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ORIGINAL ARTICLE

The management of patients with esophageal cancer and coronary artery stenosis undergoing radiotherapy or concurrent chemoradiotherapy: a single-center experience

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Summary

Purpose: *The incidence of esophageal cancer (EC) patients with coronary artery stenosis presents particular challenges. The aim of this retrospective study was to evaluate the efficiency of management on patients with both diseases treated by radiotherapy (RT) or concurrent chemoradiotherapy (CCRT).*

Methods: *Fifty-three patients with both EC and coronary artery stenosis from June 2009 to August 2012 were retrospectively analyzed. The patients received RT or CCRT with coronary artery stenosis management. Cardiac treatments often prescribed included aspirin, β-blockers, statins etc. The adverse effects, overall response rate (ORR), progression-free survival (PFS) and overall survival (OS) were analyzed.*

Results: *Most of the patients were 40-70 years old. There were 25 patients in the CCRT group and 28 patients in the RT group. The complete response (CR) rate was higher in the patients in the CCRT group than in those in the RT group (48.0 vs 21.4%; p=0.041). The median PFS was 15.9 months in the CCRT group and 11.6 months in the RT group (p=0.025). OS was 22.4 months in the CCRT group and 15.8 months in the RT group (p=0.013). Though adverse effects were less in the RT group, no significance differences in grade 3-4 toxicity were observed.*

Conclusion: *With the appropriate of coronary artery stenosis management, RT and CCRT were both tolerable and effective in EC patients with coronary artery stenosis.*

Key words: *chemoradiotherapy, coronary artery stenosis, esophageal cancer, management, radiotherapy*

Introduction

EC is the eighth most common cancer and the sixth leading cause of death from cancer worldwide [1]. Currently, RT, surgery and chemotherapy are the main treatment modalities. For early-stage EC, the standard workflow of treatment includes preoperative CCRT followed by surgery [2]. Although curative surgical resection is the first choice, almost 50% of the patients affected are not eligible at all for major surgery due to tumor invasion, technical, functional, or medical reasons at the time of diagnosis [3]. For those patients, definitive CCRT is more favorable [4]. The majority of EC patients are middle-aged or elderly people, who tend to have cardiac diseases or diabetes, lung diseases, etc. In the past, most studies focused on the therapy of cancer while barely paid

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attention to cardiac diseases which came along. For these patients, exposed to the same precipitating factors, such as tobacco smoke, hypertension and alcohol abuse, the combination of coronary artery stenosis was not uncommon. In USA, heart diseases and cancer have become the two most common causes of death [5]. It has been reported that cardiomyopathy, congestive heart failure, pericardial effusion, constrictive pericarditis, coronary artery disease (CAD), myocardial infarction, and arrythmias may result from the toxicity of chemotherapy and radiation therapy [6]. Therefore, the use of CCRT for EC patients with cardiac diseases has to be limited due to the addition of the potential cardiac toxicity from the treatment. Lauren et al. [7] found that female patients had increased odds of developing cardiac toxicity with increased dose to the heart. There was 4.0 increased odds of developing cardiac toxicity with V40 >57%. Conventional angiography used for diagnostic purposes of CAD is invasive and insufficient because of sluggishness and inaccuracy. Coronary computed tomography angiography (CCTA) is considered as a minimally invasive method of imaging and that uses x-rays to visualize blood flow in arterial and venous vessels throughout the body and with high diagnostic accuracy in the detection of significant CAD to replace the invasive conventional angiography [8-10]. In our study, CCTA was performed if necessary.

With the application of intensity modulated radiotherapy (IMRT) the radiation techniques have been considerably improved and the cardiotoxicity has been significantly reduced.

The goal of this retrospective study was to identify whether EC patients could tolerate CCRT being under treatment of CAD.

