

6.4 Staging of Breast Cancers

FDG PET is commonly used in breast cancer to determine disease spread, which can be divided into axillary nodal, mediastinal nodal, and distant metastasis assessment.

6.4.1 Axillary nodal evaluation

The presence of axillary nodal disease in breast cancer is an important factor in prognostic evaluation and determining management, and patients with invasive breast tumors typically undergo sentinel lymph node evaluation as part of the initial staging.

Several of the early studies evaluating the use of FDG PET in breast cancer looked into its utility in axillary node staging. Published reports were mixed, with several groups publishing very promising results, and others showing PET sensitivities as low as 20–30%.^{49,50}

A review of studies evaluating the utility of FDG PET in assessing axillary nodal disease using axillary nodal dissection as the gold standard shows a wide variation in reported accuracies, with a sensitivity range of 46 to 95%, specificities ranging from 66 and 100%, PPVs of 62–100%, and NPVs of 60–99%.⁵¹

The largest study⁵² was a prospective multicenter trial involving 360 women with newly diagnosed invasive breast cancer. The objective was to determine the accuracy of FDG PET in the assessment of axillary nodal metastasis using axillary nodal dissection as the gold standard. Sensitivities of 61%, specificities of 80%, PPVs of 62%, and NPVs of 79% were reported. The authors⁵² further found that false-negative axilla had significantly smaller and fewer tumor positive nodes, but that FDG PET may be highly predictive for axillary nodal disease when multiple intense foci of uptake are seen (see Fig. 6.2). These findings are not surprising and are in fact expected with current WB PET devices, in which current resolution capabilities are unlikely to detect small-volume metastatic disease in the axillary nodes.

Of further interest, the histology of the primary tumor is of importance as lobular-type carcinomas were found to have significantly lower FDG uptake compared to ductal-type carcinomas; this translates into substantially lower sensitivities of 12.5–37.5% in the detection of lobular-type nodal metastasis. These lower sensitivities are consistent with previous reports of ductal breast cancers having significantly higher FDG avidity compared with lobular type cancers,¹⁰ and correlate without previous discussion in regard to the biological differences between ductal and lobular histological subtypes.

A further review in which FDG PET was evaluated against sentinel lymph node biopsies as a gold standard found even lower sensitivities,

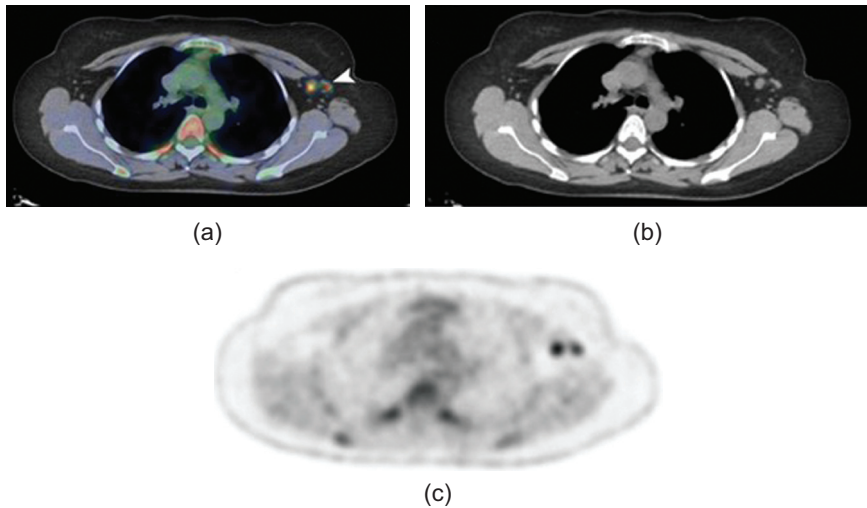


Figure 6.2 Axillary nodal metastasis.

ranging from 15 to 47%.^{53–55} Postulated reasons include the fact that sentinel lymph node histological assessments with its more detailed examination of a small number of nodes is more likely to detect foci of micrometastasis that cannot be identified with current PET detector sensitivities.

Overall, FDG PET is currently unable to replace sentinel lymph node biopsies in patients with early-stage breast cancer but may have a role in the evaluation of patients with locally advanced primary disease in which the risk of nodal metastasis is high, and the use of FDG PET might avoid the necessity of a sentinel lymph node biopsy if the results are unequivocally positive. In addition, caution in the interpretation of negative FDG PET results in primary lobular breast cancers is advised due to the generally lower FDG avidity.

