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Review

Cardiotoxicity of radiation therapy in esophageal cancer☆

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A R T I C L E   I N F O

A B S T R A C T

With a development of radiotherapeutic techniques, availability of radiotherapy data on cardiotoxicity, and slowly improving esophageal cancer outcomes, an increasing emphasis is placed on the heart protection in radiation treated esophageal cancer patients. Radiation induced heart complications encompass mainly pericardial disease, cardiomyopathy, coronary artery atherosclerosis, valvular heart disease, and arrhythmias. The most frequent toxicity is pericardial effusion which is usually asymptomatic in the majority of patients. The use of modern radiotherapy techniques is expected to reduce the risk of cardiotoxicity, although this expectation has to be confirmed by clinical data.

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1. Introduction

The incidence rate of esophageal cancer varies considerably according to geographic location. The highest rates occur in Central and Eastern Asia, and Eastern and Southern Africa, while the lowest rates are in Western Africa.[1,2] The main histological types of esophageal cancer are squamous cell carcinoma (SCC) and adenocarcinoma (AC). Smoking and alcohol consumption is considered to be the most significant risk factors for SCC, while obesity and gastroesophageal reflux disease are strong risk factors of AC.[3] Adenocarcinomas usually occur in the lower third of the esophagus and there is a high increase of this histological type in the last decades in Europe, the United States, and Australia.[4,5]

According to the guidelines, in esophageal cancer generally, radiotherapy plays a role mainly in locoregional or locally advanced disease (clinical stage IIA - IVA). It is provided as preoperative chemoradiation with subsequent surgery or even chemoradiation alone as a definitive treatment. Chemoradiation alone as a definitive therapy is preferred mainly in patients unfit for surgery or patients refusing surgery, in unresectable disease, and in cervical esophageal cancer.[6,7]

The common regimen of concurrent chemoradiotherapy is radiotherapy in a dose of 50–50.4 Gy in 5–5.5 weeks and concurrent chemotherapy, 5-fluorouracil and cisplatin. This scheme was defined as an effective definitive treatment by two ran-

domized trials. The first one, RTOG 8501, demonstrated that concurrent chemoradiotherapy is more effective than radiotherapy alone, although with lower dose of radiation.[8] The second one, Intergroup study 0123, did not confirm a survival benefit associated with a higher dose of radiation than 50.4 Gy in concurrent chemoradiotherapy.[9] Currently, other regimens of chemotherapy are accepted as similarly effective, e.g. FOLFOX, paclitaxel-carboplatin, etc.[10,11]

The preoperative chemoradiation is based on results of clinical trials and meta-analyses that confirmed a benefit of preoperative chemoradiation and surgery compared to surgery alone in esophageal cancer in terms of overall survival.[12,13] In the preoperative setting, until recently, the regimen of chemoradiation was not different compared to definitive treatment in most cases. The CROSS trial, one of the largest trial published recently, that confirmed the survival benefit of preoperative chemoradiation compared to surgery alone used radiation with a lower dose (41.4 Gy in 23 fractions in 4.5 weeks) and concurrent chemotherapy consisting of paclitaxel and carboplatin in a weekly regimen.[14] Therefore, this regimen is accepted in the preoperative setting, as well.

According to the International Commission on Radiation Units and Measurements (ICRU) reports 50 and ICRU Supplement 62, the gross tumor volume (GTV) is defined as a macroscopic primary tumor and involved lymph nodes.[15,16] It is advantageous to use FDG-positron emission tomography (PET) for precise definition of GTV.[17] The clinical target volume (CTV) includes a primary tumor, lymph nodes (GTV) and areas at risk of a microscopic spread of the disease. In general, cranial and caudal margin is recommended of at least 3 cm because of the submucosal spread and 1 cm radially. The lymph nodes at risk are included in the CTV according to the

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location of the primary tumour.[17,18] Planning target volume (PTV) includes CTV plus a margin for internal movements, mainly respiratory movements, (internal margin) and for set-up uncertainties (setup margin). The margin of 1 cm beyond the CTV is commonly used.[7,19]

It follows from the above that delineated PTV usually has an elongated cylindrical shape in the posterior part of the mediastinum and, depending on primary tumor location, it is often located beyond the heart. Although modern radiation therapy techniques have been introduced to clinical practice, the dose distribution in many cases of esophageal cancer continues to be a compromise between sparing of the lungs, heart and spinal cord.[20] Therefore, the heart is usually considered a significant organ at risk for the radiation of esophageal cancer.

2. Radiation-induced cardiotoxicity

Radiotherapy-induced cardiotoxicity has been extensively studied mainly in breast cancer[21,22] and Hodgkin's lymphoma patients.[23,24] The reason of scientific concentration on cardiotoxicity in these diagnoses is the high number of patients with breast cancer, very young age at the time of treatment of Hodgkin's lymphoma and a high number of long term survivals in both diagnoses.

