Cardiac volume reduction during radiotherapy in patients with esophageal carcinoma

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Abstract. The present study investigated the factors contributing to cardiac volume reduction (CVR) during radiotherapy (RT) in patients with esophageal carcinoma (EC). This retrospective study included patients with EC treated at National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan). Cardiac delineation was based on initial and off-cord boost (spinal cord-sparing approach) planning computed tomography images. The relationship between CVR and other relevant parameters was analyzed. A total of 58 patients with EC were investigated between January 2016 and January 2022. Univariate and multiple regression analyses revealed a statistically significant association between CVR during RT and the change ratio of the inferior vena cava (IVC) volume and body mass index (BMI) loss. In multivariate analysis of CVR of >10%, only the change in IVC volume exhibited a significant association. Conversely, CVR during RT displayed no association with heart dose-volume parameters, laboratory data, or changes in blood pressure and pulse rate. Among the 12 cases with CVR of >10%, the median movement of the left anterior descending coronary artery region (LADR) was 1.35 cm (range, 0.0-2.7 cm). In conclusion, CVR during RT was most strongly associated with changes in IVC volume, suggesting dehydration as the primary cause, rather than radiation-induced heart damage. LADR movement due to a CVR of >10% may lead to LADR radiation overdose.

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Abbreviations: EC, esophageal carcinoma; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; IMRT, intensity-modulated radiation therapy; CVR, cardiac volume reduction; IVC, inferior vena cava; LADR, left anterior descending coronary artery region; Alb, albumin; Ht, hematocrit; BUN/Cr, blood urea nitrogen to creatinine; eGFR, estimated glomerular filtration rate; sBP, systolic blood pressure; dBP, diastolic blood pressure; BMI, body mass index; PR, pulse rate; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; DVH, dose volume histogram

Key words: CVR, dehydration, dose volume parameter, LADR, EC

Introduction

Esophageal carcinoma (EC) is typically managed using curative-intent concurrent chemoradiotherapy (CCRT) as a definitive treatment option for patients who are either ineligible for or decline esophagectomy (1-3). Although CCRT is recognized as a safe and effective treatment for EC, it carries the potential for inducing adverse events, including esophageal, pulmonary, and cardiac toxicities (4).

Cardiac volume reduction (CVR) is among the observed phenomena during CCRT for EC (5-7). Suggested causes for this CVR include intravascular volume depletion attributed to dehydration which occurs when patients use or lose more fluid than they take in, and their body do not have enough water and other fluids to carry out its normal functions, a common issue encountered during hospitalization for CCRT in EC treatment (6,8,9). However, several studies have also demonstrated that acute cardiac damage may occur during CCRT for EC (6,7,10,11) and contribute to CVR (7). CVR can occur due to heart dilatation disorders caused by cardiac damage represent congestive symptoms (12). Physiological changes can also be quite different for patients with the same CVR (dehydration or heart dilatation disorders). Nevertheless, there are few reports that discuss the causes of CVR. Consequently, the cause of CVR during CCRT remains uncertain.

The left anterior descending coronary artery (LAD) is the most important coronary artery with the wide perfusion area. Recently, some studies suggested that dose to the LAD correlated with cardiac events after irradiation (13-16). In the Three-dimensional conformal radiation therapy era, CVR has not been studied extensively because the changes of dose distribution due to CVR have been reported to be small. However, in the intensity-modulated radiation therapy (IMRT) era which has dose density changes, the impact of CVR may be significant. To address these issues, we examined the correlation between factors reflecting dehydration and the parameters associated with CVR, and evaluated the cause of CVR and the impact of the CVR on movement of LAD region.

Materials and methods

Study protocol and patients. Between January 2016 and January 2022, 143 patients with EC were treated with definitive radiotherapy (RT) at National Hospital Organization Shikoku Cancer Center. Patients with the following characteristics were excluded from the study: i) Prior surgical therapy, including endoscopic treatment before RT (n=9), ii) absence of replan CT image (n=13), iii) incomplete RT (n=2), iv) deviation from the daily fraction dose of 2 Gy (n=23), v) diagnosis of cervical EC (n=5), vi) presence of double cancer (n=16), vii) occurrence of distant metastases (n=17). Subsequently, we conducted a retrospective evaluation of the remaining 58 patients with EC [male/female=49/9; median (range), 69 (48-88) years] who received definitive RT. Details of the patient characteristics are shown in Table I. This retrospective study received approval by the Ethics Committee of the National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan; approval no. RIN 2021-69).

