Oral cavity and oropharynx squamous cell carcinoma: CT texture analysis as an independent predictor of survival

Delphine Blanchot[1], Carole Durot[2], Xavier Dubernard[3], Jean-Claude Merol[1], Léa Fath[4], Marc Labrousse[1], Camille Boulagnon-Rombi[1], Christine Hoeffel-Fornes[2], Coralie Barbe[1], and Esteban Brenet[5]

[1]CHU Reims
[2]CHU Reims Imagerie Médicale
[3]Universite de Reims Champagne-Ardenne UFR de Medecine
[4]CHU Strasbourg
[5]Centre Hospitalier Universitaire de Reims

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Brief running title: CT texture analysis in oral cavity and oropharynx squamous cell carcinoma

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Key points:

1. Histological criteria of poor prognosis cannot be used pre-operatively in oral cavity and oropharyngeal squamous cell carcinoma (OOSCC) because a biopsy does not reflect all of the tumor heterogeneity
2. Image texture parameters analyzed on pre-operative contrast-enhanced computed tomography (CT) imaging could reflect tumor heterogeneity and could be associated with overall survival and event-free survival in these patients.
3. Texture parameters were evaluated: mean gray-level, standard deviation, kurtosis, skewness and entropy.
4. Mean gray-level of the histogram was significantly associated with overall survival at spatial scale filtration (SFF) 5 and with event-free survival at coarse scale (SSF) 6.
5. Pretreatment CT scan texture analysis mean gray-level may be associated with survival in patients with OOSCC.

Key words: Squamous cell carcinoma, Oral cavity, Oropharynx, Computer-assisted image analysis, Survival

Introduction

Squamous cell carcinoma (SCC) represent 90% of head and neck cancers (HNC), which is the fifth most common cancer worldwide. Oral and oropharyngeal squamous cell carcinoma (OOSCC) accounts for respectively 30% and 20% of HNC(1).

Histological prognostic factors are widely acknowledged currently and constitute an integral part of the therapeutic strategy. However, they are only obtainable after pathological examination of the entire resected specimen. Indeed, small sizes of preoperative biopsy samples may not allow assessment of the tumor differentiation degree, and may not accurately represent the nature of the entire tumor(2). It is therefore not

currently possible to determine histological prognostic factors preoperatively nor for patients who do not benefit from a surgical treatment.

CT texture analysis (CT-TA) has been reported to be a useful tool for preoperatively assessing survival in various types of cancers, such as oesophageal, colorectal, non-small cell lung cancers, hepatocellular carcinoma, metastatic melanoma and also to predict treatment response(3,4). CT-TA can indeed overcome the drawbacks related to visual analysis of tumor heterogeneity and quantify the heterogeneity reflecting spatial differences in tumor perfusion and proliferation(5).

In locally advanced head and neck squamous cell carcinoma (HNSCC), a recent study has reported the potential prognostic value of tumor texture features on overall survival(6).

The purpose of this retrospective study was to determine if contrast-enhanced CT- based texture analysis could constitute a new biomarker of overall survival (OS) and event-free survival (EFS) in patients suffering from OOSCC treated by surgical resection

Material and Methods

Patients

Consecutive patients who underwent tumor resection for OOSCC at our University Hospital from January 2008 to December 2016 were retrospectively selected. Among them, patients who had a cervical contrast-enhanced CT scan available within 3 months before surgery were included. Patients treated with first chemo and/or radiotherapy, with a history of HNSCC, with too small or not delineable lesion, or with exaggerated dental artifacts on the CT examination were excluded.

Patients were informed of the study objectives and could express their opposition to the use of their medical data. The database was constituted in accordance with the reference methodology MR004 of the Commission Nationale de l'Informatique et des Libertés (n°2206749, 13/09/2018) and followed the French authorities' requirements.

The following data were collected: age, gender, body mass index (BMI), alcohol and tobacco use, precise location of the tumor, HPV status, TNM staging, histological differentiation, resection status.

Every patient underwent close clinical-biological and radiological evaluation during the first 3 years after surgery. Primary and secondary endpoints were OS and EFS, respectively. OS was defined as the time from diagnosis until death from any cause. Patients alive at the end of follow up were censored at that time. EFS was defined as the time from diagnosis until recurrence; metastasis or death from any cause. Patients without recurrence, death or metastasis at the end of follow-up were censored at that time.

