Original Article

Variation by stage in the effects of prediagnosis weight loss on mortality in a prospective cohort of esophageal cancer patients

S. Shen,¹ J. L. Araujo,² N. K. Altorki,³ J. R. Sonett,⁴ A. Rodriguez,¹ K. Sungur-Stasik,⁴ C. F. Spinelli,³
A. I. Neugut,¹ J. A. Abrams¹

¹Department of Medicine, Columbia University Medical Center, ²Veterans' Administration New York Harbor Healthcare System, Brooklyn, New York, USA, ³Department of Thoracic Surgery, Weill Cornell Medical Center, New York, and ⁴Thoracic Surgery, Columbia University Medical Center

SUMMARY. Cancer cachexia is increasingly recognized as a poor prognostic marker for various tumor types. Weight loss in esophageal cancer is multifactorial, as patients with bulky tumors also have reduced ability to eat. We aimed to investigate the relationship between prediagnosis weight loss and mortality in esophageal cancer and to determine whether these associations vary with tumor stage. We conducted a prospective cohort study of esophageal cancer patients at two tertiary centers. We recorded baseline patient characteristics including medications, smoking, body mass index, and weight loss in the year prior to diagnosis, and collected data on treatment and outcomes. We used Cox regression modeling to determine the associations between percent weight loss and outcomes. The main outcome of interest was all-cause mortality; secondary endpoints were esophageal cancer-specific mortality and development of metastases. We enrolled 134 subjects, the majority of whom had adenocarcinoma (82.1%); median percent weight loss was 4.7% (IQR: 0%–10.9%). Increasing percent weight loss was not associated with all-cause mortality ($p_{\text{trend}} = 0.36$). However, there was evidence of significant interaction by tumor stage ($p = 0.02$). There was a strong and significant association between prediagnosis weight loss and mortality in patients with T stages 1 or 2 (adjusted HR 8.26 for highest versus lowest tertile, 95%CI 1.11–61.5, $p_{\text{trend}} = 0.03$) but not for T stages 3 or 4 ($p_{\text{trend}} = 0.32$). Body mass index one year prior to diagnosis was not associated with mortality. Prediagnosis weight loss was associated with increased all-cause mortality only in patients with early stage esophageal cancer. This suggests that tumor-related cachexia can occur early in esophageal cancer and represents a poor prognostic marker.

KEY WORDS: body mass index, cachexia, esophageal neoplasms, weight loss.

INTRODUCTION

The incidence of esophageal cancer has risen over the past several decades, primarily due to the increasing

incidence of adenocarcinoma.^{1,2} Although there have been major advances in treatment, the 5-year survival rate remains less than 20%.² Risk factors for mortality in esophageal cancer include advanced age, black race, increased tumor depth and length, poor differentiation, and greater number of positive lymph nodes.³ The literature on the effect of body mass index (BMI) on survival is inconclusive, with some studies showing that higher BMI is protective, while others show no effect on overall survival.^{4–6} Cachexia is a more recently identified prognostic marker, but has not been extensively studied in esophageal cancer.

The syndrome of cancer cachexia consists of a combination of weight loss from skeletal muscle and adipose tissue wasting, and systemic inflammation. It is estimated that cachexia is the cause of death in approximately 20% of cancer patients.⁷ In terminally ill patients with cancer, >10% weight loss is

Address correspondence to: Dr Julian A Abrams, 630 West 168th St., P&S 3-401, New York, NY 10032, USA.

Email: ja660@cumc.columbia.edu

Conflicts of Interest: The authors declare no conflicts of interest.

Specific author contributions: Study concept and design: Sherry Shen, James L. Araujo, Nasser K. Altorki, Joshua R. Sonett, Alfred I. Neugut, Julian A. Abrams; Acquisition of data: Sherry Shen, James L. Araujo, Adriana Rodriguez, Kivilcim Sungur-Stasik, Catherine F. Spinelli; Data analysis and interpretation: Sherry Shen, Julian A. Abrams; Drafting of manuscript: Sherry Shen, Julian A. Abrams; Critical revision of manuscript: Sherry Shen, James L. Araujo, Nasser K. Altorki, Joshua R. Sonett, Adriana Rodriguez, Kivilcim Sungur-Stasik, Catherine F. Spinelli, Alfred I. Neugut, Julian A. Abrams; Final approval of manuscript: Sherry Shen, James L. Araujo, Nasser K. Altorki, Joshua R. Sonett, Adriana Rodriguez, Kivilcim Sungur-Stasik, Catherine F. Spinelli, Alfred I. Neugut, Julian A. Abrams.

