Oral Oncology 49 (2013) 261–268

Contents lists available at SciVerse ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Total lesion glycolysis: A possible new prognostic parameter in oral cavity squamous cell carcinoma

Yasser G. Abd El-Hafez [a], Hosna M. Moustafa [b], Haytham F. Khalil [b], Chun-Ta Liao [c,*], Tzu-Chen Yen [d,*]

[a] Radiotherapy and Nuclear Medicine Department, South Egypt Cancer Institute, Assiut University, Egypt
[b] Department of Clinical Oncology and Nuclear Medicine, Kasr Aini Hospital, Cairo University, Egypt
[c] Department of Otorhinolaryngology, Head and Neck Surgery, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan
[d] Nuclear Medicine Department and Molecular Imaging Center, Chang Gung Memorial Hospital, Chang Gung University, Taoyuan, Taiwan

ARTICLE INFO

Article history:
Received 15 March 2012
Received in revised form 7 September 2012
Accepted 10 September 2012
Available online 1 October 2012

Keywords:
Prognosis
Oral cancer
Tumor volume
Total lesion glycolysis
Squamous cell carcinoma
Positron emission tomography computed tomography
Fluorodeoxyglucose

SUMMARY

Objectives: We sought to determine potential prognostic value of total lesion glycolysis (TLG) calculated from combined positron emission tomography/computed tomography (PET/CT) in patients with oral cavity squamous cell carcinoma (OSCC).

Materials and methods: We prospectively studied 126 patients with OSCC who underwent PET/CT before definitive treatment by radical surgery. The metabolic tumor volume (MTV) was calculated for the primary tumor according to an absolute standardized uptake value (SUV) of 3. TLG was calculated as MTV × the average SUV. The nodal SUVmax was also recorded. The median value of SUVmax and TLG were used to divide the patients into two categories (high and low). Patients were followed up until death or for at least 24 months from their surgery. Disease-free (DFS) and disease-specific survivals (DSS) were the main outcome measures.

Results: The median TLG of the primary tumor ($_T$TLG) was 71.4, and the median nodal SUVmax ($_N$SUV) was 7.5. Patients with high $_T$TLG (⩾median) had a 2-year DFS of 52% whereas the DFS was 74% for those with a low $_T$TLG ($P = 0.007$); the 2-year-DSS rates were 53% vs. 84%, respectively ($P < 0.001$). Similarly, patients with high $_N$SUVmax (⩾median) had a 2-year DFS of 42% vs. 70% for patients with a low $_N$SUVmax ($P = 0.001$); the 2-year-DSS rates were 39% vs. 78%, respectively ($P < 0.001$). In multivariate analyses, $_T$TLG, $_N$SUVmax, and pathological nodal status were independent prognostic factors for the 2-year DSS. A 3-point prognostic scoring system was formulated based on the presence or absence of the independent factors. Patients with positive neck nodes, high $_N$SUVmax, and high $_T$TLG (score 3) had a 32-fold higher risk of cancer death compared with those lacking such risk factors (2-year-DSS = 26% vs. 97%, $P < 0.001$).

Conclusion: Primary tumor TLG is an independent prognostic factor for cancer control and survival in patients with OSCC. A prognostic scoring system that includes primary tumor TLG, nodal SUVmax, and pathological neck status may be useful for risk stratification in this group of patients.

Introduction

Numerous clinical and pathological prognostic factors have been identified in patients with oral cavity squamous cell carcinoma (OSCC)[1,2]; however, the survival rate has remained substantially unchanged over the past three decades.[3] The possibility of identifying novel prognostic factors may improve risk stratification and promote the individualization of cancer treatment plans. Standardized uptake value (SUV), a semi-quantitative measure from positron emission tomography (PET), has been shown to be an independent prognostic factor in several malignancies, including head and neck cancer.[4–6] However, SUVmax suffers from a number of limitations[7] as it reflects a single pixel value,[8] which may not be entirely representative of the actual tumor heterogeneity. The calculation of total lesion glycolysis (TLG) may overcome this potential issue. TLG on PET is calculated by multiplying the SUV by the metabolic tumor volume (MTV).[9] Although the potential clinical value of TLG has been investigated in many cancers, its routine use has been hampered by the delineation method used to

* Corresponding authors. Addresses: Department of Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital, Chang Gung University, 5 Fu-Hsin Street, Gweishan, Taoyuan 333, Taiwan. Tel.: +886 3 328 1200x2744; fax: +886 3 211 0052 (T.-C. Yen), Department of Otorhinolaryngology, Head and Neck Surgery, Head and Neck Oncology Group, Chang Gung Memorial Hospital, Chang Gung University, 5 Fu-Hsin Street, Gweishan, Taoyuan 333, Taiwan. Tel.: +886 3 328 1200x8466; fax: +886 3 211 0052 (C.-T. Liao).

E-mail addresses: liaoct@adm.cgmh.org.tw (C.-T. Liao), yen1110@adm.cgmh.org.tw (T.-C. Yen).

1368-8375/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.oraloncology.2012.09.005

calculate the tumor volume. This may be especially difficult for fuzzy PET images in the absence of a real gold standard. Previous studies have shown an association of TLG with the clinical outcomes of patients with oropharyngeal tumors[10,11]; however, data on its prognostic role in patients with oral cavity cancer are scanty. Therefore, the aim of this study was to assess the potential prognostic role of TLG in patients with OSCC.

