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The revised AJCC Staging System (7th Edition) improves prognostic stratification after minimally invasive esophagectomy for esophagogastric adenocarcinoma

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Abstract

Background—Staging for esophagogastric adenocarcinoma lacked sufficient prognostic accuracy and was revised. We compared survival prognostication between American Joint Commission on Cancer (AJCC) 6th- and 7th-editions.

Methods—We abstracted data for 836 patients who underwent minimally invasive esophagectomy (MIE) for esophagogastric adenocarcinoma (n=256 neoadjuvant). Monotonicity and strength of survival trends, by stage, were assessed (log-rank test of trend chi-squared statistic) and compared using permutation testing. Overall survival (Cox regression) and model fit (Akaike Information Criterion (AIC)) were determined.

Results—A greater log-rank test of trend statistic indicated stronger survival trends by stage in AJCC-7th (152.872 vs. 167.623; permutation test p<0.001). Greater Cox likelihood chi squared value (162.957 vs. 173.951) and lower AIC (4831.011 vs 4820.016) indicated better model fit. Superior performance was also shown after neoadjuvant therapy.

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This work was presented as a poster at the 2014 Gastrointestinal Cancers Symposium on January 16, 2014 at the Moscone West Building in San Francisco, California, and at ASCO Annual Meeting 2014 on May 31, 2014 at McCormick Place Convention Center in Chicago, Illinois.

Conclusion—AJCC 7th-edition staging for esophagogastric adenocarcinoma provides superior prognostic stratification after MIE, overall and after neoadjuvant therapy compared to AJCC 6th-edition.

Keywords

Staging; Neoplasm; Esophageal Neoplasms; Adenocarcinoma; Esophagectomy; Survival

Introduction

Esophageal cancer is an aggressive disease and prognosis is poor, with 5-year survival rates less than 20% despite multimodality treatment.(1, 2) Accurate staging of cancer is important for determining appropriate treatment, facilitating survival prognostication and communicating risks, benefits and potential outcomes of various treatment options with patients.(3) Historically, the American Joint Committee on Cancer (AJCC) esophageal cancer staging has been based on a simple arrangement of increasing anatomic classifications: increasing tumor depth (T-status), regional nodal metastasis (N-status) and distant metastasis (M-status; included celiac lymph node metastasis). It became clear over time, however, that the survival outcomes predicted by the 6th-edition AJCC staging system for esophageal cancer were inconsistent with existing survival data and increasing understanding of esophageal cancer biology.(4) To overcome the known shortcomings of the 6th-edition, numerous and major changes were introduced in the seventh edition of AJCC TNM staging system.(4) These changes included: 1) T4 tumors invading local structures were sub classified as T4a (resectable cancers) and T4b (unresectable cancers); 2) nodal disease (N-classification) was stratified based on number of positive lymph nodes (N1: 1 to 2 nodes; N2: 3 to 6 nodes; and N3: > 7 nodes); 3) metastases (M classification) were redefined as M0 (no distant metastasis) and M1 (distant metastasis) and the sub classifications M1a and M1b eliminated; 4) separate staging systems for squamous cell and adenocarcinoma were delineated; 5) tumors of the gastroesophageal junction and proximal 5 cm of the stomach were classified as esophagogastric carcinoma; and 6) histologic grade and tumor location were added for early stage disease.

The new staging system was developed using pathological data derived from an international collection of 4627 patients (60% adenocarcinoma) gathered under the direction of the Worldwide Esophageal Cancer Collaboration.(5) By design, none of the patients in the database had received neoadjuvant or adjuvant therapy and the approach to esophagectomy varied widely. While exclusion of exposure to chemo/radiation provided a relatively homogenous population of patients with regard to treatment (only esophagectomy), it does not represent the current population of esophageal cancer patients undergoing esophagectomy, where neoadjuvant chemoradiotherapy is considered standard for Stage III disease and increasingly used for Stage II patients. Because neoadjuvant therapy can drastically alter the final pathologic stage compared to pretreatment clinical stage, it is not known whether AJCC 7th-edition provides accurate prognostication for patients with esophageal adenocarcinoma who have had neoadjuvant chemo/radiation in their treatment algorithm. The aim of our study was to compare the performance of AJCC 6th- and AJCC 7th-edition pathologic stage assignment in predicting survival in a cohort of

esophageal adenocarcinoma patients who underwent minimally invasive esophagectomy, overall and after neoadjuvant therapy.

