Supplemental Data

INTRODUCTION

In this study, a standardized uptake value (SUV) of 2.5 was taken as a cutoff for the detection of OPSCC tumor boundaries. After defining a volume of interest in the tumor, texture analysis was performed in two steps. First, the tumor voxel intensities were resampled within the segmented tumors to yield a limited range of values for reducing noise and normalizing images (*1*). The intensity of FDG uptake in the primary tumor was resampled to 4, 16, 32, and 64 different values. In the second step, the texture features were analyzed using SUV histogram analysis, normalized grey-level co-occurrence matrix (NGLCM), and neighborhood grey-tone difference matrix (NGTDM). Matrices describing textures on images were extracted from tumors, and textural features were subsequently computed using these matrices.

SUV HISTOGRAM ANALYSIS

First-order texture features were calculated using the original images. Histogram analysis was used for first-order texture features to identify the frequency distribution of PET image intensities. Maximum SUV, SUV variance, and SUV entropy were derived accordingly.

The maximum SUV denotes the maximum intensity in the tumor, whereas SUV variance is a measure of dispersion of voxel intensities from the mean tumor intensity. SUV variance was calculated as: $\Sigma\ (\mathrm{X}i-\mu)^2 / \mathrm{N}$, where X$i$ is the intensity of voxel i, μ denotes the mean tumor intensity of the tumor, and N is the total number of voxels of the tumor. SUV entropy – defined as an uncertainty measure of the intensity distribution within the tumor – was calculated as: $-\Sigma\ \mathrm{P}i\ \ln(\mathrm{P}i)$, where P$i$ indicates the probability of distinct resampled values. The intensity of the tumor was resampled to 4, 16, 32, and 64 different values. For example, the SUV entropy of 4 bins represents the sum of 4 probabilities multiplied by the natural logarithm of the probability values.

NORMALIZED GREY-LEVEL CO-OCCURRENCE MATRIX (NGLCM)

Second-order texture measures were used to assess the relationship between two neighboring voxels within the original image. After resampling the image intensities to 4, 16, 32, and 64 different values, second-order textural features were calculated using the NGLCM. The NGLCM indicates how frequently a voxel of resampled intensity i is neighbor to another voxel of intensity j; it includes the parameters of uniformity, entropy, dissimilarity, contrast, homogeneity, inverse different moment, and correlation, according to the following equations:

Uniformity	$\sum C_{ij}^{2}$
Entropy	$-\sum C_{ij} \log C_{ij}$
Dissimilarity	$\sum C_{ij} \lvert i - j \rvert$
Contrast	$\sum C_{ij}(i - j)^2$
Homogeneity	$\sum \frac{C_{ij}}{1 + \lvert i - j \rvert}$
Inverse difference moment	$\sum \frac{C_{ij}}{1 + (i - j)^2}$
Correlation	$\sum \frac{(i - \mu_x)(j - \mu_y)C_{ij}}{\sigma_x \sigma_y}$

C*ij* indicates the probability of a voxel of intensity *i* is neighbor to another voxel of intensity *j*. The three-dimensional NGLCM was applied in an orientation-invariant manner for the calculation of all parameters (*2, 3*).

NEIGHBORHOOD GREY-TONE DIFFERENCE MATRIX (NGTDM)

Higher-order parameters were calculated using neighborhood intensity difference matrices (NGTDM) (*4*) to describe the local features. The NGTDM are based on the differences between each voxel and the neighboring voxels in the adjacent image planes. Texture parameters derived from NGTDM resemble the human perception of the image. After resampling the image intensities, we calculated coarseness, contrast, busyness, complexity, and strength according to the following equations:

Coarseness $\left[\epsilon + \sum_{i=0}^{G_h} p_i s(i)\right]^{-1}$

Contrast $\left[\frac{1}{N_g(N_g-1)} \sum_{i=0}^{G_h} \sum_{j=0}^{G_h} p_i p_j (i-j)^2\right]\left[\frac{1}{n^2} \sum_{i=0}^{G_h} s(i)\right]$

