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BREAST SURGERY

Primary endocrine therapy can be effective in decreasing lymph node burden in hormone receptor positive breast cancers

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Background: Breast cancer is a significant global health concern. Primary endocrine therapy (PET) and primary chemotherapy (PCT) are employed to manage hormone receptor positive breast cancers in the neoadjuvant setting. We hypothesise that PET is as effective as chemotherapy to treat axillary metastases.
Methodology: All patients treated for breast cancer at Tygerberg Hospital Breast Unit during the period of 2016–2019 were included. Patients who did not receive PCT or PET were excluded, as were patients who did not undergo axillary lymph node dissection (ALND).
Results: The sample consisted of 176 patients. The median age was 49.2 years (IQR = 42.4–57.9 years; range = 25.1–84.6 years), and 174/176 (98.9%) were female. Of the 176 patients, 35/176 (19.9%) had luminal A cancers, while 141/176 (80.1%) had luminal B cancers. Among these patients, 150/176 (85.2%) underwent PCT while 26/176 (14.8%) received PET. The lymph node burdens found via ALND were similar for patients who underwent PCT (median = 25.0%; IQR = 0.0–50.0%) and PET (median = 16.8%; IQR = 0.0–89.0%; $p = 0.66$). The rates of patients with no nodal involvement were also similar for patients who underwent PCT (47/150 = 31.3%) and PET (9/26 = 34.6%; $p = 0.74$). Multivariate analysis showed that there were no significant confounding effects due to age, sex, HIV status, molecular subtype or AJCC stage.
Conclusion: Our study showed no statistically significant difference in the lymph node burden regardless of whether PET or PCT was given to patients with a hormone receptor positive breast cancer.
Keywords: breast cancer, primary endocrine therapy, primary chemotherapy, lymph node burden, hormone receptor-positive, treatment efficacy

Introduction

Breast cancer continues to be a significant global health concern, affecting millions of women annually. Its inherent molecular and clinical heterogeneity necessitates tailored treatment approaches for optimal outcomes.[1,2] Among the various subtypes, hormone receptor-positive breast cancers account for 70–80%. Such tumours often exhibit indolent growth patterns and are associated with a relatively favourable prognosis compared to hormone receptor-negative tumours.[1,2] Lymph node involvement is a determinant of breast cancer prognosis, with a higher nodal burden being associated with an increased risk of distant metastasis and poorer survival outcomes.[3]

Two main therapeutic approaches, primary endocrine therapy (PET) and primary chemotherapy (PCT), are employed to manage hormone receptor positive breast cancers in the neoadjuvant setting. The therapeutic goals of primary systemic therapy for breast cancers are to downsize the tumour to allow breast conservation surgery, downstage the axilla for surgical de-escalation, assess response to therapy, and address micrometastases in breast cancer which is considered a systemic disease.[4] The decision as to which to use is dependent on many factors, but endocrine therapy can only be considered for those who are hormone receptor positive and is generally reserved for postmenopausal women.[4-6]

PET involves the administration of hormonal agents, such as selective oestrogen receptor modulators (SERMs) or aromatase inhibitors (AIs), with the intent to suppress hormone receptor-mediated tumour growth.[7-9] On the other hand, PCT utilises cytotoxic agents to directly target rapidly dividing cancer cells. The choice between these strategies in the neoadjuvant setting is influenced by menopausal status, tumour characteristics, patient preferences, and clinical considerations.[7-9]

Both PET and PCT have demonstrated efficacy in reducing tumour size and inhibiting cell proliferation, which subsequently contributes to lymph node burden reduction.[10-13] The comparative evaluation of PET and PCT in lymph node burden reduction stems from the need to optimise treatment selection for hormone receptor-positive breast cancers.[11-14]

While both approaches exhibit efficacy in attenuating tumour growth, their differential mechanisms of action raise questions regarding their relative impact on lymph node metastasis. The potential hormonal modulation of the tumour microenvironment by PET and the direct cytotoxic effects of PCT could yield distinct patterns of lymph node

response. Understanding this is vital for tailoring treatment decisions and refining therapeutic strategies.[14]

