation therapy, cancer-directed surgery and ICU admission as dichotomous variables for each patient using CPT and ICD-9 codes for inpatient and outpatient settings. We then stratified hospital-level utilization and survival across terciles of hospital volume. Hospitals were divided evenly into terciles based on mean volume of patients attributed to each hospital. Following this, analysis of variance was used to compare differences in mean utilization and survival across terciles [10]. All tests of statistical significance were two-sided with $P < 0.05$ considered significant. We performed all analyses using Stata release 13 (StataCorp, College Station, TX).

RESULTS

Defining the Cohorts

Using our inclusion criteria (Fig. 1), we identified 905 EC and 3,293 PC patients at 138 and 375 hospitals, respectively, with Stage I or II disease. Patient tumor and socio-demographic characteristics are summarized in Table I. The mean age of EC and PC patients was 76 and 77 years, respectively. The majority of EC patients were male (73%), and the majority of PC patients were female (58%). In both cohorts, the majority of patients were white (88.7% in EC, 83.8% in PC), with black patients representing 6.7% of the EC and 8.8% of the PC cohorts, respectively. An approximately equal number of EC patients were Stage I (49.2%) and Stage II (50.8%), while there were less Stage I (25.0%) versus Stage II (75.0%) PC patients.

Overall Multimodal Cancer Care Utilization

Characteristics of multimodal cancer care utilization at the patient level are shown in Table I. The overall proportion of patients receiving chemotherapy for EC and PC was 50.7% and 52.5%, respectively. The overall proportion receiving radiation therapy was 59.8% and 35.9%, respectively. The overall proportion undergoing cancer-directed surgery was 24.4% and 31.8%, respectively. At least one ICU admission was noted for 40.2% of EC patients and 34.0% of PC patients. For EC, the proportion of patients receiving all three modalities (chemotherapy, radiation and surgery) varied across low to high volume terciles (4.7% vs. 5.9% vs. 14.1%; $P < 0.001$). This was similar for PC (5.1% vs. 9.0% vs. 14.9%; $P < 0.001$).

Using multivariable Cox proportional hazards modeling and multivariable logistic regression, we calculated risk-adjusted survival. Mean adjusted 2-year survival was 46.7% for EC and 21.7% for PC. Corresponding bivariate and multivariable hazard ratios are shown in Table II. For EC, variables independently associated with mortality in our multivariable model included advanced age, black race, single marital status, and multiple comorbidities as defined by the Charlson-Deyo comorbidity index [11]. For PC, variables independently associated with mortality included age greater than 75, black race, multiple comorbidities and more advanced AJCC stage.

Utilization of multimodal cancer care was analyzed at a hospital level, with hospitals divided into terciles of patient volume (Table III). Notably, the lowest volume hospitals treated a higher percentage of black patients in both EC and PC. The extent of variation in volume of patients treated is pronounced, with more patients treated in the highest volume tercile than in the other two terciles combined. The lowest volume hospitals treated a higher proportion of Stage I patients than higher volume hospitals for each cancer.

Improved Survival With Increased Rates of Cancer-Directed Surgery

We then evaluated the relationships between utilization of multimodal cancer care and survival across terciles (Fig. 2). The proportion of patients receiving chemotherapy and/or radiation therapy in the highest versus lowest volume hospitals was 64.7% versus 68.6% ($P = 0.318$) for EC, and 57.8% versus 51.9% ($P = 0.172$) for PC. The proportion of patients undergoing ICU admission in the highest versus lowest volume hospitals was 39.7% versus 36.7% ($P = 0.876$) for EC, and 31.4% versus 28.5% ($P = 0.637$) for PC. However, the proportion of patients undergoing cancer-directed surgery in the highest versus lowest volume hospitals was 32.9% versus 9.5% ($P < 0.001$) for EC, and 30.1% versus 12.0% ($P < 0.001$) for PC. For these same patients, 2-year overall survival was significantly higher in the highest versus lowest volume hospitals with 48.5% versus 43.1% ($P < 0.001$) in EC and 21.5% versus 19.9% ($P = 0.01$) in PC.

