Conditional Survival of Esophageal Cancer
An Analysis from the SEER Registry (1988–2011)

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Introduction: Conditional survival can provide valuable predictive information for both patients and caregivers for patients surviving over time. The purpose of this study was to estimate conditional survival for esophageal cancer patients through analysis of a national population-based cancer registry.

Methods: This retrospective cohort study analyzed 64,433 patients within the Surveillance, Epidemiology, and End Results (SEER) data set who were diagnosed with esophageal cancer from 1988 to 2011. Covariates included cancer characteristics and demographics. Overall survival (defined as time from diagnosis until death), cause-specific survival (defined as time from diagnosis until death from cancer), and 5-year conditional survivals (the probability of surviving an additional 5 years) were calculated. Significant prognostic variables of univariate and multivariable models of survival were identified.

Results: The multivariable models of overall and cause-specific survivals included gender, age group, race, relationship status, year of diagnosis, site, grade, histology, and stage group. Although all patients showed an improvement in conditional survival over time, more dramatic improvements were seen in more advanced stage groups. At the 5-year mark, conditional cause-specific survival of distant stage (defined as having spread by direct extension or metastasis to distant organs, tissues, or lymph nodes) increased from 4% to 79%, whereas regional stage increased from 18% to 77% and localized stage increased from 38% to 85%.

Conclusions: Conditional survival showed improving prognosis over time. Patients with advanced stage had the most dramatic improvement. Clinicians, caregivers, and patients with esophageal cancer can feel encouraged by the improving prognosis with each year survived. This information has practical implications regarding longitudinal follow-up guidelines and survivorship planning.

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Esophageal cancer is the eighth most common cancer and sixth leading cause of cancer death worldwide, with more than 400,000 diagnoses and 350,000 deaths annually.[1] In the United States, an estimated 18,170 new cases were diagnosed in 2014 and median age of diagnosis was 67 years.[2] Incidence rates have been increasing, especially in adenocarcinoma histology and white race.[1] Although survival of esophageal cancer has improved over the decades,[1] 5-year relative survival was still only 17% in 2014 in the United States. Prognosis depends heavily on stage and the individual's response to treatment, but prognosis also changes for each individual over time. Conditional survival demonstrates quantitatively and visually how an individual's prognosis changes over time.

The purpose of this study was to calculate the conditional survival of esophageal cancer patients in the United States. The hypothesis was that conditional survival would improve over time, especially in more advanced stages, as has been shown for other gastrointestinal tract tumors like the stomach,[3] colon,[4] and rectum.[5] The national population-based Surveillance, Epidemiology, and End Results (SEER) registry is a publicly available database that provides both large cohort size and long-term follow-up, two necessary components for studying conditional survival. These attributes are especially useful for esophageal cancer whose epidemiologic study can be difficult because of the short survival.[6]

MATERIALS AND METHODS

The data were obtained from the SEER registry of the National Cancer Institute (Bethesda, MD). SEER is a national population-based cancer registry that is globally recognized for its accuracy and completeness. It currently collects cancer incidence and survival data for over one fourth of the United States population.[7] More information on the geographic regions included as SEER regions can be found at its website.[7] Because the data from the SEER registry are de-identified and publicly available, no institutional review board approval was necessary.

The newest available SEER registry (1973–2011) found 81,686 patients who were diagnosed with esophageal cancer as their first and only cancer diagnosis using Collaborative Stage Schema. The anatomical sites included both the esophagus and esophagus/gastroesophageal junction (GEJ). Inclusion

required microscopic diagnostic confirmation, malignant tumor behavior, active follow-up, and diagnosis after the year 1988 to have sufficient information for analysis. Cases were excluded if reported by death certificate, autopsy, or hospice. Pediatric cases were excluded (age at diagnosis <18 years). These criteria resulted in 64,433 cases in the final retrospective cohort analysis.