This study aims to compare the effectiveness of PET and PCT in reducing lymph node burden, a crucial prognostic factor in breast cancer.[1,2] The findings of this study have potential implications for clinical decision-making in Southern Africa. Determining whether PET is as effective as PCT in decreasing lymph node burden can guide treatment recommendations for hormone receptor-positive breast cancers. Tailoring therapies based on lymph node involvement may enable personalised treatment plans that optimise patient outcomes while minimising unnecessary exposure to cytotoxic agents.

Methodology

All consecutive patients treated for breast cancer at Tygerberg Hospital Breast Unit from January 2016 to December 2019 were added to a manually kept database from pre-diagnosis clinic visits to post-adjuvant therapy follow-up. This database is password-protected and uses number identification. This database has ethical approval for its use by the HREC of Stellenbosch University. All non-metastatic patients undergoing primary systemic therapy were included. All patients were node positive at their original assessment. This was based on both clinical and radiological assessment as core biopsy is not routinely done on suspicious lymph nodes. Exclusion criteria included patients who did not undergo axillary lymph node dissections (ALNDs), patients who underwent sentinel lymph node biopsies (SLNBs) without ALND, those with no documented hormone receptor status, those with HER-2-enriched or triple-negative cancers, and those with no record of whether PET or chemotherapy was given (Figure 1). The rationale for excluding patients who underwent SLNB is that they were assessed as having node negative disease, so did not have known axillary disease to measure a response based on a chosen primary treatment modality. The number of patients who had a positive SLNB during this study period was too small to make any impact on our outcomes, hence the exclusion. Comparisons were made between cancer subtypes, stage and the type of primary therapy received. Surgery may be done occasionally on those with low volume systemic metastatic disease. Outcomes were determined by the lymph node burden and deposit sizes present on operative specimens. Data analysis was performed using R v4.1.1. Appropriate descriptive statistics were reported. Inferential statistics were performed using t-tests or Kruskal-Wallis tests for numerical data, and chi-square or Fisher's exact tests for categorical data. The level of significance was defined as *p*-values less than 0.05.

Results

The sample consisted of 176 patients (Figure 1). The median age was 49.2 years (IQR = 42.4–57.9 years; range = 25.1–84.6 years), and 174/176 (98.9%) were female. Of the 176 patients, 13/176 (7.4%) were HIV-positive, 138/176 (78.4%) were HIV-negative, and 25/176 (14.2%) had unknown HIV status.

Of the 176 patients, 35/176 (19.9%) had luminal A cancers, while 141/176 (80.1%) had HER-2 negative luminal B cancers. Patients with luminal A and luminal B cancers were similar in age ($p = 0.11$), sex ($p = 1.0$) and HIV status ($p = 0.13$).

The American Joint Committee on Cancer's (AJCC) staging was reported for 156 patients. Of these, 52/156 (33.3%) had stage 1 or 2 disease, while 104/156 (66.7%) had stage 3 or 4 disease. Patients with different stages of cancer were similar in age ($p = 0.29$), sex ($p = 0.26$), HIV status ($p = 0.06$) and molecular subtype ($p = 0.23$).

Of the 176 patients with luminal subtypes, 150/176 (85.2%) underwent PCT while 26/176 (14.8%) received PET. Patients who underwent PCT (median = 47.5 years; IQR = 41.3–55.8 years) were significantly younger than those who received PET (median = 64.4 years; IQR = 55.6–71.6 years; $p < 0.001$), but were similar in sex ($p = 0.27$) and HIV status ($p = 0.39$). There were no significant differences in the rates of PCT and PET use among patients with different molecular subtypes ($p = 0.18$) or different AJCC stages of cancer ($p = 0.23$).

