

Recommendations for pathologic staging (pTNM) of cancer of the esophagus and esophagogastric junction for the 8th edition AJCC/UICC staging manuals

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SUMMARY. We report analytic and consensus processes that produced recommendations for pathologic stage groups (pTNM) of esophageal and esophagogastric junction cancer for the AJCC/UICC cancer staging manuals, 8th edition. The Worldwide Esophageal Cancer Collaboration provided data for 22,654 patients with epithelial esophageal cancers; 13,300 without preoperative therapy had pathologic assessment after esophagectomy or endoscopic treatment. Risk-adjusted survival for each patient was developed using random survival forest analysis to identify *data-driven pathologic stage groups* wherein survival decreased monotonically with increasing group, was distinctive between groups, and homogeneous within groups. The AJCC Upper GI Task Force, by smoothing, simplifying, expanding, and assessing clinical applicability, produced *consensus pathologic stage groups*. For pT1-3N0M0 squamous cell carcinoma (SCC) and pT1-2N0M0 adenocarcinoma, pT was inadequate for grouping; subcategorizing pT1 and adding histologic grade enhanced staging; cancer location improved SCC staging. Consensus eliminated location for pT2N0M0 and pT3N0M0G1 SCC groups, and despite similar survival, restricted stage 0 to pTis, excluding pT1aN0M0G1. Metastases markedly reduced survival; pT, pN, and pM sufficiently grouped advanced cancers. Stage IIA and IIB had different compositions for SCC and adenocarcinoma, but similar survival. Consensus stage IV subgrouping acknowledged pT4N+ and pN3 cancers had poor survival, similar to pM1. *Anatomic pathologic stage grouping*, based on pTNM only, produced identical consensus stage groups for SCC and adenocarcinoma at the cost of homogeneity in early groups. Pathologic staging can neither direct pre-treatment decisions nor aid in prognostication for treatment other than esophagectomy or endoscopic therapy. However, it provides a clean, single therapy reference point for esophageal cancer.

KEY WORDS: epidemiology, esophagectomy, esophagogastric junction, oncology.

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INTRODUCTION

TNM is a means of recording anatomic facts about a cancer; stage grouping assembles these facts into broad classes with similar prognosis.¹ Data necessary for staging esophageal and esophagogastric junction cancer in the AJCC and UICC cancer staging manuals, 8th edition, is based on the 6-continent Worldwide Esophageal Cancer Collaboration (WECC).^{2,3} Cancer facts, patient characteristics, and survival data served as substrate for a machine-learning analysis producing *data-driven pathologic stage groups*. The AJCC Upper GI Task Force reviewed these facts and prognosis groupings and, by smoothing, simplifying, expanding, and assessing clinical applicability, produced *consensus pathologic stage*

groups. An additional machine-learning analysis and consensus produced *anatomic pathologic stage groups* based only on traditional pT, pN, and pM categories.

This manuscript reports these recommendations for pathologic staging of esophageal and esophagogastric junction cancer.

PATIENTS AND METHODS

Patients

At 33 WECC institutions (Supporting Information Appendix S1), 22,654 patients were treated for epithelial esophageal cancers.² Of these, 22,123 had treatment, survival, and pT data available. Among the latter, 13,300 patients had pathologic staging after esophagectomy, endoscopic mucosal resection, or ablation without preoperative therapy. Patient, cancer, and survival data have been published.³

Endpoint

The endpoint was all-cause mortality from first management decision. Median *potential* follow-up was 8.9 years⁴; however, median actual follow-up for surviving patients was 2.5 years, with 25% followed more than 5.1 years and 10% more than 8.4 years.²

Data

Data were collected using a common format with standardized definitions (Supporting Information Table S1). The Case Cancer Institutional Review Board of Case Western Reserve University and Cleveland Clinic Institutional Review Board approved the entire project.

Data analysis

Analytic strategy. Risk-adjusted survival for each patient was developed. Data-driven groups were formulated such that (1) survival decreased monotonically with increasing group number, and (2) survival between groups was distinctive, with no more than a 5% difference. pTNM categories comprising each group were then exposed. Homogeneity of survival within groups was determined. Subgroup analyses were performed as necessary.