Covariates included demographic variables (gender, age group, race, and marital status) and diagnostic information (year of diagnosis, site, grade, histology, and SEER historic stage group). SEER historic stage grouped esophageal cancers into localized, regional, distant, or unknown stages as follows: (1) localized—an invasive neoplasm confined entirely to the organ of origin; (2) regional—a neoplasm that has extended directly into surrounding organs or tissues, into regional lymph nodes, or both; (3) distant—a neoplasm that has spread to parts of the body remote from the primary tumor either by direct extension or by discontinuous metastasis (e.g., implantation or seeding) to distant organs, tissues, or through the lymphatic system to distant lymph nodes; or (4) unknown—information is not sufficient to assign a stage. To maximize sample size, all sites (esophagus and esophagus/GEJ), grades (I–IV, unknown), and histology (adenocarcinoma, squamous cell carcinoma, all others) were included. Esophagus site can be loosely correlated with multiple regions (cervical, upper thoracic, and mid thoracic). The lower (distal) esophagus and GEJ site can be considered as the lower thoracic region. Patients were divided into two age groups around 65 years, a typically used definition of elderly patients according to the World Health Organization.[8] Race categories were white, black, other (American Indian/Alaska native, Asian/Pacific Islander, or other unspecified), and unknown. Relationship status categories were single, married/partner, separated/divorced, widowed, and unknown. The χ^2 test was used to compare the distribution of these groups across the stage groups.

The Kaplan–Meier method was used for the initial, unadjusted univariate survival analysis. Overall survival was defined as time from diagnosis until death. Cause-specific survival was defined as time from diagnosis until death because of esophageal cancer. The log-rank test was used to identify and compare the outcome of significant covariates in univariate survival analysis. These clinically meaningful and significant prognostic variables were considered for inclusion in the final Cox proportional hazards multivariable regression models.

Five-year conditional (overall and cause specific) survivals were calculated for each of the covariates in the final multivariable regression models. Conditional survival was calculated as the proportion surviving 5 additional years, as shown in the following equation: when $S(t)$ is (overall or cause specific) survival at time t, conditional survival is $S(x + 5)/S(x)$.

Analysis was conducted using SAS v9.3 and Microsoft Excel 2010. Conditional overall survival was also calculated for the subgroup of patients diagnosed during 2004 to 2011 with an American Joint Committee on Cancer (AJCC) 6th edition stage, to compare trends using SEER historic stage versus AJCC stage. Effort was made to present only conditional survival graphs with sufficient follow-up by displaying conditional survivals of only those values calculated from Kaplan—Meier survival estimates with at least 100 patients at risk; exceptions were required for unknown marital status (<100 cases at risk at 9 years after diagnosis, which was necessary for conditional survivals at ≥4 years) and for subanalysis of cases diagnosed after 2004 (because of fewer cases, shorter follow-up, and poor survival).

RESULTS

Stage distribution was statistically different across all demographic and diagnostic covariates, as shown in Table 1; all p values from χ^2 test were less than 0.0001. For all stages, there were more patients with male gender, white race, married, diagnosed in 2000 to 2011, non-GEJ site, grades II and III, and adenocarcinoma histology. Relatively lower stage was associated with female gender, older age group, white or unknown race, widowed or unknown relationship status, non-GEJ site, lower grade, and squamous cell histology. Diagnosis during 2000 to 2011 was associated with fewer unknown stage and more distant stage group diagnoses.

Analysis of univariate overall and cause-specific survivals showed that better survival was associated with more distal site, lower stage, lower grade, adenocarcinoma histology, more recent diagnosis, younger age at diagnosis, and being married or non-widowed; all p values from log-rank test for significance were less than 0.0001. Five-year cause-specific versus overall survival of localized stage was 38% versus 29%; regional stage was 18% versus 15%; and distant stage was 4% versus 3%. Ten-year cause-specific versus overall survival of localized stage was 32% versus 19%; regional stage was 14% versus 9%; and distant stage was 3% versus 2%.

