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THE ROLE OF PET-CT IN THE CLINICAL MANAGEMENT OF ESOPHAGEAL CARCINOMA AND ITS LIMITATIONS

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ABSTRACT

In patients with oesophageal carcinoma being considered for esophagectomy, conventional staging methods include upper endoscopic gastroduodenoscopy, endoscopic ultrasonography(US), and computed tomography (CT) of the thorax and abdomen. The routine use of integrated positron emission tomography (PET)/CT with 2-[fluorine 18]fluoro-2-deoxy-d-glucose(FDG) in evaluation of patients with oesophageal carcinoma is increasing and has been reported to be useful in initial staging of oesophageal carcinoma. Methodology: This observational study retrospectively evaluated 45 consecutive patients with carcinoma esophagus which was diagnosed histologically. PET/CT is performed on an integrated scanner that combines both multisection CT and PET capabilities in two sequential gantries, avoiding the need for patient motion between the CT and PET components of the study and thereby leading to accurate coregistration of the CT and PET data. Results: In our study, 45 patients with histologically proven carcinoma esophagus were evaluated with PET-CT imaging which included 64.44% (no. 29) patients who had imaging only for staging, 31.11% (no. 14) patients for staging and response evaluation to therapy and 4.44% (no. 2) patients had treatment elsewhere and had PET-CT imaging for detection of recurrence of malignancy. Conclusion: appropriate and accurate interpretation of PET/CT results requires an appreciation of the artifacts and interpretative pitfalls that can be encountered in PET/ CT.

INTRODUCTION

The oesophagus is one of the common sites of malignancy in the gastro-intestinal tract. In patients with early-stage malignancy at presentation, esophagectomy is the treatment of choice and is potentially curative. Unfortunately, most patients have locally advanced disease at presentation, and 20%–30% have distant metastases [1]. In patients with locally advanced disease without distant metastases, esophagectomy is a potential treatment option after neoadjuvant chemotherapy and radiation therapy in those who do not develop distant metastases during therapy [2–11].

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Consequently, in all patients with potentially respectable disease, accurate staging at initial presentation and assessment of therapeutic response after neoadjuvant therapy are important in regard to optimal management.

In patients with oesophageal carcinoma being considered for esophagectomy, conventional staging methods include upper endoscopic gastroduodenoscopy, endoscopic ultrasonography (US), and computed tomography (CT) of the thorax and abdomen. The routine use of integrated positron emission tomography (PET)/CT with 2-[fluorine 18]fluoro-2-deoxy-d-glucose(FDG) in evaluation of patients with oesophageal carcinoma is increasing and has been reported to be useful in initial staging of oesophageal carcinoma, assessment of therapeutic response after neoadjuvant therapy, and detection of recurrent malignancy [12-15]. However, accurate interpretation of PET/CT results in patients with

oesophageal carcinoma requires knowledge of the technical aspects of PET/CT image acquisition and the interpretative pitfalls that may be encountered, as well as an understanding of how the disease manifests and disseminates, the staging criteria used, and the different management strategies available.

Positron emission tomography (PET)/ computed tomography (CT) has important utility and limitations in the initial staging of esophageal cancer, evaluation of response to neoadjuvant therapy, and detection of recurrent malignancy. Esophageal cancer is often treated by using a combined modality approach (chemotherapy, radiation therapy, and esophagectomy); correct integration of PET/CT into the conventional work-up of esophageal cancer requires a multidisciplinary approach that combines the information from PET/CT with results of clinical assessment, diagnostic CT, endoscopic gastroduodenoscopy, and endoscopic ultrasonography. PET/CT has limited utility in T staging of esophageal cancer and relatively limited utility in detection of dissemination to loco regional lymph nodes. However, PET/CT allows detection of metastatic disease that may not be identifiable with other methods.

PET/CT is not sufficiently reliable in the individual patient for determination of treatment response in the primary tumour. Interpretation of PET/CT results is optimized by understanding the diagnostic limitations and pitfalls that may be encountered, together with knowledge of the natural history of oesophageal cancer and the staging and treatment options available.

METHODOLOGY

This observational study retrospectively evaluated 45 consecutive patients with carcinoma esophagus which was diagnosed histologically.

Of the 45 patients, 31 patients had not received surgical treatment or chemotherapy or radiotherapy, 8 patients had received neoadjuvant therapy, 16 patients had received adjuvant therapy & surgery. 2 patients presented for the detection of recurrent malignancy. Of the 45 patients, 31 were male & 14 were female. The primary tumour was localized in the cervical oesophagus [n=10], thoracic oesophagus [n=14], and lower oesophagus [n=20]. And in 1 patient tumour was localized in both cervical & thoracic oesophagus.

