Radiotherapy and Oncology 132 (2019) 34–41

Contents lists available at ScienceDirect

Radiotherapy and Oncology

journal homepage: www.thegreenjournal.com

Original Article

A nomogram for the prediction of cerebrovascular disease among patients with brain necrosis after radiotherapy for nasopharyngeal carcinoma

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ARTICLE INFO

Article history:
Received 6 September 2018
Received in revised form 5 November 2018
Accepted 7 November 2018
Available online 21 December 2018

Keywords:
Brain necrosis
Radiotherapy
Cerebrovascular disease
Carotid stenosis
Nomogram

ABSTRACT

Background and purpose: This study sought to develop and validate a nomogram to predict cerebrovascular disease (CVD) among patients with brain necrosis after radiotherapy for nasopharyngeal carcinoma (NPC).

Materials and methods: A total of 346 eligible patients with brain necrosis after radiotherapy for NPC were divided into a training set (n = 231) and a validation set (n = 115). A multivariate Cox proportional hazards regression model was used to select the significant variables for CVD prediction in the training set. Then, a nomogram was developed based on the regression model. The performance of the nomogram was assessed with respect to discrimination and calibration. All patients were classified into high- or low-risk groups based on the risk scores derived from the nomogram. Moreover, a decision curve analysis was performed with the combined training and validation sets to evaluate the clinical usefulness of the nomogram.

Results: Four significant predictors were identified: hypertension, statin treatment, serum level of high-density lipoprotein, and interval between radiotherapy and brain necrosis. The nomogram incorporating these four predictors showed favorable calibration and discrimination regarding the training set, with a C-index of 0.763 (95% CI, 0.694 to 0.832), which was confirmed using the validation set (C-index 0.768; 95% CI, 0.675 to 0.861). Furthermore, the nomogram successfully stratified patients into high- and low-risk groups. The decision curve indicated that our nomogram was clinically useful.

Conclusion: The nomogram showed favorable predictive accuracy for CVD among patients with brain necrosis after radiotherapy for NPC and might aid in clinical decision making.

In various cancer populations, radiotherapy is associated with the development of vascular disease [1–4]. Previous studies have established an increased incidence of carotid stenosis (CAS) and ischemic stroke in patients with head and neck cancer treated with radiotherapy [4,5]. A study of 6862 patients (age >65 years) showed that five-year incidence of cerebrovascular events was 19% in patients treated with radiotherapy alone compared with 14% in patients treated with surgery plus radiotherapy; the corresponding ten-year incidence were 34% and 25%, respectively [4]. Another cohort study of patients younger than 60 years showed that the 15-year cumulative risk of stroke after radiotherapy to the neck was 12.0% [3]. And the reported intervals between radiation and first symptoms range widely from 6 months to more than 20 years [6,7]. In fact, early radiation damage is believed to be characterized by an inflammatory process centered on initial

Abbreviations: ASCVD, atherosclerotic cardiovascular disease; CAS, carotid stenosis; CFS, cerebrovascular disease-free survival; CI, confidence interval; C-index, concordance index; CVD, cerebrovascular disease; DCA, decision curve analysis; IRB, interval between radiotherapy and brain necrosis; HDL, high-density lipoprotein; IMRT, intensity-modulated radiation therapy; IQR, interquartile range; NPC, nasopharyngeal carcinoma; TIA, transient ischemic attack.

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https://doi.org/10.1016/j.radonc.2018.11.008
0167-8140/

changes in the endothelial cells, partly followed by cerebrovascular disease (CVD), including transient ischemic attack, ischemic stroke and so on [8,9]. Moreover, compared with carotid lesions caused by atherosclerosis, radiation-induced carotid lesions were significantly longer (measured by the distance between the proximal edge and distal edge) and more prone to develop restenosis [10,11].

Of those cancers treated with radiotherapy, nasopharyngeal carcinoma (NPC) is a common type of malignancy with distinct geographic areas of high risk such as Southeast Asia, East Asia, North Africa and notably, southern China. Annually, NPC leads to 87,000 incident cases and causes 51,000 deaths worldwide [12]. Based on high-quality clinical evidence, radiotherapy or chemoradiotherapy has been the major treatment for early or locoregionally advanced NPC [13]. Brain necrosis develops in 3–24% of patients between 3 months and 10 years after radiotherapy, with most cases occurring in the first two years [14]. Moreover, patients with brain necrosis after radiotherapy are more likely to develop CVD [15].

Thus, it's of great significance to distinguish patients with high risk of suffering from CVD after radiotherapy from those with low risk, and follow up with those high-risk patients closely for early detection and prevention of CVD. Though several tools for evaluating atherosclerotic cardiovascular disease (ASCVD) risk were published to provide a direction for clinical practice in various populations [16,17], traditional vascular risk factors might not play a role in radiation-induced CAS for the failure of considering the impact of radiation. In addition, standard risk prediction models derived from the general population might underestimate stroke risk in patients who have received radiotherapy [18]. To our knowledge, a prediction model has not been developed specifically to predict CVD in patients with brain necrosis after radiotherapy.

