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Original Article

Prediction of new-onset atrial fibrillation in patients with non-small cell lung cancer treated with curative-intent conventional radiotherapy

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ABSTRACT

Background: Atrial fibrillation (AF) is an important side effect of thoracic Radiotherapy (RT), which may impair quality of life and survival. This study aimed to develop a prediction model for new-onset AF in patients with Non-Small Cell Lung Cancer (NSCLC) receiving RT alone or as a part of their multi-modal treatment.
Patients and Methods: Patients with stage I-IV NSCLC treated with curative-intent conventional photon RT were included. The baseline electrocardiogram (ECG) was compared with follow-up ECGs to identify the occurrence of new-onset AF. A wide range of potential clinical predictors and dose-volume measures on the whole heart and six automatically contoured cardiac substructures, including chambers and conduction nodes, were considered for statistical modeling. Internal validation with optimism-correction was performed. A nomogram was made.
Results: 374 patients (mean age 69 ± 10 years, 57 % male) were included. At baseline, 9.1 % of patients had AF, and 42 (11.2 %) patients developed new-onset AF. The following parameters were predictive: older age (OR=1.04, 95 % CI: 1.013–1.068), being overweight or obese (OR=1.791, 95 % CI: 1.139–2.816), alcohol use (OR=4.052, 95 % CI: 2.445–6.715), history of cardiac procedures (OR=2.329, 95 % CI: 1.287–4.215), tumor located in the upper lobe (OR=2.571, 95 % CI: 1.518–4.355), higher forced expiratory volume in 1 s (OR=0.989, 95 % CI: 0.979–0.999), higher creatinine (OR=1.008, 95 % CI: 1.002–1.014), concurrent chemotherapy (OR=3.266, 95 % CI: 1.757 to 6.07) and left atrium D_{max} (OR=1.022, 95 % CI: 1.012–1.032). The model showed good discrimination (area under the curve = 0.80, 95 % CI: 0.76–0.84), calibration and positive net benefits.
Conclusion: This prediction model employs readily available predictors to identify patients at high risk of new-onset AF who could potentially benefit from active screening and timely management of post-RT AF.

Introduction

Radiotherapy (RT) is widely used in the curative-intent treatment of Non-Small Cell Lung Cancer (NSCLC) [1]. For early-stage, it serves as a noninvasive, well-tolerated alternative for medically inoperable patients or those averse to surgery [2]. Patients with locally advanced NSCLC are often treated with radical RT combined with systemic treatments (chemotherapy, immunotherapy and/or targeted therapy) [3]. However, despite considerable advantages of RT on tumor control and survival outcomes, RT-induced cardiac injuries continue to pose a significant challenge.

Atrial fibrillation (AF) is the most common rhythm disturbance resulting from unintentional cardiac radiation exposure, which can clinically manifest weeks to months after treatment initiation [4]. The

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incidence of AF during cancer treatment varies between 2 % and 16 %, depending on different factors [5]. AF may be induced or exacerbated either by anticancer treatments or by interactions with pre-existing conditions common in patients with cancer, such as aging, electrolyte abnormalities, hypoxia and malnourishment [6]. Previous studies have shown that in patients with active cancer, the incidence of AF is associated with a two-fold higher risk of thromboembolism and a six-fold higher risk of heart failure [7]. Despite well-defined associations between RT and new-onset AF, there is currently no risk estimation instrument for patients with lung cancer.

At the time of this study, there was limited evidence available exploring the risk factors for new-onset AF in patients with lung cancer treated with RT. Kim et al. identified dose constraints, considering cardiac substructures, in patients with locally advanced NSCLC treated with chemoradiotherapy [8]. Several studies have shown that AF development is potentiated by pre-existing cardiovascular diseases and older age in patients with cancer [9]. As the overall survival of patients with lung cancer improves due to the development of new therapies, there is an increased demand for a risk stratification instrument to identify patients at high risk of AF who could potentially benefit from active screening and timely management according to the ESC Guidelines on cardio-oncology for the diagnosis and management of AF [10].

