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THE ROLE OF PET/CT IN CLINICAL MANAGEMENT OF ESOPHAGEAL CANCER

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Abstract

Esophageal cancer is a cancer of the digestive system considered one of the "big killers" due to its low 5-year survival. Diagnostic imaging during preoperative staging is essential for choosing the most appropriate treatment to be performed: radical excision with curative intent, neoadjuvant therapy or a palliative approach. CT, endoscopic ultrasound, and PET scans all play a major role in the staging of patients with esophageal cancer. Positron Emission Tomography (PET), especially in combination with CT (PET-CT), has proved to be a fundamental tool for the diagnosis of esophageal carcinoma.

Keywords: *Esophageal cancer, diagnostic imaging, nuclear medicine, Ct/PET*

Introduction

Esophageal cancer is a cancer of the digestive system considered one of the "big killers" due to its low 5-year survival in a global scenario where breast cancer is currently the highest-incidence cancer. [1] [2] To date, one of the determining factors for improving survival remains early diagnosis. Imaging plays a fundamental role in tumor detection. TNM pre-treatment chemoradiotherapy or pre-surgery, although it does not appear to significantly improve the accuracy of local staging compared to other diagnostic techniques. [3] [4] Among the various diagnostic techniques, Positron Emission Tomography (PET), especially in combination with CT (PET-CT), has proved to be a fundamental tool for the diagnosis of esophageal carcinoma, particularly it has a high sensitivity for staging. In the future, further evolutions in imaging can bring improvements towards an increasingly accurate diagnosis, both in the staging phase and during therapy or the search for possible relapses, in order to obtain an ever earlier diagnosis and therefore even more targeted therapies. [5] [6] [7]

Esophageal cancer

Esophageal cancer is a relatively rare cancer, in eighth place worldwide, with an overall incidence of 3-4 cases / 100,000 inhabitants. [8] In the European Union there are an estimated 43,700 new cases / year and 20,750 deaths in men and 6,950 in women, with considerable geographical variability (3 / 100,000 in Greece,> 10 / 100,000 in France) [9] . Currently 15% of esophageal carcinomas originate from the upper 1/3 of the esophagus, 50% from the average 1/3, the remaining 35% from the lower 1/3; where the gastroesophageal junction (GEJ) is often involved, in the latter site, adenocarcinoma associated with Barrett's metaplasia is prevalent, an expression of the recent increased incidence of adenocarcinoma compared to the squamous cell variant. [10] Relatively high incidence of synchronous primary neoplasms in other districts - oral cavity, pharynx, larynx, lungs - (1-3%) or metachron (4-9%) associated with esophageal carcinoma for common risk factors. By submucosal lymphatic diffusion, synchronous esophageal lesions can also occur at a distance ("skip lesions"). [11]

In Italy, recent estimates by the Cancer Registers indicate 2,025 new cases / year in males and 548 cases / year in females with a mortality of 3-5 / 100,000 inhabitants and a number of deaths greater than 6-7 times in men over women. Risk factors for esophageal cancer vary in different geographic areas, reflecting the fact that there are socioeconomic differences. among the dominant risk factors in the European Community there are above all tobacco and alcohol for males, with a 5-10 times greater risk in smokers and a relative risk that varies between 3.0 and 7.5 in heavy drinkers; also in women, the increase in incidence in recent years is associated with a higher consumption of cigarettes. [12] Among the main risk factors known to date for esophageal adenocarcinoma are gastroesophageal reflux and its most severe complication, Barrett's esophagus. Both of these conditions have been on the rise since the early 1990s and probably the increase in both of these factors has contributed to the increase in esophageal adenocarcinoma. [13]

There is a theoretically protective role of fruit and vegetables, enrichment of the diet with beta carotene, vitamin E and selenium, while the risk appears to be increased in deficient nutritional status and increased red meat intake . [14-15] The main risk factor related to the development of esophageal adenocarcinoma is gastroesophageal reflux disease, due to excessive exposure of the mucosa to gastric acid content.[16] Due to the fact that obesity is the main risk factor for acid reflux, there is an increased risk of developing esophageal cancer in these patients. [17]

Several studies have also documented a correlation between Helicobacter pylori infection and carcinoma of the esophagus [18]: there appears to be an inverse association between Helicobacter pylori CagA-positive (cytotoxin-associated antigen A) infection and the risk of developing erosive esophagitis, Barrett's esophagus and esophageal adenocarcinoma [19-20].

