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GUIDELINES FOR CLINICAL PRACTICE

Positron emission tomography's changing significance in the treatment of esophageal cancer

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Abstract

Incidence of esophageal cancer has been rising, and Positron Emission Tomography (PET) is one tool that has shown utility and promise as a tool for staging, treatment response, and prognosis. PET delivery has evolved over time and is now frequently registered with a CT scan at the time of acquisition. However, resolution and confounders such as post-treatment radiation changes may limit clinical utility. PET has been shown to be helpful in staging, especially in evaluating for distant metastases. PET acquired after chemoradiation may give important prognostic information that can guide additional treatment decisions. Studies have had substantial variability in recommendations for the timing and manner of using PET for this purpose, and additional study is needed.

Key words: Positron emission tomography; Esophageal cancer; Staging

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INTRODUCTION

The incidence of esophageal cancer has been rising, with an estimated 146 726 new cases and 124 728 deaths worldwide[1]. The poor long term survival in patients with esophageal cancer is due partly to late detection of disease. Tumors often remain undetected until they are locally advanced or metastatic, leading to poor prognosis. Esophageal cancer staging is intended to group patients with similar prognosis for appropriate therapy. The accuracy of staging is contingent on the sensitivity and specificity of the tools available to the physician, as is ongoing management based on response to prior therapy. Positron Emission Tomography (PET) is one such tool that has increased in usage over the last several years. Investigators have sensed great promise with PET, and reports evaluating its utility have multiplied.

PET DELIVERY

PET is performed by injecting a patient with radio-labeled glucose [2-(fluorine 18) fluoro-2-deoxy-D-glucose] (FDG), which is concentrated in tissues with higher metabolic activity. Radio-labeled glucose is transported into active cells, phosphorylated, and then is unable to be metabolized further through glycolysis. The effect is concentration of decay emissions in metabolically active tissues, including cancer, as measured with a scanner.

PET is often obtained in conjunction with a CT scan using a dual gantry machine that can obtain both image

sets without moving the patient. Although this allows for a more accurate registration between the scans, the relative speed with which CT images are obtained contrasts with the relatively long period required for PET acquisition. This results in a disparity between the images. Normal organ motion within the body "smears" the PET image over time but does not have as much impact on CT scans. The variation between the CT and PET image is greatest at the diaphragm and can result in a 30%-50% change in the maximum uptake[2]. Regardless of this limitation, co-registered PET/CT is superior to PET and CT obtained separately or viewed side-by-side. Another limitation of all PET scans is the relatively low resolution inherent in the imaging process. The intensity of FDG uptake may be similar between tissue with few cells which are largely active and tissue with many cells which are moderately active in the same volume. This results in an inability to distinguish fine detail within the scan and therefore lower resolution.

The measured activity within a PET scan is calculated as the Standard Uptake Value (SUV) and is obtained by dividing the measured decay events in a given body volume by the expected decay events if the distribution of activity from the administered FDG were homogenous throughout (with attenuation and other corrections)[3]. PET scans reveal metabolically active tissue regardless of whether the activity is from malignancy, inflammation, or other causes. This, along with the limited spatial resolution mentioned previously, limits the interpretation of PET in oncologic management generally.

Regardless of PET's limitations, it has improved accuracy of staging and its value in post-therapy evaluation is recognized but not yet fully defined. There have been a number of recent studies suggesting new beneficial uses of the modality, but the findings have been somewhat mixed and are difficult to collectively summarize into a coherent, well-supported guideline.

PET holds particular appeal to oncologists because of its apparent complementarity to CT scans and other imaging obtained for staging. Staging scans have historically focused on the anatomy of the patient while PET allows for insight into the functionality of tissues by representing the metabolic activity of tumor and normal tissue. The combination of anatomic and physiologic information seems conceptually superior to anatomic information alone as it informs staging and therapeutic efforts. PET is now typically added to clinical assessment, diagnostic CT, endoscopic gastroduodenoscopy, and endoscopic ultrasonography for staging workup.

PET UTILITY IN STAGING

Patients with locally advanced disease are often treated with neoadjuvant chemoradiation followed by surgery. Several meta-analyses have shown a benefit in local recurrence, complete resection, and survival with trimodality therapy compared with surgery alone[4,5]. However, the addition of neoadjuvant therapy limits initial staging due to the absence of histopathological information. This raises the potential value of additional information that can be used for clinical staging such as through PET.