associated with worse survival.^{8,9} Among all cancers, there appears to be a direct relationship between greater percent weight loss and decreased survival, especially among patients with lower BMI at baseline.¹⁰

The incidence of weight loss in patients with esophageal cancer is among the highest of all cancer types, nearing that of pancreatic and gastric cancers; the majority of esophageal cancer patients have experienced weight loss by the time of diagnosis.^{11,12} Previous studies suggest that pretreatment weight loss of >10% is associated with worse survival in esophageal cancer patients.^{13–17} However, weight loss in esophageal cancer is multifactorial, with contributions from systemic inflammation as well as decreased caloric intake due to mechanical obstruction by bulky tumors.¹⁸ The effects of weight loss are further complicated by neoadjuvant therapy and surgery, as significant weight loss during or after treatment is also associated with decreased survival.^{19,20} A better understanding of the mechanisms that underlie weight loss in esophageal cancer and of prognostic factors at the time of diagnosis are needed in order to identify potential targets of intervention.

To address these issues, we investigated the effects of prediagnosis weight loss on outcomes in a prospective cohort of esophageal cancer patients that has previously been studied, and assessed whether these effects differed by tumor stage.²¹

MATERIALS AND METHODS

Study cohort

The study design was a prospective cohort study of adult patients with newly diagnosed, histologically confirmed primary esophageal cancer enrolled at two tertiary care centers in New York, NY, from 2009 to 2015. We enrolled 167 individuals after obtaining written informed consent. The Institutional Review Boards at Columbia University Medical Center and Weill Cornell Medical College approved the study. We excluded individuals who were enrolled >180 days following diagnosis, did not report current weight or weight one year prior to diagnosis in the questionnaire, in whom the highest degree of neoplasia was high-grade dysplasia, or who had a coexisting malignancy (besides nonmelanoma skin cancers) within 3 years before diagnosis.

Baseline assessment

Upon enrollment, we administered a questionnaire assessing baseline characteristics, including demographics, medical history, medication use, lifestyle factors, family history of cancer, smoking, and alcohol history. We used self-reported height and weight to

calculate BMI one year prior to diagnosis and percent weight change in the year prior to diagnosis. We used both patient self-report and medical records to document medical comorbidities and utilized the Charlson comorbidity index to assess disease burden, excluding esophageal cancer.²²

Tumor characteristics

From surgery and pathology reports, we ascertained each subject's diagnosis date, tumor histology, differentiation, and if applicable, human epidermal growth factor receptor-2 status (negative, positive, or equivocal). If the differentiation included two grades, we assigned the worse of the two. We used endoscopy and surgical reports to determine tumor location (esophagogastric junction, lower, mid, or upper esophagus). We classified tumor stage per the cancer staging manual of the American Joint Committee on Cancer, 7th ed.²³ We obtained pathologic T stage from operative reports in those who underwent curative resection (esophagectomy or endoscopic mucosal resection) and clinical T stage from endoscopic ultrasound reports. We used clinical T stage in our analyses unless the patient underwent surgery without neoadjuvant chemoradiation, in which case we used pathologic T stage from the resection specimen. We recorded lymph node status as positive if there was any clinical or pathologic evidence of lymph node involvement prior to neoadjuvant therapy; we classified celiac, paraesophageal, and cervical lymph node involvement as lymph node positive, not distant metastases.²³ We recorded the presence and site of distant metastases based on imaging and pathology reports.

Follow-up

We collected follow-up data on imaging, surveillance endoscopies, and treatment for each subject. We recorded deaths and date of death through review of the medical record, the Social Security Death Index, and contacting next of kin.²⁴ We classified death as esophageal cancer-specific if related to tumor burden (failure to thrive due to an inoperable tumor, obstructive disease, extensive metastases), tumor complications (hemorrhage from the tumor), or treatment complications (postesophagectomy sepsis, respiratory failure). We determined cause of death by two-investigator consensus.

Clinical endpoints and statistical analysis

The primary exposure of interest was percent weight loss in the year prior to diagnosis, which we categorized by tertiles. The primary endpoint was all-cause mortality; secondary endpoints were esophageal cancer-specific mortality and development of metastases. We defined overall survival as the time from

diagnosis to death from any cause, disease-specific survival as the time from diagnosis to death related to esophageal cancer, and metastasis-free survival as the time from diagnosis to first documented occurrence of metastasis.