Hence, the aim of this study was to develop and validate a novel nomogram for the prediction of CVD in individual patients with brain necrosis after radiotherapy for NPC to aid clinical decision making and improve ongoing treatment efforts.

Methods and materials

Patients

The current retrospective analysis of anonymous data was approved by the institutional review board. In total, 346 consecutive patients diagnosed with brain necrosis after radiotherapy for NPC between January 2005 and December 2015 from our hospital were enrolled in our study. Patients were included if they (a) underwent radiotherapy; (b) showed radiographic evidence to support the diagnosis of brain necrosis after radiotherapy; and (c) had clinical characteristics and data available. Patients were excluded if they (a) were initially hospitalized for brain necrosis after radiotherapy at another institution; (b) had CAS >50%, ischemic stroke or transient ischemic attack (TIA) prior to the diagnosis of brain necrosis after radiotherapy; (c) received radiotherapy for another type of cancer rather than NPC; or (d) had NPC recurrence or metastasis. Supplementary Fig. S1 presents the patient recruitment pathway. All enrolled patients were divided into two cohorts at a ratio of 2:1 using computer-generated random numbers. Thus, 231 patients were randomly allocated to the training cohort, whereas 115 patients were allocated to the independent validation cohort.

The clinical data were obtained by reviewing these patients' inpatient and outpatient medical records. These data included patient age, gender, hypertension status, diabetes status, cigarette smoking status, alcohol consumption status, presence of statin treatment, height, weight, total cholesterol level, triglyceride level, high-density lipoprotein (HDL) level and low-density lipoprotein level acquired from the first hospitalization due to brain necrosis after radiotherapy. The maximum radiation dose of the temporal lobe, the total radiation dose of the neck, radiotherapy method (i.e., conventional radiotherapy or intensity-modulated radiation therapy [IMRT]) and the interval between radiotherapy and brain necrosis (IRB) were also recorded. Details are shown in the supplement.

All patients were followed up and examined via bilateral carotid ultrasonography every 3 months during the first 2 years, every 6 months from years 3–5, and annually thereafter. According to the 2010 guidelines of the European Society for Vascular Surgery, asymptomatic CAS >50% with or without other symptoms or signs of atherosclerosis may be regarded as an equivalent to coronary heart disease [19]. Approximately 10–15% of all strokes follow a thromboembolism from a previously asymptomatic internal CAS >50% [20]. The 2017 guidelines of the European Society for Vascular Surgery indicate that carotid endarterectomy should be considered for symptomatic patients with 50–69% CAS[21], and a meta-analysis of the three most important randomized controlled trials, i.e., the North American Symptomatic Carotid Endarterectomy Trial, the European Carotid Surgery Trial and the Symptomatic Veterans Affairs Co-operative Study Trial indicated that carotid endarterectomy conferred a significant benefit to patients with 50–99% stenosis [22]. Therefore, the patients in our study whose carotid ultrasonography showed CAS >50% or who were hospitalized for ischemic stroke or TIA were regarded as having CVD, which was chosen as the endpoint. The study was censored in December 2017.

Construction of the nomogram

First, a univariate Cox proportional hazards regression was used to reduce the number of clinical candidate predictors based on a criterion of $P < 0.10$. Thereafter, a multivariate Cox proportional hazards regression model was applied to select the significant predictors of CVD using a backward-selection procedure using Akaike's Information Criterion [23]. Then, a nomogram was developed based on the multivariate Cox proportional hazards regression model that incorporated the selected predictors.

Assessment of nomogram performance

The concordance index (C-index) was used to assess the discrimination of the nomogram, which is equivalent to the area under the receiver operator characteristic curve [24]. The calibration of the nomogram was assessed by comparing the nomogram-predicted survival probability with the observed Kaplan–Meier estimates of survival probability. Moreover, bootstrapping using 1000 resampling procedures was performed.

Internal validation of the nomogram

The performance of the nomogram was internally validated using the validation set. A risk score for each patient was calculated as a linear combination of the selected predictors that were weighted by their respective regression coefficients of the multivariate Cox proportional hazards regression analysis performed in the training set to reflect the risk of CVD. Using the validation set, a Cox proportional hazards regression was performed using the risk score as a factor. Then, the C-index and calibration curves were derived based on the Cox proportional hazards regression analysis.

Categorization of patients into high- or low-risk groups

All patients were classified into high- or low-risk groups according to their risk score, whose threshold was identified using X-tile

plots based on score associations with CVD-free survival [25]. The log-rank test was used to compare the survival curves of the high- and low-risk groups using the training and validation sets.

Clinical usefulness of the nomogram

To estimate the clinical usefulness of the nomogram, a decision curve analysis (DCA) was performed by calculating the net benefits for a range of threshold probabilities using the combined training and validation sets [26]. As a comprehensive method for evaluating and comparing different diagnostic and prognostic models, DCA can be used to assess whether the nomogram-assisted decisions would improve patient outcomes. Detailed descriptions of the DCA are provided in the Supplementary Methods.

