Short- and long-term outcomes of definitive chemoradiotherapy in patients with esophageal carcinoma aged ≥75 years

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Abstract. The most relevant treatment modalities in elderly patients with esophageal carcinoma (EC) remain a subject of debate. Combined definitive chemoradiotherapy (CRT) is currently widely accepted as a non-surgical treatment for esophageal cancer. However, elderly patients were excluded from the majority of studies on CRT, or the proportion of elderly patients was relatively low in those studies and the number of available studies on the treatment of EC patients aged ≥75 years is limited. The aim of the present retrospective study was to analyze the safety and efficacy of CRT in patients aged ≥75 years in order to assess the short- and long-term outcomes of CRT for elderly patients with EC. In this study, based on further refinement of patient age groups and analysis of the Charlson comorbidity score, we performed a statistical analysis of factors such as short-term response, long-term survival and toxicity reactions. The results of the analysis indicated that the treatment of patients with EC aged ≥75 years with radiotherapy (RT) and chemotherapy was effective. However, we recommend that customized treatment is based on the stratification of patients into different age groups and the Charlson score, as for patients aged ≥80 years a lower-dose therapy may be more beneficial and for patients aged ≥85 years definitive CRT should be administered with greater caution.

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Abbreviations: CRT, chemoradiotherapy; RT, radiotherapy; EC, esophageal carcinoma; 5FU-CDDP, 5-fluorouracil-cisplatin; CR, complete response; OS, overall survival; uRT, unfinished radiotherapy; cRT, completed radiotherapy; dCRT, discontinued chemoradiotherapy; rCRT, reduced chemoradiotherapy; cCRT, completed chemoradiotherapy.

Introduction

Clinical trials since the 1990s have demonstrated that combined definitive chemoradiotherapy (CRT) is superior to radiotherapy (RT) alone for the treatment of esophageal carcinoma (EC) (1,2). However, the most relevant treatment modalities in elderly patients with EC remain a subject of debate. It was reported that elderly patients are less likely to undergo surgery and chemotherapy, which is partially due to their comorbidities (3,4). Currently, CRT based on the 5-fluorouracil-cisplatin (5FU-CDDP) regimen is used for the treatment with curative intent of locally advanced or inoperable non-metastatic EC (5).

The number of available studies on the safety and efficacy of CRT in elderly patients with locally advanced EC is currently limited, with a consequent lack of sufficient data regarding tolerance and short- and long-term outcomes of CRT in such patients. In two previous randomized trials that investigated the efficacy of CRT, the proportion of patients aged ≥75 years was 34.9 and 45% (6,7), which was not considered sufficient to provide adequate reference data for the treatment of patients in this age group.

Thus, we conducted a retrospective analysis in a single institution to determine the safety and efficacy of CRT in EC patients aged ≥75 years and assess the short- and long-term outcomes of CRT in such patients.

Materials and methods

Patient inclusion. The medical records of a total of 312 EC patients aged ≥75 years who had undergone non-surgical treatment at the Affiliated Tumor Hospital of Zhengzhou University (Jinshui, China) between January, 2002 and March, 2008 were retrospectively evaluated. The study protocol was approved by a suitably constituted Ethics Committee of the Affiliated Tumor Hospital of Zhengzhou University and conformed to the provisions of the Declaration of Helsinki, 1995 (as revised in Tokyo, 2004). All patients had histologically confirmed squamous EC, without distant metastases at the time of diagnosis. The general condition of the patients was evaluated using the Eastern Cooperative Oncology Group (ECOG) performance status (PS) criteria and patients with an ECOG PS of ≥4 were excluded from the study. We computed a comorbidity score for each patient using the variables included in the Charlson comorbidity index

(myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, peptic ulcer disease, mild to severe liver disease, diabetes with/without end-organ damage, hemiplegia, moderate or severe renal disease and AIDS). Each condition was weighted and the patients were assigned a score based on the Charlson index (8).

