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Worldwide Esophageal Cancer Collaboration: Clinical Staging Data

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ABSTRACT: To address uncertainty of whether clinical stage groupings (cTNM) for esophageal cancer share prognostic implications with pathologic groupings after esophagectomy alone (pTNM), we report the data—simple descriptions of patient and cancer characteristics and non–risk-adjusted survival—for clinically staged patients from the Worldwide Esophageal Cancer Collaboration (WECC). Thirty-three institutions from 6 continents submitted data using variables with standard definitions: demographics, comorbidities, clinical cancer characteristics, and all-cause mortality from first management decision. Of 22,123 clinically staged patients, 8,156 had squamous cell carcinoma, 13,814 adenocarcinoma, 116 adenosquamous carcinoma, and 37 undifferentiated carcinoma. Patients were older (62 years) men (80%) with normal body mass index (18.5 to 25 mg/kg^2, 47%), little weight loss (2.4±7.8 kg), 0-1 ECOG performance status (67%), and history of smoking (67%). Cancers were cT1 (12%), cT2 (22%), cT3 (56%), cN0 (44%), cM0 (95%), and cG2-G3 (89%); most involved the distal esophagus (73%). Non–risk-adjusted survival for squamous cell carcinoma was not distinctive for early cT or cN; for adenocarcinoma, it was distinctive for early versus advanced cT and for cN0 versus cN+. Patients with early cancers had worse survival, and those with advanced cancers had better survival than expected from equivalent pathologic classifications based on prior WECC pathologic data. Thus, clinical and pathologic classifications do not share prognostic implications. This makes clinically based treatment decisions difficult and pre-treatment prognostication inaccurate. These data will be the basis for the 8th edition cancer staging manuals

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following risk adjustment for patient, cancer, and treatment characteristics and should

direct 9th edition data collection.

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Keywords: survival, cancer staging, decision-making, prognostication, data sharing

Word count = 252

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INTRODUCTION

Initial therapeutic decisions for patients with esophageal cancer, the goal of which is to maximize survival while minimizing cancer treatment harm, are driven largely by clinical cancer staging information. Assignment of clinical stage grouping (cTNM) has, by tradition, shared pathologic stage groupings (pTNM) corresponding to cTNM, but whether prognostic significance of pTNM is shared with cTNM is uncertain.

To address this uncertainty, a 6-continent Worldwide Esophageal Cancer Collaboration (WECC) was mounted to collect patient and clinical esophageal cancer characteristics and all-cause mortality to 1) test the hypothesis that clinical and pathologic classifications share the same prognostic implications, 2) facilitate pre-treatment prognostication, 3) improve clinical decision-making, and 4) prepare for the 8th edition of the cancer staging manuals following risk adjustment. In this paper, we simply report the descriptive dataset of patient and cancer characteristics of individuals with clinically staged cancers and non–risk-adjusted survival that begin to address these aims.

PATIENTS AND METHODS

Data

In 2012, 79 institutions were invited to participate in WECC, aimed at constructing refined data-driven esophageal cancer staging for the 8th edition of the cancer staging manuals. They were invited based on known volumes, indication that they had accessible data, and location around the world. Of these, 41 institutions obtained local ethics-board approval of databases and executed data-use

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agreements with Cleveland Clinic. Data were requested in completely de-identified form (Health Insurance Portability and Accountability Act research standards) for analysis, using a set of required variables with standard definitions. Variables included demographics, comorbidities, cancer characteristics, cancer treatment, and time-related outcomes. The Case Cancer Institutional Review Board of Case Western Reserve University and Cleveland Clinic Institutional Review Board approved the entire project. This paper reports results of clinical data from 33 institutions whose data were submitted by September 30, 2014, and were cleaned and adjudicated (Appendix).

Patients

At these institutions, of 22,654 patients (eTable 1) with epithelial cancers, the majority were older men with normal body mass index, no weight loss, and 0-1 Eastern Cooperative Oncology Group (ECOG) performance status. Comorbidities were present in a minority of patients, with cardiopulmonary comorbidities predominating. Among the 22,654 patients, 22,123 had clinical staging data available before treatment. These data revealed that patients with pure adenocarcinoma were older than those with pure squamous cell carcinoma (Table 1), were far less likely to be female, were considerably larger, and were more likely to have diabetes, coronary artery disease, and hypertension; however, they were in better ECOG status and had normal FVC. Although 6 continents are represented, most patients in the dataset were treated in North America, Europe, and Asia. Patients with adenocarcinoma lived predominantly in the West and those with squamous cell carcinoma in the East.

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Endpoint

The endpoint was all-cause mortality from the first management decision. Median

potential follow-up,[1] if there were no deaths, was 8.9 years (25% >13.4 years, 10%

>20 years), but considering deaths in this elderly population with a rapidly lethal

cancer, overall median survival was 1.6 years; median follow-up for surviving

patients was 2.5 years, with 25% followed more than 5.1 years and 10% more than

8.4 years.

Data Analysis

For analysis, patients with adenosquamous and undifferentiated carcinoma (eTable

2) were considered in both the squamous cell carcinoma and adenocarcinoma

datasets. Survival was estimated using the Kaplan–Meier method, and these

estimates are accompanied by 68% confidence limits, equivalent to ±1 standard

error. Survival has been simply stratified by a number of patient and cancer

characteristics, with no risk adjustment. The hazard function for death was

estimated by a parametric temporal decomposition method (for additional details,

see http://www.lerner.ccf.org/qhs/software/hazard).[2] Continuous variables are

summarized by mean ± standard deviation and categorical variables by frequency

and percentage.

RESULTS

Clinical Cancer Characteristics

Histopathologic cell type was squamous cell carcinoma in 8,156, adenocarcinoma

in 13,814, adenosquamous carcinoma in 116, and undifferentiated carcinoma in

37. Approximately a third of all cancers were confined to the esophageal wall (cT2
or less) for both squamous cell carcinoma and adenocarcinoma (Table 2 and
eTables 3 and 4). Fewer than half the patients were free of regional lymph node
metastasis (cN0), and few cancers had distant metastases (cM). The majority of
cancers were G2/G3. Adenocarcinomas were located predominantly in the lower
esophagus, and squamous cell carcinomas in the middle and lower esophagus.
Otherwise, cancer characteristics differed only modestly.

Non–Risk-Adjusted Survival

Overall survival was 98%, 74%, 36%, and 24% at 30 days and 1, 5, and 10 years,
respectively (eFig. 1). For both histopathologic cell types, risk of death peaked at 1
year, then gradually decreased and plateaued by about 5 years to a near constant
rate of 8% per year (eFig. 2).

Clinical classifications (cTNM)

Survival was similar for patients with cTis and cT1 cancers, but better for those with
adenocarcinoma than squamous cell cancer (Fig. 1). It decreased with increasing
cT for cT2-4a cancers. Survival decreased with increasing cN for adenocarcinoma
but not for squamous cell carcinoma (Fig. 2). These decreases were much more
distinctive with increasing cT for squamous cell carcinoma than for
adenocarcinoma when stratified by cN0 (because of the better survival of patients
with cTis-cT1 adenocarcinomas [Fig. 3] and cN+ [Fig. 4]). Survival was poor in the
presence of distant metastases (cM1) (Fig. 5). Generally, patients with early
cancers had worse survival ,and those with advanced cancers better survival, than
expected from equivalent pathologic classifications based on prior WECC data.

Other cancer characteristics

Survival decreased with increasing histologic grade for G1-4 cancers (eFig. 3); however, it was considerably better for patients with G1 adenocarcinomas than those with squamous cell carcinoma. Survival increased with a more distal location of cancer within the esophagus (eFig. 4).

Other characteristics

Survival decreased with advancing age (eFig. 5) and was worse for men with squamous cell carcinoma than for women, but similar between sexes for adenocarcinoma (eFig. 6). Survival was highly heterogeneous among institutions (eFig. 7).

DISCUSSION

Appropriateness of Shared Stage Groupings

Comparing survival based on clinical cancer classifications to that of equivalent pathologic classifications based on esophagectomy alone for the 7th edition of the cancer staging manuals,[3] it is evident that prognostic implications for clinical classifications will not be equivalent to those of pathologic classifications, contrary to our initial hypothesis. The prognosis for these clinically staged early cancers was clearly worse, indicating that cTNM for these cancers was understaged compared to pTNM. This is particularly troublesome for therapeutic decisions about endoscopic therapies performed under the assumption that the cancer is early stage, without regional nodal or distant metastases. Prognostication for these early clinically staged cancers will be overly optimistic. Conversely, apparently advanced

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cTNM cancers carry a somewhat better prognosis than equivalent pTNM cancers. In part, this may be due to clinically overstaging early cancers and in part to the effect of neoadjuvant and adjuvant therapy for more advanced stage cancers. This is troublesome because it may expose patients with clinically overstaged early cancers and non-responders to unnecessary or ineffective neoadjuvant therapy.

