

## Limiting the Use of Primary Endocrine Therapy in Elderly Women With Breast Cancer

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### Abstract

Primary endocrine therapy (PET) is often included as a treatment option in elderly women with operable breast cancer. Elderly women tend to have pre-existing comorbidities and are often reluctant to undergo surgery. The benefit of surgery needs to be weighed against a relatively higher potential for operative morbidity and mortality, and a limited life expectancy. But while PET can provide relatively good locoregional control, it is not curative in nature and the possibility of local complications and metastasis remains. We retrospectively reviewed the outcome of PET in a series of 19 elderly women, older than 70 years of age, who had presented with operable non-metastatic breast cancer. Only about a third of these women were deemed medically unfit for surgery; the rest had declined surgery. Compliance was an issue, with almost half of these patients defaulting treatment and follow-up. Local control was achieved in most patients, but disease progression did occur in 5 patients. Three of these patients received additional treatment; which included surgery in 1 patient. PET should therefore not be considered an equivalent alternative to surgery in elderly women who were fit to undergo surgery. However, having observed that only 1 of the 6 deaths in our study was related to breast cancer, PET does have a role in women whose life expectancy is more likely to be limited by coexisting morbidities than the breast cancer itself.

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### Introduction

There is a tendency to opt for non-surgical interventions in elderly women with breast cancer. Although surgery offers the most effective form of locoregional control, there is concern that increased operative risk from existing comorbidities and a limited life expectancy outweigh the benefits of surgery.<sup>1,2</sup> Primary endocrine therapy (PET) appears as a viable alternative. Tumours in the elderly are often hormone responsive and tend to progress slowly, making them particularly amenable to hormonal therapy.<sup>3</sup> Although not curative, PET can confer fairly good locoregional control to allow for a reasonable quality of life. This is particularly relevant in women whose life expectancy is limited by serious comorbidities and who are expected to die with the breast cancer. PET is especially appealing to elderly Asian women, who often believe themselves to be too old and frail to undergo surgery. In this study, we

reviewed our experience with PET in a series of elderly women with operable breast cancer, focusing particularly on disease control and compliance to treatment.

Nineteen patients older than 70 years of age who had received PET were identified from clinical records spanning from 1 January 2002 to 31 December 2009. All tumours were histologically confirmed and deemed operable. Male patients and those presenting with metastatic disease were excluded. Treatment endpoints included tumour response, the need for additional locoregional treatment and the development of distant metastasis. Patient demographics, tumour characteristics and disease outcome during follow-up were obtained from the clinical records. The criteria defining human epidermal growth receptor (HER)-2 status was modified in 2007 following changes in the American Society of Clinical Oncology (ASCO) guideline

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recommendations. A test was considered positive if more than 30% of the tumour cells exhibited uniform intense membrane staining. Prior to this, a test was considered positive if strong complete membrane staining was observed in more than 10% of tumour cells.

Details of the 19 patients are included in Table 1. Median patient age was 84 years (range, 70 to 98 years). All 19 patients had at least 1 significant comorbidity; with hypertension, ischaemic heart disease and a previous history of stroke being the most common. Skin involvement (ulceration or fixation to the overlying skin) was present in 3 patients but none were associated with significant bleeding or discharge. Ipsilateral axillary nodes were palpable in 2 patients. Most patients (12 of 19) had stage II disease. All tumours were strongly estrogen receptor (ER) positive; a median of 90% of cells stained positive with an intensity of 3. Nine tumours were also progesterone receptor (PR) positive. HER-2 receptor status was not known in majority of the patients. Of these 19 patients, only 7 were documented as being medically unfit for surgery due to the severity of pre-existing comorbidities. The median follow-up interval was 28 months (range, 2 to 94 months).

Eighteen patients received tamoxifen as the first-line hormonal agent, and 1 patient received letrozole. Median duration of first-line hormonal therapy was 20 months (range, 1 to 60 months). At the end of the follow-up period, only 1 patient had completed 5 years of therapy and 4 others were still on tamoxifen. Six (32%) patients had died. Five died from causes unrelated to breast cancer and 1 from lung metastasis; none of these 5 patients had completed 5 years of tamoxifen. Seven patients (37%) had defaulted on treatment and follow-up, after a median duration of 29 months (range, 5 to 33 months). The patient on letrozole was switched to tamoxifen after 3 months because of intolerable musculoskeletal side effects but defaulted soon after. She presented again 6 months later with disease progression.

Local control was achieved in 14 of 19 patients (74%). Clinical tumour regression was noted in 8 patients, and the tumour remained stable in size in the other 6 patients. Among the 7 patients who had defaulted, clinical reduction in tumour size was documented in 3 patients and stable disease in the remaining 4. The primary tumour progressed in the remaining 5 patients, with skin ulceration and tumour fungation occurring in 2 patients. Progression had been documented after a median interval of 15 months from the time of diagnosis (range, 2 to 29 months). In 4 cases, the tumour had remained stable up until the time of progression; in the remaining case, progression was documented at the next review. One patient underwent mastectomy and axillary clearance, and continued with tamoxifen postoperatively after she declined a switch to aromatase inhibitors. The other patient received whole breast irradiation for local

