Annals of Medicine and Surgery 12 (2016) 5–7

Contents lists available at ScienceDirect

Annals of Medicine and Surgery

journal homepage: www.annalsjournal.com

Commentary

# Primary surgical treatment of locally advanced breast cancer in low resource settings

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## HIGHLIGHTS

- Optimum management of locally advanced breast cancer is multidisciplinary.
- Neoadjuvant chemotherapy is mainstay of management.
- Primary surgical treatment may be acceptable in selected patients.

## ARTICLE INFO

*Article history:*
Received 18 August 2016
Received in revised form
17 October 2016
Accepted 17 October 2016

Breast cancer is the second commonest cancer in the world, increasing in incidence (1 in 8 women) aged 45–55, and it is the second most common cause of death after lung cancer in the West [1]. Male breast cancer is a rare disease (1% of all breast cancers) and advanced male breast cancer is an even rarer entity [2,3]. The cause is not known probably because of the interaction of genetic (BRCA1, BRCA2 mutation status) and environmental factors (viruses, high fat diet, etc). Depending on referral patterns and clinical definitions between 1 in 12 and 1 in 4 patients present with locally advanced disease characterized clinically by features suggesting infiltration of the skin or chest wall by tumour or matted-involved axillary lymph nodes (Table 1) [4]. They may arise because of its position in the breast (e.g. if the lesion is peripheral), because of neglect common in the developing world, or the cancer is biologically aggressive (inflammatory cancers and the majority of those with *peau d'orange* from lymphatic blockage) and require neoadjuvant chemotherapy [4,5]. Locally-advanced breast cancer remains an important clinical problem in developing countries because of the limited use of the multidisciplinary approach in management, minimal breast awareness programmes including routine breast screening and neglect [5–10]. In contrast to early stage disease for which level 1 evidence exists for the majority of treatment options, there are few recognized therapeutic standards of care in locally advanced breast cancer particularly after first line anti HER-2 (trastuzumab) treatment [11]. All but one study published after 2010 support the surgical removal of the primary tumour in patients with stage IV disease [12–16]. Therefore, the question of primary surgical treatment of locally advanced breast cancer in resource poor settings is of certain value and interest [7–11]. Further studies in the form of well-designed prospective randomized trials are required [11].

Locally advanced breast cancer ($T_4$, $N_{0\text{-}2}$, $M_0$) is, by definition, incurable because of putative occult micrometastases [1,4,5]. However, worthwhile symptom control and extension of survival are achievable especially for those with favourable tumour biology [4,5,13,15]. Due to differences in definition and the different forms of breast cancer the five-year survival rate varies between 1 and 30%, and the overall median survival is about 2–2.5 years [6]. A minimal staging work-up which includes a thorough history, physical examination, haematology, serum biochemistry (Liver function tests, renal function, electrolytes, calcium, total proteins, albumin) should exclude metastatic disease. In many cases basic imaging with a chest X-ray, an abdominal ultrasound and a bone scan are sufficient [11,17]. Current treatments have had some impact on local control but little overall impact on survival [11]. As local and regional relapse is a major problem affecting 50% of patients, loco-regional control of breast cancer is associated with improve disease-specific survival [5–8,10,11]. Even in those patients with apparently localized disease, the majority (80%) die of metastatic disease (Table 2) [10]. Patients with hormone-sensitive disease have a much longer survival than those with insensitive (triple negative –oestrogen, progesterone, human epidermal growth factor) disease [18]. Thus, a multidisciplinary approach in breast cancer would provide the optimum management geared at eradicating or slowing down the growth of these occult metastases

*Abbreviations:* ER, Oestrogen receptor; PR, Progesterone receptor; SERMS, Specific oestrogen receptor modulators; CMF, Cyclophosphamide, methotrexate, 5-fluorouracil; HER2, Human epidermal growth factor receptor 2.

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http://dx.doi.org/10.1016/j.amsu.2016.10.003

**Table 1**
TNM (clinical) Staging (Union International Contre le Cancer-IUCC).

| T (Tumour) | N (Nodes) | M (Metastases) |
|---|---|---|
| T0: impalpable tumour<br>T1: <2 cm d, No fixation or tethering | N0: No palpable axillary lymph nodes<br>N1: Mobile palpable axillary nodes | M0: No evidence of distant metastases<br>M1: Distant metastases or contralateral lymph nodes |
| T2: 2–5 cm d, with tethering or nipple retraction<br>T3: 5–10cm d, with infiltration, ulceration or peau fd'orange, deep fixation<br>T4: >10 cm d or infiltration/ulceration > its diameter | N2: Fixed axillary nodes<br>N3: Palpable supraclavicular nodes (M1); Oedema of the arm. | |

