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Prediction of distant metastasis and survival in adenoid cystic carcinoma using quantitative ^{18}F-FDG PET/CT measurements

Won Sub Lim[a,1], Jungsu S. Oh[b,1], Jong-Lyel Roh[a,*], Jae Seung Kim[b], Soo-Jong Kim[b], Seung-Ho Choi[a], Soon Yuhl Nam[a], Sang Yoon Kim[a]

[a] Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea
[b] Department of Nuclear Medicine, Asan Medical Center, University of Ulsan College of Medicine, Seoul, Republic of Korea

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ABSTRACT

Objectives: Adenoid cystic carcinoma (AdCC) in the salivary gland shows a high rate of distant metastasis, which is related to the resulting poor prognosis. We therefore examined the role of pretreatment ^{18}F-FDG PET/CT for prediction of distant metastasis, recurrence/progression, and survival in AdCC.

Methods: This study included 52 patients who underwent pretreatment ^{18}F-FDG PET/CT scanning and subsequent treatments for AdCC. Maximum, mean, and peak standardized uptake value (SUV_{max}, SUV_{mean}, and SUV_{peak}), metabolic tumor volume (MTV), and total lesion glycolysis (TLG) were measured on ^{18}F-FDG PET/CT. Univariate and multivariate Cox proportional hazards regression analyses were used to identify associations between the quantitative measurements of ^{18}F-FDG PET, and progression-free survival (PFS), distant metastasis-free survival (DMFS), and disease-specific survival (DSS).

Results: Distant metastases were found in 20 (39%) patients: 6 (12%) at initial diagnosis and 14 (27%) during the median follow-up of 72 months after treatment. Univariate analyses showed that all the ^{18}F-FDG PET parameters of SUV_{max}, SUV_{mean}, SUV_{peak}, MTV, and TLG were significantly associated with overall PFS, DMFS, and OS (all $P < .05$). After controlling for clinicopathological variables, SUV_{max} remained an independent factor predictive of PFS ($P = .001$), while MTV and TLG were independent predictors of DMFS ($P = .009$) and DSS ($P = .017$). Patients with MTV > 14.8 mL showed a 5.9-fold higher risk of distant metastasis and a 4.2-fold higher risk of disease-specific death than those with a lower MTV.

Conclusions: Quantitative measurements using ^{18}F-FDG PET/CT are useful for predicting tumor progression, distant metastasis, and survival in patients with AdCC.

Introduction

Salivary gland cancer is a rare disease that accounts for approximately 5% of all head and neck cancers and 0.3% of all human cancers [1–3]. Salivary gland carcinoma arises in various regions of the major and minor salivary glands, presenting at least 24 different histological subtypes with different clinical features of metastasis and recurrence [4,5]. Distant metastases are relatively common in salivary gland carcinoma [6], and may be present at initial presentation or may emerge during the post-treatment period. Metastasis to a distant site is an important independent variable predictive of survival after treatment for salivary gland cancer [7].

Of the different histological subtypes, salivary duct carcinoma and adenoid cystic carcinoma (AdCC) show high rates of distant metastasis, but very different clinical behaviors in terms of metastasis. Salivary duct carcinoma is associated with an aggressive and rapid progression, frequent recurrence, and poor survival, with early development of metastasis and recurrence [8]. By contrast, AdCC exhibits a unique clinical behavior, with a tendency towards distant metastasis and late recurrence up to 30 years after initial treatment [9,10]. Distant metastasis impacts the survival of AdCC patients, with a gradual decrease in survival beyond 10 years, indicating the necessity of long-term surveillance after treatment for AdCC [11,12]. Therefore, there is an urgent need to investigate the risk factors associated with distant metastasis and recurrence, to facilitate the prediction and early identification of at-risk patients.

^{18}F-FDG PET/CT has been used as an important diagnostic and prognostic tool for head and neck cancers, including salivary gland

* Corresponding author at: Department of Otolaryngology, Asan Medical Center, University of Ulsan College of Medicine, 88 Olympic-ro 43-gil, Songpa-gu, Seoul 05505, Republic of Korea.
E-mail address: rohjl@amc.seoul.kr (J.-L. Roh).
[1] The first two authors contributed equally to this paper.

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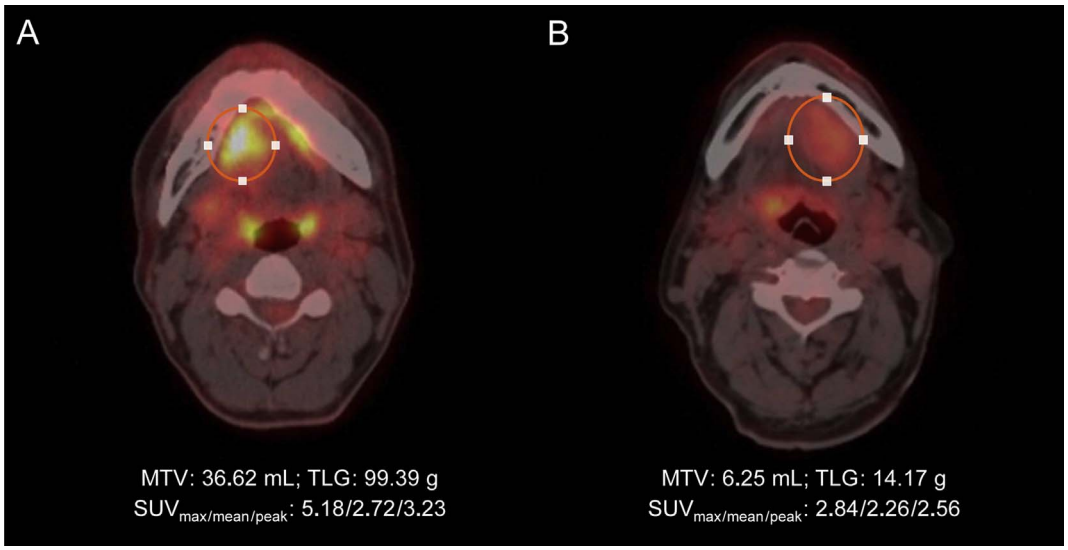