All of the covariates were also found to be significant in multivariable analysis, as shown in Table 2. Better prognosis was associated with younger age at diagnosis, non-black race, married or non-widowed relationship status, diagnosed in 2000 to 2011, more distal site, lower grade, adenocarcinoma histology, and lower stage after adjusting for other covariates. The single greatest hazard in the multivariable model was distant stage, with triple the risk of death compared with localized stage, and 3.5 times the risk of death from cancer compared with localized stage.

Conditional overall and cause-specific survivals of all patients improved dramatically over time, as shown in Figure 1*A* and *B*. Over the first 5 years after diagnosis, conditional overall survival improved from 29% to 67% in the localized stage group, 15% to 63% in the regional stage group, and 3% to 68% in the distant stage group (Fig. 1*A*). Over the first 5 years after diagnosis, conditional cause-specific survival improved from 38% to 85% in the localized stage group, 18% to 77% in the regional stage group, and 4% to 79% in the distant stage group (Fig. 1*B*). Subanalysis of the 3338 cases with AJCC 6th edition staging information showed the same trend, with conditional overall survival of stage IV increasing from 3% to 52% after 3 years, whereas stages III/II/I increased from 11%/25%/34% to 52%/68%/68%, respectively (Fig. 2), although there were fewer cases in this analysis. More dramatic increases were seen in more advanced stages.

TABLE 1. Demographic and Cancer Diagnosis Distribution of Studied Cohort by Stage Group

		Localized	Regional	Distant	Unknown	Total	*P* Value
Gender	Female	3529	4050	4490	2516	14,585	<0.0001
	%	24	28	31	17		
	Male	10,592	15,345	18,524	5387	49,848	
	%	21	31	37	11		
Age group	<65	5170	9241	11,948	2271	28,630	<0.0001
	%	18	32	42	8		
	65+	8951	10,154	11,066	5632	35,803	
	%	25	28	31	16		
Race	White	11,832	16,158	19,066	6318	53,374	<0.0001
	%	22	30	36	12		
	Black	1467	2000	2526	1053	7046	
	%	21	28	36	15		
	Other/ unknown	822	1237	1422	532	4013	
	%	20	32	36	12		
Marital status	Single	1768	2629	3507	1173	9077	<0.0001
	%	19	29	39	13		
	Married/partner	8152	11,782	13,570	3476	36,980	
	%	22	32	37	9		
	Separated/divorced	1311	2117	2673	729	6830	
	%	19	31	39	11		
	Widowed	2266	2269	2501	1847	8883	
	%	26	26	28	21		
	Unknown	624	598	763	678	2663	
	%	23	22	29	25		
Year of diagnosis	1988–1999	3926	5262	5358	3086	17,632	<0.0001
	%	22	30	30	18		
	2000–2011	10,195	14,133	17,656	4817	46,801	
	%	22	30	38	10		
Site	Esophagus	9597	13,050	14,896	5876	43,419	<0.0001
	%	22	30	34	14		
	Esophagus/GEJ	4524	6345	8118	2027	21,014	
	%	22	30	39	10		
Grade	I	1145	715	618	396	2874	<0.0001
	%	40	25	22	14		
	II	5146	6339	6268	2401	20,154	
	%	26	31	31	12		
	III/IV	5262	10,052	12,224	3188	30,726	
	%	17	33	40	10		
	Unknown	2568	2289	3904	1918	10,679	
		18	32	40	10		
Histology	Adenocarcinoma	8622	11,339	14,517	3928	38,406	<0.0001
	%	22	30	38	10		
	Squamous cell	4030	5491	5193	2769	17,483	
	%	23	31	30	16		
	All others	1469	2565	3304	1206	8544	
	%	17	30	39	14		

All p values were less than 0.0001 by χ^2 test.
GEJ, gastroesophageal junction.

