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Validation of metabolic tumor volume as a prognostic factor for oral cavity squamous cell carcinoma treated with primary surgery ☆

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SUMMARY

Background: Despite the promise of metabolic tumor volume (MTV) as a risk-stratifying marker, the retrospective design of the initial study limits its generalizability. Therefore, this study sought to validate MTV as a prognostic factor for oral cavity squamous cell carcinoma (OCSCC) treated with primary surgery within an independent data set.

Methods: The validation data set consisted of 42 patients diagnosed with OCSCC between 2008 and 2012. The original cohort consisted of 80 patients. MTV and SUVmax were calculated for the primary tumor and nodal metastasis separately, as well as combined. Before statistical analysis, MTV and SUVmax values were divided into intertertile thirds to allow for intergroup survival analysis. Validation analysis was conducted on the validation data set alone. Data from both cohorts were then combined ($n = 122$) to increase statistical power.

Results: An increase in combined MTV of 17.5 cm^3 was associated with statistically significant increase in risk of disease recurrence (HR = 19.2, $p < 0.001$) and death (HR = 9.2, $p < 0.05$). Combined SUVmax failed to predict overall (HR = 1.0, $p > 0.05$) and disease-free survival (HR = 1.0, $p > 0.05$). Increase in the MTV of the primary tumor was associated with an increase in the risk of disease recurrence (HR = 21.7, $p = 0.0001$) and risk of death (HR = 7.0, $p = 0.0001$), while increase in the MTV of the locoregional neck metastasis was not ($p > 0.05$). An MTV cutoff value of greater than 10.2 cm^3 was found to significantly affect survival.

Conclusion: Due to the reproducibility of MTV findings, this study validates MTV as an independent prognostic factor for OCSCC treated with primary surgery.

Introduction

Accounting for over 20% of all cases in North America, oral cavity squamous cell carcinoma (OCSCC) is the most common site of occurrence for head and neck mucosal cancers (HNC) [1]. Successful treatment and better prognosis has traditionally depended on tumor staging, local regional tumor extension, anatomical tumor site, histotype, lymph node involvement and locoregional disease control [2–5]. Recent developments in tumor and protein expression biomarkers have brought about the possibility of patient centered treatment options by using biomarkers to stratify patients according to risk of disease progression in order to improve survival benefits for at risk patient populations [3,4].

Pre-treatment ^{18}F-fluorodeoxydeglucose positron emission tomography with computed tomography (PET-CT) has a unique ability to systematically measure tumor burden and therefore yielded possible risk-stratifying biomarker including metabolic tumor volume (MTV) [3,4,6–9]. Derived as the product of maximum standardized uptake value (SUV_{max}) and tumor volume, MTV has been shown previously within our institution to be an independent prognostic factor for OCSCC patients treated with primary surgery [10]. Although our original study demonstrated promise for MTV as a risk-stratifying biomarker, the retrospective study design limited its generalizability. Therefore, a validation study utilizing an separate interrogation cohort of patients

☆ NB: The corresponding author has full access to the data in this study and takes responsibility for the integrity of the data and accuracy of the data analysis.

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within a different geographic area treated at the same time frame as the previous study is required to allow its use within a wide OCSCC population. The main objective of this study was then to validate the prognostic utility of MTV in OCSCC patients treated with primary surgery within an independent interrogation cohort of patients. We also sought to determine whether the primary tumor or nodal tumor MTV drives the relationship with the outcome.

Methods

Ethics approval was granted by the University of Alberta's Health Research Ethics Board (HREB PRO:000032457) and the Alberta Cancer Board.

Patients

Inclusion criteria were defined as:

1. Biopsy-proven OCSCC.
2. Treatment in Alberta with curative intent
3. Residents of Alberta > 18 years of age
4. PET-CT Scans prior to curative treatment

Exclusion criteria were defined as:

1. Previous HNC with or without treatment
2. Refusal of prescribed treatment
3. Treatment with palliative intent
4. Incomplete data sets from chart review

Our original data set analysis included 80 patients whom we previously studied [10]. The validation cohort consisted of 42 patients accrued at the same time frame as the original dataset but treated at a different tertiary cancer center. The complete cohort combined the original and validation dataset ($n = 122$).

