



The Radiotherapy-induced Cardiotoxicity in Esophagus and Stomach Cancer

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SUMMARY

The incidence of esophagus and stomach cancer is increasing; however, the novel multidisciplinary management strategies and modern technology lead an increase in the low survival outcome. Radiotherapy (RT) and chemotherapy (CT) are two essential parts of the multidisciplinary treatment which helps to increase the outcome, but causes extra toxicities. Cardiac toxicity is one of the acute and late-term concerns that are being more important as survival increases. The free oxygen radicals produced by irradiation which lead DNA damage and accompanying release of inflammatory factors cause cellular changes and fibrosis with various pathophysiological effects. The CT agents have their own cardiotoxicity mechanisms apart from the radiation damage of the irradiated portion of the heart. Both two types of treatment have toxic effects on the cellular basis of the pericardium, cardiac vascular structures, muscles of the heart, and the valvulas which turns into side effects such as pericardial effusion, myocardial infarction, heart failure, and valvular dysfunction. It is essential to carefully evaluate the patients cardiac condition before initiation of any the treatment modalities, use the most conformal RT technique which is available and prefer the neoadjuvant treatment modalities which require less radiation doses to reduce the cardiac toxicities. In addition, in the follow-up period, we must ensure that the patient is under the control of not only the surgeon or the oncologist but also the cardiologist.

Keywords: Cardiotoxicity; esophageal cancer; radiotherapy; side effect; stomach cancer.

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Introduction

Nowadays, the incidence of esophagus and stomach cancer is increasing and these cancers are usually detected in more advanced stages with high mortality rates such as 15-40% at 5-year in resectable cases.[1,2] Adjuvant and neoadjuvant strategies have been used to overcome the low survival rates achieved by surgery alone. The multidisciplinary management with surgery, radiotherapy (RT), and chemotherapy (CT) have improved the outcomes with the increasing importance of mortality and morbidity rates due to the toxicities.[3,4]

The heart is in the radiation treatment portals due to the anatomical location in the esophagus, stomach, and esophagogastric junction tumors. Radiation-induced cardiotoxicity is usually considered as a long-term side effect and most of the data about it are from the trials of long-term survivals of breast cancer and lymphoma. [5,6] There are limited data in the literature about the esophagus and stomach cancer patients as they have shorter survival rates.

Nowadays, neoadjuvant chemoradiotherapy (CRT) is a treatment of choice in the locally advanced esophagus and esophagogastric junction cancers because

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of the pathological tumor response and lesser post-operative morbidity rates and 45 grays (Gy) of RT is administered concurrently with cisplatin and 5-fluorouracil (5-FU)-based CT.[2,7] However, the CROSS trial demonstrated a survival advantage in local and distant disease control with concomitant paclitaxel and carboplatin.[8,9] The 5-year survival rates of stomach cancer treated with only surgery is more than 90% in early stages in novel series but reduces down to 35% in patients with lymph node-positive disease and stages more than IIB.[10-14] The randomized trials have shown an increase in survival rates in resectable stomach cancer with adjuvant CRT and CT compared with surgery alone.[15-17] Epirubicin, cisplatin, and 5-FU (ECF), FOLFOX (oxaliplatin, 5-FU, leucovorin), and FLOT (docetaxel, oxaliplatin, leucovorin, 5-FU) are commonly used regimens in the adjuvant setting and 5-FU + leucovorin or infusional 5-FU/oral capecitabine are preferred concomitantly with RT. Due to its close proximity to the lymphatics and the primary tumor site in esophagus and stomach cancer, the heart is in the radiation field, and the risk of toxicity may increase in concomitant CT administration. This chapter is a review on the cardiotoxicity of RT for esophagus, stomach, and esophagogastric junction tumors.

