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Development and external validation of nomograms predictive of response to radiation therapy and overall survival in nasopharyngeal cancer patients

Jae-Keun Cho [a], Gil-Joon Lee [b], Keun-Ik Yi [c], Kyu-Sup Cho [c], Nayeon Choi [b], Jong Se Kim [b], Hakyoung Kim [d], Dongryul Oh [d], Sun-Kyu Choi [e], Sin-Ho Jung [e], Han-Sin Jeong [b,1], Yong Chan Ahn [d,*,1]

[a] *Department of Otorhinolaryngology-Head and Neck Surgery and Research institute for Convergence of Biomedical Science and Technology, Pusan National University Yangsan Hospital, Busan, Republic of Korea*
[b] *Department of Otorhinolaryngology-Head and Neck Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[c] *Department of Otorhinolaryngology-Head and Neck Surgery, Pusan National University Hospital, Busan, Republic of Korea*
[d] *Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea*
[e] *Biostatistics and Clinical Epidemiology Center, Research Institute for Future Medicine, Samsung Medical Center, Seoul, Republic of Korea*

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Abstract ***Introduction:*** Large variability in the clinical outcomes has been observed among the nasopharyngeal cancer (NPC) patients with the same stage receiving similar treatment. This suggests that the current Tumour-Node-Metastasis staging systems need to be refined. The nomogram is a useful predictive tool that integrates individual variables into a statistical model to predict outcome of interest. This study was to design predictive nomograms based on the clinical and pathological features of patients with NPC.
Materials and methods: Clinical data of 270 NPC patients who underwent definitive radiation therapy (RT) alone or concurrent with chemotherapy were collected. Factors predictive of response to RT and overall survival (OS) were determined by univariate and multivariate analyses, and predictive nomograms were created. Nomograms were validated externally by assessing discrimination and calibration using an independent data set ($N = 122$).
Results: Three variables predictive of response to RT (age, histology classification and N classification) and four predictive of OS (age, performance status, smoking status and N

* *Corresponding author at:* Department of Radiation Oncology, Samsung Medical Center, Sungkyunkwan University School of Medicine, 81 Irwon-ro, Gangnam-gu, Seoul 135-710, Republic of Korea. Tel.: +82 2 3410 2602; fax: +82 2 3410 2619.
E-mail addresses: ahnyc@skku.edu, ycahn.ahn@samsung.com (Y.C. Ahn).
[1] Equal contribution by Han-Sin Jeong and Yong Chan Ahn.

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classification), in addition to T classification, were extracted to generate the nomograms. The nomograms were validated externally, which showed perfect correlation with each other.
Conclusion: The designed nomograms proved highly predictive of response to RT and OS in individual patients, and could facilitate individualised and personalised patients' counselling and care.

1. Introduction

Nasopharyngeal cancer (NPC) has distinct features among head and neck cancers (HNC) with several respects including epidemiology, aetiology and clinical manifestation [1,2]. It has been estimated that globally 84,400 cases are newly diagnosed as having NPC and 51,600 patients die of NPC each year [3]. The age-standardised prevalence rate is 15–50 per 100,000 persons, and NPC is the third most common cancer among Asians [4–7]. The prevalence rises after 20 years of age and decreases after 60 years of age, with a male–female ratio of 3:1. The median age at presentation is 40–50 years of age, which is significantly younger than that of other HNC [4,5].

Radiation therapy (RT) alone for the patients with early stage and RT concurrent with systemic chemotherapy (CCRT) for those with advanced stage have been the main standard treatment strategies, which mainly have been based on the current Tumour-Node-Metastasis (TNM) staging system. However, a large variability in the clinical outcomes has been observed among the patients with the same stage receiving similar treatment [8]. This suggests that the current TNM staging system, in which histologic subtypes, patient's characteristics and other biologic features have not been taken into account, might be inadequate for therapeutic decision and prognosis prediction [9,10]. Development of a new tool that could enhance and assist the decision-making and patient counselling would be desired.

A nomogram is a tool that enables predicting outcome of interest by providing a numerical probability by integrating multiple clinical, pathological, biochemical and treatment-related variables into a statistical model. Several nomograms have been currently employed in oncology [11–14]. An advantage of nomogram over the conventional TNM system is the predictive power of the outcome of interest on an individual patient [15–18]. In addition, the model has a potential of incorporation into the current TNM staging system [19–22]. The aims of the current study were to create predictive nomograms based on the clinical and pathological features of the NPC patients and to validate these externally.

2. Materials and methods

2.1. Patient characteristics

The current study was approved by the Institutional Review Board. We identified 332 NPC patients who underwent definitive RT alone or CCRT at the authors' institute from 1996 till 2012, and their clinical and pathological data were retrospectively reviewed. Sixty-two patients were excluded: occurrence of second primary malignancy; history of previous cancer treatments; other histologic types than nasopharyngeal carcinomas; incomplete follow-up; and systemic metastasis at the time of diagnosis. The final number of patients included to build nomograms was 270 (Table 1).

46.3% of the patients had locally advanced disease (T3–4), and 80.4% had clinically positive regional lymph node metastasis. Most patients had good to excellent performance status, and CCRT was applied mostly to the patients with either advanced T stages (T3–4) or positive lymphatic metastasis, on the ground that they were presumed to tolerate CCRT. Complete response or remission (CR) following RT was observed in 220 patients (81.5%). Forty-one patients (15.2%) experienced treatment failures: 22 with loco-regional recurrence (11 local, 6 regional, 5 loco-regional); 19 with distant metastases; and three with combined loco-regional and distant failure. Fifty-two patients (19.3%) died from any cause during the follow-up period. The 5-year overall survival (OS) and disease-free survival (DFS) of all patients were 83.1% and 84.4%, respectively (Fig. 1).

2.2. Outcome analyses and design of predictive nomograms

The demographics and disease characteristics of the patients included age, gender, smoking and alcohol intake status, Eastern Cooperative Oncology Group (ECOG) performance status, characteristics of primary tumour upon clinical and radiological examination, status of the neck lymph nodes, histologic grade according to World Health Organisation (WHO) classification [23], treatment modalities, and dose of RT. During the study period, RT technique evolved from 3-dimensional