Risk-adjusted survival. Random survival forest (RSF) methodology was used to estimate nonparametric risk-adjusted and cross-validated survival for each patient.^{5,6} Thirty-nine dichotomous, polytomous, ordinal, and continuous variables were used (Supporting Information Table S2) in separate analyses for squamous cell carcinoma (SCC) and adenocarcinoma.

All computations used open-source randomForestSRC R-software under default settings.⁷ Missing data were pre-imputed without using outcome information by random forest (RF) imputation

methodology, missForest.^{8,9} Thereafter, 1,000 survival trees were grown using log-rank splitting. Each tree was constructed using an independent bootstrap sample of size 22,123; on average, each bootstrap sample contained 63% of the patients (in-sample bootstrapped data). The remaining unused patients (37%) were referred to as out-of-bag (OOB) observations. Each tree and its corresponding OOB observations were used to calculate a patient-specific risk-adjusted OOB (cross-validated) survival function for stage grouping and patient-specific mortality value (integrated cumulative hazard for each patient) for analysis of homogeneity.⁵

Data-driven staging. From the individual survival estimates, 27 subsets of SCC patients and 19 of adenocarcinoma were produced (Supporting Information Table S3 and Figs. S1,S2). Stage groups were then formed by iteratively merging these subsets by closeness, defined as the root-mean-squared-error difference between OOB survival functions from 3–10 years, until no more than a 5% difference between adjacent groups, above and below, was observed.

Consensus pathologic staging. The AJCC Upper GI Task Force reviewed cancer categories and data-driven stage groupings. By consensus request, because pT1a/b subcategories were not available on all pT1 patients, separate RSF analysis of pT1a-1bN0M0 subcategories was performed. Consensus streamlined data-driven groups and subcategories by merging and splitting while maintaining clinical relevance and minimizing drift from data-driven groups. Finally, the AJCC Upper GI Task Force requested data-driven placement of GX and LX cancers in the consensus pathologic stage groups.

Anatomic pathologic staging. To meet UICC requirements for pure TNM groups, a regrouping of survival curves was performed to produce data-driven anatomic pathologic stage groups. Grade and location were used only in risk adjustment. The consensus process produced consensus anatomic pathologic stage groups.

Homogeneity. Within each data-driven, consensus, and anatomic stage group, homogeneity of survival was assessed as follows. OOB survival was analyzed with respect to the 39 independent variables using RF regression. Regression forests of 1,000 random regression trees were grown using mean-squared-error splitting. From each RF regression, variable importance (VIMP) of each variable was calculated by measuring the increase in OOB mean-squared error when the variable was removed from the analysis,⁶ and standardized by dividing VIMP by the variance of OOB patient mortality multiplied by 100. Standardized VIMP measured the relative importance of each independent

Table 1 Data-driven and consensus pathologic stage grouping for squamous cell carcinoma

Data-driven group	pT	pN	pM	pGrade	pLocation	Consensus stage group
1	Tis	N0	M0	N/A	Any	0
	T1a	N0	M0	G1	Any	IA [†]
	T1b	N0	M0	G1		IB [†]
2	T1	N0	M0	G2-3	Any	
	T2	N0	M0	G1	Any	
	T3	N0	M0	G1	Lower	IIA
3	T2	N0	M0	G2-3	Lower	
4	T2	N0	M0	G2-3	Upper/middle	
	T3	N0	M0	G2-3	Lower	
	T3	N0	M0	G1	Upper/middle	
5	T3	N0	M0	G2-3	Upper/middle	IIB
	T1	N1	M0	Any	Any	
6	T1	N2	M0	Any	Any	IIIA
	T2	N1	M0	Any	Any	
7	T2	N2	M0	Any	Any	IIIB
	T3	N1-2	M0	Any	Any	
	T4a	N0-1	M0	Any	Any	
8	T4a	N2	M0	Any	Any	IVA
X [‡]	T4b	N0-2	M0	Any	Any	
	Any	N3	M0	Any	Any	
	Any	Any	M1	Any	Any	IVB

