EDITORIAL

The Usefulness of Positron Emission Tomography in Nonsmall Cell Lung Carcinoma

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Lung cancer–more frequent among men and the primary cause of cancer-related death–constitutes a major health problem, with a prognosis that is generally so poor that 5-year survival scarcely reaches 15% in spite of treatment.[1]

The most frequent type of lung cancer is nonsmall cell carcinoma, which includes epidermoid carcinoma, adenocarcinoma, and large cell carcinoma. Unlike small cell carcinoma, nonsmall cell tumors are susceptible to surgical resection since they are diagnosed at stage I or II of the disease, whereas small cell tumors frequently present clinically as disseminated disease and require other primary treatment modalities such as chemotherapy and/or radiotherapy. Therefore, the diagnostic approach to lung cancer requires accurate histology, which is based on bronchoscopic specimens in 70% of cases,[2] and accurate staging of the disease, which depends on imaging techniques.

Staging in the evaluation of nonsmall cell carcinoma—using the international TNM staging system denoting tumor shape and size, node involvement, and metastasis to distant sites—establishes the extension of the disease, enabling both the selection of therapy and an assessment of prognosis. Proper staging provides information regarding tumor invasion (T) and distinguishes homolateral and contralateral node involvement, since patients with voluminous technically nonresectable homolateral nodes (N2) or with contralateral mediastinal node involvement (N3) are not susceptible to radical surgical treatment. The clinical stage (cTNM) is determined by noninvasive imaging techniques, whereas the pathologic stage (pTNM) is reached after invasive procedures such as bronchoscopy, mediastinoscopy, or thoracotomy.

In the series studied by McLoud et al[2] and Dillemans et al,[3] from 28% to 38% of patients presented mediastinal lymph node involvement at diagnosis–with computed tomography (CT) of the thorax as the standard technique for detection. However, those authors concluded that CT was less effective for detection of malignant nodes less than 1 cm in diameter and specificity varied. This situation justifies the use of other techniques such as mediastinoscopy, endoscopic ultrasonography, and even thoracotomy—invasive methods that are not free of complications. Consequently, new noninvasive diagnostic modalities, such as positron emission tomography (PET), sentinel node biopsy, and imaging with tumor and molecular markers are tools of great importance and will be used in the near future to determine the overall staging of the disease.

PET images of the radiotracer [18F] fluorodeoxyglucose (FDG; FDG-PET) enable visualization of the elevated metabolism of glucose in tumor tissue in the lungs and mediastinum. At present FDG is the most commonly used PET tracer, and the sensitivity of the technique is based on the high metabolic activity of tumor tissue, tumor volume, activity in affected tissue, and the contrast provided by surrounding healthy structures–thus enabling detection of lesions of 1 cm in diameter. Lesions of less than 1 cm are difficult to detect since the imaging process is conditioned by a PET scanner's intrinsic limit of spatial resolution and by interference caused by a patient's respiratory movements. This is not the case in examining the mediastinum, where PET can detect lesions of less than 1 cm[4]—even as small as 0.4 cm when high-resolution full ring scanners are used. Moreover, PET can provide information on the existence of distant metastases thanks to the possibility of whole-body imaging.[5,6] (Figure)

Regarding specificity, it is well known that benign inflammatory tissue has FDG uptake capacity, both in inflammatory processes and in active infectious diseases that affect the lungs,[7-10] such as histoplasmosis, tuberculosis, coccidioidomycosis, pneumonia, and granulomatosis, among others. These processes cause the appearance of false positives in scans of the mediastinum and require surgical confirmation as a precaution.

The first studies published on the use of PET in lung cancer date from 1990,[11] when PET was used for differential diagnosis. Later, many studies[12-24] comparing PET to CT scanning in lung cancer concluded that PET