Tumor staging. According to the TNM classification of the International Union Against Cancer in 2003, clinical staging was based on esophagography, esophagoscopy, color Doppler and computed tomography of the neck, chest and abdomen. Endoscopic ultrasonography, magnetic resonance imaging, bronchofiberscopy, ultrasonography or bone scintigraphy were additionally performed for individual staging.

Treatments. All patients underwent conventional two-dimensional RT or three-dimensional conformal RT. The treatment details were described previously (6). RT was performed with 6 or 8 MV linear accelerators using a standard fractionation regimen (1.8-2.0 Gy/fraction; 5 days/week) at a prescribed dose of 50-64 Gy.

Concurrent chemotherapy consisted of CDDP at a dose of 60 mg/m^2 on days 1-3 administered by bolus injection and 5-FU at a dose of 400 mg/m^2 on days 1-5 administered by continuous infusion. These chemotherapy regimens consisted of three courses administered every 3 weeks. Weekly or more frequent complete blood counts were recorded and the doses of 5-FU and CDDP were reduced by 20% if the white blood cell count was 2,500-3,500 on day 21.

Short-term response evaluation criteria. Evaluation of the short-term response of elderly EC patients to CRT was performed using the short-term Response Evaluation Criteria in Solid Tumors established by Therase *et al* (9) and based on X-ray film obtained following an esophageal barium meal. Local therapeutic failure refers to no changes in the esophageal lesions or progressive disease following RT and chemotherapy. Recurrence refers to the progression of esophageal lesions after achieving a complete response (CR) or partial response (PR) following RT and chemotherapy, reappearance of local lesions after 6 months and appearance of new lesions outside of the irradiation field.

Toxicity scoring criteria. Radiation toxicity was scored using the Radiation Therapy Oncology Group criteria (10), which included acute reactions occurring within the first 90 days of treatment, or late reactions occurring after 90 days of treatment. Chemotherapy-related toxicity was scored using the National Cancer Institute Common Toxicity Criteria, version 2.0 (11), and tabulated continually over the course of treatment. The most severe reaction was recorded as the toxicity score for the entire treatment.

Follow-up and statistical analysis. Patients were monitored weekly during the course of RT and every 3-6 months following the completion of treatment. Patient follow-up was conducted using outpatient records, ward records and telephone interviews. All endpoints were observed from the first day of treatment until death or the last follow-up contact.

Table I. Patients characteristics.

Characteristics	Patient no. (n=312)	%
Age range, years (mean±SD)		
75-79 (76.9±1.4)	193	61.86
80-84 (81.3±1.4)	88	28.20
85-89 (86.5±1.1)	24	7.70
≥90 (94.9±6.2)	7	2.24
Performance status		
0	60	19.2
1	179	57.4
≥2	73	23.4
Charlson score		
0	42	13.5
1	146	46.8
≥2	124	39.7
T stage		
T1	44	14.1
T2	149	47.8
T3	64	20.5
T4	55	17.6
N stage		
N0	177	56.7
N1	135	43.3
TNM stage		
I	102	32.7
II	129	41.3
III	81	26.0

SD, standard deviation; TNM, tumor-node-metastasis.

Statistical analysis was performed using the χ^2 test for two-proportion comparisons. The survival rates were calculated from the date of treatment initiation until death, or the last follow-up contact for surviving patients, using the Kaplan-Meier method. The differences between survival rates were assessed using the log-rank test. P<0.05 was considered to indicate a statistically significant difference. All analyses were performed using SPSS for Windows, version 18.0 (SPSS, Inc., Chicago, IL, USA).

Results

Patient and tumor characteristics. A total of 312 patients with locally advanced EC, aged ≥75 years, who were treated between January, 2002 and March, 2008, were included in this study. The patient age ranged from 75 to 107 years (median, 79 years) and 31 of the patients (9.9%) were aged ≥85 years. The patient sample included 118 women and 194 men. The prevalence of comorbidity, defined as a Charlson score of ≥1, was 86.5%. The mean total RT dose delivered was 50.7 Gy. The patient and tumor baseline characteristics are summarized in Table I.