[†]From subset analysis.[‡]Not in data-driven analysis.

variable in predicting OOB mortality within a stage group. If a group is homogeneous, standardized VIMP for all cancer facts should be near zero. Values under 5% were deemed non-significant.¹⁰

RESULTS

Data-driven pathologic stage groups

Eight data-driven stage groups, presented simply as cardinal numbers, were identified for SCC (Table 1) and 9 for adenocarcinoma (Table 2). Risk-adjusted

survival for SCC (Fig. 1A) and adenocarcinoma (Fig. 1B) monotonically decreased, was distinctive, and was generally homogeneous. Homogeneity was excellent except for groups 7 and 8 for SCC and 9 for adenocarcinoma (Supporting Information Figs. S3A,S4A). However, refinement in these groups was not possible nor clinically meaningful because survival was so poor.

Survival for pT1 adenocarcinoma was much better than for pT1 SCC. pT alone was insufficient for grouping pT1-2N0M0 adenocarcinoma and pT1-3N0M0 SCC; addition of histologic grade improved these groupings (see Tables 1 and 2). However, addition of location was necessary for grouping pT2-3N0M0 SCC. The uncommon pT1N1M0 cancer was grouped with pT3N0M0G2-3 upper/middle thoracic esophagus for SCC and pT3N0M0 for adenocarcinoma.

The adverse effect of regional lymph node and distant metastases on survival was remarkable (see Fig. 1); thus, advanced SCC and adenocarcinoma (pT4N0M0, pTanyN + M0, and pM1) shared stage groupings (see Tables 1 and 2).

Data for pT4b and pM1 were insufficient and required consensus grouping.

Consensus pathologic stage groups

By consensus, G4 was combined with G3, with further pathologic analysis required to determine histopathologic cell type. The anatomic boundary between esophagus and stomach was redefined such that cancers with epicenter no more than 2 cm into the proximal stomach are staged as esophageal cancers.

Table 2 Data-driven and consensus pathologic stage grouping for adenocarcinoma

Data-driven group	pT	pN	pM	pG	Consensus stage group
1	Tis	N0	M0	N/A	0
	T1a	N0	M0	G1	IA [†]
	T1a	N0	M0	G2	IB [†]
	T1b	N0	M0	G1-2	
2	T1	N0	M0	G3	IC
3	T2	N0	M0	G1-2	
4	T2	N0	M0	G3	IIA
5	T1	N1	M0	Any	IIB
	T3	N0	M0	Any	
6	T1	N2	M0	Any	IIIA
	T2	N1	M0	Any	
	T4a	N0	M0	Any	IIIB
7	T2	N2	M0	Any	
8	T3	N1-2	M0	Any	
	T4a	N1	M0	Any	
	T4a	N2	M0	Any	IVA
9	T4b	N0-2	M0	Any	
X [‡]	Any	N3	M0	Any	
	Any	Any	M1	Any	IVB

[†]From subset analysis.[‡]Not in data-driven analysis.