Busyness $\left[\sum_{i=0}^{G_h} p_i s(i)\right] \Big/ \left[\sum_{i=0}^{G_h} \sum_{j=0}^{G_h} ip_i - jp_j\right]$

Complexity $\sum_{i=0}^{G_h} \sum_{j=0}^{G_h} \left\{(|i-j|) \big/ \left(n^2(p_i + p_j)\right)\right\}\left\{p_i s(i) + p_j s(j)\right\}$

Strength $\left[\sum_{i=0}^{G_h} \sum_{j=0}^{G_h} (p_i + p_j)(i-j)^2\right] \Big/ \left[\epsilon + \sum_{i=0}^{G_h} s(i)\right]$

Where *P*i is the probability of occurrence of a voxel of intensity *i* and s(*i*) represents the NGTDM value of intensity *i* calculated as: Σ │*i* - A*i*│. A*i* indicates the average intensity of the surrounding voxels without including the central voxel (of intensity *i*).

The most fundamental property of NGTDM is coarseness which has been associated with the human perception of image granularity. Contrast relates to the fluctuations of intensity levels of an image. A high contrast within an image indicates that voxel intensity significantly differs between neighboring voxels. Busyness correlates with the rate of changing intensity within an image. Therefore, a busy texture is characterized by rapid changes of intensity in adjacent pixels. The complexity is a sum of normalized differences between intensity values taken in pairs. Strength integrates and summarizes the concepts of busyness and coarseness. An image with a strong texture is composed by easily definable elements.

COMPUTATIONS

The computations of the textural features were performed using a homemade software package (Chang-Gung Image Texture Analysis toolbox; CGITA; http://code.google.com/p/cgita/) implemented under MATLAB 2012a (Mathworks Inc., Natick, MA, USA).