We used Student's *t*-tests and Wilcoxon rank sum tests to analyze continuous variables, and Fisher's exact and Kruskal–Wallis tests for categorical variables. For time-to-event analyses, we used the date of diagnosis as time zero; we calculated time-to-death for individuals who died and censored all other individuals at the last time point at which they were known to be alive. For development of metastases, we only included individuals who were metastasis-free at enrollment and had ≥ 6 months of follow-up imaging.

We used the log-rank test to compare survival curves between percent weight loss tertiles. We performed univariate Cox modeling to determine the unadjusted associations between demographic, clinical, and tumor variables and mortality. We used Cox proportional hazards modeling to calculate hazard ratios (HRs) and 95% confidence intervals (CIs). We analyzed percent weight loss using a series of models: Model 1—unadjusted; Model 2—adjusted for BMI one year prior to diagnosis; Model 3—adjusted for BMI one year prior and receipt of treatment (surgery, chemotherapy, and/or radiation therapy); Model 4—final multivariable model. To build the final multivariable models, we included all variables that changed the beta coefficient for percent weight loss by $\geq 10\%$, then removed variables one at a time with the highest *p*-value that was >0.15 . In all models, we used complete subject analyses. We performed all statistical analyses using Stata 14.0 for Mac (StataCorp, College Station, TX), and defined statistical significance as $p < 0.05$.

RESULTS

Study population

We enrolled 167 patients over six years. We excluded 33 due to enrollment >180 days after diagnosis ($n = 16$), failure to report weight on questionnaire ($n = 4$), coexisting malignancy within 3 years before diagnosis ($n = 6$), high-grade dysplasia as the highest degree of neoplasia ($n = 5$), reclassification as gastric cancer ($n = 1$), or withdrawal of consent ($n = 1$). Baseline patient characteristics are shown in Table 1, and tumor characteristics are shown in Table 2. Among included subjects ($n = 134$), the mean age at diagnosis was 64.5 (SD 11.1). The majority of subjects were male (109, 81.3%) and white (119, 88.8%). Most tumors were adenocarcinoma (110, 82.1%), and located in the lower third of the esophagus or gastroesophageal junction (110, 82.1%). Ninety-four subjects underwent surgery for curative intent (71.2%) and 96 subjects received chemoradiation therapy (71.6%). The

Table 1 Baseline patient characteristics of an esophageal cancer cohort ($n = 134$) at Columbia University and Weill Cornell Medical Centers (2009–2015)

Age at diagnosis, mean (SD)	64.5 (11.1)
Sex, male (%)	109 (81.3%)
Race, white (%)	119 (88.8%)
Ethnicity, non-Hispanic (%)	119 (88.8%)
Tobacco exposure (%)	
Never	35 (26.1%)
Former	75 (66.0%)
Current	24 (17.9%)
Charlson comorbidity index, median (IQR) [†]	1 (0–1)
Charlson comorbidity index (%) [‡]	
0	66 (49.6)
1	36 (27.1)
2	14 (10.5)
3 or greater	17 (12.8)
BMI at diagnosis, median (IQR)	26.4 (23.4–29.4)
BMI one year prior, median (IQR)	28.3 (24.4–31.0)
BMI, one year prior (%)	
Underweight (15–20)	9 (6.7%)
Normal (>20 –25)	29 (21.6%)
Overweight (>25 –30)	54 (40.3%)
Obese (>30)	42 (31.3%)
Weight loss in pounds, median (IQR)	10 (0–20)
Weight loss (%)	
No weight loss	39 (29.1%)
>0 , $<5\%$	31 (23.1%)
≥ 5 , $<10\%$	28 (20.9%)
$\geq 10\%$	36 (26.9%)

[†]Esophageal cancer was excluded from Charlson comorbidity index score.

[‡]Data missing in 1 individual.

BMI, body mass index; IQR, interquartile range; SD, standard deviation.

Table 2 Tumor characteristics of an esophageal cancer cohort ($n = 134$) at Columbia University and Weill Cornell Medical Centers (2009–2015)

Histology (%)	
Adenocarcinoma	110 (82.1%)
HER-2 positive [‡]	18 (25.7%)
Squamous cell carcinoma	24 (17.9%)
Grade (%)	
Well or moderately differentiated	48 (35.8%)
Poor	62 (46.3%)
Unknown	24 (17.9%)
Location (%)	
Gastroesophageal junction and lower third	110 (82.1%)
Middle and upper third	24 (17.9%)
T stage (%)	
T1–T2	49 (36.6%)
T3–T4	63 (47.0%)
Tx	22 (16.4%)
Lymph node status (%) [‡]	
Negative	46 (34.3%)
Positive	86 (64.9%)
Metastatic disease (%)	
No	123 (91.8%)
Yes	11 (8.2%)

[†]70 out of 110 (63.6%) adenocarcinomas assessed for HER-2 status.

