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Original Article

Late cardiac toxicity of neo-adjuvant chemoradiation in esophageal cancer survivors: A prospective cross-sectional pilot study

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ABSTRACT

Purpose: Although cure rates in esophageal cancer (EC) have improved since the introduction of neoadjuvant chemoradiation (nCRT), evidence for treatment-related cardiac toxicity is growing, of which the exact mechanisms remain unknown. The primary objective of this study was to identify (subclinical) cardiac dysfunction in EC patients after nCRT followed by surgical resection as compared to surgery alone.

Materials and Methods: EC survivors followed for 5–15 years after curative resection with (n = 20) or without (n = 20) nCRT were enrolled in this prospective cross-sectional pilot study. All patients underwent several clinical and diagnostic tests in order to objectify (sub)clinical cardiac toxicity including cardiac CT and MRI, echocardiography, ECG, 6-minutes walking test, physical examination and EORTC questionnaires.

Results: We found an increased rate of myocardial fibrosis (Linear late gadolinium enhancement (LGE) 4 vs. 1; p = 0.13; mean extracellular volume (ECV) 28.4 vs. 24.0; p < 0.01), atrial fibrillation (AF) (6 vs. 2; p = 0.07) and conduction changes in ECG among patients treated with nCRT as compared to those treated with surgery alone. The results suggested an impact on quality of life in terms of worse role functioning for this patient group (95.0 vs. 88.8; p = 0.03).

Conclusion: Based on our analyses we hypothesize that in EC patients, radiation-induced myocardial fibrosis plays a central role in cardiac toxicity leading to AF, conduction changes and ultimately to decreased role functioning. The results emphasize the need to verify these findings in larger cohorts of patients.

Although cure rates of esophageal cancer (EC) patients have been improved since the introduction of neo-adjuvant chemoradiation (nCRT), radiation-induced cardiac toxicity might jeopardize the beneficial effect of this treatment. The CROSS trial showed a significant increase in survival rates for patients treated with nCRT prior to surgery compared to patients treated with surgery alone with acceptable acute and perioperative toxicity [1,2]. Quality of life was similar in both groups at one year after treatment [3]. Therefore, nCRT became the standard treatment for EC in large parts of the world. However, after thoracic radiotherapy for haematological malignancies, lung or breast cancer, radiation-induced cardiac and pulmonary toxicity has increasingly been acknowledged as a clinically relevant problem [4–6]. SEER database studies including EC patients showed more cardiac deaths among irradiated patients as opposed to those treated with surgery [7,8]. Recent studies comparing, modern organ sparing radiotherapy techniques like IMRT or proton therapy with more conventional techniques found lower rates of all cause or cardiac morbidity and mortality [9-11]. Furthermore, higher (cardiovascular) postoperative complication rates were found in irradiated patients as well as patients treated with less advanced radiotherapy techniques [12-15].

These findings suggest that treatment-related cardiovascular morbidity is a clinically relevant problem in EC patients. In retrospective studies, high rates of atrial fibrillation, pericardial effusion, heart failure and cardiac wall motion disorders have been described [16-19]. However, so far, prospective imaging studies have not been systematically performed in EC patients. Moreover, information of the biological mechanisms resulting in cardiovascular toxicity is lacking. Therefore, assessment of subclinical cardiac

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toxicity using advanced cardiac imaging techniques may provide a better understanding of these mechanisms and may identify targets to prevent cardiac toxicity in the treatment of EC.

Therefore, the main objective of this prospective hypothesis-generating cross-sectional pilot study was to identify subclinical and clinical cardiopulmonary abnormalities in EC survivors after nCRT followed by resection and compared to patients treated with surgery alone.