Principal Findings

Clinical staging appeared to be adequate for separating early stage cTis-1N0M0 cancers from more advanced stage cancers, with survival better and more distinctive for adenocarcinoma than squamous cell carcinoma, but discrimination among early cancers was poor. Discrimination among advanced cancers was slightly better, but of questionable practical value. These observations highlight the deficiencies of current clinical staging.

WECC and Data Assemblage

WECC data for the 7th edition staging manuals was based on pathologic staging of patients undergoing esophagectomy alone.[3-5] This new WECC effort included collecting clinical staging data for patients undergoing all treatments. The number of patient characteristic variables was greater and the data more complete than in the prior WECC effort. Thus, this was a global effort of considerable magnitude across geography, institutions, patients, cancer characteristics, and treatments. These data will be the basis for the 8th edition cancer staging manuals following risk adjustment for all these variables.

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Clinical Patient Characteristics

In this WECC experience, esophageal cancer was found to be a disease of older men, although more so for adenocarcinoma than squamous cell carcinoma. Because the majority of patients underwent treatment with curative intent, most had good to excellent performance status, and no weight loss. Comorbidities were numerous and clinically significant; collection of these data was essential for risk adjustment of all-cause mortality.

Clinical Cancer Characteristics

The majority of cancers were locally advanced, with invasion into the adventitia (cT3) and metastases to regional lymph nodes (cN+). However, except for cancers so advanced that only palliative therapy was offered, there were a sufficient number of patients to provide a wide spectrum of clinically staged esophageal cancers.

Histologic grade 2 and 3 predominated in both cell types. There was a smaller proportion of grade 1 cancers in this dataset than in the prior WECC effort,[1] because it includes more than esophagectomy-only patients. G4 cancers were uncommon. Location was predominately lower thoracic esophagus; few patients had adenocarcinoma of the middle thoracic esophagus and rarely of the upper thoracic esophagus. Distribution of location for squamous cell carcinoma, although skewed to the middle and lower thoracic esophagus, will be sufficient to permit analysis of the effect of location on risk-adjusted survival. No patient with cervical esophageal cancer was included in the dataset, because this location was staged as a head and neck cancer in the 7th edition cancer staging manuals.[4,5]

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Non–Risk-Adjusted Survival

The endpoint for this study was all-cause mortality. This was chosen because it is a hard endpoint not requiring interpretation. Recording multiple patient comorbidities will permit extensive risk adjustment, which provides a truer reflection of death due to cancer than the softer endpoint of disease-specific mortality.[6-8]

Overall survival was similar for squamous cell carcinoma and adenocarcinoma. This surprising fact reflects important differences in patient and cancer characteristics between these groups. Except for cTisN0M0 and cT1N0M0 cancers, unadjusted survival was more distinctive when combining cT with cN. Survival was distinctive for histologic grades cG1-G4 and location. Regardless of histopathologic cell type, survival curves for cancer characteristics "pinched" together compared with pathologic staging.[3] This "regression toward the mean" has many possible explanations, including 1) understaging of early clinically staged cancers accentuated by the ceiling of cTis, 2) failure to use, or ineffectual use of, staging modalities such as endoscopic mucosal resection (EMR), EUS-FNA (endoscopic ultrasound-directed fine needle aspiration), and CT-PET for suspected early stage cancers, 3) overstaging of advanced clinically staged cancers due to a floor of cT4b, cN3, and cM1, and 4) unpredictability of effectiveness of neoadjuvant treatment (downstaging) of advanced clinically staged cancers, resulting in intermediate survival for some of these cancers that have poor pretreatment prognosis. This highlights the need for risk adjustment and a type of multivariable analysis that accounts for treatment effects as well as patient and cancer characteristics.

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Strengths and Limitations

Currently, this is the best attempt at providing worldwide clinical esophageal cancer staging data. However, clinical staging was not uniform among centers or across continents, and these heterogeneities generated heterogeneous survival. Patients treated in North America, Europe, and Asia predominated. Unlike most registry data, WECC collected more patient and cancer characteristics and specific treatments. However, values for some variables were not recorded (missing data). Patients included in the study were undoubtedly biased away from metastatic cancer and palliative treatment. Data were similarly limited for untreatable patients, such as those with T4b and M1 cancers.

The dataset also reflects temporal changes in treatment from esophagectomy alone to neoadjuvant therapy for advanced cancer. Nevertheless, older data on esophagectomy alone, which may seem a limitation, are crucial for developing pathologic staging of advanced esophageal cancers.

A limitation of this pure data presentation is that it does not account for patient variables that affect all-cause mortality; the interplay among TNM, histopathologic cell type, histologic grade, and cancer location in part due to the unique lymphatic anatomy of the esophagus; and the confounding of treatment effects, temporal factors, etiology, diagnosis, and clinical decision-making around the world.

Clinical Staging Implications

Today, esophagogastroduodenoscopy (EGD) and biopsy are necessary for determining location, histopathologic cell type, and histologic grade; EMR and EUS

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for cT; EUS-FNA for cN; and CT-PET for cM and cN; supplemented by ancillary imaging, aspiration, or biopsy.

Comprehensive clinical staging as described is problematic because of varying cost limitations and regional availability of staging modalities. Minimal worldwide standards for clinical staging must be set with worldwide adherence expected. Recording how clinical stage was obtained is necessary to determine quality of clinical staging. There is a need for more accurate and precise clinical staging modalities. Addition of other patient and cancer characteristics will permit better treatment decisions and more accurate pre-treatment prognostication.

Conclusions

Comparing these clinical data with WECC pathologic data for the 7th edition cancer staging manuals,[3] it became evident that clinical stage classifications did not share the same prognostic implications as pathologic stage classifications after esophagectomy alone. The pinching of survival data makes pre-treatment prognostication difficult, providing overly optimistic prognostication for patients with early clinical stage cancers and overly pessimistic prognostication for those with clinically advanced stage cancers. This makes clinical decision-making difficult.

These clinical staging data will be the basis for the 8th edition cancer staging manuals following risk adjustment for many confounding variables. These findings should direct data collection for the 9th edition. This is a milestone in the clinical staging of esophageal cancer and provides direction for future advancements.

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ACKNOWLEDGMENTS

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FIGURE LEGENDS

Figure 1: Survival by clinical cT classifications. Kaplan-Meier estimates accompanied by vertical bars representing 68% confidence limits, equivalent to ±1 standard error. **A,** Squamous cell carcinoma. **B,** Adenocarcinoma.

Figure 2: Survival by clinical cN classifications. Format is as in Fig. 1. **A,** Squamous cell carcinoma. **B,** Adenocarcinoma.

Figure 3: Survival by cT classifications for cN0 cancers. Format is as in Fig. 1. **A,** Squamous cell carcinoma. **B,** Adenocarcinoma.

Figure 4: Survival by cT classifications for cN+ cancers. Format is as in Fig. 1. **A,** Squamous cell carcinoma. **B,** Adenocarcinoma.

Figure 5: Survival by clinical cM classifications. Format is as in Fig. 1. **A,** Squamous cell carcinoma. **B,** Adenocarcinoma.

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Table 1. Patient characteristics of those with pure squamous cell carcinoma and pure adenocarcinoma of the esophagus

Characteristic	n^a	Squamous Cell Carcinoma (total n=8,156) No. (%) or Mean ± SD	n^a	Adenocarcinoma (total n=13,814) No. (%) or Mean ± SD
Demographics				
Age (years)	8,077	61 ± 9.9	13,373	63 ± 10
Female	8,156	2,455 (30)	13,812	1,882 (14)
Body mass index (mg/kg^2)	4,427	22 ± 3.7	7,226	27 ± 5.1
Weight loss (kg)	4,590	1.9 ± 4.9	6,726	2.8 ± 9.2
Comorbidities				
ECOG performance status	3,104		3,178	
0		739 (24)		1,156 (36)
1		549 (18)		1,755 (55)
2		1,269 (41)		178 (5.6)
3		540 (17)		80 (2.5)
4		7 (0.23)		11 (0.35)
Diabetes	7,436	322 (4.3)	11,606	1,430 (12)
IDDM	7,365	58 (0.79)	11,127	185 (1.7)
NIDDM	7,365	193 (2.6)	11,127	766 (6.9)
Coronary artery disease	4,263	269 (6.3)	6,117	993 (16)
Arrhythmia	3,862	79 (2)	4,127	119 (2.9)
Hypertension	5,734	1,120 (20)	9,168	2,753 (30)
Peripheral arterial disease	4,811	114 (2.4)	6,937	235 (3.4)

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Smoker	5,094	3,664 (72)	9,457	6,439 (68)
Past	4,412	1,442 (33)	7,553	2,993 (40)
Current	4,412	1,540 (35)	7,553	1,542 (20)
FEV1 (% of predicted)	3,823	96 ± 21	5,605	95 ± 20
FVC (% of predicted)	3,468	110 ± 21	3,922	100 ± 18
Creatinine (µmol/L)	2,686	76 ± 17	1,448	75 ± 28
Bilirubin (µmol/L)	2,583	12 ± 6.2	1,019	11 ± 6.8
Decade	8,129		13,798	
1970-1979		127 (1.6)		45 (0.33)
1980-1989		1,291 (16)		427 (3.1)
1990-1999		1,427 (18)		3,441 (25)
2000-2009		3,185 (39)		7,614 (55)
2010-2014		2,099 (26)		2,271 (16)
Continent	8,156		13,814	
North America		1,937 (24)		7,814 (57)
Europe		1,473 (18)		4,143 (30)
Asia		4,041 (50)		360 (2.6)
Australia		597 (7.3)		1,280 (9.3)
South America		80 (0.98)		209 (1.5)
Africa		28 (0.34)		8 (0.058)

Note: Patient characteristics of those with adenosquamous and undifferentiated carcinoma are shown in eTable 2.

a. Patients with data available.