Methods

Patient population

This retrospective analysis was made based on the data of 53 patients (39 male and 14 female), who were admitted to the Qianfoshan Hospital affiliated to Shandong University between June 2009 and August 2012 with locally advanced EC combined with coronary artery stenosis. This study had been approved by the institutional committee on human research and a written informed consent was obtained from each patient prior to treatment. The recruited patients were administered RT with or without cisplatin as initial treatment.

Inclusion criteria

The following inclusion criteria were used: (1) Age 18 years or older; (2) histological or cytological diagnosis of EC; (3) no history of previous chemotherapy or RT; (4) ECOG score of 0-1 and no evidence of distant metastases; (5) signed informed consent; (6) previous clinical history of coronary artery stenosis proved by CCTA with or without clinical symptoms; (7) history of hypertension with well controlled medication; (8) life expectancy of at least 3 months; (9) considered inoperable due to advanced stage (clinical T3-4,N0-1,M0) or patient medically unfit for surgery based on multidisciplinary opinion. Locally advanced tumors were defined as those with a diameter up to 3 cm, or with involvement of adjacent structures [11].

Patients who had renal impairment, distant metastases, acute or previous myocardial infarction, or history of another malignancy were excluded from this study.

A total of 73 patients diagnosed with EC and coronary artery stenosis were identified and included initially in the study during the period from June 2009 to August 2012. Among these, 2 patients were lost to follow up because of bad coordination and 53 patients met the eligibility criteria and were evaluated. After joint consultation or discussion by a multidiscipinary team that included surgical, radiation and medical oncologists, pathologists and cardiologists, treatment recommendations were finalized. Patients meeting the following criteria received radical RT: clinical stage T1-3, N0, M0 disease; age <65 years: refused to receive chemotherapy; with poor lung function. The remaining patients were assigned to CCRT group.

Radiotherapy and chemotherapy

Patients were treated with IMRT/three-dimensional conformal radiotherapy (3D-CRT) and RT was delivered by a linear accelerator device with 6 mV photons. A total dose from 59.4 to 63 Gy, 9 Gy in 5 fractions a week (1.8 Gy/fraction) was delivered. For each patient, the enhanced contrast CT images were acquired at 5 mm intervals through the entire thorax and used for delineation of the esophagus and involved lymph nodes.

Gross tumor volume (GTV) included both the esophageal tumor and metastatic lymph nodes (with short axis diameter ≥10 mm). The clinical target volume (CTV) was defined as the GTV with 3 cm cephalad and caudal margins and 1 cm radial-lateral margins, including any grossly involved nodal site. The planning target volume (PTV) was expanded from the CTV by a 0.5 to 1.0-cm margin to account for daily setup variations and uncertainties. The inverse treatment planning system Eclipse (Eclipse 10.0 software; Varian Medical Systems, Palo Alto, USA) was used for RT. The dose was prescribed to the isocentre. The aim was to cover the PTV with 95% of the prescribed dose. Portal imaging films were obtained on the first day and then once a week before treatment. Total doses were corrected for the inhomogeneity of irradiated tissue.

The doses for the organ at risk (OAR) were as fol-

lows: maximal dose to the spinal cord <45 Gy, mean dose 9-21 Gy; dose to the heart, V40 ≤40-50%; percentage of total lung volume received ≥ 20 Gy (V20), <27% dose to the thoracic stomach, V40 ≤ 40–50%.

Concurrent chemotherapy

Cisplatin 30 mg/m^2 was infused over 1h with hydration weekly. Chemotherapy was administered before RT on day 1 of each week of the therapeutic cycle. Complete blood counts and 12-lead ECG were done weekly before each cisplatin infusion, while liver and kidney function tests were performed every 3 weeks. For patients receiving CCRT, RT began on day 1 of chemotherapy.

Coronary artery stenosis management

The management of the patients with CAD aimed to control symptoms, prevent the progression of atherosclerosis, and prevent the development of acute coronary syndrome. Cardiac treatment included the use of aspirin, statins, β-blockers, ACE inhibitors and thrombolytics. Aspirin was recommended to be continued throughout the treatment. Statins have been shown to be beneficial for patients with ischemic heart disease. β-blockers can reduce the ischemic stress with carefully titration. ACE inhibitors were prescribed for patients with left ventricular systolic dysfunction. For each patient, blood pressure was measured every day, troponin levels were tested once a week and echocardiography was performed when necessary.

