Original Article

Cancer of the Esophagus and Esophagogastric Junction

Data-Driven Staging for the Seventh Edition of the American Joint Committee on Cancer/ International Union Against Cancer Cancer Staging Manuals

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BACKGROUND: Previous American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) stage groupings for esophageal cancer have not been data driven or harmonized with stomach cancer. At the request of the AJCC, worldwide data from 3 continents were assembled to develop data-driven, harmonized esophageal staging for the seventh edition of the AJCC/UICC cancer staging manuals. **METHODS:** All-cause mortality among 4627 patients with esophageal and esophagogastric junction cancer who underwent surgery alone (no preoperative or postoperative adjuvant therapy) was analyzed by using novel random forest methodology to produce stage groups for which survival was monotonically decreasing, distinctive, and homogeneous. **RESULTS:** For lymph node-negative pN0M0 cancers, risk-adjusted 5-year survival was dominated by pathologic tumor classification (pT) but was modulated by histopathologic cell type, histologic grade, and location. For lymph node-positive, pN+M0 cancers, the number of cancer-positive lymph nodes (a new pN classification) dominated survival. Resulting stage groupings departed from a simple, logical arrangement of TNM. Stage groupings for stage I and II adenocarcinoma were based on pT, pN, and histologic grade; and groupings for squamous cell carcinoma were based on pT, pN, histologic grade, and location. Stage III was similar for histopathologic cell types and was based only on pT and pN. Stage 0 and stage IV, by definition, were categorized as tumor in situ (Tis) (high-grade dysplasia) and pM1, respectively. **CONCLUSIONS:** The prognosis for patients with esophageal and esophagogastric junction cancer depends on the complex interplay of TNM classifications as well as nonanatomic factors, including histopathologic cell type, histologic grade, and cancer location. These features were incorporated into a data-driven staging of these cancers for the seventh edition of the AJCC/UICC cancer staging manuals. ***Cancer*** **2010;116:3763–73.** *© 2010 American Cancer Society.*

KEYWORDS: TNM, histopathologic cell type, histologic grade, random forests analysis, cancer location, survival.

For esophageal cancer, previous editions of the American Joint Committee on Cancer and International Union Against Cancer (AJCC/UICC) cancer staging manuals were neither data driven nor harmonized with stomach cancer.[1,2] Stage groupings were based on a simple, orderly arrangement of increasing anatomic tumor (T), then lymph node (N), then metastatic (M) classifications. Although these nondata-driven stage groupings have been useful prognostically, they did not take into account the growing body of literature concerning factors associated with survival, including both anatomic and nonanatomic cancer characteristics. Among these are the interplay of T and N classifications[3]; the prognostic importance of the number of cancer-positive lymph nodes[3-5]; histopathologic cell type[6]; histologic grade[7]; cancer location, including at the esophagogastric junction[8,9]; and differences in cancer characteristics between East and West.[10]

Therefore, the AJCC Lung and Esophageal Task Force spearheaded an initiative to develop a data-driven, revised cancer staging system for the seventh edition of the *AJCC Cancer Staging Manual*. In response, the Worldwide Esophageal Cancer Collaboration (WECC) was formed and assembled worldwide data on esophageal and esophagogastric junction

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cancers.[11] This article presents the data, novel analytic methods, and resulting data-driven stage groupings for cancers of the esophagus and esophagogastric junction for the seventh edition of the AJCC/UICC cancer staging manuals.[12]

MATERIALS AND METHODS

Patients

Data-driven staging was based on data from 13 institutions on 3 continents. At these institutions, 4627 patients underwent surgery alone for adenocarcinoma, squamous cell carcinoma, or undifferentiated cancer of the esophagus or esophagogastric junction—hereafter termed *esophageal cancer*—and had complete follow-up for all-cause mortality.[11] Characteristics of these patients and their cancers are presented in Table 1.[11]

Deidentified data were approved for use in research by each site's institutional review board, and data use agreements were executed when required. The entire project was approved by the Case Cancer Institutional Review Board of Case Western Reserve University.

Endpoint

All-cause, time-related mortality, including operative mortality, was the endpoint for the current analysis. Median follow-up was 2.1 years, and 5% of patients were traced beyond 10 years. This seemingly short follow-up was because of the lethality of esophageal cancer.

Variables Available for Analysis

This analysis focuses on anatomic pathologic TNM classifications and nonanatomic prognostic factors, including cancer location (Table 2), length, histopathologic type (Table 2), histologic grade (Table 2), number of regional lymph nodes resected, number of regional cancer-positive lymph nodes, and resection margin. All factors were reviewed for consistency among institutions. In addition, the analysis took into account institution, country, hemisphere, year of operation, patient age, sex, and race. In this report, pN+ indicates regional lymph node metastases, regardless of the number (pN1 in previous AJCC/UICC classifications).

Strategy for Cancer Stage Grouping

The goal of cancer staging is to group cancer characteristics such that they reflect decreasing patient survival with increasing stage group (monotonicity), difference in survival between groups (distinctiveness), and similar survival within a group (homogeneity). In addition, by convention, stage 0 is tumor in situ (Tis)N0M0 (high-grade dysplasia), and stage IV is M1 (distant metastatic disease). This makes only stages I, II, and III available for stage grouping. Ideally, cancer stage groupings should be equally spaced in survival.