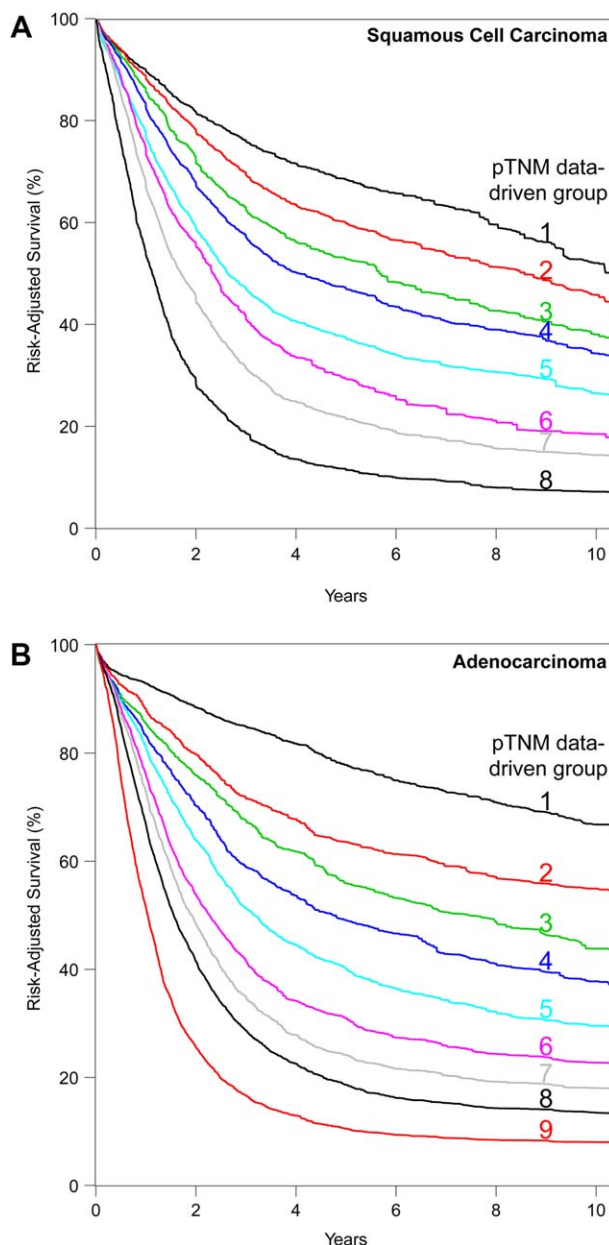


Fig. 1 Risk-adjusted survival of data-driven pathologic stage groups. (A) Squamous cell carcinoma. (B) Adenocarcinoma.

Squamous cell carcinoma. Consensus produced seven changes from the data-driven stage groups, which increased the number of stage subgroups from 8 to 9 and the number of entries from 19 to 20 (Table 1).

By consensus request, pT1 was subcategorized as pT1a and pT1b (Supporting Information Fig. S5A), producing three subsets: pTis, pT1aN0M0G1, and pT1aN0M0G2-3 plus pT1bN0M0G1-3.

Despite similar survival to pT1N0M0G1 cancer, pTis was placed alone into consensus stage 0 (Fig. 2A). The remaining data-driven group 1 was divided by pT1 subcategories and grade into consensus stage groups IA (pT1aN0M0G1) and IB (pT1bN0M0G1). Consensus stage group IB was completed by placing data-driven group 2 members pT1N0M0G2-3 and pT2N0M0G1 into consensus

group IB. Data-driven stage groups 3 and 4 were consolidated into consensus stage group IIA along with pT3N0M0G1 lower thoracic esophageal cancer from data-driven stage group 2. These two changes removed location as a category for pT2N0M0 and pT3N0M0G1 cancers.

Data-driven stage groups 5–7 were identical to consensus stage groups IIB, IIIA, and IIIB. The consensus process divided data-driven group 8 into two subgroups: IVA and IVB. pT4bN1-2N0M0 cancer was placed into consensus stage group IVB.

For any location, if grade is unknown, pT1aN0M0GX is pStage IA, pT1bN0M0GX is pStage IB, pT2N0M0GX is pStage IIA, and pT3N0M0GX is pStage IIB. For any grade, if location is unknown, pT3N0M0LX is pStage IIB.

