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Original Article

Can we safely reduce the radiation dose to the heart while compromising the dose to the lungs in oesophageal cancer patients?

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ABSTRACT

Purpose: The aim of this study was to evaluate which clinical and treatment-related factors are associated with heart and lung toxicity in oesophageal cancer patients treated with chemoradiation (CRT). The secondary objective was to analyse whether these toxicities are associated with overall survival (OS).
Materials and methods: The study population consisted of a retrospective cohort of 216 oesophageal cancer patients treated with curative CRT. Clinical and treatment related factors were analysed for OS and new pulmonary and cardiac events by multivariable regression analyses. The effect of these toxicities on OS was assessed by Kaplan Meyer analyses.
Results: Multivariable analysis revealed that pulmonary toxicity was best predicted by the mean lung dose. Cardiac complications were diverse; the most frequently occurring complication was pericardial effusion. Several cardiac dose parameters correlated with this endpoint. Patients developing radiation pneumonitis had significantly worse OS than patients without radiation pneumonitis, while no difference was observed in OS between patients with and without pericardial effusion. OS was best predicted by the V45 of the lung and tumour stage. None of the cardiac dose parameters predicted OS in multivariable analyses.
Conclusion: Cardiac dose volume parameters predicted the risk of pericardial effusion and pulmonary dose volume parameters predicted the risk of radiation pneumonitis. However, in this patient cohort, pulmonary DVH parameters (V45) were more important for OS than cardiac DVH parameters. These results suggest that reducing the cardiac dose at the expense of the dose to the lungs might not always be a good strategy in oesophageal cancer patients.

Over the last decade, increasing numbers of oesophageal cancer patients have been treated with radiotherapy, either in the neo-adjuvant setting followed by surgery or as definitive treatment. Due to neo-adjuvant CRT, cure rates have improved [1,2]. As a consequence, the number of oesophageal cancer survivors at risk of developing late toxicity is has risen correspondingly.

Traditionally, radiotherapy planning for these patients has aimed at adequate target coverage while focussing on dose limitation for the spinal cord and lungs in order to prevent radiation-induced toxicities. In recent years, there has been an increasing awareness of radiation-induced cardiac toxicity. In breast cancer patients, prediction models for cardiac toxicity [3,4] indicate a linear increase of the risk of major coronary events by 7.4% per Gray.

However, in the radiotherapy treatment of oesophageal cancer the radiation dose to the heart is generally much higher and oesophageal cancer patients generally have less favourable cardiovascular risk profiles. Therefore, prediction models describing the relationship between dose parameters and cardiac events developed in breast cancer patients cannot be automatically extrapolated to oesophageal cancer patients.

Limited data currently exists for radiation-induced cardiac toxicity in oesophageal cancer patients. Grade III cardiac toxicities are observed in about 10 percent of these cases and occur relatively early after treatment. Numerous dose volume parameters of the heart are significantly associated with a variety of cardiac toxicity endpoints. However, multivariable prediction models for cardiac toxicity are not available and it remains unclear which threshold dose levels should be used in routine clinical practice [5–9]. Nevertheless, in some studies, including of patients with lung and

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oesophageal cancer, significant associations were found between cardiac dose and OS, suggesting that cardiac toxicity is a relevant and possibly underestimated problem in the treatment of these patients [10–16].

Even with modern photon techniques, such as IMRT and VMAT, attempts to reduce cardiac dose is generally accompanied by higher dose levels to the lungs, thus increasing the risk of pulmonary toxicity. The optimal balance between cardiac and pulmonary toxicity and its influence on overall survival remains to be determined.

The main objective of this study was therefore to evaluate which clinical and treatment-related factors are associated with cardiac and/or lung toxicity in oesophageal cancer patients after definitive CRT. The secondary objective was to determine whether these toxicities are associated with OS.

Methods and materials

The study population of this retrospective cohort study consisted of 216 oesophageal cancer patients who had been referred to the department of radiation oncology in Osaka for definitive CRT from January 2007 to December 2013. All patients had histologically confirmed carcinoma of the oesophagus and were staged using CT scans of the neck, chest and abdomen and endoscopic evaluation. When local treatment was considered, endoscopic ultrasound was performed. Based on these findings, patients were restaged according to the 7th edition of the AJCC cancer staging manual [17].