Key: *ECOG,* Eastern Cooperative Oncology Group; *FEV1 (%),* forced expiratory volume in 1 second (percent of predicted); *FVC (%),* forced vital capacity (percent of predicted); *IDDM,* insulin-dependent diabetes mellitus; *NIDDM,* non–insulin-dependent diabetes mellitus; *SD,* standard deviation.

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Table 2. Clinical cancer characteristics of patients with pure squamous cell carcinoma and pure adenocarcinoma of the esophagus

Characteristic	Squamous Cell Carcinoma (n=8,156) No. (%)	Adenocarcinoma (n=13,814) No. (%)
cT		
cT0	19 (0.3)	160 (1.5)
cTis	67 (1.1)	214 (2)
cT1	556 (8.9)	1,469 (14)
cT2	1,327 (21)	2,346 (22)
cT3	3,297 (53)	6,094 (57)
cT4a	1,000 (16)	385 (3.6)
cTX	1,890	3,146
cN		
cN0	2,522 (40)	5,009 (47)
cN+	3,785 (60)	5,725 (53)
cN1	1,520 (79)[a]	256 (73)[b]
cN2	371 (19)[a]	82 (23)[b]
cN3	45 (2.3)[a]	15 (4.2)[b]
cNX	1,849	3,080
cM		
cM0	7,850 (96)	12,981 (94)
cM1	306 (3.8)	833 (6.0)
Grade[c]		
cG1	307 (9.2)	370 (11)
cG2	1,494 (45)	1,367 (42)
cG3	1,519 (46)	1,553 (47)
cG4[d]	0 (0)	0 (0)
cGX	4,836	10,524

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Location		
cUpper	990 (13)	97 (0.83)
cMiddle	3,573 (48)	456 (3.9)
cLower	2,938 (39)	11,137 (95)
cLocationX	655	2,124

Note: Clinical characteristics of patients with adenosquamous and undifferentiated carcinoma are shown in eTable 4.

a. Data available for 1,936 patients.

b. Data available for 353 patients.

c. G1, well differentiated; G2, moderately well differentiated; G3, poorly differentiated; G4, undifferentiated.

d. G4 cancers are reported in eTable 4.

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APPENDIX: Worldwide Esophageal Cancer Collaboration: participating institutions and investigators

Institution	Location	Investigators
Beijing Cancer Hospital, Peking University	Beijing, China	Ken N. Chen
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Erasmus Medical Center	Rotterdam, The Netherlands	Bas P.L. Wijnhoven Jan van Lanschot Sjoerd Lagarde
Fourth Hospital of Hebei Medical University	Shijiazhuang, Hebei; China	Jun-Feng Liu
Fox Chase Cancer Center	Philadelphia, PA; USA	Walter J. Scott Donna Edmondson
Groote Schuur Hospital, University of Cape Town	Cape Town; South Africa	Riette Burger
Guy's & St. Thomas' Hospitals	London, UK	Andrew R. Davies Janine Zylstra
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Hospital Universitario del Mar	Barcelona; Spain	Manuel Pera
Hôpital Nord	Marseille; France	Xavier B. D'Journo
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University of Texas MD Anderson Hospital	Houston, TX; USA	Wayne L. Hofstetter Arlene Correa Stephen G. Swisher
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University Medical Center Utrecht	Utrech, The Netherlands	Richard van Hillegersberg
University of Alabama at Birmingham	Birmingham, AL; USA	Robert J. Cerfolio
Hospital de Clinicas, University of Buenos Aires	Buenos Aires; Argentina	Luis Durand Roberto De Antón
The University of Chicago, Department of Surgery	Chicago, IL; USA	Mark K. Ferguson
University of Hong Kong Medical Center, Queen Mary Hospital	Hong Kong; China	Simon Law
University of Michigan	Ann Arbor, MI; USA	Mark B. Orringer Becky L. Marshall
University of Montreal	Montreal, Quebec; Canada	André Duranceau Susan Howson
University of Pittsburgh Medical Center	Pittsburgh, PA; USA	James D. Luketich Arjun Pennathur Kathy Lovas
University of Rochester	Rochester, NY; USA	Thomas J. Watson
University of São Paulo	São Paulo; Brazil	Ivan Cecconello
West China Hospital of Sichuan University	Chengdu, Sichuan; China	Long-Qi Chen
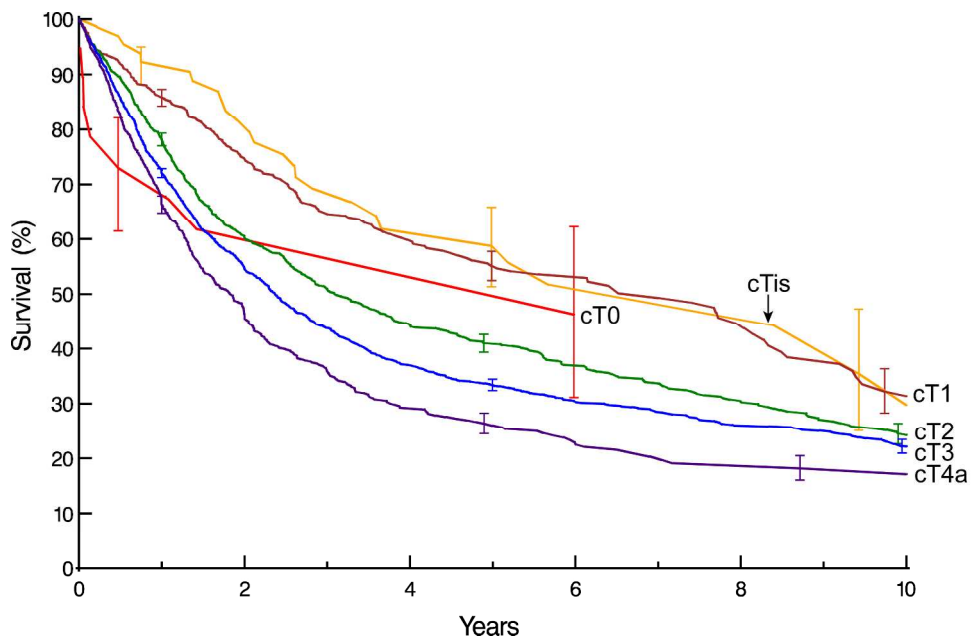
Survival by clinical cT classifications. Kaplan-Meier estimates accompanied by vertical bars representing 68% confidence limits, equivalent to ±1 standard error. A, Squamous cell carcinoma.
233x145mm (300 x 300 DPI)
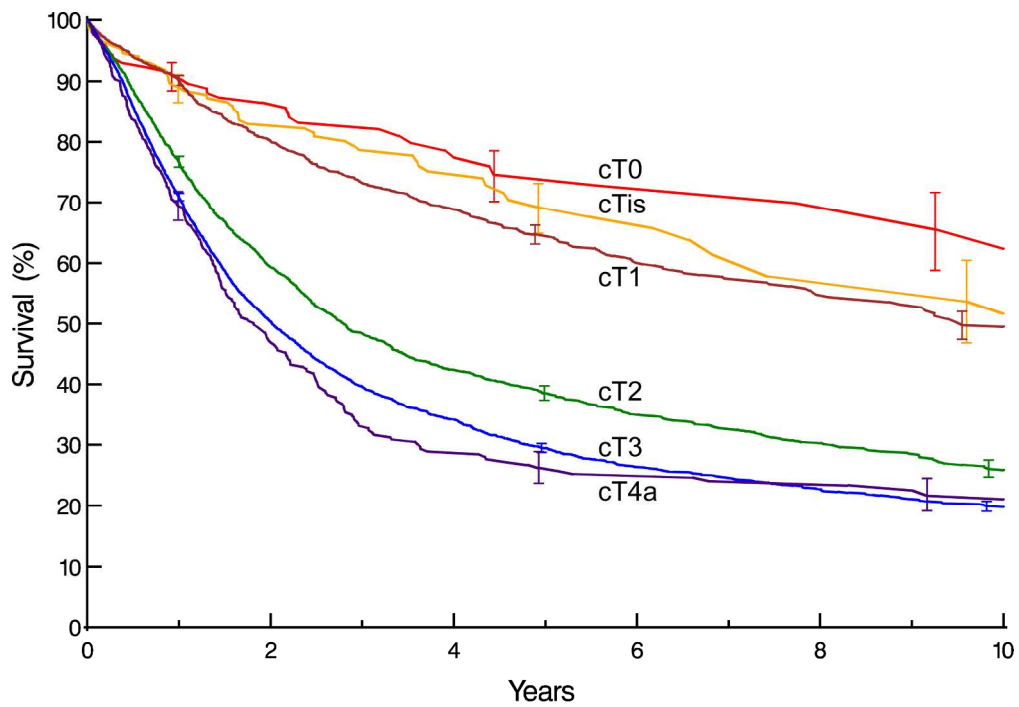
Survival by clinical cT classifications. Kaplan-Meier estimates accompanied by vertical bars representing 68% confidence limits, equivalent to ±1 standard error. B, Adenocarcinoma.