Data Analysis

An in-depth description of the generalizable methodology developed for cancer staging and applied to esophageal cancer has been presented in the statistical literature.[13] The analytic technique extends familiar recursive partitioning that results in a single survival tree, which is unstable.[14] Random forest techniques grow a forest of 1000 trees using random sampling (bootstrap) techniques, and the results of such a forest are averaged to obtain a stable result. An abbreviated summary of these details follows.

Risk-adjusted survival

Random survival forests (RSF) methodology[15,16] produced a survival curve for each patient that was risk-adjusted for all variables listed in Table 1 plus individual institution, country of institution, and hemisphere in the world, as follows[13]: A forest of 1000 random bootstrap survival trees was grown using log-rank splitting. On average, each tree was grown from 63% of the data (bootstrapped data); the remaining unused data (37%) are referred to as out-of-bag (OOB) data. Each tree and its corresponding OOB data were used to generate an OOB survival curve for each patient in the OOB dataset. Growing 1000 trees yielded approximately 370 OOB survival curves for each patient, and these curves were averaged to yield a risk-adjusted OOB ensemble survival curve for each patient. From these curves, risk-adjusted 5-year survival was extracted.

An OOB ensemble cumulative hazard function (cumulative hazard is minus the logarithm of survival) also was calculated for each patient. These were summed over observed survival times to yield the risk-adjusted, predicted mortality for each patient (OOB ensemble mortality).[15]

Template stage groups

Patients were then ordered by increasing OOB ensemble mortality and divided into 10 randomly spaced *template stage groups*. Risk-adjusted OOB ensemble survival curves for patients were averaged within each group. This procedure was repeated independently 1000 times, and group survival curves represent the average of these repetitions.

Table 1. Patient and Cancer Characteristics

Characteristic	n[a]	No. of Patients (% of n)
Demographics		
Age: Mean ± SD, y	4625	62 ± 11
Men	4626	3562 (77)
Race	3587	
Caucasian		2339 (65)
Asian		1168 (33)
Other		80 (2.2)
Continent	4627	
North America		2295 (50)
Europe		1164 (25)
Asia		1168 (25)
Cancer characteristics		
Cancer location	4344	
Upper one-third		177 (4.1)
Middle one-third		1172 (27)
Lower one-third		2,995 (69)
Cancer length: Mean ± SD, cm	2229	3.3 ± 2.5
Pathologic tumor classification	4609	
pTis		335 (7.3)
pT1[b]		1040 (23)
pT2		755 (16)
pT3		2329 (51)
pT4		150 (3.3)
Pathologic lymph node status	4616	
pN0		2584 (56)
pN1[c]		2032 (44)
No. of regional lymph nodes positive for cancer	4507	
0	2584	(57)
1	547	(12)
2	353	(8)
3	218	(5)
4	165	(4)
5	117	(3)
≥6	523	(12)
No. of lymph nodes resected	3921	
0	42	(1.1)
1-5	986	(25)
6-10	740	(19)
11-15	558	(14)
16-20	444	(11)
21-25	337	(8.6)
26-30	219	(5.6)
31-35	152	(3.9)
36-40	112	(2.9)
≥41	331	(8.4)
Pathologic metastasis classification	4564	
pM0		4208 (92)
pM1[d]		356 (7.8)
Histopathologic cell type	4595[e]	
Adenocarcinoma		2775 (60)
Squamous		1834 (40)
Undifferentiated		7 (0.15)
Histologic grade	3816	
G1		1228 (32)
G2		1257 (33)
G3		1324 (35)
G4		7 (0.18)

(Continued)

Table 1. (Continued)

Characteristic	n[a]	No. of Patients (% of n)
Resection margin status	4123	
R0		3572 (87)
R1		434 (11)
R2		117 (3)
Era	4627	
1970s		36 (0.78)
1980s		1118 (24)
1990s		1846 (40)
2000s		1627 (35)

SD indicates standard deviation

[a] The number of patients who had values available.

[b] pT1a disease was present in 262 patients, and pT1b disease was present in 244 of 506 patients in whom this distinction was made.

[c] Terminology from 6th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) cancer staging manuals: pN1 indicates any number of positive regional lymph nodes, not including celiac lymph nodes.

[d] Terminology from 6th edition of the American Joint Committee on Cancer/International Union Against Cancer (AJCC/UICC) cancer staging manuals: M1a indicates metastasis to the supraclavicular or celiac lymph nodes, and M1b indicates distant metastases. pM1a disease was present in 104 patients, and pM1b disease was present in 122 of 226 patients in whom this distinction was made.

[e] In 21 patients, both cell types were present.

Construction of monotonic and distinctive proposed stage groups

To construct *proposed stage groups* from these template stage groups, we used random forest regression (RF-R).[17,18] This required 10 RF-R analyses, 1 for each template stage group. Each analysis generated a forest of 1000 random bootstrap regression trees. Standardized variable importance (VIMP) for each variable was calculated by measuring the increase in OOB mean-square error when a variable was removed from the regression.[17] Standardized VIMP represents the averaged stability of a variable within a template stage group. A standardized VIMP >5% was used to identify variables for stratifying cancers into distinctive stage groups with monotonically decreasing survival.