Caustic injuries are another risk factor. In fact, the development of esophageal carcinoma was observed in 1-7% of patients with a history of ingestion of caustics. [21] The period of time between ingestion and the appearance of carcinoma, mainly in the middle third of the esophagus, can have a long latency of up to 50 years. [22]

Finally, among the pathologies that predispose to the development of esophageal carcinoma there are the Plummer-Vinson syndrome, achalasia and tylosis. [23]

Histologically, squamous cell carcinoma and adenocarcinoma are the most frequent histotypes (International Classification of Diseases for Oncology 30). 60% of squamous cell carcinomas are located in the middle third, 30% in the distal third and 10% in the proximal third of the esophagus. Adenocarcinoma, often associated with Barrett's esophagus and intestinal metaplasia and dysplasia, tends to be localized in the distal third [24]. Rarer epithelial histotypes include adenosquamous, adenocystic, mucoepidermoid, pseudosarcomatous and undifferentiated carcinoma. Small cell carcinomas, which often present high systemic aggression, constitute a small percentage, about 1%, occur more frequently in the middle or distal third and may be associated with ectopic hormone production. Among non-epithelial tumors, leiomyosarcomas are the most common mesenchymal tumors, usually presenting as large neoplastic masses with large hemorrhagic and necrotic pictures, lymphomas, carcinoids, carcinosarcomas and malignant melanomas are rarer. [25]

Staging

Correct staging of esophageal cancer and determination of the histotype are essential for proper planning of esophageal cancer therapy. [26]

The extent of esophageal cancer is described by the TNM classification. Parameter T, in particular, describes the depth of tumor invasion, N indicates lymph node involvement and M implies the presence of any distant metastases.

Imaging

Diagnostic imaging during preoperative staging is essential for choosing the most appropriate treatment to be performed: radical excision with curative intent, neoadjuvant therapy or a palliative approach. [27] To date, the gold standard for initial diagnosis is endoscopic examination with biopsy. Endoscopy allows a reliable evaluation of the mucosa, but on the contrary, it is not useful for identifying the depth of tumor invasion within the esophageal wall. This has given great importance to the combined use of esophagogastroduodenoscopy (EGD) and endosonography, which however has limitations in patients with marked strictures. [28]

CT

CT is one of the noninvasive imaging methods used for staging esophageal cancer. The first goal of staging is the assessment of the extent of the disease, in order to plan a correct radiotherapy or neoadjuvant chemotherapy. CT offers the possibility to evaluate the tumor invasion of adjacent organs, first of all the trachea, bronchi, aorta and pericardium, as well as the presence of hematogenous or lymphogenic metastases. Signs of invasion of adjacent organs are considered: involvement of paraesophageal fat, compression or dislocation of the airways, involvement of the circumference of the aorta for more than 90 °, the presence of tracheoesophageal or bronchoesophageal fistula or cortical erosion of the bodies vertebral. [29]

Normal thickness of the esophageal wall on CT, when the esophagus is distended, is usually less than 3mm and any thickness greater than 5mm is considered abnormal . CT has a sensitivity of 90% in discriminating between T1/T2 lesion and T3/T4 lesion and, in this respect, it is superior to PET, but is inferior to the latter in the identification of distant

metastases (64% vs 90 %), since even a normal-sized lymph node could contain microscopic metastatic foci that are beyond the detection level offered by CT. CT has indeed shown low sensitivity in the identification of metastatic periesophageal lymph nodes measuring less than 7 mm and if the CT shows distant metastases, it makes other procedures, such as PET and ultrasound endoscopy, unnecessary. [30]

