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Challenges at the Cochin Cancer Research Centre - PET/CT in Breast Cancer - Boon or Bane? - Lessons learnt from the Royal Marsden experience

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1. Abstract

18F-fluorodeoxyglucose positron emission tomography with integrated computed tomography (18F-FDG PET/CT) can be used for evaluation of response in Metastatic Breast Cancer (MBC). This article aimed to review literature with special reference to clinical practice guidelines from the Royal Marsden Hospital, London. I made a systematic search in Embase, PubMed/Medline, and Cochrane Library using a modified PICO model. The population was MBC patients and the intervention was PERCIST or RECIST. Quality assessment was performed using the QUADAS-2 checklist. A total of 1975 articles were identified. After screening by title/abstract, 78 articles were selected for further analysis of which 2 duplicates and 39 abstracts/out of focus articles were excluded. The remaining 31 articles provided useful information, but only one met the inclusion and none of the exclusion criteria. This was a retrospective study of 65 patients with MBC showing one-year progression-free survival for responders versus non-responders to be 59% vs. 27% ($p = 0.2$) by RECIST compared to 64% vs. 0% ($p = 0.0001$) by PERCIST.

This systematic literature review identified a lack of studies comparing the use of RECIST (with CE-CT) and PERCIST (with FDG-PET/CT) for response evaluation in metastatic breast cancer. The available sparse literature suggests that PERCIST might be more appropriate than RECIST for predicting prognosis in patients with MBC.

2. Introduction

The morbidity and mortality related to breast cancer remains high necessitating the optimization of role of imaging in breast cancer management. Functional imaging approaches are being increasingly used in breast cancer management, the principal advantage over anatomical imaging being that sites of active disease are (Figure 1) accurately assessed. A particularly exciting development in recent years has been that of the advent of positron emission tomography/ computed tomography (PET/CT) scanners providing functional information regarding disease status (defining sites of active/inactive disease) combined with the anatomical definition of CT.

The principal tracer used in clinical PET to date is 2-(fluorine-18) fluoro-2-deoxy-D-glucose (18F-FDG). The extent of 18F-FDG uptake in tumors is directly related to the number of viable tumour cells. In addition, the number of viable tumor cells expressing the cell surface glucose transporter 1 (GLUT- 1) best correlates with the extent of 18F-FDG uptake by the tumor; GLUT-1 being over expressed in breast cancer [1].

Here I will outline the role of PET/CT in breast cancer patients citing excerpts The Royal Marsden Hospital in London. The assessment of primary/axillary nodal disease will briefly be reviewed followed by the role of 18F-FDG PET/CT in defining metastatic disease, treatment response assessment, and disease recurrence. Likely future applications of PET in breast cancer will also be briefly addressed (Figure 2).