Compared with patients in the RT group, patients in the CCRT group were more often prescribed aspirin (66 vs 43%; p=0.004), β-blockers (61 vs 46%; p=0.018), and thrombolytics (9.0 vs 0.3%; p=0.0001). There was no intergroup difference in the use of aspirin and β-blockers.

If there were symptoms, such as chest pain and tightness, ECG was performed regularly; 24-hour ambulatory ECG and echocardiography were performed as needed.

Treatment and toxicity evaluation

Treatment response evaluation was made according to Response Evaluation Criteria in Solid Tumors 1 month later after the completion of CRT by enhanced contrast CT of the thorax and the upper abdomen [12]. Based on only the longest diameter of all lesions: complete response (CR) was defined as the disappearance of all target lesions, without appearance of new lesions; partial response (PR) was defined as a decrease of 30% or more in the sum of the longest diameters of all lesions, referring to the sum of baseline longest diameters; progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameters of target lesions, referring to the smallest sum of longest diameters recorded since the treatment started or the appearance of one or more new lesions; stable disease (SD) was defined as neither sufficient lesion shrinkage to qualify for PR nor sufficient lesion growth to qualify for PD, referring to the smallest sum of longest diameters since the treatment started. Toxicity evaluation of the treatment was evaluated according to National Cancer Institute Common Toxicity Criteria, version 3.0 [13].

Treatment continued until disease progression or unacceptable toxicity. If severe toxicity occurred during the course of treatment, chemotherapy was suspended until recovery and restarted with the chemotherapy dose reduced by 25% in the subsequent cycle. The patients typically underwent follow-up examinations every 3–6 months after the completion of treatment.

Statistics

Age, sex, and baseline comorbidities between the CCRT group and the RT group were registered and analyzed. The primary endpoint of the study was to determine the ORR, defined as the total number of patients with CR and PR. The secondary endpoints were OS, PFS, toxicity and tolerance to treatment. OS was calculated from study inclusion to death from any cause, PFS was defined as the time from treatment initiation to PD or death from any cause. Univariate analysis was performed and factors with p<0.05 were included in Cox regression multivariate analysis. All statistical analyses were performed using SPSS statistical software (SPSS Inc, Chicago, Ill). The x^2 test was used for categorical variables, and the Student's t-test was used for continuous variables. Survival curves were constructed using the Kaplan–Meier method and differences between variables were examined using two-sided log-rank test. A two-tailed p<0.05 was considered as statistically significant. 95% CI were also calculated.

Results

Patient characteristics

Of 53 eligible patients, 25 received concurrent CCRT and 28 radical RT alone. Baseline demographics and clinical characteristics are summarized in Table 1.

Seventy-five percent of the patients were smokers, 50.9% were treated for hypertension and 26.4% for diabetes. At the time of inclusion, all patients were asymptomatic. The median age was 60 years (range 37-79) in the RT group and 62 years (range 39-76) in the CCRT group. Gender, ECOG PS, stage, and the number of chemotherapy cycles showed no statistically significant difference in both groups (p>0.05). The details of cardiac treatments are summarized in Table 2. There was no difference in the use of aspirin and β-blockers between the groups. Among patients with thrombocytopenia (platelet count <150 per