This study aimed to develop and evaluate a nomogram for new-onset AF using a wide range of potential clinical factors as well as dose-volume measures on cardiac substructures in patients with stage I-IV NSCLC treated with curative-intent conventional photon RT.

Methods

Study population

We retrospectively included adult patients (≥18 years old) with stage I to oligometastatic stage IV NSCLC treated with curative-intent conventional photon RT between 2015 and 2022 at the Department of Radiation Oncology of the Maastricht University Medical Center (Maastro Clinic). The AJCC 7th edition was used for staging [11]. Patients with previous chest irradiation, two primary tumors requiring synchronous irradiation, incomplete RT course, enrollment in RT-related clinical trials or lack of access to cardiac evaluations were excluded. The study was approved by the Institutional Review Board (W21-11-00042).

RT planning and treatment

Details about the RT process have been published previously [12,13]. Briefly, a 4-dimensional planning Computed Tomography (CT) scan was obtained, combined with a Fluorodeoxyglucose −Positron Emission Tomography (FDG-PET) CT scan for patients with lymph node involvement. The administration of intravenous contrast was made based on the judgment of the radiation oncologist. The Gross Tumor Volume (GTV) was contoured and an edited 5 mm margin was added to derive the Clinical Target Volume (CTV). The planning target volume was created individually according to the movement and the set-up uncertainty (on average 8 mm from the CTV). Organs-at-risk (OARs) were contoured as previously published [12,13]. Conventional fractionation schemes included 45 Gy (1.5 Gy BID), 65 Gy (45 Gy/1.5 Gy BID followed by 20 Gy/2 Gy BID) or 60–66 Gy (2 Gy QD). Isotoxic dose escalated schedules were used as previously reported [12,14]. Treatment planning was performed using Eclipse v11 (Varian Medical Systems, Palo Alto, CA). The physicists and radiation oncologists approved the final treatment plan after careful assessment of plan robustness, quality and interplay effects. Most patients were treated with free-breathing. However, breath-hold technique was utilized in patients with respiratory tumor motion greater than 1 cm. Patient positioning was verified on a daily basis using cone beam CT and adapted if necessary. Adaptive RT protocols for the target volumes were implemented since 2018 [15].

Potential clinical predictors

The following clinical variables were selected as candidate predictors for statistical modeling based on expert opinion and the literature [16]: basic characteristics (age, gender and body mass index), tumor specifications (stage, histology, laterality and location), cancer treatments (surgery, chemotherapy and immunotherapy), RT (given dose, fractions and duration), baseline electrocardiographical parameters (heart rate, PR, QRS intervals and QTc according to Bazett), lung function tests (Forced Expiratory Volume in one second, FEV1 and Diffusing Capacity of the Lungs for Carbon Monoxide, DLCO), blood biomarkers (glucose, sodium, potassium, creatinine and C-reactive Protein, CRP), comorbidities (diabetes, hypertension, cardiac diseases and procedures, chronic obstructive pulmonary disease, obstructive sleep apnea, vascular, autoimmune and thyroid diseases), performance status, smoking and alcohol use.

Dose-volume parameters

The cardiac chambers (right atrium, left atrium, right ventricle and left ventricle) were contoured according to the multi-atlas mapping approach using an open-source deep learning model developed by Finnegan et al. [17]. Using the same model, the conduction nodes (sino-atrial, SAN and atrioventricular, AVN) were geometrically contoured, defined as sphere of radius 10 mm located based on other substructure contours [18]. In addition to the six automatically cardiac substructures, whole heart manually contoured by treating radiation oncologists was considered for dose-volume extraction. Automatic contours were reviewed to detect misleading contours which could affect the dose-volume extraction [F.T.].

The following parameters were calculated for the whole heart and four chambers: volume in cc, minimum, mean and maximum doses in Gy and V_{5Gy} toV_{60Gy} with increments of 5 Gy (V_x refers to the percentage of the structure receiving at least x Gy). For geometrically contoured conduction nodes, minimum, mean and maximum doses were calculated. The GTV of the primary tumor (GTVp) and lymph node(s) (GTVn) were also extracted.