The RT Technique in Esophageal, Stomach, and Esophagogastric Junction Tumors

The aim of the RT is to deliver a high dose to the tumor volume while delivering a minimal dose to the surrounding normal tissue. The location of the primary tumor is the major determinant of the treatment field in neoadjuvant/adjuvant RT administration of esophagus, stomach, and esophagogastric junction tumors. The Clinical Target Volume for the primary tumor (CTV primary) is determined by adding 1 cm anterior-posteriorly and 3-4 cm in upper-lower direction to the primary tumor (in neoadjuvant setting) or tumor bed/residual organ (in adjuvant setting), and also the related regional lymphatic nodes (paraesophageal, aorticopulmonary, subcarinal, paracardial, peri-gastric, and celiac) are contoured (CTV nodal) depending on the primary tumor location. The Planning Target Volume (PTV) is generated by adding 1-1.5 cm margin to the CTV to cover the tumor motion due to physiological movements such as breathing, heartbeat, peristalsis, and set-up errors (physical/personal). The surrounding normal tissues such as heart, coronary arteries, and lung should also be contoured. At least 95% of the PTV

should be covered by 95-98% of the total irradiation dose. Normal tissues' tolerance doses must be carefully evaluated. The heart is usually in the high dose region in RT plans of esophagus and stomach cancer because of the anatomic position and proximity. Besides, the advanced RT techniques such as intensity-modulated radiotherapy (IMRT), volumetric arc therapy (VMAT), and proton therapy provide lower doses in OARs such as heart and lung.[3,18] Witt et al.[19] reported that cardiac structures are better protected with advanced RT techniques such as IMRT (step-and-shoot), VMAT, and helical tomotherapy than with the 3-D conformal RT (3DCRT). While there was no statistically significant difference in median heart doses, a significant difference was observed in high dose volumes and ≥ 35 Gy doses in the study. They found the volume of heart receiving 35 Gy (V35) was 30% in the IMRT arm compared to 54% in the 3DCRT arm ($p=0.03$). Respectively, the V40 was 18% compared to 45% ($p<0.01$) and the V45 was 11% compared to 20% ($p<0.01$).

The Pathophysiology of Radiation-induced Cardiac Toxicity

The vascular damage caused by the DNA strand damage due to the free oxygen radicals produced by irradiation is the basic pathophysiological mechanism of radiation-induced cardiac toxicity. In addition, tumor necrosis factor and interleukin (IL)-1,6,8 which are released in the early phases of RT administration cause acute inflammation, while IL-4 and transforming growth factor- β are responsible for the fibrosis.[20] The histological indicators of cardiac injury induced by RT are diffuse fibrosis with normal-shaped myositis in the interstitium of the myocardium, narrowing of the capillary and the arterial lumens, irregularity of the membrane of endothelium, thrombosis, and damage on the wall.[21-23] The ratio of capillary/myositis decreases almost 50%. This causes myocardial cell death, ischemia, and fibrosis. Pericardial effusion (PE), fibrosis, and rarely cardiac tamponade can be observed due to the shift of the normal pericardial adipose tissue with collagen and fibrin.[24]

The Cardiotoxicity of RT

The mean cardiac dose was 4.9 Gy in the trial that Darby et al.[5] have evaluated the correlation between radiation dose and cardiac events in breast cancer survivors. They demonstrated that the relative risk of ischemic

cardiac disease increases 7.4% for every 1 Gy of mean cardiac dose. The mean cardiac dose is much lower in the RT plans of breast cancer compared to those of esophagus and stomach cancer. However, due to the lower survival of the esophagus and stomach cancer patients, enough time interval to observe the late cardiac toxicities such as ischemic cardiac disease cannot reach most of the time. RT-induced cardiotoxicity is observed either in the acute or late-term. Side effects observed during RT/CRT applications and in the first 6 months after treatment are defined as "acute," and the side effects observed in the following months and years are defined as "late" side effects. Each treatment modality has their own side effects in multidisciplinary management; however, concomitant or sequential treatment administration can increase the side effects.