FUNCTIONAL IMAGING

The role of functional imaging with nuclear medicine techniques oncology (and in esophageal cancer) is well established and continues to expand rapidly. [31-33] Many reports have demonstrated the utility of scintigraphy in the evaluation of functional oesophageal pathology (such as achalasia and sclerodermia) and in differentiating normal from abnormal oesophageal function. [34] The role of the radionuclide esophagogram in the diagnosis and management of achalasia, oculopharyngeal muscular dystrophy and its complications, tracheoesophageal fistulae, pharyngeal and esophageal diverticulae, gastric transposition, and fundoplication is established. [35-36]

Nuclear medicine imaging techniques have an advantage, since they by principle are functional modalities, using radioactive pharmaceuticals to map physiological processes. [37] Moreover, changes in function often precede anatomical changes, thereby allowing for evaluation of biological changes in tissues on shorter timescales.[38] This is typically applied for evaluating the response of tumours to treatment. [39]

PET

PET is a tomographic imaging technique that allows for accurate non-invasive in-vivo measurements of a whole range of regional tissue functions in man. [40] By using different tracers, a multitude of physiological, biochemical and pharmacokinetic parameters can be measured. [36]These include blood flow (perfusion), blood volume (vascularity), oxygen utilisation, glucose metabolism, pre- and post-synaptic receptor density and affinity, neurotransmitter release, enzyme activity, drug delivery and uptake, gene expression, etc. [41-42]

T staging

FDG PET showed high sensitivity (95%) and specificity (> 90%) in the preliminary evaluation of squamous cell carcinoma and esophageal adenocarcinoma. [43] Among the limitations of this method are the absence of correlation between the intensity of FDG absorption and the depth of tumor invasion in the esophageal wall, and a high number of false negatives in small lesions, below the limit of 3-5 mm spatial resolution of PET imaging. [44]

FDG PET and CT have comparable sensitivity in the staging of esophageal cancer. [45] However, PET offers less sensitivity than endosonography in evaluating wall invasion, due to difficulties in anatomical correlation of results. [46] [47]

N staging

The detection of locoregional lymph node metastases (N staging) has considerable prognostic relevance. CT with contrast medium has a high sensitivity to this indication but limited specificity. PET, on the other hand, has a specificity of 100% for the N stage of esophageal carcinoma, but with a sensitivity limited to 45%. [48]

The spatial resolution of conventional PET scanners is insufficient to positively distinguish locoregional lymph node metastasis from primary tumor involvement. Peripheral lymph nodes can be more accurately identified, however. [49]

[18F] FDG PET has been used in recent studies in combination with [11C] choline PET to allow more accurate evaluation of mediastinal lymph nodes, without, however, demonstrating a significant diagnostic improvement: the sensitivity of [18F] FDG

PET it was 100% versus 73% of the [11C] choline PET. [50-54]

M staging

Detection of distant metastases from esophageal cancer (M staging) is a critical factor in determining the need for surgery. The presence of lymph node or organ metastases is considered a contraindication as it is related to a poorer prognosis with an increase in morbidity and related risks. Involvement of locoregional lymph nodes appears to be an essential factor in determining the prognosis in patients without evidence of distant metastasis. [55]

FDG PET has a sensitivity of 69% and a specificity of 93% in the identification of distant metastases (Luketich et al. 1999), compared to only 46% and 74% for CT [49] However, FDG PET showed 78% higher sensitivity (versus 46%) and 90% specificity (versus 69%), even when compared with CT plus endosography. [56]

Detection of Recurrence

Early diagnosis of tumor recurrence after surgery, combined with radical therapy, can improve prognosis. High-resolution CT with contrast media, after esophageal resection, allows the locoregional evaluation of postoperative findings with the identification of any lymph nodes involved. [57]

