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Chemoradiation is a Tolerable Therapy for Older Adults with Esophageal Cancer

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Abstract. *Introduction: Esophageal adenocarcinoma (EC) is increasing in incidence. Chemoradiation (CRT) is regarded as an acceptable alternative to surgery for the management of locally advanced EC. Ten-20% of EC patients are over the age of 75 years. There are limited data regarding efficacy and tolerability of CRT for the treatment of EC in the elderly. Patients and Methods: We retrospectively reviewed EC cases ≥70 years of age treated with CRT at a single institution. Clinical data, regarding therapy administered and outcome, were obtained from records. Clinical prognostic variables were analyzed against survival in a univariate model using the log rank test and in a multivariate model using Cox proportional hazards analysis. Results: Thirty consecutive patient records were identified. Commonly used chemotherapy agents included 5-fluorouracil, cisplatin, paclitaxel and oxaliplatin. There was no significant correlation between age and survival. The dose of chemotherapy or radiation was unrelated to any of the toxicities (p-values >0.16). The most common grade 3 or 4 toxicities were dehydration, hypotension, mucositis and pneumonitis. On multivariate analysis, adenocarcinoma histology (p=0.0094) and higher radiation dose (p=0.0158) were associated with improved survival. The median survival of the patients was 10 months. Conclusion: CRT was tolerable for older patients with EC. Close monitoring for dehydration, nutritional compromise and pulmonary toxicity is required.*

Esophageal adenocarcinoma (EC), which accounts for 1% of all malignancies in the United States, is increasing in incidence (1). Most patients with EC have locoregional or advanced disease at diagnosis and face a serious prognosis. Esophagectomy, the treatment of choice for locoregional disease, is associated with significant morbidity, particularly in the elderly (2). It is estimated that 10-20% of patients with EC are older than 75 years (3). Older patients are often excluded from esophagectomy and chemoradiation with curative intent is regarded as an acceptable alternative. However, there are limited data on the feasibility or efficacy of chemoradiation administered with a curative intent in the older population. The purpose of our study was to determine the outcome of older patients (>70 years) who received chemoradiation therapy for EC. This study addresses the major toxicity and survival concerns that limit enthusiasm for offering aggressive therapy to older patients with this disease.

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Key Words: Esophageal cancer, combined modality therapy, aged.

Patients and Methods

We retrospectively analyzed the medical records of patients with adeno- or squamous EC ≥70 years of age treated at Roswell Park Cancer Institute (RPCI), USA, with concurrent chemo- and radiation therapy from 1999 to 2004. Data from the RPCI tumor registry database were used with Institutional Review Board (IRB) approval. Criteria for inclusion in our review included: i) patient age 70 years or more, ii) histological diagnosis of esophageal adeno- or squamous carcinoma, iii) treatment with chemotherapy and concurrent radiation and iv) therapy administered at RPCI. Medical records were systematically examined for treatments administered, including chemotherapy and radiation therapy and their respective doses. Laboratory data for all treated patients were obtained from the medical records and tabulated. All clinical notes and hospitalization records were reviewed and all grade 3 or 4 toxicities were tabulated. Patient survival and current patient status information was obtained from the tumor registry. Statistical analysis was performed as indicated below.

Patient and disease characteristics (Table I): Data were available on 30 patients who received concurrent chemoradiation (CRT) during the study period. The median age was 72.5 years (range: 70-86 years). The male to female ratio was 4:1. The histology was adenocarcinoma in 28 and squamous cell carcinoma in 2 patients. Most patients (67%) were stage II or III (AJCC classification) on diagnosis. The data are updated through May 2004.

Chemotherapy. Chemotherapy was administered to all patients on an outpatient basis. Commonly used regimens included 5-fluorouracil (5-FU) as a single agent (n=5) or in combination with cisplatin (n=13) or oxaliplatin (n=8). Four patients received paclitaxel (Table II). 5-FU was given as a continuous infusion in all cases. Cisplatin

Table I. *Patient characteristics.*

Characteristic	Number of patients
Age -	
70 years	2
>70 years	28
Sex -	
Male	24
Female	6
Morphology -	
Adenocarcinoma	28
Squamous	2
AJCC Stage	
Stage 0 (TisNoMo)	0
Local: Stage I – II b.	16
Regional: Stage III.	10
Stage IV (Any T, Any N, M1)	4

Table II. *Chemotherapy.*

Drug	Number of patients	Dose range (mg/m^2/week)	Median dose (mg/m^2/week)
5-FU	26	325 - 2000	1220
Cisplatin	13	27.2 - 36.4	36.3
Oxaliplatin	8	30.9 - 46.4	46.4
Paclitaxel	4	50 - 80	80

was administered every 3 or 4 weeks. Oxaliplatin was administered every 2 weeks. The median dose intensity and range of doses/week for each of these drugs are depicted in Table II.