The cardiotoxicity rate during the neoadjuvant CRT course for esophagus and stomach cancer is 21% and the radiation-induced cardiac toxicity rate after the multimodal treatment is 11% (5-44%) and most often observed within the first 2 years.[25,26] The most common acute cardiac toxicity is in the form of pericarditis and can become chronic. The late toxicities are coronary artery disease, congestive heart failure (CHF), myocardial infarction (MI), cardiomyopathy, valvular dysfunctions, PE, and arrhythmias.[3,4,19] coronary artery disease is due to the intimal damage of the coronary arteries in the RT field which ends up with atherosclerosis.[3,21] The damage is observed after 10-15 years of completion of the treatment. The valvular dysfunctions which are most commonly observed in the aortic or the mitral valves are the result of fibrosis and accompanying calcification may be determined.[3] The right valvular replacement is less common than the left independent of the RT dose, suggesting that the high pressure of the systemic circulation has a role in the pathogenesis. Myocardial fibrosis causes diastolic dysfunction and fibrosis in conduction system cells causes rhythm disturbances.[3,27-29] In addition, the concurrent CT agents have their own toxicity profiles such as cisplatin causes ischemia, MI, and venous thrombosis; 5-FU causes ischemia and MI, while paclitaxel causes ventricular arrhythmia, bradycardia, bundle branch blocks, atrioventricular block, and CHF.[3,30,31]

A retrospective trial which evaluated 123 esophagus cancer patients who were treated either with neoadjuvant CRT or surgery alone showed that 16% of the patients had grade ≥ 3 side effects (25% in the CRT vs. 10% in the surgery alone arm, $p=0.04$), 3% had grade 4 cardiac toxicity, none of the patients had grade 5 toxicity.[19] The observed grade ≥ 3 side effects were

five acute coronary syndrome, two newly diagnosed CHF, eight arrhythmia, one cardiac arrest, three PE, and one episode of pericarditis and the median time to event was 3.7 months in the CRT and 1.7 months in the surgery alone arm. This study did not demonstrate any additional cardiotoxicity of the concomitant CRT agent. The multivariate analyses showed that the history of a previous cardiac disease ($p<0.01$, HR 3.45, 95% CI 1.41-8.32) and neoadjuvant CRT ($p<0.01$, HR 3.45, 95% CI 1.35-9.09) affects the risk of cardiac death. Interestingly, there was no relationship between the RT technique (IMRT, 3DCRT) or dose and cardiac side effects or between the total heart dose and survival. However, we must consider that advanced RT techniques were used in this study and this is one of the most important issues when having risk factors such as neoadjuvant CRT or previous cardiac disease history. Takeuchi et al.[32] evaluated cardiac toxicity in 83 esophagus cancer patients in their study using a biological dose-volume histogram (DVH). At median 58 months follow-up time, the grade 2, 3, 4, and 5 cardiac side effects were observed in 49, nine, three, and zero patients, respectively. They observed symptomatic PE (16%) at median 17.5 month, angina pectoris in 2 patients at 27th and 47th months (grade 3 and 4, respectively), arrhythmia in 3 patients (4%) at 34th, 59th, and 109th months (grade 2, 5, and 3, respectively), and grade 5 valvular failure in one patient (1%) at 110th month.

The RT-induced Cardiotoxicity-PE, Arrhythmia

PE is the most common type of cardiotoxicity of CRT administrations with a prevalence of 48% and being diagnosed more often by recent routine diagnostic imaging procedures.[33] Pericarditis or PE can be observed after 6-12 months after RT course.[3] It is usually self-limiting and asymptomatic but can be progressive and may cause heart failure and death.[26] The inflammatory processes are accepted as the cause of PE.[34] Arrhythmia may be another manifestation of radiation-induced cardiotoxicity, yet less is known about the relationship between RT and arrhythmia. Likewise, paclitaxel can induce ventricular arrhythmia, bradycardia, and various degrees of atrioventricular conduction defects.[3] Morota et al.[35] evaluated the late cardiotoxicity in esophagus cancer patients who were treated with CRT. They found that the prevalence of grade ≥ 2 cardiotoxicity (PE, valvular replacement, cardiac failure, and cardiac ischemia) was 6% and detected 10 months after treatment in a follow-up period of 26 months. The