Table II. Patient stratification by clinical stage, treatment modality and treatment completion.

Stage	CRT			RT	
	cCRT	rCRT	dCRT	cRT	uRT
T					
T1	13	6	5	16	4
T2	47	22	22	44	14
T3	21	9	8	19	7
T4	18	10	7	15	5
N					
N0	55	26	23	52	21
N1	44	21	19	42	9
TNM					
I	31	15	13	33	10
II	40	19	17	39	14
III	28	13	12	22	6

CRT, chemoradiotherapy; RT, radiotherapy; cCRT, completed chemoradiotherapy; rCRT, reduced chemoradiotherapy; dCRT, discontinued chemoradiotherapy; cRT, completed radiotherapy; uRT, unfinished radiotherapy; TNM, tumor-node-metastasis.

Treatment progress. A total of 124 patients did not receive systemic chemotherapy and underwent RT alone due to comorbidities, personal choice or other reasons; 30 of these patients (24.2%) did not complete the planned RT regimen [unfinished RT group (uRT)] and 94 patients (75.8%) completed the planned RT regimen (cRT group). A total of 188 patients received comprehensive treatment with CRT, of whom 42 (22.3%) discontinued the treatment [discontinued CRT group (dCRT)], 47 (25%) underwent a reduction in the dose of chemotherapy or the planned radiation dose by 10% after 1 cycle of CRT [CRT reduction group (rCRT) and 99 (52.7%) completed the treatment [completed chemotherapy group (cCRT)]. There were no significant differences among the T, N and clinical staging data distribution in each group (Table II). With regard to the proportion of patients who completed CRT and RT, the difference was statistically significant (χ^2=16.967; P=0.000).

Additionally, a statistical analysis was performed for age, PS and Charlson score of 42 patients from the dCRT group, 47 patients from the rCRT group and 30 patients from the uRT group (Table III). In the dCRT group, the differences between patients with a PS of ≥2 and those with a PS of <2 were not statistically significant (χ^2=2.914; P=0.088), whereas the differences between patients with a Charlson score of ≥2 and those with a score of <2 were statistically significant (χ^2=33.599; P=0.000). Patients aged ≥85 years accounted for 90.9% of the dCRT group (20/22) and patients aged <85 years accounted for 13.3% (22/166) of the group; the difference between these two age groups was statistically significant (χ^2=67.521; P=0.000). In the rCRT group, the difference between patients with a PS of ≥2 and those with a PS of <2 was statistically significant (χ^2=13.061; P=0.000). The difference between the patients with a Charlson score of ≥1 and those with a score of 0 was statistically significant (χ^2=6.596; P=0.01). Patients ranging in age from 75 to

79 years accounted for 22.1% (25/113) of the rCRT group, whereas patients aged 80-84 years accounted for 37.7% (20/53) of the rCRT group, with a statistically significant difference between these two age groups (χ^2=4.450; P=0.035).

Short- and long-term response evaluation. The CR rates in the chemotherapy, RT and reduced-dosage groups were 52.5 (52/99), 38.3 (36/94) and 46.8% (22/47), respectively. The comparison of the CR rate of the CRT group to that of the RT group revealed a statistically significant difference (χ^2=3.935; P=0.047). The comparison of the CR rate among the chemotherapy and dosage-reduction groups revealed no statistically significant difference (χ^2=0.417; P=0.519).

A statistical analysis of overall survival (OS) was performed in the rCRT, cCRT and RT groups at 1, 3 and 5 years of follow-up, respectively. At 1, 3 and 5 years, the OS was 59.6 (n=28), 17.0 (n=8) and 10.6% (n=5), respectively, in the rCRT group; 60.6 (n=60), 17.2 (n=17) and 11.1% (n=11), respectively, in the cCRT group; and 58.5 (n=55), 2.1 (n=2) and 0% (0), respectively, in the RT group. Furthermore, the comparison of the OS rates between the rCRT and cCRT groups revealed no statistically significant difference (P=0.905, 0.982 and 0.932, respectively). There were no significant differences in the OS rate between the RT and the CRT groups in the first year (P=0.767); however, the OS rates at 3 and 5 years were significantly lower compared to those in the other two groups (P=0.000 and 0.001).