210x145mm (300 x 300 DPI)

Survival by clinical cN classifications. Format is as in Fig. 1.
A, Squamous cell carcinoma.

210x145mm (300 x 300 DPI)

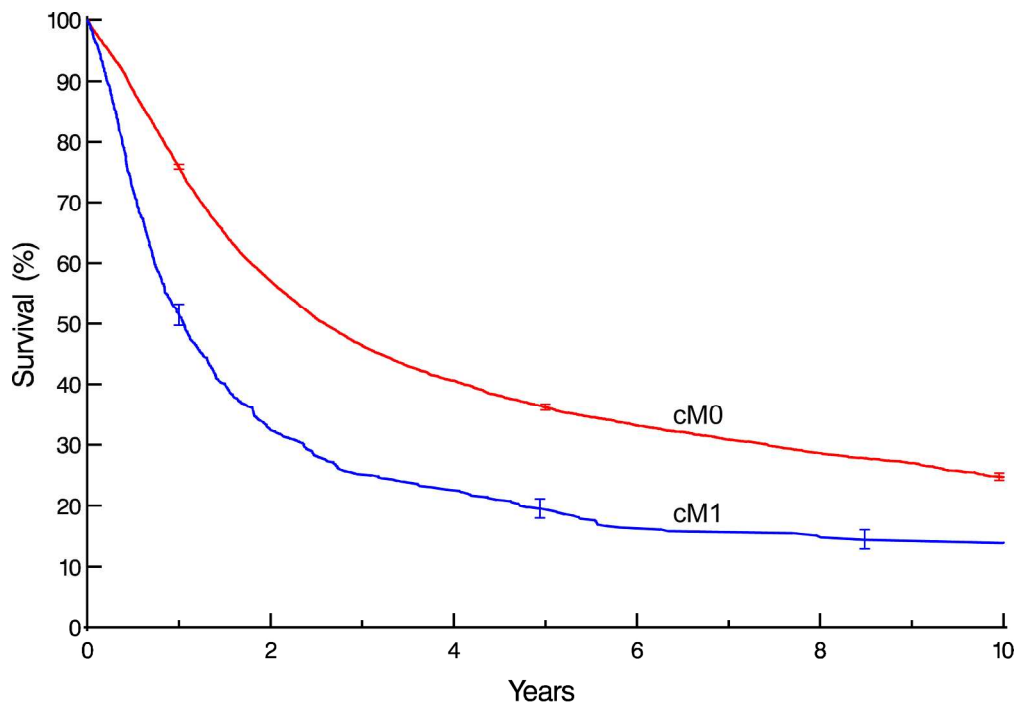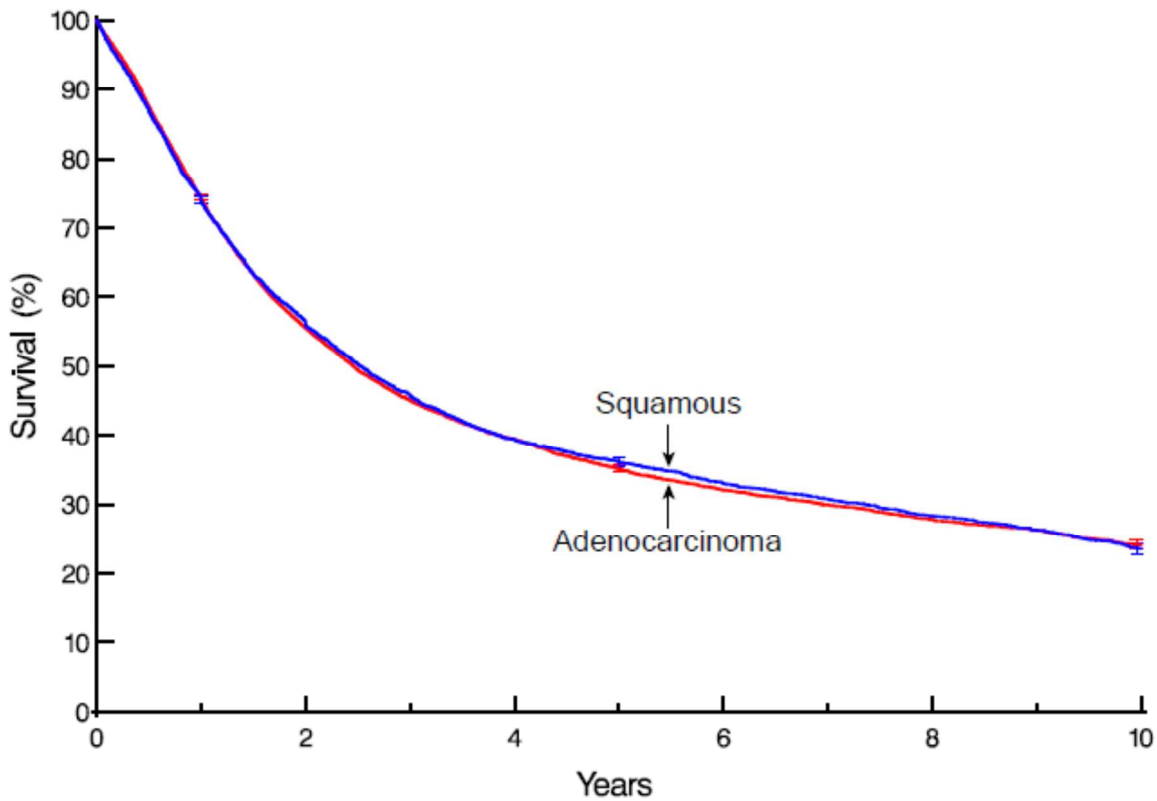Survival by clinical cN classifications. Format is as in Fig. 1. B, Adenocarcinoma.

210x145mm (300 x 300 DPI)

Survival by cT classifications for cN0 cancers. Format is as in Fig. 1. A, Squamous cell carcinoma.
210x145mm (300 x 300 DPI)

Survival by cT classifications for cN0 cancers. Format is as in Fig. 1. B, Adenocarcinoma.
210x145mm (300 x 300 DPI)

Survival by cT classifications for cN+ cancers. Format is as in Fig. 1. A, Squamous cell carcinoma.
210x145mm (300 x 300 DPI)

Survival by cT classifications for cN+ cancers. Format is as in Fig. 1. B, Adenocarcinoma.
210x145mm (300 x 300 DPI)

Survival by clinical cM classifications. Format is as in Fig. 1. A, Squamous cell carcinoma.