Image Acquisition and Analysis

All patients underwent a 64-section contrast-enhanced CT scan (Discovery HD 750; GE Healthcare) covering the cervical region to the chest. Acquisition parameters were as follows: tube voltage, 120 kVp; section collimation, 64x1.25 mm; helical pitch, 1.375; scan time per spiral, 0.7s; image reconstruction thickness, 2.5 mm.

CT-TA was performed on the pretreatment CT examination using the commercially available TexRAD software (TexRAD Ltd). An ENT-specialized radiologist blinded to all data selecteded the CT image demonstrating the lesion largest cross-sectional area. The region of interest (ROI) was manually delineated around the tumor.

CT-TA was performed in a two-step process including image filtration and histogram quantification. Spatial scale image filtration (SSF) extracted features with different texture scales, as follows: fine (SFF=2, object radius of 2 mm), medium (SFF=3-5, 3-5 mm), coarse (SFF=6, 6mm) and without filter (SFF=0) , by using a Laplacian of Gaussian spatial band-pass filter (Figure1). Quantification of the histogram distribution within the ROI allowed the extraction of five texture parameters: mean gray-level intensity, standard deviation of

the gray-level histogram distribution (SD), entropy, kurtosis, and skewness. The mean value of each texture parameters among lesions was calculated.

Statistical analysis

Quantitative variables are reported as mean ± standard deviation and qualitative data as number and percentage. The survival curves were established by the Kaplan-Meier method. Multivariate analyses were performed to identify independent predictors of OS and EFS. To take into account the correlation between the estimates of each texture parameter from the different filter values as well as the small number of events compared with the number of included covariates, multivariate L1 (least absolute shrinkage and selection operator—Lasso) penalized Cox regression models logistic regression models were built in order to select clinical and texture parameters(7). The regularization parameter was determined by using fivefold cross-validation. The Lasso method allows variable selection by shrinking down to zero coefficient weights for variables non-related to outcome. Variables with non-zero coefficients were selected as potential predictors of outcome and integrated into multivariable Cox regression analyses in order to estimate associated hazard ratios (HR) and their 95% confidence intervals (CI 95%).

For each texture parameter associated with outcome in multivariate analysis, a receiver operating characteristic (ROC) curve was constructed to identify the most relevant threshold.

A p value < 0.05 was considered statistically significant. Analyses were performed using SAS version 9.4 (SAS Inc, Cary, NC, USA) and R version 3.6 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient characteristics

A total of 42 patients, 32 men and 10 women, with 21 people in each group of oropharyngeal and oral SCC were included. The main clinical, radiological and pathological characteristics of patient are shown in Table 1.

Overall survival analysis

Median follow-up time was 34 months with 50% of global survival rate at 3 years of follow up. The Lasso penalized Cox regression analysis identified as potential predictors of OS: standard deviation (p =0.0082) at medium scale (SSF = 4), mean gray-level (p =0.0010) at medium scale (SSF = 0), mean gray-level (p =0.0312) at medium scale (SSF = 5) and age at diagnosis (p =0.0436). In multivariate Cox regression analysis, mean gray-level at medium scale (SSF = 5) and age at diagnosis were significantly associated with overall survival (HR = 1.07 [1.02; 1.12], p =0.003 and HR = 1.08 [1.03; 1.13], p =0.001, respectively) (Table 2A).

When dichotomized at the optimal threshold identified using ROC curve, mean gray-level greater than 5.89 at medium scale (SSF = 5) was significantly associated with lower survival time (HR = 3.7 [1.4; 10.2], p =0.01) (Figure 2A).

Event-free survival analysis

The Lasso penalized Cox regression analysis identified as potential predictors of EFS: standard deviation (p =0.0194) at medium scale (SSF = 4), mean gray-level (p =0.0411) at coarse scale (SSF = 6), mean gray-level (p =0.0040) at medium scale (SFF=0), mean gray-level (p =0.0180) at medium scale (SFF=3) and age at diagnosis (p =0.0732). In multivariate Cox regression analysis, mean gray-level at coarse scale (SSF = 6) (HR = 1.06 [1.02; 1.12],p =0.006), standard deviation at medium scale (SSF = 4) (HR=1.03 [1.003; 1.07], p =0.03) and age at diagnosis were significantly associated with EFS (HR = 1.11 [1.05; 1.17],p =0.002) (Table 2B).

When dichotomized at the optimal threshold identified using ROC curve, mean gray-level greater than -7.63 at coarse scale (SSF = 6) (HR = 2.4 [1.0; 5.9], p =0.06, figure 2B) and standard deviation greater than 32

at medium scale (SSF = 4) (HR = 2.6 [0.9; 7.2], $p = 0.07$, figure 2C) tended to be associated with lower survival time.