Homogeneity within stage groups

RF-R was then used to assess homogeneity of survival within proposed stage groups. OOB ensemble mortality was the response, and T classification, number of cancer-positive lymph nodes, location, and histologic grade were the regressors. One RF-R analysis was used for each stage group. Survival homogeneity (0% to 100%) was calculated by dividing the OOB error (mean-square error) by the variance of OOB mortality within each group. A value of 100% represents perfect homogeneity.

Final stage groupings

Proposed stage groupings were submitted to AJCC and UICC consensus panels that focused on harmonization with gastric cancers, particularly with respect to T3/T4 and N classifications and esophagogastric junction and cardia cancers; consistency with rules for defining stages 0 and IV; T classifications; separation by histopathologic cell type; review of nonanatomic cancer characteristics; and validation against existing databases not included in WECC data. Consensus was reached that pT4 cancers in this population were resectable (pT4a), and unresectable cancers that were not represented in the data were assigned to pT4b.

Finally, the resulting consensus stage groupings were submitted for harmonization with stomach cancer. Particular attention was given to cancers of the esophagogastric junction and cardia and to T3/T4 and N classifications.

Risk-adjusted survival curves for the resulting final stage groups were calculated by averaging OOB ensemble patient survival curves stratified by stage. Because stage groups that involved pN0 cancers were different for adenocarcinoma and squamous cell cancers, averaging was stratified by histopathologic cell type for these groups.

RESULTS

Template Stage Groups

The 10 template stage groups demonstrated successively decreasing survival (monotonicity) at nearly all times, with nonoverlapping standard errors after about 2 years

Table 2. Definitions of Anatomic and Nonanatomic Cancer Characteristics

Anatomic classification

Location

International Classification of Diseases for Oncology coding recognizes 3 anatomic compartments traversed by the esophagus: cervical, thoracic, and abdominal. It also arbitrarily divides the esophagus into equal thirds: upper, middle, and lower. However, the clinical importance of the primary site of esophageal cancer is related less to its position in the esophagus than to its relation to adjacent structures.

Cervical esophagus

Anatomically, the cervical esophagus lies in the neck and is bordered superiorly by the hypopharynx and inferiorly by the thoracic inlet, which lies at the level of the sternal notch. Typical endoscopic length measured from the incisors is 15 cm to <20 cm.

Upper thoracic esophagus

The upper thoracic esophagus is bordered superiorly by the thoracic inlet and inferiorly by the lower border of the azygos vein. Typical endoscopic length from the incisors is 20 cm to <25 cm.

Middle thoracic esophagus

The middle thoracic esophagus is bordered superiorly by the lower border of the azygos vein and inferiorly by the inferior pulmonary veins. Typical endoscopic length from the incisors is 25 cm to <30 cm.

Lower thoracic esophagus/esophagogastric junction (EGJ)

The lower thoracic esophagus is bordered superiorly by the inferior pulmonary veins and inferiorly by the stomach. Because it is the end of the esophagus, it includes the EGJ. Cancers with an epicenter in the lower thoracic esophagus or EGJ or located within the proximal 5 cm of the stomach (cardia) that extend into the EGJ or esophagus (Siewert III) were stage grouped similar to adenocarcinoma of the esophagus. Typical endoscopic length from the incisors is 30 cm to 45 cm.

Nonanatomic classification

Histopathologic type

Squamous cell carcinoma

Adenocarcinoma

Undifferentiated

Histologic grade (G)

GX: Grade cannot be assessed—stage grouping as G1

G1: Well differentiated

G2: Moderately differentiated

G3: Poorly differentiated

G4: Undifferentiated—stage grouping as G3 squamous

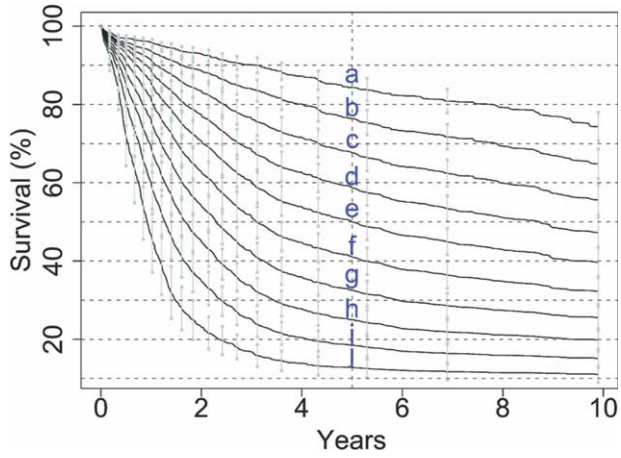

Figure 1. This chart illustrates the 10 monotonic and distinctive template stage groupings (lines a-j). The 10 template stage groups demonstrated successively decreasing survival (monotonicity) at nearly all times with nonoverlapping standard errors after about 2 years (distinctiveness). Vertical gray bars represent standard errors.