Atrial fibrillation

The new-onset AF was defined as the first documented episode of AF in patients with no prior diagnosis, irrespective of the duration or the presence and severity of AF-related symptoms. Additionally, AF was considered in patients with pre-existing AF who were in a period of remission but later developed AF following the initiation of RT. Only diagnoses confirmed by treating cardiologists, based on electrocardiogram (ECG) or Holter monitoring, were considered as events.

Statistical analysis

Stepwise logistic regression with backward selection was performed to develop the clinical, dose-volume and combined prediction models. The predictive power of dose-volume measures were evaluated using the Area Under the receiver operating characteristic Curve (AUC). Top dose and volume measures with the highest AUCs and no correlations were used as the input for multivariable analysis. The predictors from clinical and dose-volume models were used to build the combined model. The multivariable model was selected based on minimizing the Akaike information criterion value. The inherent class imbalance was addressed using the Synthetic Minority Oversampling Technique (SMOTE) [19].

Internal validation using 1000 bootstrap samples was performed for optimism-correction of the AUCs and calibration measures. Decision Curve Analysis (DCA) was used to assess the clinical utility of the prediction models in decision making comparing to the “treat none” and

"treat all" benchmarking strategies. The Positive Predictive Values (PPVs) and Negative Predictive Values (NPVs) were calculated for the optimal threshold determined using the Youden index method as well as all threshold probabilities with positive net benefits. A nomogram was developed based on the clinical and dose-volume predictors that remained in the combined model. All analyses were performed in R v.4.3.1 (R Foundation for Statistical Computing).

Results

A total of 374 patients with a mean age of 69 ± 10 years and 57 % male gender were included. The overall stage was I in 76 (20 %), II in 50 (13 %), III in 206 (55 %) and IV in 42 (11 %) patients. Squamous-cell carcinoma was identified in 131 (35 %) patients. Tumor laterality was on the left side in 155 (41 %) and on the right side in 219 (59 %) patients. The tumor was predominantly located in the upper, middle and lower lobes in 217 (58 %), 17 (4.5 %) and 110 (29 %) patients, respectively, and 30 (8 %) patients had tumor located in the mediastinum or hilar area.

Pulmonary resection was performed in 62 (17 %) patients prior to RT. A total of 79 (21 %) and 152 (41 %) patients received sequential and concurrent chemotherapy, respectively. The chemotherapy agents were cisplatin-etoposide in 113 (30 %), carboplatin-etoposide in 24 (6.4 %) and other combinations in 94 (25 %) patients. Moreover, 36 (9.6 %) patients received adjuvant durvalumab. Nivolumab or pembrolizumab was used as the standard of care in 13 (3.5 %) patients with advanced NSCLC. About 36 % and 19 % of the patients had a history of cardiac diseases and procedures, respectively. At baseline, 34 (9.1 %) patients had AF, and a total of 42 (11.2 %) patients developed new-onset AF during a three-year follow-up. Further statistics on the patients' characteristics and treatments are presented in Table 1.

The mean volume of the whole heart was 833 ± 220 cc and the mean and maximum doses to the whole heart were 6.4 ± 5.9 Gy and 47.9 ± 25.2 Gy, respectively. The following substructures received the highest doses, respectively: left atrium (35.9 ± 26.7 Gy), SAN (25.8 ± 23.5 Gy), right atrium (22.3 ± 22.3 Gy), left ventricle (15.7 ± 19.9 Gy), right ventricle (13.8 ± 15.9 Gy) and AVN (5.8 ± 8.8 Gy). The mean GTVp and GTVn were 56.5 ± 100 cc and 17.3 ± 36 cc, respectively.

In multivariable analysis, the following variables remained in the clinical model: older age (OR=1.037,95 % CI: 1.011 to 1.065), being overweight or obese (OR=1.847, 95 % CI: 1.185 to 2.88), alcohol use (OR=3.957, 95 % CI: 2.42 to 6.47), history of cardiac procedures (OR=1.899, 95 % CI: 1.072 to 3.362), tumor located in the upper lobe (OR=1.905, 95 % CI: 1.155 to 3.142), higher FEV1 (OR=0.989, 95 % CI: 0.98 to 0.999), higher creatinine (OR=1.007, 95 % CI: 1.001 to 1.013) and concurrent chemotherapy (OR=3.243, 95 % CI: 1.782 to 5.902).