Radiation. Doses of external beam radiation ranged from 45-64.8 Gy with 1.8 Gy per fraction. CT simulation was used for all patients. Clinical target volume (CTV) was defined as gross tumor volume (GTV) plus 3-5 cm superior to the highest extension and inferior to the lowest extension of the tumor with a 2-cm radial margin. Planning target volume (PTV) was defined as CTV plus 1-cm margin. For oblique-fields planning, the radial margin was reduced if necessary to give a minimum 1-cm margin to the spinal cord in order to respect the spinal cord tolerance dose of 45 Gy.

Megavoltage equipment (≥6 MV) was used, typically treating anterior-posterior / posterior-anterior fields to 39.6 Gy and delivering the remaining dose using off-spinal-cord oblique fields.

Toxicities. Significant grade 3 or 4 toxicities are enumerated in Table III. Grade 3 or 4 hematological toxicities occurred in five patients, one patient requiring blood transfusion. Four patients required hospitalization for febrile neutropenia. Twelve patients experienced mucocutaneous toxicity as a consequence of 5-FU, which responded to dose modifications. Sixteen patients required hospitalization during treatment, most commonly for dehydration and hypotension (n=15). Pulmonary complications including pneumonitis were noted in six patients.

Table III. *Grade 3 or 4 toxicities of chemoradiation.*

Toxicity	Number of patients
Hematological -	
Anemia	1
Neutropenia	4
Mucositis	12
Gastrointestinal -	
Dehydration	15
Diarrhea	5
Pulmonary	6
Cardiac	2
Neurological -	
Neuropathy	2
Hospitalizations	16

Table IV. *Univariate results.*

	Frequency	Median survival	95% CI	*p*-value†
Overall	30	10	(8, 17)	-
Age of diagnosis				
≤72.5	15	10	(6, 19)	0.9896
>72.5	15	12	(8, 28)	(0.2281)
Histology				
Adenocarcinoma	24	12	(9, 28)	0.0054
Squamous	6	6	(3, 8)	
Type of chemo				
one agent	14	14	(6, 28)	0.4674
two agents	16	9.5	(8, 17)	
5-FU				
<1240	13	10	(6, 19)	0.4524
≥1240	13	15	(8, 29)	(0.7560)
Cycles				
1	13	9	(6, 29)	0.6416
>1	17	12	(8, 28)	
Radition dose (Gy)				
<50.4	11	9	(5, 13)	0.0808
≥50.4	19	13.5	(8, 29)	(0.0205)

† *P*-value of log-rank test of homogeneity. *P*-value in parentheses from Cox proportional hazards model treating the predictor as continuous variable.

Patient survival. Patient survival was calculated from the date of diagnosis until demise. Data were censored through May 2004. Of the thirty patients, only two were alive as of May 2004. Most patients died of recurrence: local (n=6) and distant metastatic disease (n=7). There were seventeen patients who were never disease-free (persistent disease). There was no treatment-related mortality. The median survival was 10 months (range: 3-45 months) (Figure 1).

Statistical analysis. Descriptive statistics, such as frequencies and relative frequencies, were computed for all categorical variables. Numeric variables were summarized using simple descriptive statistics such as the mean, median, standard deviation and range.