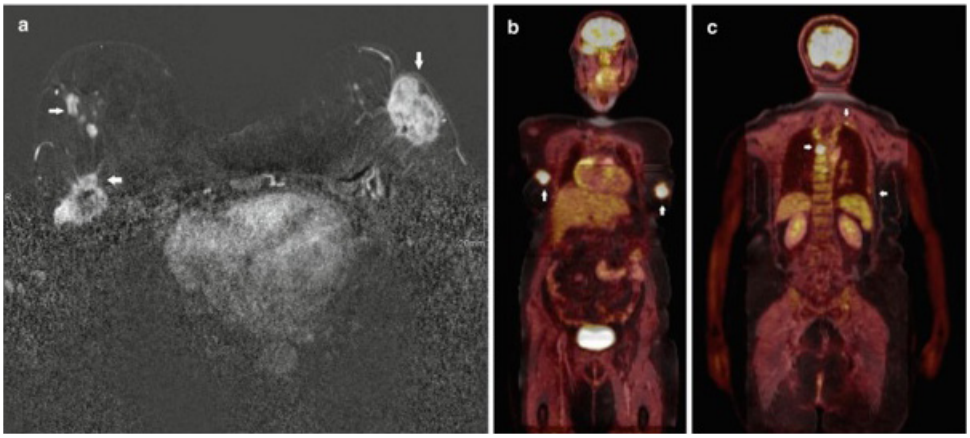

Figure 1: A 66-year-old female with bilateral biopsy proven multicentric breast cancers underwent whole-body 18F-FDG PET/MRI which enables "one stop" staging of both locoregional and distant disease (histology: right invasive ductal carcinoma NOS, G2, ER/PR positive, HER2 negative, p53 weakly positive (10%), MIB-1 20% positive; left invasive ductal carcinoma NOS G2, ER/PR positive, HER2 weakly positive (20%), p53 weakly positive (10%), MIB-1 10% positive). (a) Contrast-enhanced axial T1 subtracted breast MRI image shows multicentric disease on the right (arrows) involving the skin, nipple, and chest wall and a dominant left breast mass (arrow) involving the nipple; bilateral T4 tumors (b, c) Coronal fused whole-body PET/MRI images show bilateral FDG avid breast tumors (arrows) (b) and multiple FDG avid osseous metastases (arrows) (c). PET/MRI also revealed bilateral FDG avid axillary and supraclavicular nodes (not shown). Overall stage T4, N3, M1.

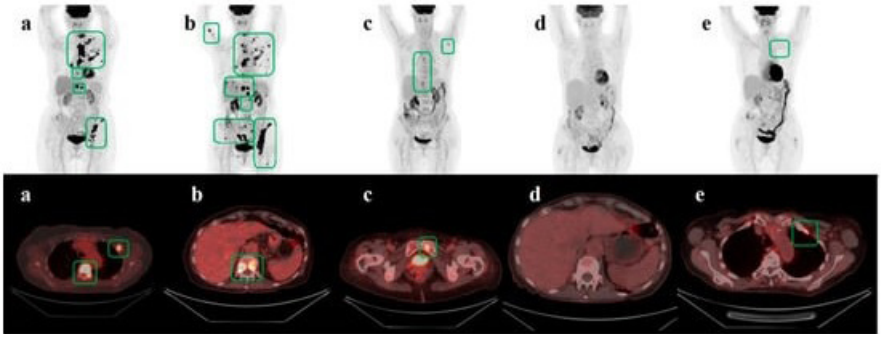

Figure 2: The figure shows serial FDG-PET/CT images (a–e) for a patient with primary treatment for ductal carcinoma in situ in 2011; Van Nuys, gr. III. No adjuvant chemotherapy or radiotherapy was given after surgery. Baseline FDG-PET/CT in February 2017 (a) showed metastases in bone and lymph nodes. She was treated with thoracic radiotherapy and a first series of TDM1. Follow-up scan in April (b) showed progressive metabolic disease possibly due to delayed initiation of treatment. The patient received five more series of TDM1. A third scan in May 2017 (c) showed partial metabolic regression before the patient received the sixth and seventh series of TDM1. The scan from July 2017 (d) showed complete metabolic regression. Treatment was stopped thereafter due to side-effects. The control scan in February 2018 (e) showed a tiny bone lesion suspicious of relapse. TDM1 = Trastuzumab Emtansine. Green squares outline metastatic lesions.

3. Methods

A search was performed to identify mainly all published randomized controlled trials and systematic reviews in the English language literature. An additional search was performed to identify relevant unpublished systematic reviews. These publications comprised both retrospective and prospective studies of variable methodological quality. The consequences of false-positive and false-negative test results when evaluating the clinical usefulness of tests, as well as the impact of 18F-FDG PET/CT on the management of cancer patients, were also reviewed. I made a systematic search in Embassy, PubMed/Medline, and Cochrane Library using a modified PICO model. The population was MBC patients and the intervention was PERCIST or RECIST. Quality assessment was performed using the QUADAS-2 checklist. A total of 1975 articles were identified. Quality assessment was performed using the QUADAS-2 checklist. A total of 1975 articles were identified. After screening by title/abstract, 78 articles were selected for further analysis of which 2 duplicates and 39 abstracts/out of focus articles were excluded. The remaining 31 articles provided useful information, but only one met the inclusion and none of the exclusion criteria.