Maximum dose delivered to the left atrium (D_{max}) showed the highest AUC (0.61, 95 % CI: 0.57 to 0.66) for predicting the risk of new-onset AF among the dosimetric measures. The dosimetric and volume measures ranked by AUC are shown in Table S1. The following predictors were included in the dose-volume model: heart volume (OR=1.002, 95 % CI: 1.001 to 1.003) and left atrium D_{max} (OR=1.012, 95 % CI: 1.005 to 1.019). After combining the clinical and dose-volume predictors, heart volume was removed from the combined model. Table 2 shows the details on the clinical, dose-volume and combined prediction models.

As shown in Fig. 1, the combined model showed the best discrimination power for new-onset AF prediction with an apparent and optimism-corrected AUC of 0.82 (95 % CI: 0.78 to 0.85) and 0.80 (95 % CI: 0.76 to 0.84), respectively. The calibration curve showed good conformation of the predicted probabilities versus the actual outcomes for probabilities ranging between 0.1 and 0.9. Moreover, decision curve analysis showed higher net benefits of the combined model across the majority of the threshold probabilities compared to the clinical and dose-volume models. The PPV and NPV for the optimal threshold of 0.42 were 65 % and 85 %, respectively. Moreover, the PPVs and NPVs for all

Table 1
Patient characteristics.

Characteristic	N=374 [a]
Age at RT	69 ± 10
Male gender	213 (57 %)
Body mass index	
Normal	148 (40 %)
Underweight	24 (6.4 %)
Overweight or obese	202 (54 %)
WHO performance status	
0	37 (9.9 %)
1	224 (60 %)
2	84 (22 %)
3	29 (7.8 %)
Overall stage	
I	76 (20 %)
II	50 (13 %)
III	206 (55 %)
IV	42 (11 %)
Histology	
Squamous cell	131 (35 %)
Non-squamous cell	243 (65 %)
Tumor laterality	
Left	155 (41 %)
Right	219 (59 %)
Tumor location	
Upper	217 (58 %)
Lower	110 (29 %)
Middle [b]	17 (4.5 %)
Mediastinum or hilum	30 (8 %)
Heart rate (bpm)	81 ± 18
PR interval (ms)	157 ± 28
QRS interval (ms)	94 ± 20
QTc interval (ms)	433 ± 29
Lung resection	62 (17 %)
Chemotherapy	
Sequential	79 (21 %)
Concurrent	152 (41 %)
Immunotherapy	
Durvalumab	36 (9.6 %)
Pembrolizumab or nivolumab	13 (3.5 %)
RT dose (Gy)	61.59 ± 4.54
RT fractions	26 ± 4
RT duration (days)	36 ± 6
Glucose (mmol/L)	6.8 ± 2.4
Sodium (mmol/L)	138.7 ± 3.3
Potassium (mmol/L)	4.4 ± 0.5
Creatinine (μmol/L)	87 ± 37
CRP (mg/L)	33 ± 50
FEV1 (%)	73 ± 22
DLCO (%)	64 ± 20
COPD	131 (35 %)
Obstructive sleep apnea	14 (3.7 %)
Diabetes	
NIDDM	40 (11 %)
IDDM	25 (6.7 %)
Hypertension	232 (62 %)
Cardiac disease	136 (36 %)
Cardiac procedure	72 (19 %)
Vascular disease	68 (18 %)
Autoimmune disease	41 (11 %)
Thyroid disease	32 (8.6 %)
Smoking	
Never	21 (5.6 %)
Current	93 (25 %)
Former	260 (70 %)
Alcohol	
Never	144 (39 %)
Current	193 (52 %)
Former	37 (9.9 %)

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease; CRP, C-reactive Protein; DLCO, Diffusing Capacity of the Lungs for Carbon Monoxide; FEV1, Forced Expiratory Volume in 1 s; IDDM, Insulin Dependent Diabetes Mellitus; NIDDM, Non-Insulin Dependent Diabetes Mellitus; RT, Radiotherapy; WHO, World Health Organization.