6.4.2 Mediastinal and internal mammary nodal evaluation

The presence of mediastinal or internal mammary nodal metastasis in patients with breast cancers has important implications in management and is generally associated with poorer prognosis.^{56,57} In contrast to the equivocal findings in axillary nodal assessment, there have been consistently encouraging results regarding the use of FDG PET in the detection of mediastinal and axillary nodal disease.

A retrospective review of 73 patients using FDG PET and CT data reported PET sensitivities, specificities, and accuracies of 85%, 90% and 88%, respectively, in the assessment for mediastinal or internal mammary nodal disease, in contrast to 54%, 85% and 73% for CT evaluation.⁵⁸ The recognition of disease in the internal mammary or mediastinal regions (see Fig. 6.3) has prognostic implications, as metastasis to the internal

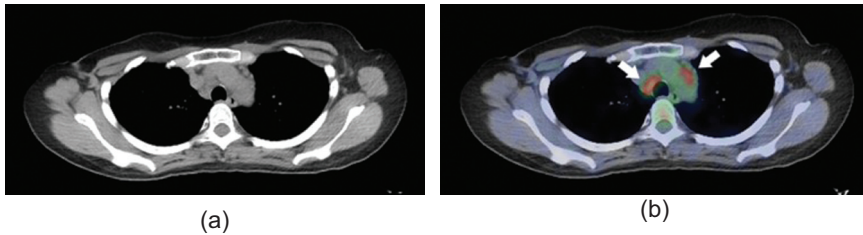


Figure 6.3 Mediastinal nodal metastasis.

mammary nodal chain has been reported to occur in a substantial portion of patients, up to 25% as reported in some studies, and is associated with a poorer prognosis.^{59–60} Further reports have suggested that the presence of internal mammary nodal disease as evidenced by FDG uptake is predictive of failure patterns consistent with such involvement.⁶¹ In addition, the identification of such disease sites has therapeutic implications, as changes to locoregional treatment such as extensions of radiotherapy fields, or more aggressive systemic therapies may be performed depending on findings.

6.4.3 Distant metastasis and overall staging impact of FDG PET

The use of FDG PET in the evaluation of distant metastasis and its general utility as a single tool staging modality is very promising, with several studies demonstrating the increased sensitivity and utility of FDG PET over current conventional techniques.

In one of the earlier studies⁶² using FDG PET in staging for breast cancers, WB PET imaging was performed on 57 patients with suspected recurrent or metastatic disease. Encouraging findings were reported: 93% sensitivity, 79% specificity, 82% PPV and 92% NPV of FDG PET in detecting recurrent or metastatic disease.

Heusner et al.⁶³ from the University Hospital Essen, Germany, demonstrated the technical feasibility and utility of a dedicated PET/CT protocol in breast cancers in which a general WB PET/CT scanner is utilized to perform PET/CT mammography. In a follow-up study,⁶⁴ the same authors evaluated the diagnostic accuracy of an all-in-one protocol of WB FDG PET/CT and integrated FDG PET/CT mammography, and compared it to the diagnostic accuracy of a multimodality algorithm for initial breast cancer staging. Forty women with suspected breast cancers were evaluated, and the combination FDG PET/CT protocol was able to demonstrate good accuracies in local disease (95%), nodal disease (80%), and distant metastasis (100%) assessment. Of interest, FDG PET/CT was reported to have greater accuracy in detecting lesion focality compared to MRI, and

there was an overall 12.5% change in patient management with FDG PET/CT imaging.

A study evaluating the effect of adding FDG PET to conventional screening in patients with locally advanced breast cancer was performed by van der Hoeven et al.⁶⁵ Forty-eight patients were evaluated with PET, and in 8% of the patients, FDG PET correctly detected distant metastasis not seen with routine evaluations. The authors concluded that the addition of FDG PET to standard work-ups for patients with locally invasive breast cancers may lead to the detection of unsuspected distant metastasis and could contribute to a more accurate staging and stratification of patients.

Similar findings were reported by the group from Hospital Clinic of Barcelona, in which a prospective study involving 60 consecutive patients with large (>3 cm) primary breast cancer was imaged using WB FDG PET/CT and compared to typical conventional investigations.⁶⁶ The reported sensitivities and specificities for lymph node assessment was 70% and 100%, respectively, and for distant metastasis it was 100% and 98%, respectively. In contrast, the detection of distant metastasis with conventional imaging was reported with 60% sensitivity and 83% specificity, and FDG PET resulted in a change in the initial staging in 42% of patients.