Patients and Methods

Patient selection and data acquisition

We reviewed all patients (n=836) with esophagogastric adenocarcinoma who underwent minimally invasive esophagectomy, the preferred approach to esophagectomy at our center (1/1/1997–07/31/2011). For this study, only patients having minimally invasive esophagectomy were included to minimize confounding of approach to operation on the completeness of pathologic staging (such as potential differences in node dissection between a transhiatal esophagectomy and minimally invasive esophagectomy) and survival. Endoscopic ultrasound and computed tomography or positron-emission testing were used to determine pretreatment clinical stage; 256 patients with locoregionally advanced disease (e.g. bulky lymphadenopathy or bulky tumor at laparoscopic staging, or at the discretion of the referring medical oncologist) by pretreatment staging underwent neoadjuvant chemo- and/or radiotherapy followed by minimally invasive esophagectomy. Exposure to adjuvant therapy was documented for 619 patients; 38% of patients overall and 45% of neoadjuvant patients. Patient demographics, treatment-related, and tumor-specific variables were abstracted and described in Table 1. Using T-status, N-status, and M-status, a pathologic stage was calculated for each patient as per AJCC 6th-edition, while T-status, number of positive lymph nodes, mass location, degree of tumor differentiation, and M-status were used to calculate AJCC 7th-edition pathologic stage assignment. Median survival time was defined as time from esophagectomy to date of last living contact or death. This study was approved after institutional board review.

Description of Minimally Invasive Esophagectomy

All patients underwent minimally invasive esophagectomy as previously described, with either a cervical (McKeown) or intrathoracic (Ivor Lewis) anastomosis.(6–9) Regardless of the location of the anastomosis, laparoscopic mobilization of the gastric conduit with extensive abdominal lymph node dissection, including the periceliac, perigastric and paraesophageal lymph node packets, was performed in all patients. Routine pyloroplasty is performed to facilitate postoperative gastric emptying and a feeding jejunostomy tube inserted for early nutritional supplementation. The esophagogastric anastomosis is performed in the upper thorax or neck.

Statistical analysis

Statistical analysis was performed using R version 3.0.0, SPSS version 22 and STATA 13. Descriptive statistics were summarized with frequencies and percentages for categorical variables and median with interquartile (IQR) for continuous variables for the entire cohort and then stratified by type of treatment (primary surgery versus neoadjuvant therapy followed by esophagectomy). After assignment of AJCC 6th- and AJCC 7th-edition stage, the assigned stages were examined to identify concordant and discordant (i.e. reclassified) stage assignment and to determine whether stage-specific survival in the reclassified cases was similar to survival of cases who were not reclassified. Where sufficient number of

reclassified cases allowed, pairwise Kaplan-Meier log-rank test was used to compare survival for upstaged and downstaged subsets. Because the full dataset includes pathologically Stage 0 patients with high grade dysplasia as well as pathologically Stage 0 patients who have complete response to neoadjuvant therapy, with no residual invasive cancer in the esophagectomy specimen, comparisons using the full dataset excluded Stage 0 patients.

Homogeneity, discriminatory ability and monotonicity were calculated as per criteria to evaluate the performance of each staging system, described by Ueno and colleagues (10, 11). Monotonicity and strength of survival trends, by stage, were assessed with the log-rank test of trend chi-squared statistic. In order to facilitate statistical comparison of these test of trend statistics, a permutation test was carried out on the difference between chi-squared statistics for the two staging systems, in a method similar to that described by Kassis and colleagues.(12)

In addition to these test of trend comparisons, overall survival models were compared using the Cox regression likelihood ratio chi-squared statistic. Akaike Information Criterion (AIC) was used to assess model fit. A smaller AIC value indicates better model fit. Discriminatory power was assessed with concordance index (Harrell's c-index),(13) and prediction error was assessed with the integrated Brier score (IBS); both of these metrics were calculated by R software package "pec".(14) Lower IBS values indicate better prediction.