[a] Values presented as n (%) or mean ± SD.

[b] Middle lobe is only for right-sided patients.

Table 2
Multivariable analysis on clinical and dose-volume measures to predict the risk of new-onset AF in patients with NSCLC treated with curative-intent conventional RT.

Prediction **models**	**OR (95 % CI)**	**P**
Clinical model		
(Intercept)	0.005 (0.001 to 0.044)	< 0.001
Age at RT	1.037 (1.011 to 1.065)	0.006
Body mass index		
Normal	[Reference]	
Underweight	1.366 (0.462 to 4.035)	0.6
Overweight or obese	1.847 (1.185 to 2.88)	0.007
Alcohol		
Never	[Reference]	
Current	3.957 (2.42 to 6.47)	< 0.001
Former	0.666 (0.241 to 1.842)	0.4
Cardiac procedure (yes vs no)	1.899 (1.072 to 3.362)	0.028
Tumor location		
Lower	[Reference]	
Upper	1.905 (1.155 to 3.142)	0.012
Middle	0.171 (0.02 to 1.436)	0.1
Mediastinum or hilum	1.494 (0.635 to 3.516)	0.4
FEV1 (%)	0.989 (0.98 to 0.999)	0.031
Creatinine (μmol/L)	1.007 (1.001 to 1.013)	0.016
Chemotherapy		
Sequential	[Reference]	
Concurrent	3.243 (1.782 to 5.902)	< 0.001
None	0.734 (0.368 to 1.466)	0.4
Dose-volume model		
(Intercept)	0.071 (0.03 to 0.164)	< 0.001
Heart volume (cc)	1.002 (1.001 to 1.003)	< 0.001
Left atrium D_{max} (Gy)	1.012 (1.005 to 1.019)	0.001
Combined model		
(Intercept)	0.002 (0.001 to 0.011)	< 0.001
Age at RT	1.04 (1.013 to 1.068)	0.004
Body mass index		
Normal	[Reference]	
Underweight	1.37 (0.442 to 4.25)	0.6
Overweight or obese	1.791 (1.139 to 2.816)	0.012
Alcohol		
Never	[Reference]	
Current	4.052 (2.445 to 6.715)	< 0.001
Former	0.589 (0.208 to 1.672)	0.3
Cardiac procedure (yes vs no)	2.329 (1.287 to 4.215)	0.005
Tumor location		
Lower	[Reference]	
Upper	2.571 (1.518 to 4.355)	< 0.001
Middle	0.206 (0.024 to 1.799)	0.2
Mediastinum or hilum	2.085 (0.868 to 5.004)	0.1
FEV1 (%)	0.989 (0.979 to 0.999)	0.034
Creatinine (μmol/L)	1.008 (1.002 to 1.014)	0.006
Chemotherapy		
Sequential	[Reference]	
Concurrent	3.266 (1.757 to 6.07)	< 0.001
None	1.134 (0.54 to 2.382)	0.7
Left atrium D_{max} (Gy)	1.022 (1.012 to 1.032)	< 0.001

threshold probabilities for risk stratification of patients into high- and low-risk groups are presented in Table S2.

Fig. 2 shows the nomogram of the combined model. Transparent Reporting of a multivariable prediction model for Individual Prognosis or Diagnosis (TRIPOD) checklist was adhered to ensure the clarity and sufficient reporting of the details of the prediction model (Table S3).

Discussion

Given the advancements in lung cancer treatments and improved overall survival of the patients, active surveillance for post-RT AF is crucial to ensure timely treatment initiation. It could also help to develop preventive strategies and facilitate the patient-physician discussions. Therefore, we developed a prediction model utilizing readily available predictors at the time of RT planning to estimate the risk of new-onset AF in patients with stage I to oligometastatic stage IV NSCLC.