Mahner et al.⁶⁷ evaluated 119 consecutive patients with newly diagnosed locally advanced breast cancer or patients with suspected recurrent metastatic disease (see Fig. 6.4), and imaging was correlated with histopathology and clinical followup. Reported FDG PET sensitivities and specificities were 87% and 83%, respectively, in the detection of distant

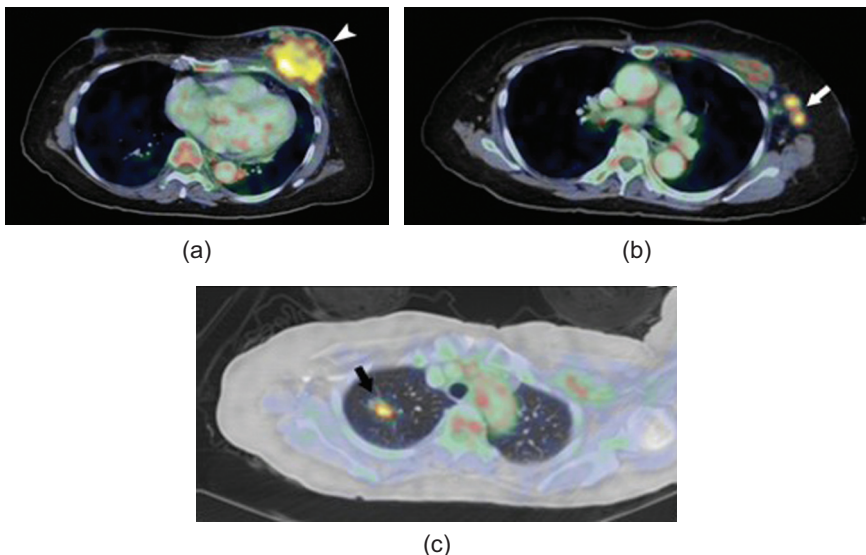


Figure 6.4 Metastatic breast cancer.

metastasis, compared to conventional imaging modality sensitivity of 43% and specificity of 98%.

The overall impact of FDG PET on clinical management is significant. An interesting study investigating the impact of FDG PET from the referring physician's perspective concluded that there was a major impact on the management of breast cancer patients, influencing both clinical staging and management in more than 30% of cases.⁶⁸

6.5 Response Assessment

Imaging plays an important role in determining the response of tumors to systemic or locoregional treatments, predominantly in the settings of neoadjuvant treatment and metastatic disease. Prior to the advent of functional imaging, morphologic or size-based criteria have been traditionally used to measure response, but there were several limitations that include delays in significant size changes, reproducibility of measurements, and lack of correlation to clinical endpoints such as overall survival and time to tumor progression. These potentially may be addressed with functional imaging.

Approximately 10–15% of patients present with locally advanced breast cancer,⁶⁹ and neoadjuvant treatment (see Fig. 6.5) is becoming standard treatment for such patients to both improve surgical options and to provide prognostic information.⁷⁰ Patients with complete response or minimal residual disease typically have longer disease-free and overall survival rates.⁷¹ Techniques that allow prediction of therapeutic response at early time points could potentially halt ineffective treatments early.

Typical morphological approaches to neoadjuvant treatment response evaluation have limitations, and it is often difficult to determine or stratify the response. In 1989, the use of the FDG radiotracer in breast cancer was

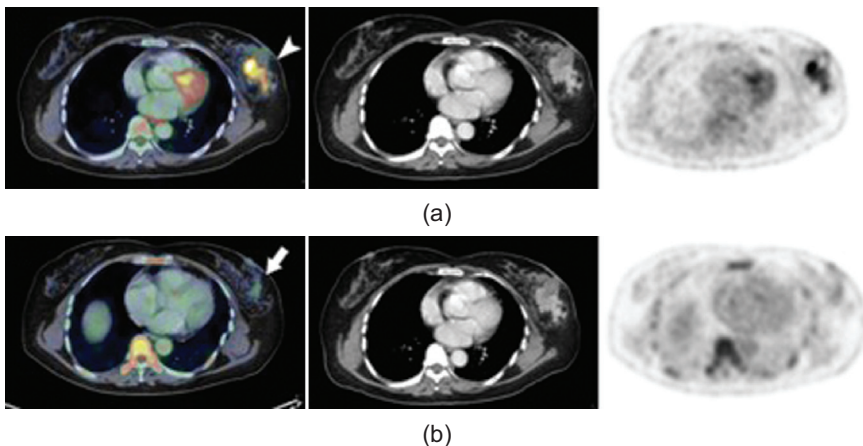


Figure 6.5 Neoadjuvant breast cancer therapy.