A similar trend was seen in conditional overall and cause-specific survivals of the higher grade group as well (Fig. 3*A* and *B*). When grouped by site (Supplementary Figure 1, Supplemental Digital Content 1, http://links.lww.com/JTO/A869), histology (Supplementary Figure 2, Supplemental Digital Content 2, http://links.lww.com/

TABLE 2. Final Cox Proportional Hazards Model Multivariable Regression with Effect Estimates for Overall Survival (Defined as Time from Diagnosis until Death from All Causes) and Cause-Specific Survival (Defined as Time from Diagnosis until Death due to Cancer)

	Overall Survival			Cause-Specific Survival		
	Hazard Ratio	95% Confidence Interval of Hazard Ratio	*P* Value	Hazard Ratio	95% Confidence Interval of Hazard Ratio	*P* Value
Gender						
Female	1 (baseline)			1 (baseline)		
Male	1.1	1.09–1.14	<0.0001	1.1	1.07–1.12	<0.0001
Age group						
<65	1 (baseline)			1 (baseline)		
65+	1.4	1.40–1.45	<0.0001	1.3	1.31–1.36	<0.0001
Race						
White	1 (baseline)			1 (baseline)		
Black	1.2	1.12–1.19	<0.0001	1.1	1.10–1.17	<0.0001
Other	0.9	0.84–0.91	<0.001	0.9	0.84–0.91	<0.0001
Unknown	0.6	0.53–0.73	<0.0001	0.6	0.50–0.72	<0.0001
Relationship status						
Single	1 (baseline)			1 (baseline)		
Married/partner	0.8	0.79–0.83	<0.0001	0.8	0.80–0.84	<0.0001
Separated/divorced	1.0	0.94–1.01	0.17	1.0	0.94–1.01	0.1536
Widowed	1.1	1.06–1.13	<0.0001	1.1	1.06–1.14	<0.0001
Unknown	0.9	0.87–0.96	0.0001	0.9	0.87–0.97	0.001
Year of diagnosis						
1988–1999	1 (baseline)			1 (baseline)		
2000–2011	0.8	0.80–0.83	<0.0001	0.8	0.79–0.83	<0.0001
Site						
Esophagus	1 (baseline)			1 (baseline)		
Esophagus/GEJ	1.0	0.94–0.98	0.0003	1.0	0.94–0.98	<0.0001
Grade						
I	1 (baseline)			1 (baseline)		
II	1.2	1.14–1.25	<0.0001	1.2	1.18–1.30	<0.0001
III/IV	1.4	1.33–1.46	<0.0001	1.5	1.41–1.56	<0.0001
Unknown	1.2	1.17–1.28	<0.0001	1.3	1.21–1.34	<0.0001
Histology						
Adenocarcinoma	1 (baseline)			1 (baseline)		
Squamous cell	1.1	1.12–1.17	<0.0001	1.1	1.12–1.17	<0.0001
All others	1.1	1.11–1.17	<0.0001	1.2	1.12–1.19	<0.0001
Stage						
Localized	1 (baseline)			1 (baseline)		
Regional	1.4	1.38–1.45	<0.0001	1.6	1.54–1.63	<0.0001
Distant	3.0	2.91–3.06	<0.0001	3.5	3.44–3.63	<0.0001
Unknown	2.0	1.90–2.02	<0.0001	2.1	2.05–2.20	<0.0001

GEJ, gastroesophageal junction.

JTO/A870), year of diagnosis (Supplementary Figure 3, Supplemental Digital Content 3, http://links.lww.com/JTO/A871), gender (Supplementary Figure 4, Supplemental Digital Content 4, http://links.lww.com/JTO/A872), age at diagnosis (Supplementary Figure 5, Supplemental Digital Content 5, http://links.lww.com/JTO/A873), race (Supplementary Figure 6, Supplemental Digital Content 6, http://links.lww.com/JTO/A874), or relationship status (Supplementary Figure 7, Supplemental Digital Content 7, http://links.lww.com/JTO/A875), the conditional survivals increased more uniformly so that the relative relationship between subgroups was maintained over time.