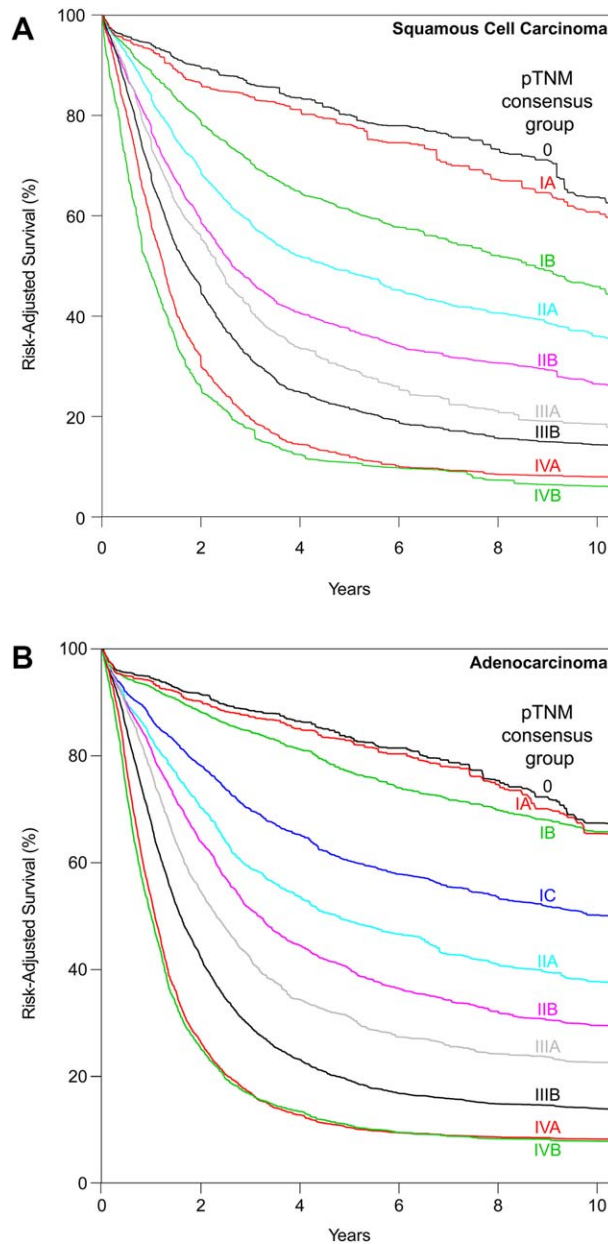


Fig. 2 Risk-adjusted survival of consensus pathologic stage groups. (A) Squamous cell carcinoma. (B) Adenocarcinoma.

The consensus process caused deterioration in homogeneity in stages 0, IIA, IIIB, IVA, and IVB (Supporting Information Fig. S3B).

Adenocarcinoma. Consensus produced nine changes from the data-driven stage groups, which increased the number of stage subgroups for adenocarcinoma from 9 to 10 and entries from 15 to 18 (Table 2).

By consensus request, pT1 was subcategorized as pT1a and pT1b (Supporting Information Fig. S5B), producing survival curves clearly clustered into three subsets: pTis and pT1aN0M0G1, pT1aN0M0G2 and pT1bN0M0G1-2, and pT1a/T1bN0M0G3. Survival of patients with pT1 adenocarcinoma was much better than for SCC.

Despite similar survival to pT1N0M0G1 cancer, pTis was placed alone into consensus stage group 0 (Fig. 2B). The remaining data-driven group 1 was divided by T1 subcategories into consensus stage groups IA (pT1aN0M0G1) and IB (pT1aN0M0G2 and pT1bN0M0G1-2). Data-driven groups 2 and 3 were amalgamated into consensus group IC, and groups 4 and 5 became consensus groups IIA and IIB, respectively. Data-driven group 6, minus pT4aN0M0, became consensus group IIIA. Data-driven groups 7 and 8 plus pT4aN0M0 from data-driven group 6 were amalgamated into consensus group IIIB after removing pT4aN2M0.

Data-driven group 9 was divided into two subgroups: IVA and IVB. pT4aN2M0 and pT4bN1-2M0 were placed into consensus stage group IVA.

Table 3 Data-driven and consensus anatomic pathologic stage grouping for squamous cell carcinoma

Data-driven group	pT	pN	pM	Consensus stage group
1	Tis	N0	M0	0
2	T1a	N0	M0	IA [†]
	T1b	N0	N0	IB [†]
3	T2	N0	M0	IIA
4	T3	N0	M0	IIB
	T1	N1	M0	
5	T1	N2	M0	IIIA
	T2	N1	M0	
6	T2	N2	M0	IIB
	T3	N1-2	M0	
	T4a	N0-1	M0	
7	T4a	N2	M0	IVA
X [‡]	T4b	N0-2	M0	
	Any	N3	M0	
	Any	Any	M1	IVB

[†]From subset analysis.[‡]Not in data-driven analysis.