Out of 45 patients, 11 patients had PET-CT imaging for both staging and for the evaluation of response to therapy.

Patients are required to fast for approximately 4–6 hours prior to PET-CT to enhance FDG uptake by tumours as well as to minimize cardiac uptake. They are instructed to avoid caffeinated or alcoholic beverages but can have water during this period. Before injection of FDG, the blood glucose level is measured; a level of less than 150mg/dL is desirable. Good control of blood glucose is essential because the uptake of FDG into cells is competitively inhibited by glucose, as they use a common transport mechanism (glucose transporters [GLUT]) for facilitated transport into both normal and tumour cell. Patients are also instructed to avoid any kind of strenuous activity prior to the examination and following injection of the radioisotope to avoid physiologic muscle uptake of FDG. All oncology patients with the exception of those being studied for head and neck malignancy are given water-soluble iodinated contrast media orally for bowel opacification. The typical dose of FDG is 10 mci injected intravenously. Patient activity and speech are limited for 20 minutes immediately following injection of the radioisotope to minimize physiologic uptake by muscles. To our knowledge, there are no contraindications to FDG administration. Imaging is initiated approximately 60 minutes following the injection of FDG. A whole-body PET study (neck through pelvis) follows an enhanced whole-body CT study. The CT study takes approximately 60–70 seconds to complete and the PET study takes approximately 30–45 minutes, depending on the coverage required.

PET/CT is performed on an integrated scanner that combines both multi section CT and PET capabilities in two sequential gantries, avoiding the need for patient motion between the CT and PET components of the study and thereby leading to accurate co registration of the CT and PET data. Patients undergo fasting for at least 6 hours before the PET/CT study. PET images are acquired during shallow breathing in the two-dimensional mode for 3 minutes per bed position 60–90 minutes after intravenous administration of 555–740 MBq of FDG. PET images are reconstructed by using standard vendor-provided reconstruction algorithms that incorporate ordered subset expectation maximization. Attenuation correction of PET images is performed by using attenuation data from the CT component of the examination; emission data are corrected for scatter, random events, and dead-time losses by using the manufacturer's software.

RESULTS

Our study group included 45 patients with histologically proven carcinoma esophagus with age ranging from 29 years to 81 years (mean age 63 years) . Of them, 30 patients were male and 15 were female.

The site of primary tumour was localized to lower oesophagus in 23 patients, mid oesophagus in 11 patients, upper oesophagus in 10 patients and 1 patient had tumour involving upper and mid oesophagus.

Of them 29/45 patients has PET-CT imaging done for staging alone,14/45 patients had PET-CT imaging for both staging and for response evaluation to therapy and 2 patients had PET-CT imaging for detection of recurrence of malignancy. Of the 29 patients who underwent PET-CT for staging, 11 patients had uptake at the tumoral site with no loco regional nodal or distant metastases, 2 patients had uptake of the tumour and the loco regional nodes with no distant metastases, 4 patients had uptake at the tumour with locoregional nodes and

regional nodal metastases. 6 patients had uptake at the tumor with loco regional and distant metastases. 1 patient had no uptake at the site of tumour with uptake in the locoregional nodes and distant metastatic sites. This patient had surgery and adjuvant chemoradiation. On follow up scan, there was no focal oesophageal thickening or metabolic uptake at the tumoral site. 1 patient had no uptake at the site of tumor or in the nodes, but showing uptake in the distant metastatic regions. This patient had neoadjuvant radiotherapy.

2 patients had no tumoral uptake with uptake in the locoregional and regional nodes and 2 patients had no uptake at the tumoral site, locoregional or distant metastases. Of this, 1 patient had neoadjuvant chemotherapy and follow up scan showed thickening of the gastroesophageal junction (about 1.0cms thickness) with no metabolic activity, and another patient had surgery with adjuvant chemoradiation. Out of 29 patients who underwent PET-CT for staging of the carcinoma, 20 patients underwent surgery and adjuvant therapy, 3 patients underwent neoadjuvant chemotherapy, 1 patient was diseased after surgery (due to postoperative complication) and the remaining 5 patients were lost to follow up. Of the 29 patients only 8 had follow up PET-CT for response evaluation of treatment. Of this 2 patients showed complete response, 2 patients showed partial response, 1 patient showed stable disease whereas 3 patients showed disease progression.