4. Primary Staging

The evaluation of primary or axillary breast cancer disease status is not an "indication" for 18F-FDG PET/CT imaging. When PET studies are performed on patients with breast cancer, a significant proportion of primary breast cancers can be detected, including multifocal, bilateral, and occult disease. Likewise, a significant proportion of "involved axillae" will also be detected. PET often elegantly demonstrates axillary level I, II and III disease, including occult disease in a significant proportion of patients as well as

small volume nodal chain involvement [2].

For staging primary breast cancer, a number of studies have demonstrated that PET is not sufficiently accurate compared with the conventional breast work-up which includes triple assessment, including mammography, ultrasound, cyto/histology, and Magnetic Resonance Imaging (MRI) where indicated. Accuracy of whole body 18F-FDG PET/CT imaging in the detection of primary breast cancer depends on the lesion size; 0/4 stage pT1a tumors (0.5cm or smaller) and 1/8 pT1b tumors were detected by PET [3].

False negative findings are also observed with slow-growing or well-differentiated tumors, non-invasive, tubular, ductal carcinoma in situ and lobular tumors (a histological subtype which can often be 18F-FDG PET" negative" or low grade, although they can be FDG avid in a small proportion of patients [4].

It should also be recognized that 18F-FDG is a glucose ligand, therefore, not truly a tumor-specific agent. False positive uptake is therefore observed with inflammatory or infectious lesions and for a short period after biopsy or surgery (Figure 3).

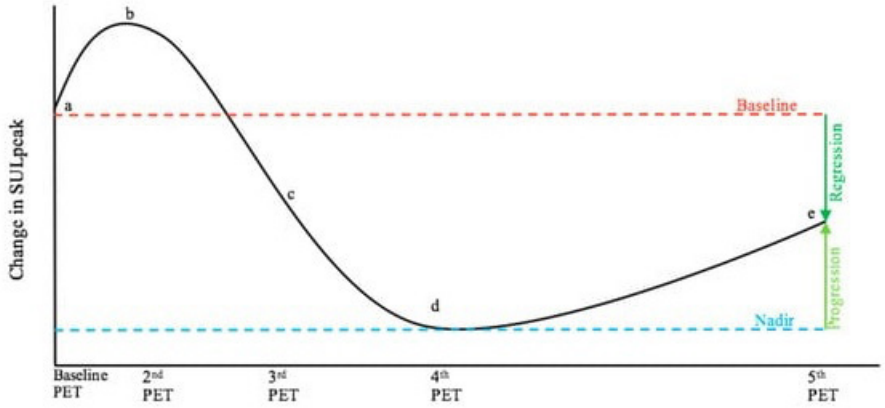

Figure 3: The graph is a theoretic illustration showing the curve for the continuous variable of SULpeak in a fictive patient that corresponds to the patient course illustrated in Figure 2, where (a) to (e) now represent corresponding fictive SULpeak values. The bone lesion in (e) is considered suspect for metastasis. The patient would be categorized to have partial metabolic regression, when compared to baseline (a) as suggested by PERCIST 1.0, but progressive metabolic disease would be concluded when compared to nadir (d). which may be more clinically relevant. SULpeak= peak standardized uptake value normalized to lean body mass.

While there is some interest in the potential use of 18F-FDG PET for axillary nodal staging, current whole body PET/CT scanners are not quite of sufficient accuracy to replace the current "gold standard" of sentinel lymph node biopsy (SLNB) in routine clinical practice. PET will demonstrate axillary level I, II, and III disease and is particularly useful in the detection of level II and level III involvement where disease is invariably occult, enabling appropriate surgical and radiotherapy treatment planning pre-operatively [5]. It is now an accepted practice for breast surgeons to perform axillary dissections, without SLNB, where a PET is considered confidently positive for axillary nodal involvement, based on semi-quantitative Standard Uptake Value (SUV). Conversely, because a "PET negative axilla" may reflect a 'false negative' finding, an SLNB should be performed.

Precise anatomical information can be given on extra-axillary sites including internal mammary chain and supraclavicular disease. Unlike CT alone, PET is able to detect occult small volume nodal disease in these distributions and also enables treatment planning such as radiotherapy.