We found that left atrium D_{max} was the most predictive factor among the dosimetric measures on cardiac substructures. In line with our finding, Kim et al. found that maximum radiation dose exposed to the left atrium (≥55.8 Gy) was associated with increased risk of new-onset AF in patients with locally advanced NSCLC treated with chemoradiotherapy [8]. A post-hoc analysis of the IDEAL-CRT trial has also shown that left atrium maximum dose > 64 Gy was associated with post-RT electrocardiographical changes in patients with locally advanced NSCLC [20]. A recent study has shown that baseline left atrial enlargement was a significant predictor of post-RT supraventricular arrhythmia in patients with NSCLC [21]. Another study reported that the onset of AF was associated with the dose received by the pulmonary veins, which anatomically drain into the left atrium [22]. The synthesis of these findings provide compelling evidence to support the theory that the dose to the base of the heart is associated with post-RT cardiac events and overall survival [23,24]. The base of the heart is the most fixed point of the heart defined as the union of the atria and the great vessels connected to them, which are the inlets and outlets to the circulation system. This region also includes the coronary ostia and the sinoatrial node, which stimulates cardiac contraction as the origin of the electrical impulse. Therefore, possible inflammation, fibrosis or ischemia induced by incidental irradiation of the base of the heart can jeopardize critical physiological processes.

Our results showed that patients with higher baseline creatinine level were significantly at higher risk of developing AF. This finding is supported by a recent longitudinal population-based cohort study on 9,288 individuals showing that lower kidney function at baseline, quantified as the estimated glomerular filtration rate based on serum creatinine and cystatin C, was associated with an increased risk of incident AF in middle-aged and elderly men and women [25]. Another study was conducted among 235,818 individuals participating in a voluntary health checkup program in Japan, which showed that higher baseline creatinine level increased the risk of new-onset AF [26]. Similarly, several studies have shown that chronic kidney disease is associated with the incidence of AF [27,28]. One of the mechanisms explaining the association between kidney function and AF might be described by the cardiorenal syndrome, a term that encompasses the complex and pathological interactions between the cardiovascular system and the kidneys [29]. These findings suggest that kidney dysfunction is a risk factor for AF, which can improve the prediction of AF among cancer survivors.

Similar to our results, impaired lung function, namely reduced FEV1 has been reportedly associated with an increased risk of AF [30,31]. It has been shown that patients with restrictive or obstructive lung function impairments had approximately 1.4-fold higher risk of new-onset AF compared to those with normal lung function [32]. Previous studies have suggested several possible mechanisms for this association, including hypoxia, use of COPD treatments, systemic inflammation and increased sympathetic nerve activation [33]. As many patients with lung cancer suffer from reduced lung function due to various factors, it is essential to consider FEV1 for assessing the risk of new-onset AF.

Patients with the tumor located in the upper lobes showed a significantly higher risk of new-onset AF. Several reasons may account for this finding. First, tumors in the upper lobes can exert greater mechanical pressure on critical nearby structures, including the pulmonary veins and atria. This increased pressure may disrupt normal electrical conduction pathways within the heart, contributing to atrial remodeling and development of AF. Second, higher concentration of locoregional tumor-related products such as cytokines, growth factors and inflammatory mediators can induce local inflammation and oxidative stress in the adjacent cardiac tissues, potentially promoting arrhythmogenesis [34]. Third, previous studies have shown that in healthy individuals, the volume of the upper lobes were larger than that of the lower lobes both at the end of inspiration and expiration [35]. Therefore, upper lobe tumors can potentially affect a larger portion of the lung's overall capacity, which in turn may influence cardiac function and predispose to AF.