The rest 14/45 who have had follow up PET-CT scan after initial staging of the disease. Out of which, 7 patients underwent neoadjuvant therapy (4 patients chemotherapy, 2 patients radiotherapy and 1 patient chemoradiation) , 6 patients underwent surgery and adjuvant radiotherapy and 1 patient underwent surgery and chemotherapy. Of this, 2 patient showed complete response, 6 patient showed partial response, 4 patient showed stable disease and 2 patient showed disease progression. Two patients had treatment elsewhere and underwent PET-CT scan in our institute for the detection of recurrence of malignancy, both of which did not show recurrence.

Of the 45 cases, all the 23 cases of lower esophageal carcinoma were operated with adjuvant chemo or radiotherapy. Of the 11 cases of carcinoma mid esophagus, 4 were operated based on its lower location and the remaining was treated with neoadjuvant chemo or radiotherapy. And there were 10 upper esophageal and 1 upper and mid esophageal carcinoma which were treated with neoadjuvant chemo or radiotherapy.

Table 1. Indication for PET/CT imaging

Indications for PET-CT	No. of patients
Staging	29
Staging and response evaluation	14
Follow up for recurrence	02
Total	45

Table 2. 29/45 patients who had PET-CT imaging for staging alone

Staging	Number of patients
Only primary tumor uptake	11
Primary tumor uptake + locoregional metastasis	2
Primary tumor uptake +locoregional +regional nodal metastases	4
Primary tumor uptake +locoregional +distant metastases	6
Only distant metastases	1
Only locoregional +distant metastases	1
Locoregional +regional metastases	2
No uptake at the tumor site or the nodal metastases	2

Table 3. Treatment after PET-CT (29/45)

Treatment	Number of patients
Neoadjuvant chemotherapy	3
Surgery + adjuvant chemotherapy	12
Surgery +adjuvant radiotherapy	8

Table 4. PET-CT imaging for both staging and response evaluation to therapy (14/45)

Staging	Number of patients
Primary tumor uptake +locoregional metastases	2
Primary tumor uptake +locoregional +regional nodal metastases	7
Only primary tumor uptake	2
Primary tumor uptake +locoregional +distant metastases	2
Only distant metastases	1

Table 5. Response evaluation to treatment (14/45)

Response	Number of patients
Complete response	2
Partial response	6
Stable disease	4
Disease progression	2

Table 6. Treatment after PET-CT (14/45)

Treatment	Number of patients
Neoadjuvant chemotherapy	4
Neoadjuvant radiotherapy	1
Neoadjuvant chemoradiation	1
Surgery +adjuvant radiotherapy	7
Surgery +adjuvant chemotherapy	1

Table 7. PET-CT imaging for the detection of recurrence of malignancy (2/45)

Staging	No. of Patient	Recurrence
Primary tumor uptake +locoregional metastases	1	No
Primary tumor uptake + locoregional & regional metastases	1	No

DISCUSSION

In our study, 45 patients with histologically proven carcinoma esophagus were evaluated with PET-CT imaging. PET-CT has important utility in the initial staging, evaluation of response to therapy and detection of recurrent malignancy.

The location of primary tumor was maximum in the lower esophagus. 51.11% (n - 23) patients had tumor localized to the lower esophagus, 24.44% (n - 11) patients in the mid esophagus and 22.22% (n - 10) patients in the upper esophagus. 2.22% (n- 1) patient had tumor involving upper and mid esophagus.

Our study included 64.44% (n- 29) patients who had PET-CT imaging only for staging, 31.11% (n- 14) patients for staging and response evaluation to therapy and 4.44% (n -2) patients had treatment elsewhere ,had PET-CT imaging in our institute for detection of recurrence of malignancy.

Among 29 patients who underwent PET-CT for staging , different stages of the disease was obtained based on the TNM staging . It was staged based on the uptake at locoregional nodes, regional nodes or distant metastases.

One patient had no uptake at the site of tumor with uptake in the locoregional nodes and distant metastatic sites. This patient had surgery and adjuvant chemoradiation. On follow up scan, there was no focal esophageal thickening or metabolic uptake at the tumoral site.

One patient had no uptake at the primary site of tumor or in the nodes, but showing uptake in the distant metastatic regions. This patient had neoadjuvant radiotherapy. 2 patients had no tumoral uptake with uptake in the locoregional and regional nodes and 2 patients had no uptake at the tumoral site, locoregional or distant metastases. Of this, 1 patient had neoadjuvant chemotherapy and follow up scan showed thickening of the gastroesophageal junction (about 1.0cms thickness) with no metabolic activity, and another patient had surgery with adjuvant chemoradiation.