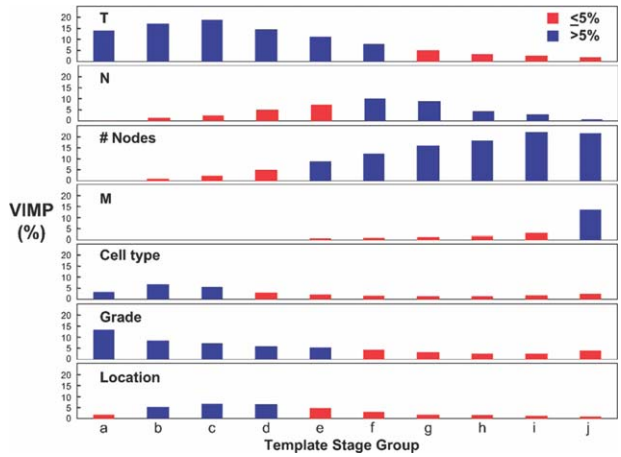

Figure 2. This chart illustrates the standardized variable importance (VIMP) of anatomic and nonanatomic cancer characteristics (tumor classification [T], 6th edition lymph node classification [N], metastatic classification [M], cell type, number of cancer-positive lymph nodes, histologic grade, and location) within each template stage grouping (a-j). Blue bars depict VIMP >5%, and red bars depict VIMP ≤5%.

(distinctiveness) (Fig. 1). This illustrates that survival after esophagectomy for cancer is both highly variable and spans the entire range from a very good prognosis to an exceedingly poor prognosis.

Monotonic and Distinctive Stage Groups

The impact of anatomic and nonanatomic cancer characteristics on predicted 5-year survival within each template stage group is depicted in Figure 2. pT is important in groups with best to intermediate survival (Figure 2, columns a-f), but not in those with poor survival. Conversely, pN is important in groups with intermediate to poor survival (Fig. 2, columns f-j). However, the number of cancer-positive lymph nodes is a better predictor and becomes dominant for groups with poor survival (Fig. 2, columns e-j). pM is important in the stage group with the poorest survival (Fig. 2, column j), confirming this stage grouping definition.

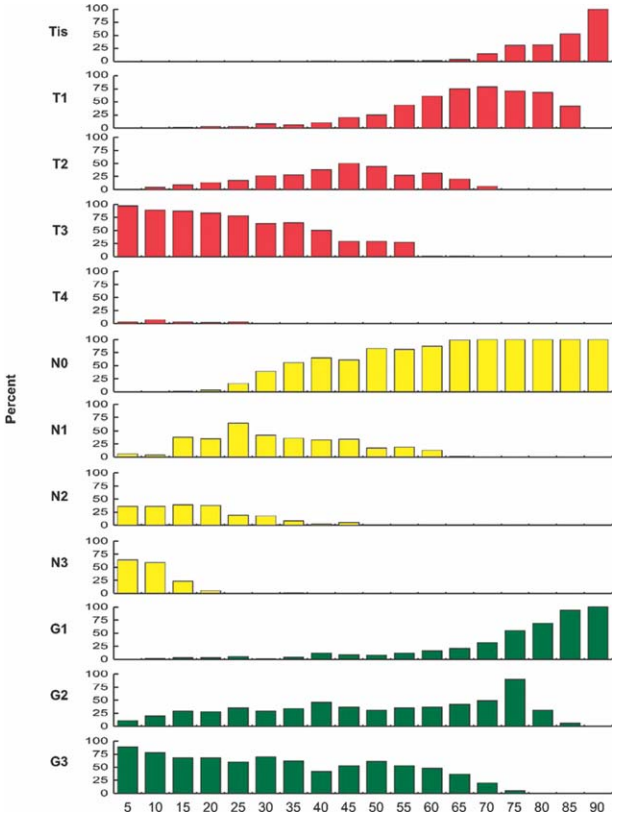

Figure 3. The percentages of patients with adenocarcinoma who have given cancer characteristics (tumor classification [T], 7th edition lymph node classification [N], and histologic grade [G]) are illustrated in 5% increments of risk-adjusted 5-year survival.

Table 3. Stage Groupings for the Seventh Edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals: Adenocarcinoma

Stage	T	N	M	G
0	Tis (HGD)	0	0	1
IA	1	0	0	1-2
IB	1	0	0	3
	2	0	0	1-2
IIA	2	0	0	3
IIB	3	0	0	Any
	1-2	1	0	Any
IIIA	1-2	2	0	Any
	3	1	0	Any
	4a	0	0	Any
IIIB	3	2	0	Any
IIIC	4a	1-2	0	Any
	4b	Any	0	Any
	Any	3	0	Any
IV	Any	Any	1	Any

T indicates tumor classification; N, lymph node status; M, metastasis; G, histologic grade; Tis, tumor in situ; HGD, high-grade dysplasia.

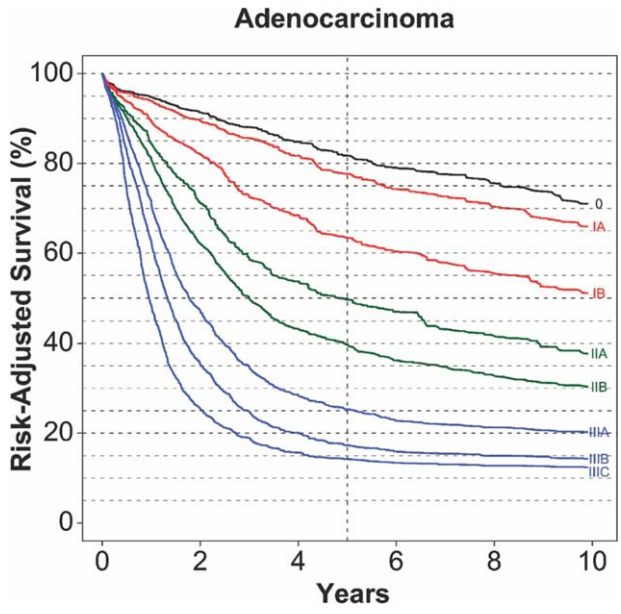

Figure 4. Risk-adjusted survival is illustrated for patients with adenocarcinoma according to stage groups for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer cancer staging manuals.

