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Analysis of primary endocrine therapy in patients older than 70 years with breast cancer rejecting surgery from a single unit in South Africa including COVID-19 issues

Research Letter to the Editor

Breast cancer in older patients is characterized as a heterogeneous disease, coupled with a more significant proportion having associated concurrent comorbidities, thereby increasing the risk of non-cancer-related deaths [1]. Geriatric and clinical assessments are imperative for offering appropriate treatment decisions to patients, as some exhibit enhanced life expectancy, which are prime candidates for more aggressive treatment strategies. In contrast, more conservative approaches might be beneficial for patients with existing comorbidities. Neoadjuvant chemotherapy (NACT) is a well-established treatment approach in patients with triple-negative and HER-2 positive localized breast cancer [2]. On the other hand, the role of NACT in patients with endocrine sensitive tumors remains uncertain. A meta-analysis of 20 clinical studies with 3490 patients demonstrated that primary endocrine therapy (PET), even as monotherapy, is associated with comparable response rates compared to NACT in patients with estrogen receptor (ER) positive tumors. PET is associated with considerably lower toxicity, indicating that PET could be reevaluated as a potential alternative in the appropriate patient [3]. The International Society of Geriatric Oncology (SIOG) and European Society of Breast Cancer Specialists (EUSOMA) breast cancer guidelines recommend surgery as the optimal treatment for patients with ER-positive, HER2-negative disease. At the same time, PET should only be offered to older patients with ER-positive tumors who have a short estimated life expectancy (<2–3 years) and who are considered unfit for surgery after optimizing medical conditions patients who refuse surgery. The involvement of a geriatrician as part of the team is strongly recommended to assess the life expectancy accurately, comorbidities as competing causes of mortality, drug safety, drug–drug interactions, treatment compliance, and manage reversible comorbidities. In this setting, it is reasonable to choose PET in the form of tamoxifen or an aromatase inhibitor, based on potential side-effects and patient preferences [4].

This retrospective study aimed to evaluate a subset of patients with endocrine sensitive breast cancer, refusing to undergo surgery or were not eligible for surgery. PET was decided as the initial treatment of choice, following extensive discussion between the patient and the treating clinician.

In the current climate of COVID-19, this study demonstrates how PET can create a viable alternative for those patients over 70 years of age, preceding surgery, and highlights the importance of patient navigation. At the Netcare Breast Care Centre (NCBC), located at Milpark Hospital in Johannesburg, South Africa, all newly diagnosed older patients with breast cancer and their families were counseled by the treating specialists and nurse navigators of their diagnosis, the importance of taking adequate decision time, optimizing medical comorbidities before planned surgery, and misconception of mastectomies as primary treatment options. In parallel, patients were assessed by a specialist anesthetist and physician/cardiologist with an interest in older patient anesthesia to confirm surgical safety. Before initiating treatment, all patients were discussed in the weekly NCBC multidisciplinary tumor board, and feedback was given to the patients.

Patients opting to be managed by PET instead of surgery were counseled of the importance of regular clinical with or without sonographic tumor assessments. The end-point of this retrospective study was to determine the time to progression. The primary tumor and regional nodes were evaluated at baseline. Follow-up consisted of at least bi-annual clinical with or without radiological assessments. For the purpose of this study, older patients were defined as patients 70 years and older at the time of diagnosis [5]. Patients to be eligible for this analysis were required to be receptor-positive and electing not to undergo surgery as a primary treatment mode. The analysis was performed on patients presenting at the NCBC between January 2012 and December 2017. Ethics clearance to conduct this study was covered under the Midas Protocol (Netcare Trial Number: TRIAL-2017-0035, Pharma Ethics Ref No: 170416525). Demographic, histological, and staging information was collected. Patients with basal-like/triple-negative breast cancers and patients who underwent primary surgery or oncology treatment within six weeks of diagnosis were excluded. The type of endocrine therapy used was noted. Patients who successfully completed the 6-month PET course with no complications or heightened toxicity levels were counseled for further surgery. If surgical salvage was required for progressive disease, the time to surgery was recorded. Additionally, patient mortality and cause were recorded.