There is also some evidence for greater FDG uptake in triple-negative cancers, raising the possibility for future PET use in staging specific tumor subtypes [6].

Currently, although moderately sensitive, PET is not routinely used for primary disease or axillary workup. Very useful clinical information can be provided in a significant number of cases when a PET study is performed in patients with breast cancer including the evaluation of local and distant disease.

5. Distant Metastatic Disease

Converse to the assessment of primary disease, a large number of world-wide studies clearly demonstrate that PET/CT is the "single" most accurate imaging modality now available to stage metastatic disease. This technique provides both soft tissue and bony staging, often revealing unsuspected metastases in up to 30% of patients, with resultant management change [7].

The strengths of PET/CT are the fact that it is a whole-body scanning modality, accurately assessing the soft tissues, viscera, and skeleton with "one" test and with the ability to define the sites of active tumor.

The technique is particularly effective in demonstrating small (sub 5-10 mm) metastatic nodal sites of involvement and bony disease. With anatomical CT imaging the significance of small (sub 1 cm) sites of change (adenopathy) is difficult to assess (eg. In axillary levels II and III, the internal mammary and mediastinal stations); PET can indicate pathology in small nodes, in patients otherwise

thought to be "disease free". As mentioned above, the lack of a tumor-specific PET tracer raises the risk of false-positive studies. For example, entities such as sarcoidosis will cause increased FDG accumulation, with mediastinal and bilateral hilar nodal uptake [8].

Therefore, it is important to always interpret scan findings in the clinical context and use all the imaging findings in order to provide an accurate diagnosis. A useful rule in daily clinical practice is that" 'a 'positive' ^{18}F-FDG PET does not always imply malignancy and a 'negative' ^{18}F-FDG PET does not always imply that malignancy is absent.

Technetium-99m methylene diphosphonate (99m Tc MDP) bone scintigraphy is conventionally used to assess the skeleton but is not a specific technique as an osteoblastic response is imaged. False positive uptake is seen with a degenerative change, trauma, inflammation, and infection. In addition, bone scan is not sensitive in the context of lytic metastatic disease when a significant osteoblastic response may not occur, and areas of resulting photopaenia can be difficult to identify [9].

CT bony window assessment is insufficiently sensitive for staging. MRI, although a sensitive technique, is targeted to certain parts of the skeleton, not currently being a whole-body-scan modality in clinical practice. Diffusion-weighted MRI is an interesting new technique, with protocols being developed in relation to whole-body imaging. However, this technique remains of research interest and has not been sufficiently developed at present for routine clinical practice [10].

^{18}F-FDG PET is a more specific modality than bone scan as it demonstrates sites of viable tumour cells in the skeleton. The other significant benefit of PET over bone scan is the improved accuracy in the detection of lytic metastatic disease. As lytic disease is associated with a more aggressive breast cancer and a worse prognosis, an earlier and more accurate detection by ^{18}F-FDG PET is of particular importance [11]. A large retrospective study from the Royal Marsden Hospital, London evaluating 233 ^{18}F-FDG PET studies over a 4-year period found that PET/CT was particularly useful in evaluating lytic disease [12].

The entity of the bone scan-negative PET-positive patient with bony metastatic disease is now clearly recognized; these patients virtually always have lytic lesions. If a "negative bone scan" is observed in a patient, where the clinical index of suspicion of bony disease is high, in the context of bone pain or a raised alkaline phosphatise, an ^{18}F-FDG PET scan should be considered.

^{18}F-FDG PET is also extremely useful for liver disease evaluation. The concept of the indeterminate liver lesion is well known on ultrasound, CT, and liver MRI, which sometimes requires biopsy. However, this can constitute risk to the patient if the lesion is in a challenging anatomical location or is hyper vascular. The key advantage of PET over MRI in the evaluation of liver lesions is that benign vascular liver lesions such as haemangiomas, focal nodular hyperplasia, and adenomas, with "atypical appearances" on CT and MRI are FDG negative. Conversely, liver metastases from breast cancer, including small liver metastatic lesions are PET positive [13].

