Oral Oncology 67 (2017) 37–45

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Validation of published nomograms and accordingly individualized induction chemotherapy in nasopharyngeal carcinoma

Pu-Yun OuYang [a,1], Lu-Ning Zhang [b,1], Yao Xiao [a,1], Xiao-Wen Lan [a], Xiao-Min Zhang [a], Jun Ma [a], Fang-Yun Xie [a,*]

[a] Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, Guangzhou, Guangdong, China
[b] Department of Oncology, The First Affiliated Hospital of Guangdong Pharmaceutical University, Guangzhou, China

ARTICLE INFO

Article history:
Received 12 November 2016
Received in revised form 19 January 2017
Accepted 23 January 2017
Available online 7 February 2017

Keywords:
Concurrent chemotherapy
Induction chemotherapy
Intensity-modulated radiotherapy
Nasopharyngeal carcinoma
Nomogram

ABSTRACT

Objectives: We have attempted to validate two published nomograms in nasopharyngeal carcinoma (NPC) and individualize induction chemotherapy (IC) accordingly.
Materials and methods: From 2007 to 2011, 920 patients were included in the study. The validity of the nomograms was assessed by Harrell's concordance index (C-index), areas under the curve (AUC), and calibration curves. Disease-free survival (DFS) and overall survival (OS) by IC were evaluated in and out of risk stratified patients with and without propensity score matching analysis.
Results: Compared with the 7th edition of the Union for International Cancer Control (UICC) staging system, Tang's nomogram better discriminated DFS (C-index 0.629 versus 0.569, $P = 0.002$; AUC 0.635 versus 0.576, $P = 0.018$), whereas Yang's nomogram had no advantage in predicting OS (C-index 0.648 versus 0.606, $P = 0.184$; AUC 0.643 versus 0.604, $P = 0.157$). Calibration curves indicated good agreement between predicted and observed DFS or OS probability. Without risk stratification, patients achieved no benefit from IC in DFS ($P \geqslant 0.101$) or OS ($P \geqslant 0.370$). However, among 580 high-risk patients stratified by Tang's nomogram, IC improved five-year DFS from 68.8 to 74.8% ($P = 0.072$), and OS from 82.6 to 87.9% ($P = 0.065$), and the improvement of DFS and OS increased to 9.3% ($P = 0.019$) and 7.3% ($P = 0.036$), respectively, in 426 propensity-matched patients.
Conclusions: Tang's nomogram helps to stratify stage III-IVa-b NPC, and IC is beneficial to high-risk patients in clinical practice.

Introduction

Nasopharyngeal carcinoma (NPC) is a squamous cell carcinoma that occurs in the epithelial lining of the nasopharynx. Radiotherapy is the primary treatment modality because of the anatomical location of the carcinoma and its sensitivity to irradiation. As a result of the non-specific nature of nasal and aural symptoms and the difficulty in making a clinical examination of the nasopharynx, almost 70% patients are initially diagnosed with locoregionally advanced disease [1]. The addition of induction chemotherapy (IC) before radiotherapy was expected to shrink tumor volume, lower tumor burden, and reduce the radiation dose to organs at risk. Unfortunately, phase III randomized controlled trials demonstrated no survival benefit from the addition of IC to two-dimensional radiotherapy alone [2–5]. In the era of concurrent chemoradiotherapy, the efficiency was quite contradictory [6–9]. Hence, the main issues focused on the magnitude of survival benefit in clinical practice, and the effective way to individualize IC.

Classic tumor-related prognostic factors, such as Epstein-Barr virus (EBV) deoxyribonucleic acid (DNA) [10], in addition to numerous patient characteristics, such as sex [11], pretreatment level of lactate dehydrogenase (LDH) [12], hemoglobin (Hb) [13],

Abbreviations: AUC, areas under the curve; BMI, body mass index; CC, concurrent chemotherapy; CI, confidence interval; C-index, concordance index; CRP, C-reactive protein; CT, computed tomography; DFS, disease-free survival; DNA, deoxyribonucleic acid; EBV, Epstein-Barr virus; Hb, hemoglobin; HR, Hazard ratio; IC, induction chemotherapy; IMRT, intensity-modulated radiotherapy; LDH, lactate dehydrogenase; MRI, magnetic resonance imaging; NPC, nasopharyngeal carcinoma; OS, overall survival; PET/CT, positron emission tomography and computed tomography; ROC, receiver operating characteristic; UICC, Union for International Cancer Control.

* Corresponding author at: Department of Radiation Oncology, Sun Yat-sen University Cancer Center, State Key Laboratory of Oncology in South China, Collaborative Innovation Center for Cancer Medicine, No. 651 Dongfeng Road East, Guangzhou 510060, China.
E-mail address: xiefy@sysucc.org.cn (F.-Y. Xie).
[1] Co-first authors.

http://dx.doi.org/10.1016/j.oraloncology.2017.01.009
1368-8375/

and body mass index (BMI) [14], have been reported to independently correlate with treatment outcomes. A combination of these predictors was anticipated to create clinical risk groups by disease severity and aid in clinical decision-making. Recently, several nomograms [15–17] have been developed, which seem to perform well in internal validation to predict outcomes. However, none of them have been externally validated in a pure cohort of patients who have been diagnosed with locoregionally advanced disease and irradiated with uniform intensity-modulated radiotherapy (IMRT). More importantly, the application of a nomogram to stratify patients and individualize induction chemotherapy has not been well-studied.