A positive association between cardiac procedures and AF has been confirmed by several studies [36]. In addition, we found that an

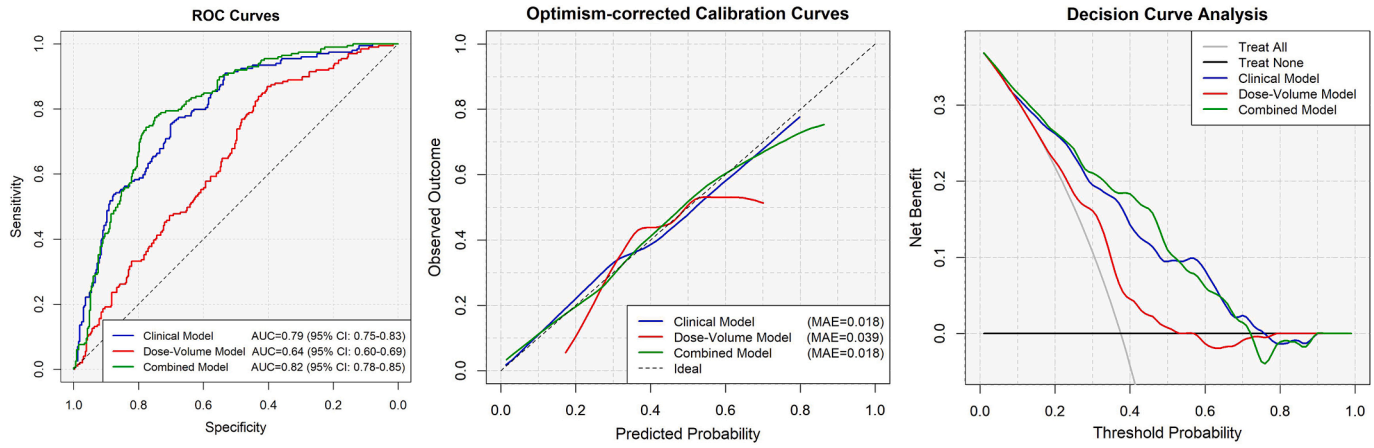

Fig. 1. Receiver Operating Characteristic Curves (ROCs), calibration curves and decision curve analysis of the clinical, dose-volume and combined prediction models for estimating the risk of new-onset AF in patients with NSCLC treated with curative-intent conventional RT.