Materials & methods

In this pilot study, we included 40 EC survivors who were treated 5 to –15 years ago. Twenty patients were treated with nCRT followed by surgery. Since the EC population is generally older with several (cardiopulmonary) comorbidities, 20 patients treated with surgery only were included as a control group. During the time frame 2002–2010, our hospital participated in the CROSS trial. At that time, multimodality treatment was not considered standard of care and therefore we expected to include EC survivors with comparable baseline cardiopulmonary risk factors. Because of the limited number of survivors, we included patients that were 2 years before, during and 2 years after the recruitment period of the CROSS trial. Thereafter, nCRT was considered standard of care. nCRT was given according to the CROSS trial with a total dose of 41.4 Gy in 23 fractions combined with weekly concurrent carboplatin and paclitaxel [1]. 3-Dimensional conformal radiotherapy was used during this time frame. Beam directions usually consisted of two opposing beams, adding a third, lateral beam to decrease the dose to the heart. According to the protocol, the volume of lung tissue receiving 20 Gray (V20) did not exceed 30%, the V40 of the heart did not exceed 30%, and the V30 of the liver did not exceed 60%.

The current study was approved by the local ethics committee and registered in clinicaltrials.gov (NCT03396614). All patients treated for EC with curative surgery plus or minus neoadjuvant CRT were selected from our institutional database. After verification of survival and disease status with their general practitioners, we contacted patients whether they were willing to participate in this study. In total, 36 nCRT patients and 40 control patients were contacted. Written informed consent was given by 22 and 26 patients respectively. Inclusion was done in order of response.

Participants visited our hospital for one day. They were interviewed on issues concerning medical history and physical functioning. In addition, the EORTC Quality of life questionnaires (EORTC-QLQ), measuring cancer patients' physical, psychological and social health (C-30) and OES-18, focusing on EC cancer patients, were completed. After a routine physical examination, a 6-minute walking test (6MWT) was performed as measurement for functional capacity and physical fitness [20,21]. Blood biomarkers were taken to evaluate myocardial damage: NT pro BNP is considered an early biomarker for heart failure and is prognostic for cardiac events and overall survival [22] and HS-TNT is considered as a measurement for myocardial necrosis and predicts the development of heart failure and overall survival as well [23].

Echocardiography was performed according to the guidelines of the European Association of Cardiovascular Imaging [24]. This protocol included assessments of right and left systolic and diastolic function parameters, strain imaging, valve disorders and signs of pulmonary hypertension.

An ECG triggered CT-scan was performed on a dual source CT-scanner without contrast enhancement in order to quantify the number of coronary calcifications. This was calculated and expressed as the Coronary Artery Calcium (CAC) score based on the Agatston method [25].

A cardiac MRI scan was performed during breath hold and ECG monitoring on a 1.5 Tesla MRI scanner (Magnetom Avanto-fit, Siemens Healthineers, The Hague, Netherlands). T1 images were acquired with and without contrast enhancement in order to assess patterns of myocardial fibrosis and to enable T1 mapping to quantify myocardial abnormalities. Cine and delayed enhancement images (4 chamber, 2 chamber and short axis) were acquired for functional evaluation and measurements [26,27]. Results of the imaging techniques were assessed while being blinded for treatment group and medical history.

In order to identify possible relationships between dose distribution parameters and diagnostic tests, detailed information on cardiac radiation dose distributions was collected. The radiotherapy planning CT scan, 3D treatment plan and delineated structures were transferred to the Mirada Medical treatment planning system (version 1.2.0). Additional contouring of substructures, and the left ventricular myocardial segments of the heart was subsequently performed according to previously published guidelines [28,29]. These retrospective data were exported to our research database.

As this trial was designed as a pilot study, it was not powered for statistically significant ($p < 0.05$) differences between the two groups. We consider differences up to a p value below 0.20 relevant for further analyses and worthwhile presenting. Binary endpoints were analysed using a logistic regression analysis, while for continuous endpoints a linear regression analysis was performed. To compensate for potential imbalances between the groups we tested and corrected for confounding variables. Mean values were used in presenting the data.

Results

Forty patients were included in this study, of which 20 received nCRT prior to surgery and 20 were treated with surgery only. An overview of patient characteristics, cardiac risk factors, clinical events at baseline and during follow up is presented in Table 1.

In the surgery only group, patients were older (74 vs 67.8 years, $p = 0.04$), and the median follow up after treatment was significantly longer (126 vs 88 months, $p = 0.01$). No statistically significant differences were found in clinical cardiac or pulmonary events except for cardiac arrhythmia. In the nCRT group, 6 patients were diagnosed with atrial fibrillation vs. 2 in the control group ($p = 0.11$, age corrected $p = 0.07$).