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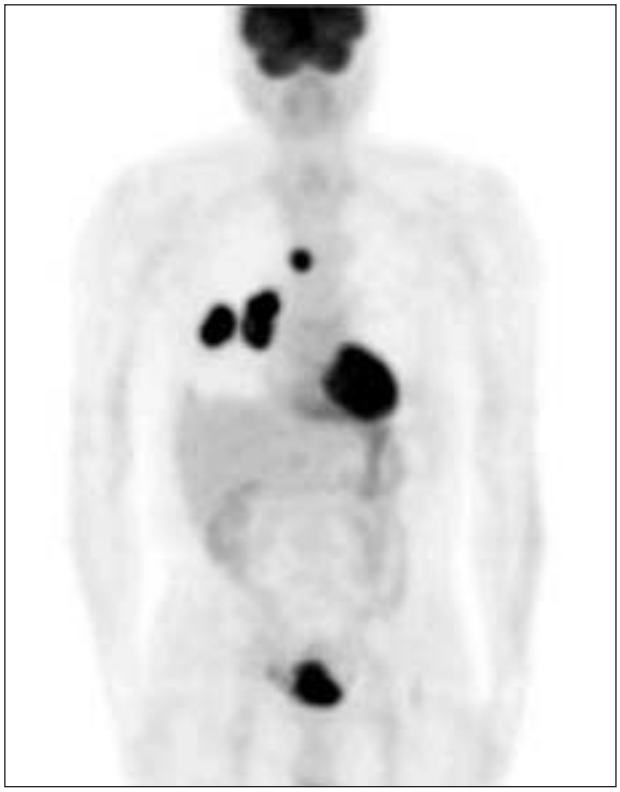

Figure. Patient with right lung cancer in stage T2 (>3 cm) N1-N2 (ipsilateral:paratracheal, hilar).

is useful for staging. The information the two techniques provide differ with respect to the staging of mediastinal lymph nodes, such that for CT, sensitivity ranges from 56% to 81% and specificity ranges from 56% to 94%, whereas PET obtains a significantly higher sensitivity, ranging from 73% to 100%, and specificity, ranging from 81% to 85%. Diagnostic accuracy for PET is also significantly superior: CT, 59% to 85%; PET, 80% to 100%.

Another more recent study[25] evaluated the diagnostic yield of CT, PET, and endoscopic ultrasonography (EUS) in the staging of lung cancer in candidates for surgery. While sensitivity for accurate staging of mediastinal extension of the disease was superior using EUS (94%) compared to CT (57%) and PET (73%), PET specificity was 83% compared to 71% with EUS and 74% with CT. The negative predictive value was 70% with CT, 79% with PET, and 92% with EUS. Diagnostic accuracy was 67% with CT, 79% with PET, and 82% with EUS. Likewise the study showed that diagnostic accuracy improved with a combination of CT and PET (88%), reaching a percentage similar to that of EUS-directed fine needle aspiration (91%).

PET has a major advantage over CT scanning: high negative predictive value in the mediastinum since a positive mediastinal image must be verified by histology in order to rule out false positives; if the image is negative, however, mediastinoscopy can be avoided in as many as 12% of cases according to some authors.[26] Hence, PET staging of lung cancer can change the therapeutic approach as demonstrated in a study by Pietermann et al,[24] who found that of 102 patients who had been staged by standard methods, 42 were found to be in a more advanced stage and 20 in an earlier stage according to PET.

The demonstrated prognostic value of PET has also made this modality useful in assessing lung cancer. In pulmonary lesions the degree of uptake, determined semiquantitatively by the standardized uptake value (SUV), gives information on the degree of lesion differentiation. There is a direct relation between the degree of FDG uptake of a lesion and its malignancy. Numerous studies[27-30] have shown that the SUV varies according to the type of tumor. For example, the histologic type that shows the highest SUV is squamous cell carcinoma, followed by adenocarcinoma, and finally bronchioloalveolar carcinoma, which can present false negatives in PET imaging. Jeong et al[27] ran a multivariate analysis of various factors of possible prognostic value in patients with nonsmall cell carcinoma, including the quantitative information provided by FDG-PET. They found that a higher stage and a SUV greater than 7 in a pulmonary lesion were adversely correlated with survival.

In another study, Pandit et al[31] correlated PET findings with those of pathology and CT/magnetic resonance, as well as clinical observations, in treated and untreated patients. They determined the prognostic value of studies in which PET was positive. They found that, in cases where the PET image was positive, overall survival was significantly poorer than in the cases with negative images; moreover, there was a significant negative correlation between maximal SUV and survival for those patients who had received treatment. Hence FDG accumulation has prognostic value in nonsmall cell lung carcinoma; that is to say, less accumulation is related to longer survival and, according to Pugsley et al,[32] this is due to the correlation between FDG uptake by the tumor and cell proliferation as assessed by Ki-67 expression.

PET is, therefore, a noninvasive diagnostic modality that is capable of detecting alterations in cellular metabolism and that is more reliable than other techniques for staging nonsmall cell lung cancer. The high cost of PET may be compensated for by a decrease in the need for invasive diagnostic procedures and by avoiding inappropriate surgical interventions, making the procedure cost-effective. Accordingly, PET might be indicated for many, though not all, patients with lung neoplasms.[33,34]

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