ORIGINAL ARTICLE

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The Contribution of Curative Dose Radiotherapy to Primary Disease with Concurrent Chemotherapy on Survival in Patients with Metastatic Esophageal Cancer

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Abstract

Objective: Chemotherapy (CT) is the standard treatment for patients with metastatic esophageal cancer. Primary tumor progression is one of the important reasons for morbidity and mortality. Several studies have shown that aggressive treatment of primary tumors in metastatic patients may contribute to survival. In this study, patients with metastatic esophageal cancer and who received radiotherapy (RT) to the esophagus were evaluated.

Methods: Patients with metastatic esophageal cancer treated with esophageal RT were retrospectively evaluated. ECOG 3-4 patients were not included. Analyzes were performed with SPSS 22.0 (SPSS Inc., IBM Corp., Armonk, NY). Kaplan-Meier, Log-rank, and Cox-regression tests were used for the analysis.

Results: Forty-seven patients between 2009 and 2016 were evaluated. The median age was 61 (44-85); 60% of the patients were female. Eighty-nine percent of the histological subtype was squamous cell carcinoma. The mean RT dose was 45 Gy (20-68 Gy). Thirty percent of the patients had concurrent CT. The median overall survival (OS) was 14 months. 45 Gy and higher RT doses and concurrent CT were associated with better OS in univariate analysis (p=0.009, p=0.03). The median OS was nine months in patients receiving <45 Gy, and 20 months in patients who received RT ≥45 Gy; 24 months in patients who received concurrent CT, and 13 months in patients who did not. There was no significant prognostic factor in multivariate analysis.

Conclusion: Forty-five Gy and higher dose RT with concurrent CT after standard treatment may contribute to survival in metastatic esophageal cancer patients with good performance scores.

Keywords: Esophageal cancer, metastasis, radiotherapy, chemoradiotherapy

INTRODUCTION

Esophageal cancer ranks seventh in terms of incidence (604,000 new cases) and sixth in overall mortality (544,000 deaths) (1). East part of Turkey has the highest rates of esophageal cancer in the country and forms the bulk of daily oncology practice (2,3). According to the surveillance, epidemiology, and end results (SEER) data, 40% of the cases were diagnosed with the metastatic stage. Even if initially diagnosed as localized disease, the 5-year survival rate is below 50% (4).

Chemotherapy (CT) is the standard treatment approach for patients with metastatic esophageal cancer. However, survival rates are low. Primary tumor progression is one of the critical reasons for morbidity and mortality. Aggressive treatment of primary tumor in metastatic patients may contribute to survival. The best evidence for local radiotherapy (RT) for metastatic disease comes from prostate and nasopharyngeal cancer (5-7).

We, therefore, examined retrospectively survival outcomes associated with RT ± CT among patients with initially diagnosed

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metastatic esophageal cancer. We examined whether or not definitive dose RT with concomitant CT improves overall survival (OS) in patients presenting with metastatic esophageal cancer.

METHODS

We included patients with esophageal cancer who were metastatic stage at the time of diagnosis and confirmed histo-pathologically. All patients were staged with diagnostic endoscopy, radiological imaging including computed tomography scan of the chest, abdomen, and pelvis, and/or 18-fluoro-deoxyglucose positron emission tomography scan. All patients were classified according to the seventh edition of the American Joint Committee on Cancer staging manual. The patients were first treated with CT, and referred to the radiation oncology department for RT. Patients with stable disease and who had complete or partial responses were evaluated for RT. ECOG 3-4 patients were excluded from the study.

The treatment decision (RT doses and CT schema) was made by the treating physician. Patients were divided into three subgroups according to the treatment they received. Group 1 consisted of patients receiving just RT with a total dose of 30 Gy in ten fractions, which is generally applied as palliative doses. Group 2 consisted of patients receiving only RT with curative doses ≥45 Gy in 25-28 fractions. Group 3 consisted of patients receiving RT with curative doses combined with CT. Target volumes are defined according to the pre-CT scanning. All radiologically positive lymph node areas and primary lesions were included in the field. Elective lymph nodes were not treated. Local treatments for metastatic sites were not included in the analysis. After RT, the patients underwent regular clinical assessments and follow-up scans with 3-4 months of time-intervals for an objective assessment of the response. OS was the main objective and was defined as the time from diagnosis until death from any cause.

Statistical Analysis

All data were evaluated with SPSS 22.0 (SPSS Inc., IBM Corp., Armonk, NY). The Kaplan-Meier test was used for survival analysis. The Log-rank test and the Cox-regression test were used for the univariate analysis and multivariate analysis, respectively. The p value of less than 0.05 was considered statistically significant.