The most famous sign and symptoms of dehydration is thirst, but a reliable early indicator of dehydration may not be thirsty, particularly elderly. Therefore, several examination results were used for indicators of dehydration. Dehydration indicators such as serum albumin (Alb), hematocrit (Ht), serum blood urea nitrogen to creatinine (BUN/Cr) ratio, and estimated glomerular filtration rate (eGFR) were collected. Systolic blood pressure (sBP), diastolic blood pressure (dBP), pulse rate (PR), and body mass index (BMI) were recorded during initial and off-cord boost computed tomography (CT) simulations. The timings of measurements for sBP, dBP, PR, and BMI within a day followed a not-rigid schedule. These data were obtained from their medical records. Inferior vena cava (IVC) volume (long diameter x short diameter) was measured in initial and off-cord boost CT images. Dose volume parameters and field length were collected in initial treatment plans.

Treatment. RT was administered using a 10 MV X-ray from a linear accelerator (Varian Medical Systems, CA, USA) at a total dose of 60 Gy (initial elective nodal irradiation, 40 Gy; off-cord boost irradiation, 20 Gy) with a daily fraction dose of 2 Gy targeted at the EC region. Off-cord boost CT images were typically acquired at a dose of 36 Gy.

Eclipse planning system (Varian Medical Systems, CA, USA) was used to create treatment plans. CT scans with 3-mm slices were acquired during free breathing without cardiac synchronization (HiSpeed NX/I Smart Gantry system; General Electric Healthcare, Little Chalfont, UK). The gross tumor volume (GTV) was defined as the primary tumor and metastatic lymph nodes. The primary tumor was identified using CT [(18F)fluoro-D-glucose positron emission tomography/CT and/or endoscopic findings]. The clinical target volume (CTV) for the primary tumor was defined as the tumor volume plus 2-3 cm margins in the craniocaudal direction and 0.5 cm margins in the other directions. The CTV for metastatic lymph nodes was defined as any metastatic lymph node volume plus 0.5 cm margins in all directions. In the initial elective nodal irradiation, prophylactic CTV, which might present microscopic metastatic tumors, was also included based on the physician's discretion and was contoured with reference to the Japan Esophageal Society Guidelines (17,18). The planning target volume (PTV) was defined as the overall CTV plus margins (0.5 cm) in all directions.

Chemotherapy concurrent with their radiotherapy consisted of cisplatin (70 mg/m^2 on days 1 and 29) and 5-fluorouracil (700 mg/m^2 on days 1-4 and 29-32) in principle. Among these, the doses were decreased if necessary [13 patients received low-dose cisplatin (85% dose, 1; 80% dose, 2; 75% dose, 4; and 50% dose, 6), and 1 patient received low-dose 5-fluorouracil (75% dose) before off-cord boost CT simulation].

Imaging evaluation. CT images were obtained before the initial plans and off-cord boost plans. The structure of the entire heart was contoured on the initial planning CT images according to the cardiac contouring atlas for radiotherapy (19), with appropriate window settings (window width=500 Hounsfield units and window level=50 Hounsfield units). All contouring procedures were performed by the same radiation oncologist and confirmed by the other two radiation oncologists. The structure of the whole heart was contoured on both CT images for the initial plans and on CT images for off-cord boost plans. A pericardial dose-volume histogram (DVH) was generated using the treatment planning system. The percentage of heart volume that received >20 Gy (V20) and the mean heart dose (Dmean) were collected as the predicted factors of CVR. IVC volume was measured at the confluence of the hepatic veins with the IVC.

In patients with CVR of >10% which is visually distinct CVR in cone-beam CT image, the LADR was contoured on initial and off-cord boost planning CT images according to the contouring atlas of the LADR (20). The LADR from the cranial (the level above the LAD branches from the left main coronary artery) to the caudal (the level of the apex of the heart) was divided equally into two parts, and the LADR movement was measured at the midpoints of the LADR.

Statistical analysis. Factors affecting the CVR during RT were examined using simple and multiple linear regression analyses. Data are presented as regression coefficients with 95% confidence intervals (CIs) and P-values. Univariate and multivariate logistic regression analyses were performed for factors affecting CVR of >10%. Statistical significance was defined as $P<0.05$. Statistical analyses were performed using the JMP software (JMP version 14.3.0; SAS Institute, Cary, NC, USA).

Results

Clinical characteristics. The median percent of CVR during RT treatment was 2.61% (range, -8.26-19.26%). Twelve patients (20.69%) had CVR of >10%, and 13 patients (22.41%) had CVR of ≤10%, >5%. The median percentage of IVC diameter change during RT was 5.27% (range, -17.07-56.52%).

Linear regression analysis to predict CVR during RT. In the univariate analysis, baseline IVC volume, change ratio of IVC volume, and change ratio of BMI loss were correlated with the

Table I. Patient characteristics.