[‡]Data missing in 1 individual.

HER-2, human epidermal growth factor receptor 2.

median follow-up time for the entire cohort was 25.1 months (IQR: 9.7–43.7) and 36.6 months (IQR: 24.7–59.2) among subjects who were still alive at the time of analysis.

The median BMI one year prior to diagnosis was 28.3 (IQR: 24.4–31.0) and at time of diagnosis was

26.4 (IQR: 23.4–29.4) (Table 1). The median weight loss in the year prior to diagnosis was 10 pounds (IQR: 0–20), with a median 4.7% weight loss (IQR: 0–10.9). Sixty-four subjects (47.9%) experienced $\geq 5\%$ weight loss, and 36 (26.9%) had $\geq 10\%$ weight loss. In multivariable logistic regression analysis, greater percent weight loss was significantly associated with greater BMI one year prior to diagnosis, non-white race, squamous cell histology, and higher T stage. History of hyperlipidemia was associated with less weight loss.

All-cause mortality

At the end of the follow-up period, 59 individuals had died, corresponding to a 3-year overall survival of 54.0% (95%CI 44.4%–62.7%). Greater percent weight loss was significantly associated with all-cause mortality in univariate analyses (unadjusted HR 2.92 for highest vs. lowest tertile, 95%CI 1.47–5.78, $p_{\text{trend}} = 0.002$) and when adjusted for BMI (HR 3.09 for highest vs. lowest tertile, 95%CI 1.55–6.16, $p_{\text{trend}} = 0.001$) (Table 3). However, there was no significant association between greater percent weight loss and all-cause mortality in the final multivariable model, which adjusted for BMI, receipt of treatment, and histology (HR 1.53 for highest vs. lowest tertile, 95%CI 0.68–3.44, $p_{\text{trend}} = 0.36$). When we restricted the analyses to patients who underwent surgery with curative intent, we found that the association between weight loss and all-cause mortality was qualitatively similar (adjusted HR 2.27 for highest vs. lowest tertile, 95%CI 0.95–5.43). There was no association between BMI one year prior to diagnosis and all-cause mortality in the full cohort (adjusted HR 1.00, 95%CI 0.95–1.06).

We found evidence of significant interaction ($p = 0.02$) between percent weight loss and T stage. Among patients with T stages 1 or 2, percent weight loss was strongly and significantly associated with all-cause mortality, adjusted for BMI one year prior to diagnosis (HR 6.97 for highest vs. lowest tertile, 95%CI 1.39–34.8, $p_{\text{trend}} = 0.01$), but not in patients with T stages 3 or 4 (HR 1.48 for highest vs. lowest tertile, 95%CI 0.60–3.66, $p_{\text{trend}} = 0.43$). The association remained significant when adjusted for receipt of treatment among those with T stages 1 or 2 (HR 8.26 for highest vs. lowest tertile, 95%CI 1.11–61.5, $p_{\text{trend}} = 0.03$). No other variables remained in the final multivariable model for T stages 1 or 2.

Esophageal cancer-specific mortality

A total of 37 subjects (62.7% of deaths) died of esophageal cancer. There was a nonsignificant trend toward increased esophageal-cancer-specific mortality with increased weight loss in unadjusted analyses (HR 2.06 for highest vs. lowest tertile, 95%CI 0.93–4.55, $p_{\text{trend}} = 0.08$) and when adjusted for BMI one year prior to diagnosis (HR 2.14 for highest vs. lowest tertile, 95%CI 0.96–4.76, $p_{\text{trend}} = 0.06$). The association was markedly attenuated with further adjustment in the final multivariable model (HR 1.00 for highest vs. lowest tertile, 95%CI 0.40–2.50, $p_{\text{trend}} = 0.99$) (Supplementary Table S1). There was no association between BMI one year prior to diagnosis and esophageal cancer-specific mortality in the full cohort (adjusted HR 1.03, 95%CI 0.97–1.10). We found no evidence of interaction between T stage and percent weight loss, but given the interaction in all-cause mortality, we stratified the analyses and found no major qualitative differences between the strata.