On the other hand, esophageal cancer is a rare diagnosis in young people. The highest incidence is at an older age (>65 years of age).[25,26] And, despite modern treatment approaches, the prognosis of esophageal cancer is not good regardless of a curative therapeutic approach. The 5-year overall survival is often less than 30% in unselected locally advanced esophageal cancer patients,[27,28] although there are studies with trimodality therapy (preoperative chemoradiation and surgery) with 5-year overall survival ≥45%.[29,30] Furthermore, some heart diseases can be caused by similar risk factors as esophageal cancer, like smoking and alcohol in SCC, and obesity in AC. Therefore, the cardiotoxicity of radiation in esophageal cancer is described in literature much less than in diagnoses mentioned above.

Radiation induced heart complications encompass mainly: pericardial disease, cardiomyopathy, coronary artery atherosclerosis, valvular heart disease, and arrhythmias. Pericardial disease can present itself as acute pericarditis or chronic pericardial effusion, often asymptomatic. Cardiomyopathy is usually characterized pathologically as diffuse fibrosis of the myocardium that can result in decreased ejection fraction and sometimes in arrhythmias. Radiation enhances the atherosclerotic process in coronary arteries and may lead to myocardial infarction. Radiation induced valvular disease means focal leaflet fibrosis, valve calcifications and stenosis, and these changes cause reduced ejection fraction and valve regurgitation. Arrhythmias are usually supraventricular.[31,32]

3. Radiation-induced heart toxicity in esophageal cancer

The higher risk of cardiac death in survivors after radiation for esophageal cancer was noted in an analysis of the Surveillance, Epidemiology, and End Results (SEER). Garzai et al. analyzed 5630 patients treated from 1973 to 2012 for esophageal cancer. There was higher probability of cardiac death among patients after radiotherapy compared to no radiation group ($p < 0.0001$) and in lower esophageal carcinomas compared to upper and middle esophageal carcinomas ($p = 0.01$ and $p = 0.04$, resp.).[33]

Data from SEER were earlier analyzed also by Frandsen et al. with the aim of evaluating the risk of heart disease related death following radiation therapy for esophageal cancer. They found a total number of 40,677 esophageal cancer patients with 26,377 of them having received radiation as a part of their initial therapy. While the overall survival for all patients at 5-, 10- and 20-year

was 19.7%, 11.8% and 4.5%, resp., the absolute risk of heart disease related death was 2.8%, 5.3% and 9.4%, resp. According to primary tumor location, the highest risk of heart disease related death was for mid-esophageal tumors.[34]

The review of Beukema et al. analyzed published data on cardiotoxicity and radiation dose parameters between 1970 and 2013. They identified 13 relevant papers with total number of 781 patients treated with radiotherapy in dose of 30–70 Gy. Based on an analysis of these papers they concluded that the overall incidence of clinically relevant cardiotoxicity was 10.8% (data available in six papers). Most events occurred within 2 years after the treatment. Pericardial effusions were the most common cardiac toxicity with an actuarial rate of 48%, although in most cases these effusions were asymptomatic and were found using imaging methods.[35]

Retrospective study of Ogino et al. found a probability of symptomatic radiation-induced cardiac complications 13.8% at 5 years, based on data from follow-up in 58 long term survivors after chemoradiotherapy for esophageal cancer. The most frequent complications were pericardial effusion and atrial tachyarrhythmias.[36]

The clinical and dosimetric factors influencing the risk of pericardial effusion after definitive radiochemotherapy for esophageal cancer were evaluated by Wei et al. They reported in 101 patients a development of pericardial effusion in 27.7% at a median of 5.3 months. The effusion was revealed at follow-up CT as asymptomatic complication. The risk of pericardial effusion increased significantly with a mean pericardial dose of 26.1 Gy and V30 of the pericardium greater than 46 % (13% vs. 73%, $p = 0,001$.[37]

Fukada et al. retrospectively analyzed 167 patients treated between 2001 and 2010 with concurrent chemoradiation. At the median follow-up of 29 months, pericardial effusion of all grades developed in 35.9% patients with an onset in median of 6 months. Symptomatic pericardial effusion (grade ≥ 3) developed in 8.4% patients with a median of 22 months (4–108 months). The average mean pericardial dose was 43.2 Gy in patients with symptomatic pericardial effusion, and it was significantly higher compared to 36.2 Gy in those with asymptomatic pericardial effusion ($p < 0.05$) and 26.7 Gy in those without pericardial effusion ($p < 0.001$). Pericardial V30 to V45 was significantly greater in patients with symptomatic effusion than in those with asymptomatic pericardial effusion ($p < 0.05$).[38]

