Review Article, PET/CT.

The Impact of ^{18}F-FDG-PET/CT in Esophageal Cancer

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INTRODUCTION:

Esophageal cancer is the sixth most common cause of cancer deaths worldwide. It is endemic in many parts of the world, particularly in the third world countries, where it is the fourth most common cause of cancer deaths. The highest rates are found in Asia, stretching from northern Iran through the central Asian republics to north-central China, with squamous cell carcinoma is responsible for 95% of all esophageal cancers worldwide. Accurate radiological assessment of esophageal carcinomas is vital to stratify patients according to the TNM classification into appropriate treatment options. A multimodality approach is used with the mainstay of assessment using EUS and MDCT. EUS is superior to CT in T staging and N staging of loco-regional disease, whereas CT has a role in the assessment of distant nodal and M staging of disease [(1)].

Both EUS and CT have limitations concerning response assessment, and FDG-PET has emerged as a useful modality in this setting. Guidelines on the diagnosis and staging of patients with esophageal cancer are reported by The Society of Thoracic Surgeons. The most common tests used to initially identify and diagnosis esophageal cancer are upper gastrointestinal tract contrast studies and upper endoscopy with biopsy [(2)].

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PET/CT combines functional information provided by PET with anatomic information provided by CT. Two- and three dimensional image reconstructions may be rendered as a function of a common software and control system. The tracer commonly used in oncological PET imaging is fluorine-18 fluorodeoxyglucose [FDG] and is a glucose analog that is taken up by glucose-using cells and undergoes phosphorylation by hexokinase, an enzyme whose mitochondrial form is at much higher levels in rapidly-growing malignant tumors. FDG is absorbed by the cells causing intense radiolabeling of areas with high glucose such as the brain and most cancers. This process is used for diagnosing, staging, and monitoring of malignant tumors. Various metrics are used clinically to determine the FDG uptake of lesions and differentiate benign from malignant or inflamed areas [(3)].

PET/CT in initial staging of esophageal cancer

Primary lesion [T stage]:

The T descriptor is determined according to the extent of invasion by the primary tumor through the mucosal layers of the esophagus and into the adventitia and adjacent organs. A higher T classification is associated with a greater likelihood of nodal metastatic disease and poorer long-term survival.

FDG-PET has a limited role in T staging as its value is limited by its low spatial resolution. It may fail to detect small primary oesophageal lesions [5–8 mm] and hence sensitivity is reduced in detecting early-stage of disease. In ***Kato et al,*** showed that PET/CT has low sensitivity of 43 % in stage 1. However, it showed better sensitivity in advanced disease; especially stage 4 with overall sensitivity of 80 %. Sensitivity of FDG-PET is also reduced in non-FDG-avid oesophageal tumors such as well- differentiated tumors [(4)].

Regional lymph-nodes [N stage]:

FDG-PET/CT is a useful tool in evaluating nodal disease, although uptake in loco-regional nodes maybe hampered by uptake in the primary tumor itself. These include supraclavicular and left gastric nodes. The main advantage of PET is in identifying disease in normal-sized lymph nodes and differentiating between inflammatory and metastatic enlarged lymph nodes, thus limiting the need for invasive procedures such as mediastinoscopy.

Multiple studies ***Kato et al***, have shown the diagnostic sensitivity, specificity and accuracy for PET in detection of individual lymph node metastases are significantly better than CT [(4)].

Also, they showed that FDG-PET in staging esophageal cancer showed that it had a sensitivity of 57 % but high specificity of 85 %. Another meta-analysis of nodal staging with PET/CT rather than PET revealed similar findings with PET/ CT resulting in a sensitivity of 55–62 % but specificity of 76–96 % [4, 5].

Metastatic evaluation [M stage]:

PET/CT allows detection of metastatic disease, which may not be identifiable with other methods. It has been shown to improve preoperative staging and prevent inappropriate intervention, and even in patients not suitable for surgery, the detection of unsuspected metastases can guide palliative management [6].

The most common sites for metastatic disease are lungs, liver, bones and adrenals. PET/CT upstaged 15 % patients from M0 to M1, especially those with T3 tumors and downstage 7 % from M1 to M0. This was confirmed in another prospective study which showed that PET/CT correctly upstaged 20 % and downstage 5 % patients sparing unnecessary surgery in those with disseminated disease. PET/CT can also detect unsuspected synchronous tumors, which occur in 5.5 % of patients with esophageal malignancy. These most commonly occur in the stomach, head and neck and colon but have also been found in the kidney, thyroid and lung [5].