Target volume delineation was performed on a 3D planning CT scan. The clinical target volume (CTV) consisted of the primary tumour and suspicious lymph nodes with a 2–3 cm margin in cranio-caudal direction along the oesophagus and 5–10 mm margin in the transversal plane. An additional margin of 5–10 mm was taken from CTV to PTV in all directions. For T2 and T3 tumours and in the case of positive lymph nodes, an area of elective nodal irradiation was delineated depending on the location of the tumour. For all these patients, the mediastinum was treated to a total dose of 40 Gy. For upper and middle thoracic tumours, the supraclavicular region was included in the elective nodal area as well. For the middle and distal tumours, the truncal region was included in the target volume and in some cases, elective nodal irradiation was omitted based on poor clinical condition or very poor prognostic factors.

For each patient, the whole heart (WH) and its substructures, including the right and left atria (RA and LA, resp.) and right and left ventricles (RV and LV, resp.) were contoured using an automatic delineation tool based on the atlas by Feng et al. [18]. Since the pericardium cannot be identified on CT images, we used a surrogate pericardium (PC), by creating a 3D structure with the WH contour as inner border and the WH + 5 mm as outer border. The lungs were delineated and considered as one organ.

Treatment was given on a daily basis, using 10 MV photons in 1.8–2.0 Gy daily fractions to a total dose of 50.4–66.0 Gy (median dose: 60 Gy). All patients were treated with 3D-conformal radiotherapy (3D-CRT). In 205 out of 216 patients, radiotherapy was combined with chemotherapy which mostly consisted of 5-FU infusions combined with cisplatin. In case of renal dysfunction or poor performance status a combination of 5-FU with nedaplatin (8) or docetaxel (14) was administered. Only few patients received neo-adjuvant (9) and/or adjuvant (7) chemotherapy as well.

All patients were subjected to a follow up program consisting of follow up visits every 3–6 months for the first 2 years and every 6 months thereafter. Each visit included a physical test, blood test, oesophageal endoscopy and CT scan of the neck, chest and abdomen. Hospital charts of all patients were reviewed for the occurrence of complications and tumour status. Late toxicities were assessed in accordance with the Common Terminology Criteria for Adverse Events version 4.0.

The dose distributions were recovered from the treatment planning system. Dose-volume parameters including doses to whole heart, substructures of the heart and lungs in 5% bins and mean doses were imported in the database.

The clinical endpoints were newly diagnosed cardiac and pulmonary events and overall survival. Dose-volume histogram (DVH) parameters, treatment and patient-related parameters as mentioned in Tables 1 and 2 were included as potential risk factors. Cardiac events were analysed as a composed endpoint for all cardiac events as listed in Table 3, but also separately as their aetiologies may be different. Tumour-related parameters, like stage, N-status and elective irradiation, were not taken into account in the logistic regression analyses because of their correlation with DVH parameters. However, for OS these known prognostic factors for OS were included in the multivariable Cox regression analysis.

To analyse possible associations of clinical and treatment-related factors with cardiac and lung toxicity, univariable logistic regression analysis was performed, using a cut-off level of p-value <0.2. The selected parameters were tested for multicollinearity using an R-square threshold >0.8. Clinical factors were excluded in case of a high number of missing data and in case the number of equivalent cases in one group was smaller than 10% (Table 2).

The remaining clinical and dosimetric parameters were included in a multivariable forward stepwise logistic regression analysis based on largest significant log-likelihood differences, which was performed in SPSS. Variables were added to the final model when the model significantly improved ($p < 0.05$) based on the likelihood ratio test. For the OS analyses a forward stepwise multivariable cox regression was used based on the log-likelihood. To test the internal validity, the entire variable selection for both the toxicities and survival was repeated in 1000 bootstrap samples (i.e. with replacement). The selected model optimism was evaluated by calculating the difference between the performance of the models in each bootstrap and in the original sample, according to the TRIPOD statement.[19] Both the area, and the adjusted area under de ROC curves are presented in order to quantify the predictive power of the analyses.

Finally, the effect of the toxicities on OS was analysed using Kaplan Meier analyses.