Trends in Stage III Patients

While we chose to primarily study Stage I and II patients, we performed an additional subgroup analysis in Stage III patients, to assess for any differences across hospital volume. In esophageal cancer, we found survival to be similar across terciles from low to high volume (27.2% vs. 27.6% vs. 29.7%; $P = 0.358$). Chemotherapy use was higher in high volume hospitals, but the difference across terciles was not statistically significant (66.2%

vs. 62.7% vs. 75.1%; $P = 0.230$). Rates of radiation were similar (74.0% vs. 70.9% vs. 73.3%; $P = 0.903$). Rates of surgery were still statistically significantly higher in high volume hospitals (9.1% vs. 16.0% vs. 29.9%; $P < 0.005$).

For Stage III patients alone in pancreatic cancer, we found survival to be similar across terciles from low to high volume (7.3% vs. 7.8% vs. 7.7%; $P = 0.637$). Chemotherapy use was higher in high volume hospitals, but the difference was not statistically significant (49.6% vs. 55.7% vs. 61.0%; $P = 0.108$). Rates of radiation were similar across terciles (38.6% vs. 47.6% vs. 40.2%; $P = 0.202$). Rates of surgery were similar across terciles (3.4% vs. 3.4% vs. 5.4%; $P = 0.456$).

DISCUSSION

Esophageal and pancreatic cancer patients treated at high-volume hospitals had significantly higher adjusted survival rates compared to patients treated at low-volume hospitals. There was no association between volume of patients treated at a given hospital and likelihood of receiving other modality therapies, including chemotherapy, radiation therapy or ICU care. However, these same esophageal and pancreatic cancer patients were statistically significantly more likely to undergo cancer-directed surgery if treated at high-volume hospitals. No prior studies have evaluated overall volume of patients treated and receipt of multimodal cancer treatments in the context of long-term cancer outcomes. Our results suggest survival differences that are directly associated with increased utilization of cancer-directed surgery and not necessarily any appreciable differences in the receipt of other treatments.

Practical implications of this study include evidence that a “volume-effect” for cancer outcomes in Stage I and II esophageal and pancreatic cancers extends beyond just immediate postoperative outcomes to long-term (2-year) survival. Further, it appears that these observed differences in long-term outcomes are largely attributable to receipt of surgical resection as opposed to other cancer treatments. The key aspect of high quality cancer care for EC and PC may include referral for resection at higher volume hospitals.

Previous studies have shown a significant surgical volume-outcome relationship for resection of both esophageal and pancreatic cancers. Two large meta-analyses (1995–2010 and 2000–2011) confirmed the presence of a consistent hospital-level volume-outcome relationship for esophagectomy, although different studies have stratified groups using very different volume cutoffs [12,13]. Another regional study in California demonstrated that patients receiving care at low versus high surgical volume hospitals for both esophageal and pancreatic cancer resections demonstrated that having Medicaid insurance as well as being black or Hispanic, were significant relative risk factors for undergoing pancreatic cancer resection at a low volume hospital, and being uninsured was separately associated with significant relative risk for not receiving pancreatic cancer resection at a high-volume hospital [14]. While many previous studies have demonstrated a relationship between surgical volume and outcomes, our study differs from these in that we used the volume of incident cancer cases treated at hospitals to define the cohort, rather than volume of surgical resections. Deriving our cohort in this way allows us to have a clearer picture of the extent to

which other aspects of multimodal cancer care might differ by hospital volume, irrespective of whether a patient undergoes resection. When viewed through this lens, the results of our study show a different kind of volume-outcome relationship for these same cancers. Namely, hospitals that treat more patients overall using any modality had improved overall outcomes, which appear to be related to higher rates of resection.

Despite the clear surgical volume-outcome relationship for these procedures, one recent study has shown that 70.3% of esophagectomies and 33.8% of pancreatectomies, are in fact performed at low volume hospitals [15]. Patient factors that were associated with an increased likelihood of surgery in a low-volume hospital included non-white race, non-private insurance, and greater comorbidities. This study also demonstrated significantly higher rates of inpatient mortality and length of stay for those patients receiving surgery at low-volume hospitals. Patients in our study had a lower overall likelihood of undergoing resection if treated in a low volume hospital, and consistent with these prior findings, patients who were treated at low volume hospitals had worse survival. Another prior SEER-Medicare analysis of the relationship between hospital cancer surgery volume and 5-year survival did demonstrate lower receipt of adjuvant therapy for pancreas cancer in low-volume hospitals [16]. Our present study adds to this by including patient and survival data for all incident cases at a given hospital, and this perhaps gives a better hospital profile for cancer treatment in general. Second, it appears that, given our results, over time, lower volume hospitals have improved their use of adjuvant therapy. However, this relative effect could be due to other factors, such as shifts in surgical referral patterns to higher volume hospitals.