At the time of analysis, patients in the nCRT group reported higher fatigue scores (EORTC QLQ-C30) 13.8 vs 9.1 ($p = 0.13$) and

Table 1
Patient population including cardiac complications at baseline and during/after treatment.*

	Surgery($n = 20$)	CRT + Surgery($n = 20$)
Age (yrs)	74.0 [46–91]	67.8 [50–81]
Follow up after treatment (months)	126	88
WHO 0 vs higher (%)	60	55
BMI	25.4	25.0
Current smoker	3	1
Hypertension	6(5)	7(4)
Diabetes Mellitus	3(3)	6(7)
Hypercholesterolaemia	5(3)	7(7)
Coronary artery disease	4(2)	2(1)
Arrythmia**	2(0)	6(1)
Heart failure	2(2)	1(0)
peripheral thrombosis	1(0)	2(0)
Peripheral arterial disease	0(0)	1(0)
Valvular replacement	1(1)	0(0)
COPD	1(0)	2(2)

ns = non-significant.
* Between brackets numbers before esophagectomy.
** Arrythmias (AF) were most often diagnosed within the first half year after treatment.

lower role functioning scores 88.6 vs 95.0. (p = 0.13). These differences could be explained by the differences in the questions "Were you tired" (p = 0.07), "Were you limited in doing your work" (p = 0.03) and "were you limited in doing your hobbies" (p = 0.01) and not by the effect on social or family life. When correcting for age, the difference in role functioning was statistically significant between the groups (p = 0.03). No differences were found in pulmonary symptoms (EORTC QLQ-LC13).

The results regarding laboratory findings, ECG and 6-min walking test are summarized in Table 2. QTc intervals on ECG were significantly shorter in the nCRT patients. No other signs for conduction disorders were found.

Thoracic CT-scans were performed in all patients. CAC scores were less reliable in 6 patients because of cardiac interventions (CABG and coronary stents). However, scores of these patients did not influence the conclusion: there was no difference between the groups.

Functional and dimensional parameters were measured using echocardiography and cardiac MRI. No significant differences were seen between the two treatment groups regarding signs of pulmonary hypertension, systolic or diastolic dysfunction and valve disorders. A significant difference in myocardial wall thickness of the septum (p = 0.04) was observed, but when correcting for age, the effect of radiotherapy on this parameter became non-significant (Table 3). A complete overview of these data is added as supplementary data (Sup 1).

A linear pattern of cardiac late gadolinium enhancement (LGE) which is considered a sign of local non ischemic fibrosis [30] was observed in 4 out of 18 irradiated patients vs. in 1 out of 20 non-irradiated patients (Fig. 1, p = 0.13). Within the nCRT group, the mean radiation dose to the heart (MHD) was significantly higher (26.6 vs. 21.8 Gy, p = 0.01) in patients showing linear LGE. T1 mapping was performed in these patients [31]. Mean extracellular volume (ECV) value is an objective quantitative measurement of myocardial fibrosis of the left ventricle, and was calculated by using both the T1 native and the T1 post contrast map [27]. In multilevel analysis, myocardial segments showing this linear LGE (10 vs 262) indeed showed higher ECV values (p = 0.01), received a higher radiation dose (p = 0.03) and these patients had higher hs-TNT (p = 0.03) values.

As the prevalence of atrial fibrillation (AF) was higher among nCRT patients compared to the surgery alone group (6 vs. 2, p = 0.07), we performed additional analyses in order to unravel the possible mechanisms behind this complication and its consequences for physical functioning (Table 4).

Patients with AF received markedly higher radiation doses to the heart, especially to the atria. This was not only seen in the entire group investigated but also when the analysis was restricted to the irradiated patient group. However, in this analysis, it did not become statistically significant in most substructures of the heart (supplement 2).