Results

All new cardiopulmonary complications during follow up are summarized in Table 3. Radiological changes in the lungs were only scored as radiation pneumonitis if they remained after the use of antibiotics. In 60 out of 216 patients (27.8%), radiologic features of radiation-induced pneumonitis were observed on follow up CT scans. 3 patients experienced clinical symptoms requiring steroids (grade 2), 6 of them were hospitalized (grade 3), another 4 patients eventually died of this complication (grade 5).

Univariate logistic regression analysis showed that most lung dose parameters and some cardiac substructure dose parameters were significantly associated with pneumonitis. Of the clinical factors, only diabetes mellitus (DM) was associated with this endpoint (suppl. Data Fig. 7). Multivariable logistic regression analysis showed that radiation pneumonitis was best predicted by the mean lung dose (MLD) only, with an odds ratio of 1.18 per Gy MLD (this model had an AUC of 0.67 (adjusted AUC after bootstrapping = 0.63)).

Bootstrap analysis confirmed the robustness of the selection of the MLD into the model. Calibration plots of the observed vs. calcu-

Table 1
Tumour and treatment characteristics.

Stage 1	73(34.7%)
Stage 2	57(26.3%)
Stage 3	78(36.2%)
Stage 4	8(3.7%)
N0	102(47.2%)
N1/N2/N3	114(52.8%)
Tumour location	
Cervical	47(21.8%)
Mid	114(52.8%)
Distal/GE junction	55(23.2%)
Pathology	
SCC	212(98%)
Other	4(2%)
Prescribed dose	60 Gy(50.4–66.0)
Elective irradiation	135(62.5%)
Chemotherapy	205(94.9%)

lated risk of complications using the Hosmer-Lemeshow test showed a good performance of the model as well (suppl. data Figs. 1 and 2). In 69 out of 216 (31.9%) patients, pericardial effusion (PE) was seen on the follow up CT scans. Nine of these patients developed clinical symptoms of heart failure. Two other patients presented with heart failure without signs of pericardial effusion. They both had a cardiac history (1 valvular disease, 1 ischaemic heart disease). Other cardiac events were diverse and are listed in Table 3. The numbers of the separate toxicities were too low for reliable modelling procedures. Combining clinical cardiac events did not result in a predictive model. In univariate analysis, most cardiac, but no lung, dose volume-parameters were related to PE. None of the clinical factors were significantly associated with PE (suppl. Data Fig. 8). In the multivariable analysis, PE was significantly associated with the volume of the RV receiving a dose higher than 35 Gy (V35): OR = 1.03 (95%CI 1.017–1.039). This model had an AUC of 0.73 (95% CI 0.66–0.80).

However, most dose volume parameters, including the mean dose values of the WH, pericardium and RV, performed similarly well in predicting PE (Table 4). Most of the heart parameters were highly correlated so we eventually decided to present three models for PE with the mean dose to the RV, the whole heart and to the pericardium as explanatory variables, to facilitate a comparison with results from the literature and use of the models in routine daily practice. All models are presented in Table 4 and the model using the mean pericardial dose is depicted in Fig. 1.

The bootstrap procedure and calibration curves again confirmed the robust selection of dose volume parameters in the model (suppl. data Figs. 3, 4); the adjusted AUC's are included in Table 4. With a median follow up of 27 months, 97 out of 216 patients developed locoregional failures. The median disease-free survival was 64 months (95% CI 58.7–69.3 months). The median OS was not reached.

Univariable analysis showed that all lung as well as several cardiac dose parameters were associated with OS. However the high dose pulmonary DVH parameters performed significantly better in predicting this endpoint (suppl. Data Fig. 9). Significant clinical factors for worse OS were high tumour stage, high WHO-score, diabetes mellitus (DM), positive lymph nodes and the use of elective radiotherapy. In the Cox-regression analysis, the V45 of the lungs, DM and tumour stage remained significantly associated with OS. The final model is presented in Table 4.

After the bootstrapping procedure, the same variables were selected and included in the preferred model. The adjusted AUC was 0.69 (suppl. Data Fig. 5).

Kaplan Meier analyses with regard to the effect of these toxicities on OS showed a significantly worse OS for patients presenting with radiation-induced pneumonitis (p = 0.013). Patients presenting with pericardial effusion had similar OS as compared to those without pericardial effusion. All analyses are summarized in Fig. 2.