There were several limitations to our study. We retrospectively examined a cohort of patients who were all age 65 or older and within the Medicare population. Thus, these results may not be generalizable to younger patients. However, the median ages at diagnosis of esophageal and pancreatic cancer patients are 67 and 71, respectively, ages which would be well-reflected within the Medicare cohort [17]. Another limitation is the lack of ability to determine the extent of actual benefit from each of the treatment modalities to individual patients. For example, while resection may be done with curative intent, a major postoperative complication could lead to decreased survival compared to receipt of a well-tolerated chemoradiation treatment regimen, and thus the relationship between optimal treatment and optimal patient outcomes is complex, with many unmeasured factors likely playing a role. Notably, PC survival in our studied cohort was lower than in other studied cohorts. There are several potential reasons for this. First, our SEER-Medicare data is limited to Medicare patients >65 years old in SEER regions, and thus younger patients undergoing resection are not captured. Second, by including non-operative patients in our cohort, it is likely that we are studying a group that has a higher comorbidity burden, which likely contributes to this worse survival, even in Stage I or II disease. Finally, the granularity present in SEER-Medicare does not allow for a “deeper dive” that might show differences within subgroups of patients receiving different modalities and doses of chemotherapy and radiation therapy. A future study examining this would provide more insight into appropriate use of chemotherapy and radiation therapy regimens across hospitals.

CONCLUSIONS

In summary, when stratified by overall volume of patients treated, long-term survival and utilization of cancer-directed surgery are both statistically significantly higher at high-volume hospitals, while receipt of chemotherapy and radiation therapy are no different across hospital volumes for all patients with Stage I and II esophageal and pancreatic cancers. Further study must be done to better understand potential barriers to receipt of surgical resection for patients who are cared for at lower volume hospitals. Our study highlights the need to improve referral for surgical resection when clinically appropriate, as the impact on survival is significant and lasting.

Acknowledgments

Dr. Healy is supported by NIH T32CA009672-24 and Dr. Wong is supported by AHRQ1K08 HS20937-01 and American Cancer Society RSG-12-269-01-CPHPS.

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Appendix

CD-9 and CPT Codes Used in Identification of Medicare Claims

	ICD-9 codes	CPT codes
Cancer-directed surgery	Esophageal:42.32, 42.33, 42.39, 42.40, 42.41, 42.42, 42.5x, 42.6x, 43.99 Pancreatic:52.5x, 52.6, 52.7, 52.96	
Chemotherapy	V58.1, 99.25	J9000–J9999, Q0083–Q0085
Radiation therapy	V58.0, V66.1, V67.1, 92.2, 92.3, 92.4	77401–77499, 77520, 77523, 77750–77799, G0256, G0261

Fig. 1.

Development of cohorts of patients with esophageal, and pancreatic cancers within the Surveillance, Epidemiology, and End Results— Medicare database incident cases 2005– 2009, with follow-up through 2011.

Fig. 2. Mean multimodal cancer care utilization across terciles of hospital volume for (a) esophageal and (b) pancreatic cancers.

TABLE I

Patient Characteristics in Cohorts for Esophageal and Pancreatic Cancers

	Esophageal cohort	Pancreatic cohort
Patients	905	3,293
Hospitals	138	375
Mean age (sd)	76 (± 7)	77 (± 7)
Male (%)	659 (72.8)	1,392 (42.3)
Race (%)		
White	803 (88.7)	2,758 (83.8)
Black	61 (6.7)	290 (8.8)
Other	41 (4.5)	245 (7.4)
AJCC stage (%)		
I	445 (49.2)	824 (25.0)
II	460 (50.8)	2,469 (75.0)
Modality of therapy		
Cancer-directed surgery	221 (24.4)	1,047 (31.8)
Chemotherapy	459 (50.7)	1,729 (52.5)
Radiation therapy	541 (59.8)	1,183 (35.9)
Rates of ICU admission	364 (40.2)	1,119 (34.0)

sd, standard deviation; AJCC, American Joint Committee on Cancer; ICU, intensive care unit.

Percent totals may not tabulate to 100% as each patient may have received multiple therapeutic modalities.

Also shown is overall use of multimodal cancer care in cohorts for patients with AJCC Stage I and II esophageal and pancreatic cancers. Values represent total counts of patients who received a given therapy, with percentage of cohort in parentheses.