Table 1. Patient characteristics

Characteristics	*CRT (N=25)*	*RT (N =28)*	*Total (N=53)*	*p value*
Gender				
Male	18	21	39	0.809
Female	7	7	14	
Age (years)				
≤60	9	12	21	0.619
>60	16	16	32	
ECOG performance status				
0-1	20	24	44	0.589
2	5	4	9	
Smoking				
Current	2	1	3	0.709
Former	17	20	37	
Never	6	7	13	
Hypertension				
Yes	6	6	12	0.827
No	19	22	41	
Hyperlipidemia				
Yes	13	14	27	0.887
No	12	14	26	
Diabetes mellitus				
Yes	6	8	14	0.713
No	19	20	39	
Tumor location				
Cervical	4	5	9	0.805
Upper thoracic	6	6	12	
Middle thoracic	11	14	25	
Low thoracic	4	3	7	
Pathology				
Adenocarcinoma	4	3	7	0.579
Squamous cell carcinoma	21	25	46	
Clinical stage				
II	10	8	18	0.390
III	15	20	35	
Tumor diameter, cm				
<5	21	20	41	0.284
≥5	4	8	12	
Weight loss (over 3 months), %				
≤5	18	23	41	0.388
>5	7	5	12	

CRT: chemoradiotherapy, RT: radiotherapy, ECOG: Eastern Cooperative Oncology Group

μL), oral aspirin was withdrawn. During CCRT cisplatin dose was adjusted properly in some patients to suit their physical condition.

Efficacy

Treatment efficacy is shown in Table 3. CR was seen in 12 patients and PR in 10 in the CCRT group, and in 6 patients and 12 patients in the RT group. The ORR was 88% in the CCRT group compared with 64.3% to the RT group (p=0.045). Median PFS was 15.9 months (95% CI 10.2–21.6) in the CCRT group and 11.6 months (95% CI 10.3–12.9) in the RT group (Figure 1). OS was 22.4 months (95% CI 18.0–26.8) in the CCRT group and 15.8 months (95% CI 14.0–17.6) in the RT group (Figure 2). The differences were significant in PFS (p=0.025) or OS (p=0.013) between the two groups.

Table 2. Management of coronary disease in patients undergoing CRT

Medicines	*Usage*
β-blocker	Continued if already taking. Maintain to moderate blood pressure and keep heart rate of 70 beats per min.
Statins	Recommended for patients with high cardiac risk and cancer.
Aspirin ACE inhibitors	Continue 100 mg per day. For patients with left ventricular systolic dysfunction

ACE: angiotensin-converting enzyme

Table 3. Treatment efficacy

Response	*CCRT N (%)*	*RT N (%)*	*p value*
CR	12 (48.0)	6 (21.4)	0.041
PR	10 (40.0)	12 (42.9)	0.833
SD	2 (8.0)	6 (21.4)	0.173
PD	1 (4.0)	4 (14.3)	0.201
ORR	22 (88.0)	18 (64.3)	0.045

CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, ORR: overall response rate, CCRT: concurrent chemoradiotherapy, RT: Radiotherapy

Toxicity

During the hospital stay, none of the patients experienced acute coronary syndrome or any significant rise in troponin levels. No death was observed.

Adverse events are shown in Table 4. Leukopenia, febrile neutropenia and anaemia were the most common significant hematologic toxicities (p=0.001, p=0.007, and p=0.045, respectively), while fatigue and radiation-induced esophagitis were the most common non-hematologic toxicities (p=0.012 and p=0.014, respectively) in both groups. Grade 3 or 4 neutropenia was higher in the CCRT group (20.0%) than in the RT (7.0%). Grade 3 or 4 febrile neutropenia (4.0%) and thrombocytopenia (7.0%) were also seen in CCRT group, but not in the RT group. Grade 3 or 4 radiation-induced esophagitis was 40.0 vs 21.4% and 12 vs 7% in the CCRT and RT groups (p=0.142), while it was