Fig. 1. Measurement of standardized uptake value (SUV), metabolic tumor volume (MTV), and total lesion glycolysis (TLG). The region of interest (circled) was set to include the adenoid cystic carcinoma with metabolic activity, and the software automatically calculated the SUV_{max}, SUV_{mean}, SUV_{peak}, and MTV. Patient A (62-year-old man) had an early distant metastasis at 5 months, while patient B (65-year-old man) had been disease-free for 124 months since treatment for adenoid cystic carcinoma arising in the sublingual gland.

carcinoma [13–16]. ^{18}F-FDG PET or PET/CT is more sensitive than CT alone for detecting metastatic diseases of the neck and distant sites, and for diagnosing post-treatment recurrence [13]. However, the prognostic role of quantitative measurements of ^{18}F-FDG PET/CT scans has rarely been reported in terms of the prediction of distant metastasis in AdCC of the head and neck. Recent reports show that maximum standardized uptake value (SUV_{max}) measured on pretreatment ^{18}F-FDG PET/CT scans can predict distant metastasis in head and neck AdCC [17,18]. Moreover, volumetric PET parameters, e.g., metabolic tumor volume (MTV) and total lesion glycolysis (TLG), have emerged as being potentially better predictors of treatment [19,20]. However, these studies mostly enrolled patients with head and neck squamous cell carcinoma. Therefore, we hypothesized that quantitative measurements on pretreatment ^{18}F-FDG PET/CT could predict distant metastasis and prognosis in AdCC. This study therefore examined the role of quantitative ^{18}F-FDG PET/CT measurements for the prediction of distant metastasis and survival in head and neck AdCC patients.

Methods

Patients

Using the electronic hospital medical record system, patients who were diagnosed with pathologically proven AdCC between 2005 and 2014 were reviewed. The inclusion criteria were patients who underwent pretreatment whole body ^{18}F-FDG PET/CT and subsequent surgical or non-surgical treatment for previously untreated AdCC of the head and neck. The exclusion criteria were recurrent disease at presentation ($n = 6$), lack of available ^{18}F-FDG PET/CT imaging data ($n = 33$), a previous history of head and neck cancer or other major second cancer ($n = 2$), and early loss to follow-up of < 2 years after treatment ($n = 4$). Fifty-two patients were included in the final analyses of this study. Tumors at presentation were staged using the tumor-node-metastasis (TNM) system according to the American Joint Committee on Cancer Staging manual (7th ed. 2010) [21]. This study was approved by the institutional review board of our hospital, and the requirement for informed consent from each patient was waived.

Patients with local or locoregional diseases commonly underwent complete extirpation of the tumors. Modified neck dissection was performed in patients with clinical cervical lymph node involvement. Patients with adverse pathological features, e.g., a positive resection margin, nodal positivity, perineural invasion, and lymphovascular invasion [22], that were defined by surgical pathology, underwent postoperative radiotherapy at a median dose of 61 Gy (range, 57–70 Gy) delivered in single daily fractions of 1.8 or 2.0 Gy for 5 days/week for 5–8 weeks. Chemotherapy was performed in some patients with distant metastases, initially in combination with radiotherapy and then continuing alone afterwards. All study patients underwent careful examinations at every visit to the clinic, with visits being scheduled for every 1–3 months during the first year, every 2–4 months during the second year, every 4–6 months during the third, fourth, and fifth years, and annually thereafter [23]. Any recurrent or new lesions suspected of malignancy were imaged with CT/MRI and/or ^{18}F-FDG PET/CT scanning, and were then biopsied for tissue confirmation.

Imaging analysis

The study patients underwent ^{18}F-FDG PET/CT evaluations on a variety of different PET/CT equipment, including Biograph Sensation 16/TruePoint 40 Siemens scanners (Siemens Medical Systems, Knoxville, TN, USA), and Discovery STE 8, Discovery 690, and Discovery 710 GE scanners (GE Healthcare, Milwaukee, WI, USA). The patients fasted for at least 6 h to ensure a serum glucose concentration of < 150 mg/dL (range, 63–145 mg/dL) prior to an intravenous injection of ^{18}F-FDG (370–650 MBq), which was followed by the PET scanning. The techniques used for image reconstruction and equalization of the SUVs from different PET scans followed those reported in a previous study [24]. Harmonization of the SUVs from the multiple PET systems was performed using previously reported standard methods [25,26]. ^{18}F-FDG-PET activity was determined by calculating the SUV from the decay-corrected activity in the tissue divided by the injected dose of ^{18}F-FDG per lean body mass of the patient. SUV values were obtained for volumes of interest (VOIs) placed over primary tumors visible on the PET images (Fig. 1). Intensity values were automatically converted to SUVs, and SUV_{mean}, SUV_{max}, SUV_{peak}, MTV, and TLG were measured for each patient. For MTV calculations, the contouring margins of the primary tumor were delineated using the SUV 2.0 isocontour. TLG was calculated as MTV $\times$ SUV_{mean}.

Statistical analysis

Distant metastasis-free survival (DMFS) was the primary endpoint of this study. Progression-free survival (PFS) and disease-specific survival (DSS) were secondary endpoints. DMFS and PFS were calculated from