Table 3 Hazard ratios with 95% confidence intervals for the associations between prediagnosis weight loss and risk of all-cause mortality in a prospective cohort of esophageal cancer patients, 2009–2015

	First tertile	Second tertile	Third tertile	p_{trend}
All patients				
Model 1	1 (referent)	2.34 (1.20–4.71)	2.92 (1.47–5.78)	0.002
Model 2	1 (referent)	2.44 (1.23–4.84)	3.09 (1.55–6.16)	0.001
Model 3	1 (referent)	2.09 (1.00–4.37)	2.02 (0.94–4.33)	0.09
Model 4	1 (referent)	1.94 (0.93–4.07)	1.53 (0.68–3.44)	0.36
T Stages 1 & 2				
Model 1	1 (referent)	4.68 (1.17–18.8)	5.75 (1.15–28.6)	0.01
Model 2	1 (referent)	4.70 (1.17–18.9)	6.97 (1.39–34.8)	0.008
Model 3	1 (referent)	5.69 (1.06–30.5)	8.26 (1.11–61.5)	0.03
Model 4 [†]	n/a	n/a	n/a	n/a
T Stages 3 & 4				
Model 1	1 (referent)	1.65 (0.68–3.96)	1.45 (0.59–3.58)	0.45
Model 2	1 (referent)	1.69 (0.70–4.12)	1.48 (0.60–3.66)	0.43
Model 3	1 (referent)	1.52 (0.61–3.78)	0.82 (0.30–2.21)	0.64
Model 4	1 (referent)	1.19 (0.47–3.00)	0.64 (0.23–1.75)	0.32

Model 1: unadjusted.

Model 2: adjusted for BMI one year prior to diagnosis.

Model 3: adjusted for BMI one year prior to diagnosis and treatment received.

Model 4 (full model): adjusted for BMI one year prior to diagnosis, treatment received, and histology.

[†]Model 3 represents the full model for the stratum of T stages 1 & 2.

Development of metastases

A total of 94 patients were metastasis free at baseline and had ≥ 6 months of follow-up surveillance imaging; 22 of these subjects (23.4%) developed metastases. We found no significant association between percent weight loss and development of metastatic disease in unadjusted analyses (HR 1.33 for highest vs. lowest tertile, 95%CI 0.46–3.84), or in the final multivariable model (HR 0.71, 95%CI 0.21–2.38) (Supplementary Table S2).

DISCUSSION

In our prospective cohort of esophageal cancer patients, there was no significant association between greater percent weight loss and all-cause mortality in the final model adjusted for BMI, treatment received, and tumor histology. Interestingly, the association between percent weight loss and all-cause mortality differed markedly by tumor stage. We found a strong, significant effect of weight loss on survival in patients with T1 or T2 tumors, but no association in those with T3 or T4 tumors. These results suggest that tumor-related cachexia can occur early in esophageal cancer and may represent a poor prognostic marker.

Weight loss is associated with decreased survival in many cancer types. In post-hoc analyses of chemotherapy clinical trials of colon cancer patients, weight loss was independently associated with poorer survival.^{25,26} In a study of gastric cancer patients, pre-diagnosis weight loss was associated with higher post-operative mortality.²⁷ Weight loss is also a poor prognostic marker in nongastrointestinal cancers, where tumor mass does not directly affect caloric intake. In a retrospective analysis of cervical cancer patients treated with chemotherapy, $>10\%$ weight loss prior to treatment was a predictor of poor outcome.²⁸ Among lung cancer patients treated with radiation $\pm$ chemotherapy, $>5\%$ pretreatment weight loss was associated with worse survival.²⁹ Weight loss may reflect muscle wasting; sarcopenia, demonstrated by low lumbar skeletal muscle indices on cross-sectional imaging, has also been associated with poorer prognosis.³⁰

Weight loss is also associated with decreased survival in esophageal cancer. In a multicenter retrospective analysis of esophageal cancer patients treated with chemoradiation, pretreatment weight loss of $\geq 10\%$ was significantly associated with worse survival in multivariate analyses adjusted for tumor location and volume.¹⁷ Two other retrospective analyses of esophageal cancer patients also reported associations between pretreatment weight loss and survival.^{13,16} In a more recent study of patients who underwent surgery, preoperative weight loss of $>10\%$ was associated with a modest but significant increase in 5-year

mortality (HR 1.34).³¹ However, these studies did not assess for differing effects of weight loss by tumor size. In esophageal cancer, weight loss is likely due to a combination of cachexia and decreased caloric intake due to dysphagia caused by bulky tumors. Thus, conclusions that can be drawn from these studies are limited regarding the relative contributions of these factors to weight loss and survival.