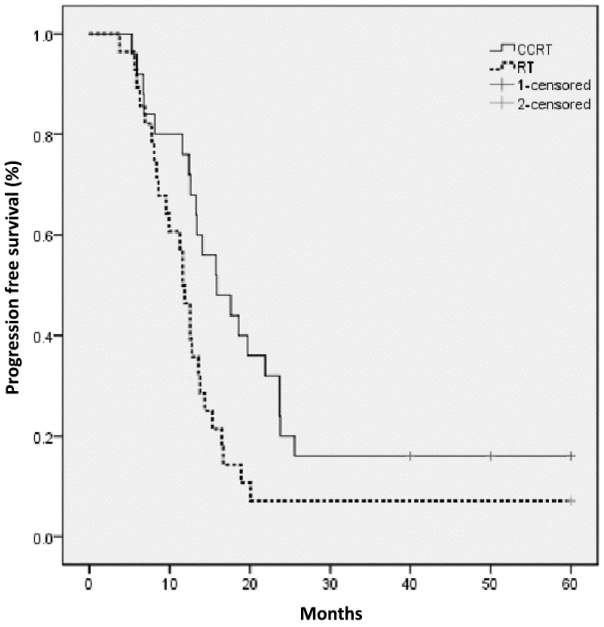

Figure 1. Progression-free survival in the CCRT and RT groups. Median PFS was 15.9 months (95% CI 10.2–21.6) in the CCRT group and 11.6 months (95% CI 10.3–12.9) in the RT group (p=0.025).

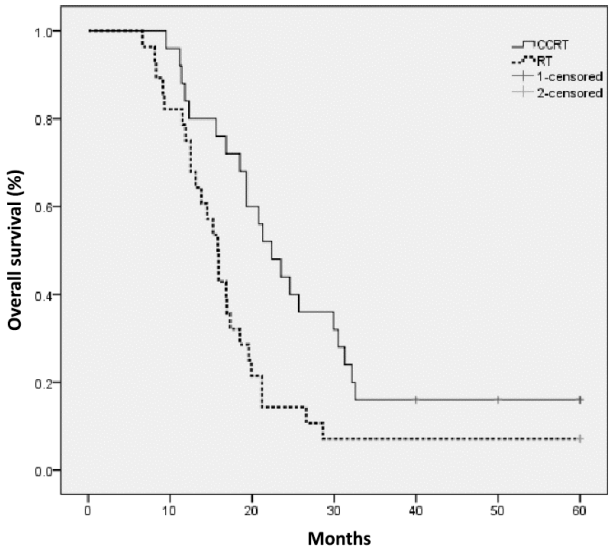

Figure 2. Overall survival in the CCRT and RT groups. OS was 22.4 months (95% CI 18.0–26.8) in the CCRT group and 15.8 months (95% CI 14.0–17.6) in the RT group (p=0.013).

Table 4. Treatment-related toxicity

Toxicity	*Grades 3-4*			*All grades*		
	CCRT	*RT*	*p value*	*CCRT*	*RT*	*p value*
Leukocytopenia	5	2	0.168	24	15	0.001
Febrile neutropenia	1	0	0.285	19	11	0.007
Anaemia	2	1	0.486	22	18	0.045
Thrombocytopenia	2	0	0.127	7	4	0.306
Nausea	3	1	0.246	15	10	0.077
Vomiting	2	1	0.486	13	8	0.082
Anorexia	3	0	0.059	10	6	0.142
Fatigue	2	0	0.127	20	13	0.012
Diarrhea	1	0	0.285	6	2	0.087
Constipation	1	1	0.935	8	4	0.124
Abnormal liver function	5	1	0.060	1	0	0.285
Renal toxicity	0	0	-	0	0	
Radiation esophagitis	10	6	0.142	25	22	0.014
Radiation pneumonitis	3	2	0.546	8	7	0.572
Acute coronary syndrome	0	0	-	0	0	
Myocardial ischemia	0	0	-	2	0	0.127
Pericardial effusion	1	0	0.285	3	2	0.546

RT: radiotherapy, CCRT: concurrent chemoradiotherapy

12 vs 7% (p=0.546) for radiation-induced pneumonitis without treatment-related deaths. Pericardial effusion was more frequent in the CCRT group than in the RT group (12 vs 7% for all grades, no grades 3 or 4 were found in both groups).