If grade is unknown, pT1aN0M0GX is pStage IA, pT1bN0M0GX is pStage IB, and pT2N0M0GX is pStage IIA.

The consensus process had little effect on the homogeneity of stage groupings compared with the data-driven groupings (Supporting Information Fig. S4B).

Anatomic pathologic stage groups

Despite slightly different data-driven stage groupings for SCC and adenocarcinoma, anatomic pathologic stage groupings were identical for both histopathologic cell types (Table 3).

Squamous cell carcinoma. Data-driven anatomic pathologic staging produced seven groups (Table 3). Consensus increased the number of stage subgroups to 9, with the number of entries increasing from 13 to 15.

Survival of pTis was much better than all pT1N0M0 cancers (Fig. 3A). Thus, data-driven group 1 became anatomic pathologic stage group 0. Data-driven group 2 was divided by T1 subcategories into consensus anatomic stage groups IA (pT1aN0M0) and IB (pT1bN0M0). Stage IIA solely comprised pT2N0M0 patients. Stage IIB was pT3N0M0 and pT1N1M0 cancers. Stage grouping of advanced cancers (III and IV) was identical to consensus pathologic stage grouping recommendations.

Homogeneity was disrupted within anatomic pathologic groups 0, IIA, and IIB when G and location were removed from staging (Supporting Information Fig. S3C).

Adenocarcinoma. Data-driven anatomic pathologic staging produced eight groups (Table 4). Consensus increased the number of stage subgroups to 9, with the number of entries increasing from 14 to 16.

Changes were similar for SCC except that pT4aN0M0 in data-driven group 5 was amalgamated with data-driven groups 6 and 7, producing anatomic

stage group IIB after removal of T4aN2M0 (Table 2 and Fig. 3B). Stage grouping of advanced cancers (III and IV) was identical to consensus pathologic stage grouping.

For adenocarcinoma, homogeneity was disrupted within anatomic pathologic group I when G was removed from staging (Supporting Information Fig. S4C).

DISCUSSION

Principal findings

TNM categories are unchanged except for addition of peritoneal invasion to T4a. However, non-anatomic category G4 was eliminated and anatomic boundary of cancers in the esophagogastric junction was narrowed. Survival of stage I adenocarcinoma was better than SCC. For pT1-3N0M0 SCC and pT1-2N0M0 adenocarcinoma, T alone was inadequate. Stage grouping for N0M0 cancers was enhanced by subdividing pT1 into pT1a and pT1b subcategories and by adding histologic grade. For pT2-3N0M0 SCC, location was also important. Consensus removed location as a category for pT2N0M0 and pT3N0M0G1 SCCs. For both SCC and adenocarcinoma, stage IIA and IIB cancers had somewhat different category compositions, but they were associated with similar survival. Metastases markedly reduced survival, so that T, N, and M were sufficient for grouping advanced cancers. Advanced cancers had similar survival regardless of histopathologic cell type, histologic grade, or cancer location.

Consensus maintained the definition of stage 0, ignoring that pTis survival was similar to early invasive carcinoma. In contrast, broadening the definition of stage IV acknowledged that pT4N+ and pN3 cancers had dismal survival equivalent to distant metastases. However, the subgroups of stage IVA and IVB were consensus driven.

Anatomic pathologic staging based on pTNM alone rendered stage groups of SCC and adenocarcinoma identical, but with loss of homogeneity for earlier stage cancers.

7th versus 8th edition

Generally, the 7th edition^{11,12} was an improvement over the 6th, as single institution reviews attest¹³⁻¹⁷; however, shortcomings were also noted.¹⁸⁻²¹ Aware of deficiencies in the 7th edition, four goals for pathologic staging were realized²²: improving homogeneity of stage I and IV by broadening definitions, improving homogeneity of stage IIA and IIB SCC and stage IIB adenocarcinoma by amassing more data, assessing other non-anatomic cancer characteristics, and adding treatment other than esophagectomy. Changes from edition 7 are summarized in Box 1.