Characteristic	No. of patients (%)
Age	
<70 years	29 (50.0)
≥70 years	29 (50.0)
Sex	
Male	49 (84.5)
Female	9 (15.5)
PS	
0	24 (41.4)
≥1	34 (58.6)
BMI	
<25 kg/m^2	24 (41.4)
≥25 kg/m^2	34 (58.6)
Stage	
1	16 (27.6)
2	20 (34.5)
3	19 (32.7)
4	3 (5.2)
Location	
Upper thoracic	7 (12.1)
Mid thoracic	26 (44.8)
Lower thoracic	25 (43.1)
Smoking	
Yes	43 (74.1)
No	9 (15.5)
Unknown	6 (10.4)
Hypertension	
Yes	24 (41.4)
No	34 (58.6)
Hypercholesterolemia	
Yes	4 (6.9)
No	54 (93.1)
Chemotherapy	
Yes	55 (94.8)
Low dose	17 (65.5)
Standard dose	38 (29.3)
No	3 (5.2)

PS, performance status; BMI, body mass index. The cut-off value of BMI was 25 (26).

degree of CVR (Table II). In addition, age, dBP change ratio, and PR change ratio tended to correlate with the degree of CVR (Table II). In the multivariate analysis, only the change ratio of the IVC volume was correlated with the degree of CVR (Table II).

The movement of LADR in patients with severe CVR (>10%) during RT. Twelve patients were analyzed to evaluate the effect of CVR of >10% on the LADR movement. For these 12 patients, the median movement of LADR was 1.3 cm (range, 0-2.7 cm). The patient with the largest LADR movement (2.7 cm) had the largest change ratio in CVR (19.62%) and IVC volume (56.5%). This patient had small changes in sBP (103-101 mmHg) and dBP (76-63 mmHg), but the PR showed large changes (70-102 mmHg).

Discussion

In our study, the change ratio of the IVC volume was exclusively associated with the degree of CVR during RT. Conversely, changes in blood pressure, pulse rate, BMI loss, laboratory data, and heart dose did not exhibit any significant correlation with the CVR during RT. Additionally, patients experiencing CVR of >10% demonstrated substantial LADR movements.

Dehydration stands out as the foremost reason for hospitalization in patients undergoing RT for EC (6,8,9). The IVC serves as an indicator of dehydration (21). In our study, the change ratio of the IVC volume correlated with the degree of CVR during RT. This suggests that dehydration is the primary cause of CVR during RT. However, in our study, several parameters that are typically used as indicators of dehydration, such as variations in blood pressure, pulse rate, and laboratory data, were not correlated with CVR during RT. Blood pressure and pulse rate can be influenced by diurnal variations and the degree of rest, factors that may have been challenging to control given the retrospective nature of our study. Furthermore, laboratory data are typically used to gauge dehydration in patients with normal renal function. However, the administration of cisplatin + 5-fluorouracil during CCRT in patients with EC can frequently lead to myelosuppression and/or nephrotoxicity (22-24), making it challenging to accurately assess dehydration using these parameters. Therefore, the primary cause of CVR seems to be dehydration. However, few clinical features have been presented to conveniently presume CVR during RT. In clinical practice, cisplatin + 5-fluorouracil is a chemotherapy regimen that induces dehydration and it is difficult to prevent dehydration at present. Therefore, CVR should be assessed in EC patients treated with CCRT, and re-planning should be conducted if necessary.

Several studies have demonstrated that radiotherapy to the heart can damage cardiac function, leading to cardiac impairment (6,7,10,11,13-16,25). Furthermore, some studies have suggested that cardiac damage can occur in the early stages of RT in patients with EC, and that the percentage of heart volume receiving a high dose may influence the extent of cardiac damage (7,11). Wang *et al* proposed that heart dilatation disorders, including cardiac impairment, contribute to CVR during RT (7). However, heart dilatation disorders generally result in a dilated IVC (12). Moreover, no studies, including ours, have demonstrated a correlation between DVH during cardiac irradiation and CVR during RT (6,7). Therefore, although cardiac impairment may also play a role, the primary cause of CVR during RT appears to be dehydration.

This suggests that CVR may occur in patients with EC treated with IMRT, even with cardiac dose reduction. Although the effect of the CVR on dose distribution is reported to be small in 3DCRT planning (6), it can

Table II. Factors associated with cardiac volume changes during radiotherapy treatment.