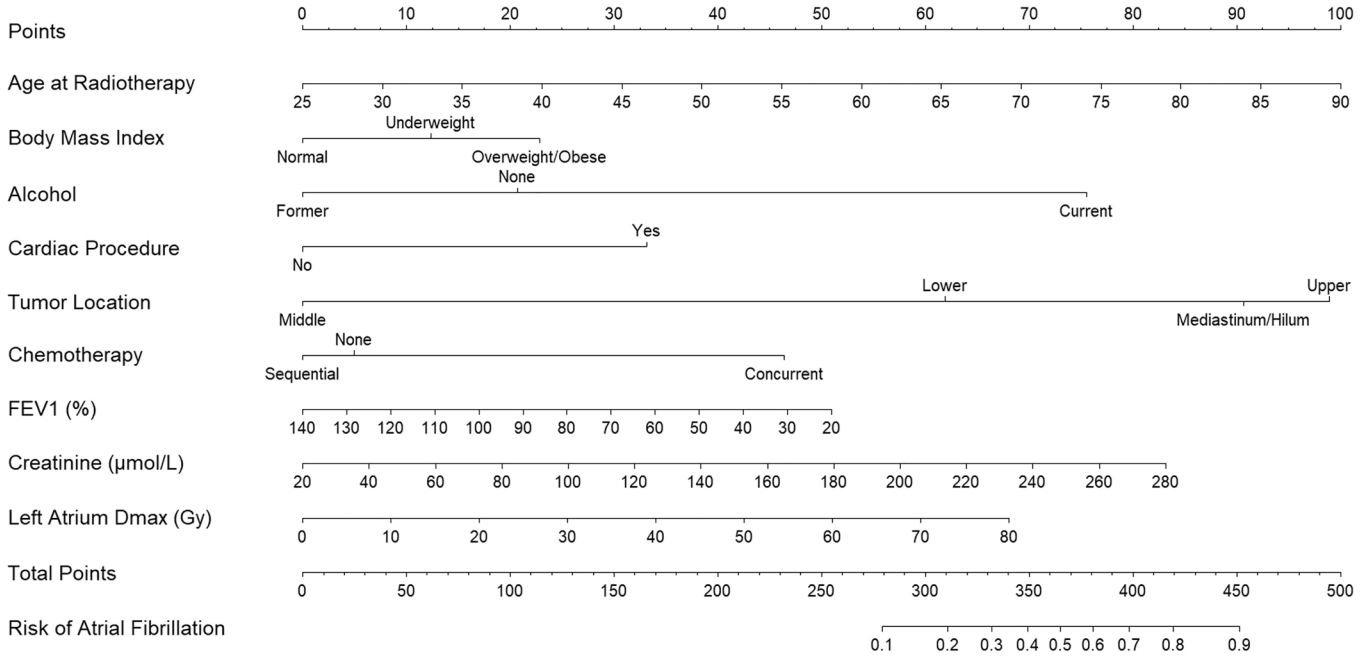

Fig. 2. Nomogram of the combined model for predicting the risk of new-onset AF in patients with NSCLC treated with curative-intent conventional RT.

enlarged heart, was a significant risk factor for post-RT AF in the dose-volume model. Enlarged heart is not strictly a disease. However, it can signal the presence of another health condition, which results in cardiac overload (e.g. uncontrolled hypertension, obesity, alcohol abuse, stress, thyroid disorders or chronic lung diseases) [37]. The higher susceptibility of patients with excess body weight [38] and older patients [16] to the incidence of AF has been previously documented. Consistent with our results, the toxic effect of chemotherapy has been shown in previous papers [39]. Our results indicate that concurrent chemoradiotherapy is associated with an increased risk of AF compared to sequential administration. Amongst the identified risk factors, alcohol consumption is a well-known, modifiable risk factor for incident AF, with further dose–response associations published elsewhere [40].

According to the latest ESC Guidelines on cardio-oncology, a standard 12-lead ECG remains as the standard diagnostic tool for AF [10]. The nomogram developed in this study could potentially be used for active screening of patients at high risk of AF to identify asymptomatic episodes of AF before severe clinical manifestation. This allows the rationale for timely management of AF following the "ABC pathway" (Atrial fibrillation Better Care) [41]. Additionally, preventive lifestyle recommendations, including weight management [42], moderation of alcohol consumption [43] and engagement in moderate physical activities [44], can be discussed during patient-physician consultations to mitigate the risk of AF. Moreover, some technologies may be considered as viable options to further decrease the radiation dose to the base of the heart, such as deep inspiratory breath-hold, magnetic resonance-guided RT and proton therapy [45–47].

The present study has some limitations. First, since this study was conducted retrospectively, there is a possibility of bias in the data. Second, inaccuracies related to the auto-contouring of cardiac substructures may have resulted in uncertainties in dosimetric measures. However, upon visual inspection, the automated contours appeared to be satisfactory. Third, lack of an external validation dataset may have resulted in optimistic performance measures. However, optimism-correction was performed to correct the model performance estimates. Future studies incorporating further potential predictors, such as cardiac biomarkers, and employing other machine learning algorithms to identify non-linear associations could potentially help to improve the

prediction accuracy.

In conclusion, the developed model showed good patient-level predictions and had higher net benefits compared to the benchmarking strategies in decision analysis. Using easily obtainable predictors, the model could be used as a potentially useful and cost-effective instrument to identify those patients at high risk of developing new-onset AF after RT. The model has the potential to help clinicians in gaining insights into patients for whom RT adjustment, post-RT active screening or lifestyle recommendations would be advantageous.

CRediT authorship contribution statement

Fariba Tohidinezhad: Writing – original draft, Visualization, Validation, Resources, Methodology, Formal analysis, Data curation, Conceptualization. **Leonard Nürnberg:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Femke Vaassen:** Writing – review & editing, Methodology, Data curation, Conceptualization. **Rachel Ma ter Bekke:** Writing – review & editing, Supervision, Methodology, Data curation, Conceptualization. **Hugo Jwl Aerts:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Lizza El Hendriks:** Writing – review & editing, Supervision, Methodology, Investigation, Conceptualization. **Andre Dekker:** Writing – review & editing, Project administration, Methodology, Funding acquisition, Conceptualization. **Dirk De Ruysscher:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Alberto Traverso:** Writing – review & editing, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

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.

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Appendix A. Supplementary material

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