DISCUSSION

This is the first analysis to describe overall conditional and cause-specific survival for esophageal cancer. Two studies

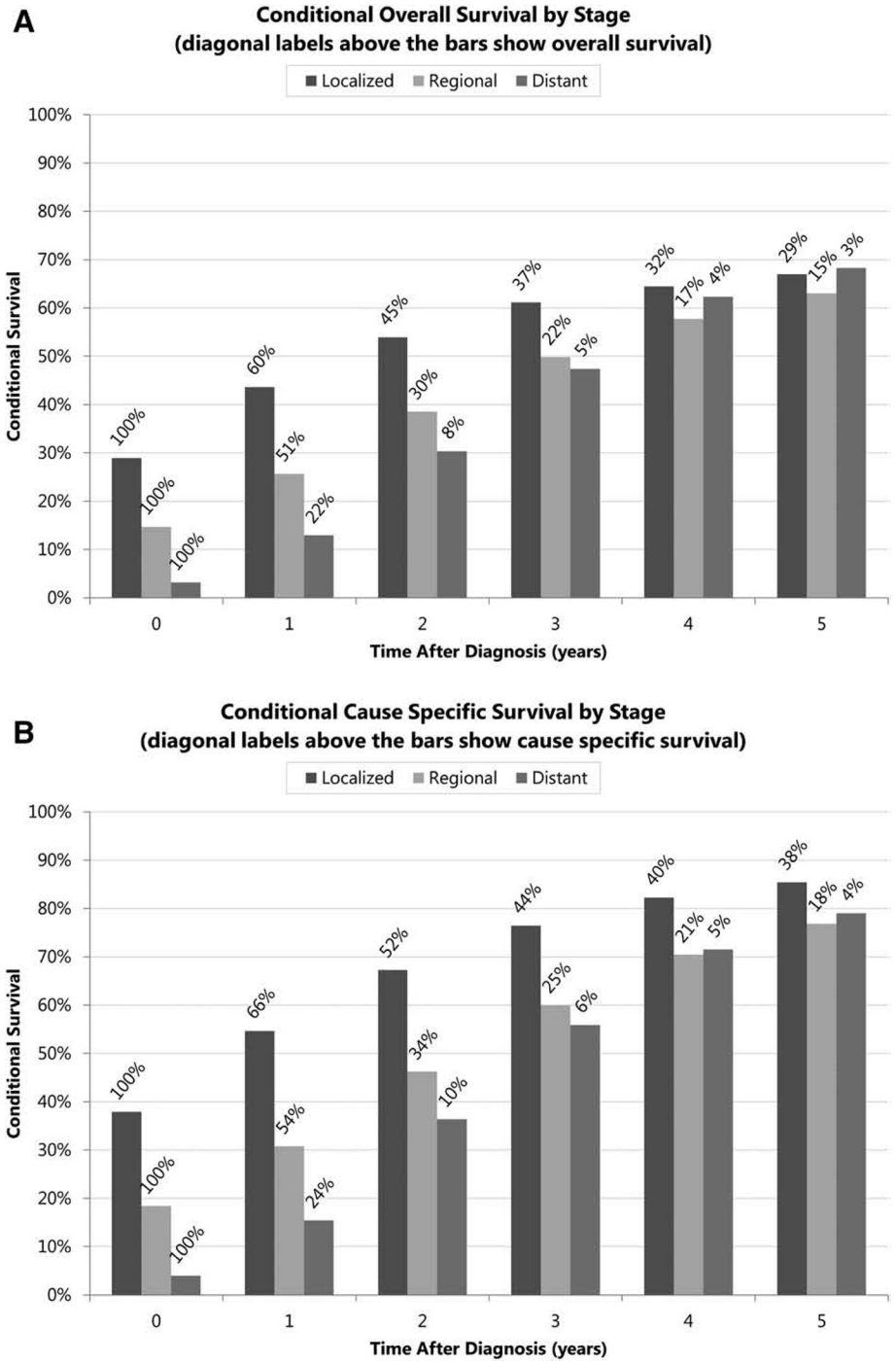

FIGURE 1. Five-year conditional overall survival (*A*) and cause-specific survival (*B*) of esophageal cancer patients by SEER historic stage group, calculated from Kaplan–Meier survival estimates, with diagonal labels above the bars showing overall survival and cause-specific survival from diagnosis, respectively.

of perioperative mortality published what they called conditional survival: one following esophagectomy or gastrectomy for esophagogastric cancer[9] and another following surgery for non-metastatic colon, esophageal, gastric, liver, lung, pancreatic, or rectal cancers.[10] What they actually calculated was survival excluding perioperative mortality (survival among patients who did not die within 30 or 60 days of surgery). These are different from the more standard 5-year conditional survival calculated here.