In order to get more insight in causal relationships between toxicity and OS, we reanalysed OS data censoring the patients having a radiation pneumonitis. The same variables remained significant for OS (Stage, DM and V45 lung). Performing the same analyses on patients who developed radiation pneumonitis, the heart dose (V55 heart) was the only predictor significantly predicting OS (Suppl. Table 1).

Discussion

In this paper, we aimed to identify clinical and/or dosimetric parameters that are related to cardiac and/or pulmonary toxicity in oesophageal cancer patients and analysed its effect on overall survival. The total prescribed dose in this patient group was relatively high which explains the OS compared favourable to the literature and the relatively high complication rates in this patient group. This allowed us to develop a multivariable prediction model for both heart and lung toxicity and report a comprehensive analysis of these toxicities in oesophageal cancer patients. Cardiac and pulmonary toxicities are clinically relevant side effects and deci-

Table 2
Clinical risk factors.

Parameter				
Age at start treatment	median	68[40–88]		
Seks	female	36(17%)		
	male	180 (83%)		
WHO 0 vs 1 or higher	0	169(78%)		
	>0	46(21%)		
		Yes	No	Unknown
Family history (cadiovasc disease)**		12(6%)	83(38%)	121(56%)
Smoking		185 (86%)	29(13%)	2(1%)
Use of alcohol		193 (89%)	21(10%)	2(1%)
Any cardiac history*		26 (12%)	190(88%)	
Diabetes Mellitus		27(12%)	189(88%)	
Hypercholesterolaemia		22(10%)	194(90%)	
Hypertension		81(37%)	135(63%)	
COPD**		2(1%)	214(99%)	
High BMI (≥26)**		15(7%)	201(93%)	

* Any cardiac history, ischaemic event, rhythm disorders, heart failure, valve disorders.
** Not taken into analysis because of too many missing values or low numbers per group.

Table 3
Follow up and toxicity.

New pulmonary events	
Radiation pneumonitis grade 1	47(22%)
Radiation pneumonitis grade 2	3(1%)
Radiation pneumonitis grade 3	6(3%)
Radiation pneumonitis grade 4	0(0%)
Radiation pneumonitis grade 5	4(2%)
New cardiac events	
Pericardial effusion grade 2	60(28%)
Pericardial effusion grade 3	9(4%)
Angina pectoris any grade	3(1%)
Myocardial infarction any grade	4(2%)
Heart failure any grade	8(4%)
Arythmia any grade	8(4%)
Valvular disease any grade	1(0%)
Survival status at last FU	
Alive, no evidence of disease	105(49%)
Alive with recurrent disease	33(15%)
Dead by index tumor	57(26%)
Dead by toxicity	5(2%)
Dead intercurrent disease	16(7%)

sions on the preferred dose distribution in an individual patient should be based on the risk of toxicity of both organs at risk.

Regarding pulmonary toxicity, there is only limited data on the risk of radiation pneumonitis in oesophageal cancer patients treated with definitive CRT. The published papers do not provide an odds- or hazard ratio for radiation pneumonitis in this patient group [20,21].

Our model on pericardial effusion is in line with other retrospective publications [7,22,23]. Dose response relationships with different cardiac dose parameters were described in all of these publications. Hayashi, et al. presented the odds ratios of several cardiac DVH parameters related to PE. Our odds ratios seemed to be slightly lower but remained within their 95% confidence intervals [22]. Wei et al. analysed doses both to the pericardium and whole heart and also found a stronger association for the pericardial dose vs. mean heart dose on PCE, indeed suggesting a local inflammatory effect [23].

To determine which toxicity is most relevant and consequently which organ at risk should be prioritized in our planning strategies, we finally focused on OS as an endpoint. In the multivariable analysis, we found that the dose to the lungs but not the radiation dose to the heart influenced OS significantly in this patient population. Moreover, the subgroup of patients with radiation pneumonitis had a worse OS in Kaplan Meier analysis, as opposed to the patients diagnosed with pericardial effusion, a side effect which did not seem to influence OS. However, when repeating the survival analyses censoring patients with a RP, the same variables remained significant for OS, suggesting the clinical diagnosis of radiation pneumonitis itself might not be the cause for worse OS. In the patient group presenting with radiation pneumonitis, we found the heart dose the most important predictor for OS.

