

## CORRELATION BETWEEN STANDARDISED UPTAKE VALUE AND HISTOPATHOLOGY OF OESOPHAGEAL CARCINOMA: A SINGLE-CENTRE ANALYSIS

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Received: 9 April 2015 / Accepted: 17 April 2015

### Abstract

**Aim:** This study aims to evaluate the correlation between oesophageal cancer histopathology and the standardised 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 CT (<sup>18</sup>F-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 male. The mean age was 52.6 years (standard deviation  $\pm$  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 was 7%. Mean maximum SUV (SUVmax) for SCCa was  $12.6 \pm 5.14$  and  $10.5 \pm 6.2$  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:** Fluorodeoxyglucose, oesophageal adenocarcinoma, oesophageal squamous cell carcinoma, positron emission tomography/computed tomography, standardised uptake value

### Introduction

Oesophageal cancer is the eighth most common cancer worldwide, with nearly 456,000 new cases diagnosed in 2012 (3% of the total).<sup>[1]</sup> It is a leading cause of cancer mortality amongst men. The incidence ranges from 2.5 to 5.0 for men and 1.5–2.5 for women per 100,000

population. It has a relatively poor prognosis with a 5-year survival of 6–11%.

Worldwide, squamous cell carcinomas (SCCa) are 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.<sup>[2]</sup> 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.<sup>[3]</sup>

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In the 1960s and 1970s, the 5-year survival of patients with oesophageal cancer was only about 5%. At present, nearly 20% of patients survive at least 5 years after the diagnosis of oesophageal cancer.<sup>[1]</sup> 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 fluorodeoxyglucose (FDG) uptake.

### Methods

This study was carried out in the Department of Nuclear Medicine at Shaukat Khanum Memorial Cancer Hospital and Research Centre (SKMCH and 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 positron emission tomography/computed tomography (PET/CT) scan using 18F-FDG (<sup>18</sup>F-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 and 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 tumour, node and metastasis international staging system. Each specimen was classified based on glandular formation in adenocarcinoma and keratin pearl formation for squamous cell carcinoma and was also categorised 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 h before the scan and then received a dose of 300 MBq (0.21 mCi/kg body weight) of <sup>18</sup>F-FDG intravenously. Uptake period in a quiet room was 60 min. Thereafter, images were acquired from the base of the skull to the mid-thigh with 3 min 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 80 mA was used for attenuation correction and lesion localisation. Dual interpretation of scans was performed by certified radiologists and nuclear medicine physicians. Maximum standardised uptake value (SUV<sub>max</sub>) 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 localisation. 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 male and 118 (41%) were female [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 SCCa and 75 (25.5%) were adenocarcinomas.

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].

**Table 1: Gender-based distribution of histopathological categories (n=289)**

Gender	n (%)	Adenocarcinoma n (%)	Squamous cell Ca n (%)
Female	118 (41)	12 (10)	106 (90)
Male	171 (59)	62 (37)	108 (63)

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

Type	n (%)	Differentiation	n (%)	Mean SUV+S.D
Squamous cell carcinoma	214 (74.5%)	Well	29 (13.5%)	13.4±4.1
		Moderate	151 (70.6%)	12.6±5.1
		Poor	34 (15.9%)	12.5±6.1
Adenocarcinoma	75 (25.5%)	Well	21 (30%)	9.6±6.9
		Moderate	34 (48.6%)	11.2±5.7
		Poor	15 (21.4%)	10.3±6.2
		Signet ring cell	5 (7%)	4.5±1.8

SUV: Standardised uptake value, SD: Standard deviation

**Table 3: T-stage distribution (n=289)**

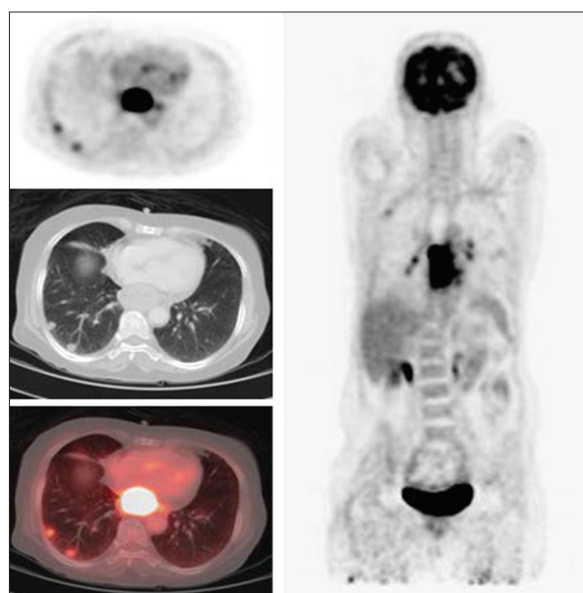
T-stage	n (%)
T1	1 (0.3)
T2	2 (0.7)
T3	155 (53.6)
T4	131 (45.3)