Statistical analyses

We created the X-tile plots to select the optimum cutoff risk score using X-tile software version 3.6.1 (Yale University School of Medicine, New Haven, CT, USA). All other statistical tests were performed using R statistical software version 3.4.2. All statistical tests were two-tailed, and *P*-values <0.05 were considered significant. Details are available in the supplement.

Results

Patient clinical characteristics

The characteristics of the patients in the training and validation sets are summarized in Table 1 and Supplementary Table S1. Patients with CVD comprised 22.1% (51/231) and 23.5% (27/115) of the training and validation sets, respectively, and no significant difference was found between them ($P = 0.769$). The median follow-up time was 1.8 years (interquartile range [IQR] 1.0–3.4) for the training set and 1.8 years (IQR 0.8–3.1) for the validation set. Additionally, the clinical baseline characteristics showed no significant differences between the training set and the validation set ($P = 0.130$–0.904).

Table 1
Characteristics of patients in the training and validation sets.

	Training set ($n = 231$)	Validation set ($n = 115$)
Gender		
Male	169 (73.2)	88 (76.5)
Female	62 (26.8)	27 (23.5)
Age (years)	50 (44–57)	48 (43–57)
Hypertension		
Without	187 (81.0)	96 (83.5)
With	44 (19.0)	19 (16.5)
Diabetes		
Without	183 (79.2)	83 (72.2)
With	48 (20.8)	32 (27.8)
Statin treatment		
Without	181 (78.4)	87 (75.7)
With	50 (21.6)	28 (24.3)
Cigarette smoking		
No	149 (64.5)	82 (71.3)
Yes	82 (35.5)	33 (28.7)
Alcohol consumption		
No	191 (82.7)	99 (86.1)
Yes	40 (17.3)	16 (13.9)
BMI (kg/m^2)	21.6 (19.9–23.2)	21.6 (19.4–23.6)
TC (mmol/L)	5.3 (4.5–6.0)	5.2 (4.6–6.3)
TG (mmol/L)	0.9 (0.6–1.3)	0.9 (0.6–1.2)
HDL (mmol/L)	1.4 (1.1–1.6)	1.4 (1.2–1.7)
LDL (mmol/L)	3.3 (2.8–3.8)	3.3 (2.7–4.0)
D_{max} of the temporal lobe (Gy)	70.0 (69.6–72.0)	70.0 (69.9–72.0)
Total radiation dose of the neck (Gy)	60.1 (60.0–64.0)	60.1 (60.0–64.1)
Radiotherapy methods		
Conventional radiotherapy	180 (77.9)	93 (80.9)
IMRT	51 (22.1)	22 (19.1)
Chemotherapy		
Without	87 (37.7)	39 (33.9)
With	144 (62.3)	76 (66.1)
IRB (years)	3.9 (2.6–6.6)	3.3 (2.5–5.2)
Follow-up time (years)	1.8 (1.0–3.3)	1.8 (0.8–3.1)
CVD		
Without	180 (77.9)	88 (76.5)
With	51 (22.1)	27 (23.5)

Data are shown as numbers (%) or medians (interquartile ranges). No difference was found between the training data set and the validation data set regarding either the clinical characteristics or the follow-up data ($P = 0.130$–0.904). *Abbreviations*: BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; D_{max} of the temporal lobe, the maximum radiation dose of the temporal lobe; IMRT, intensity-modulated radiation therapy; IRB, the interval between radiotherapy and brain necrosis; CVD, cerebrovascular disease.

Construction of the nomogram

According to the univariate Cox proportional hazards regression analysis, five candidate clinical variables were found to meet the threshold of $P < 0.1$, including age, hypertension, statin treatment, serum HDL and IRB. Among these factors, four significant predictors (hypertension, statin treatment, serum HDL and IRB) were identified by the subsequent multivariate Cox proportional hazards regression model (Table 2 and Supplementary Table S2). Moreover, the hazard ratio associated with the serum HDL level suggested that it was a protective factor, whereas the other predictors indicated the progression of CVD, of which statin treatment is discussed in detail in the Discussion section. The predictive nomogram that integrated all the significant predictors for the CVD-free survival (CFS) rate was then developed (Fig. 1). The formula for calculating the total point of the nomogram is as follows: $3.096 \times$ I (with hypertension) + $3.012 \times$ I (with statin treatment) − $3.571 \times$ HDL + $0.200 \times$ IRB + 10.714. The indicator function (I) is equal to 1 if the statement in the parentheses is true and is equal to 0 otherwise.

Assessment of the nomogram performance

The nomogram yielded a C-index of 0.763 (95% confidence interval [CI], 0.694 to 0.832) using the training set. A generally accepted approach suggests that a C-index of more than 0.75 reflects clearly useful discrimination [27,28]. Therefore, the nomogram showed satisfactory discrimination in the training set. The calibration curves for the CFS rate at 1, 3 and 5 years after the diagnosis of brain necrosis showed favorable agreement between the nomogram prediction and actual observation, indicating good calibration of the nomogram (Fig. 2A to C).