age (>75 years) was the only significant factor affecting the late cardiopulmonary toxicity (29% in older vs. 3% in younger). Bosch et al.[36] compared 96 esophagus cancer patients treated with neoadjuvant CRT (41.4 Gy/carboplatin+paclitaxel) with an equally paired control group who were treated with surgery alone. The significantly more arrhythmia (20.4% vs. 34.4%), pneumonitis (27.1% vs. 51%), and PE (12.5% vs. 24%) were reported in CRT arm. The multivariate analysis demonstrated an increased risk with neoadjuvant CRT in all side effects (odds ratio [OR] for arrhythmia: 2.215, OR for pneumonitis: 2.896; OR for PE: 2.268).

The irradiation of the pericardium increases the risk of PE independently of the dose.[33] The first of the studies defining clinical and dosimetric factors for pericardial and pleural effusion risk is the University of Michigan series.[37] PE was observed in 9% of the patients who were treated with computed tomography-based 3DCRT, observed in the first 8 months after the completion of the treatment. The only factor associated with this was that the daily fraction dose used in treatment is 3.5 Gy. The mean and maximum cardiac doses were found to be significant after the doses were converted to the Linear Quadratic Model. In the retrospective study of Wei et al.[33] which was a review of 101 esophagus cancer patients treated with CRT, the incidence of PE was 28% and the median time to PE was 5.3 (1-16.7) months after RT. The dose-volume value of pericardium had a better correlation with PE than the dose-volume value of the heart. The PE risk decreased from 73% to 13% at 18 months after treatment when the pericardial dose was <26.1 Gy. The strongest prognostic factor was V30 of the pericardium to be >46%. They highlighted that it is important to reduce the high doses to pericardium as low as possible to reduce the PE risk. Similarly, Witt et al.[19] demonstrated cardiac V45 >33% predicts PE in uni- and multivariate analyses. Takeuchi et al.[32] used a DVH calculating the α/β ratio as 3 for the OARs and evaluated the cardiac side effects. The multivariate analyses showed that V80-BED of pericardium and median-BED of heart were related with symptomatic PE. Five-year symptomatic PE development risk was 58% in those with V80-BED \geq 27.4%, 5% in those with low ($p<0.001$), and 54% in those with a mean-BED value of \geq 61.7Gy-BED, and 5% in those with low.

The RT-induced Cardiotoxicity-heart Failure

Another of the most common side effects is heart failure. Left ventricular ejection fraction (LVEF) may re-

duce 4-5% after CRT.[38,39] The total dose of heart is an important issue in RT administrations. Mukherjee et al.[38] evaluated the effect of heart doses on cardiac functions in their retrospective analyses of 15 patients who were treated with CRT (45-50 Gy/1.8-2 G with concurrent cisplatin+5-FU \pm paclitaxel). They observed a significant decrease (from 63% to 58%) in ejection fraction (EF) in 80% of patients at the 1st month after CRT. Similarly, in Tripp et al.'s[39] study, the mean EF was 59% before CRT and decreased to 54% after treatment, but that was not clinically significant. The first of the EF changes was observed in 1.5 months after treatment. In both studies, the relationship between doses could not be evaluated due to the small number of patients.

