CORRELATION BETWEEN STANDARDIZED UPTAKE VALUE AND HISTOPATHOLOGY OF OESOPHAGEAL CARCINOMA: A SINGLE CENTER ANALYSIS

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Abstract:

Aim: To evaluate the correlation between oesophageal cancer histopathology and the Standardized Uptake Value (SUV) of the primary lesion on Positron Emission Tomography/Computed Tomography (PET/CT) scan.

Methods: We reviewed clinical data of consecutive newly diagnosed oesophageal cancer patients who underwent positron emission tomography with 2-deoxy-2-[fluorine-18]fluoro- D-glucose integrated with computed tomography (¹⁸F-FDG PET/CT) between September 2009 and July 2014.

Results: A total of 289 baseline scans were performed in this 55 month period. Of these, 171 (59%) were males. The mean age was 52.6 years (standard deviation SD +/- 12.4 years). On histological review, 214 were squamous cell carcinomas (SCCa) and 75 were adenocarcinomas. Of the SCCa, 15.9% were poorly differentiated, 70.6% were moderately differentiated, and 13.5% were well differentiated. Of the adenocarcinomas, 20% were poorly differentiated, 45% were moderately differentiated, 28% were well differentiated and signet ring cell were 7%. Mean SUVmax for SCCa was 12.6 +/- 5.14 and 10.5 +/- 6.2 for adenocarcinomas. In bivariate analysis, being a female was associated with a higher SUV in the primary lesion by 1.66 units (p=0.011) compared to males. Adenocarcinomas were associated with a lower SUV by 2.14 units (p=0.004) compared to SCCa. In bivariate analysis, no significant correlation was found between the T stage of the tumour and the SUVmax of the primary tumour (p=0.339). Multivariate analyses showed no association of the SUV of the primary oesophageal tumour with the degree of differentiation of either SCCa or adenocarcinoma. There was no correlation between the SUVmax of the primary lesion and the presence or activity level of a metastatic focus, whether visceral or nodal.

Conclusion: At our centre three fourths of patients with oesophageal carcinoma had squamous cell carcinoma on histology. Adenocarcinoma is associated with a lower SUV compared to SCCa. There is no association between the SUVmax and degree of differentiation of the primary oesophageal cancer.

Key Words: oesophageal squamous cell carcinoma, oesophageal adenocarcinoma, PET-CT, FDG, SUV

Introduction:

Oesophageal cancer is the eighth most common cancer worldwide, with nearly 456,000 new cases diagnosed in 2012 (3% of the total).¹ It is a leading cause of cancer mortality among men. The incidence ranges from 2.5 to 5.0 for men and 1.5 to 2.5 for women per 100,000 population. It has a relatively poor prognosis with a 5-year survival of 6% - 11%.

Worldwide, SCCa is the most common type of cancer of the oesophagus, although adenocarcinoma is more prevalent in the West. Similarly, in Pakistan, SCCa is the most frequent histology.² Various factors
including smoking, poor oral health, low fresh fruit and vegetable intake and the patient’s socioeconomic status have been found to influence the histopathological type of oesophageal cancer. In the 1960’s and 1970’s, the 5 year survival of patients with oesophageal cancer was only about 5%. Currently, nearly 20% of patients survive at least 5 years after the diagnosis of oesophageal cancer. In hopes of further improving survival, it is important to understand the metabolic signature of this cancer and to evaluate the correlation between the histology and the level of FDG uptake.

Methods:

This study was carried out in the Department of Nuclear Medicine at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH&RC), a 189-bed cancer specialist centre in Lahore, Pakistan. We reviewed the medical records of all gastroesophageal cancer patients who were referred to our department for a baseline staging PET/CT scan using 18F FDG during a period of 55 months from September 2009 to July 2014. We included in the study all patients who had a proven histopathology of primary oesophageal carcinoma. This study was approved by the Institutional Review Board at SKMCH&RC.

Pathology:

All histopathological specimens were reviewed by experienced pathologists using standard techniques. Immunohistochemical staining was performed when appropriate. The pathological stage was assessed using the TNM international staging system. Each specimen was classified based on glandular formation in adenocarcinoma and keratin pearl formation for squamous cell carcinoma and were also categorized according to differentiation.