Prognostic factor analysis

Univariate analysis of OS is presented in Table 5, and shows that age, hyperlipidemia, chemotherapy, pathology and ECOG PS were significant indicators of poor prognosis (p<0.05). Table 6 shows the results of multivariate analysis in which the

Table 5. Univariate analysis for overall survival

Prognostic factors	*HR*	*95%CI*	*p value*
Age (>60 vs ≤60)	2.688	1.136-6.360	0.024
ECOG PS (0-1 vs 2)	0.017	0.002-0.138	0.001
Smoking history (yes vs no)	0.519	0.041-6.523	0.611
Hyperlipidemia (yes vs no)	0.215	0.065-0.710	0.012
Pathology (adenocarcinoma vs squamous cell carcinoma)	0.028	0.003-0.294	0.003
Clinical stage (II vs III)	0.283	0.071-1.130	0.074
Tumor diameter (cm^3) (<5 vs ≥5)	1.035	0.279-3.832	0.959
Weight loss (over 3 months), % (≤5 vs >5)	0.235	0.026-2.094	0.194
Chemotherapy (yes vs no)	0.067	0.024-0.185	0.001

HR: hazard ratio, CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status

Table 6. Multivariate analysis for overall survival

Prognostic factors	*HR*	*95%CI*	*p value*
Age (>60 vs ≤60)	2.799	1.360-10.487	0.037
ECOG PS (0-1 vs 2)	0.255	0.099-0.657	0.005
Smoking history (yes vs no)	0.750	0.243-7.313	0.716
Hyperlipidemia (yes vs no)	0.242	0.104-0.566	0.001
Pathology (adenocarcinoma vs squamous cell carcinoma)	0.046	0.019-0.761	0.037
Clinical stage (II vs III)	0.508	0.277-1.136	0.099
Tumor diameter (cm^3) (<5 vs ≥5)	1.236	0.395-3.862	0.716
Weight loss (over 3 months), % (≤5 vs >5)	0.550	0.263-1.149	0.112
Chemotherapy (yes vs no)	0231	0.078-0.684	0.012

HR: hazard ratio, CI: confidence interval, ECOG PS: Eastern Cooperative Oncology Group performance status

significant predictors retained their value.

Discussion

For the usual patient, CCRT can improve the outcome of locally advanced EC despite its adverse effects. A phase II study by Shim et al. found that concurrent CCRT with docetaxel and cisplatin was well tolerated with promising efficacy [14]. Rawat et al. [15] retrospectively analyzed 45 eligible patients with locally advanced squamous cell carcinoma and proved that CCRT had similar survival time and toxicity compared to CCRT combined with surgery. Cardiotoxicity is a rare adverse event with modern RT technologies. For patients with CAD, use of aspirin, β-blockers, statins, and coronary revascularization could improve prognosis [16-18]. Patients with CAD combined with EC have been largely excluded from all trials of acute coronary syndrome; hence, the cardiotoxicity induced by CCRT has seldom been estimated. Although this retrospective study is based on the data from a single institute, we evaluated the efficiency and toxicity of CCRT in patients with locally advanced EC. We found that ORR of the CCRT group was higher compared to the RT group (88 vs 64.3%). PFS was more favorable in the CCRT group (95% CI 10.2–21.6, p=0.025). OS was also significantly superior in the CRT group (95% CI 18.0–26.8 p=0.013). Grade 3 and 4 toxicities were similar in both groups. Though leukopenia, febrile neutropenia, anaemia and thrombocytopenia were significantly higher in the CCRT group than in the RT group, there were no treatment-related deaths. CAD and cancer share common risk factors, such as smoking and alcohol abuse. In recent decades, cancer and cardiovascular disease are the leading causes of mortality and morbidity worldwide [19]. There is a moderately increased risk of tobacco-related cancers among survivors of coronary artery stenosis. Elderly patients with cancer also suffer from other serious comorbidities, especially heart and vascular disease. Among cancer patients aged > 70 years the prevalence of heart and vascular disease is 20% [20]. Previous studies seldom investigated the survival of cisplatin-based chemotherapy concurrent with RT for EC patients with CAD. We found that treatment of EC in the general population is also applicable to the CAD population under good management.