REFERENCES

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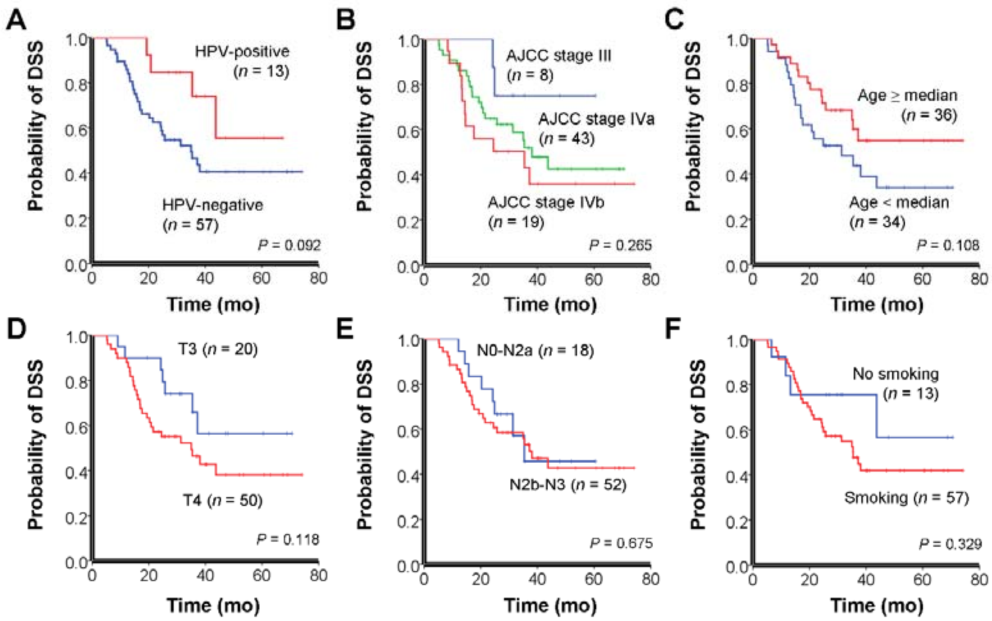
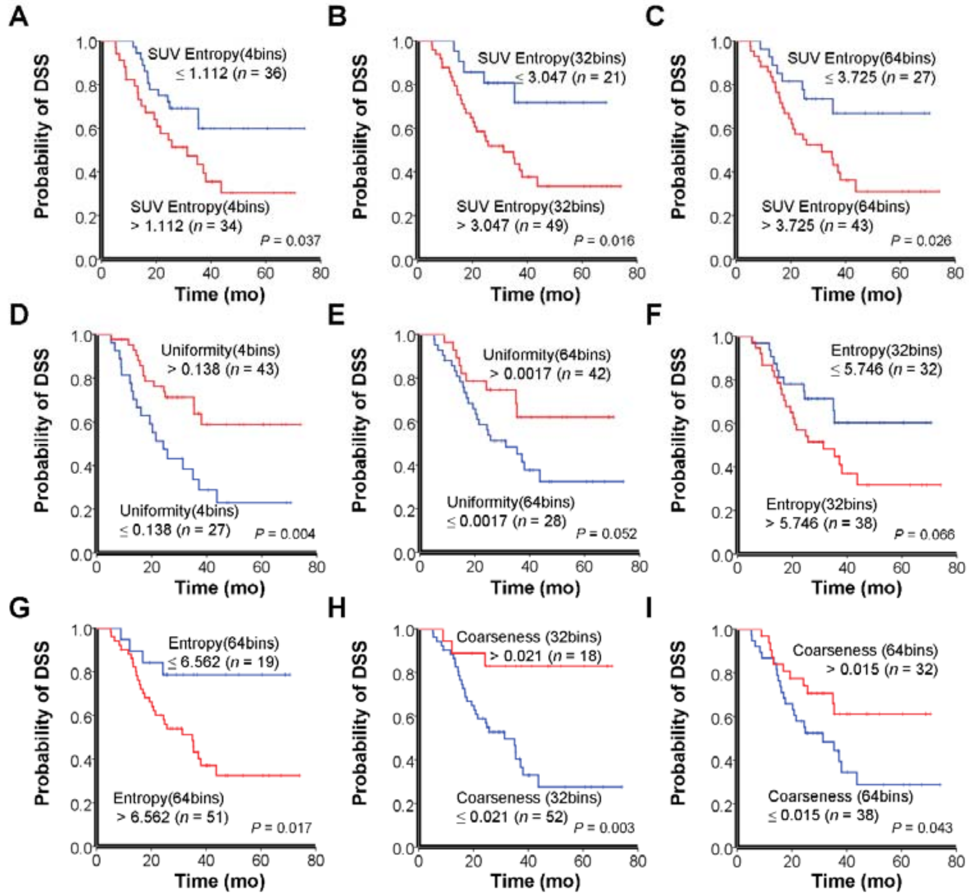


Supplemental Figure 1. Kaplan-Meier estimates of disease-specific survival (DSS) rates according to the presence of HPV infections (A), AJCC stage (B), age (C), T4 stage (D), N-stage (E), and smoking (F). The *P* values according to the log-rank test are reported in the insets.



Supplemental Figure 2. Kaplan-Meier estimates of disease-specific survival (DSS) according to different cutoffs for the ^{18}F-FDG PET texture features. The *P* values according to the log-rank test are reported in the insets.

SUPPLEMENTARY TABLE

Supplementary Table 1

Cutoff values for PET parameters

Texture features	Cutoff	AUC*	*P*
Histogram analysis			
SUV entropy (4 bins)	1.112	0.681	0.009
SUV entropy (32 bins)	3.047	0.646	0.035
SUV entropy (64 bins)	3.725	0.666	0.017
Normalized grey level co-occurrence matrix			
Uniformity (4 bins)	0.138	0.336	0.018
Uniformity (64 bins)	0.0017	0.342	0.023
Entropy (32 bins)	5.746	0.674	0.012
Entropy (64 bins)	6.562	0.681	0.009
Neighborhood grey level difference matrix			
Coarseness (32 bins)	0.021	0.359	0.043
Coarseness (64 bins)	0.015	0.362	0.047

*AUC: area under curve