6. Limitations

Limitations of ^{18}F-FDG PET include the lack of ability to effectively evaluate the neuroaxis. Metastatic lesions in the brain parenchyma and leptomeningeal disease are difficult to identify on PET due to physiological FDG brain uptake [14].

Although PET will detect moderate or larger volume intracranial metastases, and leptomeningeal disease in a small number of patients, gadolinium-enhanced MRI of the craniospinal axis is the gold standard modality for CNS evaluation. However, an area where PET is increasingly useful is with gamma knife intracranial surgery. This technique is being used in a proportion of patients with breast cancer depending on the number of intracranial deposits, thereby avoiding Whole-Brain Radiotherapy (WBRT). Post gamma knife, active or recurrent disease can be very difficult to differentiate from radio necrosis on MRI imaging. Correlation and fusion of post-gamma knife PET cranial studies with MRI is useful in this context as radio necrosis is PET negative and active/recurrent disease is 18F-FDG avid [15].

PET also has difficulties in fluid compartment assessment. Due to the tumor cell density being low in fluid, 18F-FDG PET will not differentiate benign from malignant fluid. Hence, the technique will not differentiate benign from metastatic pleural or pericardial effusions or ascites. In a study of ascites of undetermined origin, the sensitivity, specificity and accuracy of ^{18}F-FDG PET/CT in detecting the primary cause of ascites were 63.3%, 70.0%, and 65.0%, respectively [16].

It is critical to always evaluate these anatomical compartments on the underlying CT aspect of ^{18}F-FDG PET/CT when analyzing PET data. Likewise, although a PET signal will usually be seen in the context of omental/peritoneal disease infiltration, a significant PET signal may not be seen with fin e peritoneal stranding/infiltration. This highlights the importance of reviewing the peritoneal spaces on the anatomical CT fusion component of PET.

Despite the few limitations, clinicians need to recognize that in a proportion of patients, disease will be detected by this new, more sensitive imaging modality at an earlier stage and smaller anatomical volume than with "CT or bone scan."

Given that ^{18}F-FDG PET/CT is the most sensitive current imaging modality to define metastatic disease there is clearly an argument that it should be used as the first-line investigation in patients with metastatic breast cancer. This would reduce the need for serial investigations which may include plain films, bone scintigraphy, CT, MRI, and biopsy prior to a ^{18}F-FDG PET/CT scan. As ^{18}F-FDG PET/CT accurately defines the disease status early in the patient's workup, the management pathway can become more efficient and

cost effective.

7. Assessing Response to Treatment

^{18}F-FDG PET/CT is useful in assessing response to a number of different types of treatment, particularly hormone/endocrine therapy, chemotherapy, radiotherapy, and surgery. It is also now being used with radiofrequency (RF)/ laser ablation and post-cyber knife therapy [17, 18].

The large Royal Marsden Hospital PET/Breast Cancer series [12] showed that 18F-FDG PET/CT studies over a 4-year period at this institution were useful in the management of patients, with up to one-third of all studies performed for response evaluation.

Because PET will give a very useful indication of the overall "active" disease burden, it provides clinicians with important information regarding the timing and use of non-toxic treatment/ maintenance strategies, such as hormone treatment for example, where " metabolic low volume" active disease, or "metabolic low intensity"(low SUVmax), disease remains and the need for / use of more toxic systemic single/ combination chemotherapy treatment strategies (where metabolically large volume and/or intensely FDG-avid disease is present).

8. Early Treatment Response Assessment

The early assessment of treatment response is a particularly exciting use of functional imaging, as metabolic changes in tumors occur before morphological (anatomical) changes occur. The early differentiation of responding from non-responding patients would allow for alteration / discontinuation of ineffective treatment, improving patient morbidity and mortality, and also leading to public health care savings.