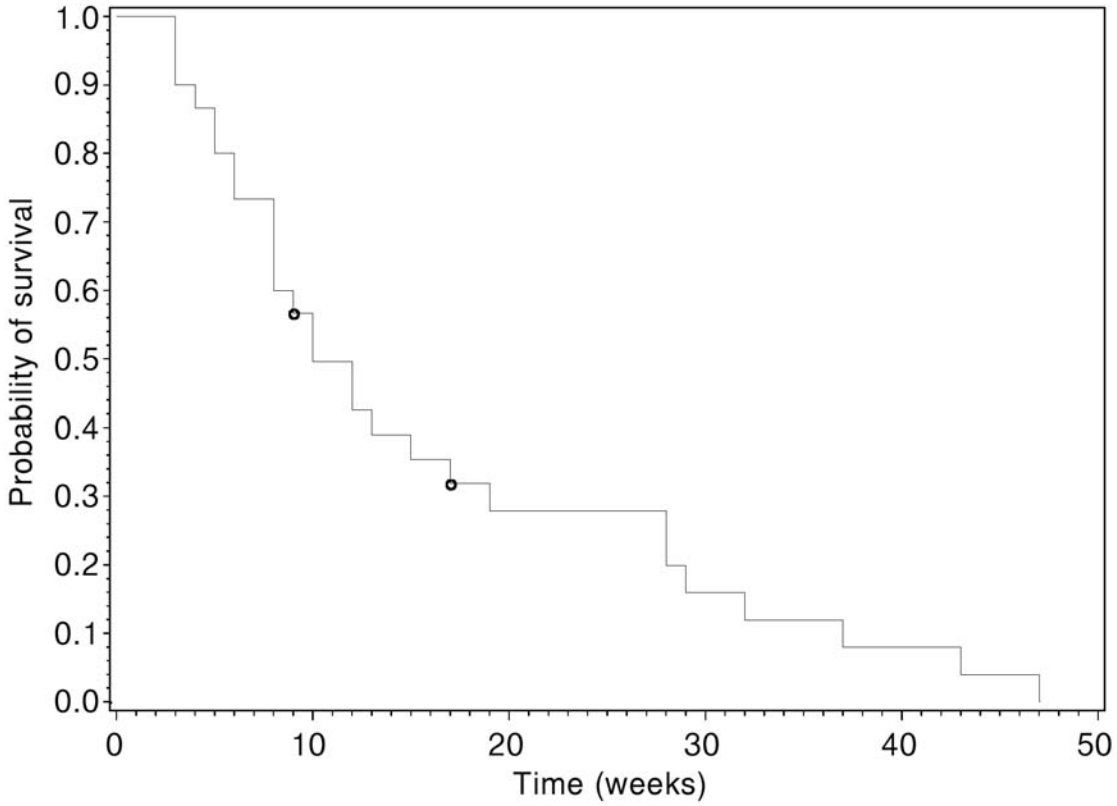

Figure 1. *Kaplan-Meier survival curve (circles represent censored values).*

The estimated survival distribution was obtained using the Kaplan-Meier method. Using this distributional estimate, summary descriptive statistics such as the median survival were obtained and the corresponding 95% confidence interval was computed. To evaluate differences in the survival distribution with respect to variables of interest, the log-rank test was used in the case of categorical predictors and Cox proportional hazards model was used in the case of continuous variables. Continuous variables were also analyzed after dichotomization for ease of graphical examination. The Cox model was further used in a multivariate setting in which all significant predictors in the univariate analyses were considered simultaneously (Table IV). To examine if age or dose was related to the occurrence of grade 3/4 toxicities, logistic regression was used. Model assumptions were evaluated using standard diagnostic tools and a nominal significance level of 0.05 was used throughout.

Results

Both histology and radiation dose showed statistical significance when analyzed together in a multivariate model with *p*-values of 0.009 and 0.02, respectively (Figures 2 and 3). Grade 3 or 4 toxicities were separately evaluated in terms of potential relationships with dose and age, *via* logistic regression, and with survival, using the log-rank test (see Table IV). The dose of chemotherapy or radiation was unrelated to any of the toxicities ($p>0.16$). Increasing age was found to be statistically significantly related to an increase in dehydration ($p<0.05$). Pulmonary toxicity was found to have a significant negative effect on survival ($p<0.05$). The above results are presented in Figure 4.

Discussion

The demographics of esophageal and gastric cancer have been changing in the United States over the past several decades. While the incidence of esophageal squamous cell carcinoma and distal gastric carcinoma has declined, adenocarcinomas of the esophagus and proximal stomach have increased in number, particularly among white males. Adenocarcinoma of the esophagus affects older adults. Based on current projections by the U.S. Bureau of the Census, by the year 2030, one in five Americans or 20.1% of the population will be >65 years of age (4, 5). We are likely to treat increasing numbers of older adults with EC. Treatment guidelines for these patients are needed. Approximately 50% of patients present with locoregional disease. Surgery is the treatment of choice for EC in its early stages, but is associated with significant morbidity. Poon *et al.* reviewed their experience with esophagectomy in 167 patients, who were 70 years of age