Internal validation of the nomogram

The formula for calculating the risk score is as follows: $1.121 \times$ I (with hypertension) + $1.090 \times$ I (with statin treatment) − $1.293 \times$ HDL + $0.072 \times$ IRB. The indicator function (I) is equal to 1 if the statement in the parentheses is true and is equal to 0 otherwise. The favorable calibration of the nomogram was confirmed using the validation set (Fig. 2D to F). Additionally, the nomogram also showed good discrimination with a C-index of 0.768 (95% CI, 0.675 to 0.861) in the validation set. Therefore, our nomogram performed well using both the training and validation sets.

Categorization of patients into high- or low-risk groups

After obtaining the risk scores from the nomogram, the patients were classified into low- and high-risk groups according to the optimal cutoff value of 0.04 generated by the X-tile plots

Table 2
Risk factors for CVD among patients with brain necrosis after radiotherapy.

Variable	Univariate Cox Regression		Multivariate Cox Regression	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Gender (Male vs. Female)	0.853 (0.437–1.667)	0.642	–	–
Age (years)	1.053 (1.020–1.087)	0.001*	–	–
Hypertension (Without vs. With)	3.530 (2.003–6.219)	<0.001*	3.068 (1.691–5.566)	<0.001*
Diabetes (Without vs. With)	1.177 (0.600–2.308)	0.636	–	–
Statin treatment (Without vs. With)	3.324 (1.904–5.805)	<0.001*	2.975 (1.657–5.344)	<0.001*
Cigarette smoking (No vs. Yes)	1.183 (0.670–2.086)	0.562	–	–
Alcohol consumption (No vs. Yes)	1.320 (0.657–2.649)	0.435	–	–
BMI (kg/m^2)	0.967 (0.872–1.072)	0.520	–	–
TC (mmol/L)	1.029 (0.808–1.310)	0.818	–	–
TG (mmol/L)	1.169 (0.820–1.667)	0.388	–	–
HDL (mmol/L)	0.304 (0.134–0.692)	0.005*	0.274 (0.122–0.618)	0.002*
LDL (mmol/L)	1.174 (0.886–1.556)	0.264	–	–
D_{max} of the temporal lobe (Gy)	0.957 (0.870–1.053)	0.366	–	–
Total radiation dose of the neck (Gy)	0.996 (0.943–1.052)	0.881	–	–
Radiotherapy methods (Conventional Radiotherapy vs. IMRT)	1.243 (0.616–2.506)	0.544	–	–
Chemotherapy (Without vs. With)	0.900 (0.512–1.584)	0.715	–	–
IRB (years)	1.113 (1.065–1.163)	<0.001*	1.075 (1.027–1.125)	0.002*

Abbreviations: CVD, cerebrovascular disease; BMI, body mass index; TC, total cholesterol; TG, triglyceride; HDL, high-density lipoprotein; LDL, low-density lipoprotein; D_{max} of the temporal lobe, the maximum radiation dose of the temporal lobe; IMRT, intensity-modulated radiation therapy; IRB, the interval between radiotherapy and brain necrosis; HR, hazard ratio; CI, confidence interval.

* $P < 0.05$.