Cachexia is a syndrome of skeletal muscle mass depletion which occurs due to systemic inflammation, mechanical changes, anorexia, and neuroendocrine changes.³² When muscle loss contributes to physical burden and disability, it is categorized as frailty. Among cancer patients, frailty is associated with increased risk of all-cause and postoperative mortality, treatment complications, and is a risk factor for morbidity and mortality from cardiovascular disease.^{33–36} We speculate that patients with early stage tumors and greater weight loss may have had marked cancer-related cachexia and increased frailty, and were thus at greater risk of disease- and treatment-related complications and death. In our cohort, we found no association between weight loss and mortality in patients with advanced stage tumors. We speculate that weight loss due to decreased caloric intake secondary to dysphagia may not lead to frailty in the same fashion as tumor cachexia.

A second potential reason for the association between weight loss and mortality in earlier stage tumors is that cachexia may be a marker of more aggressive cancer, conferring worse prognosis. In pancreatic cancer patients, weight loss is associated with decreased survival in those undergoing resection or receiving palliative treatment compared to those with stable weight, suggesting a decreased treatment response.^{37,38} However, in our cohort there was no association between weight loss and esophageal cancer-specific mortality or development of metastases.

Cancer cachexia reflects a state of systemic inflammation; various circulating inflammatory markers are associated with worse outcomes in esophageal cancer. Elevated serum C-reactive protein and IL-6 levels are associated with weight loss and negatively affect survival.^{39,40} High serum CRP and IL-6 levels are also associated with increased risk of disease progression, tumor invasion, lymph node metastasis, and poorer response to chemotherapy.^{40–43} Elevated blood neutrophil: lymphocyte ratio, another potential marker of systemic inflammation, has been associated with disease recurrence, disease-specific mortality, and all-cause mortality in esophageal cancer.⁴⁴

The main strength of this study is the prospective cohort design, which allowed adjustment for potential confounders collected at baseline. We minimized recall bias by enrolling study participants shortly after diagnosis, and reduced selection bias, as outcomes were not known at the time of enrollment. Finally, we

obtained near complete follow-up data on treatment and surveillance over several years to assess for recurrence and metastases.

This study also has certain limitations. We used self-reported and not measured weights. However, studies show that self-reported weights are highly reliable, accurate, and correlate well with measured weights.⁴⁵ We reviewed the medical charts in a subset of our patients and found a strong correlation between reported and measured heights and weights (data not shown). This study included a relatively small sample size that was heterogeneous with regard to treatment received, and was limited to two tertiary care centers in the same region, which may limit the generalizability of our results. We did not collect data on dysphagia, frailty, inflammatory markers, or nutritional status at baseline, which would have provided a clearer understanding of how weight loss contributes to mortality.

In conclusion, in a prospective cohort study, greater prediagnosis weight loss was associated with significantly increased all-cause mortality among patients with early stage esophageal cancer. Greater percent weight loss in early esophageal cancer may serve as a marker of more severe systemic inflammation, cachexia, and worse prognosis. Future studies should aim to verify our results and correlate weight loss with inflammatory markers and cachexia as well as dysphagia scores and frailty indices to elucidate further the mechanisms by which weight loss affects survival in esophageal cancer.

SUPPLEMENTARY DATA

Supplementary data are available at [DOTESO](#) online.

ACKNOWLEDGMENTS

We would like to acknowledge Christian Espino and Kazeem Abdul for their help with subject enrollment. Support was provided by: The Scholarly Projects Program and the Sara and Arnold P. Friedman Award at Columbia University College of Physicians and Surgeons (SS); a Career Development Award (K07 CA132892) and an Administrative Supplement (CA132892-02S1) from the National Cancer Institute (JAA).

