



Predictive and prognostic value of CT based radiomics signature in locally advanced head and neck cancers patients treated with concurrent chemoradiotherapy or bioradiotherapy and its added value to Human Papillomavirus status

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ABSTRACT

Objectives: To explore prognostic and predictive value of radiomics in patients with locally advanced head and neck squamous cell carcinomas (LAHNSCC) treated with concurrent chemoradiotherapy (CRT) or bioradiotherapy (BRT).

Materials and Methods: Data of 120 patients (CRT vs. BRT matched 2:1) were retrospectively analyzed. A total of 544 radiomics features of the primary tumor were extracted from radiotherapy planning computed tomography scans. Cox proportional hazards models were used to examine the association between survival and radiomics features with false discovery rate correction. The discriminatory performance was evaluated using receiver operating characteristic curve analysis.

Results: Multivariate analysis showed a 24-feature based signature significantly predicted for OS (HR = 0.3, $P = 0.02$) and progression-free survival (PFS) (HR = 0.3, $P = 0.01$). Combining the radiomics signature with p16 status showed a significant improvement of prognostic performance compared with p16 (AUC = 0.78 vs. AUC = 0.64 at 5 years, $P = 0.01$) or radiomics signature (AUC = 0.78 vs. AUC = 0.67, $P = 0.01$) alone. When patients were stratified according to this combination, OS and PFS were significantly different according to the 4 sub-types (p16+ with low/high signature score; p16– with low/high signature score) ($P < 0.001$). Patients with high signature score significantly benefited from CRT (vs. BRT) in terms of OS ($P = 0.004$), while no benefit from CRT in patients with low signature score.

Conclusion: Our analysis suggests an added value of radiomics features as prognostic and predictive biomarker in HNSCC treated with CRT/BRT. Moreover, the radiomics signature provided additional information to HPV/p16 status to further stratify patients. External validation of such findings is mandatory given the risk of overfitting.

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Introduction

The current standard of care for patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC) is concurrent

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chemoradiotherapy (CRT), although it is associated with frequent severe acute and late toxicities [1]. In the recent years there has been a growing interest in increasing the benefit/risk ratio in human papillomavirus (HPV)-positive patients [2,3]. Due to improved prognosis, CRT could be safely postponed in HPV positive patients, reducing toxicity while not jeopardizing survival. Despite the overall good prognosis for HPV+ population, a substantial proportion of these patients remain at risk of recurrence and death [4]. Current recogni-

tion of prognostic factors mainly based on tobacco exposure, TNM classification, performance status and comorbidities. Additional biomarkers are needed to further stratify patients and select candidates for studies testing de-intensification approaches.

Generally, tissue or blood sampling is required to evaluate most of the biomarkers. Invasive biopsies performed with that purpose are prone to sampling bias and may not be able to accurately reflect true heterogeneity of the entire tumor. Easily-obtainable, noninvasive prognostic biomarkers that allow assessment of tumor heterogeneity are lacking.

Inspired by the high-throughput success of the “omics”, there has been resurgent interest in radiomics, which converts imaging data into a high dimensional mineable feature space, by using a large number of automatically extracted data-characterization algorithms [5]. Radiomics can provide a more comprehensive view of the entire tumor. Recent studies demonstrated that radiomics features had significant associations with clinical factors and underlying genomic patterns in various cancer types, thus showed strong prognostic performance [6–9]. In head and neck cancers, computed tomography (CT) imaging is routinely used for patient management, including diagnosis, radiation treatment planning and surveillance. Therefore, radiomics has significant clinical potential without adding additional imaging studies.

The purpose of this investigation was to develop a radiomics signature to estimate overall survival (OS) in patients with locally advanced head and neck squamous cell carcinomas (LAHNSCC) treated with concurrent chemoradiotherapy (CRT) or bioradiotherapy (BRT) and assess its incremental value to *Human Papillomavirus* (HPV) and clinical risk factors for individual OS estimation, and also to explore its predictive value.

Materials and methods

Patients

The retrospective cohort consisted of 120 patients with pathologically-confirmed head and neck squamous cell carcinoma (HNSCC), stage III–IVb according to American Joint Committee on Cancer (AJCC)/ International Union for Cancer Control (UICC) TNM classification 2010. Patients received total radiation dose of 70 Gy, ≥ 2 cycles of concurrent CDDP or ≥ 3 cycles of concurrent cetuximab were selected from the former study cohort of 265 patients [10,11]. Patients were matched according to each T and N stages, with a 2:1 ratio of CRT vs. BRT patients. Institutional research ethics board approval was obtained.