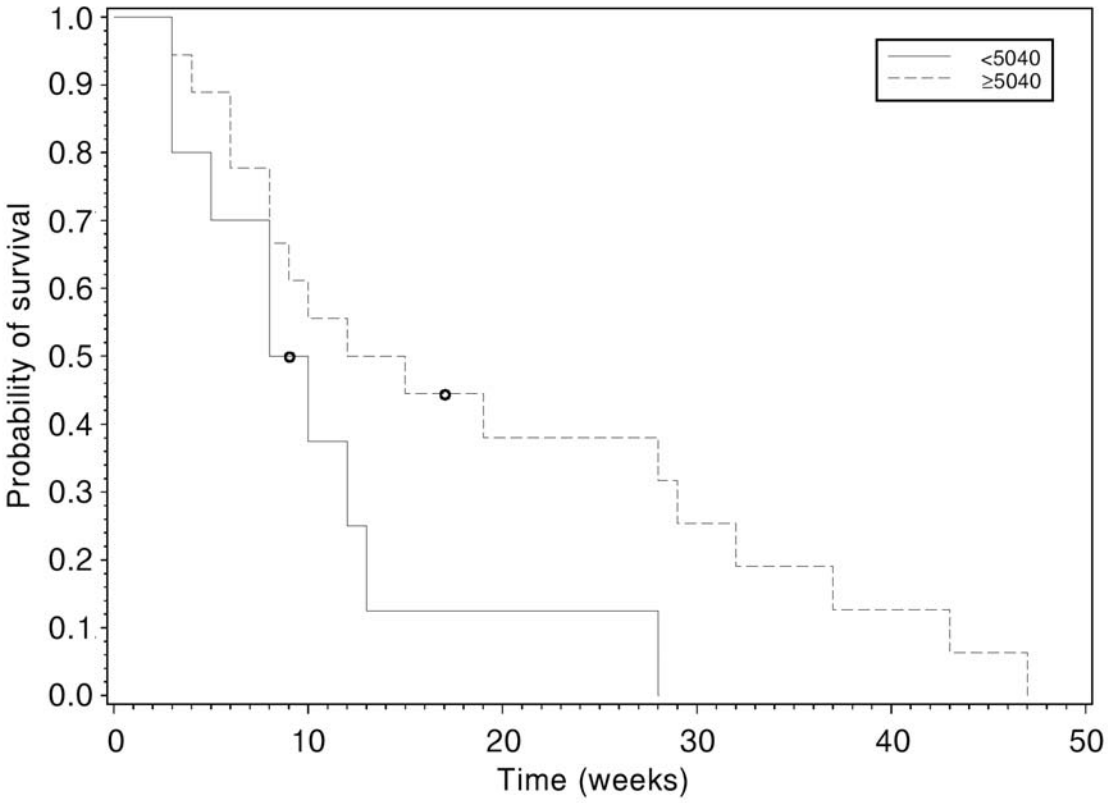

Figure 2. *Kaplan-Meier survival curves by dose of radiation: <5040 cGy ot ≥5040 cGy. (circles represent censored values).*