References

- Pohl H, Sirovich B, Welch H G. Esophageal adenocarcinoma incidence: are we reaching the peak? *Cancer Epidemiol Biomarkers Prev* 2010; 19: 1468–70.
- Siegel R L, Miller K D, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015; 65: 5–29.
- Eloubeidi M A, Desmond R, Arguedas M R, Reed C E, Wilcox C M. Prognostic factors for the survival of patients with esophageal carcinoma in the U.S.: the importance of tumor length and lymph node status. *Cancer* 2002; 95: 1434–43.
- Kayani B, Okabayashi K, Ashrafian H *et al*. Does obesity affect outcomes in patients undergoing esophagectomy for cancer? A meta-analysis. *World J Surg* 2012; 36: 1785–95.
- Scarpa M, Cagol M, Bettini S *et al*. Overweight patients operated on for cancer of the esophagus survive longer than normal-weight patients. *J Gastrointest Surg* 2013; 17: 218–27.
- Blom R L, Lagarde S M, Klinkenbijn J H, Busch O R, van Berge Henegouwen M I. A high body mass index in esophageal cancer patients does not influence postoperative outcome or long-term survival. *Ann Surg Oncol* 2012; 19: 766–71.
- Warren S. The immediate causes of death in cancer. *Am J Med Sci* 1932; 184: 610–5.
- Maltoni M, Pirovano M, Scarpi E *et al*. Prediction of survival of patients terminally ill with cancer. Results of an Italian prospective multicentric study. *Cancer* 1995; 75: 2613–22.
- Chuang R B, Hu W Y, Chiu T Y, Chen C Y. Prediction of survival in terminal cancer patients in Taiwan: constructing a prognostic scale. *J Pain Symptom Manage* 2004; 28: 115–22.
- Martin L, Senesse P, Gioulbasanis I *et al*. Diagnostic criteria for the classification of cancer-associated weight loss. *J Clin Oncol* 2015; 33: 90–99.
- Laviano A, Meguid M M, Inui A, Muscaritoli M, Rossi-Fanelli F. Therapy insight: cancer anorexia-cachexia syndrome—when all you can eat is yourself. *Nat Clin Pract Oncol* 2005; 2: 158–65.
- Daly J M, Fry W A, Little A G *et al*. Esophageal cancer: results of an American College of Surgeons Patient Care Evaluation Study. *J Am Coll Surg*. 2000; 190: 562–72; discussion 572–563.
- Stahl M, Wilke H, Stuschke M *et al*. Clinical response to induction chemotherapy predicts local control and long-term survival in multimodal treatment of patients with locally advanced esophageal cancer. *J Cancer Res Clin Oncol* 2005; 131: 67–72.
- Polee M B, Hop W C, Kok T C *et al*. Prognostic factors for survival in patients with advanced oesophageal cancer treated with cisplatin-based combination chemotherapy. *Br J Cancer* 2003; 89: 2045–50.
- Kelsen D P, Ginsberg R, Pajak T F *et al*. Chemotherapy followed by surgery compared with surgery alone for localized esophageal cancer. *N Engl J Med* 1998; 339: 1979–84.
- Streeter O E, Jr, Martz K L, Gaspar L E *et al*. Does race influence survival for esophageal cancer patients treated on the radiation and chemotherapy arm of RTOG #85-01? *Int J Radiat Oncol Biol Phys* 1999; 44: 1047–52.
- Crehange G, Bosset M, Lorchel F *et al*. Tumor volume as outcome determinant in patients treated with chemoradiation for locally advanced esophageal cancer. *Am J Clin Oncol* 2006; 29: 583–7.
- Deans D A, Tan B H, Wigmore S J *et al*. The influence of systemic inflammation, dietary intake and stage of disease on rate of weight loss in patients with gastro-oesophageal cancer. *Br J Cancer* 2009; 100: 63–9.
- Adenis A, Tresch E, Dewas S *et al*. Clinical complete responders to definite chemoradiation or radiation therapy for oesophageal cancer: predictors of outcome. *BMC Cancer* 2013; 13: 413.
- D'Journo X B, Ouattara M, Loundou A *et al*. Prognostic impact of weight loss in 1-year survivors after transthoracic esophagectomy for cancer. *Dis Esophagus* 2012; 25: 527–34.
- Araujo J L, Altorki N K, Sonett J R *et al*. Prediagnosis aspirin use and outcomes in a prospective cohort of esophageal cancer patients. *Therap Adv Gastroenterol* 2016; 9: 806–14.
- Charlson M E, Pompei P, Ales K L, MacKenzie C R. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–83.
- Edge S B, Compton C C. The American Joint Committee on Cancer: the 7th edition of the AJCC cancer staging manual and the future of TNM. *Ann Surg Oncol* 2010; 17: 1471–74.
- Quinn J, Kramer N, McDermott D. Validation of the Social Security Death Index (SSDI): an important readily-available outcomes database for researchers. *West J Emerg Med*. 2008; 9: 6–8.
- Lavin P, Mittelman A, Douglass H, Jr, Engstrom P, Klaassen D. Survival and response to chemotherapy for advanced colorectal adenocarcinoma: an Eastern Cooperative Oncology Group report. *Cancer* 1980; 46: 1536–43.
- Mitry E, Douillard J Y, Van Cutsem E *et al*. Predictive factors of survival in patients with advanced colorectal cancer: an