210x145mm (300 x 300 DPI)

Survival by clinical cM classifications. Format is as in Fig. 1. B, Adenocarcinoma.
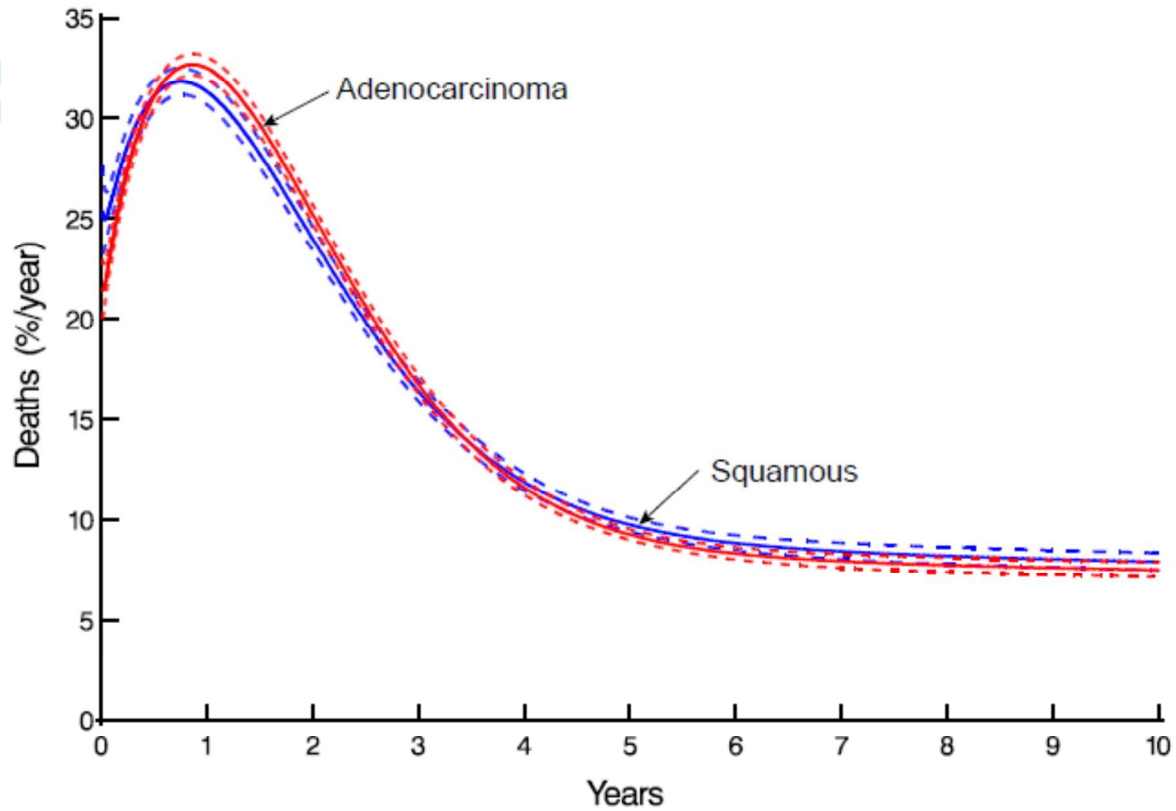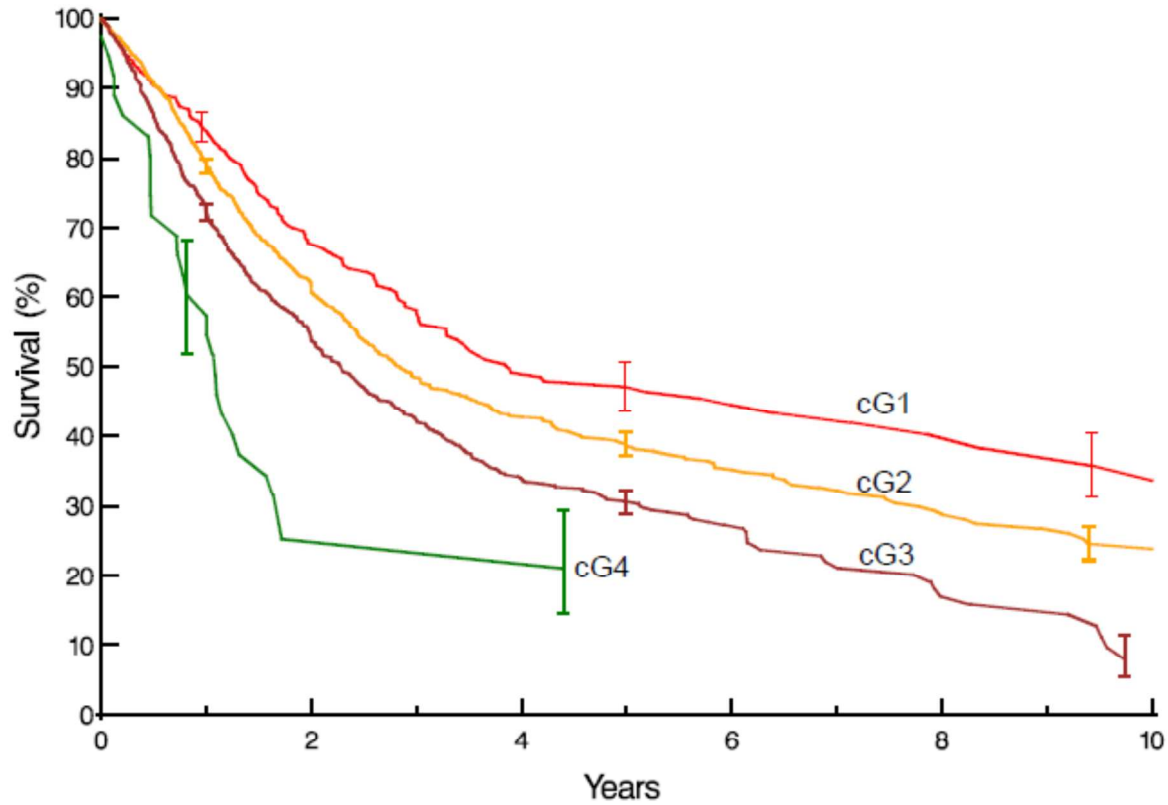
210x145mm (300 x 300 DPI)

eFigure 1. All-cause mortality after clinical staging of esophageal cancer patients.

Vertical bars on Kaplan–Meier estimates represent 68% confidence limits, equivalent to
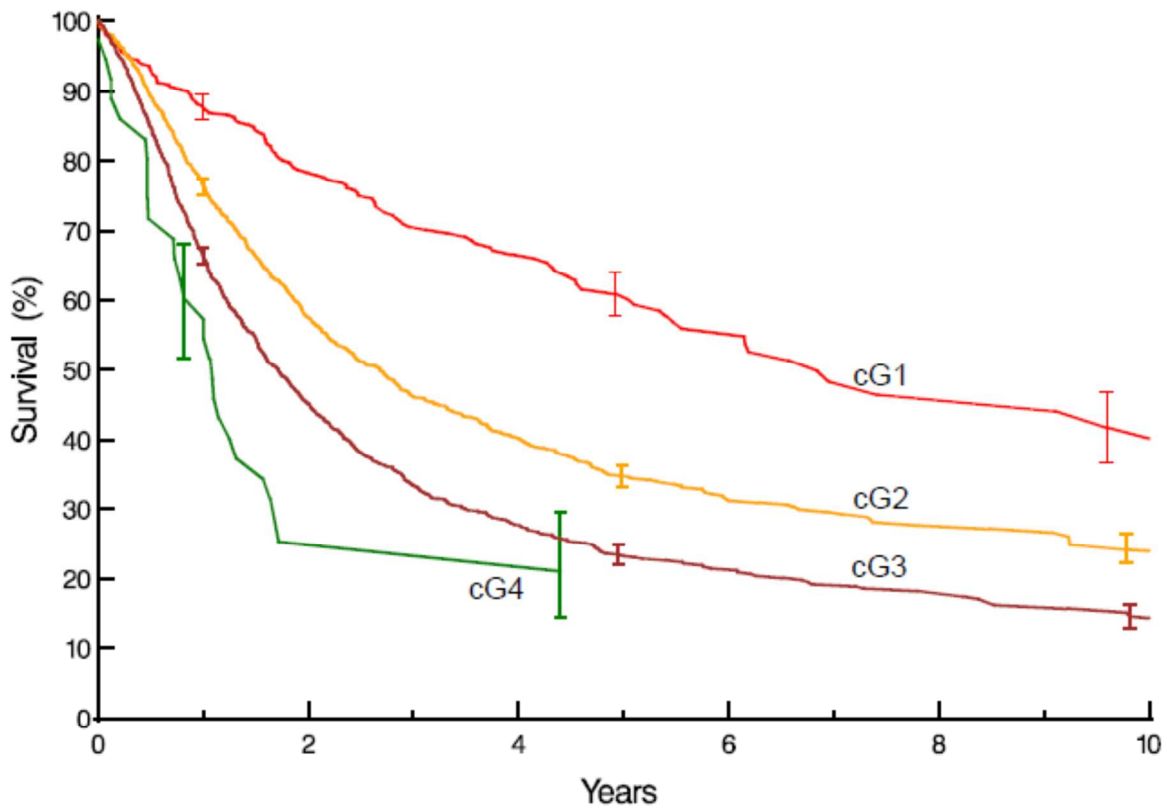
±1 standard error.

eFigure 2. Instantaneous risk of death (hazard function). Dashed lines represent 68% confidence limits.