^{18}F-FDG PET/CT scanning of metastatic breast cancer has the ability to detect rapid and significant reduction in glucose metabolism in responding patients, whereas no significant reduction is seen in non-responding patients. Although the optimum time for the investigation of treatment response has not yet been established, the response / non-response differentiation is possible as early as day 8 after the first cycle of chemotherapy. The use of SUVs for serial response evaluation is part of our routine daily clinical practice, baseline marker SUVmax (standard uptake value maximum) levels being documented with marker levels at different body sites of involvement, such as primary breast, nodal, lung, liver, and bone marker measurements. This allows a serial semi-quantitative PET analysis, as well as visual scan analysis, on subsequent studies as demonstrated in the large clinical series audit of Royal Marsden Hospital [12]. The role of MRI is also under active investigation in treatment response in the neoadjuvant setting [19].

Early assessment of complete tumor destruction following RF ablation (RFA) or laser therapy of liver metastases and a subsequent follow-up of RFA sites is difficult with conventional imaging. Ultrasound, CT, and MRI all have limitations with regard to sensitivity and specificity. PET is a modality which is particularly useful in this regard, enabling both early assessment of complete/incomplete tumor destruction and also being a sensitive and an accurate modality in subsequent follow-up [20- 22].

In addition to visual PET analysis, the semi-quantitative SUVmax measurement is also very useful in providing a semi-objective measurement regarding bone disease status. Although PET/CT can be used "early" for response evaluation and has been usually performed within 1 week of chemotherapy in certain tumor types, a practical issue is the presence of physiological bone marrow reactivation due to chemotherapy, which will cause a generalized increased marrow activity on 18F-FDG PET/CT studies [23]. In general, it is better to delay the "Early Response Evaluation" PET study, in the context of assessing bone response, for as long as possible; for example, if the patient is on a weekly chemotherapy regimen, to perform the PET at day 6 or day 5 (i.e., circa 1 or 2 days before the next treatment cycle is due), thus reducing the extent of marrow reactivation effects.

The above principle also applies to previous radiotherapy fields – metabolic photopaenia being shown on PET at treated and responding radiotherapy field sites (a few months and onwards after radiotherapy). This is also very useful for defining disease recurrence/tumor activity within previous radiotherapy beds, disease recurrence showed an increased PET signal, recurrence often being difficult to objectively define on CT or MRI, with clinical problems of patient pain and changing tumor markers often also being an issue in this clinical scenario.

Have published the largest study on response evaluation using CE-CT and RECIST in patients with MBC. They found that the RECIST criteria showed poorer correlation with survival for MBC than for colorectal cancer and non-small cell lung cancer. This result was unchanged whether patients in the stable disease group were considered as responders, tumor-static responders, or non-responders [23].

Regarding the use of FDG-PET/CT, current literature indicates PERCIST to be a valid method for response evaluation in MBC. However, the only study that directly compared PERCIST from FDG-PET/CT and RECIST from CE-CT was a retrospective study with some limitations, such as a relatively small patient group (n = 65) and therapy regimes from multiple protocols including cytotoxic, hormone, target therapies, and a combination of these. Breast cancer subtype and hormone receptor status also varied, giving a highly heterogeneous patient group [24].

The PERCIST guidelines recommend measuring either SULpeak in the hottest one lesion or the sum of SULpeak in up to five lesions. The impact of analyzing one or up to five lesions was investigated by [25]. who assessed response in 60 patients using SULpeak of the most FDG-avid lesion (PERCIST1) and by the change in sum for SULpeak for five lesions (PERCIST5). The two

approaches gave responses that were equally (and significantly) correlated to progression-free survival and disease-specific survival. The authors concluded that there was little difference between using one or five lesions for response evaluation with PERCIST. Analysis of up to five lesions means that any progressive metabolic disease will not be ignored as SULpeak might increase less in a single lesion than in the sum of several lesions. Progressive metabolic disease might be underestimated for the same reason. It is worth noting that [26] found alternative threshold values for all metrics when applying ROC analysis on the metabolic indices, which slightly improved the performance of SUVpeak and total lesion glycolysis. This suggests that there might be more optimal threshold values for metrics than those specified by PERCIST.

When using FDG-PET/CT for evaluation of targeted treatment [27]. found that this modality had a significant correlation with clinical outcomes, suggesting that it might be useful for response evaluation in the setting of patients receiving targeted treatment.