	Univariate analysis			Multivariate analysis		
Variable	Coefficients	95% CI	P-value	Coefficients	95% CI	P-value
Baseline IVC vol.	0.0002	0.0001-0.0003	0.010	0.0001	-0.0001-0.249	0.191
IVC vol. change	0.228	0.147-0.308	<0.001	0.183	0.095-0.270	<0.001
Age	-0.002	-0.005-0.0001	0.062	-0.001	-0.003-0.001	0.356
sBP change	0.103	-0.034-0.240	0.139	-	-	-
dBP change	0.087	-0.014-0.188	0.090	0.039	-0.046-0.125	0.358
BMI loss	0.785	0.157-1.412	0.015	0.246	-1.141	0.390
PR change	-0.050	-0.167-0.067	0.396	-	-	-
eGFR change	-0.043	-0.124-0.038	0.295	-	-	-
Ht change	0.110	-0.154-0.373	0.409	-	-	-
BUN change	-0.013	-0.071-0.044	0.648	-	-	-
Alb change	0.002	-0.223-0.226	0.987	-	-	-
Cr change	-0.056	-0.136-0.024	0.169	-	-	-
V20	0.0001	-0.0001-0.0002	0.380	-	-	-
Dmean	0.0004	-0.003-0.004	0.828	-	-	-
Field length	-0.001	-0.005-0.003	0.585	-	-	-

IVC, inferior vena cava; vol. volume; sBP, systolic blood pressure; dBP, diastolic blood pressure; BMI, body mass index; PR, pulse rate; eGFR, estimated glomerular filtration rate; Ht, hematocrit; BUN, blood urea nitrogen; Alb, albumin; Cr, creatinine; V20, volume receiving 20 Gy; Dmean, mean dose.

significantly impact the dose distribution in IMRT, a more precise radiation method than 3DCRT. Although there were no detailed prospective analyses of adverse cardiac events, several studies have suggested that doses to the LAD may be associated with late cardiac adverse events such as major adverse cardiac events (MACEs), which include myocardial infarction, coronary revascularization, or death resulting from ischemic heart disease (13-16). In our study, because of the limited CT image quality from free breathing and the absence of cardiac synchronization, evaluating LAD movement was not feasible. Instead, we contoured the LADR as accurately as possible and evaluated its movement between the initial and off-cord boost-plan CT scans. We observed significant LADR movement caused by CVR of >10%, suggesting that substantial changes in LADR dose distribution might occur during IMRT planning and may increase the cardiac adverse event. Although further detailed evaluation with cardiac synchronization and breath-hold CT images is warranted, some studies showed that higher LAD doses may increase cardiac adverse events (13-16). Therefore, the increased LADR dose due to significant LADR movement form CVR of >10% may be associated with a higher risk of cardiac adverse events and unfavorable prognosis. To address these issues, we recommend reducing the intensity of the oblique entry beam from the front left to the back right in IMRT planning, considering the LADR as the path of the additional beam. Moreover, because few clinical features are available for predicting CVR, cone-beam CT for the evaluations of CVR 2-3 weeks after the commencement of IMRT treatment may be necessary to identify the need for replanning.

However, our study has some limitations due to its retrospective design. First, the sample size was small, which may have contributed to the discrepancies between our results and those of previous studies regarding changes in sBP, dBP, and PR. Moreover, although we used the CVR cutoff value of 10%, we believe that calculation of the appropriate clinically significant CVR cutoff value with Receiver Operating Characteristic analysis should be performed using a larger sample size in the future. Second, the use of CT images obtained during free breathing without cardiac synchronization may introduce uncertainty in LADR contouring. In our study, LADR variation from free breathing and without cardiac synchronization was judged by three observers (radiation oncologists) to be sufficiently small to have an acceptable impact on contouring. However, the variation in right coronary artery region (RCAR) due to free breathing without cardiac synchronization was deemed too large for reliable contouring. Therefore, further studies are required in the future for evaluating the changes of RCAR dose distribution. Finally, because chemotherapy was used in almost all patients (94.8%) in this study, it is unclear whether this result would apply to cases treated with radiotherapy alone. Despite these limitations, our study offers valuable insights for daily clinical practice, especially in IMRT planning, as there have been limited reports on CVR during CCRT for patients with EC and no reports on LADR movement due to CVR.

In conclusion, the primary cause of CVR during RT for patients with EC appears to be dehydration, as evidenced by the correlation between the change in IVC diameter and the degree of CVR. Notably, the substantial movement of LADR

due to large CVR highlights the importance of monitoring CVR during RT, particularly in IMRT with cardiac dose reduction.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

All authors had full access to the data in the study, confirmed the authenticity of all the raw data, and take responsibility for the integrity of the data and the accuracy of the data analysis. KM and AM designed the study. KM, YH, HK and KN collected patient data and drafted the manuscript. KM, YH, HK, AM and KN collaborated for discussions. KM prepared the manuscript and YH edited the manuscript. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the Institutional Research Committee and the 1964 Declaration of Helsinki and its later amendments. The present study was approved by the Ethics Committee of National Hospital Organization Shikoku Cancer Center (Matsuyama, Japan; approval no. RIN 2021-69). The need for informed consent was waived due to the retrospective nature of the study.

Patient consent for publication

Not applicable.

Competing interests

Not applicable.

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