eFigure 3. Survival by histologic grade (cG1, well differentiated; cG2, moderately

differentiated; cG3, poorly differentiated; cG4, undifferentiated). Format is as in eFig. 1.
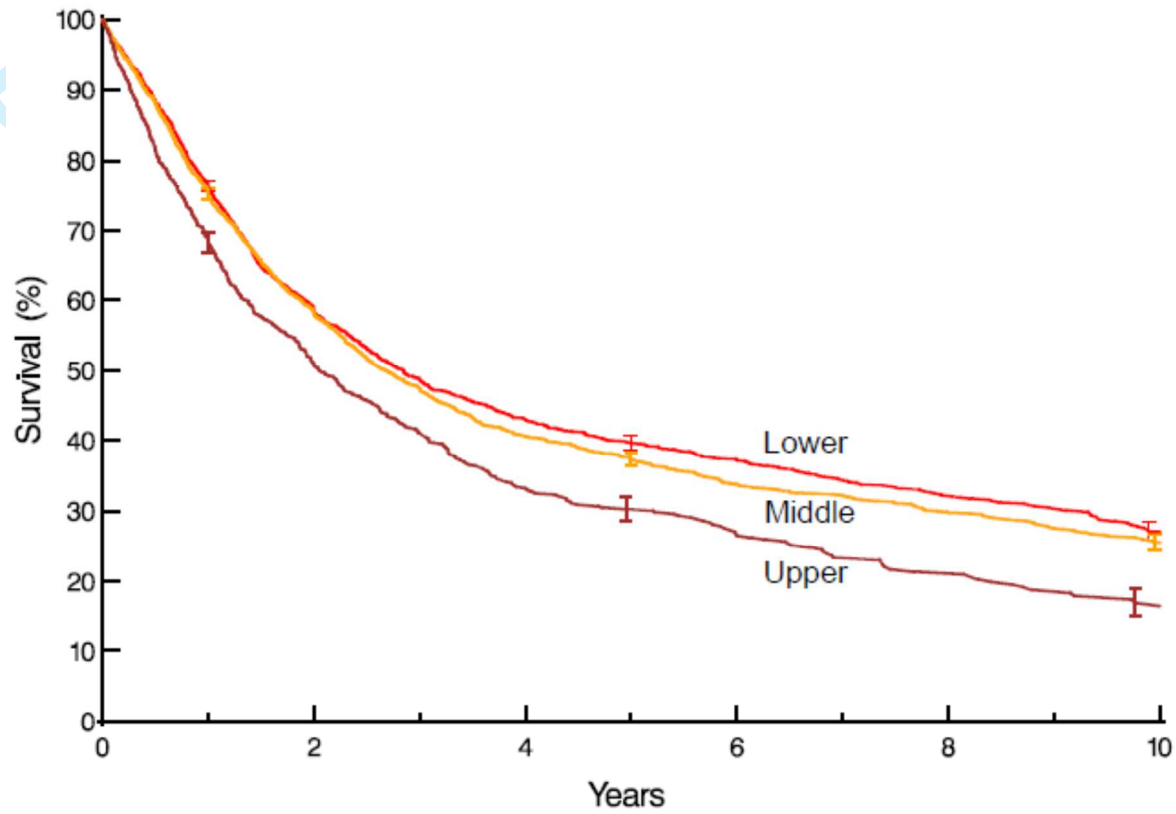
A, Squamous cell carcinoma.

eFigure 3. Survival by histologic grade (cG1, well differentiated; cG2, moderately differentiated; cG3, poorly differentiated; cG4, undifferentiated). Format is as in eFig. 1.
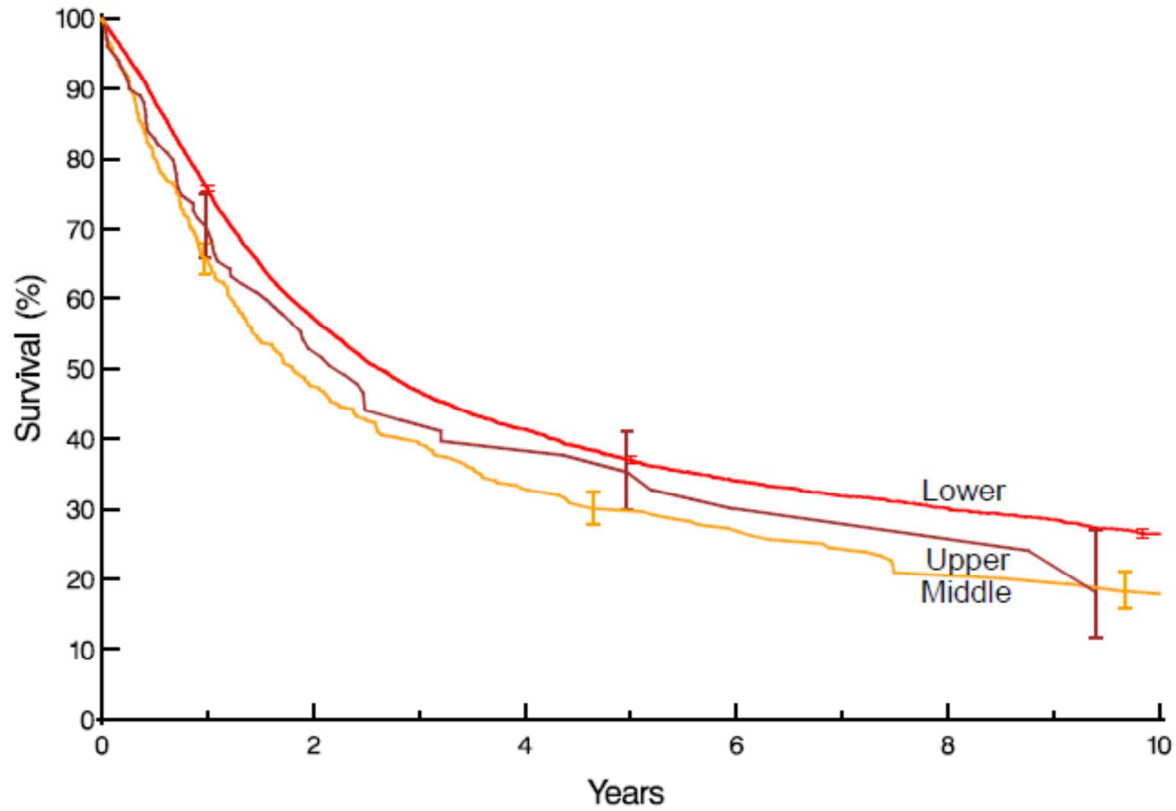
B, Adenocarcinoma.

eFigure 4. Survival by upper extent of cancer in the esophagus (location: upper, middle, lower). Format is as in eFig. 1.

A, Squamous cell carcinoma.

eFigure 4. Survival by upper extent of cancer in the esophagus (location: upper, middle,

lower). Format is as in eFig. 1.

B, Adenocarcinoma.
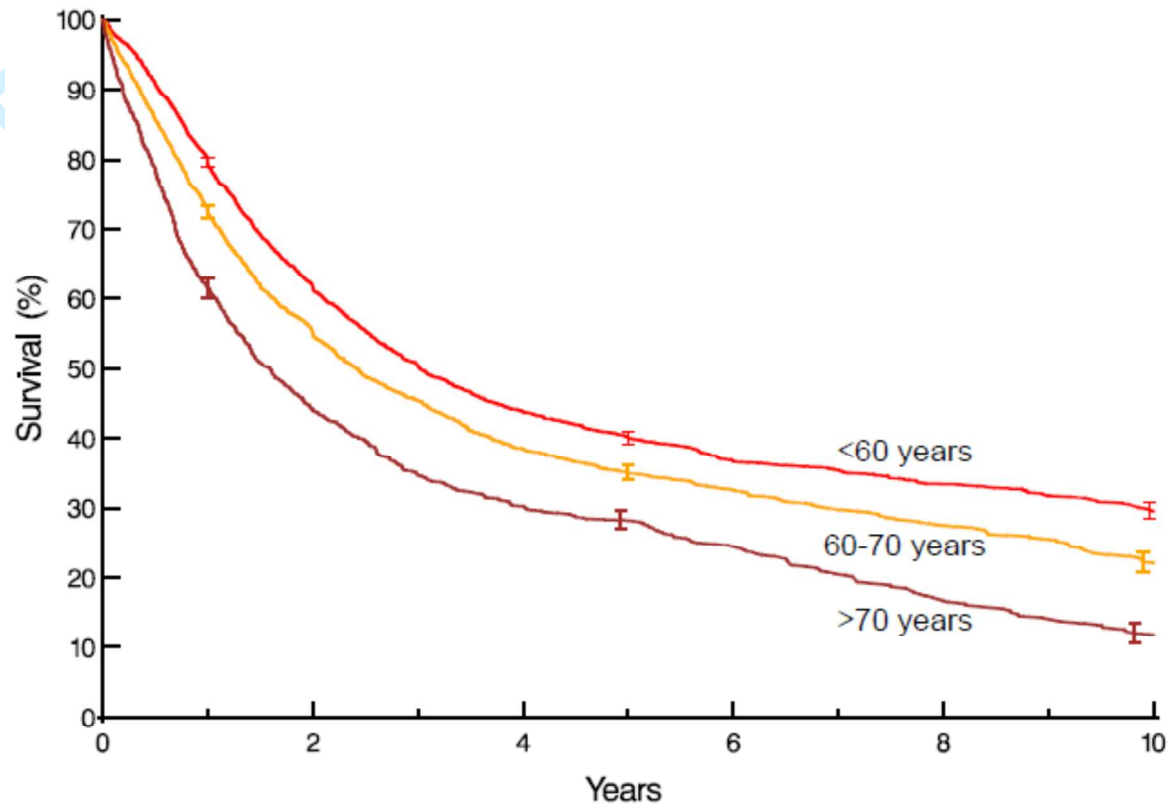
eFigure 5. Survival by patient age (<60, 60-70, >70 years). Format is as in eFig. 1.