9. Liver Response

Ultrasound and CT (MRI when required) are useful modalities for liver metastatic disease evaluation. However, in a proportion of patients, objective or convincing objective response evaluation can be difficult with these modalities, particularly with the "workhorse modality" of CT in the situation where widespread liver abnormality is often present. It can be very difficult to evaluate whether liver disease is progressing, active, responding, or showing a mixed response.

Akin to the situation of PET providing a signal in the context of widespread bone infiltration, PET is very useful for defining the control of liver disease or disease reactivation. Experience at the Royal Marsden Hospital finds PET particularly useful in the context of liver residual changes and "Liver Pseudocirrhosis of Malignancy" [12], the PET simply being "negative" in in the context of a controlled "fibrotic" liver, whereas the metabolic volume and metabolic intensity (SUVmax) of liver disease activity/ reactivation can be clearly visualised and documented on PET. This is important, as extensive liver involvement / active disease is a life threatening situation in breast cancer, the PET providing information regarding liver disease status and therefore enabling appropriate treatment.

10. Limitations and Caveats

Small (sub 7mm in particular) lung nodules can be beyond the resolution of current PET scanners, therefore, it is important to always scrutinize the underlying CT anatomical lung window component of ^{18}F-FDG PET/CT scan. As discussed above, fluid compartment assessment is also limited.

Kruk Enberg deposits can also be misinterpreted in pre-menopausal women. This is because cyclical physiological ovarian activity can be seen as a normal appearance on ^{18}F-FDG PET/CT imaging. While in a post-menopausal woman, adnexal 18F-FDG increased activity is considered to usually reflect disease involvement, in a pre-menopausal woman again due consideration needs to be given to the CT appearance in the adnexum, occasionally a trans-vaginal ultrasound or Pelvic MRI being needed for further clarification [28].

Pleurodesis is a situation where care is needed regarding the interpretation of PET data/response evaluation. Pleurodesis incites an intense inflammatory reaction, with activated macrophages and granulation tissue; these cells will of course take up the FDG radiotracer (which is a glucose analogue). When PET imaging is performed post pleurodesis, one invaraiably sees an intense PET activity encasing a hemithorax. Furthermore, serial SUVmax measurements are not helpful in this situation, as the degree of pleurodesis metabolic activity can "wax and wane" for a number of months and years following the procedure [12]. On a very detailed analysis, the sites of increased pleurodesis-related PET activity usually correspond to "typical high-attenuation CT sites of pleurodesis change" on the underlying CT aspect of PET, however. Pleural disease recurrence / progression is usually shown by an increase in pleurally based soft tissue change on review of the underlying CT aspect of PET (as well as associated PET changes) and/ or re-accumulation / a significant increase in pleural fluid volume.

^{18}F-FDG PET/CT is very useful for bone response evaluation, including post-surgery and post radiotherapy, as described earlier. A potential pitfall when reporting PET studies is in the context of vertebroplasty procedures, however [29].

This is because "high attenuation" vertebroplasty cement" (shown on the CT aspect) causes an "attenuation correction artefact" on PET studies, implying a "PET positive" appearance (reminiscent of active disease). Again, as always for appropriate patient data interpretation / reporting it is very important to analyse the underlying CT soft tissue and bone window appearances of ^{18}F-FDG PET/CT and not to just assess PET data in "isolation." If a high-attenuation typical "cement" appearance is seen on CT, then evaluation of the source "non-attenuation" corrected PET data on the workstation is appropriate. An "attenuation correction artefact signal" will not be seen on the source data. These steps will avoid the possibility of calling "false positive" sites of disease.

11. The Concept of "Oligo metastatic" Disease

PET is critical for the appropriate selection of patients with metastatic breast cancer for novel treatment strategies such as surgery for "oligometastatic disease" (e.g., sternal disease resection and chest wall reconstruction) or planning potential liver RFA. PET is able to define the disease extent and is crucial for the detection of clinically important occult disease.

The use of novel techniques such as RFA has led to improved patient quality of life, prolonged survival, reduced requirements for toxic systemic chemotherapy treatments, and improved overall outcomes [30].