Toxicity reactions. Adverse toxicity reactions ≥grade 3 or reactions that were life-threatening were recorded. The frequency of toxicity reactions was 30.3, 14.9, 42.9, 18.1 and 23.3% in the cCRT (30/99), rCRT (7/47), dCRT (18/42), RT (17/94) and uRT (7/30) groups, respectively. Among these, the incidence of adverse toxicity reactions ≥grade 3 in the dCRT group was significantly higher compared to that in the other groups; the

Table III. Patient stratification by performance status, Charlson score and age.

Variables	dCRT, n/total (%)	rCRT, n/total (%)	uRT, n/total (%)
Performance status			
0	10/51 (19.6)	8/51 (15.6)	2/9 (22.2)
1	22/108 (20.4)	24/108 (22.2)	15/71 (21.1)
≥2	10/29 (34.5)	15/29 (51.7)	13/44 (29.5)
Charlson score			
0	4/36 (11.1)	3/36 (8.3)	0/6 (0)
1	20/126 (15.9)	35/126 (27.7)	2/20 (10.0)
≥2	17/26 (65.4)	9/26 (34.6)	28/98 (28.6)
Age (years)			
75-79	14/113 (12.4)	25/113 (22.1)	17/76 (22.4)
80-84	8/53 (15.1)	20/53 (37.7)	8/35 (22.9)
85-89	17/19 (89.5)	2/19 (10.5)	3/9 (33.0)
≥90	3/3 (100.0)	-	2/4 (50.0)

dCRT, discontinued chemoradiotherapy; rCRT, reduced chemoradiotherapy; uRT, unfinished radiotherapy.

Table IV. Causes of death in the CRT and RT treatment groups.

	CRT (n=172)			RT (n=124)	
Causes of death	cCRT, n (%)	rCRT, n (%)	dCRT, n (%)	cRT, n (%)	uRT, n (%)
Tumor					
Recurrence	15 (17.0)	8 (19.0)	28 (66.7)	16 (17.0)	22 (73.3)
Relapse	30 (34.1)	14 (33.3)	-	30 (31.9)	-
Metastasis	20 (22.7)	9 (21.4)	-	35 (37.2)	-
Relapse and metastasis	5 (5.7)	3 (7.2)	-	4 (4.3)	-
Treatment-related	2 (2.2)	1 (2.4)	8 (19.1)	3 (3.2)	1 (3.3)
Underlying disease	13 (14.8)	3 (7.2)	5 (11.9)	4 (4.3)	6 (20.0)
Other	3 (3.4)	4 (9.5)	1 (2.3)	2 (2.1)	1 (3.3)

CRT, chemoradiotherapy; RT, radiotherapy; cCRT, completed chemoradiotherapy; rCRT, reduced chemoradiotherapy; dCRT, discontinued chemoradiotherapy; uRT, unfinished radiotherapy; cRT, completed radiotherapy.

difference was statistically significant between the cCRT and rCRT groups (χ^2=4.000; P=0.046) and between the RT and CRT groups (χ^2=3.907; P=0.048). Adverse toxicity reactions ≥grade 3 did not differ significantly between the RT and the rCRT group (χ^2=0.226; P=0.635).

Cause of death. During follow-up, a total of 296 deaths were recorded. The mortality rate due to tumor-related factors in the cCRT, rCRT, dCRT, RT and uRT groups was 79.5, 80.95, 66.7, 90.4 and 73.3%, respectively (Table IV). The mortality rate due to underlying disease in the cCRT group was significantly higher compared with that in the other groups (14.8%). Additionally, the mortality rate was significantly higher in the dCRT group compared with that in the other groups (19.1%) and mortality due to distant metastasis in the RT alone group was also higher compared with that in the other groups (37.2%).