- individual data analysis of 602 patients included in irinotecan phase III trials. *Ann Oncol* 2004; 15: 1013–17.
- 27 Haugstvedt T K, Viste A, Eide G E, Soreide O. Factors related to and consequences of weight loss in patients with stomach cancer. The Norwegian multicenter experience. *Norwegian Stomach Cancer Trial. Cancer* 1991; 67: 722–9.
- 28 Kastritis E, Bamias A, Bozas G *et al*. The impact of age in the outcome of patients with advanced or recurrent cervical cancer after platinum-based chemotherapy. *Gynecol Oncol* 2007; 104: 372–6.
- 29 Jeremic B, Shibamoto Y. Pre-treatment prognostic factors in patients with stage III non-small cell lung cancer treated with hyperfractionated radiation therapy with or without concurrent chemotherapy. *Lung Cancer* 1995; 13: 21–30.
- 30 Kimura M, Naito T, Kenmotsu H *et al*. Prognostic impact of cancer cachexia in patients with advanced non-small cell lung cancer. *Support Care Cancer* 2015; 23: 1699–708.
- 31 van der Schaaf M K, Tilanus H W, van Lanschot J J *et al*. The influence of preoperative weight loss on the postoperative course after esophageal cancer resection. *J Thorac Cardiovasc Surg* 2014; 147: 490–95.
- 32 Anandavadivelan P, Lagergren P. Cachexia in patients with oesophageal cancer. *Nat Rev Clin Oncol* 2016; 13 (3): 185–98.
- 33 Handforth C, Clegg A, Young C *et al*. The prevalence and outcomes of frailty in older cancer patients: a systematic review. *Ann Oncol* 2015; 26: 1091–101.
- 34 Brown J C, Harhay M O, Harhay M N. The Prognostic Importance of Frailty in Cancer Survivors. *J Am Geriatr Soc* 2015; 63: 2538–43.
- 35 Dumurgier J, Elbaz A, Ducimetiere P, Tavernier B, Alperovitch A, Tzourio C. Slow walking speed and cardiovascular death in well-functioning older adults: prospective cohort study. *BMJ* 2009; 339: b4460.
- 36 Newman A B, Simonsick E M, Naydeck B L *et al*. Association of long-distance corridor walk performance with mortality, cardiovascular disease, mobility limitation, and disability. *JAMA* 2006; 295: 2018–26.
- 37 Davidson W, Ash S, Capra S, Bauer J, Cancer Cachexia Study G. Weight stabilisation is associated with improved survival duration and quality of life in unresectable pancreatic cancer. *Clin Nutr* 2004; 23: 239–47.
- 38 Bachmann J, Heiligensetzer M, Krakowski-Roosen H, Buchler M W, Friess H, Martignoni M E. Cachexia worsens prognosis in patients with resectable pancreatic cancer. *J Gastrointest Surg* 2008; 12: 1193–201.
- 39 Huang Y, Feng J F, Liu J S, Chen Q X. Prognostic role of serum C-reactive protein in esophageal cancer: a systematic review and meta-analysis. *Ther Clin Risk Manag* 2015; 11: 89–94.
- 40 Groblewska M, Mroczko B, Sosnowska D, Szmitkowski M. Interleukin 6 and C-reactive protein in esophageal cancer. *Clin Chim Acta* 2012; 413: 1583–90.
- 41 Oka M, Yamamoto K, Takahashi M *et al*. Relationship between serum levels of interleukin 6, various disease parameters and malnutrition in patients with esophageal squamous cell carcinoma. *Cancer Res* 1996; 56: 2776–80.
- 42 Nozoe T, Saeki H, Sugimachi K. Significance of preoperative elevation of serum C-reactive protein as an indicator of prognosis in esophageal carcinoma. *Am J Surg* 2001; 182: 197–201.
- 43 Fujiwara H, Suchi K, Okamura S *et al*. Elevated serum CRP levels after induction chemoradiotherapy reflect poor treatment response in association with IL-6 in serum and local tumor site in patients with advanced esophageal cancer. *J Surg Oncol* 2011; 103: 62–8.
- 44 Sharaiha R Z, Halazun K J, Mirza F *et al*. Elevated preoperative neutrophil: lymphocyte ratio as a predictor of postoperative disease recurrence in esophageal cancer. *Ann Surg Oncol* 2011; 18: 3362–9.
- 45 Bowman R L, DeLucia J L. Accuracy of self-reported weight: a meta-analysis. *Behavior Therapy* 1992; 23: 637–55.