Table 1. Details of Patient and Tumour Characteristics (n = 19)

| Characteristic                       | n (%)        |
|--------------------------------------|--------------|
| Median age (years)                   | 84 (70 – 98) |
| Ethnicity                            |              |
| Chinese                              | 17 (89.5)    |
| Malay                                | 2 (10.5)     |
| Comorbidities                        |              |
| Yes                                  | 19 (100)     |
| No                                   | 0            |
| Median tumour size (mm)              | 45 (10 – 70) |
| Disease stage at presentation        |              |
| I                                    | 2 (10.5)     |
| IIa                                  | 7 (36.8)     |
| IIb                                  | 5 (26.3)     |
| IIIa                                 | 2 (10.5)     |
| IIIb                                 | 3 (15.9)     |
| IV                                   | 0            |
| Oestrogen receptor (ER) status       | 19 (100)     |
| Positive                             | 0            |
| Negative                             |              |
| Progesterone receptor (PR) status    | 9 (47.4)     |
| Positive                             | 10 (52.6)    |
| Negative                             |              |
| HER-2 status                         |              |
| Positive                             | 2 (10.5)     |
| Negative                             | 5 (26.3)     |
| Unknown                              | 12 (63.2)    |
| Reasons for no surgical intervention |              |
| Medically unfit for surgery          | 7 (36.8)     |
| Declined surgery                     | 12 (63.2)    |

HER-2: Human epidermal growth receptor-2

control when the tumour progressed despite a switch from letrozole to tamoxifen; she subsequently received megestrol acetate following radiotherapy. Three of these 5 patients had also developed distant metastasis; 2 patients developed bone metastases and one developed lung metastases. The patient with lung metastases received no further treatment and died 24 months later; patient and family had declined further treatment including PET. One patient with bone metastases received radiotherapy to the left shoulder for pain control, while the other remained asymptomatic and was continued on hormonal therapy alone. Both patients declined a switch to aromatase inhibitors and continued to receive tamoxifen. Both were alive at the end of the follow-up period.

## Discussion

As the average life expectancy increases, clinicians can expect to encounter more elderly women with breast cancer. Many elderly women are reluctant to undergo surgery.

Some are fearful of the potential operative morbidity, others have a fatalistic outlook and there are those who are not convinced of the need for treatment given the absence of bothersome symptoms such as pain. PET is therefore often included in discussions regarding management. Similar to other published reports, adequate locoregional control, without the need for additional local therapy, was achieved in the majority of our patients.<sup>4-7</sup> The tumour response rate observed in our study was similar to that reported in a study from the Netherlands.<sup>8</sup> On the other hand, Osborn et al had reported lower rates of disease progression, but several differences in the study design preclude a direct comparison.<sup>9</sup> The study had included only patients treated by a single consultant and compared to ours, many more patients had received an aromatase inhibitor. PET may slow distant progression to some extent as well, since only 3 patients in our study developed distant disease. Our observation that more women died from non-breast cancer specific causes strengthens the case for PET in women who are more likely to die from pre-existing comorbidities than from the breast cancer.<sup>10</sup> Overall, PET was well tolerated and none of the patients reported serious adverse reactions.

However, compliance appeared to be a major issue. Excluding those who died, close to half of the remaining patients defaulted treatment and follow-up. Many may disregard the need for treatment given the absence of worrisome symptoms. Also, lack of tumour regression, even if it remains stable, may sometimes be misinterpreted as ineffective hormonal therapy. Defaulting treatment leaves open the possibility of these women re-presenting later with uncontrolled disease, when further hormonal therapy alone is often no longer effective. Surgery may eventually be needed for locoregional control; however, the extent of resection may be so extensive as to require skin cover of the postmastectomy defect. Radiotherapy is an alternative, but complete pathological response is rare and radiation cannot be given past a maximum dose. Furthermore, surgery on postirradiated skin is associated with more frequent wound complications.

As observed from our study, more than half the women who received PET were in fact medically fit to undergo surgery. Avoiding surgery and more definitive locoregional control at the start may in fact make later management more difficult since many of these women would survive long enough to develop complications from disease progression. It is probably prudent for the clinician to attempt to address the reasons behind this reluctance to undergo surgery rather than offer PET upfront. A review of our records showed that over the same period, 261 women older than 70 years of age had undergone curative surgery without major complications. This is significantly lower than that reported in a study from the Netherlands where overall, 12%

to 29% of women older than 75 years of age were treated with PET during a 20-year period from 1988 to 2008; this varied significantly between hospitals, ranging from 9% to 44%.<sup>8</sup> Mastectomy, and even axillary clearance, can be safely performed under thoracic paravertebral anaesthesia should the risks of general anaesthesia be considered to be too high in selected patients<sup>11</sup>. Apart from reducing the operative risk, paravertebral anaesthesia also provides excellent pain control and facilitates recovery<sup>12</sup>.

## Conclusion

In conclusion, we found that PET offered adequate disease control and was generally well tolerated in elderly women with operable breast cancer. However, compliance appeared to be a significant issue. Furthermore, we observed that many women who opted for PET were in fact fit to undergo surgery. Since PET is not curative and complete pathological response is uncommon,<sup>13</sup> disease progression remains possible and these women may eventually still need surgery or other local treatments. PET should therefore be recommended as an alternative to surgery only to those women who are deemed more likely to succumb from pre-existing comorbidities than from the breast cancer itself. Continued follow-up and close monitoring remains important in these patients to allow for early detection and second-line treatment in the event of disease progression, in order to avoid a poor outcome and preserve the quality of life.

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