Discussion:

Our study suggests that OOSCC heterogeneity as evaluated by CT-texture analysis is an independent predictor of overall survival in patient treated by surgical resection. Indeed, pretreatment mean gray-level values were significantly associated with OS at medium texture scale (SFF=5) and significantly associated with EFS at coarse texture scale (SFF=6).

Tumors are heterogeneous both on genetic and histopathological levels with intratumoral spatial variation in the cellularity, angiogenesis, haemorrhage, and areas of necrosis. Tumors with high intratumoral heterogeneity have been shown to have a poor prognosis, which could be secondary to intrinsic aggressive biology or treatment resistance(5).

Over the past decade, texture analysis has increasingly been investigated as a method to predict survival in patients with a wide spectrum of cancers(4,8–10). In head and neck cancers, Zhang et al. (6) found entropy and skewness on CT-TA to be associated with the OS of patients with locally advanced OOSCC treated by induction chemotherapy with cisplatin, 5-fluorouracil, and docetaxel.

In the filtration-histogram approach for CT-TA, "mean" reflects the measure of uniformity of the histogram corresponding to the gray-level values within a ROI. We hypothesize that gray level uniformity of primary oral and oropharyngeal tumors may be linked with hypervascularization and thus may reflect tumor angiogenesis.

Limitations of our study include the use of a monocentric retrospective design with possible known bias. However, to reduce this bias, the evaluation of imaging and histopathology was conducted blinded and independently to each other. Moreover, patient sample is small. Many patients had to be eliminated from the study before performing CT-TA because of marked dental artifacts. The effects of metallic artifacts on CT-TA are not fully known or described; therefore, for this pilot study, we tried to collect subjects without any dental artifacts to limit this factor as a potential confounder.

Conclusion:

Our study suggests that pretreatment tumor values derived from contrast-enhanced CT-TA may help predict survival in patients with resectable OOSCC. This is an exploratory study and a larger number of patients are needed to validate the performance of the predictive model for each subsite.

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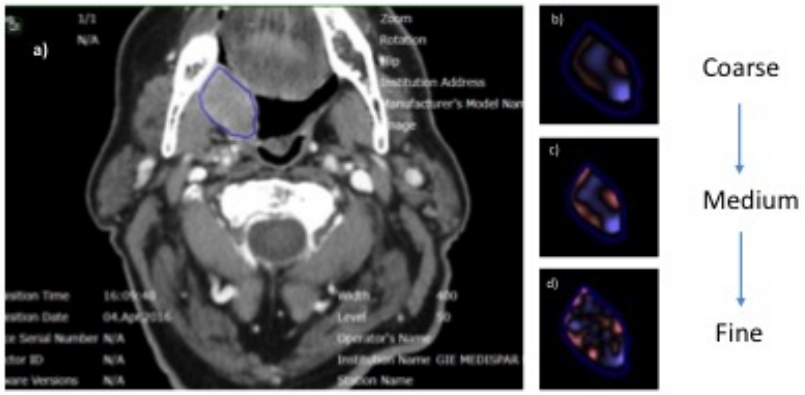

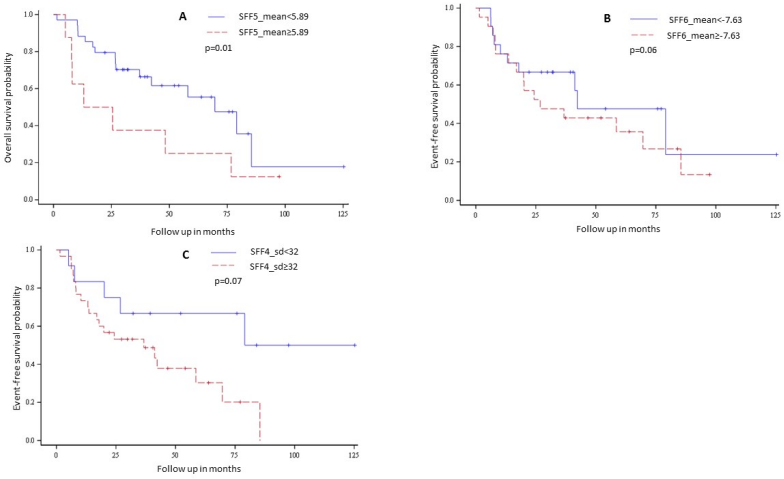

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