Imaging:

Imaging was performed on a dedicated Phillips Gemini TOF PET/CT scanner. Patients were asked to fast for at least 4 hours prior to the scan and then received a dose of 300 MBq (0.21 mCi/kg body weight) of 18F-FDG intravenously. Uptake period in a quiet room was 60 minutes. Thereafter images were acquired from the base of the skull to the mid-thigh with 3 minute acquisition for each of 8-9 bed positions. If skeletal metastases were found, additional images to include the limbs were obtained. A contrast-enhanced CT scan (CeCT) with a voltage of 70 – 140 kVp and tube current of 80mA was used for attenuation correction and lesion localization. Dual interpretation of scans was performed by certified radiologists and nuclear medicine physicians. Maximum SUV was determined by drawing regions of interest on attenuation corrected FDG images around the primary tumour and metastatic lesions.

An iodinated CeCT was obtained for attenuation correction of PET images as well as for anatomical localization. Iodinated contrast was not used if there was a documented history of contrast allergy in the past or if serum creatinine was above 1.4 mg/dl. Patients were encouraged to void before scanning, and 8 oz of water were given to distend the stomach just before imaging.

We evaluated the correlation of SUV with basic patient demographics, histopathology and the degree of differentiation. In addition, the SUV of the primary tumour site was compared to the presence or absence of metastases and to the level of uptake in metastatic lesions, whether nodal or visceral.

Results:

Patient Characteristics:

Of the 289 patients, 171 (59%) were males and 118 (41%) were females (table 1). The mean age was 52.6 years (standard deviation (SD) +/− 12.4 years). Histopathological review of the primary oesophageal tumour showed that 214 (74.5%) were squamous cell carcinomas and 75 (25.5%) were adenocarcinomas.
Table 1: Gender based distribution of histopathological categories (n = 289)

<table>
<thead>
<tr>
<th>Gender</th>
<th>n (%)</th>
<th>Adenocarcinoma n (%)</th>
<th>Squamous Cell Ca n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>118 (41%)</td>
<td>12 (10%)</td>
<td>106 (90%)</td>
</tr>
<tr>
<td>Male</td>
<td>171 (59%)</td>
<td>62 (37%)</td>
<td>108 (63%)</td>
</tr>
</tbody>
</table>

Table 2: Histopathological classification and average SUV of oesophageal carcinoma (n = 289)

<table>
<thead>
<tr>
<th>Type</th>
<th>n (%)</th>
<th>Differentiation</th>
<th>n (%)</th>
<th>Mean SUV ±S.D</th>
</tr>
</thead>
<tbody>
<tr>
<td>Squamous Cell Carcinoma</td>
<td>214 (74.5%)</td>
<td>Well</td>
<td>29 (13.5%)</td>
<td>13.4 ±4.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>151 (70.6%)</td>
<td>12.6 ± 5.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor</td>
<td>34 (15.9%)</td>
<td>12.5 ± 6.1</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>75 (25.5%)</td>
<td>Well</td>
<td>21 (30%)</td>
<td>9.6 ± 6.9</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Moderate</td>
<td>34 (48.6%)</td>
<td>11.2 ± 5.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Poor</td>
<td>15 (21.4%)</td>
<td>10.3 ± 6.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Signet Ring Cell</td>
<td>5 (7%)</td>
<td>4.5 ± 1.8</td>
</tr>
</tbody>
</table>

Of the SCCa, 34 (15.9%) were poorly differentiated, 151 (70.6%) were moderately differentiated, and 34 (15.9%) were well differentiated. Of the adenocarcinomas, 15 (21.4%) were poorly differentiated, 34 (48.6%) were moderately differentiated, and 21 (30%) were well differentiated (table 2).

The mean SUVmax for SCCa was 12.6 ±5.14 and 10.5 ±6.2 for adenocarcinomas. For SCCa the mean SUVmax on baseline scanning for poorly-, moderately-, and well-differentiated carcinomas was 12.5 (SD: 5.6), 12.6 (SD: 5.1), and 13.4 (SD: 4.1) respectively. For adenocarcinomas, the corresponding mean SUV max were 10.3 (SD: 6.2), 11.2 (SD: 5.7), and 9.6 (SD: 6.9) respectively.

Based on the T stage of the primary tumour; 0.3% were T1, 0.7% T2, 53.6% T3 and 45.3% T4 tumours. (Table 3)

In bivariate analysis, being a female was associated with a higher SUV in the primary lesion by 1.66 units (p=0.011) compared to males. Adenocarcinomas were associated with a lower SUV by 2.14 units (p=0.004) compared to SCCa. Bivariate analysis showed no significant correlation between the T stage of the tumour and the SUVmax of the primary tumour mass (p=0.339).