AF has hemodynamic consequences which resulted in lower ejection fractions and higher NT pro BNP levels. Additionally, AF patients performed worse on the 6-minutes walking test (64.6 vs. 74.7% of predicted, p = 0.10). The most common cause of AF in the general population is hypertension and atrial dilatation (LAVI). In this study, a borderline significant association was found between LAVI and AF (p = 0.10). However, when combining this factor with a radiation dose parameter in the multivariate regression analyses, both parameters became statistically significant (p = 0.02) with a high AUC (0.93).

Discussion

The aim of this hypothesis-generating pilot study was to identify late subclinical cardiac toxicity after nCRT for esophageal cancer. An overview of these results is visualized in Fig. 2. The results suggest an effect on myocardial fibrosis and an increased rate of AF. In this small population of patients treated with nCRT followed by surgery, the prevalence of AF was higher than after surgery alone (p = 0.07 (corrected for age)). These findings are in line with those from several previous reports, showing an increased incidence of AF after thoracic irradiation [11-13,32].

There might be a causal relationship between myocardial fibrosis and the development of AF. Most patients who develop AF have fibrosis in the atrial wall (e.g. as a consequence of hypertension, valvular disease and atrial dilatation [33]). When looking at the patient group with AF in the current study, a relatively high radiation dose was given to the atria because of its close proximity to the target volume. Given the linear dose response relationship with fibrosis that we found in the left ventricular myocardial wall [31], it is likely that the atrial walls developed fibrosis as well. These findings are supported by preclinical studies, in which fibrosis was associated with decreased end diastolic diameter of the irradiated atria [34]. Unfortunately, ECV cannot be measured in an atrial wall since the walls are too thin. Although both mechanisms (wide atria as measured by LAVI and radiation dose to the atria) were only related to AF with borderline significance in this population, we evaluated these variables both in a multivariate analysis and found that they became statistically significant with high discriminating power (AUC 0.93). These findings suggest that myocardial fibrosis as induced by radiotherapy is a second mechanism in the development of AF in this irradiated population.

Other investigators suggested that inflammatory reactions may also lead to AF [34]. Indeed, if the interval between treatment and onset of the arrhythmia is short, local inflammation due to nCRT

Table 2
Questionnaires, blood tests, ECG, 6MWT.*

	Surgery (n = 20)	CRT + Surgery (n = 20)	p value	Age corrected p value
Global health (EORTC QLQ-C30)	72.1 (2.9)	70.4 (2.7)	ns	ns
Physical functioning (EORTC QLQ-C30)	89.3 (2.5)	88.0 (2.0)	ns	0.15
Role functioning (EORTC QLQ-C30)	95.0 (3.3)	88.8 (2.4)	0.13	0.03
Emotional functioning (EORTC QLQ-C30)	94.7 (1.7)	91.9 (2.4)	ns	ns
Cognitive functioning (EORTC QLQ-C30)	90.6 (2.5)	96.3 (1.6)	0.07	ns
Fatigue (EORTC QLQ-C30)	9.2 (2.1)	13.8 (2.1)	0.13	0.15
ECG				
PQ time (ms)	182 (6.7)	175 (6.7)	ns	ns
QRS complex (ms)	94 (2.7)	90 (2.3)	0.18	0.11
QT (Bazet corrected) (ms)	432 (4.1)	423 (3.4)	0.10	0.03
6-minute walking test (% predicted)	74.6 (3.4)	70.9 (3.6)	ns	
Blood tests				
HS-TNT (ng/L)	14.0 (1.9)	10.6 (1.0)	0.13	ns
NT-pro BNP (ng/L)	250 (93.2)	362 (108.1)	ns	0.19

* Standard error of the mean (SEM) between brackets.

Table 3
Imaging echo, CT and MRI.**

	Surgery (20)	CRT + Surgery (20)	*p* value	Age corr
CAC score (CT scan)	735 (249)	350 (173)	0.20	ns
Left atrium Volume Index (LAVI ml/m^2)	35.1 (3.6)	30.1 (2.5)	ns	ns
Number of patients with MRI	20	18		
Intramural contrast enhancement (LGE)	1	4	0.12	0.13
Mean ECV *	24.0 (0.3)	28.4 (0.3)	<0.01	<0.01
Septum thickness (mm)	9.9 (0.4)	8.7 (0.4)	0.04	0.14

* Only eligible results (n = 27).
** Standard error of the mean between brackets.