A median of 11.0 lymph nodes (IQR = 8.0–14.0) were harvested during ALND, with a median lymph node burden (portion of lymph nodes containing malignant tissue) of 23.6% (IQR = 0.0–52.3%). Of the 176 patients who underwent ALND, 56/176 (31.8%) had no nodal involvement. No information was available on whether treatment-related changes were present in these nodes.

The lymph node burdens found via ALND were similar for patients who underwent PCT (median = 25.0%; IQR = 0.0–50.0%) and PET (median = 16.8%; IQR = 0.0–89.0%; $p = 0.66$). Among patients who underwent PCT, 47/150 (31.3%) had no nodal involvement, and among patients who underwent PET, 9/26 (34.6%) had no nodal involvement, with no significant differences between these groups ($p = 0.74$). Multivariate analysis showed that there were no significant confounding effects due to age, sex, HIV status, molecular subtype or AJCC stage (Figure 2).

The median size of the largest malignant deposits in the lymph nodes harvested was 6.1 mm (IQR = 4.0–11.0 mm). The largest malignant deposits in the lymph nodes of patients who underwent PCT (median = 6.0 mm; IQR = 4.0–10.0 mm) and PET (median = 9.4 mm; IQR = 5.0–11.9 mm) were similar ($p = 0.19$). Multivariate analysis showed that there were no significant confounding effects due to age, sex, HIV status, molecular subtype or AJCC stage.

Of the entire cohort, extracapsular nodal spread was only reported in 120 patients and was present in 81/120 (67.5%) of these patients. The rates of extracapsular spread were similar in patients who underwent PCT (67/102 = 65.7%) and those who received PET (14/18 = 77.8%; $p = 0.31$). Multivariate analysis showed that there were no significant

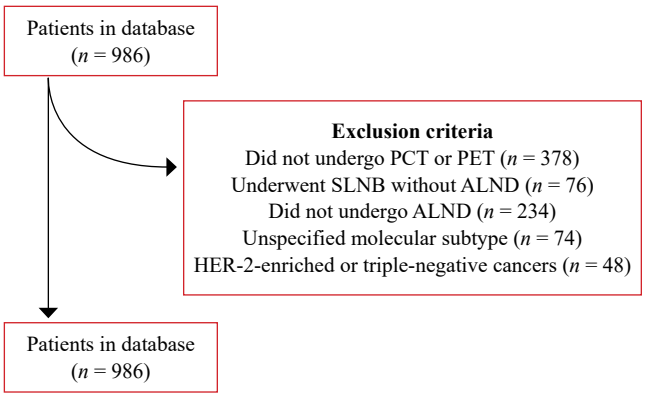

Figure 1: Consort diagram showing study sample

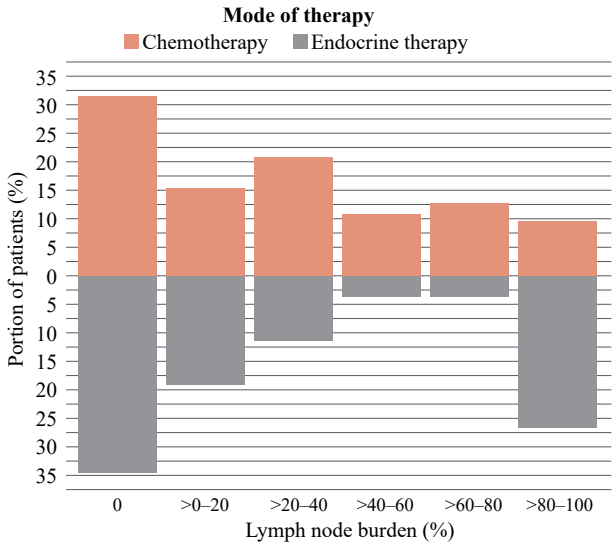

Figure 2: Histogram comparing lymph node burden at ALND for patients who received PCT and PET

confounding effects due to age, sex, HIV status, molecular subtype or AJCC stage.