Results

Patients were predominantly Caucasian males in their 6th decade, with a slightly younger age, and fewer comorbidities (including smoking and obesity) present in patients receiving neoadjuvant therapy. (Table 1) Tumor characteristics in patients receiving neoadjuvant therapy showed a trend toward slightly larger tumor size, with a higher proportion of poorly differentiated tumors. These patients were more likely to receive adjuvant therapy compared to primary esophagectomy patients. Median overall survival after esophagectomy was 25.7 months (IQR 10.1–48.8). For patients managed with primary esophagectomy, median survival was 29.8 months (IQR 11.8–56.6) compared to 18.6 months (IQR 8.2–36.1 months) after neoadjuvant therapy followed by esophagectomy. Median survival for each stage, stratified by AJCC 6th- and 7th-edition staging system, is shown in Figure 1.

In the overall cohort, AJCC 7th-edition restaged 165 patients (19.7%) compared to AJCC 6th-edition stage assignment, as shown in Table 2. AJCC 7th-edition stage assignment upstaged 107 (12.8%) patients and down-staged 49 (5.9%). The most common reason for upstaging was the shift of 77 T3, node-negative patients from Stage 2a in AJCC 6th- to Stage 2b in AJCC 7th-edition. For the 77 cases who were upstaged to AJCC 7th-edition Stage 2b, median survival was 31.9 months (95% CI 25.4–38.3). When we compared these cases to the 2b cases who were stage-concordant in the AJCC 6th- and 7th-editions, there was a trend toward worse survival in the reclassified AJCC 7th-edition 2b cases (p=0.09). Another 29 patients shifted from IIb to IIIa based on N2 designation (3–5 positive lymph nodes). When we examined their survival, there were no differences in survival between upstaged AJCC-7th IIIa and stage-concordant AJCC-7th IIIa cases (log-rank p=0.989). The

most frequent down-staging was from IIa to Ib, including 32 patients with T2 depth of invasion who were downgraded to Stage Ib because tumor grade was well- to moderately-differentiated. Survival in cases were down-staging from AJCC 6th- to AJCC 7th-edition was observed was also analyzed. Median survival for stage-concordant Ib cases was not reached, with worse survival in the down-staged Ib cases (median 38.9; 95% CI 33.1-44.7) compared to the stage-concordant Ib cases ($p=0.048$). A total of 17 patients with celiac-positive lymph nodes were down-staged from stage IVa because celiac nodes are considered part of the regional lymphadenectomy in AJCC 7th-edition rather than representing metastatic disease as they did in AJCC 6th-edition staging. Because of the small numbers of stage-discordant cases upstaged to IIIc and down-staged from AJCC 6th-edition Stage IVa ($n=10$), analysis of these cases is not shown.

Comparison of the prognostic value of AJCC-6th and AJCC-7th in the overall cohort

All numeric values below compare AJCC 6th- vs. AJCC 7th-edition, respectively. A greater log-rank test of trend statistic indicated stronger survival trends by stage in AJCC 7th-edition (152.872 vs. 167.623). Using permutation testing, this difference in survival trend statistics was significant ($p<0.001$). The AJCC 7th-edition model also had superior model fit for the assigned stages and survival compared to AJCC 6th-edition as indicated by a greater Cox regression likelihood chi squared value (162.957 vs. 173.951), and lower AIC value (4831.011 vs 4820.02). Harrell's concordance index (0.655 vs. 0.677) demonstrated greater discriminatory power, and the integrated Brier scores (0.174 vs. 0.172) showed slightly lower prediction error, in the AJCC 7th-edition.

Comparison of the prognostic value of AJCC 6th- and AJCC 7th-edition after neoadjuvant therapy

Having established the superior performance of the AJCC 7th-edition staging system over AJCC 6th-edition in the overall cohort, we then sought to determine whether this holds true within the subset of patients who received neoadjuvant therapy. For this subset analysis, patients with pathologic stage 0, i.e. no residual tumor in the esophagus, resected lymph nodes or distant metastasis, were included to determine whether the staging system correctly stratifies survival after neoadjuvant therapy across the full range of possible responses to treatment.