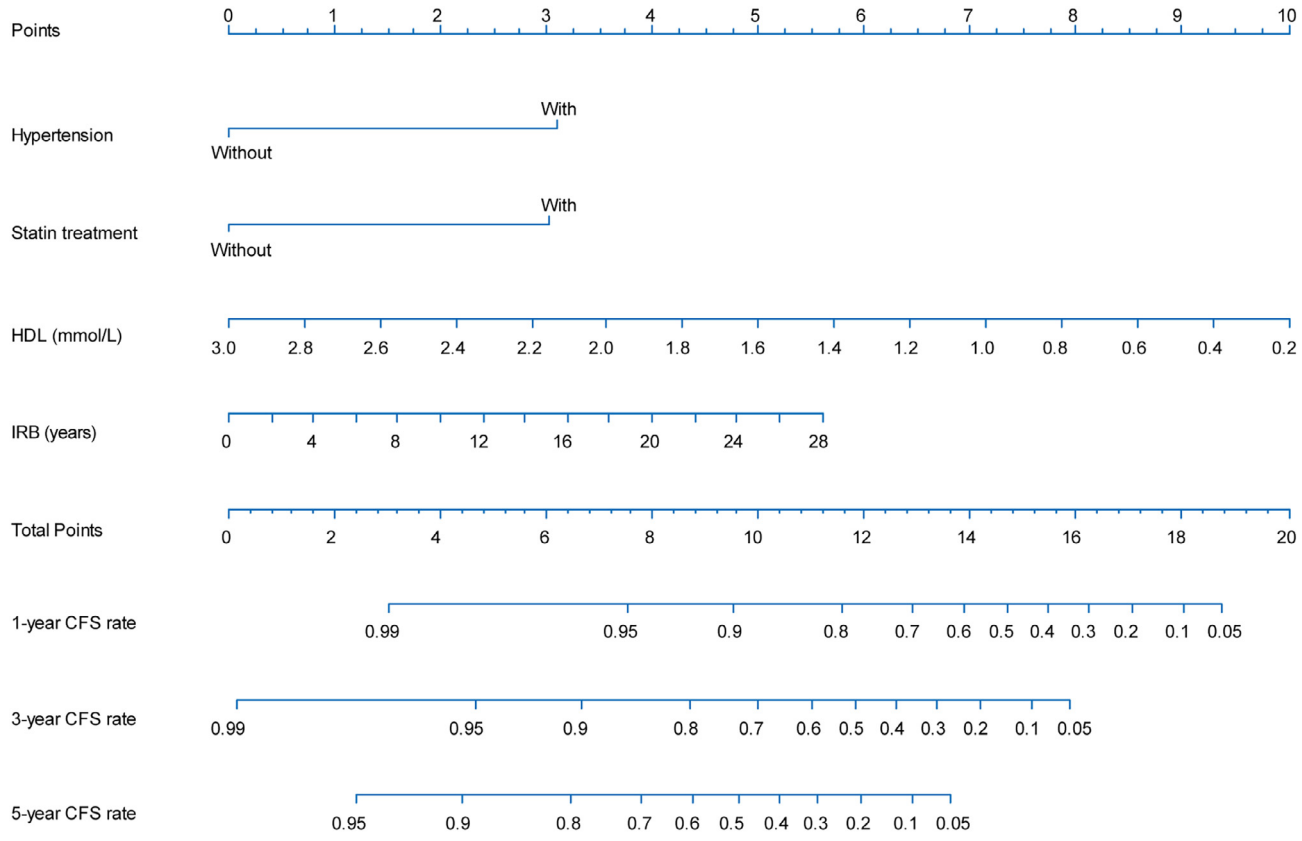

Fig. 1. Nomogram to predict 1-, 3- and 5-year CFS rates for patients with brain necrosis after radiotherapy. Points were assigned for hypertension, statin treatment, IRB and HDL level by drawing a line upward from the corresponding values to the "Points" line. The sum of these four points, plotted on the "Total points" line, corresponds to predictions of 1-, 3- and 5-year CFS. *Abbreviations*: CFS, cerebrovascular disease-free survival; HDL, high-density lipoprotein; IRB, the interval between radiotherapy and brain necrosis.