Cisplatin has been used extensively as antineoplastic agent for many years. Although uncommon, cardiotoxicity associated with cisplatin has been observed [21]. In our study, only 8% of the patients presented symptoms attributed to cisplatin-induced cardiotoxicity: one patient developed hypertension and another one myocardial ischemia. On the other hand, no patient presented symptoms due to radiation-related cardiotoxicity. Cisplatin induced hypertension, which may be worsened by the intravenous saline infusions required for the administration of the drug. Nieto

et al. have reported that patients with mediastinal irradiation are susceptible to cisplatin-based chemotherapy. Myocardial ischemia and acute coronary syndrome have also been reported, mostly in older patients [22]. Cisplatin-associated thrombosis has also been reported and can lead to direct endovascular damage by free radical induced lipid peroxidation in endothelial cells which can cause intimal thickening and platelet aggregation [23]. In our study, however, acute thrombosis has not been observed, maybe due to the frequent use of aspirin.

In older trials, with the use of outdated radiation techniques and more volume of heart exposed, it was suggested that the excess of non-cancer related deaths mainly came from heart and vascular toxicities. Radiation therapy is shifting from the use of traditional techniques and conventional fractionations to IMRT and rapid arc techniques. Though it did not annihilate the risk for subsequent heart and vascular disease, the new megavoltage techniques have significantly reduced the irradiated cardiac volume and facilitated sparing the heart and coronary vessels from unnecessary irradiation.

In our study, the most common toxicity was apparently radiation-related esophagitis. Therapy-related grade 3 or 4 dysphagia requiring percutaneous endoscopic gastrostomy tube feeding was observed in 3 (6%) patients. Myocardial ischemia (4%) has also been seen in the study, however, these side effects were well amenable to treatment. Early cardiac toxicity from radiotherapy results from direct cellular toxicity through apoptosis, necrosis, and endothelial cell injury, leading to increased vascular permeability and stromal oedema. Delayed vascular toxicity includes epithelial nuclear atypia and development of multinucleate stromal fibroblasts, with subsequent intimal thickening, fibrinoid necrosis, medial hyalinization and parenchymal atrophy. Although radiation-induced toxicity is a late and irreversible effect that can manifest even 10–15 years after radiation therapy, most of our patients had locally advanced disease stage and thus usually could not survive enough to see the delayed toxicity. Other studies have evaluated in-field toxicities of RT, especially lung and heart toxicities after esophageal RT and demonstrated less treatment-related toxicity of IMRT compared to 3D-CRT [24,25]. However, previous studies conducted in esophageal CCRT correlating dose-volume parameters and risk of cardiotoxicity had significant variations in dose, fractionation, radiation technique, and definition of cardiac volumes for radiation dosimetry.

The present study has several limitations. A median follow-up of 16.7 months was rather short for patients with EC. Therefore, long-term cardiac complications demonstrated in EC patients, including coronary artery sclerosis, myocardial infarction, cardiomyopathy, valvular disease, and conduction abnormalities, would typically not be observed in this narrow interval. This limitation can partially be attributed to the overall poor prognosis of EC.

This study showed that a simple therapy, such as aspirin and β-blockers, saves lives in cancer patients with CAD, with limited side effects. Due to the proven benefits of medical and revascularization therapy in coronary artery stenosis, a prospective trial of such therapy in cancer patients would be unethical. Hence, we simply advocate the development of a prospective registry for cancer patients with CAD among the leading oncological centers of the world.

In conclusion, our results show that with appropriate management of CAD, anticancer treatments such as RT and CCRT can be well tolerated. Medical therapy improves survival. Furthermore, our results also suggest that, despite the hematological adverse events, CCRT was well tolerated from patients with good PS. Further prospective randomized studies are needed to understand the effect and to propose guidelines for daily practice.

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