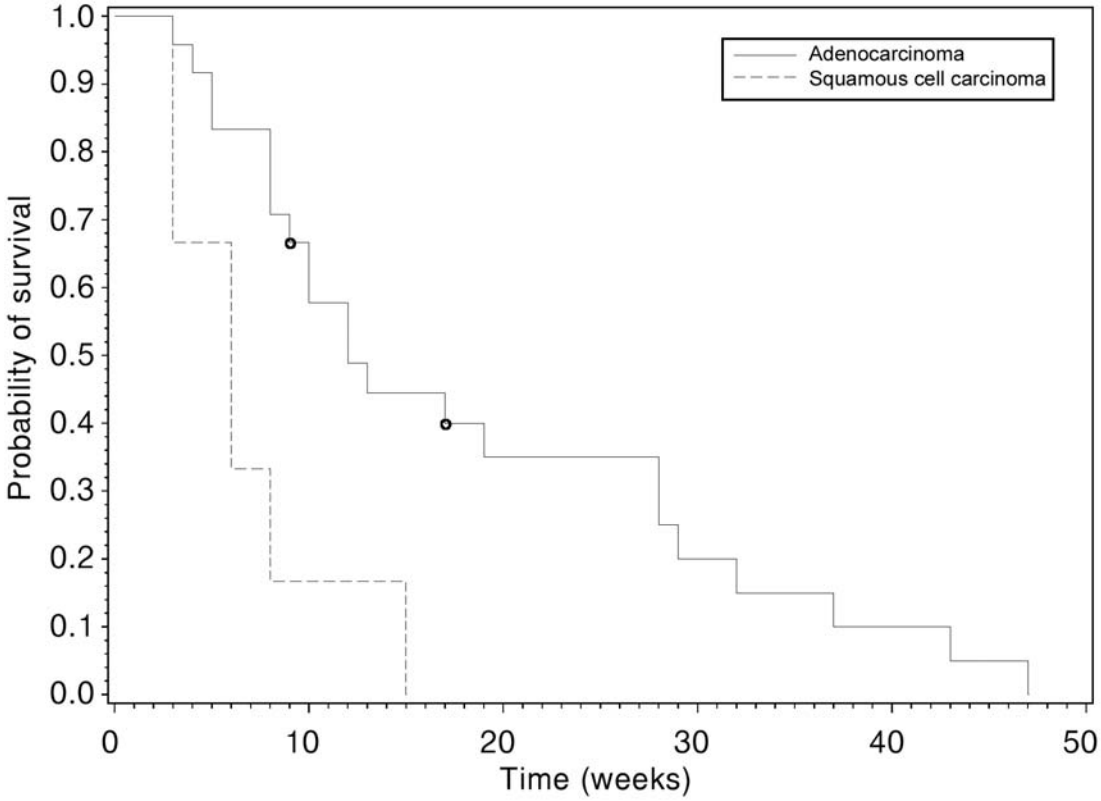

Figure 3. *Kaplan-Meier survival curves by histology (circles represent censored values).*

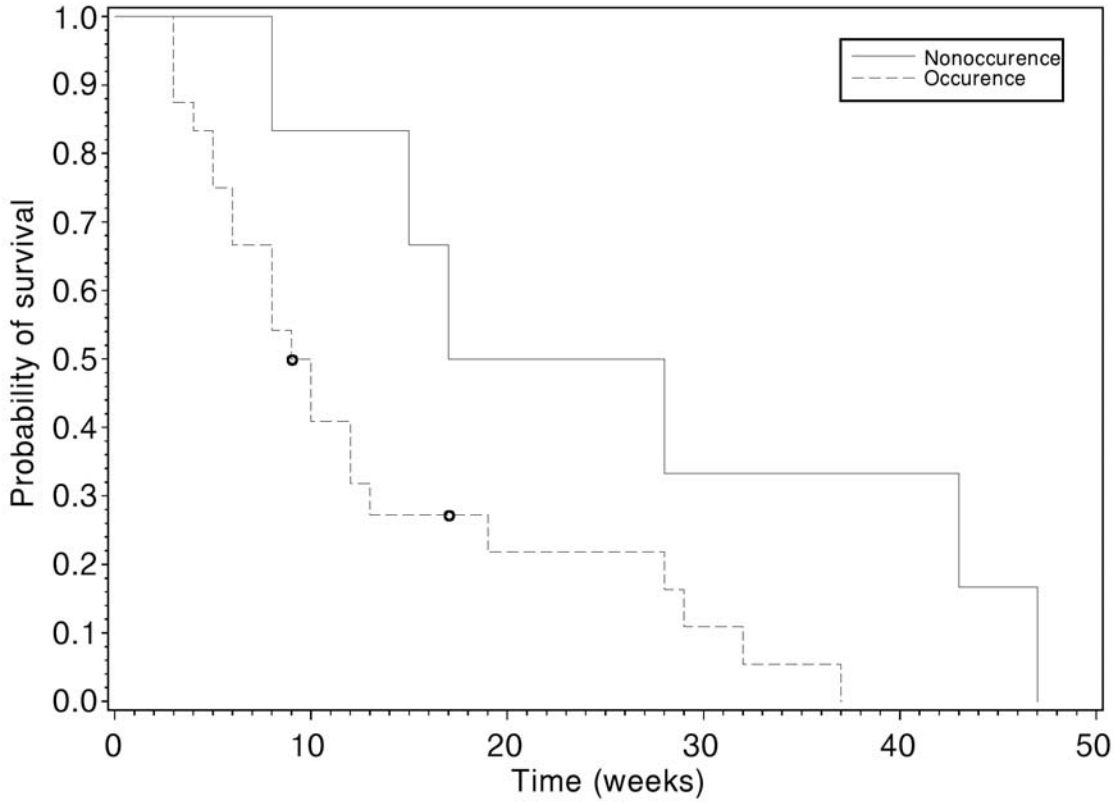

Figure 4. *Kaplan-Meier survival curves by pulmonary toxicity event (circles represent censored values).*