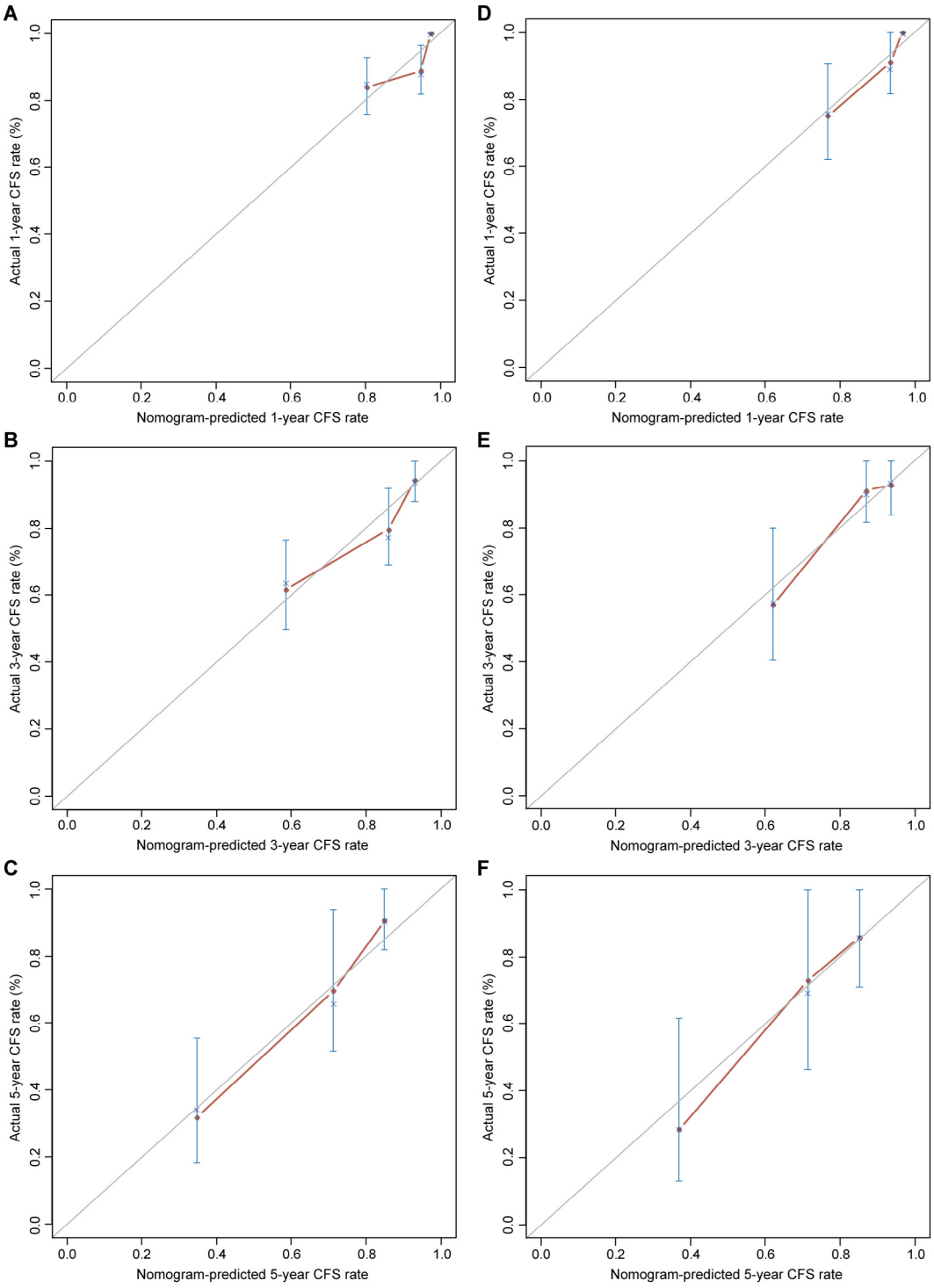

Fig. 2. Calibration curves of the nomogram. The observed CFS is shown compared with the nomogram at 1 year (A), 3 years (B) and 5 years (C) using the training set and validation set (D to F), respectively. The calibration curves depict the calibration of the nomogram in terms of the agreement between the predicted risk of CVD and the observed CVD outcomes. The 45-degree gray line represents a perfect prediction, and the pink solid lines represent the predictive performance of the nomogram. The distance between the pink solid line and the ideal line represents the superior predictive accuracy of the nomogram. *Abbreviations*: CFS, cerebrovascular disease-free survival; CVD, cerebrovascular disease.

(Supplementary Fig. S2). Notably, significant discrimination between the CFS of the high- and low-risk patients was observed using the training set (Fig. 3A), which was confirmed using the validation set (Fig. 3B). Therefore, our nomogram can successfully distinguish patients with high risk of CVD after diagnosis of brain necrosis from those with low risk.

Clinical usefulness of the nomogram

The DCA demonstrated that when the threshold probabilities exceeded 2% at 1 year, ranged between 4.7% and 85.6% at 3 years, and between 6.4% and 86.7% at 5 years, the use of the nomogram to predict CVD provided greater net benefit than the "treat all" or

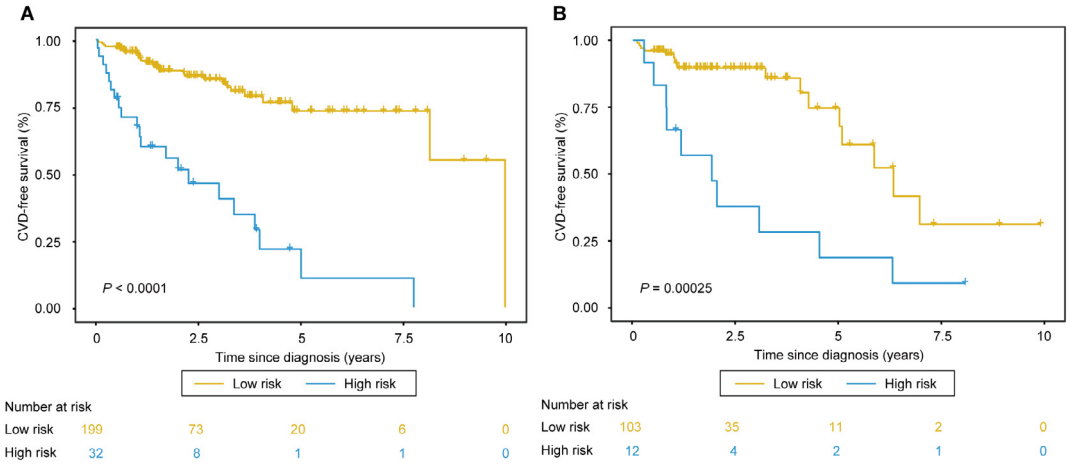

Fig. 3. Kaplan–Meier survival curves of the training and validation sets categorized into low- and high-risk groups. A significant association between the risk score and CFS was observed using the training set (A) and confirmed using the validation set (B). Abbreviation: CFS, cerebrovascular disease-free survival.