In studies using three-dimensional functional cardiac imaging to evaluate cardiac toxicity due to RT, it was reported that perfusion anomalies and wall ischemia increased in the irradiated group, but there was no significant difference in functional parameters (LVEF, end-diastolic volume, and systolic volume).[40] Seventy percent of perfusion defects were detected in a high-dose region of the heart (\geq 45 Gy). In another study, although perfusion defect was detected in approximately 1/3 of the esophageal and lung cancer patients treated with CRT, no relationship was shown with symptomatic cardiac events.[41] An increase in cardiac events has been observed after CRT in those with a history of arrhythmias or CHF. In the prospective study of Hatakenaka et al.,[42] 31 patients with esophageal cancer treated with CRT underwent cardiac MRI before, during, and after treatment. The patients were divided into low and high-dose groups according to their mean left ventricular (LV) doses. In the low dose (mean LV dose <0.6 Gy) group, in the low-dose group (mean SV dose <0.6 Gy), LVEF was reported significantly decreased (before treatment: 62.7% vs. during: 59.8% vs. after: 60.6%; $p<0.05$). In the high-dose (mean LV dose 3.6-41.2 Gy) group, left ventricle end-diastolic volume index (before: 69.1% vs. after: 57.0% mL/m²), LV stroke volume index (38.6 vs. 29.9 mL/m²), and LVEF (56.9% vs. 52.8%) parameters were decreased significantly after treatment. In addition, LV wall movement abnormalities were observed in segment 8, 9, and 10. Heart rate was increased after treatment compared with pre-treatment rate. In another functional study evaluating myocardial activity with FDG-PET involvement, a decrease in FDG uptake was observed shortly after treatment, especially in the lateral myocardial wall.[43] However, it failed to show a correlation between cardiac toxicity and uptake of the myocardium. On the other hand, mean heart dose,

V20 (79.7% vs. 67.2%), V30 (75.8% vs. 61.9%), and V40 (69.2 vs. 53.8%), was significantly high in the patients who experienced symptomatic cardiac toxicity. The cut of values for V20, V30, and V40 was 70%, 65%, and 60%, respectively. However, these findings should be verified by studies with higher patient numbers.

The RT-induced Cardiotoxicity-Ischemic Diseases

Secondary ischemic diseases are commonly observed in patients treated with RT or CRT. Ischemic events are observed not only in late-term but also in the first 2 years after treatment.[26] RT should not be counted as the only risk factor for ischemic heart events. In these patients, there are additional factors that increase the risk of ischemic diseases such as advanced age, smoking, and obesity history. In addition, it should be kept in mind the agents that increase thrombus risks, such as cisplatin and 5-FU, are used as radiosensitizers in the treatment of these patients.[44]

Protection of RT-induced Cardiotoxicity

It would not be accurate to claim that cardiac events seen after RT are caused only by radiation. Advanced age, a history of cardiovascular disease, or other cardiac risk factors (smoking, hypertension, hyperlipidemia, etc.) also play a role in the increase of RT-related cardiotoxicity.[5,31,45] It is important to evaluate and treat these risk factors to reduce the risk.[3] While disease-specific survivals are prolonged, care should be taken to tolerate doses of the heart in treatment planning to avoid an increase in the risk of death due to cardiac side effects. In the literature, there are data showing a relationship between radiation-induced cardiac toxicity and dose-volume values in this patient group.[4,33,37] However, based on the current literature, it is recommended to choose plans in which the lowest dose is given to cardiac structures and coronary arteries, although clear values have not been defined for prevention from cardiac toxicity.[3] The total doses of >30-35 Gy and fraction dose of >2 Gy should be avoided whenever possible in the heart. According to Quantec recommendation, a mean heart dose <26 Gy and V30 <46% should be for RT to keep the risk of pericarditis <15%.[4] It is important to deliver a lower dose of radiation to the cardiac structures without compromising the positive impact of RT on cancer survival. The 3DCRT or more advanced techniques (IMRT, VMAT/Image-guided RT) or proton therapy can help to protect cardiac structures.

[3,18,19,46] It should be kept in mind that RT-induced cardiac damage may occur in the early period as well as in the long term and may be progressive, and so if the heart is in the treatment field, a cardiologist should be included to the follow-up team.[3]

Conclusion

As the incidence of esophagus and stomach cancer is increasing, and the survival is getting longer by the multidisciplinary treatment approach, long term cardiac side effects become a bigger concern. Every effort must be made to deliver as low as possible radiotherapy doses to the heart by using the highest conformal RT technique evaluable. Last but not the least, patients must be followed by both the oncologists and the cardiologists during the follow-up period.

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