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Biomarkers in HNSCC

Improving the prediction of overall survival for head and neck cancer patients using image biomarkers in combination with clinical parameters

Tian-Tian Zhai [a,b,*], Lisanne V. van Dijk [a], Bao-Tian Huang [b], Zhi-Xiong Lin [b,*], Cássia O. Ribeiro [a], Charlotte L. Brouwer [a], Sjoukje F. Oosting [c], Gyorgy B. Halmos [d], Max J.H. Witjes [e], Johannes A. Langendijk [a], Roel J.H.M. Steenbakkers [a], Nanna M. Sijtsema [a]

[a] Department of Radiation Oncology, University Medical Center Groningen, University of Groningen, The Netherlands; [b] Department of Radiation Oncology, Cancer Hospital of Shantou University Medical College, China; [c] Department of Medical Oncology, University Medical Center Groningen, University of Groningen; [d] Department of Otolaryngology, University Medical Center Groningen, University of Groningen; and [e] Department of Maxillofacial Surgery, University Medical Center Groningen, University of Groningen, The Netherlands

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ABSTRACT

Purpose: To develop and validate prediction models of overall survival (OS) for head and neck cancer (HNC) patients based on image biomarkers (IBMs) of the primary tumor and positive lymph nodes (Ln) in combination with clinical parameters.

Material and methods: The study cohort was composed of 289 nasopharyngeal cancer (NPC) patients from China and 298 HNC patients from the Netherlands. Multivariable Cox-regression analysis was performed to select clinical parameters from the NPC and HNC datasets, and IBMs from the NPC dataset. Final prediction models were based on both IBMs and clinical parameters.

Results: Multivariable Cox-regression analysis identified three independent IBMs (tumor Volume-density, Run Length Non-uniformity and Ln Major-axis-length). This IBM model showed a concordance (c)-index of 0.72 (95%CI: 0.65–0.79) for the NPC dataset, which performed reasonably with a c-index of 0.67 (95%CI: 0.62–0.72) in the external validation HNC dataset. When IBMs were added in clinical models, the c-index of the NPC and HNC datasets improved to 0.75 (95%CI: 0.68–0.82; $p = 0.019$) and 0.75 (95%CI: 0.70–0.81; $p < 0.001$), respectively.

Conclusion: The addition of IBMs from the primary tumor and Ln improved the prognostic performance of the models containing clinical factors only. These combined models may improve pre-treatment individualized prediction of OS for HNC patients.

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Head and neck cancer (HNC) accounts for about 0.65 million new cancer cases and 0.35 million cancer deaths worldwide every year [1]. Based on the Surveillance, Epidemiology, and End Results (SEER) data, the 5-year overall survival (OS) for HNC patients is approximately 60% [2]. The introduction of more intensified treatment regimens has resulted in improved OS rates, however the number of patients developing locoregional failure or distant metastases remains substantial [3,4]. To enable more personalized treatment approaches, risk stratification is becoming increasingly important [5]. Risk stratification in HNC requires new, robust and prognostic parameters to identify patients with different risk profiles for locoregional recurrence, distant metastasis and death [6–8].

In routine clinical practice, the TNM staging system is used to guide treatment decision-making often in combination with other classical prognostic factors such as performance status, tumor characteristics and age [9,10]. However, patients with similar prognostic factors may have different outcome [6,7] and thus new prognostic factors are needed to improve outcome prediction accuracy when added to prediction models based on classical prognostic factors only.

Recent studies have demonstrated the potential value of image biomarkers (IBMs), which are significantly associated with OS and complications in HNC, thoracic, pancreatic and colorectal cancer [11–13]. IBMs can be extracted from medical images and provide quantitative information regarding intensity, shape and textural characteristics of the region of interest [14–17]. By extracting

* Corresponding authors at: Department of Radiation Oncology, University Medical Center Groningen, P.O. Box 30001, 9300 RB Groningen, The Netherlands (T.-T. Zhai). Department of Radiation Oncology, Cancer Hospital of Shantou University Medical College, 515031 Shantou, China (Z.-X. Lin).
E-mail addresses: t.zhai@umcg.nl (T.-T. Zhai), zxlin5@qq.com (Z.-X. Lin).

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IBMs, the three-dimensional morphological tumor information can be transformed into multi-dimensional and mineable data [5,18]. Furthermore, IBMs enable decoding of a general prognostic phenotype existing in different cancer types, which may widen the scope of application [11].

Although many IBMs are significantly associated with outcome, it remains unclear to what extent the addition of IBMs improves the predictive power of models only consisting of classical prognostic factors, such as TNM staging and performance status. The aim of this study was to test whether the performance of prediction models for OS could be improved by the addition of IBMs compared to models based on solely classical prognostic factors for nasopharyngeal cancer (NPC) patients. Furthermore, the ability to generalize the prognostic value of IBMs for different tumor types was determined by externally validating this value for other HNC subtypes.

Materials and methods

Patient demographics and treatment

This retrospective study was composed of 289 consecutive NPC patients. Patients were treated with (chemo-)radiotherapy between January 2010 and June 2011 at the Cancer Hospital of Shantou University Medical College. All patients received a pre-treatment computed tomography (CT) scan (Philips Brilliance CT Big Bore Oncology Configuration, Cleveland, OH, USA; voxel size: $1.0 \times 1.0 \times 3.0$ mm; scan voltage: 120 kV; convolution kernel: Philips Healthcare's B) for radiotherapy planning. Patients were primarily treated with intensity-modulated radiotherapy (IMRT) and received a total dose of 70.4 Gy with fractions of 2.2 Gy in 6.5 weeks (5 fractions per week).