Esophageal cancer is often treated with combined modality approach (chemotherapy, radiotherapy and esophagectomy) In our study, all the 23 cases of lower esophageal carcinoma were operated with adjuvant chemo or radiotherapy. Of the 11 cases of carcinoma mid esophagus, 4 were operated based on its lower location and the remaining were treated with neoadjuvant chemo or radiotherapy. And there were 10 upper esophageal and 1 upper and mid esophageal carcinoma which were treated with neoadjuvant chemo or radiotherapy. 5 patients were lost to follow up which was a major drawback in our study.

Assessment of treatment response was made using RECIST 1.1 CRITERIA. In our study, we had response evaluation in 22 patients, of which 4 patients showed complete response, 8 patients showed partial response, 5 patients had a stable disease whereas 6 patients showed disease progression.

Two patients had treatment elsewhere and underwent PET-CT scan in our institute for the detection of recurrence of malignancy, both of which did not show recurrence.

And seven primary studies conducted by Chatterton et al, 2009 [16], Cheze-Le Rest et al, 2008 [17], Hsu et al, 2009 [18], Hu et al, 2009 [19], Noble et al, 2009 [20], Okada et al, 2009 [21], and Shimizu et al, 2009 [22]) also showed the significant impact of PET and PET/CT on the clinical management, prognostic stratification of patients with newly diagnosed esophageal cancer, prediction of regional and locoregional lymph nodes, and improvement on the accuracy of pretreatment staging. Another study by Chandawarkar et al [23] and Kobori et al [24] demonstrated in their studies that PET has a greater

diagnostic efficacy in the detection of tumour adenopathies.

And thus to conclude, PET-CT has a major role in the clinical management of esophageal carcinoma by initial staging, evaluation of response to treatment and detection of recurrence.

Although most esophageal carcinomas appear FDG avid at PET/CT, the reduced spatial and contrast resolutions of PET/CT limit visualization of the anatomic extent of the primary mass and preclude evaluation of the depth of local tumor invasion in most cases. Early-stage carcinomas, in particular, may not be detectable at all with either CT or PET/CT.

PET/CT has relatively limited utility for detection of metastatic dissemination to locoregional lymph nodes .FDG uptake within periesophageal lymph nodes that are anatomically close to the primary tumor is difficult to differentiate from uptake within the esophagus itself owing to the limited spatial resolution of PET-CT.

Furthermore, microscopic metastatic disease within lymph nodes may not demonstrate sufficient FDG uptake for detection with PET . In addition, FDG uptake within lymph nodes can occur in benign disease such as granulomatous infection (particularly in regions of endemic histoplasmosis or tuberculosis) or sarcoidosis. In many cases, a confident interpretation of benign disease is not possible. The commonest sites of visceral metastases (M1b) include the lungs, liver, bones, and adrenal glands .However, metastases from esophageal cancer can occur in unusual and unexpected locations and can be radiologically occult when traditional imaging methods such as CT are used for detection. Uncommon sites of organ metastases include the brain, skeletal muscle, subcutaneous tissues, thyroid gland, and pancreas. In therapeutic response criteria with PET/CT, the most important parameters to consider are the specificity and negative predictive value for detecting residual macroscopic tumor (or the sensitivity and positive predictive value for detecting a pathologic response), which determine the utility of these criteria for assessing the suitability of esophagectomy in the individual patient; that is, patients who have residual viable macroscopic tumor after neoadjuvant therapy (according to PET/CT criteria) may benefit more from nonsurgical management rather than proceeding to esophagectomy. Conversely, it is important to be able to predict a good therapeutic response to neoadjuvant therapy with high sensitivity and positive predictive value in order not to deny potentially curative surgery to these patients.

Response Evaluation Criteria in Solid Tumors 1.1(RE-CIST 1.1) was used for the radiologic assessment of response to therapy. RECIST 1.1 defines four response categories: complete response, partial response, stable dis-ease, and progressive disease.

CONCLUSION

PET/CT is useful in patients with esophageal cancer, for initial staging**,** response evaluation to treatment and for assessment of treatment response.

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CONFLICT OF INTEREST:

The authors declare that they have no conflict of interest.

STATEMENT OF HUMAN AND ANIMAL RIGHTS

All procedures performed in human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This article does not contain any studies with animals performed by any of the authors.

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