Data collection

The original data set consisted of all patients diagnosed with an OCSCC within the North and Edmonton Health Zones in Alberta between January 1, 2008 and January 1, 2012. The validation data set consisted of all patients diagnosed with an OCSCC in the Central, Calgary, and South Health Zones within Alberta between January 1, 2008 and January 1, 2012. Both the validations as well as the original cohorts of patients were identified within the Alberta Cancer Registry (ACR) first by a data analyst. The ACR, established in 1942, is a population-based registry that records and maintains data of all new cancer cases, their treatments, and resulting deaths occurring in the province. The ACR is operated by Alberta Health Services Cancer Care and follows patients longitudinally and prospectively [11].

Demographic, survival and clinicopathologic data were extracted from the ACR database. A physical review of outpatient, inpatient, and cancer clinic records was undertaken to confirm data accuracy and extract relevant patient, tumor, treatment, follow-up, survival data, as well as Eastern Cooperative Oncology Group (ECOG) performance scores [12]. Charlson Comorbidity Index (CCI) scores, which were not included in the ACR database, were calculated using relevant comorbidities taken from individual chart review [13]. Date of diagnosis was defined as the date of pathologically confirmed OCSCC.

Staging

Staging of the tumors was clinical and according to the seventh edition of the American Joint Committee on Cancer (AJCC) TNM staging manual [14].

Treatment

All patients underwent curative surgical resection consisting of tumor ablation with variations of primary closure, locoregional or free tissue transfer reconstruction, and uni- or bilateral neck dissection. Patients receiving radiation therapy (RT) or combined chemoradiation therapy (CRT) for distant metastases or palliation were not included. S-RT patients underwent surgical resection and adjuvant RT within 6–8 weeks post-operatively. Total adjuvant RT doses ranged from 6000 to 6600 Gy given at 2 Gy per fraction. S-CRT patients received surgical resection followed by adjuvant CRT within 6–8 weeks of their operation. Single agent cisplatin or carboplatin based CRT protocols were used exclusively for all patients.

PET-CT imaging protocol

All patients were scanned using a Gemini TF 16-slice PET-CT scanner system (Philips Healthcare, Andover, MA). Patients were fasted a minimum of 4 h before imaging (typically from midnight the night before). ^{18}F-fluorodeoxyglucose (FDG) was injected intravenously at a dose of 5.18 MBq/kg. A 60-min uptake period was waited prior to imaging.

PET imaging

With the patient in a supine position, PET scans were acquired in two separate acquisitions. Initially a scan was performed from the top of the shoulders to the mid-thigh level with the arms elevated. Scan times of 1 min per bed acquisition were used for patients weighing less than 100 kg and 2 min for patients with a weight of 100 kg or greater. A second PET scan was performed from the mid brain level to the carina with the arms down at an acquisition time of 2 min per bed position.

CT imaging

After each PET images acquisition a corresponding CT scan was performed for both anatomic assessment and attenuation correction. This was typically performed with the administration of IV contrast. After the initial PET, 100 mL of intravenous contrast (Omnipaque 300, GE Healthcare, Buckinghamshire, UK) was injected at a rate of 3.5 mL/s followed by 25 mL of saline at 3.0 mL/s. A helical CT acquisition was obtained from the top of the shoulders to the mid-thigh level using dose modulation with a maximum 250 mAs, 120 kVp, and a contrast delay of 28 s. After the second PET acquisition a second IV contrast bolus of 40 mL at 1 mL/s followed by 10 mL at 2.5 mL/s followed by 25 mL saline at 2 mL/s was administered. A second helical CT acquisition was then performed from the mid-brain to the carina using dose modulation with a maximum 350 mAs, 120 kVp, and 50 s contrast delay.

Image reconstruction

The PET images were reconstructed using vendor supplied ASTONISH time-of-flight iterative reconstruction with CT-based attenuation correction (Philips Healthcare, Andover, MA). The CT images through the neck were reconstructed for display with 1 mm slice thickness at 1 mm intervals. The CT images through