Dual Target Molecular Imaging in precision management of breast cancer: The time has come

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1. Introduction

In the early days, the efficacy of evaluation of available treatment options in estrogen positive breast cancer (ER +ve BrCa) was dependant on randomized double blind placebo controlled trials to determine the efficacy of a particular treatment and there was paucity of biomarkers for prognostication and prediction. The estrogen receptor (ER) is a prognostic and predictive biomarker in breast cancer and the expression of this receptor helps to determine the nature of treatment which is required in this set of patients. (1)

Currently, there are various bio marker assays which are used in ER +ve BrCa for prognostication and prediction of outcomes to various treatment protocols or chemotherapeutic drugs. ER +, Erb B-1+ and/or ErbB-2+ (epidermal growth factor receptor and HER2/nue) primary breast cancer responds well to Letrozole. It also responds to Tamoxifen but these responses are infrequent. This suggest that signaling of these factors through ER depends on ligand and growth promoting effects of these receptor by tyrosine kinase on ER + breast cancer can be inhibited by potent estrogen deprivation therapy (2). Similarly, the relationship of 21-gene recurrence score (RS) assay with the likelihood of distant recurrence in these group of patients have also been reported (3). Common variants on chromosome 5p12 have also been used (4).

2. Overview & Review of literature

In breast cancer, correct staging and early diagnosis is the key factor in patient management. Imaging in breast cancer has evolved from purely morphological imaging to molecular imaging in current times and this has had a significant impact on patient management. 18F fluro-deoxy-glucose PET-CT (FDG) exploits the high glucose turnover in cancer cells as compared to normal cells (5,6) and has become the standard of care in breast cancer staging, response evaluation, restaging and metastatic work-up (7,8,9,10,11,12,13). It must also be kept in mind that granulocytes and activated lymphocytes also exhibit significantly increased glucose uptake and in many occasions it creates a diagnostic dilemma in interpretation of FDG. (14,15) In addition to this, fluoroestradiol labeled with F-18 (FES) has been found to bind ER with high affinity and has been studied in vitro with good results and has currently reached the bed side in the form of imaging with PET-CT. This can evaluate ER expression in all disease sites, in both primary and metastatic disease. The sensitivity and specificity for detection of ER +ve breast cancer has been 84% and 98% respectively (16,17,18,19,20). Currently there has been an attempt to test the ability of FES to predict pathologic response to neo-adjuvant therapy (NACT) by FES imaging (21,22) The authors concluded that FES uptake was a determinant factor in choosing either NACT or endocrine therapy. The patients having ER-rich tumors defined by immunohistochemistry (IHC) but poor FES uptake are better treated with NACT as compared to endocrine therapy (22). The study also focuses on the diagnostic accuracy of FES imaging of primary ER +ve breast tumors. It was found that there was 92% positive agreement between FES imaging and ER α immunohistochemistry (21). In another study, it was also reported that pre-therapy FES SUV max was lower in pathologic responders than non-responders. (23).

3. Discussion

The value of FES imaging has been documented in few current studies in literature. Similarly, the value of FDG imaging in breast cancer has already been documented in the overall management of the disease. The data of dual target (FES & FDG) imaging in the same patient is however lacking in literature. It has been contemplated that the FES PET examination combined with a FDG (which is a surrogate marker of glucose metabolism) PET examination in the same patient could potentially improve the predictive power of risk stratification and evaluating response in hormone positive breast cancer. FDG evaluates the glucose utilization by the tumor and can demonstrate tumour aggressiveness. In this context we would like to draw attention to the recently published study from our group in which we have performed FES and FDG imaging both in staging and restaging of hormone positive breast cancer (24) in the same patient within one week interval. Lesion detection sensitivity was compared for a total number

of lesions, and for non hepatic ones, as normal bio-distribution of FES in the liver makes detection of hepatic lesions difficult. We analyzed 154 lesions in 10 ER positive breast cancer patients. FDG picked up 142 lesions with a sensitivity of 92.21% whereas the sensitivity of FES was 75.32 %. The sensitivity of FES improved to 85.29% when hepatic lesions were excluded from the analysis. FES was also able to characterize 27.5% FDG indeterminate lesions, thereby having an impact on the management in 20% of the patients. The receptor status plays an important role in predicting outcome as well as has a significant role in personalizing treatment protocols. Hormone positivity has an impact on both treatment planning and prognosis and therefore imaging the estrogen receptor (ER) will have an important role. FES correctly characterized FDG positive (false positive) mediastinal lymph nodes which creates interpretational problems especially in our Asian subcontinent. On analysis of the correlation between ER expression and SUV max of FDG and FES lesions by Spearman rank test we found a positive co-relation between ER expression and FES median SUV max. We also calculated the *P* values and *P* trend between the level of ER expression and the FDG or FES SUV max using Kruskal-Wallis test and Jonckheers-Terpstra test, respectively. *P* value was not significant with the level of ER expression and the SUV max in either of the tracers. However, a positive trend was noted with FES SUV max and ER expression (*P* trend 0.011). Negative trend of ER expression with FDG uptake was also appreciated (*P* trend 0.118). We were also able to validate the fact that subcutaneous skin nodules could well be characterized with the help of FES PET along with a periampullary mass lesion as an uncommon site of metastasis in another. Both of these cases were proven by cytology. The impact on management was noticed in the form of detecting bone and lymphnodal metastatic sites not appreciated otherwise (24). We are aware that measurement of ER expression is done by biopsy at the time of primary diagnosis. Estrogen is involved in the growth of both normal and cancerous breast tissues. Its activity is mediated by ER receptor and its positivity in breast cancer cells has a profound impact on treatment and patient outcome. With the background knowledge of tumor heterogeneity, a uniform expression of receptor in the breast tumor is an exception rather than a rule. At the same time, the expression in primary tumour and the metastatic sites may be of different intensity which may further prompt the need to use both of these imaging simultaneously. We were also able to demonstrate the migration from hormone positive status to hormone negative status leading to a change in the therapeutic approach and personalizing the treatment protocols. We have thus been able to prove the hypothesis that both FDG and FES study should be done routinely in ER positive breast cancer for guiding management strategies. In our series, FES showed incremental value not only by characterizing FDG positive lesions but also showed exclusive lesions in 7.4% of

cases. FES PET scan in combination with FDG PET can be used as a problem solving modality in deciding the treatment regimen. Our initial results point to this fact and highlight the spectrum of metastatic sites which can be documented. A common rule of thumb could be that well differentiated hormone positive tumor with FDG uptake less than the FES uptake is unlikely to benefit from cytotoxic chemotherapy alone and would be an ideal candidate for combination therapy and vice versa where a poorly differentiated tumour with higher FDG concentration in comparison to FES will benefit from cytotoxic chemo-therapeutic regimen alone (25). Inter-pretation should be cautious in patient with hepatic metastasis for reasons cited previously. Nonetheless, FES PET can be used along with FDG PET in strongly ER expressing patients for better specificity, evaluation of disease extent and impact on management.

4. Conclusion

It is therefore quite certain that in the coming years and in future, the treatment of breast cancer has a very high potential to be personalized based on biological characteristics depicted in-vivo by both FDG and FES molecular imaging.

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