A meeting abstract by German investigators calculated conditional survival using 25,306 SEER cases diagnosed between 1988 and 2004.[11] It is unclear from the abstract exactly what selection criteria or analytical methods they used. Their "multivariate [sic]" analysis does not seem to have included stage, site, grade, histology, year of diagnosis, or age group. Dubecz et al.[11] showed the same dramatic increase in conditional overall survival in more advanced stages, with slightly lower conditional survival values (58%, 56%, and

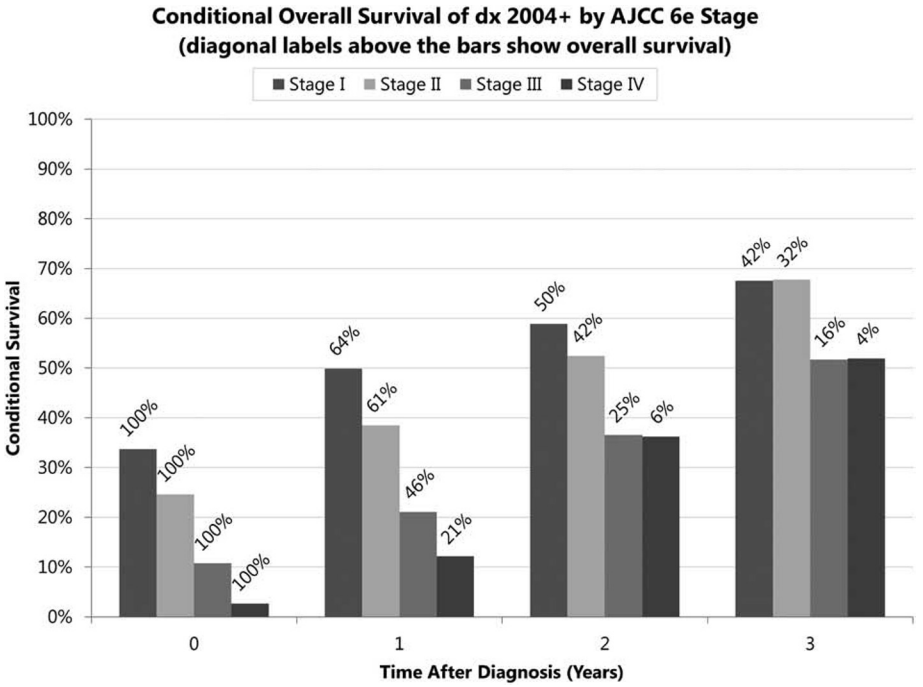

FIGURE 2. Five-year conditional cause-specific survival of esophageal cancer patients by American Joint Committee on Cancer (AJCC) 6th edition stage, calculated from Kaplan–Meier survival estimates, with diagonal labels above the bars showing cause-specific survival from diagnosis.

61% for localized, regional, and distant SEER historic stages after 5 years, compared with the current, larger analysis, 67%, 63%, and 68%, respectively). Other gastrointestinal tract[3–5] and solid tumors[12–15] show a similar pattern, with the 5-year conditional survival of higher stage disease increasing more rapidly and starting to approach the conditional survivals of lower stages over time. As shown in Figure 1*B*, although conditional cause-specific survival of distant stage increases from 4% to 15% after just 1 year, this is only for the 24% who survive for 1 year. Likewise, although conditional cause-specific survival of distant stage increases to almost 20-fold over 5 years (from 4% to 79%), this is only for the 4% who are still alive at the 5-year mark following the original diagnosis.