Histopathologic cell type is important in groups with the best survival (Fig. 2, columns a-c); patients with adenocarcinoma had better survival than patients with squamous cell carcinoma in these groups. Increasing histologic grade influenced survival similar to, but to a lesser degree than, pT (Fig. 2, columns a-e). Cancer location influenced survival in groups with good survival (Fig. 2, columns b-d). This suggested that, for pN0 cancers, pT, histopathologic cell type, histologic grade, and location should determine these early stage groupings, and the number of cancer-positive lymph nodes and distant metastasis should determine late-stage groups.

Figure 3 illustrates the impact and interplay of cancer characteristics on 5-year survival for adenocarcinoma (squamous cell carcinoma is not shown). Generally, survival is better for patients with early-stage adenocarcinoma than for patients with early-stage squamous cell carcinoma. Well-differentiated pN0M0 cancers predominate early-stage adenocarcinomas, but not squamous cell carcinomas. Generally, pT classification increases as survival decreases for both histopathologic cell types of pN0 cancers. For pN+ cancers, as the number of cancer-positive lymph nodes increases, survival decreases, but there is a dependence on pT. The pattern of survival with respect to pT of these pN+ cancers is similar between histopathologic cell types. The final stage groups that were constructed from the analysis and corresponding survival curves are shown in Table 3 and Figure 4 for

Table 4. Stage Groupings for the Seventh Edition of the American Joint Committee on Cancer/International Union Against Cancer Cancer Staging Manuals: Squamous Cell Carcinoma

Stage	T	N	M	G	Location
0	Tis (HGD)	0	0	1	Any
IA	1	0	0	1	Any
IB	1	0	0	2-3	Any
	2-3	0	0	1	Lower
IIA	2-3	0	0	1	Upper, middle
	2-3	0	0	2-3	Lower
IIB	2-3	0	0	2-3	Upper, middle
	1-2	1	0	Any	Any
IIIA	1-2	2	0	Any	Any
	3	1	0	Any	Any
	4a	0	0	Any	Any
IIIB	3	2	0	Any	Any
IIIC	4a	1-2	0	Any	Any
	4b	Any	0	Any	Any
	Any	3	0	Any	Any
IV	Any	Any	1	Any	Any

T indicates tumor classification; N, lymph node status; M, metastasis; G, histologic grade; Tis, tumor in situ; HGD, high-grade dysplasia.

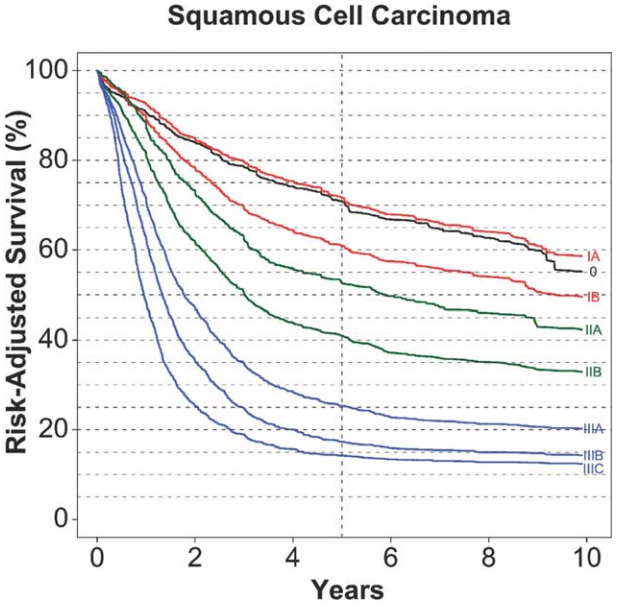

Figure 5. Risk-adjusted survival is illustrated for patients with squamous cell carcinoma according to stage groups for the seventh edition of the American Joint Committee on Cancer/International Union Against Cancer cancer staging manuals.