As above, all numeric values below compare AJCC 6th- vs. AJCC 7th-edition, respectively. Similar to the overall cohort, AJCC 7th-edition staging showed stronger survival trends across stages compared to AJCC 6th-edition as indicated by a greater log-rank test of trend statistic (25.237 vs. 32.994, permutation test $p=0.008$), greater Cox regression likelihood chi-squared values (27.841 vs. 38.901), and lower AIC values (1629.225 vs. 1618.164). Finally, AJCC 7th-edition continued to show greater discriminatory power (Harrell's concordance index 0.606 vs. 0.628), and lower prediction error (integrated Brier scores 0.182 vs. 0.176), compared to AJCC-6th, even after neoadjuvant therapy. The ideal set of survival curves show successive survival curves that consistently decrease at least as much or more over time as the preceding survival curve; in this scenario, there is a separation of curves as time progresses from time 0 without subsequent overlap or crossing. While analysis shows that monotonicity is better for AJCC 7th- compared to AJCC 6th-edition,

examination of survival curves for both the primary surgery cohort and for the neoadjuvant cohort suggest that in smaller series of patients (compared to the expansive dataset used by the Worldwide Esophageal Cancer Collaboration), monotonicity is far from ideal. For example, as shown in Figure 1, median survival for the overall cohort for Stage 1b and Stage 2a is 58.3 and 58.8 months, respectively, while median survival for 3b and 3c is 14.22 and 14.13 months respectively. Even when considering the cohort undergoing primary surgery separately from the neoadjuvant therapy group, the median survival curves for overall survival in Stage 3b and 3c patients have minimal separation in the primary surgery cohort while there is overlap for Stage 0 (complete pathologic response) and Stage 2a as well as Stages 2b and 3a. (Figure 2 and Figure 3, respectively)

Discussion

In this study, we have examined the application and strengths of the 7th-edition AJCC staging system for esophageal adenocarcinoma in a large cohort of patients who underwent minimally invasive esophagectomy, with a separate analysis in patients who underwent neoadjuvant therapy. We observed stronger monotone trend and greater discriminatory power with AJCC 7th-edition; this superior performance was observed in the overall cohort and in the subset of patients who underwent minimally invasive esophagectomy after neoadjuvant therapy. Using permutation analysis, we have shown that the differences between the two staging systems are statistically significant, indicating that AJCC 7th-edition provides better prognostication information compared to AJCC 6th-edition. These findings support the use of AJCC 7th-edition staging system over the use of the AJCC 6th-edition system for esophageal adenocarcinoma. By improving the assignment of patients within survival stages, appropriate treatment decisions, such as recommendations for esophagectomy in higher risk early-stage cases and neoadjuvant and/or adjuvant therapy, will be facilitated and patients will be better informed about their overall prognosis.

The inclusion of tumor grade, location and histology in the AJCC 7th-edition TNM staging system represents a major departure from previous versions, which relied entirely on tumor depth, a binary node status, and presence of distant metastasis (which included celiac node disease). Based on survival data from the pathologic specimens of more than 4000 esophageal cancer cases treated with surgery alone, the inclusion of these additional variables clearly improved stage stratification over AJCC 6th-edition in our analysis. One of the major changes in the new staging system is to incorporate the number of lymph nodes with metastatic disease given the well-documented importance of nodal status, including number of nodes removed and the number of nodes positive.(15–18) We utilize a minimally invasive approach in our center; this approach, which is similar to Rizk and colleagues,(19) includes an perigastric and periesophageal lymphadenectomy. Since our median lymph node dissection exceeds the minimum recommended number, thus maximizing identification of all positive nodes,(18, 20, 21) this change in node classification may explain the improved differentiation of stages seen in our study with AJCC 7th-edition.

In addition to stratifying lymph node status by number of positive nodes, another major change was the reassignment of celiac lymph nodes from metastatic disease to regional nodal disease. AJCC 7th-edition no longer considers involvement of celiac lymph node as an

evidence of metastatic disease. This is because of data (22) (23) showing that patients classified to have metastatic disease based on celiac lymph node involvement have survival which is comparable to patients with regional lymph nodes metastasis. In our study, the number of patients down-staged in AJCC 7th-compared to AJCC 6th-edition for this reason was too small to make any meaningful comparisons.