or greater. They found a significantly higher rate of medical complications as compared with a group of 570 patients less than 70 years of age (2). On the other hand, Sabel *et al.* retrospectively reviewed 413 patients with EC, treated at a single center and examined the post operative complications following esophagectomy in relation to patient age. They noted no significant differences between patients younger or older than 70 years of age, for estimated blood loss, intraoperative transfusions, length of stay, overall morbidity, or mortality. Only postoperative myocardial infarction and atrial fibrillation were increased in the older group (6). Yet, despite surgical resection, 5-year survival is less than 30% in locally advanced disease (7, 8). Post-operative morbidity and mortality are related to surgical volume and access to esophagectomy is limited to tertiary care centers. Most patients with EC in the U.S. are treated with non- surgical approaches including concurrent CRT (9, 10).

CRT is based on the results of the RTOG trial 85-01 (11), in which patients were randomized to receive either radiation alone or four cycles of 5-FU and cisplatin; the first two cycles concurrently with radiation. Patients who received CRT demonstrated significant improvement in median survival (14 *vs.* 9 months) and 5-year survival over those who received radiation alone. Since this study, CRT has become the standard of care in inoperable patients. Several newer agents are being incorporated into chemoradiation strategies. However, these trials commonly include patients <70 years of age. No prospective clinical trials, to our knowledge, have investigated CRT strategies specifically for the elderly. Possible reasons for the poor representation of older EC patients in clinical trials include the following: fewer trials are specifically designed for elderly patients; physicians, patients and family members may perceive older patients as less likely to benefit from or tolerate intensive treatment and older people are more likely to have other health problems (co-morbidities). There is a lack of financial, logistic and social support for participation of older patients in trials. Further, elderly patients may have more advanced disease on diagnosis due to less intensive screening. Yet, there is evidence to indicate that, across a range of tumor types, elderly patients have a survival similar to that of comparable younger patients (12). According to the 'Analysis of Patterns Of Care Study' in Japan, age was not a significant prognostic risk factor for esophageal cancer patients treated with radiation therapy (13). Radiation therapy may represent an important treatment modality for the elderly as well as for younger esophageal cancer patients.

In our study, CRT was tolerated by most patients. There was no significant correlation between age and survival. The

most common grade 3 or 4 toxicities observed were dehydration, hypotension, mucositis and pneumonitis. Hospitalization for dehydration and hypotension was required for 50% of the patients. Thus, close monitoring of nutritional and hydration status of these patients is necessary. The dose intensity of chemotherapy was unrelated to survival. The dose of radiation correlated with survival, suggesting that suboptimal doses may be deleterious in this population. The median survival of the patients in our review was 10 months. There was no treatment-associated mortality. Disease progression or metastasis were the most common causes of death. Adenocarcinoma had a significantly superior survival as compared to squamous cell carcinoma.

Our results compare well with the existing literature. Uno *et al.* studied 22 older patients with esophageal cancer. All patients were 75 years of age and older and received CRT with 5-FU. The median survival of this population was 9 months. Grade 3 or 4 toxicities occurred in 2 patients (14). Lorchel *et al.* reported the feasibility of CRT in patients older than 75 years of age with esophageal cancer. Seventeen patients received CRT with 5-FU and cisplatin in their study. Grade 2 toxicities were noted in 14 cases. Ten patients were free of disease for up to 44 months (15).

The chemotherapy agent of choice in this setting is unclear. Although 5-FU was the commonest agent used in our group of patients, as noted above, cisplatin has been used safely by others in the elderly. Studies in non-small lung cancer have indicated the feasibility of cisplatin-based chemotherapy in elderly patients with good performance status and adequate renal function (16). Radiation dose correlated with survival in our patient population on multivariate analysis, such a correlation has not yet been reported in this population to our knowledge. As noted in the results section, increased radiation doses did not correlate with increased toxicity. Adenocarcinoma histology was associated with improved survival in our study. This finding has also been reported by Siewert *et al.* (17).

Although our study had a limited number of patients, to our knowledge this is the largest reported study of older adults with esophageal cancer receiving chemoradiation therapy. In our experience this treatment is tolerable. However, dehydration, mucositis and pneumonitis can be dose limiting and careful follow-up for these toxicities is required. Prospective clinical studies of elderly EC patients are required.

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