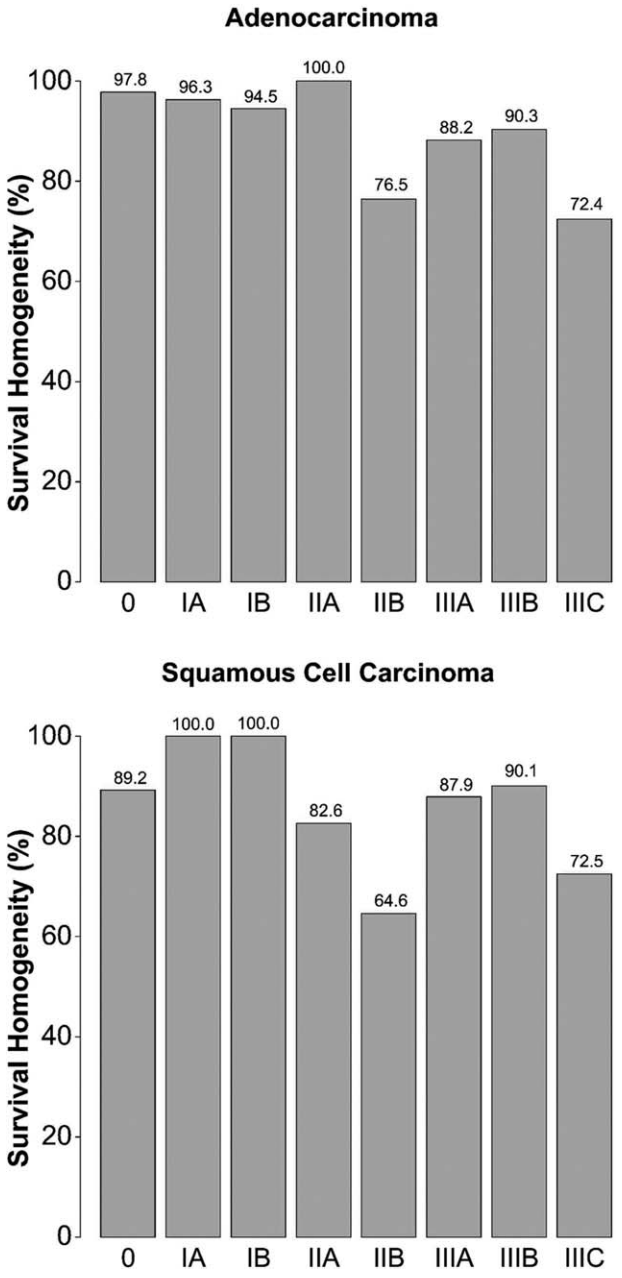

Figure 6. Risk-adjusted 5-year survival homogeneity is illustrated for (*Top*) adenocarcinoma stage groups and (*Bottom*) squamous cell carcinoma stage groups.

adenocarcinoma and in Table 4 and Figure 5 for squamous cell carcinoma.

Homogeneity Within Stage Groups

Within the proposed stage groups, homogeneity varied, in large part because of the necessity to restrict the extremes, thus limiting number of stage groups. Homogeneity was particularly good for early-stage cancers, worse for stage IIB and IIIC cancers, and good for stage IIIA and IIIB cancers (Fig. 6).

Figure 7 illustrates how achieving homogeneity within stage groups required taking the interplay among cancer characteristics into account. Survival was homogeneous when poorly differentiated pT1 adenocarcinomas were grouped with well and moderately differentiated

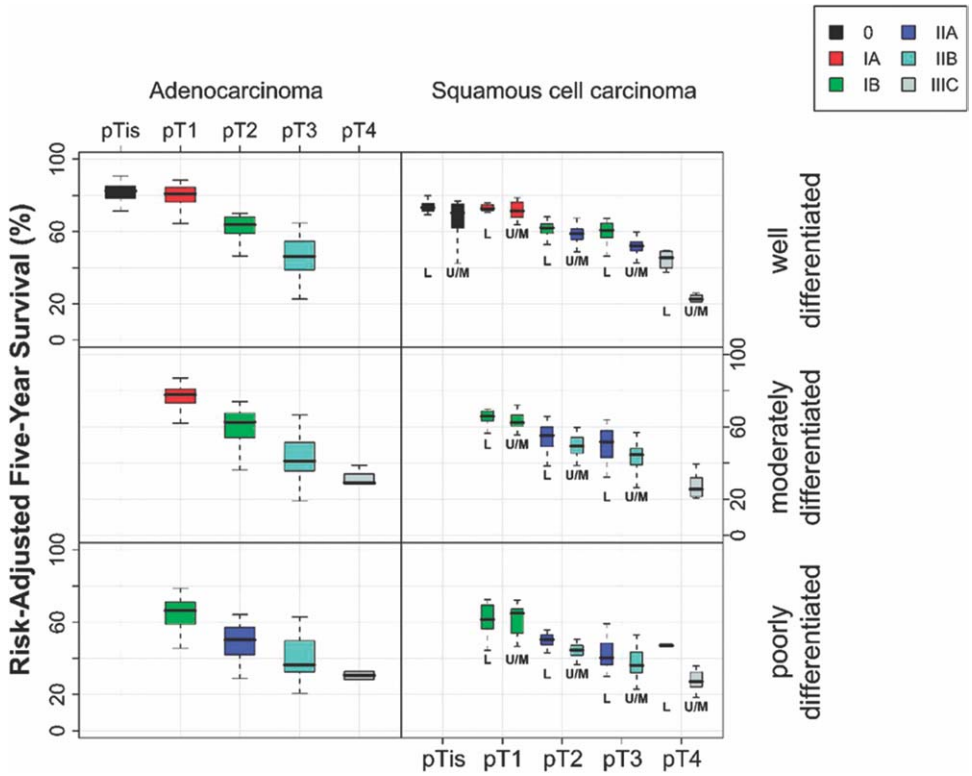

Figure 7. This is a box-and-whiskers coplot of risk-adjusted 5-year survival for patients with negative lymph node status and no metastases stratified according to histopathologic cell type, histologic grade, pathologic tumor (pT) classification, and cancer location. pTis indicates pathologic tumor in situ; L, lower; U/M, upper-middle. The boxes encompass 50% of values, the horizontal bar within each box indicates the median value, and whiskers extend to 1.5 times the interquartile range. Proposed stage groups are indicated by color (see key, top right).

pT2 adenocarcinomas. However, histologic grade did not play a role for pT3/pT4 adenocarcinomas. For squamous cell carcinoma, these patterns were more complex, because location also came into play.