While AJCC has introduced many positive changes that appear to have improved prognostication accuracy for patients with esophagogastric adenocarcinoma, it was derived entirely from pathological data from esophageal cancer patients who underwent primary surgical resection alone.(4). Therefore, the generalizability of the new classification for patients who also received neoadjuvant therapy, which has the potential to drastically alter the final pathologic stage compared to the pretreatment clinical stage through the intended reduction and/or elimination of viable tumor, required further validation. Nearly one-third of our patients received neoadjuvant therapy, allowing sufficient numbers to perform a stratified analysis comparing the two staging systems in the subset of patients who received neoadjuvant therapy. Similar to the overall cohort, we found that AJCC 7th-edition performed better than AJCC 6th-edition in patients who received induction therapy. Gaur and colleagues also came to the same conclusion in their study; they also found the new staging system to be superior to AJCC 6th-edition in predicting survival in esophagogastric adenocarcinoma patients who underwent surgery with or without induction therapy.(24) In their cohort, all patients had adenocarcinoma and 61% of patients received neoadjuvant therapy. In contrast to our study, they analyzed data in the overall cohort and in the surgery alone cohorts. Taken together with our findings, these data show that AJCC 7th-edition provides better prognostic information for patients who receive induction therapy before definitive surgery than does AJCC 6th-edition esophageal cancer staging system.

We recognize that our study has several limitations, some of which are inherent to retrospective studies, including completeness of data and inability to account for unmeasured factors with potential to introduce bias. These limitations were minimized by extensive chart review using consistent data definitions and utilizing a second abstractor for data verification. Potential strengths of our study include homogenous histology (adenocarcinoma only), a consistent operative approach (minimally invasive esophagectomy) and a single surgeon (JDL) performing the majority of surgeries, thereby reducing the bias of approach to esophagectomy and surgeon experience. However these strengths may be considered as potential weaknesses as they may impact the generalizability of our study results.

The AJCC 7th-edition esophageal cancer staging system appears to be the first step towards a data-driven staging system for esophageal cancer with inclusion of non-anatomic variables like histology and tumor grade. However, there are clearly deficits in the current system, as evidenced by our finding that patients who were upstaged to IIb have a trend toward worse survival compared to the other patients in the higher stage to which they were assigned. Similarly, we found that survival was worse in the down-staged Ib cases compared to those whose stage remained Ib from the 6th-edition to the 7th-edition. We also found that monotonicity, though significantly better for AJCC 7th-edition, was not present for several of the stages in both primary surgery patients and in patients who received neoadjuvant

therapy. These findings highlight the limitations in our current understanding of the factors influencing survival from esophageal adenocarcinoma, particularly in the intermediate stage groups and, despite better risk stratification with AJCC 7th-edition, there are likely other factors contributing to overall survival that are not yet measured.(25) Lymphovascular invasion (LVI),(26, 27) and tumor budding(28) in esophageal carcinoma have been shown to be independent prognostic factors and may warrant consideration for inclusion in future staging algorithms. Similarly, factors which take tumor biology into account can also prove invaluable in prognosticating survival. For example, gene-expression profiles and copy number,(29–31) mucin core proteins,(32) angiogenic and growth factor levels (33), inhibitors of apoptosis,(34) tumor cell expression of erythropoietin-receptor (EPO-R),(35) preoperative plasma fibrinogen and serum albumin level (FA score),(36) and cell signaling pathways(37) have all been shown to predict prognosis in esophageal cancer, and may serve as potential biomarkers in future editions of staging system.

Conclusions

In conclusion, we found that AJCC 7th-edition esophageal cancer staging system improves prognostic stratification of surgically resected esophagogastric adenocarcinoma patients, including patients who received neoadjuvant therapy, when compared with the 6th-edition. To improve upon the current system, future editions will likely expand beyond pathologic variables to include tumor-specific biomarkers.

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Figure 1. Stage Specific Median Survival by AJCC 6th-versus 7th-edition staging system
 Median survival for AJCC-6th edition Stage 1 and AJCC-7th-edition Stage 1b has not been reached and is, therefore, not included. Stage 0 is not included in the analysis for the overall cohort due to inclusion of both high-grade dysplasia only patients undergoing surgical resection and patients with complete pathologic response after neoadjuvant therapy for locoregionally advance disease.