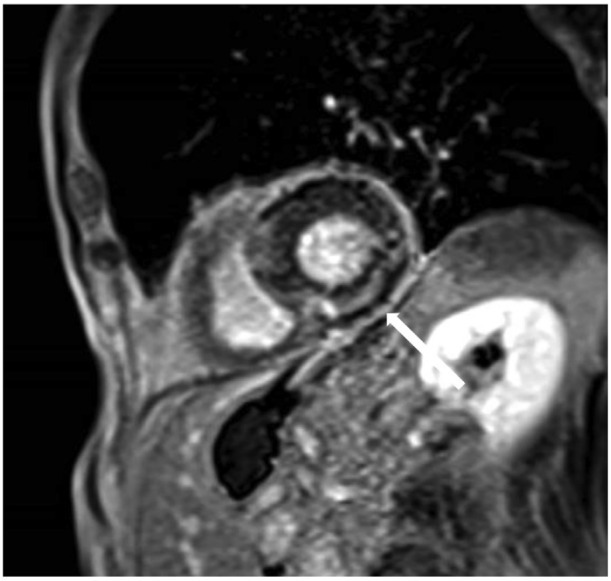

Fig. 1. Linear late gadolineum enhancement, a sign of non ischaemic fibrosis.

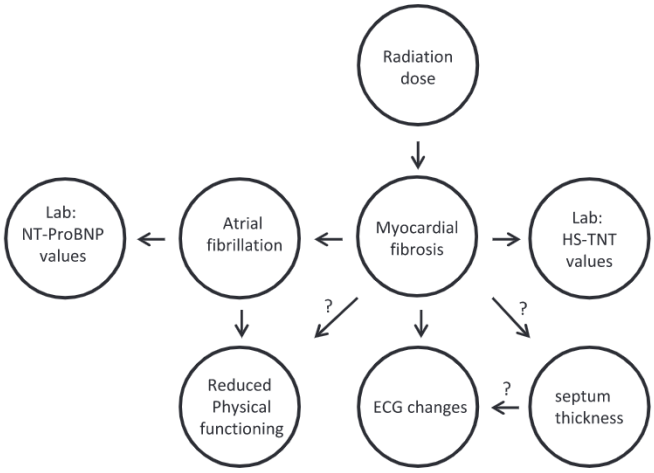

Fig. 2. Overview of relevant findings.

eventually leading to fibrosis could be one of the mechanisms. However, in this cross-sectional study with assessments of cardiac abnormalities 5–10 years after treatment this question remains unanswered.

Development of AF is a clinically relevant adverse event. Patients with AF are at higher risk of developing a stroke. Moreover, AF may cause or enhance heart failure and patients require hospitalization more frequently. Moreover, AF patients have worse overall survival rates [35,36].

In the current study, we were not able to identify cardiac systolic or diastolic dysfunction secondary to myocardial fibrosis based on ultrasound measurements. This could be explained by the small sample size and the fact that many of the echocardiographic parameters were not assessable because of poor acoustic windows. Therefore, we were not able to analyse sufficient parameters for an adequate diastolic function assessment nor to perform strain imaging. Another reason could be the selection bias as we only included long term survivors.

Table 4
Differentiating factors in patients with or without (a history) of atrial fibrillation.**