Esophageal cancer uses the AJCC TNM staging convention to represent primary, nodal, and metastatic disease respectively. The T stage depends on the invasiveness of the primary tumor and is well-appreciated with endoscopic ultrasound. PET scans may have value in determining the size and location of the primary malignancy, and thereby may be used to assist in radiation treatment planning target delineation, but these do not influence the T stage[6,7]. There are other limitations to PET in regard to primary tumor evaluation as well. Although most esophageal malignancies are hypermetabolic and manifest on PET, lesions less than 1 cm may be too small to be detected. Also, the spatial resolution of PET is inadequate to contribute to the T stage by suggesting a degree of invasion with any certainty even when it is positive.

PET may improve the accuracy of the N stage by distinguishing metabolically active lymph nodes from enlarged benign nodes. However, the low resolution of PET imaging makes it difficult to distinguish loco-regional lymph nodes from direct primary tumor extension, and metabolically active nodes may reflect sarcoidosis, granulomatous disease, reactive nodes, or other non-malignant conditions. Using PET for N staging also shares the T stage limitation of failing to identify microscopic disease or gross disease less than 1 cm.

The area in which PET has the greatest utility in esophageal cancer staging is in the assessment of distant metastases, the M stage. PET/CT may detect metastatic disease at unusual sites that may otherwise have been overlooked, and has thereby been shown to improve staging and prevent inappropriate surgery for patients with metastatic disease.

PET UTILITY IN TREATMENT RESPONSE

Patients with persistent disease after neoadjuvant therapy and prior to surgery have a poorer outcome and may best be managed without surgery[8,9]. A PET scan may be helpful in more accurately determining patient response to treatment to facilitate choosing appropriate additional therapy.

There have been mixed reports on this topic. A reduction in SUVmean or SUVmax between pre- and post-treatment PET scans was a predictor of pathologic response in some series, but the cutoff point varied widely between the studies (e.g. 10% to 80%) and typically has been chosen tailored to a retrospective data set rather than prospectively evaluated[8,10-14]. In other studies, persistent uptake within the primary tumor site on a single post-treatment PET correlated with residual viable tumor and poor survival[9,15-17]. However, the specific SUVmax value used in these series as a cutoff varied from 2.5 to 4.0, and unfortunately other recent studies similarly designed have concluded that a single post-therapy PET scan is not adequate in determining

response within the primary tumor[18-20].

There are several issues that may contribute to the disparate findings among these studies. Some studies examined only adenocarcinoma patient response while others were exclusively squamous cell carcinoma. Most were mixed. This may explain the relatively large difference in SUVmax cutoff values used to assess treatment response. Additionally, negative findings often remain unpublished and could be under-represented in the published literature. Retrospective studies are also widely understood to suffer from bias, and that seems particularly relevant in a group of studies with similar conclusions but widely disparate objective data.

Another possible reason for the range of findings in studies that address PET as a tool to assess clinical response is the changing technical format of PET administration. Earlier studies routinely obtained PET without CT using a separate transmission scan for attenuation correction. PET/CT uses CT data to perform attenuation correction and the difference in time acquisition results in mismatching. This may be corrected using respiration-averaged CT, but because independent PET was used for many of the earlier studies while PET/CT has been used most frequently recently may explain some of the disparity in findings. There are also disparities between treatment centers in FDG dose and attenuation correction procedures[2].

A potential limitation of post therapy PET is the esophagitis and ulceration that is induced by chemoradiation during treatment and which manifests as increased uptake on PET. Reactive uptake in non-malignant tissues increases three or more weeks after treatment, but tumor tissue uptake may not yet have diminished within the first week or two after treatment. The timing of PET is important to minimize the potential masking of high uptake in actual persistent disease[20,21].

PET has also been used as an assessment of treatment response after brief chemotherapy and prior to the full course of chemoradiation. This holds advantages for the group of patients who have a poor response to chemoradiation because surgical outcome is poorer after trimodality therapy than it would have been if surgery had not been delayed for neoadjuvant therapy. Lordick *et al*[22] reported in the Municon trial on the utility of PET when used as an earlier assessment of neoadjuvant treatment response. Patients were divided into responder and non-responder groups after administering two weeks of preliminary chemotherapy. Non-responders were allowed to proceed directly to surgery without additional neoadjuvant therapy while responders received the full course of chemoradiation. The results suggested the feasibility of a PET-guided treatment algorithm for esophageal cancer. Another study showed that PET/CT after two cycles of chemotherapy predicts pathologic response to neoadjuvant therapy and long-term outcome with a sensitivity of 93% and a specificity of 95%[10].

CONCLUSION

PET is useful in esophageal cancer for staging and evaluation of treatment response. However, this is only true when PET is carefully interpreted with awareness of its limitations. An awareness of the scientific basis for PET will allow physicians to interpret the results within the patient's overall clinical history, including timing of PET acquisition prior to biopsies and other procedures that confound results. Specific prognostic information and appropriate treatment management in response to PET evaluation will become better defined as additional studies, particularly prospective trials, are published in the future.

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