RESULTS

Forty-seven patients who were diagnosed with synchronous metastatic esophageal cancer and referred to the radiation oncology department for esophageal RT between 2009 and 2016 were evaluated. Sixty percent of the patients were female, and 40% were men. The median age of the patients was 61 (44-85) years. The most common metastatic sites were the liver, lung, distant lymph nodes, and bone. All patients were polymetastatic and without visceral crisis. Eighty-nine percent of the histological subtype was squamous cell carcinoma. Forty-seven percent of the tumors were located proximally, and the rest were located distally. The ECOG performance distribution of the patients was ECOG 0 in 3 (6%) patients; ECOG 1 in 10 (21%) patients and ECOG 2 in 34 (72%) patients. The distribution of T stage of the primary tumor was T2 in 1 (2%) patient; T3 in 40 (85%) patients, T4a in 3 (6%) patients; and T4b in 4 (7%) patients. The distribution of the N stage of the primary tumor was N1 in 2 (4%) patients; it was N2 in 12 (26%) patients, and N3 in 33 (70%) patients.

All patients had completed the CTs (2-6 cycles) for metastatic esophageal cancer. Cisplatin fluorouracil or paclitaxel carboplatin combination was used. RT was applied to 73% of patients with 2D-conventional and 27% of patients with the 3D-conformal method. The mean RT dose was 45 Gy (20-68 Gy). Fifty-one percent of the patients were Group 1 patients who had palliative doses (lower than 45 Gy, hypo-fractionation); 25% of the patients were group 2 who received a curative dose (45 Gy and higher, conventional fractionation) RT. Patients with group 3 who received concurrent CT were 24% of all patients. Concomitant CT regimens were 2 area under the curve carboplatin and 60 mg/m^2 paclitaxel weekly or cisplatin 60 mg/m^2 and 5-fluorouracil 1.000 mg/m^2 every 3 weeks.

All patients completed RT as planned. Patients who were given concurrent CT also completed their treatment without interruption. There were no patients who interrupted treatment due to treatment toxicity in our study. Mild esophageal toxicity was experienced in 39 patients; of 32 side effects 9 (23%) were grade 1 and 30 (77%) were grade 2. The median OS was 14 (5-74) months. Older age (≥65 years old), ECOG performance status, anatomical location of the tumor, T and N stages were not associated with survival outcome ($p<0.05$) in the univariate analysis (Table 1). 45 Gy and higher RT doses and concurrent CT applications were associated with better OS in the univariate analysis ($p=0.009$, $p=0.03$) (Figure 1A). One-year OS was 43% in patients receiving lower than 45 Gy and 56.5% in patients who received RT over 45 Gy, and the median OS was nine months and 20 months, respectively (Figure 1B). Median OS was 24 months in patients who received concurrent CT and 13 months in patients who did not (Figure 1C). There was no significant prognostic factor in multivariate analysis ($p<0.05$) (Table 1).

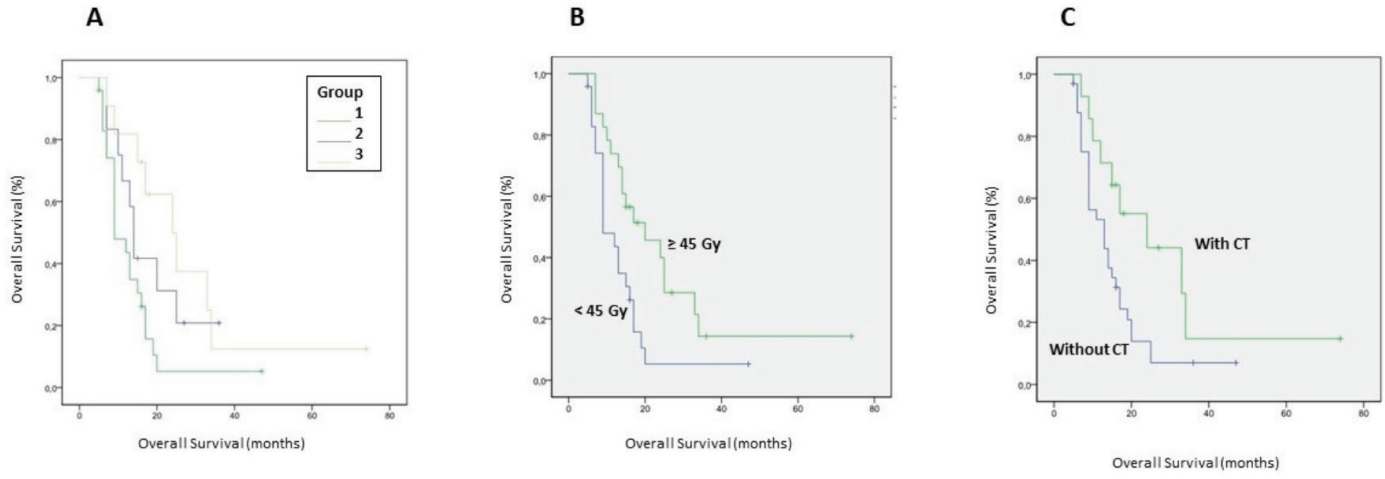

Figure 1. Overall survival curves according to the treatment groups (A), overall survival curves according to the RT dose groups (B), overall survival curves according to the concomitant CT status (C)