A, Squamous cell carcinoma.

eFigure 5. Survival by patient age (<60, 60-70, >70 years). Format is as in eFig. 1.

B, Adenocarcinoma.

eFigure 6. Survival by sex. Format is as in eFig. 1.

A, Squamous cell carcinoma.

eFigure 6. Survival by sex. Format is as in eFig. 1.
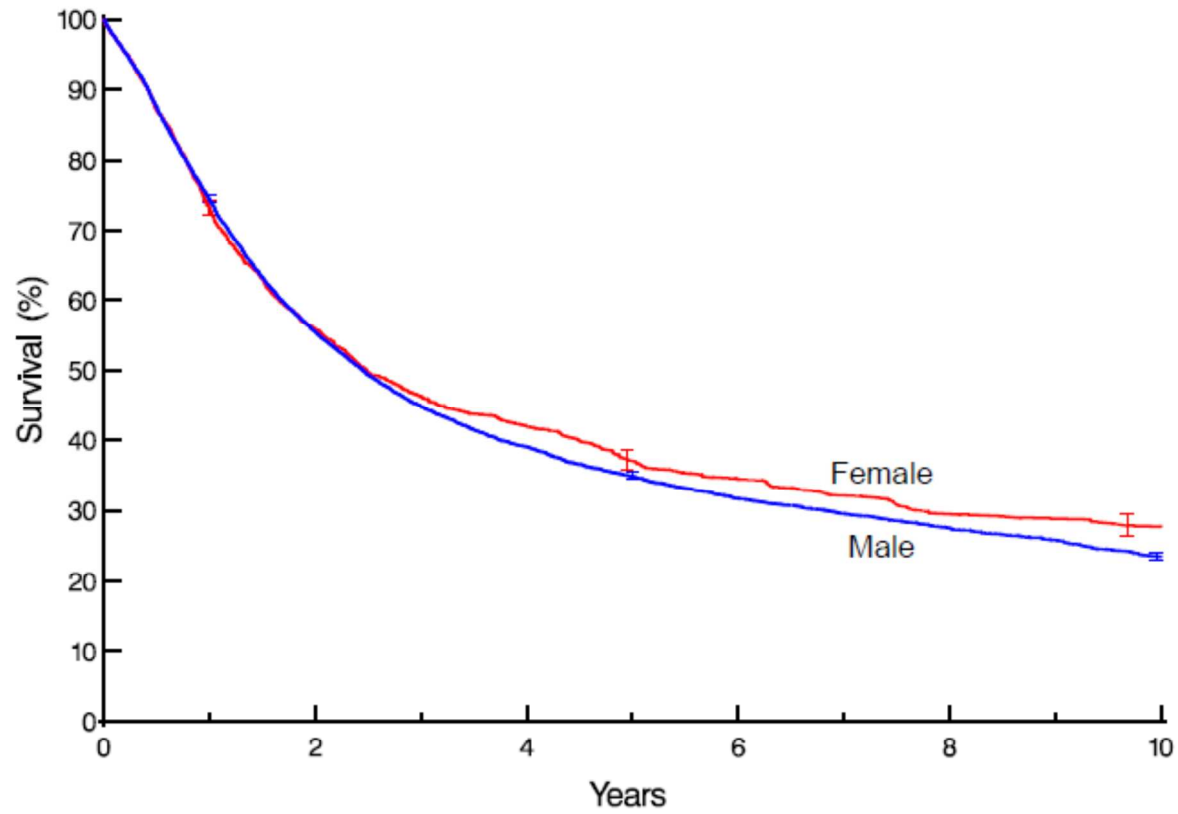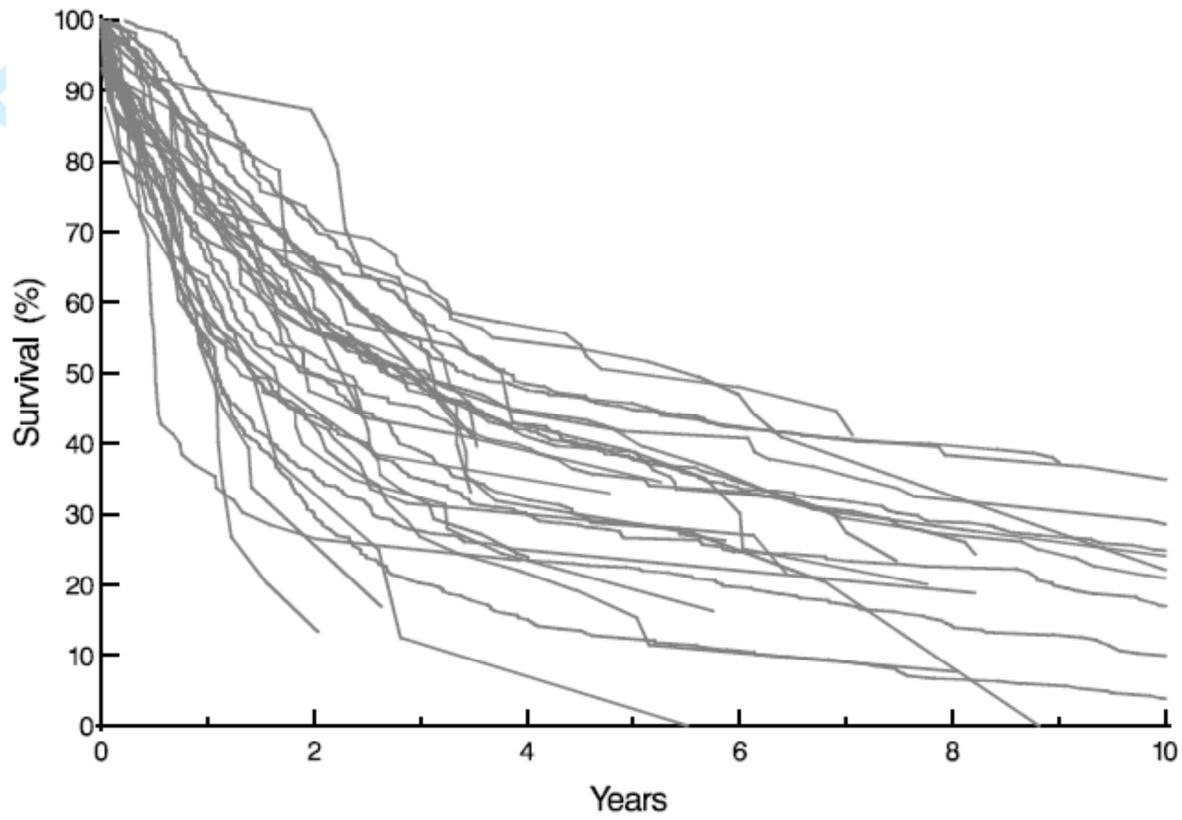
B, Adenocarcinoma.

eFigure 7. Survival by institution where clinical staging was performed.