One hundred and twenty-two patients were accrued in this study. Patient characteristics and treatment outcomes are summarized in Fig. 1 and Table 1. The median age at diagnosis was 78 years (range: 70 to 94 years) most showing ductal carcinoma, (n = 105, 86.07%), followed by lobular carcinoma (n = 15,12.30%), and bi-phenotypic ductal lobular carcinoma (n = 2, 1.64%). One hundred and seventeen patients (95.90%) were treated with tamoxifen, and the remaining five patients (4.09%), received an aromatase inhibitor. Patients were assessed regularly and discussed the possibility of surgical management. During the first three months of treatment, 120 (98.36%) patients remained on PET with no clinical or radiological evidence of disease progression. At six months, 118 (96.72%) patients remained on PET. At nine months, 111
(90.98%) remained on PET, while at twelve months, 82 (67.21%) remained on treatment. Disease progression was documented in eleven patients (9.01%), non-treatment compliance in eleven patients (9.01%), there were three patients (2.45%) with no evidence of disease progression who elected to have surgery within the first six months of endocrine treatment. In total, during the study period, 27 (22.13%) patients died of associated co-morbidities not related to breast cancer, and two patients (1.64%) developed other cancers (one patient had non-small cell lung cancer, and one patient colon cancer). Endocrine therapy was well tolerated with no obvious detrimental effects on associated co-morbidities.

Advanced age is considered a risk factor for breast cancer. In Sub-Saharan Africa, the older age population increases from 46 million in 2015 to a projected 157 million by 2050 [6]; this trend is observed globally. Therefore, it is likely that breast cancer in older adults will become a health care burden in the future. However, there is limited evidence-based data related to screening and management strategies specifically focused on this patient population. Currently, the COVID-19 pandemic has resulted in challenges to our ability to safely perform surgery in older adult patients. In light of this infection, updates to international guidelines recommending endocrine therapy for patients with hormone-sensitive disease included the ‘Cancer Care Triage and Management: Breast Cancer Patients’ laid out by the American College of Surgeons in May of this year [7].

Part of the dilemma facing treating physicians is the “need and desire to treat” versus the concept of “do no further harm.” The balancing act of this treatment scale is particularly evident in older adults. One can argue both sides of the case - to treat or not to treat. Recent publications highlighted the overdiagnosis of breast cancer (the detection of cancer that would not be associated with death or symptoms), resulting in overtreatment [8]. This concept applies to our older adult population.

Moreover, this could lead to unnecessary aggressive surgical procedures and overuse of adjuvant treatments such as chemotherapy and

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**Fig. 1.** Figure a: Kaplan-Meier plot showing the time to discontinuation of primary endocrine therapy; Figure b: Kaplan-Meier plot showing the overall survival of the entire cohort of patients on primary endocrine therapy.
Table 1
Patient characteristics and clinical outcomes.