Our higher survivals are reasonable given that Dubecz et al.[11] used an older release of the same SEER registry. Patients diagnosed in 2000 to 2011 had better outcomes than those from 1988 to 1999 in both univariate and multivariable survival analyses. This is consistent with established national trends[1] and is likely a result of a combination of factors including advances in treatment methods, better use of combined modalities, and changes in dominant histology type. Incidence of adenocarcinoma has been increasing while that of squamous cell carcinoma has been decreasing[1]; adenocarcinoma had better overall and cause-specific survivals than squamous cell carcinoma in both univariate and multivariable survival analyses.

There are many possible reasons for the greater increase in conditional survival for more advanced stages. Stage is thought to be the single most important prognostic factor.[1] In our multivariable analysis as well, the largest predictors of hazard were advanced stages (Table 2). Unlike localized or regional stages, distant stage includes a much wider spectrum of disease; distant stage could mean one distant lymph node, or it could mean widely metastatic cancer. In a subanalysis of cases diagnosed after 2004, when SEER started including AJCC 6th edition stage, localized stage group was mostly stage I (ranging stages I and II), regional stage group was mostly stages II and III (ranging stages I–IV), and distant stage group was mostly stage IV (ranging stage I–IV). This would exacerbate the range in therapies received by patients with distant stage because of different treatment options, aggressiveness of and patients' tolerance of these treatments, and varying goals of treatment. Initial mortality was high from more advanced stages, with 1-year cause-specific survival of only 24%, but the patients who did survive 1 or 2 years may have been those with relatively less severe disease and thus better survival.

SEER can provide data to quantify the potential impact of different modalities and their sequence of administration including preoperative therapy.[16] The generation of outcome prediction tools using these data may serve as decision aids for patients and practitioners.[16,17] One limitation of using SEER data is the lack of detailed treatment information. Treatment information is limited to surgery or radiation therapy received within 4 months of diagnosis; it does not have treatments started later or details on the specific agents that comprised systemic therapies. Dubecz et al.[11] included surgery as a covariate, but we did not feel that there were adequate details regarding surgery or other treatment information to include it in the analysis without potentially compromising the quality of the results because of incomplete treatment information.

The grade may not be as reliable as some of the other tumor characteristics because central pathology review was not and cannot be performed for all of the cases in the SEER database. Another limitation is the inconsistency of staging information and potential understaging, particularly in older cases. SEER's historic stage is certainly useful, but AJCC staging information provides much finer classifications and is the basis of modern clinical decision making and prognostic