TABLE II

Bivariate and Multivariate Cox Proportional Hazards Analysis of Patient and Tumor Factors and Survival for Esophageal and Pancreatic Cancers

	Esophageal cancer		Pancreatic cancer	
	Bivariate HR (95%CI)	Multivariable HR (95%CI)	Bivariate HR (95%CI)	Multivariable HR (95%CI)
Age				
65–69	—	—	—	—
70–74	1.37 (1.03–1.82)	1.39 (1.04–1.85)	1.13 (0.99–1.28)	1.13 (0.99–1.28)
75–79	1.58 (1.18–2.10)	1.59 (1.19–2.12)	1.30 (1.14–1.47)	1.28 (1.13–1.45)
80	2.27 (1.75–2.96)	2.23 (1.70–2.92)	1.98 (1.76–2.23)	1.94 (1.72–2.18)
Gender				
Male	—	—	—	—
Female	1.12 (0.92–1.37)	1.03 (0.83–1.28)	1.04 (0.96–1.12)	0.92 (0.85–1.00)
Race				
White	—	—	—	—
Black	1.62 (1.19–2.21)	1.57 (1.14–2.17)	1.21 (1.06–1.38)	1.19 (1.04–1.36)
Other	1.18 (0.78–1.78)	1.12 (0.74–1.70)	1.06 (0.91–1.23)	1.08 (0.94–1.26)
Marital status				
Married	—	—	—	—
Single	1.43 (1.19–1.71)	1.30 (1.07–1.59)	1.33 (1.23–1.44)	1.25 (1.14–1.36)
Urban/rural area				
Big metro	—	—	—	—
Metro	1.19 (0.98–1.44)	1.26 (1.04–1.53)	1.05 (0.96–1.14)	1.06 (0.97–1.15)
Urban	0.65 (0.38–1.09)	0.83 (0.49–1.41)	1.03 (0.86–1.22)	1.04 (0.87–1.24)
Less urban	1.17 (0.78–1.77)	1.41 (0.93–2.14)	1.08 (0.92–1.26)	1.13 (0.97–1.32)
Rural	1.06 (0.56–1.99)	1.27 (0.68–2.41)	1.01 (0.71–1.44)	1.09 (0.77–1.55)
Comorbidities				
0	—	—	—	—
1	1.31 (1.03–1.66)	1.25 (0.99–1.59)	1.06 (0.96–1.16)	1.08 (0.98–1.18)
2	1.63 (1.29–2.08)	1.54 (1.21–1.97)	1.53 (1.38–1.69)	1.47 (1.33–1.63)
AJCC stage				
I	—	—	—	—
II	1.03 (0.86–1.24)	1.07 (0.90–1.29)	1.04 (0.95–1.14)	1.17 (1.07–1.28)

HR, hazard ratio; CI, confidence interval.

TABLE III

Patient and Tumor Characteristics Across Terciles of Hospital Volume for (a) Esophageal and (b) Pancreatic Cancers

Volume tercile	1 (low)	2	3 (high)	<i>P</i> *
(a) Esophageal cancers				
Patients	211	239	455	
Hospitals	51	44	43	
Mean age (sd)	76.5 (±7.9)	74.9 (±6.6)	75.5 (±6.8)	0.058
Race (%)				<0.001
White	173 (82.0)	212 (88.7)	418 (91.9)	
Black	31 (14.7)	17 (7.1)	13 (2.9)	
Other	7 (3.3)	10 (4.2)	24 (5.3)	
AJCC stage (%)				0.375
I	112 (53.1)	118 (49.4)	215 (47.3)	
II	99 (46.9)	121 (50.6)	240 (52.8)	
(b) Pancreatic cancers				
Patients	394	735	1,666	
Hospitals	128	126	121	
Mean age (sd)	77.6 (±7.0)	77.3 (±7.4)	76.5 (±6.9)	<0.01
Race (%)				<0.01
White	310 (78.7)	602 (81.9)	1,846 (85.3)	
Black	46 (11.7)	67 (9.1)	177 (8.2)	
Other	38 (9.6)	66 (9.0)	141 (6.5)	
AJCC stage (%)				<0.001
I	131 (33.3)	195 (26.5)	498 (23.0)	
II	263 (66.8)	540 (73.5)	1,666 (77.0)	

sd, standard deviation; AJCC, American Joint Committee on Cancer.

Numbers may not add to 100% due to rounding.

* Calculated using Pearson χ^2 test or analysis of variance as appropriate.