Discussion

The improvements in general healthcare and increased life expectancy have resulted in an increased number of elderly patients with EC. It was previously reported that, at 75 years of age, life expectancy is >10 years (12) Therefore, provided there are no major comorbidities, elderly patients with EC may benefit from curative treatment. Our results indicated that CRT was an effective treatment for EC patients aged ≥75 years. Our results also indicated that patient selection and the short- and long-term outcomes of CRT for elderly patients were considered acceptable, which is in accordance with the results reported in previous studies (7,13). Our study mainly focused on those patients who required treatment discontinuation or a reduction in treatment dose.

Age and comorbidity were associated with significant difficulties during treatment, particularly in patients treated

with CRT. Our results indicated that an age of 75 years did not affect the frequency of adverse events. It was previously reported that tolerance to 5-FU was the same in elderly and younger patients (14). Furthermore, a previous study on patients with advanced esophagogastric adenocarcinoma suggested that cisplatin-based chemotherapy toxicities did not increase with age (15). Those results indicated that age criteria alone may not suffice for the guidance of therapy and a better characterization of patients using the Charlson score is required. However, the number of studies on the safety and efficacy of selective CRT treatment in patients with EC aged ≥75 years based on the Charlson score is limited.

In this study, we demonstrated that, based on the completion of treatment, the tolerance of patients who received RT alone was satisfactory and the completion rate was superior to that of patients who underwent CRT; our results were in accordance with the findings of previous studies (1,2). In our study, the proportion of patients with a Charlson score of ≥2 who discontinued their treatment was significantly higher in the dCRT group compared to that in the other groups, although there were no differences in the PS. Anderson et al (13) reported that there was a correlation between a Charlson score of ≥2 and grade 3 or 4 toxicity. In the present study, the proportion of patients aged ≥85 years in the dCRT group was significantly higher compared with that of patients aged ≤85 years and the number of patients with ≥3 grade toxicity in this group was also higher compared to that in the other groups. This suggested that chemotherapy in EC patients aged ≥85 years should be administered with greater caution. No studies on the effects of CRT in EC patients aged ≥75 years are currently available.

The comparison of patients with a Charlson score of 0 and those with a Charlson score of ≥1 indicated that the proportion of patients who experienced rCRT was higher in the latter group. Additionally, in patients with a PS of ≥2, the number who experienced rCRT was significantly higher compared to those with a PS of ≥1. Patients with a Charlson score of ≥1 experienced more adverse events of grade ≥2 and a delay in undergoing chemotherapy (7). The comparison of patients aged <80 years with those aged ≥80 years revealed that the proportion of patients experiencing a rCRT was higher among those aged ≥80 years. Furthermore, the number of patients with toxicity reactions of grade ≥3 was lower in the rCRT group compared to that in the cCRT group, but there were no significant differences with regards to CR and OS. This regimen may be an appropriate adjustment for older EC patients who cannot tolerate standard therapy and exhibit a high comorbidity rate. Previous studies suggested that a PS of <2 was one of the factors affecting survival (7); according to the results of the present study, in the assessment of patient treatment, tolerance was not as sensitive as the Charlson score.

With regard to mortality, tumor-related factors were the primary cause; furthermore, the rate of distant metastasis in the RT alone group was higher compared with that in the CRT group. This was consistent with corresponding results from previous studies (3,16). With the extension of the survival time in the cCRT group, the mortality rate due to underlying disease was higher compared to that in the other groups.

In conclusion, we demonstrated that CRT is an effective treatment for EC patients aged ≥75 years; however, individualized treatment is recommended in accordance with further age regrouping and pretreatment in line with the Charlson score. For patients aged ≥80 years, a lower-dose therapy was found to be more effective and for those aged ≥85 years, CRT should be administered with greater caution.

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