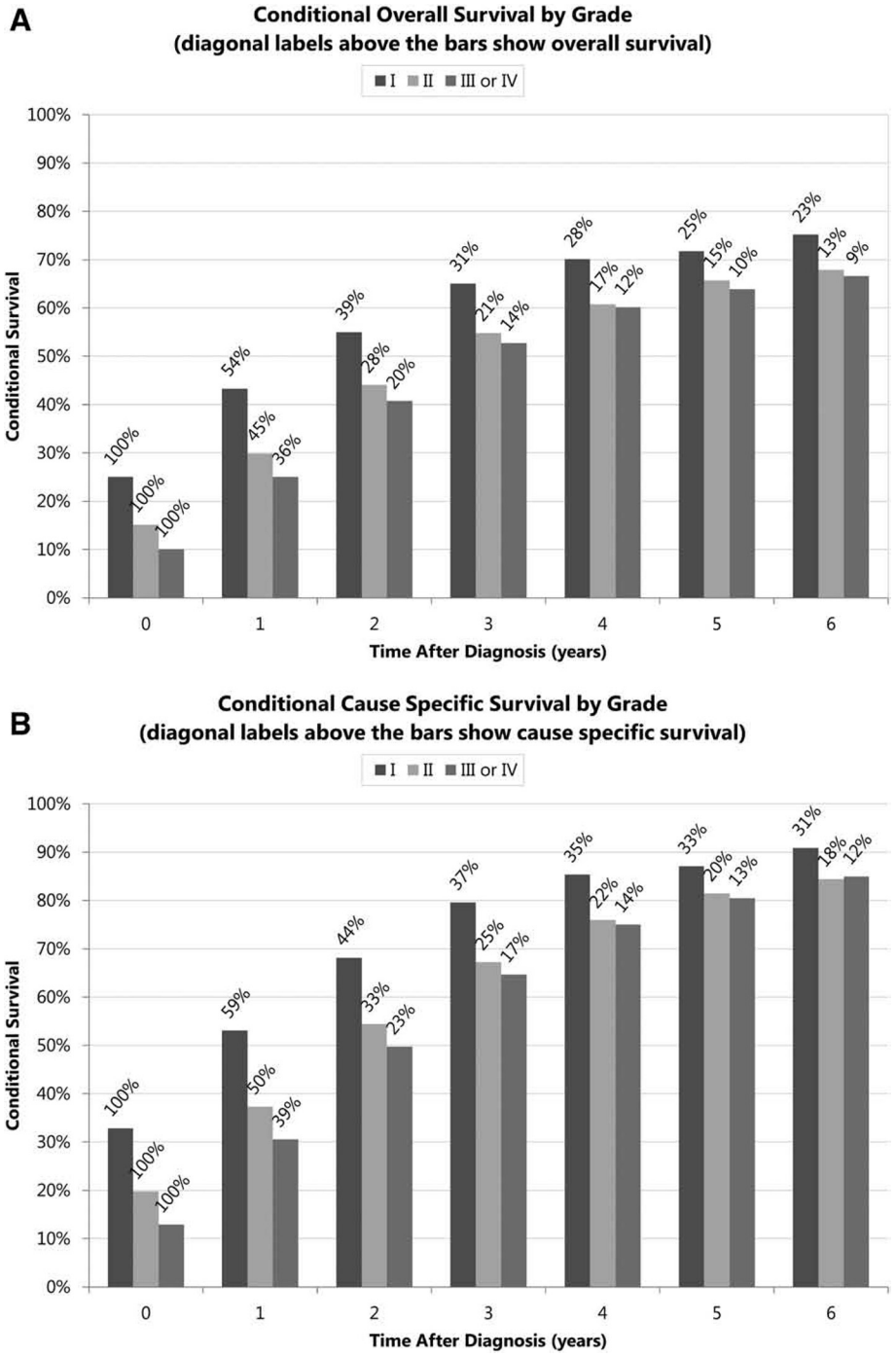

FIGURE 3. *A,* Five-year conditional overall survival (*A*) and cause-specific survival (*B*) of esophageal cancer patients by grade, calculated from Kaplan–Meier survival estimates, with diagonal labels above the bars showing overall survival and cause-specific survival from diagnosis, respectively.

assessment. For esophageal cancer in the SEER registry, AJCC stage information is only available as 6th edition for cases diagnosed during or after 2004. The quality of diagnostic procedures may have led to understaging of patients, which could artificially inflate the survival of more advanced stages.

Subanalysis of conditional overall survival using only this subgroup diagnosed during 2004 to 2011 found the same conclusion as using SEER historic stage. Because of recent data with limited follow-up, conditional survival could only be calculated up to 3 years after diagnosis for this subanalysis, and stages III and IV in particular had very small sample sizes (111 and 53 at risk after 3 years) because of the poor survival of advanced stages, resulting in potentially less representative results. Follow-up time is particularly important for conditional survival because the conditional survival calculated at the 2-year mark, for instance, requires follow-up information until at least 7 years after diagnosis. The SEER registry is a useful resource because it has long-term follow-up information for many tumor types, including esophageal cancer.

CONCLUSIONS

This is the first known study of conditional survival for esophageal cancer. Conditional overall and cause-specific survivals here provide visual and quantitative evidence of the changing prognosis of a patient over time. Patients with more advanced stages in particular can feel encouraged by their improving prognosis with every year survived. Conditional survival is a valuable resource in cancer survivorship and should continue to be investigated with other databases with more treatment and staging information and longer follow-up. In summary, conditional survival can be a useful tool to predict survival for esophageal patients, their family and friends, and healthcare professionals.

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