Materials and methods

Patients

The institutional review board for Human Research of the Chang Gung Memorial Hospital (Taoyuan, Taiwan) approved the study. All patients provided written informed consent. The common eligibility criteria were a histological diagnosis of OSCC; previously untreated tumor scheduled for radical surgery; no other suspected distant metastatic lesions detected by imaging (including magnetic resonance imaging/computed tomography and FDG-PET); and a willingness to undergo computed tomography-guided biopsy or surgical exploration, if necessary. The exclusion criteria included the presence of a fasting blood glucose higher than 200 mg/dL, a previous diagnosis of another malignancy, and/or the refusal or inability to receive definitive treatment for the disease.

All of the study participants underwent an extensive preoperative evaluation, including FDG-PET, within 2 weeks before surgery. This included medical history and complete physical examination, flexible fiberoptic pharyngoscopy, complete blood count and routine blood biochemistry panel, computed tomography or magnetic resonance imaging scans of the head and neck, chest radiography, bone scan, and liver ultrasonography. Patient staging was performed according to the 1997 American Joint Committee on Cancer (AJCC), 5th edition, staging criteria.[12]

PET/CT imaging

Patients were asked to fast for at least 6 h before the start of the PET study. Serum glucose level was determined at the time of intravenous injection of 370 MBq (10 mCi) of ^{18}F-FDG. PET/CT images were acquired using a combined PET/CT scanner (Discovery ST 16, GE Healthcare) according to the previously published standardized protocol.[13] The data were transferred via the Digital Imaging and Communications in Medicine (DICOM) protocol to a processing workstation (Siemens Syngo MI.PET/CT 2010A). The primary tumor volume was measured using a semi-automatic contouring software (Siemens TrueD, Siemens Medical Solutions). The tumor boundaries were identified and drawn largely enough to include all the tumor volume and carefully enough to exclude areas of physiological uptake. An isocontour connecting the outlines of the volume of interest (VOI) was set using different approaches, adopting a fixed threshold fraction of the peak FDG uptake in the tumor. The threshold level was selected using different cutoff values for the SUV (i.e. 2.5, 3.0, 3.5 and 4.0). In addition, different fixed percentages of the maximum SUV were used (i.e. 30%, 40%, 50%, 60% and 70% of the SUVmax).[14,15] Of the nine different delineation methods, only one was chosen to calculate the MTV and TLG. The choice was based on the best correlation observed between the maximum axial tumor diameters obtained from the generated volumes using the different approaches and the maximum axial tumor diameters obtained from the histopathological examination. To minimize the partial volume effect (PVE) of the primary tumor volume, patients with T1 disease were excluded.[16]

Total lesion glycolysis was calculated by multiplying the selected PET volume by the average SUV within that volume:

$$\text{TLG} = (\text{MTV}) \times (\text{Average SUV})$$

Surgery and adjuvant therapy

The primary tumors were excised with $\geqslant 1$ cm safety margins (both peripheral and deep margins). Classic radical or modified neck dissections (levels I–V) were performed in patients with clinically positive nodal disease. Supra-omohyoid NDs (levels I–III) were performed in clinically node-negative patients. Bilateral NDs were performed if the primary tumor reached or crossed the midline sagittal plane of the oral cavity.

The tumor margins were cryosectioned. If a margin was positive, additional tissue was excised and cryosectioned to ensure that the margin was free of tumor. The surgical defects were repaired with primary closure or reconstructed immediately by plastic surgeons using free or local flaps.

Postoperative radiotherapy (RT) was performed in patients with stage pT4 tumors, pathologic positive lymph nodes, or pathologically close margins ($\leqslant$4 mm). RT was scheduled within 4–8 weeks after surgery. The prescribed dose was 1.8–2 Gy/fraction daily, given 5 d/wk. The total radiation dose was 66 Gy for patients with multiple positive neck lymph nodes and/or extracapsular spread (ECS) and 60 Gy for the remaining patients. Concomitant chemoradiotherapy (CCRT) with cisplatin-based agents was administered to patients with ECS or metastases in multiple lymph nodes.[17]

Follow-up protocol

All of the patients were followed up until death or for at least 24 months from the date of surgery. The initial tumor response was evaluated with CT or MRI in combination with a clinical physical examination 2–3 months after the completion of the definitive treatment. Selected patients received a ^{18}F-FDG PET scan. During the follow-up, neck ultrasound, serial images, and clinical physical examinations were arranged. In the presence of visible neck nodes or lesions of the mucosa, biopsies were recommended.

Statistical analysis

Descriptive statistics were summarized using frequencies, percentages, means ± standard deviations, or medians and ranges, as appropriate.

Because of their skewed distribution, SUVmax and TLG values were compared in patients with different clinicopathological characteristics using the Mann–Whitney *U* test (for two-group comparison) or the Kruskal–Wallis test (for three or more subgroups). The median values of SUVmax, average SUV, MTV and TLG were used as cut-offs to divide the patients into two groups (i.e., more than or equal to the median vs. lower than the median).

The primary study endpoint was cancer-specific mortality. Disease-free survival (DFS) and disease-specific survival (DSS) were computed using the Kaplan–Meier method starting from the date of surgery to the date of confirmed event or the last follow-up (for censored patients). The events for the calculation of DFS included the development of local/regional recurrence or distant metastases. Cancer-related mortality was used for the calculation of the DSS. Univariate analysis of DFS and DSS was performed using the Kaplan–Meier method and compared among different subgroups using the log-rank test. Variables with P value < 0.05 were further selected for multivariable analyses (MVA), which was performed using the Cox proportional hazards model with a forward selection procedure. The variables which showed significance in the MVA for the prediction of DSS were used to formulate a risk score based on the presence or absence of the independent factors. In all analyses, P values < 0.05 (two-tailed) were considered statistically significant.