As EBV DNA is currently the most attractive potential biomarker to complement the TNM (tumor, node, and metastases) classification [18] and correlate with tumor burden [19] and treatment outcomes of NPC [20], we compared the performance of two published nomograms [15,16] that utilized EBV DNA. We also evaluated the role of IC in and out of risk stratified patients by nomogram.

Materials and methods

Patient's eligibility

This study was approved by the Institutional Review Board at Sun Yat-sen University Cancer Center, and individual informed consent was waived given the anonymous analysis of routine data. All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. From January 2007 to October 2011, patients that met the following criteria were eligible for this study: (1) newly diagnosed with World Health Organization type 2 or 3 NPC, (2) staged with III-IVb (T1-2N2-3M0 and T3-4N0-3M0, based on the 7th edition of the Union for International Cancer Control [UICC] staging system in 2010), (3) aged 18 or older, (4) treated with IMRT plus concurrent chemotherapy (CC) with or without IC, and (5) had known BMI, EBV DNA, C-reactive protein (CRP), LDH, and Hb before treatment.

Treatment

The cumulative radiation doses were 66 Gy or greater to the primary tumor, 60 Gy or greater to the involved neck area, and 50 Gy or greater to potential sites of local infiltration and bilateral cervical lymph nodes area in 30–33 fractions. Further IMRT information was detailed previously [21]. Concurrent chemotherapy consisted of cisplatin/nedaplatin administered weekly for up to seven cycles or every three weeks for two to three cycles. IC consisted of docetaxel/paclitaxel plus cisplatin/nedaplatin, or cisplatin/nedaplatin plus fluorouracil, or docetaxel/paclitaxel plus cisplatin/nedaplatin plus fluorouracil given every three weeks for two to three cycles before IMRT.

Follow-up

Patients were observed at least once every three months during the first three years and every six months thereafter. Detailed history and physical examinations were performed at each follow-up visit. Nasopharyngoscopy with or without biopsy, magnetic resonance imaging (MRI) of the head and neck, chest radiography or computed tomography (CT), abdominal sonography or CT, whole-body bone scan, or [18F] fluorodeoxyglucose positron emission tomography and computed tomography (PET/CT) were performed to detect possible locoregional relapse and/or distant metastasis. Salvage treatment, including re-irradiation, surgery, and/or chemotherapy, was delivered to patients with confirmed relapse, distant metastasis, or persistent disease.

Statistical analysis

The variables required for Tang's nomogram [15] to predict disease free survival (DFS) were age (18–29/30–39/40–49/50–59/$\geqslant$60), sex, BMI (<18.5/18.5–22.9/22.9–27.5/$\geqslant$27.5), T-classification, N-classification, EBV DNA (<10^3/10^3–10^4/10^4–10^5/10^5–10^6/$\geqslant 10^6$), CRP (<1.0/1.0–3.0/$\geqslant$3.0), LDH (<245/$\geqslant$245), and Hb (<113/113–151/$\geqslant$151). Additionally, Yang et al. [16] included the following variables in their nomogram to predict overall survival (OS): age (<45/$\geqslant$45), sex, LDH (<166/$\geqslant$166), CRP (<1.49/$\geqslant$1.49), T-classification, N-classification, and EBV DNA (<3760/$\geqslant$3760). DFS was calculated from the date of treatment to the first relapse at any site, death from any cause, or the date of the last follow-up visit. OS was defined from the date of treatment to death from any cause.

There are two aspects in the evaluation of model performance: discrimination and calibration. To assess discrimination, Harrell's concordance index (C-index) was determined based on a Cox model with DFS or OS and the nomogram-calculated total points of each patient as the only covariate. Additionally, a receiver operating characteristic (ROC) curve of the nomogram-calculated total points to predict DFS or OS was drawn, and the areas under the curve (AUCs) were calculated. It is generally accepted that the C-index or AUC value can range from perfect concordance (1.0) to random predictions (0.5). Discrimination of nomograms was compared with that of the 7th edition of the UICC staging system. Calibration plots were used to compare nomogram-predicted probabilities with observed outcomes; in a perfectly calibrated nomogram, the observed and predicted outcomes aligned along the 45-degree line of the calibration plot.

To mimic randomized controlled trials, the propensity score matching method [22] was used to identify matched groups by IC with balanced characteristics to reduce known biases. Propensity scores were computed by logistic regression for each patient based on the following covariates: age, BMI, EBV DNA, LDH, T-classification, N-classification, and clinical stage. Patients were then matched without replacement at the ratio of 1:1 on those scores. Covariates balance was examined by the Chi-square (χ^2) test or Fisher's exact test and standardized difference [23] in the unmatched and matched cohorts.

Statistical analyses were performed using IBM SPSS Statistics version 23.0, Stata version 14.1, and R version 3.3.1. Two-sided $P < 0.05$ was considered to be significantly different.

Results

Patients

A total of 920 patients were included in the study. The median follow-up (range) was 56 months (3–109 months). As listed in Table 1, obvious differences were observed between our cohort and previous training cohorts in tumor stage and treatment modes. Apart from similar distributions of sex, histology, LDH, Hb, and BMI, patients in our cohort were much younger and had higher levels of EBV DNA and CRP.

Validation

Tang's nomogram showed a significantly higher ability of discrimination than the 7th edition of the UICC staging system in predicting the DFS rate, with a C-index of 0.629 (95% confidence interval [CI], 0.589–0.668) versus 0.569 (95% CI, 0.534–0.605) ($P = 0.002$). The ROC curve also justified the better performance of Tang's nomogram (AUC 0.635, 95% CI 0.591–0.680 versus AUC 0.576, 95% CI 0.537–0.615, $P = 0.018$, Fig. 1A). When compared