PET/CT in Follow up of Esophageal Cancer

There have been variable results in the use of PET for assessment of treatment response as post-radiotherapy esophagitis can also demonstrate significant uptake and it is important to wait 8–12 weeks post radiotherapy to avoid false positives [6]. FDG decrease after therapy in responders has been shown to correlate closely to histopathological outcome and a pathologic response within tumor has been reported to correspond to decreases in SUV max of 35–60 % between initial staging PET and re-evaluation imaging. It is can be a means of evaluating treatment response and can identify responders to neo-adjuvant therapy [7].

Persistent FDG uptake [with an SUV $\geq$ 4] on a single post-treatment scan has been shown to correlate with residual tumor and poor survival [8].

Weber et al. found that PET/CT performed after two cycles of chemotherapy allowed prediction of long-term outcome with a sensitivity and specificity of 93 and 95 %, respectively, suggesting there may be a more useful role for PET/CT in early treatment monitoring, especially of this can be performed within two weeks of treatment, before esophagitis developed.

However, identification of PET-positive lymph nodes after completion of chemotherapy is a predictor of poor prognosis in patients scheduled for surgery and FDG-PET lymph node status after neo-adjuvant chemotherapy is more important than that before chemotherapy [(9)].

Metabolic PETCT Parameters:

The standardized uptake value [SUV] is commonly calculated and reported today as a prognostic marker. There are several ways to estimate SUV, two commonly used parameters are the SUV max and SUV mean that are based on the maximum and mean pixel values respectively within an ROI. Metabolic tumor volume [MTV] and total lesion glycolycis [TLG] are additional markers that prove to have significant prognostic values. Patients undergo a series of primary diagnostic procedures which define the type and extend of the disease. There is increasing interest for the application of PET/CT and make it more standardized and quantitative. Computer methodologies offer robust tools for the automation and standardization of the measurements and could significantly enhance the role of PET/CT in diagnosis and treatment uptake [(10)].

Different metabolic PET/CT SUV parameters;

SUV max, SUV mean = [SUV-bw] and SUV peak = [SUV-bw/size: 1 cm3] ***(Table 1)***.

Table (1): Different metabolic PET/CT SUV parameters**.**

SUV Parameter	Definition	Advantages	Disadvantages
SUV_{max}	Highest voxel value within the ROI	Independent of ROI size, less observer dependent than SUV_{mean}, more reproducible than SUV_{mean}	More susceptible to image noise
SUV_{mean}	Mean value of all voxels within the ROI	Less sensitive to image noise	More sensitive to ROI definition, subject to intra- and interobserver variability
SUV_{peak}	Mean value of radiotracer uptake within the ROI surrounding the pixel with the highest activity	Combines reproducibility of SUV_{max} and image noise reduction of SUV_{mean}	Reduced accuracy in the assessment of small lesions, compared with SUV_{max}; limited availability of the required automated measurement software

Ziai, 2016 [(11)].

Standardized Uptake Value [SUV]:

Standardized Uptake Value [SUV]. These methods have found wide acceptance because of their convenience. They are based on the concentration in tissues, corrected to the amount injected and the body weight. The determination of SUV is dependent on identical patient preparation and adequate scan quality that is similar between the baseline and follow-up studies. Ideally, the scans should be performed on the same scanner with comparable injected doses of 18F-FDG and comparable uptake times before scanning. Absolute and rigorous standardization of the protocol for PET is required to achieve reproducible SUVs.

Weber et al, has argued that any drop in SUV of more than 20% is significant and should be called a response. Using a 1,5 cm region of interest [ROI], they showed in gastric and esophageal cancers that declines in FDG uptake of 20% - 35% after 1-2 doses of therapy are predictive of outcomes, with the larger the drop, the greater being the beneficial effect [(9)].

Total Lesion Glycolysis [TLG]:

The MTV is a volumetric quantitative measurement of tumor cells with high glycolytic activity, while the mean SUV is the mean value of metabolic activity in a chosen region, and so it is a good representative of whole tumor activity.

Thus, unlike the SUV max, which represents only the most metabolically active part of the tumor, the TLG represents the entire tumor burden because tumor size and degree of FDG uptake are, assessed simultaneously [(12)].

Larson et al, evaluated only the primary tumor for response. The evaluation was done based on a change in the total lesion glycolysis in the post-treatment scan, compared to the total lesion glycolysis in the pre-treatment scan. This value was termed TLG or the Larson-Ginsberg Index [LGI] [(13)].

The total lesion glycolysis [TLG] is a composite parameter that was introduced by Larson et al in 1999. It was intended to measure global metabolic changes of the entire tumor lesion.

It is calculated by multiplying the **metabolic tumor volume** [MTV] by the SUV mean [(14)].

$$TLG = MTV \times SUV\ mean$$

Among various other authors, ***Kiyohara et al***, showed that changes in MTV and TLG between pre-and post-treatment scans may be a useful index in the prediction of therapeutic response for various cancers.