These findings suggest that worse OS can be caused by radiation dose to both organs at risk, but the biological mechanism remains unknown. Given the prognostic significance of a heart dose parameter in the radiation pneumonitis patient group, and not in the whole group, a possible explanation can be found in the physiological interaction of the heart and lungs.

In preclinical studies, this interaction between heart and lung irradiation was objectified. Combining radiation on heart and lungs resulted in a synergistic effect on cardiopulmonary toxicity in rats. On pathologic examinations this interaction seemed to be caused by small vascular damage in lung tissue and perivascular fibrosis in heart tissue, resulting in pulmonary hypertension and reduced diastolic function [24,25].

Clinically, worse OS rates after (higher dose) thoracic radiotherapy despite better local control also suggests underreported toxicity, perhaps even unrecognized toxicity [10,24]. In several (SEER) database studies, higher cardiac death rates were reported in distal tumours and with the use of "older radiotherapy techniques" suggesting radiation induced toxicity of the heart [12,25–27]. More recent publications, like ours, are able to present DVH data on different critical organs and its relation to overall survival. Although several papers have been published on the correlation of cardiac dose with OS, there are reasons to be cautious of increasing the dose to the lungs in an attempt to spare the heart. The correlations found with cardiac dose in the literature might have been a reflection of the absence of cardiac toxicity models while lung toxicity models have been available for a longer period of time, resulting in strict planning criteria for the V20 of the lungs and the mean lung dose. Furthermore, in several of the earlier mentioned trials, not only the dose to the heart but total dose to the lungs was predictive for OS as well [11,16,28–30].

Altogether it is important to consider both heart and lungs as organs at risk in the treatment of thoracic indications. Especially in VMAT or IMRT techniques, cardiac dose reduction will be at the expense of a higher lung dose. Proton therapy on the other hand can reduce both the radiation dose to the heart and lungs. In a recent trial randomizing between photon and proton CRT, a significant reduction of treatment related complications was seen; the total toxicity score was 2.3 times lower after proton radiotherapy, compared to IMRT treated patients [31]. Therefore, it is preferable to combine both heart and lung DVH parameters in these prediction models. These models should originate from

Table 4
NTCP models on toxicity endpoints using a logistic regression analysis and cox regression models on overall survival.

Endpoint (logistic regression)	Explanatory variable	Intercept	Odds ratio	CI (95%)	Significance	Performance	Adjusted AUC
Radiation pneumonitis (Nagelkerke R^2 = 0.08)	Mean dose lung	−2.56	1.18	[1.07–1.30]	0.00	AUC 0.67 [0.58–0.75]	0.63
Pericardial effusion (Nagelkerke R^2 = 0.17)	Mean dose pericard	−3.26	1.11	[1.06–1.16]	0.00	AUC 0.73 [0.66–0.80]	0.70
Pericardial effusion (Nagelkerke R^2 = 0.16)	Mean dose heart	−3.11	1.09	[1.05–1.12]	0.00	AUC 0.72 [0.65–0.79]	0.69
Pericardial effusion (Nagelkerke R^2 = 0.20)	Mean dose RV	−3.24	1.08	[1.05–1.11]	0.00	AUC 0.73 [0.67–0.80]	0.71
Endpoint (cox regression)	Explanatory variable		Hazard Ratio	CI (95%)	Significance	performance	Adjusted AUC
Overall Survival (Cox regression)	V 45 Lung		1.23	[1.09–1.39]	0.00		
	Stage I and II vs Stage III and IV		2.34	[1.38–3.96]	0.00		
	Diabetes		0.33	[0.13–0.83]	0.02		
						AUC 0.73 [0.67–0.80]	AUC 0.70