Figure 8 demonstrates that 1 or 2 positive lymph nodes for pT1 or pT2 cancers placed patients into a homogeneous stage group with pT3N0M0 cancers. In contrast, stage group IIIC was somewhat heterogeneous in survival but was dominated by advanced T classification or large lymph node burden, and it included cancers for which there was a paucity of data, such as the unusual combination of pT1N3 or pT4 well-differentiated cancers.

DISCUSSION

Framework for Developing Esophageal Cancer Stage Groups

The framework within which cancer stage groupings are developed includes 1) *principles* of stage grouping according to monotonicity, distinctiveness, and homogeneity; 2) *definitions* of stages 0 and IV, with 3 remaining major stage groups; and 3) *extent* of cancers expressed by anatomic TNM classifications. The transition from template stage groups, to proposed stage groups, to final stage groups demonstrated that the framework makes developing monotonic, distinctive, and homogeneous groups challenging. This is because a small number of groups must encompass all invasive esophageal cancer that is not distantly metastatic, and this requires a coarse categorization of important prognostic variables, such as the number of positive lymph nodes.

In addition, and rightly so, the AJCC/UICC required that esophageal and gastric staging be harmonized. Consensus meetings and parallel analysis with the Digestive Cancer Task Force demonstrated that, compared with patients who had other gastric cancers, patients with adenocarcinoma of the esophagogastric junction and gastric cardia (Siewert II and III) had distinctively worse survival and were staged best as distal esophageal adenocarcinoma.

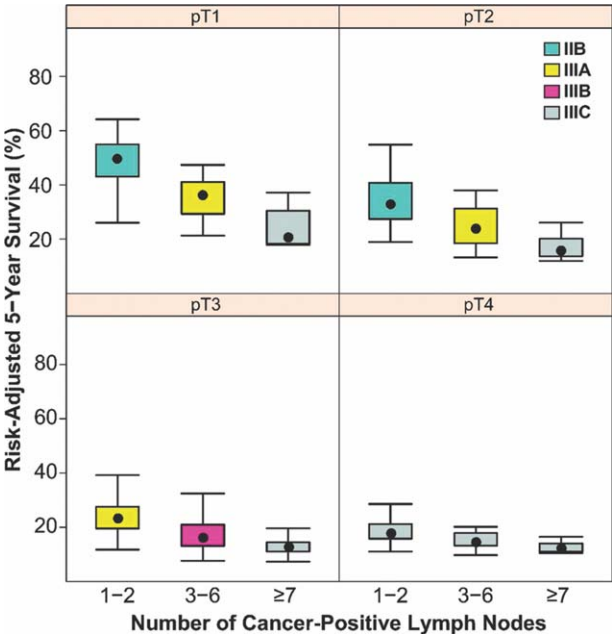

Figure 8. This is a box-and-whiskers coplot of risk-adjusted 5-year survival for patients with positive lymph node status; pathologic T1 (pT1), pT2, pT3, and pT4 tumors; stage IIB through IIIC cancer of the esophagus or the esophageal junction; and no metastases stratified according to the number of cancer-positive lymph nodes (1-2, 3-6, or ≥7). Boxes and whiskers are depicted as described for Figure 7.

Previously, the definition of a regional lymph node was ambiguous. The longitudinal nature of the intramural lymphatic plexus permits lymphatic metastases orthogonal to the depth of tumor invasion.[19] Implications of the longitudinal nature of lymphatic drainage are that the anatomic site of the cancer and the lymph nodes to which lymphatics drain from that site may not be the same. Although lymph nodes are observed along the course of the esophagus, they generally are concentrated. The major hubs occur at the pulmonary hilum and the distal esophagus, esophagogastric junction, and cardia. Therefore, regional lymph nodes were defined as periesophageal lymph nodes extending from the cervical nodes to the celiac nodes.

In the past, esophageal cancer stage grouping was based only on TNM. However, the current analysis demonstrated the importance of and need for considering nonanatomic cancer classifications as well. This resulted in separate groupings for adenocarcinoma and squamous cell carcinoma (these groups differ only in stages I and II), incorporation of the histologic grade for stage I and IIA adenocarcinomas, and histologic grade and location for stage I and II squamous cell cancers.

The Analysis

Unlike previous approaches to stage grouping, the current analysis first isolated cancer characteristics of interest from other factors that influenced survival, such as patient age, by generating risk-adjusted survival curves for each patient. Also, previous approaches began by placing cancer characteristics into proposed groups; we first grouped patients into distinctive template stage groups using monotonically decreasing, risk-adjusted survival without regard to cancer characteristics. Then, anatomic and nonanatomic cancer characteristics that were important for template stage group composition were identified. Finally, because of requirements to have a small number of simply describable groups, the homogeneity principle guided both amalgamation and segmentation of cancer characteristics between adjacent template groups to arrive at the proposed stage groups.