Number at risk

Stage 0	81	(8)	60	(2)	49	(2)	32
Stage 1a	140	(20)	103	(8)	72	(5)	47
Stage 1b	62	(11)	49	(6)	33	(7)	21
Stage 2a	18	(2)	14	(4)	9	(3)	2
Stage 2b	80	(17)	54	(14)	29	(3)	15
Stage 3a	65	(18)	44	(22)	16	(4)	7
Stage 3b	62	(40)	21	(11)	9	(3)	4
Stage 3c	67	(36)	27	(16)	10	(4)	4
Stage 4	3	(3)	1	(0)	0	(0)	0

Figure 2.

Kaplan-Meier survival curves stratified by AJCC 7th-edition staging assignment for esophageal adenocarcinoma treated with primary esophagectomy

Figure 3.

Figure 2. Kaplan-Meier survival curves stratified by AJCC 7th-edition staging assignment for esophageal adenocarcinoma treated with neoadjuvant therapy followed by esophagectomy

Table 1

Patient demographics and characteristics for all patients and stratified by primary surgery versus neoadjuvant therapy followed by esophagectomy

Characteristics	Overall Cohort	Treatment Modality		p-value
		Primary Surgery	Neoadjuvant Therapy	
	n=836	n=580	n=256	
Age at operation [median, IQR]	65 [57–73]	66 [59–74]	63 [54–70]	<0.001
Male Sex	707/836 (85)	484/580 (83)	223/256 (87)	0.177
Caucasian Race	816/836 (98)	566 (98)	250 (98)	0.951
History of Smoking	627/836 (75)	423/578 (73)	204/256 (80)	0.045
Age-adjusted Charlson Comorbidity Index	2 [1, 4]	3 [0–5]	1.5 [0–4]	<0.001
Body Mass Index	28.4 [25.2, 32.6]	28.8 [25.9–32.9]	27.2 [23.9–31.2]	<0.001
Pathologic Findings				
Positive Margin Status	15/833 (2)	12/577 (2)	3/256 (1)	0.573
Number of Lymph Nodes Examined	21 [15, 29]	22 [15–30]	20 [15–27]	0.096
Tumor Size	3.5 [2.0, 5.3]	3.4 [1.9–5]	4.0 [2–5.5]	0.059
Tumor Differentiation				0.003
Well	50/687 (7)	46/490 (9)	4/197 (2)	
Moderately	295/687 (43)	210/490 (43)	85/197 (43)	
Poorly	342/687 (50)	234/490 (48)	108/197 (55)	
Tumor Location				0.365
Upper or Mid Esophagus	9/789 (1)	8/533 (2)	1/256 (0.4)	
Lower Esophagus	269/789 (34)	179/533 (34)	90/256 (35)	
GEJ/Cardia	510/789 (65)	346/533 (65)	164/256 (64)	
Use of adjuvant therapy	238/619 (38)	135 (35)	103 (45)	0.013

Table 2

Distribution of pathologic stage in esophageal adenocarcinoma patients as determined by AJCC-6th and AJCC-7th editions

AJCC-6th th Edition Staging	AJCC-7th th Edition Staging										Total
	Stage 0	Stage IA	Stage IB	Stage IIA	Stage IIB	Stage IIIA	Stage IIIB	Stage IIIC	Stage IV		
Stage 0 ^a	115									115	
Stage I		155	46							201	
Stage IIA			32	28	77					137	
Stage IIB					58	29		1		97	
Stage III						81	89	86		256	
Stage IVa					1	3	3	10	13	30	
Total	115	155	78	28	136	113	92	106	13	836	

^a Stage 0 indicates Barrett's esophagus with high-grade dysplasia only for the primary surgery cohort. In the neoadjuvant therapy cohort, stage 0 represents complete pathologic response with no residual invasive tumor following induction therapy in the resected esophagus or the resected lymph nodes.

(Gray boxes indicate consistency in stage grouping between the AJCC-6th and 7th editions. The remaining cases were either upstaged or down-staged.)