Table 3: T stage distribution (n = 289)

<table>
<thead>
<tr>
<th>T Stage</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1</td>
<td>1 (0.3%)</td>
</tr>
<tr>
<td>T2</td>
<td>2 (0.7%)</td>
</tr>
<tr>
<td>T3</td>
<td>155 (53.6%)</td>
</tr>
<tr>
<td>T4</td>
<td>131 (45.3%)</td>
</tr>
</tbody>
</table>

In multivariate analyses, SUV of the primary oesophageal tumour was not associated with age (p=0.06), gender (p=0.54), or the degree of differentiation of the primary tumour (p=0.76). In addition, there was no statistically significant correlation between the SUVmax of the primary lesion and the presence or activity level of a metastatic focus, whether visceral or nodal (p=0.45).

Discussion:

Although survival from oesophageal cancer is improving, it still remains fairly poor. The initial tumour stage depends on the depth of tumour invasion, involvement of regional lymph nodes, and
the presence or absence of metastatic disease.\textsuperscript{4} Accurate pre-treatment work-up is critical to stage the disease, so that under-treatment and/or unnecessary over-treatment is avoided. Treatment strategies should follow guideline recommendations, and should be developed after multidisciplinary evaluation.

Several studies have already shown that PET/CT scan is superior to oesophageal ultrasound and CT scan in the evaluation of metastases at the time of baseline staging. The SUV max has been shown to correlate with tumour differentiation in various malignancies including lung cancer, head and neck cancer, and oesophageal carcinoma. One study evaluated 102 pancreatic adenocarcinoma patients and found that the SUV was related to the histologic grade, that it might be a competitive predictor for patient survival and that prognosis could be stratified according to SUV\textsuperscript{5}.

However, for oesophageal cancer, the available evidence suggests a mixed picture. Mu et al. found no association between SUV max and the degree of differentiation or clinical stage of oesophageal cancer.\textsuperscript{6} Similarly, Sun et al studied 112 patients with oesophageal squamous cell cancer and found no significant correlation between the SUV max and the clinical stage or the degree of tumour differentiation. They also saw no significant difference in patients’ gender, age, or N and M stage in relation to the SUVmax after controlling for tumour length.\textsuperscript{7} However, a meta-analysis by Pan et al comprehensively reviewed the available literature and concluded that the SUV in oesophageal cancer patients can serve as a prognostic indicator.\textsuperscript{8} Similarly, Feng et al. studied 68 patients with oesophageal cancer and found a statistically significant difference in SUVmax between the poorly differentiated group and the moderately or well differentiated group ($r=0.781$, $P=0.000$). They also found a statistically significant increase in the SUVmax of oesophageal lesions with nodal metastases compared to those without.\textsuperscript{9} The sample size was, however, relatively small, and may have affected the quality of the data.

Our study showed a statistically significant correlation between the histology and the SUV of the
primary lesion. Further analysis showed no statistically significant difference in the SUV based on the degree of differentiation of either adenocarcinoma or SCCa. We also saw no correlation between the SUV of the primary tumour and the presence or the degree of uptake in metastatic lesions, whether nodal or visceral. In terms of tumour histopathology, we found that 74% of our sample had squamous cell carcinoma while 25% had adenocarcinoma. This finding is in marked contrast to the data reported from the western hemisphere, where, over the last 4 decades, there has been a rising incidence of oesophageal adenocarcinoma. In the US, according to the National Cancer Institute’s Surveillance, Epidemiology and End Result (SEER) programme, compared to 1974-1975, there was a >350% increase in annual rate of adenocarcinoma by 1992-1994.10 Adenocarcinoma in the early 1980’s accounted for <15% of all oesophageal cancers and by the 1990s it represented >60% of all oesophageal carcinomas. In contrast, Ali et al. have reported data on 69 patients in the northern areas of Pakistan and found that 92.5% cases of oesophageal malignancy were squamous cell carcinoma, while only 5% were adenocarcinoma.12 More work is needed to understand these histopathological variations.

Limitations:

Data was gathered in a retrospective fashion. At our institution, the acceptance criteria for treatment of oesophageal cancer patients limit open acceptance of all patients. Patients with metastatic pulmonary lesions visible on chest X-ray at presentation are not accepted for further management at our hospital and are referred to outside hospitals.

Conclusion: At our centre, three-fourths of patients with oesophageal carcinoma presented with squamous cell carcinoma. Adenocarcinoma is associated with a lower SUV compared to SCCa. There is no association between the SUVmax and degree of differentiation of the primary oesophageal cancer.

References