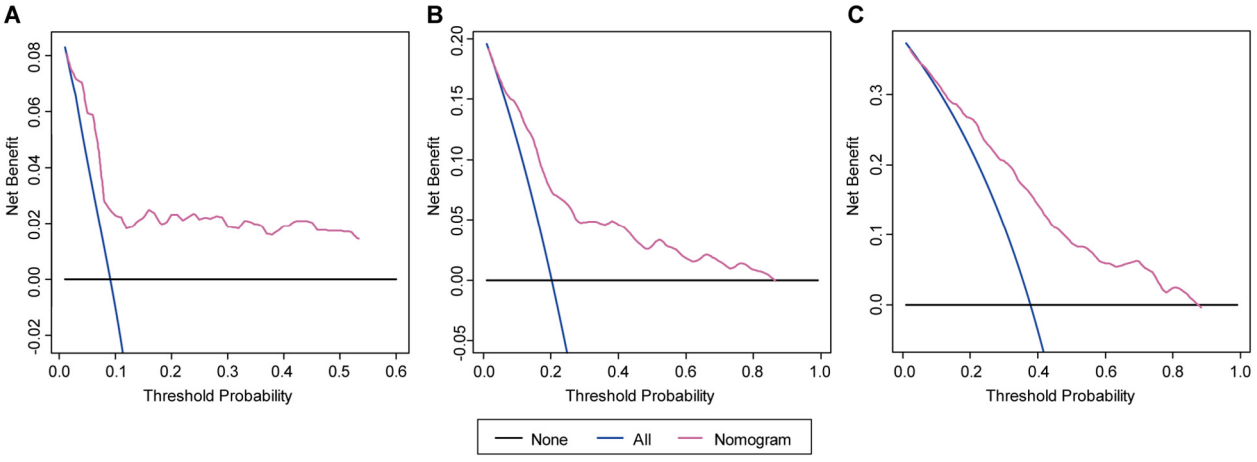

Fig. 4. DCA of the nomogram. Decision curves for CFS at 1 year (A), 3 years (B) and 5 years (C) were applied to the nomogram. The *x*-axis represents the threshold probability. The *y*-axis measures the net benefit. The black line depicts the net benefit of the strategy of treating no patients. The blue line depicts the net benefit of the strategy of treating all patients. The pink line represents the nomogram. The net benefit was calculated by subtracting the proportion of all patients who are false positive from the proportion who are true positive, weighting by the relative harm of forgoing treatment compared with the negative consequences of an unnecessary treatment. The threshold probability is where the expected benefit of treatment is equal to the expected benefit of avoiding treatment. For example, if the possibility of CVD development in a patient is over the threshold probability, then a CVD treatment strategy should be adopted. *Abbreviations*: DCA, decision curve analysis; CFS, cerebrovascular disease-free survival; CVD, cerebrovascular disease.

"treat none" strategies, which indicated the nomogram to be clinically useful (Fig. 4). For example, if the personal threshold probability of a patient is 50% (i.e., the patient would opt for treatment if his probability of CVD was >50%), then the net benefit is 0.017 at 1 year, 0.030 at 3 years, and 0.088 at 5 years when using the proposed nomogram to predict his probability of CVD and make the decision of whether to undergo treatment, with added benefit than either the regimen where all patients are assumed to have CVD or the regimen where no patients are assumed to have CVD.

Discussion

Evidence is mounting that radiotherapy contributes to vascular disease [1–4]. In fact, patients with brain necrosis after radiotherapy are more likely to develop CVD. A study demonstrated that patients with radiation-induced temporal lobe necrosis had an increased mean intima-media thickness, a higher frequency of plaques and much faster flow velocities of the middle cerebral arteries and internal carotid arteries than those without temporal lobe necrosis [15]. Furthermore, among patients with unilateral temporal lobe necrosis, the flow velocities of the middle cerebral arteries ipsilateral to the temporal lobe necrosis were more rapid than those of the contralateral (non-lesion) side [15]. Despite serious implications once it occurs, CVD does not garner sufficient attention among patients with brain necrosis after radiotherapy.

Currently, treatment for CAS, when clinically indicated, is either carotid endarterectomy or stents, which may reduce the risk of ischemic stroke yet carrying risks of severe (70–99%) ipsilateral CAS, procedural myocardial infarction and procedure-related disabling or fatal stroke [29,30]. Radiation-associated CAS is more difficult to treat surgically because of arterial wall fibrosis, tissue plane scarring, ill-defined planes of dissection, and risks of scar disruption and restenosis [31–33]. As another alternative, carotid angioplasty and stenting for high-grade radiation-induced CAS (≥70%) are associated with a higher rate of in-stent restenosis (≥50%) than that for atherosclerotic stenosis [11]. Therefore, there is great need to predict the risk of CVD in patients with brain necrosis after radiotherapy, and follow up with those high-risk patients closely for early detection and prompt interventions.

To improve primary prevention and management, several tools have been developed to predict the risk of ASCVD [16,17]. One well-known example is the Cardiovascular Risk Reduction Model,

which aims to assess a value-based payment approach toward a reduced 10-year predicted risk of ASCVD by applying the cardiovascular preventive management strategy of aspirin therapy in appropriate patients, blood pressure control, cholesterol management and smoking cessation (i.e., the "ABCS" approach) [16]. The Prediction for ASCVD Risk in China Project also developed effective tools with satisfactory performance regarding 10-year ASCVD risk prediction in a Chinese population [17].

However, when the QStroke (2014) score, which provides a valid measure of absolute stroke risk in a general population of patients free of stroke or TIA [34], was used to determine the 10-year risk of CVD in patients receiving radiotherapy, it was unable to correctly categorize any patient as high risk and only categorized 2.5% as intermediate risk. Yet, 76% of these patients did in fact have CAS in one or both arteries, suggesting that CAS due to radiotherapy is independent of traditional risk factors and that standard risk prediction models derived from the general population are not applicable [18]. Therefore, a well-performed risk prediction tool for CVD among patients with brain necrosis is greatly needed and may aid in addressing this challenge.