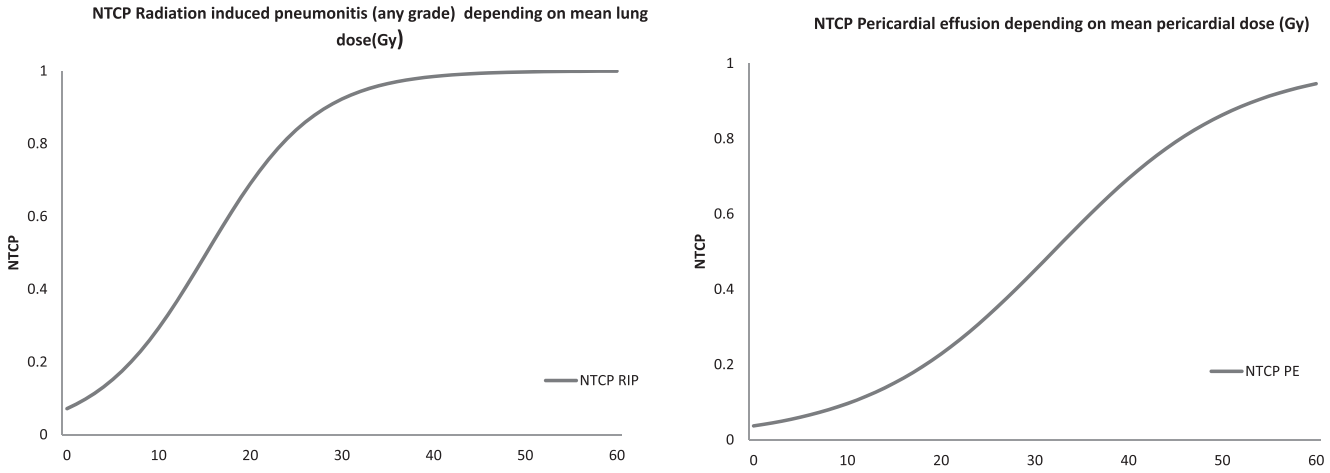

Fig. 1. NTCP curves on radiation induced pulmonary and cardiac toxicities.

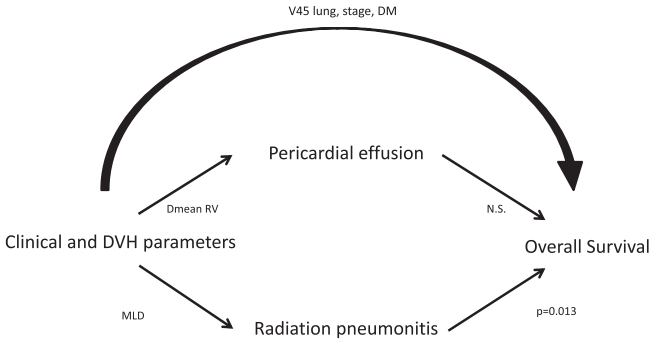

Fig. 2. Overview of the performed analyses and its relationships and predictive factors (Vmean RV = mean dose on the right ventricle, MLD = mean lung dose, DM = diabetes Mellitus).

prospective data and be validated in independent cohorts to be robust against institutional differences. A further understanding of the mechanisms behind these toxicities can facilitate the development of these models and make them more robust in different patient groups by not only selecting the best performing variables in that cohort of patients but including the most (clinically) relevant parameters [32]. Besides this, more knowledge in mechanisms will help in early detection and preventive measurements in these patient groups.

We did not find a convincing explanation for the better survival of diabetic patients in this multivariable model. The difference in overall survival in these diabetic patients in univariate analysis became apparent after 20 months, suggesting it was not tumour related but might be patient or therapy related as the highest risk for tumour recurrence is within the first two years (Fig. 7, suppl. data). Diabetic patients had a significantly higher dose to the lungs and experienced radiation pneumonitis more frequently but, in these patients, it did not seem to influence overall survival as much as it did in the non-diabetic patients. A possible explanation might be a stricter follow up in these patients in which more preventive measurements might have been taken. A stricter patient selection for the curative treatment schedule might be another explanation.

Summarizing, cardiac dose volume parameters predicted the risk of pericardial effusion and pulmonary dose volume parameters predicted the risk of radiation pneumonitis. However, in this patient cohort, pulmonary DVH parameters (V45) were more important for OS than cardiac DVH parameters. These results suggest that reducing the cardiac dose at the expense of the dose to the lungs might not always be a good strategy in oesophageal cancer patients.

Declaration of interest

The authors declare the following financial interests/personal relationship which may be considered as potential competing interest: The Department of radiation oncology has research agreements with IBA and RaySearch Laboratories. J.A. Langendigk received non-financial support and other from IBA and RaySearch Laboratories and a fee from IBA for giving a presentation at a symposium and giving consultancy. This has been paid to UMCG Research B.V. All other authors have no conflicts of interest to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2020.05.033.

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