	AF (n = 8)	no AF (n = 32)	*p* value	Age corrected *p* value
Mean RT dose right atrium (Gy)	18.4 (4.5)	9.7 (2.3)	0.09	0.05
Mean RT dose left atrium (Gy)	26.3 (5.8)	13.0 (2.9)	0.05	0.02
Mean RT dose right ventricle (Gy)	21.1 (4.7)	10.9 (2.3)	0.07	0.03
Mean RT dose left ventricle (Gy)	11.9 (3.0)	7.8 (1.7)	ns	ns
Left ventricular ejection fraction (%)	51.5 (5.8)	59.4 (1.4)	ns	0.04
Right ventricular ejection fraction (%)	46.0 (4.5)	50.7 (1.1)	0.13	0.13
6-minute walking test (%predicted)	64.8 (6.2)	74.7 (2.6)	0.10	
Global health (EORTC QLQ-C30)	62.5 (5.2)	73.4 (2.0)	0.03	0.03
Physical functioning (EORTC QLQ-C30)	84.4 (3.1)	89.7 (1.8)	0.18	ns
Dyspnoea total (QLQ LC-13)	1.8 (0.3)	1.4 (0.1)	0.07	0.08
NT pro BNP (ng/L)	852.9 (260.8)	169 (32.8)	0.01	0.01
HS TNT (ng/L)	15.8 (4.1)	11.4 (1.0)	0.16	0.17
Mean ECV (%)	27.9 (0.8)	26.1 (0.5)	0.13	0.11
Log. regression analyses predicting AF	regression coefficient		p value	AUC
Left atrium volume index (LAVI ml/m^2)	0.08		0.1	0.65
Mean left atrium dose (Gy)	0.05		0.06	0.69
LAVI/left atrium dose*	0.11/0.11		0.02/0.02	0.93

* Multivariate analysis with corresponding regression coefficients and p values per predicting item.
** Standard error of the mean between brackets.

Surprisingly, we did not find a difference in coronary calcifications as measured by the CAC-score between the two treatment groups. In this study population, known prognostic factors such as hypertension, age and diabetes were associated with higher calcium scores. Nor did we find any relationship between radiation dose and CAC score. This might also be explained by the small sample size and the fact that we analysed long-term survivors, whereas patients with cardiovascular risk factors might have experienced cardiac complications and mortality sooner after treatment [11]. In addition, most coronary arteries are located in lower dose regions as opposed to the radiation dose in e.g., breast cancer patients. Therefore, coronary problems might be less important in this patient group.

In the current study, the relaxation time after ventricle contraction (QTc interval) and the width of the QRS complex were significantly shorter in the irradiated group (Table 2). We did not find a good explanation for the changes in QTc time. This can be caused by differences in heart rate, prior infarctions, or the use of cardiac medication. The shorter QRS complex can, however, be caused by myocardial fibrosis (ECV values) as detected on MRI as described earlier in a large, otherwise healthy, study population [37]. In this paper, both shorter QRS complexes and lower voltages were seen in linear correlation with age and ECV values (supplementary 3). In addition to the shorter QRS complex we indeed found a microvoltage ECG in 2 (vs 0) of the irradiated patients. Our results are therefore in line with these findings. Lower voltages ECG's can be caused by, for example, pericardial effusion, pericardial fibrosis and by an infiltrating cardiomyopathy [38], which are known complications after irradiation of the heart [39,40]. The thinner septum between the ventricles may actually also be in line with these findings as thinner myocardial walls (fibrosis) may result in lower voltage ECG's. These findings could be relevant as prognosis in otherwise healthy adults with low voltage ECG's is worse [41].

We did correct for age difference between the groups in these analyses because age has been well recognized as a prognostic factor for cardiac comorbidities. We realized there was a difference in interval after treatment as well. Theoretically, this may influence the number of cardiac events, but this did not seem to change significance levels and therefore did not have an effect in this population.

It should be stressed that this was a relatively small cross sectional hypothesis-generating pilot study and therefore neither definitive conclusions nor causality based on these results can be drawn. Furthermore, while the patients group of this study were treated using 3-dimensional radiotherapy, current techniques such as IMRT or proton therapy have reduced the dose to critical organs such as the heart, and thus, in future studies, lower toxicity rates would be expected. However, the clinical diagnosis of AF and ECG changes of the heart, as described in the current study, can be related to radiation dose dependent myocardial fibrosis as seen on MRI. These clinically relevant findings can provide further insight into the mechanisms behind radiation induced cardiac complications, which need to be further explored. More information is needed on consequent clinical symptoms and cardiac dysfunction in order to estimate the possible benefit of primary and secondary preventive measures.

In conclusion we hypothesize that in EC patients, radiation-induced myocardial fibrosis plays a central role in cardiac toxicity leading to AF, conduction changes and ultimately to decreased role functioning. The results emphasize the need to verify these findings in larger cohorts of patients.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2021.11.029.

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