| Patient characteristics | Treatment |
|-------------------------|-----------|
| Age                     |           |
| Median                  | 78 years  |
| Range                   | 70 to 91 years |
| Number of patients      | 122       |
| Gender                  |           |
| Female                  | 121       |
| Male                    | 1         |
| Side                    |           |
| Left                    | 62        |
| Right                   | 56        |
| Bilateral               | 4         |
| Nodal Status            |           |
| N0                      | 104       |
| N1                      | 10        |
| N2                      | 2         |
| N Unknown               | 6         |
| Grade                   |           |
| 1                       | 24        |
| 2                       | 76        |
| 3                       | 6         |
| Unknown                 | 6         |
| Histology               |           |
| Ductal                  | 105       |
| Lobular                 | 15        |
| Biphenotypic            | 2         |
| Primary tumor size      |           |
| T1                      | 48        |
| T2                      | 59        |
| T3                      | 1         |
| T4                      | 14        |
| Estrogen receptor       |           |
| ER Positive 6/8         | 7         |
| ER Positive 7/8         | 7         |
| ER Positive 8/8         | 100       |
| ER Positive intensity unknown | 4   |
| ER Bilateral positive left side 8/8; positive right side 8/8 | 4 |
| Progesterone receptor   |           |
| PR Negative             | 8         |
| PR Positive 2/8         | 1         |
| PR Positive 3/8         | 4         |
| PR Positive 4/8         | 6         |
| PR Positive 5/8         | 11        |
| PR Positive 6/8         | 18        |
| PR Positive 7/8         | 12        |
| PR Positive 8/8         | 54        |
| PR Positive intensity unknown | 4 |
| PR Bilateral positive left side 0/8; right side 8/8 | 1 |
| PR Bilateral positive left side 6/8; right side 6/8 | 1 |
| PR Bilateral positive left side 7/8; right side 7/8 | 1 |
| PR Bilateral positive left side 8/8; right side 8/8 | 1 |
| HER2 receptor           |           |
| HER2 negative           | 115       |
| Bilateral HER2 negative | 3         |
| Bilateral left side HER2 positive; right sideHER2 negative | 1 |
| HER2 unknown            | 3         |
| Molecular subtype       |           |
| Luminal A               | 84        |
| Luminal B               | 29        |
| TMN classification [11] |           |
| Stage 1                 | 41        |
| Stage 2                 | 68        |
| Stage 3                 | 13        |
| Treatment               |           |
| Primary endocrine therapy type |   |
| Tamoxifen               | 111       |
| Aromatase inhibitors (AI) | 5  |
| Clinical outcomes       |           |
| Primary endocrine therapy duration |   |
| Patients on PET at 3 month follow-up | 120 |
| Patients on PET at 6 month follow-up | 118 |
| Patients on PET at 9 month follow-up | 111 |
| Patients on PET at 12 month follow-up | 82 |
| Reason for discontinuation of primary endocrine therapy |   |
| Disease progression     | 11        |
| Non-compliance          | 11        |
| Elected surgery, no progression | 3 |
| Death due to other cancers (lung and colon) | 2 |
| Death due to non-cancer related causes | 27 |

Radiation, accompanied by their associated side-effects and reduction in quality of life. The counter-argument is not treating or undertreating breast cancer, therefore, omitting to treat early-stage disease, possibly allowing subsequent disease progression and the resultant need for more aggressive surgery, radiotherapy, and chemotherapy. The more severe complication of this approach may result in disease progression and death resulting from metastatic disease. The high burden of frailty and comorbidity in the older adult patient population adds to the complexity of treatment. The majority of the older adult patients initiated on PET, included in this analysis, consisted of those who refused surgery, as the primary indication for being placed on PET. Simultaneously, a smaller group was deemed not fit for primary surgery due to comorbidities. Thus, it is not unreasonable to recommend PET to older patients displaying Luminal-A breast cancer, particularly if the patient refuses surgery. This study demonstrates that PET is a safe approach in patients over the age of 70 years. Our data shows that 96% of patients did not have significant complications during the first six months of treatment, and 9% of the patients developed disease progression within 18 months of PET.

A potential outcome predictor for hormone-sensitive breast cancer is the use of the preoperative endocrine prognostic index (PEPI score) during endocrine therapy [9]. This index considers treatment-related interval changes, including the ER status, Ki67 proliferation index, histological grade, pathological tumor size, node status, and treatment response.

Areas for future research should include investigating the impact of medical co-morbidities, geriatric assessments, the Charlson comorbidity index, and genetic tumor profiling to refine the selection criteria of patients benefiting from treatment with PET [10]. Furthermore, well-designed prospective studies should evaluate the interactions of endocrine therapy with patient co-morbidities.

The limitations of this study relate to the retrospective nature of the research, the complexities in controlling for selection bias, and the lack of a control group; however, this hypothesis-generating study should provide the framework for further research in this rapidly evolving field.

Declaration of competing interest
CB, TS, VS, YR have no conflict of interest to declare. BLR reports personal fees, advisory boards and speaker engagements from Novartis South Africa, personal fees, advisory boards and speaker engagements from Eli-Lilly South Africa, personal fees, advisory boards and speaker engagements from AstraZeneca South Africa during the conduct of the study.

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