Previous proposed revisions of esophageal cancer staging have examined goodness of fit or *P* values to test for a statistically significant effect; in the current analysis, we focused instead on predictiveness for future patients. This was done using machine learning analytic techniques that made no a priori assumptions about patient survival, as do model-based analyses, which may assume proportional hazards, a particular formulation of a risk factor model, and a specific form for interaction terms. An important limitation of model-based analysis is the discovery of complex interactions (interplay) among cancer characteristics and nonlinear behavior. RSF methodology is able to identify these interactions between variables and nonlinear effects.

Principal Findings

Stage 0 and stage IV were not data driven but were restricted by definition, as noted previously. In results that are not included in this report, this resulted in survival equivalence of stage 0 and IA well-differentiated pT1a (intramucosal) cancers. Similarly, there was equivalence between stage IV cancers and some advanced cancers that had ≥10 positive lymph nodes. In the absence of positive lymph nodes, only histologic grade was necessary for the subclassification of pT1 and pT2 adenocarcinoma (stages IA, IB, and IIA) and pT1 squamous cell cancers (stages IA and IB). For pT2 and pT3 squamous cell carcinomas (part of stage IB, stage IIA, and part of stage IIB), both histologic grade and cancer location were necessary.

The dominant classification that affected the remaining stage groups was the number of positive lymph nodes. Although each additional positive lymph node was

associated with decreased survival, classification of the number of positive lymph nodes that was suggested by the analysis and that was harmonious with gastric regional lymph node classifications was chosen. This large database also demonstrated the previously unappreciated interplay of T and N+ that is the basis for much of the subclassification of stages IIB and III. No need was established to exclude celiac lymph nodes from the lymph node count; therefore, celiac lymph nodes were considered regional lymph nodes. The purported survival difference between East and West was not observed after histopathologic cell type, histologic grade, and cancer location were considered in the analysis.

Translation to Clinical Staging

Unlike lung cancer, for which clinically staged advanced cancer data were available, similar data for esophageal cancer were not. Therefore, staging was based on the pathologic classification of surgically resected cancers. Nevertheless, these classifications can be determined clinically, although with inaccuracies inherent in the clinical staging of all cancers. Endoscopy with biopsy yields accurate cancer location, histologic cell type, and histologic grade. Endoscopic ultrasound (EUS) permits determination of T classification with variable accuracy, particularly for T2 cancers.[20-23] EUS and fluorodeoxyglucose-positron emission tomography predict N status and the number of lymph nodes, but this requires that endoscopic ultrasonographers and nuclear radiologists be informed that they must count clinically positive lymph nodes.[24-26]

Limitations

This staging system is based on esophageal cancer treated by surgery alone. Therefore, it does not represent the natural history of the disease (information that cannot be obtained). However, by restricting the dataset in this way, the data are not confounded with preoperative or postoperative chemoradiotherapy, which may alter survival.

Data used for this staging system also were strictly limited to pathologic classification.[2] These data were considered less subject to institutional and technologic variation than clinical staging. Because this is a surgical series, certain cancers, such as pT4 and pM1, are under represented or are not represented (surgical selection). Consensus was used to fill in these few gaps at the extreme of poor survival.

The staging system methodology used is self-validating. Nevertheless, validation against data external to those used for developing the system is important. Not shown are data informally supporting the staging system by the National Comprehensive Cancer Network during AJCC and UICC acceptance testing.

Each institution had its own template for data collection and for intensity and completeness of patient follow-up, and not all institutions provided the same data fields. Although no site visits could be conducted to verify data, 2 factors give us confidence in the data. First, all countries require at least semimandatory reporting of cancer cases. Second, extensive data checks were made for reasonableness, and this initiated data validation activities for all centers. Because deidentified data were provided, goodness of follow-up could not be determined. Consistent with past stage grouping, this proposal used cancer classifications based on pathology. Finally, all-cause mortality was used as the endpoint, like all analyses for the AJCC Lung and Esophagus Task Force.[27] Because mortality was constant from the time of operation to 18 months,[11] perioperative mortality (2% within 30 days) was not arbitrarily eliminated. Cancer-specific mortality was not used in this analysis, because distinguishing between cancer-related and noncancer-related deaths is unreliable outside the confines of prospective clinical trials. Nevertheless, all-cause mortality is confounded by true noncancer-related deaths. Therefore, risk adjustment was used to compensate for this effect.

In conclusion, data-driven staging of esophageal and esophagogastric junction cancers using worldwide data and random forest analysis has allowed the construction of stage groupings that include nonanatomic cancer characteristics and harmonize with stomach cancer staging. Although it is constrained by definitions for stage groups, survival monotonically decreases with increasing stage group, is distinctive between groups, and is homogeneous within each group.

The Future

The next revision of cancer staging is scheduled for 2016. The addition of new centers, continued accrual of patients, updating of current data, addition of clinically staged advanced cancers, and consideration of new cancer characteristics provide WECC the opportunity to produce further refined, data-driven staging recommendations for the eighth edition of the AJCC/UICC cancer staging manuals.

Although stage groupings are important for data collection, group analysis, and cancer reporting, they are inadequate for individual patient prognostication and optimal decision making. Therefore, future efforts should

be directed toward developing a patient-specific (personalized) prognostication and strategic decision tool.

CONFLICT OF INTEREST DISCLOSURES

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