Discussion

The study sample size of 176 patients provides a reasonable basis for analysis, offering a representation of patients with hormone-positive breast cancers who underwent various primary systemic therapies and allows for an examination of the effects of these treatments on lymph node involvement.

One of the key observations from the study is the lack of statistically significant differences in lymph node involvement at axillary dissection between patients who received PCT and PET. This finding challenges the conventional belief that PCT is more effective than PET in reducing lymph node burden.[4,15,16] Various studies have previously explored the efficacy of PCT versus PET, with mixed findings regarding the impact on lymph node involvement.[4,15,16] Some studies have indicated that PCT can result in a greater reduction in lymph node burden, when compared to PET, especially in patients with high risk molecular subtypes, but others have shown similar outcomes between the two approaches with the luminal subtypes.[4,16-17] While PCT is often associated with a more rapid reduction in tumour size and lymph node involvement, PET's gradual effects might lead to comparable outcomes over time.[4,15-18] This underscores the importance of considering the timeline of treatment responses when evaluating lymph node involvement. In the PROACT trial, clinical axillary downstaging after three months of endocrine therapy, compared to baseline, was seen in 43.4% of patients treated with anastrozole and in 38.5% of patients treated with tamoxifen. Unfortunately, in this trial, axillary surgeries were not addressed.[18] The optimal surgical management after PET remains unknown and more research is needed to determine the appropriate patient population for axillary surgery de-escalation after PET.

The age distribution of patients receiving different primary therapies is also noteworthy. Patients who underwent PCT were significantly younger than those who received PET. This age-related difference could be attributed to various factors, such as treatment preferences, overall health status and the fact that PET is not as effective in premenopausal women unless ovarian function is ablated. Therefore, selection bias is based on existing evidence.[18,20-23]

The similarity in extracapsular nodal spread seen following both PET and PCT also corresponds with previous research which suggests that some types of nodal spread will remain unaffected by primary therapies. This reflects the impact of specific tumour biology as opposed to the specific treatment chosen.[24]

However, it is essential to interpret these findings cautiously and consider potential confounding variables that might influence the treatment choices and subsequent outcomes. Future studies with larger sample sizes or more focused patient populations may provide further clarity on this matter.

The study has several limitations. Firstly, the retrospective nature of the study has the potential to introduce selection bias. Secondly, factors not explored in this study, such as tumour genetics, patient comorbidities, and treatment adherence, could influence the outcomes observed. Thirdly, the duration of PET and the therapy given is also not known for all patients, due to poor follow-up and numerous base facilities that do not include Tygerberg Hospital. Fourthly, the group of patients receiving PET is underrepresented in comparison to those that received PCT. Fifthly, our patient population under review is also too small to make any meaningful conclusions. Long-term follow-up data on recurrence rates and survival would provide a more comprehensive understanding of the implications of different primary therapies on patient outcomes. It may also be useful to look at the tolerability and compliance of both treatments. Finally, the majority of cases did not undergo pre-treatment biopsy of the nodes and the axilla could have been over-staged based only on clinical and radiological grounds. Furthermore, no treatment-related changes were captured during the data collection; thus, in patients with no nodal involvement at surgery, it is uncertain whether this is due to treatment response or an over-staged axilla pre-treatment.

Conclusion

The results of this small study sample suggest that PET may be as effective as PCT in reducing lymph node burden in node positive hormone-positive breast cancers. While no statistically significant differences were observed, the findings underscore the complexity of treatment decisions in breast cancer management. Clinicians should carefully consider patient characteristics, tumour biology, and individual preferences when choosing between PCT and PET. Further research with larger prospective cohorts and longer follow-up periods is warranted to confirm and expand upon these findings, ultimately informing more personalised and effective treatment strategies for hormone-positive breast cancer patients.

Conflict of interest

The authors have no conflicts of interest to declare.

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Ethical approval

Ethical approval was obtained from the Stellenbosch University Research Ethics Committee (HREC number: N19/04/049).

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