A, Squamous cell carcinoma.
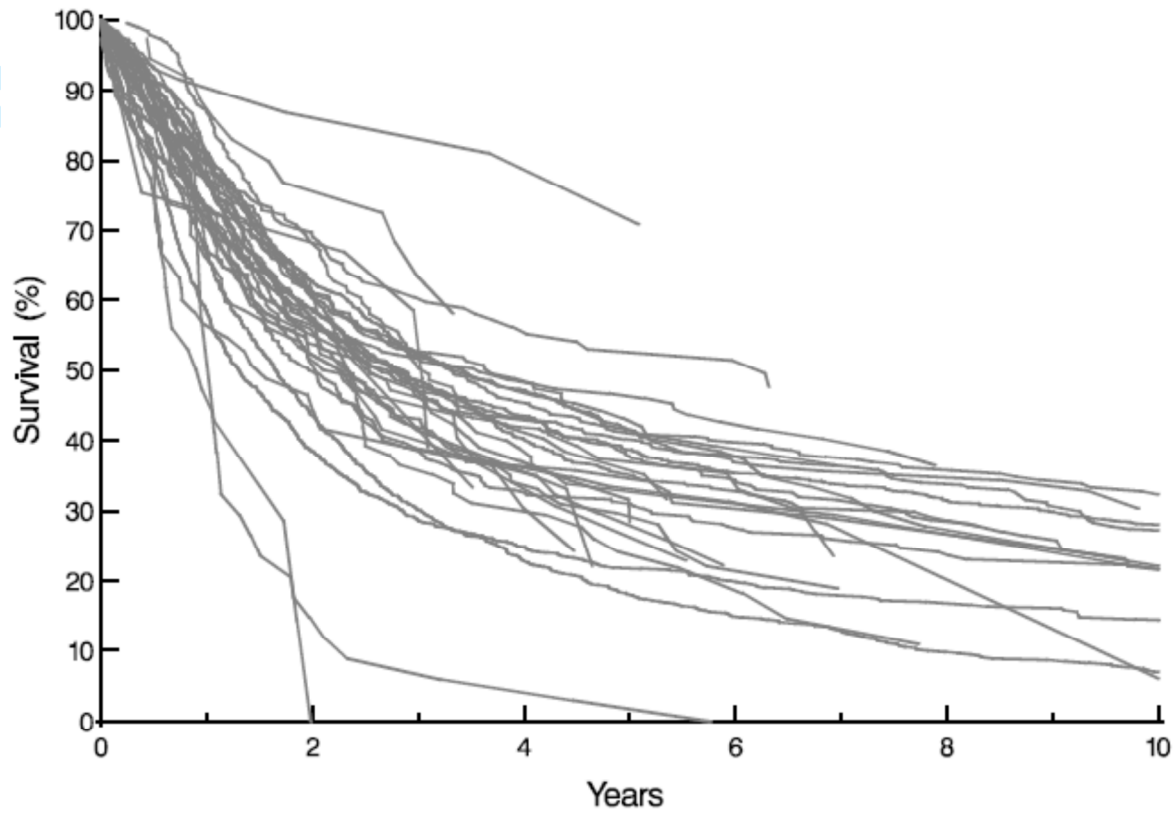
eFigure 7. Survival by institution where clinical staging was performed.

B, Adenocarcinoma.

eTable 1. Patient characteristics in entire WECC database

Characteristic	n^a	All No. (%) or Mean ± SD (n=22,654)
Demographics		
Age (years)	21,950	62 ± 10
Female	22,651	4,488 (20)
Body mass index (m/kg^2)	11,969	25 ± 5.1
Weight loss (kg)	11,632	2.6 ± 8.5
Comorbidities		
ECOG performance status	6,380	
0		1,932 (30)
1		2,338 (37)
2		1,466 (23)
3		626 (9.8)
4		18 (0.28)
Diabetes	19,653	1,797 (9.1)
IDDM	19,085	245 (1.3)
NIDDM	19,085	984 (5.2)
Coronary artery disease	10,671	1,304 (12)
Arrhythmia	8,264	207 (2.5)
Hypertension	15,305	3,970 (26)
Peripheral arterial disease	12,042	353 (2.9)
Smoker	14,935	10,384 (70)
Past	12,310	4,563 (37)
Current	12,310	3,196 (26)
FEV1 (% of predicted)	9,657	96 ± 20
FVC (% of predicted)	7,505	104 ± 20
Creatinine (µmol/L)	4,216	75 ± 22
Bilirubin (µmol/L)	3,655	12 ± 6.4

Decade	22,608	
1970-1979		173 (0.77)
1980-1989		1,732 (7.7)
1990-1999		4,916 (22)
2000-2009		11,216 (50)
2010-2014		4,571 (20)
Continent	22,654	
North America		9,885 (44)
Europe		5,849 (26)
Asia		4,448 (20)
Australia		1,936 (8.5)
South America		498 (2.2)
Africa		38 (0.17)

a. Patients with data available.

Key: *ECOG,* Eastern Cooperative Oncology Group; *FEV1 (%),* forced expiratory volume in 1 second (percent of predicted); *FVC (%),* forced vital capacity (percent of predicted); *IDDM,* insulin-dependent diabetes mellitus; *NIDDM,* non–insulin-dependent diabetes mellitus; *SD,* standard deviation.

eTable 2. Patient characteristics of those with adenosquamous and undifferentiated carcinoma

Characteristic	n^a	Adenosquamous Carcinoma (total n=116) No. (%) or Mean ± SD	n^a	Undifferentiated Carcinoma (total n=37) No. (%) or Mean ± SD
Demographics				
Age (years)	110	61 ± 10	28	59 ± 11
Female	116	20 (17)	37	6 (16)
Body mass index (mg/kg^2)	70	24 ± 4.4	23	25 ± 4.1
Weight loss (kg)	74	2.5 ± 8.5	18	9.4 ± 24
Comorbidities				
ECOG performance status	39		3	
0		8 (21)		1 (33)
1		7 (18)		2 (67)
2		19 (49)		0 (0)
3		5 (13)		0 (0)
4		0 (0)		0 (0)
Diabetes	96	6 (6.3)	35	5 (14)
IDDM	95	1 (1.1)	32	0 (0)
NIDDM	95	4 (4.2)	32	2 (6.3)
Coronary artery disease	51	3 (5.9)	6	2 (33)
Arrhythmia	41	1 (2.4)	4	0 (0)
Hypertension	92	18 (20)	22	5 (23)
Peripheral arterial disease	62	0 (0)	10	1 (10)
Smoker	94	68 (72)	21	13 (62)
Past	81	32 (40)	18	7 (39)
Current	81	23 (28)	18	3 (17)

FEV1 (%)	58	97 ± 15	17	96 ± 18
FVC (%)	50	110 ± 20	16	100 ± 21
Creatinine (µmol/L)	32	74 ± 13	10	67 ± 40
Bilirubin (µmol/L)	31	11 ± 4.3	1	5.1
Decade	116		37	
1970-1979		1 (0.9)		0 (0)
1980-1989		10 (8.6)		4 (11)
1990-1999		19 (16)		5 (14)
2000-2009		66 (57)		24 (65)
2010-2014		20 (17)		4 (11)
Continent	116		37	
North America		42 (36)		10 (27)
Europe		39 (34)		14 (38)
Asia		33 (28)		4 (11)
Australia		0 (0)		0 (0)
South America		1 (0.86)		9 (24)
Africa		1 (0.86)		0 (0)

a. Patients with data available.

Key: *ECOG,* Eastern Cooperative Oncology Group; *FEV1 (%),* forced expiratory volume in 1 second (percent of predicted); *FVC (%),* forced vital capacity (percent of predicted); *IDDM,* insulin-dependent diabetes mellitus; *NIDDM,* non–insulin-dependent diabetes mellitus; *SD,* standard deviation.

eTable 3. Clinical cancer characteristics of patients with esophageal cancer in the WECC database

Characteristic	All (n=22,123) No. (%)
cT	
cT0	179 (1.0)
cTis	281 (1.6)
cT1	2,038 (12)
cT2	3,693 (22)
cT3	9,465 (56)
cT4a	1,395 (8.2)
cTX	5,072
cN	
cN0	7,570 (44)
cN+	9,585 (56)
cN1	1,793 (78)[a]
cN2	456 (20)[a]
cN3	60 (2.6)[a]
cNX	4,968
cM	
cM0	20,975 (95)
cM1	1,148 (5.2)
Grade[b]	
cG1	681 (10)
cG2	2,867 (43)
cG3	3,095 (46)
cG4	37 (0.55)
cGX	15,443

Location	
cUpper	1,090 (5.6)
cMiddle	4,059 (21)
cLower	14,169 (73)
cLocationX	2,805

a. Data available for 2,309 patients.

b. G1, well differentiated; G2, moderately well differentiated; G3, poorly differentiated; G4,

undifferentiated.

eTable 4. Clinical cancer characteristics of patients with adenosquamous and undifferentiated carcinoma

Characteristic	Adenosquamous Carcinoma (n=116) No. (%)	Undifferentiated Carcinoma (n=37) No. (%)
cT		
cT0	0 (0)	0 (0)
cTis	0 (0)	0 (0)
cT1	10 (11)	3 (13)
cT2	14 (15)	6 (25)
cT3	60 (65)	14 (58)
cT4a	9 (9.7)	1 (4.2)
cTX	23	13
cN		
cN0	29 (32)	10 (42)
cN+	61 (68)	14 (58)
cN1	17 (85)[a]	0 (0)[b]
cN2	3 (15)[a]	0 (0)[b]
cN3	0 (0)[a]	0 (0)[b]
cNX	26	13
cM		
cM0	108 (93)	36 (97)
cM1	8 (6.9)	1 (2.7)
Grade[c]		
cG1	4 (12)	0 (0)
cG2	6 (18)	0 (0)
cG3	23 (70)	0 (0)
cG4	0 (0)	37 (100)
cGX	83	0

Location		
cUpper	3 (3.1)	0 (0)
cMiddle	20 (21)	10 (33)
cLower	74 (76)	20 (67)
cLocationX	19	7

a. Data available for 20 patients.

b. Data available for 0 patients.

c. G1, well differentiated; G2, moderately well differentiated; G3, poorly differentiated; G4,

undifferentiated.