FDG PET proved to be very effective in detecting local recurrences and new distant metastases. PET was able to identify recurrences in 12% of patients with negative morphological imaging results in CT and endoscopic ultrasound. PET has been shown to have a sensitivity of 100% and a specificity of 57% in identifying relapses near the anastomosis. Endosonographic imaging has instead also reached a sensitivity of 100%, but with a higher specificity, reaching as much as 93%. In the case of PET, most of the false positive results near the anastomosis are due to inflammatory changes, especially in cases where endoscopic dilation is performed within a few days. [58]

PET was more sensitive than morphological imaging (94% versus 81%) and with the same specificity (82%) for detecting recurrences far from the anastomosis and distant metastases. PET provided additional information in 27% of patients, revealing lesions that were not revealed by morphological imaging.

Evaluating Treatment Response

Patients diagnosed with advanced esophageal cancer (T3 or T4, clinical stage III) are initially referred for neoadjuvant chemotherapy before surgery.

Contrast-enhanced CT is able to detect shrinkage of the primary tumor and possible lymph node metastases. PET is also used in assessing the response to chemotherapy. Response to chemotherapy after two or three cycles was evaluated in a study in 14 patients with esophageal cancer. A reduction in FDG absorption of over 30% was observed, which was interpreted as a positive response as it correlated with patient survival. [59]

Evaluation with PET-CT

PET-CT has produced promising results in the assessment of locoregional lymph nodes. An initial study found that PET-CT was superior to PET and CT alone in detecting disease involvement and therapy planning. [60]

N staging

A single-center study found that integrated PET-CT was superior to CT or PET alone in the initial diagnosis of lymph node metastases from esophageal cancer. [61] In 45 patients with esophageal squamous cell carcinoma, preoperative PET-CT demonstrated a significant increase in sensitivity (93%), accuracy (92%) and negative predictive value (98%) compared to PET alone in

detecting lymph node metastases. locoregional. [62]

Evaluating treatment response

In two retrospective studies conducted on 79 and 88 patients with esophageal cancer, respectively, to determine the ability of FDG PET-CT to assess response to neo adjuvant therapy, PET-CT was able to provide functional information on response to therapy with a high rate of false positive results in the assessment of response to treatment, allowing for better patient selection and individual treatment stratification. [63]

Regarding the assessment of treatment response, it was found that a negative result with combined PET-CT did not distinguish between a circumscribed viable residual tumor and a complete and histologically confirmed remission after treatment for esophageal carcinoma. FDG PET is also unable to detect a very small residual tumor. In addition, inflammatory changes due to mucosal ulceration or peri or post-therapeutic esophagitis can hinder evaluation of the treatment outcome and lead to false positive results with PET-CT. [64]

FDG PET-CT is useful for detecting distant metastases from esophageal carcinoma in the initial and interim staging of patients on neoadjuvant therapy. [65] Therefore, FDG PET-CT performed during neoadjuvant induction chemotherapy and subsequent chemoradiotherapy allows modification of the treatment strategy by not referring patients with distant metastases for surgery. [66]

Conclusions

Even today, esophageal cancer has a high mortality, mainly due to early lymph node involvement. Precise pretreatment staging of esophageal cancer is crucial in the initial evaluation of affected patients to determine the most appropriate treatment options for the specific stage.

CT, endoscopic ultrasound, and PET scans all play a major role in the staging of patients with esophageal cancer. CT is useful in determining whether the patient can undergo resection or has distant metastases that limit surgery. Endoscopic ultrasound is the best diagnostic technique for determining the depth of tumor invasion and the presence of regional lymph node involvement. PET, on the other hand, is very useful for the evaluation of distant metastases and for restaging after neoadjuvant therapy. Each modality has its advantages and disadvantages; therefore, all three should be considered complementary modalities for the staging of esophageal cancer.

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