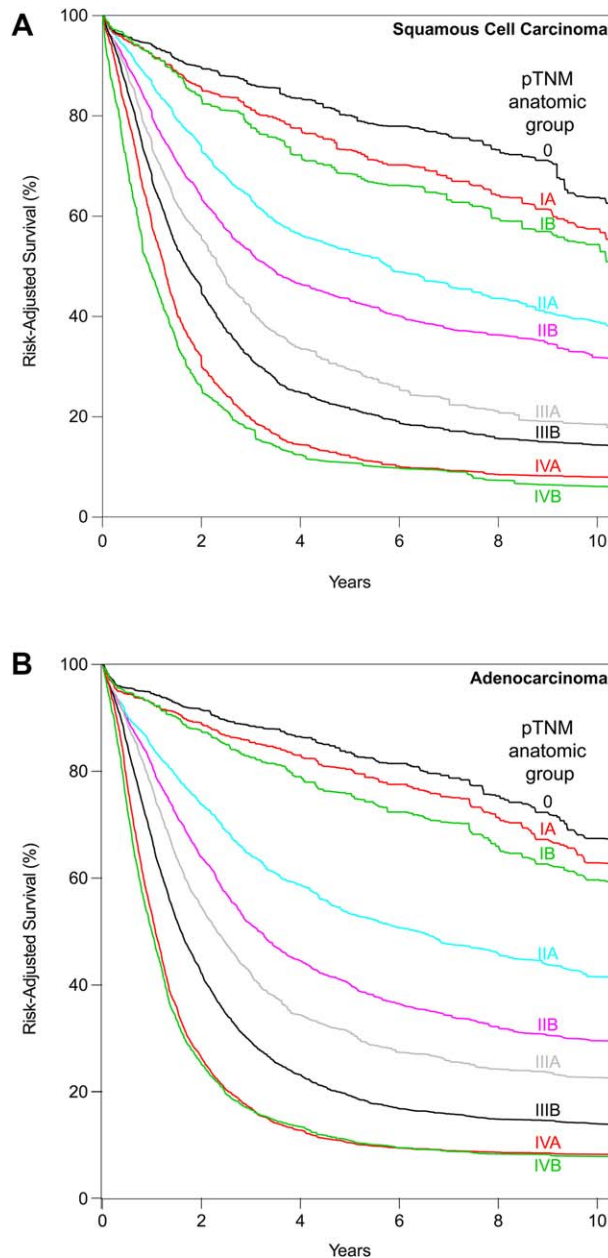


Fig. 3 Risk-adjusted survival of anatomic pathologic stage groups. (A) Squamous cell carcinoma. (B) Adenocarcinoma.

Squamous cell carcinoma. AJCC consensus would not relax the definition of stage 0. Subcategorizing T1 allowed Stage IA to be more distinctive in the 8th edition and restricted to pT1aN0M0G1. This change relegates all other T1N0M0 to stage IB. pT2N0M0 and pT3N0M0 cancers, grouped identically in the 7th edition, are more homogeneous in the 8th edition. In the 7th edition, pT2-3N0M0 cancers occupied three subgroups: IB, IIA, and IIB. In the 8th edition, location is removed as a category for pT2N0M0 cancers, and they are either stage IB (pT2N0M0G1) or stage IIA (pT2N0M0G2-3). pT3N0M0 cancers are confined to stage IIA and IIB in the 8th edition. All but pT3N0M0G2-3 upper/middle (stage IIB) thoracic esophageal cancer are now placed into stage IIA. 8th edition stage IIB is restricted to pT3N0M0G2-3

upper/middle thoracic esophageal cancers and pT1N1M0 cancers. pT2N1M0 cancers are moved from stage IIB in the 7th edition to join pT1N2M0 and form stage IIIA in the 8th edition, again improving homogeneity. 7th edition stage IIIA members pT3N1M0 and pT4aN0M0, stage IIIB pT3N2M0 cancers, and stage IIIC pT4aN1M0 cancers form stage IIIB in the 8th edition. All other stage IIIC cancers of the 7th edition become stage IVA in the 8th edition.