The mean SUVmax for SCCa was  $12.6 \pm 5.14$  and  $10.5 \pm 6.2$  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 SUVmax was 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 ( $P=0.339$ ).

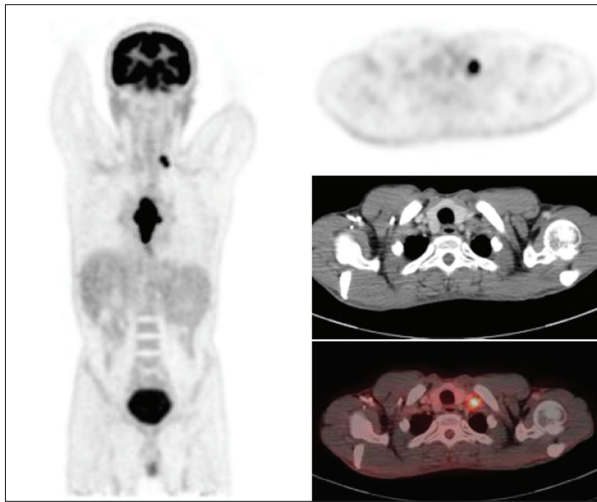
In multivariate analyses, SUV of the primary oesophageal tumour was not associated with age ( $P=0.06$ ), gender ( $P=0.54$ ) or the degree of differentiation of the primary tumour ( $P=0.76$ ). In addition, there was no statistically significant correlation between the SUVmax of the primary lesion and the presence or activity level of a metastatic focus, whether visceral or nodal ( $P=0.45$ ) [Figures 1 and 2].



**Figure 1:** 18F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography images of a 50-year-old female with well-differentiated adenocarcinoma of the mid-oesophagus, showing intense FDG uptake in the primary tumour site (standardised uptake value [SUV] of 13) together with metastatic mediastinal and hilar nodes. Significantly increased uptake is also seen in metastatic pulmonary nodules (SUV of 5.5)

## 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.<sup>[4]</sup> Accurate pre-treatment workup is critical to stage the disease so that undertreatment and/or unnecessary overtreatment is avoided. Treatment strategies should follow guideline recommendations and should be developed after multidisciplinary evaluation.



**Figure 2:** 18F-fluorodeoxyglucose positron emission tomography/computed tomography images of a 36-year-old male with well-differentiated squamous cell carcinoma showing intense FDG uptake in the mid to distal oesophagus (standardised uptake value [SUV] SUV of 12.3). Increased uptake is also seen in regional nodes as well as in a metastatic left supraclavicular lymph node (SUV of 8)

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 SUVmax 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.<sup>[5]</sup>

However, for oesophageal cancer, the available evidence suggests a mixed picture. Mu *et al.* found no association between SUVmax and the degree of differentiation or clinical stage of oesophageal cancer.<sup>[6]</sup> Similarly, Sun *et al.* studied 112 patients with oesophageal squamous cell cancer and found no significant correlation between the SUVmax 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.<sup>[7]</sup> 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.<sup>[8,9]</sup> 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.<sup>[8]</sup> 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 past 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 programme, compared to 1974–1975, there was a >350% increase in annual rate of adenocarcinoma by 1992–1994.<sup>[10]</sup> Adenocarcinoma in the early 1980s accounted for <15% of all oesophageal cancers, and by the 1990s, it represented >60% of all oesophageal carcinomas.<sup>[11]</sup> In contrast, Ali *et al.* have reported data on 69 patients in the northern areas of Pakistan and found that 92.5% of cases of oesophageal malignancy were squamous cell carcinoma, while only 5% were adenocarcinoma.<sup>[12]</sup> More work is needed to understand these histopathological variations.

### Limitations

Data were gathered in a retrospective fashion. At our institution, the acceptance criteria for the 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.

### Conflict of Interest

The authors declare that they have no conflict of interest.

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