12. Pet and Prognostication

In breast cancer PET will provide prognostic information on treatment responsiveness and whether the particular regimen can be used again in future for example, also highlighting when treatment resistance has developed.

PET can show treatment response to hormone and systemic chemotherapy. This provides very useful clinical information. For example, if a patient has a substantial "PET metabolic volume" and "PET metabolic intensity" (SUVmax) and early response to agents such as capecitabine, or vinorelbine/herceptin, or avastin, this provides useful treatment prognostic information. It implies that continued treatment with this regimen is reasonable and may be used again in future, in the event of patient relapse. Serial PET studies may be performed, to confirm ongoing treatment responsiveness, until PET shows that treatment resistance to a particular regimen has developed. "Resistance" to the particular regimecan eventually develop after it has been used two to three times in a treatment pathway. In other cases, the PET may show that the SUVmax levels do not change substantially, for example the SUVmax may change from 10 to 9, in which case the patient is not particularly responsive to the particular regimen in question, and a different regimen may be considered.

Unfortunately, unlike the situation of PET in some other tumor types such as Hodgkin's lymphoma, PET will not provide prognostic information regarding "durability of treatment response in breast cancer [31].

A patient may show a complete metabolic "switch off" of disease activity on PET imaging, for example (metabolic complete response/ remission CR). The NPV of PET CR in Hodgkin's lymphoma is 82-90%. This does not apply for PET and breast cancer. A PET CR in breast cancer does not provide any prognostic information regarding the durability of response. Despite a PET CR, the patient's breast cancer can reactivate at any future time. The key consideration after achieving PET CR in breast cancer is treatment consolidation and maintaining a non-toxic treatment strategy.

13. Current and Future Practice

Given the current resource limitations of ^{18}F-FDG PET/CT, conventional work-up / assessment, bone scan and CT, currently remain the "workhorse" modalities to define metastatic / recurrent disease and assess treatment response. Clearly, CT is a suitable modality in a vast majority of patients (>99%) in this regard. Current recommendations for ^{18}F-FDG PET/CT should be the following:

1. a small percentage of patients where there is true clinical/ imaging equivocation / uncertainty regarding recurrent/ metastatic disease status (and where clinical management will be influenced by the result), as PET is very useful in this regard as a diagnostic problem-solving tool;

2. where treatment response cannot be reliably assessed by other means, PET provides a useful signal for response evaluation.

As ^{18}F-FDG PET/CT becomes more widely available, patient management pathways will change, and ^{18}F-FDG PET/CT is likely to be used early and extensively in the management of patients with metastatic breast cancer. Functional imaging will have an increasing role to play in patient management in years to come.

14. Conclusion

^{18}F-FDG PET/CT is fundamental for the appropriate and optimal management of breast cancer patients. With current clinical radiotracers and technology, it is not accurate enough to be used in routine clinical practice in the context of primary breast disease, axillary nodal assessment, conventional work-up remaining the gold standard (although PET when performed in a breast cancer patient will provide useful primary breast and axillary staging information in a significant number of patients). However, the converse is true regarding defining recurrent disease, re-staging metastatic disease extent, and for treatment response assessment; PET proves to be a very useful diagnostic imaging problem solving tool in the context of imaging or clinical uncertainty. ^{18}F-FDG PET/CT is currently the most accurate imaging modality available for defining recurrent / metastatic disease, a key advantage being a whole-body assessment (soft tissue, nodal, visceral, and bony sites) with one test. Despite the fact that current ^{18}F-FDG PET/CT cannot rule out microscopic disease, it does provide a reliable assessment of the true extent of macroscopic metabolically active disease. It is also a highly effective and useful test to define treatment response, key strengths being early response assessment and the differentiation of active from inactive disease sites. Bony response assessment is a particularly exciting area – this being difficult with other imaging approaches. As ^{18}F-FDG PET/CT resource becomes more widely available in the coming years, it is likely that patient management pathways will change, with ^{18}F-FDG PET/CT being increasingly widely used early in the breast cancer disease course.

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