Thus, we attempted to construct a nomogram to predict the CFS rate at 1, 3 and 5 years after the diagnosis of brain necrosis after radiotherapy. In this study, four significant predictors (hypertension, statin treatment, serum HDL level and IRB) were identified using a multivariate Cox proportional hazards regression model. Of these predictors, statin treatment was unexpectedly associated with a positive coefficient in the risk prediction model (indicating a higher risk for those receiving statin therapy). In fact, estimating the consequence of a given therapy on risk simply by changing a risk factor level or removing adverse risk factors in our cohort equation (or any other similar risk-prediction equations) leads to inaccurate conclusions. Although clinical trial data demonstrated that lipid-lowering treatments lowered the risk for CVD, the prediction model we developed was not designed to reflect this change. Individuals who are treated with antihyperlipidemic therapies are at higher CVD risk because of the longer burden and severity of elevated serum lipids, regardless of whether such medications are taken regularly. Rather, another possible interpretation for this observation is that lowering blood lipids using medications does not reduce CVD risk to the same level as that of an individual whose blood lipid levels in the absence of medication were always lower, and this warrants further investigation. This interpretation is similar to a result of the Framingham Heart Study, which showed that the greatest atrial fibrillation-attributable risk of all the modifiable risk factors was hypertension and its treatment [35].

To provide an easy-to-use tool for clinicians, we developed a nomogram based on a multivariate Cox proportional hazards regression model (Fig. 1), which showed satisfactory calibration (Fig. 2) and discrimination using the training set (C-index, 0.763) and the validation set (C-index, 0.768). Furthermore, the nomogram successfully stratified patients into high- and low-risk groups, and the high-risk group showed a significantly greater probability of having CVD (Fig. 3). Therefore, our nomogram may serve as a precise and reliable predictive tool for CVD in patients with brain necrosis after radiotherapy, which may aid patient management.

The vital and ultimate argument for the application of the nomogram is based on the need to assess the additional treatment or examination requirements of individual patients. However, the clinical consequences of a particular level of discrimination or degree of miscalibration cannot be captured by the performance of a risk-prediction model [36–38]. Therefore, a DCA was applied to evaluate the clinical utility of the nomogram. The decision curves showed that when the threshold probabilities exceeded 2% at 1 year, ranged between 4.7% and 85.6% at 3 years, and between 6.4% and 86.7% at 5 years (Fig. 4), the use of the nomogram provided greater benefit than either the treat-all-patients approach or the treat-none approach.

Additionally, prior studies suggested that the screening of high-risk patients for asymptomatic CAS might be cost effective [39]. However, lack of authoritative guidelines for brain necrosis as well as CVD after radiotherapy leads to relatively arbitrary follow-up strategies based on clinical experience, especially for those asymptomatic patients with stable or resolved imaging brain necrosis lesions. Consequently, some patients may miss the good timing to prevent or treat CVD. Therefore, our nomogram may serve as a favorable tool to distinguish patients with high risk of CVD from those with low risk, and follow up with those high-risk patients closely. The high-risk patients might represent a subset of those who might benefit the most from more frequent noninvasive evaluations, including routine carotid bruit auscultation and imaging (with ultrasonography, computed tomographic angiography, or magnetic resonance angiography) for several years after a diagnosis of brain necrosis after radiotherapy. Furthermore, the use of antihypertensive treatment, hypoglycemic agents, lipid-lowering therapies and smoking and alcohol cessation might be pursued more aggressively for high-risk patients.

The limitations of our study should be considered. First, this retrospective study may have potential selection biases. For instance, enrolled patients received either conventional radiotherapy or IMRT, and majority of the patients received conventional radiotherapy which may be less considered for head and neck cancer currently [40]. The performance of our nomogram is required to be determined in patient population received radiotherapy in various approaches [41,42]. Second, the clinical factors selected as potential predictors for CVD after the diagnosis of brain necrosis after radiotherapy were based on our clinical experiences and previously published studies [16]. Unrecorded clinical characteristics might also be associated with CVD. Because a portion of patients received radiotherapy in other hospitals, it was difficult to retrospectively obtain comprehensive and detailed information of patients. Therefore, we failed to include other potential risk factors as candidate clinical variables in our study. Third, although our prediction model achieved favorable predictive power for CVD, a multicenter validation study or even prospective study should be performed to confirm the performance of our predictive model in subsequent investigations.

In summary, the nomogram we developed has potential use as an individual tool to predict CVD in patients with brain necrosis after radiotherapy. Additional external validation is warranted to determine the performance of our nomogram before its implementation into clinical practice.

Study funding

This work was supported by the National Key R&D Program of China (2017YFC1307500, 2017YFC1307504, 2016YFC1300600), National Natural Science Foundation of China (No. 81471249, 81622041 and 81820108026), the Major Program of Collaborative Innovation Specialized in Livehood Science Topics (201604020097), the Science and Technology Planning Project of Guangdong Province (2016A050502016) and the Tip-top Scientific and Technical Innovative Youth Talents of Guangdong special support program (No. 2016TQ03R559) to Yamei Tang; the National Natural Science Foundation of China (No. 81872549), Science and Technology Planning Project of Guangzhou (201704030033) and the Young Teacher Training Program of Sun Yat-sen University (17ykpy38) to Yi Li.

Conflicts of interest

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.radonc.2018.11.008.

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