Adenocarcinoma. AJCC consensus would not relax the definition of stage 0. Subcategorizing T1 required an increase from 2 stage I subgroups in the 7th edition to 3 in the 8th edition, improving distinctiveness. 7th edition stage IA pT1N0M0G1-2 cancers are now stage IA (pT1aN0M0G1) and stage IIB (pT1aN0M0G2

Table 4 Data-driven and consensus anatomic pathologic stage grouping for adenocarcinoma

Data-driven group	pT	pN	pM	Consensus stage group
1	Tis	N0	M0	0
2	T1a	N0	M0	IA [†]
	T1b	N0	M0	IB [†]
3	T2	N0	M0	IIA
4	T3	N0	M0	IIB
	T1	N1	M0	
5	T1	N2	N0	IIIA
	T2	N1	M0	
	T4a	N0	M0	IIIB
6	T2	N2	M0	
7	T3	N1-2	M0	
	T4a	N1	M0	
	T4a	N2	M0	IVA
8	T4b	N0-2	M0	
X [‡]	Any	N3	M0	
	Any	Any	M1	IVB

[†]From subset analysis.[‡]Not in data-driven analysis.

and pT1bN0M0G1-2) cancers in the 8th edition. 7th edition stage IB becomes 8th edition IC. Stage IIA is unchanged. All 8th edition changes from IIB on are identical to those reported for SCC.

Strengths and limitations

Many believe that cancer-specific survival represents the ultimate disease-specific survival. However, this soft endpoint is plagued by our ability to detect persistence of cancer after treatment. Once patient demographics, comorbidities, and treatments are accounted for (risk-adjusted survival), and in this analysis, continent and institution as well, the residual information contained in all-cause mortality becomes a better endpoint²³⁻²⁵ (Supporting Information Fig. S6).

Although the strength of WECC is worldwide representation, this also imposes limitations similar to those of large national and international registries. In WECC, these related to institutional, country, and continent heterogeneity of etiology, diagnosis, treatment, and pathologic characterization of esophageal cancer. All data were provided by individual institutions with no independent audit against medical record documentation. Similarly, there was no core pathology laboratory to review pathologic specimens for histopathology of the cancer, histologic grade, lymphovascular invasion, lymph node count, cancer genetics, or other special studies. There was, however, intense cross-tabulation of the data at the data center for interval and cross-institutional consistency. Data elements with clear inconsistencies were reported to the institution and, when possible, the data were corrected. Symptomatic differences were also identified; treatment of adenocarcinoma, for example, appeared to be more consistent across continents and sites than SCC (Supporting Information Fig. S6).

Imputation was necessary for missing data in some risk-adjustment variables, and some patients who did not have complete pTNM data or survival information were excluded. Although we attempted to incorporate less invasive treatments in the analysis, the number of patients receiving such treatment was small.

Clinical implications

Consensus and anatomic pathologic staging erased some important cancer variables. Despite the rigid definition of stage 0, pTis behaves like a pT1N0M0G1 cancer. Although location was used only to stage pT3N0M0G2-3 SCCs, it is an essential prognosticator for all pT2-3N0M0 SCCs. Stage IIB is an interesting group wherein 'T meets N'; survival of the uncommon superficial pT1 cancers with one or two regional nodal metastases is similar to the more common, deeply invasive pT3 cancers free of regional nodal metastases. Stage III further defines the T and N axis. Confirmation that survival of patients with most locally advanced cancers was similar to that of patients with distant metastases allowed relaxation of the formerly rigid definition of Stage IV.

CONCLUSIONS

Pathologic staging can neither direct pre-treatment decisions after the fact nor aid in prognostication for treatment other than esophagectomy or endoscopic treatment, and it must be remembered that what is important for stage grouping of populations is not necessarily helpful for the individual patient. This separation of decision-making and prognostication is supported by WECC data² and will be addressed in future papers. However, 8th edition pathologic staging provides an important, clean, single therapy reference point for esophageal cancer.

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