Pericardial disease as the most frequent cardiac toxicity of chemoradiation for esophageal cancer was also discussed in the study of Ishikura et al. The symptomatic pericarditis was revealed in 10% of 78 patients in complete remission. Other severe cardiac complications were myocardial infarction (2 cases) and heart failure (2 cases).[39]

Ogino et al. evaluated 86 patients with a minimum 24 months of follow-up after concurrent chemoradiotherapy for esophageal cancer. Pericardial effusion was revealed during follow-up at CT in 49 pts. (57%), but symptomatic effusion was only in 5 patients (6%). The pericardial V50 in patients with symptomatic effusion ranged between 17.1 and 21.7%; therefore, the authors recommend the threshold for the pericardial V50 ≤ 17%.[40]

Konski et al. evaluated 102 pts. treated with preoperative or definitive chemoradiotherapy for esophageal cancer and found a 12-month actuarial incidence of any cardiotoxicity of 20.4%, and 8.5% when symptomatic toxicities were considered. There was significantly higher mean heart V20, V30 and V40 in patients with symptomatic cardiotoxicity and the authors recommended that these parameters should be kept below 70%, 65%, and 60%, resp. In this study women had higher probability to develop symptomatic cardiotoxicity ($p = 0.0013$) or any cardiotoxicity ($p = 0.0046$).[41]

The higher risk of cardiotoxicity for women was noted in retrospective study of Tait et al. This study evaluated 100 males and 27 females after preoperative or definitive chemoradiation and found heart complication of grade ≥ 3 in 16 males (16%), but in 12 females
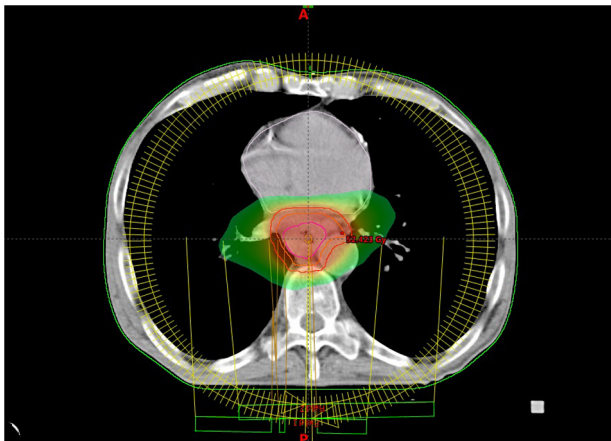
Fig. 1. Heart-sparing radiotherapy using volumetric modulated arc therapy (VMAT) in esophageal cancer. The volume irradiated with a dose greater than 25 Gy is displayed.

(44%). The risk of cardiotoxicity in females was 4.15 times higher (95% CI 1.63–10.50, p = 0.0017) than in males. The most frequent complication was pericardial effusion (23 cases).[42]

Lester et al. evaluated the risk of cardiopulmonary toxicity depending on age in 571 patients treated with preoperative chemoradiation and surgery at three US centers. The rate of cardiotoxicity including atrial fibrillation and other arrhythmias, myocardial infarction, and congestive heart failure, was significantly higher in patients older than 65 years than in younger (25% vs. 13%, p < 0.001).[43]

Recent paper of Hayashi et al. evaluated cardiotoxicity in 80 patients treated with chemoradiotherapy for invasive squamous cell superficial esophageal cancer. With a median follow-up of 73 months, thirteen patients developed severe cardiac events: ischemic heart diseases (7 pts.), pericardial effusion (3 pts.), atrial fibrillation (1 pt.), and sudden death. The 5-year rate of severe cardiac events was 16.3%. The ratio of irradiated to the total heart volume and the absolute heart's exposure to radiation was significantly higher in patients who developed a cardiac event. The authors found volume cut-off of 280 ml of the heart irradiated with a dose higher than 50 Gy (V50) with a risk ratio of 16.80 (95% CI, 4.94–53.07).[44]

4. Modern techniques in radiation therapy

The dose that the heart receives is greatly dependent on the location of the target volume, but also on the irradiation technique. Historically, conventional radiotherapy has almost not evaluated dose-volume parameters for organs at risk. Three-dimensional conformal radiotherapy (3D-CRT) introduced treatment planning based on three-dimensional computer tomography. Modern software made it possible to calculate dose in target volumes and organs at risk, as well as include dose-volume histograms and, based on these data, we obtained the possibility to find an association between dose-volume parameters and clinical data of radiation toxicity.