All patients received either one of the following two treatments between June 2006 and October 2012: definitive radiotherapy (RT) concomitantly with cisplatin (100 mg/m² every 3 weeks on days 1, 22, and 43) or cetuximab (initial loading dose of 400 mg/m² one week prior to RT, followed by weekly injection at 250 mg/m² during RT). Patients received either three-dimensional conformal radiotherapy (3D-CRT) or intensity-modulated radiotherapy (IMRT). External beam definitive RT was delivered with a total dose of 70 Gy to the gross tumor volume (GTV) in 35 fractions (range 30–35 fractions) at 5 fractions per week, with median overall treatment time of 49 days (range 39–70 days). A dose of 60 Gy and 50–54 Gy were delivered to the intermediate- and low-risk clinical target volume (CTV). The CTVs were each expanded using 3–5 mm margins to generate their respective planning target volumes (PTV). Patient assessments in follow-up were previously described [10].

CT imaging, image segmentation and radiomics analysis

Planning CT of radiotherapy was performed according to standard clinical scanning protocols at Gustave Roussy with a Siemens

Somatom Sensation Open 24-slice scanner (Siemens Medical Solutions, Forchheim, Germany). The most common pixel spacing was (0.98 mm, 0.98 mm, 3 mm) for CT.

The GTV of primary tumor (GTV-T) as region of interest was manually contoured on all CT slices by a radiation oncologist with expertise in identifying head and neck cancers. The segmentation was performed by using the treatment planning system (TPS) of ISOGRAY (DOSIsoft, Cachan, France).

The images and structures were exported from TPS in DICOM (Digital Imaging and Communications in Medicine) format. All image analysis was performed with the OncoRadiomics™ research software using Matlab R2012b (OncoRadiomics.com) [6]. In total, 544 radiomics image features were defined and were divided in four groups: (I) tumor intensity, (II) shape, (III) texture and (IV) wavelet features. Detailed definitions of all features and the extraction methods were previously described [6].

Pathology

Three μ m thick sections were cut from the paraffin-embedded pretreatment biopsy specimens. HPV status was determined by p16 expression staining with immunohistochemistry (IHC). We considered p16 as positive when nuclear staining was $>75\%$ of cells. Cytoplasmic only staining was considered as negative. All assessments were performed by the same experienced pathologist, who was blinded to the clinical and follow-up data.

Statistical and bioinformatic analysis

Survival rates were calculated with the Kaplan–Meier method. Survival times were defined as the time from the beginning of radiotherapy until either the time of first event or the date that the patient was last known to be alive (censored). Events were death from any cause for OS, death or tumor progression for progression-free survival (PFS), death or locoregional recurrence for loco-regional control (LRC), and death or distant metastasis for distant metastasis-free survival (DMFS). Survival curves were compared using the log-rank test.

Hierarchical clustering was applied to reveal the grouping patterns of patients. The correlation between the radiomics feature clusters and clinicopathologic variables were analyzed by chi-square test. Both traditional prognostic factors and radiomics features underwent univariate Cox proportional hazards model (CPHM) analysis. To adjust for multiple comparisons, a false discovery rate (FDR) correction was performed for radiomics features, and the FDR-corrected *p* values were calculated using the Benjamini and Hochberg method. The radiomics features selected as candidate indicators under UVA were conducted with the principal component analysis (PCA). Variables with a *p* value <0.1 on UVA entered the multivariate Cox regression analysis (MVA). In the Cox model, continuous variables (PS, T, N, Charlson index, age and radiomics signature score) were dichotomized. To allow appropriate dichotomization, the Youden index was utilized to choose a suitable cutoff point for the radiomics signature score with optimum sensitivity and specificity according to receiver operating characteristic curve (ROC) for predicting 5-year overall survival. The robustness of prognostic performance of the radiomic signature was assessed using 10-fold cross validation by dichotomizing patients according to the survival or death status at 5 years (censored subjects within 60 months were excluded). Two-sided *P* values <0.05 were considered to indicate a significant difference. The above analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA) and R software version 3.2.4.

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