However, in current practice, clinical oncology guidelines do not yet include MTV measurements or TLG in characterizing the response to treatment [14].

Application of PET/CT of metabolic parameters in esophageal cancer:

Multiple previous studies were done to try to establish the relationship between metabolic parameters of PET/CT and the outcome and survival of oesophageal cancer patients treated with neo-adjuvant or definite chemo radiotherapy, some studies showed no relationship between these parameters and outcomes while in the studies that did establish a relationship it was mostly TLG and MTV that showed significant relationship.

Soydal et al, in a prospective study of 22 patient which aimed to explore prognostic importance of definition of preoperative metabolic tumor volume in esophageal cancer patients found a statistically significant relationship between MTV and survival times.

However it could not define a threshold for MTV to predict disease prognosis because of the limited number of patients. Total metabolic tumor volume had a significant effect on survival (p=0.045) according to Cox proportional hazards regression analysis. One unit increase in MTV caused 1.1 fold increases in hazard, at any time [15].

Hong et al, reported that, SUV, MTV, and TLG were measured to predict their prognostic role in overall survival (OS) in 38 esophageal cancer patients who had undergone ^{18}F-FDG PET/CT before radiotherapy. TLG demonstrated higher sensitivity and specificity for predicting OS than MTV and SUV; and a better OS was observed in patients with low TLG compared to those with high TLG in locally advanced disease (OS, 46.9 months; 95% confidence interval [CI], 33.50-60.26 vs. 25.3 months; 95% CI, 8.37-42.28; P=0.003) [16].

In ***Li et al,*** study to evaluate if pre-treatment metabolic tumor volume and total lesion glycolysis are useful prognostic factors for esophageal squamous cell cancer patients. The study included 86 patients with ESC with different stages prospectively enrolled. 18F-FDG PET/CT scans were performed before the treatment. SUV max, MTV, and TLG were measured for the primary esophageal lesion and regional lymph nodes. Results of the study showed that MTV and TLG proved to be good indexes in predicting outcome for the ESC patients. An MTV value of 15.6 ml and a TLG value of 183.5 were optimal threshold to predict the overall survival (OS).

The areas under the curve (AUC) for MTV and TLG were 0.74 and 0.70, respectively. Kaplan-Meier analysis showed an MTV less than 15.6 ml and a TLG less than 183.5 to indicate good media survival time (p value <0.05). In the stage III-IV patient group, MTV could better predict the OS (P < 0.001), with a sensitivity and specificity of 0.80 and 0.67, respectively [(17)].

In ***Venkat et al,*** study, 76 patients were included in the study and both pre and post therapy PET/CT scans were included, results showed Pre CRT MTV and pre CRT TLG were independently predictive of response (MTV; cut off = 33,1 and p = 0.004 while TLG; cut of=153 and p=0.007, and percentage change in MTV independently predicted for overall survival. Further study is needed to determine if MTV and TLG values can help define which patients will most benefit from radiation dose escalation and Esophagectomy. By contrast, SUV max and SUV peak before or after CRT did not significantly predict for pCR. Percent change of SUV max, SUV peak, MTV and TLG also did not predict for pCR [(18)].

In ***Li et al,*** retrospective study including 134 patients the study showed that TLG and its percentage change during and after treatment have prognostic value regarding OS of EC patients. The same holds true for MTV.

However, in our study baseline SUV max did not have any prognostic value (p=0.4). The results also suggested that MTV1 and TLG1 (of initial PET/CT) were both associated with OS. The optimal prognostic threshold for OS (per the ROC and Youden index) were10.5 mL for MTV1 and 59.8 [(19)].

Whereas, ***Jayachandran et al,*** evaluated 37 patients with esophageal cancer treated with either neo-adjuvant (21) or definitive (16) CRT. They evaluated MTV and TLG values calculated using absolute (SUV 2.0, 2.5 and 3.0) and relative (50% of SUV max) threshold methods, as well as MTV ratio values defined as pre CRT MTV/ post CRT MTV for each SUV threshold. They found no correlation between pre CRT parameters and TRG (tumor regression grade) or OS. Post CRT MTV2.5 and TLG2.5 had the greatest correlation with both TRG and OS [(20)].

Also, ***Elimova et al,*** a small prospective trial of 31 patients found no PET parameters (before, during or post CRT) to be predictive of pathological response. TLG, however, was predictive of OS. There was association between OS and baseline TLG (p=0.03) at the optimal cutoff TLG value of 75.15 [(21)].

To conclude: metabolic parameter including MTV and TLG as quantitative metabolic parameters seems to be valuable as prognostic factor in esophageal cancer.

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