RT: Radiotherapy, CT: Chemotherapy

Table 1. Univariate and multivariate analysis of variables affecting overall survival

	p*	p**	95% confidence interval
Age group ≤65 >65	0.491	0.677	0.410-10.784
ECOG ECOG 0 ECOG 1 ECOG 2	0.219	0.869	0.408-7.477
Pathology group Squamous cell carcinoma Adenocarcinoma	0.032	0.088	0.841-12.214
Tumor location Upper Lower	0.377	0.839	0.452-1.906
T stage T2 T3 T4	0.291	0.600	0.693-1.953
N stage N1 N2 N3	0.561	0.601	0.315-1.953
RT dose group <45 Gy ≥45 Gy	0.009	0.642	0.157-10.346
Concomitant CT group Yes No	0.033	0.453	0.121-3.672
Treatment modality Palliative Radiotherapy Chemoradiotherapy	0.028	0.948	0.186-6.270

*Log-rank test, **Cox regression test, RT: Radiotherapy, CT: Chemotherapy

DISCUSSION

In this retrospective study, we found a significant improvement in OS with definitive dose RT to the primary tumor and concurrent CT in metastatic esophageal cancer patients. The standard treatment is CT, and the treatment aims to reduce the symptoms, improve the quality of life, and control the disease. Nevertheless, the prognosis of metastatic esophageal cancer remains poor. The five-year survival rate is 4%, and the median OS is 4-12 months in stage IV esophageal cancer (8). In this study, the median OS is relatively higher than the literature with median 14 months.

Several retrospective and prospective studies have suggested that RT could improve survival in metastatic esophageal cancer (9-11). In a large observational study, 12,683 newly diagnosed metastatic esophageal cancer patients were evaluated according to the treatment type that they received. Compared with CT alone, definitive dose RT was associated with improved survival (8.3 vs. 11.3 months, p=0.001) (9). CT plus palliative dose RT was associated with slightly inferior outcomes (8.3 vs. 7.5 months, p=0.001). They suggest that definitive dose RT may play a role in selected patients whose survival is threatened by local diseases such as airway invading, luminal obstructing tumors. In that study, just 24% of the tumors had an SCC histopathologic subtype contrary to our study, in which 87% of the tumors had SCC. The radiosensitive biological nature of SCC may influence the oncological results like our study in which OS was 24 months with definitive dose RT combined with CT.

In a study 5.970 metastatic esophagus cancer patients from the SEER database evaluated with propensity score analysis (11). RT significantly improved the OS in metastatic SCC of esophageal

cancer especially in younger age [hazard ratio (HR): 0.82; 95% confidence interval (CI): 0.68-0.99], white race (HR: 0.87; 95% CI: 0.76-0.99) and with CT (HR: 0.86; 95% CI: 0.75-0.98) but not in adenocarcinoma histology (median OS for RT group vs. no-RT group- 8.0, 7.6-8.4 vs. 9.0, 8.5-9.5, p=0.073).

In a phase II randomized trial, 60 patients with stage IV SCC esophageal cancer were randomly assigned to CT alone, and concurrent CT with RT. Concurrent chemoradiation was well tolerated and associated with more prolonged progression-free survival (12). The possible mechanism for the role of primary tumoral RT in metastatic disease is unknown. The historical role of RT is to control the local disease with maximal tumoral cell damage. However, RT also has immune-modulatory effects on unirradiated tumoral areas. There is an ongoing study investigating the anti-tumor T-cell response and abscopal effect of palliative RT combined with pembrolizumab in metastatic esophagus, stomach, or gastroesophageal junction cancer patients. They aimed to lead to an increase in tumor-infiltrating cytotoxic T-cells, circulating cytotoxic T-cells, and a reduction in immunosuppressive regulatory T-cells and myeloid-derived suppressor cells in metastatic sites.

Dysphagia, which was not subject to this study, is a common cause of morbidity and requires palliation in metastatic esophageal cancer. The best method for palliation of dysphagia has not been established. RT provides a long-term relief of dysphagia in many retrospective and prospective trials (13-15). A combination CT with RT improves symptoms of dysphagia and has a positive impact on survival in advanced and metastatic esophageal cancer with acceptable toxicity (16,17).

Study Limitations

The primary limitation of the study is the retrospective nature and the small sample size. Selection bias may favor patients who had more aggressive treatment. Disease and treatment-related heterogeneity may influence the results. The metastatic burden of the tumor, which may have an impact on oncological outcomes, is also not evaluated in this study. The majority of people in this series were SCC so the applicability to adenocarcinoma patients are limited. The addition of RT to metastatic sites is a different issue and may influence the results.

CONCLUSION

In patients with metastatic esophageal cancer, 45 Gy and higher dose RT with concurrent CT may contribute to OS in the selected patients after standard treatment. Extensive prospective studies are needed.

Ethics

Ethics Committee Approval: The present study was approved by the University of Health Sciences Turkey, Erzurum Regional Training and Research Hospital (02.12.2019, 2019/15-136).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: M.T., M.K., O.Ö., H.B., K.A.A.K., Concept: M.T., M.K., Design: M.T., M.K., Data Collection or Processing: M.T., M.K., O.Ö., H.B., K.A.A.K., Analysis or Interpretation: M.T., M.K., Literature Search: M.T., M.K., Writing: M.T., M.K., O.Ö., H.B., K.A.A.K.

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