The development of computer technology, as well as availability of modern imaging techniques and tools during radiotherapy planning and radiotherapy application, enabled the improvement of organ at risk sparing. For a definition of GTV, it is appropriate to use hybrid PET/CT. Similarly, the dose distribution is improved using modern irradiation techniques, mainly intensity-modulated radiation therapy (IMRT) and its variants, including volumetric modulated arc therapy (VMAT) or tomotherapy (Fig. 1).

Image-guided radiotherapy means acquisition of two orthogonal images or cone-beam CT before individual fraction of radiation, matching the reference images and individual setup corrections. IGRT enables reduction of set-up margins and, subsequently, a dose reduction in organs at risk during radiotherapy planning. The motion during the respiratory cycle can be significant, mainly in lower esophageal tumors.[45] It is possible to verify the movement of target volumes and organs at risk during respiratory cycle using 4D-computer tomography, and in the case of an advantage of irradiation in specific phase of respiratory cycle it is possible to use respiratory control techniques for irradiation (respiratory gating, tracking etc.). Recently, proton therapy has been increasingly discussed because of advantageous dose distribution.[19]

There are several papers comparing dosimetric isodose plans using modern irradiation techniques. Chen et al. compared IMRT, tomotherapy and 3D-CRT techniques and found better sparing of the heart (V30 and V45) in IMRT and tomotherapy although lung V10 was more acceptable in 3D-CRT.[46] Similarly, Choi et al. noted better heart protection using IMRT and VMAT compared to 3D-CRT in V20, V30, and V40 parameters.[47] Kataria et al. found dosimetric advantages of the VMAT technique compared to IMRT, although the data for the heart were not statistically significant.[48] On the other hand, Wu et al. compared isodose plans of VMAT, IMRT and 3D-CRT and, although they found a better protection of the heart, they recommended 3D-CRT as a feasible and cost-effective option for middle thoracic esophageal cancer radiotherapy.[49]

Xu et al. retrospectively analyzed 65 patients with thoracic esophageal cancer treated with the VMAT technique using 4D-CT and PET based planning and compared plans and results with 130 pts. treated with the IMRT step and shoot technique (ssIMRT). With a median follow-up of 14.3 months in the VMAT group and 31.8 months in the ssIMRT group, there was no difference in overall survival or recurrence-free survival in statistical analysis. Dosimetric analysis did not reveal a significant difference for heart parameters V30 and V40, V5 was higher, while V50 was lower in the VMAT group compared to ssIMRT. The differences in cardiac toxicity were not statistically significant between the groups.[50] Hirano et al. compared proton therapy, IMRT and 3D-CRT plans in CT data of 27 esophageal cancer patients treated with proton therapy. Proton therapy reached a better dose distribution compared to IMRT and 3D-CRT in the heart and lung sparing. Clinically, four patients (15%) developed late pericardial effusion of grade 2 after proton therapy.[51]

Similarly, Ling et al. compared proton therapy, IMRT, and 3D-CRT in 10 esophageal cancer patient CT data. That study did not find a benefit of IMRT compared to 3D-CRT, but proton therapy was beneficial in lower heart doses compared to both, IMRT and 3D-CRT.[52] Similarly, dosimetric study of Shiraishi et al. reported that proton therapy is associated with significantly lower radiation exposure to the whole heart and cardiac substructures than IMRT.[53]

Clinical data of intensity-modulated proton therapy in 19 pts. with esophageal cancer was recently published by Prayongrat et al. With a median follow-up of 17 months, they noted only two grade 2 toxicities: pericardial effusion and atrial fibrillation.[54]

Despite modern radiation techniques in use, there can be a higher risk of heart complications in the case of dose escalation. Venkat et al. compared treatment results after preoperative chemoradiation with prescribed dose of 56 Gy a 50.4 Gy. Radiation was applied as IMRT and planned using 4D-CT. Although the higher dose was associated with better treatment results in terms of better pathologic complete response rate (56.2% vs. 30.0%), 3-year locoregional control (93.8% vs. 78.5%; p = 0.022), 3-year freedom from failure (73.7% vs. 52.2%; p = 0.051), there was a statistically significant increase in postoperative atrial fibrillation (30.1% vs. 12.5%; p = 0.036).[55]

5. Conclusion

With a development of radiotherapeutic techniques, availability of radiotherapy data on cardiotoxicity, and slowly improving esophageal cancer outcomes, an increasing emphasis is placed on the heart sparing in radiation treated esophageal cancer patients. Modern techniques and tools improve the dose distribution with organ at risk sparing, including heart protection, and, therefore, the risk of cardiotoxicity is expected to be reduced when using these techniques. Naturally, expectations must be confirmed by clinical data. However, it is equally important, even at this time, to be aware of the cardiotoxicity risk in patients irradiated for esophageal cancer.

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Conflict of interest

None declared.

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