An additional set of 298 consecutive HNC patients (including 4.4% NPC patients) was treated with definitive radiotherapy, either combined or not, with chemotherapy or cetuximab at the University Medical Center Groningen between November 2007 and May 2013. For all patients, a pre-treatment CT-scan (Somatom Sensation Open, Siemens, Forchheim, Germany; voxel size: $1.0 \times 1.0 \times 2.0$ mm; scan voltage: 120 kV; convolution kernel: B30) was acquired for radiotherapy planning. Radiotherapy consisted of primarily three-dimensional conformal radiotherapy or IMRT to a total dose of 70 Gy with fractions of 2 Gy in 6–7 weeks (6 or 5 fractions per week).

Inclusion criteria were as follows: confirmed primary tumor with pathological diagnosis, standard contrast-enhanced planning CT-scan, treatment with curative intent, and OS data available.

Clinical parameters

All clinical parameters including age, gender, tumor location, treatment modality, human papilloma virus (HPV) status (only for oropharyngeal cancer (OPC)) and World Health Organization performance status (WHO PS) [19] were derived from medical records. Dose-volume information of the primary tumor (PT) and positive lymph nodes (pLN) was derived from the radiotherapy planning system (mean dose, $V50$, $V60$, $V70$, $V80$, $D_{90\%}$, $D_{95\%}$ and $D_{98\%}$). Tumor (T) and positive lymph node (N) stage were defined according to the 6th edition of the American Joint Committee on Cancer Staging Manual [10].

CT image biomarkers

The PT and pLN were delineated for the NPC and HNC datasets on the planning CT-scan by experienced head and neck radiation-oncologists. In-house software was used to extract the IBMs, developed using common formulas in Matlab R2014a (Mathworks, Natick, USA). Twenty-four CT intensity and 20 geometric IBMs were directly derived from every delineated structure (the PT, all pLN and the pLN with the largest volume). The intensity IBMs were obtained from the histogram of all voxel values, such as median of the voxels and entropy of the voxels. Geometric IBMs, such as volume, compactness and major axis length, were calculated from the three-dimensional shape and size of the contoured structures. Ninety textural CT IBMs from both the PT and the pLN with the largest volume were defined to quantify the heterogeneity of tissue. They were derived from three different matrices: the gray level co-occurrence matrix (GLCM) [15], gray level run-length matrix (GLRLM) [16] and gray level size-zone matrix (GLSZM) [17]. GLCM describes the gray level transition, GLRLM and GLSZM describe the directional and volumetric gray level repetition. They were calculated from the three-dimensional contoured structures. More details on feature extraction and used algorithms are described in our previous publication [20]. The lymph node IBMs from patients without lymph node metastasis were defined as 0.

Data analysis

The endpoint of this study was OS, defined as the time from the first day of radiotherapy to the date of death from any cause. Patients alive were censored at the date of last follow up. An overview of the analysis design is shown in Fig. 1.

Step 1: Clinical models

Potential clinical parameters that were considered for their prognostic ability in the NPC and HNC datasets included age (>median vs. ≤median), gender (female vs. male), T-stage (T3–T4 vs. T1–T2), N-stage (N2–N3 vs. N0–N1), treatment modality (RT with systemic treatment vs. RT only), WHO PS (1–3 vs. 0) and dose parameters (>median vs. ≤median). HPV status assessed by p16 immunohistochemistry and DNA polymerase chain reaction (OPC positive vs. others) was included in the analysis for the HNC dataset, as this is a strong risk factor for oropharyngeal cancer [10,21,22]. Due to the known difference in etiology between NPC and HNC, two multivariable clinical prediction models were created: one based on the NPC and the other on the HNC dataset.

Step 2: IBM model

IBM variables were pre-selected to reduce the probability of over-fitting. If the Pearson correlation between pairs of IBMs was larger than 0.80, then the IBM with the lower univariable association with OS was omitted from further analysis [23,24]. All pre-selected potential IBMs were analyzed for their prognostic power, using their median value (>median vs. ≤median) in the NPC dataset as the threshold value in the univariable analysis. After selection of the independent prognostic factors, the threshold values were optimized by testing the values around the median. A multivariable IBM model was developed based on the NPC dataset only. Finally, the thresholds of IBMs for the NPC dataset were used for the HNC dataset to externally validate the IBM model.

Step 3: Combined models

All clinical parameters from the NPC and HNC datasets and pre-selected IBMs from the NPC dataset were merged into multivariable analysis and the coefficients (β) of the features were refitted to the NPC dataset and HNC dataset respectively, to generate the combined IBM-NPC and IBM-HNC models.

Normal Q–Q probability plot, cumulative frequency (*P*–*P*) plot and the Kolmogorov–Smirnov test were used to test the normality of all potential clinical parameters and IBMs. The chi-square test was used to compare the rates and an independent sample t-test was used to compare normally distributed variables between different groups. Univariable Cox regression analysis was performed

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