**Table 2**
Significance of clinical staging of Breast cancer.

| Early breast cancer $T_{0\text{-}3,}$ $N_{0\text{-}1,}M_0$ | Locally advanced breast cancer ($T_{4,}$ $N_{0\text{-}2,}M_0$) | Late breast cancer $M_1$ |
|---|---|---|
| Operable, curable<br>50% mortality | Neoaduvant treatment to make operable<br>80% mortality | Not curable<br>Inoperable<br>Palliative care<br>(100%mortality) |

and improve survival (Table 3) [6]. Appropriate adjuvant chemotherapy would improve the disease-specific survival and chance of cure [19–22]. Knowledge of the basic oestrogen (ER), progesterone (PR) and human epidermal growth factor type 2 receptor (HER2) tumour biomarkers would thus optimize treatment but may not be available in resource poor settings (Table 3). Anti-HER-2 agent (trastuzumab) although expensive has effectively led to change in the natural history of the disease with a substantial improvement in survival [11,21]. The overall survival of the ER positive locally advanced breast cancer, the most frequent subtype has remained stable since the early nineties. Thus the inexpensive anti-oestrogen (tamoxifen) and the current aromatase inhibitors have been an acceptable option for the first line treatment of postmenopausal women in low income countries [7]. Tumours that express C-erB2 oncogene are likely to be resistant to CMF chemotherapy and hormonal treatment. The BRCA1-associated breast tumour has the worse prognosis especially if associated with negative ER-PR receptors, the proteases urokinase and cathepsin D, increased S phase fraction and aneuploidy [18]. Tumour markers (if initially elevated) are useful in evaluating response to treatment particularly in patients with non-measurable metastatic disease [11]. Neoadjuvant chemotherapy downstages the breast and axilla and enhance surgical loco-regional control. Being a systemic disease, it has the initial benefit, of immediately attacking the putative occult micrometastases and can completely clear axillary metastases as assessed by standard histological examination in approximately 23% of patients with locally advanced breast cancer [19–22]. The use of anti-Her2 (biological) therapies have further increased the rates to 40–60% [21]. Although, a pathological complete response (pCR) indicates favourable biology and prognosis [19,22], a school of thought in oncology may query whether neoadjuvant chemo/radiotherapy actually alters the initial tumour biology. It may have no effect on the way the original stage of the tumour predicted the possibility of occult metastases, and therefore incurability [23].

Although axillary clearance does not improve survival as death is from distal metastases, it removes axillary disease and prevents regional recurrence, allows assessment of the nodal status for prognostic purposes and selection for adjuvant treatment and avoids the need for axillary radiation [24]. In patients with clinically palpable nodes a full axillary clearance is the treatment of choice. However, axillary clearance to level II (medial border of pectoralis minor and just below the axillary vein) offers satisfactory disease control for the majority of cases and best cost-benefit. The higher the level of clearance, the higher will be the morbidity (i.e. stiff shoulder, lymphoedema, axillary vein thrombosis). Skip lesions are rare and if level III nodes are affected it is likely that the level IV nodes (supraclavicular nodes) are also involved which is equivalent to metastases ($M_1$) [24,25]. Only rarely is tumour found encasing the axillary vein and this is usually fairly easy to dissect off. For the small group of patients less than 60 years of age with medially placed tumours, internal mammary node biopsy through the second intercostal space is required to identify those who require adjuvant chemotherapy [24]. Recurrent axillary disease represents residual untreated disease and usually occurs with metastases at other sites requiring appropriate systemic therapy with or without local treatments [19,22,25]. Treatment of the axilla is either by dissection or radiotherapy but not both due to the increased risk of lymphoedema and disabling shoulder stiffness [24,25]. Post-mastectomy radiotherapy would improve disease-free survival of patients with high risk of local recurrence i.e. large tumour size (>5cm), *peau d'orange,* heavy nodal involvement, poor histological grade and vascular involvement [14,26]. By combining appropriate systemic therapy and radiotherapy, response rates of over 80% have been reported and over two thirds of patients retain loco-regional control at death [5,8,10,11,15]. Thus, the optimum management of locally-advanced breast cancer requires a multidisciplinary approach. Although neoadjuvant treatment strategies are the mainstay of management, selected patients with nodal

**Table 3**
Factors affecting choice of systemic treatment for locally advanced breast cancer.

| Hormonal treatment | Chemotherapy | Targeted molecular therapy (Trastuzumab) |
|---|---|---|
| Slow growing or indolent disease<br>Oestrogen receptor positive cancer<br>Elderly or unfit patients | Inflammatory cancer<br>Oestrogen receptor negative cancer<br>Rapidly progressive cancer | Oestrogen –negative tumours (express high HER2 receptors)<br>PR-negative<br>Human Epidermal growth factor Receptor 2 positive<br>Early stage breast cancer<br>Metastatic breast cancer |

involvement only, in low resource areas may benefit from a safe, expeditious and effective loco-regional control with simple mastectomy and an en-bloc level II axillary clearance [5,8,11,15]. The oncological outcome will, however, depend on the presence or absence of micrometastasis [5,6,17–19]. ER determination by immunohistochemistry should at least be available in low resource areas for optimization of treatment selection with regard to adjuvant treatment and prognosis [7,27].

## Ethical approval

The 'perspectives' paper did not require any Ethical approval.

## Please state any sources of funding for your research

None.

## Authors' contributions

EPW is the surgeon and main author who drafted the manuscript. FAE is a gynaecologist who carried out some of the literature search. All authors read and approved the final manuscript.

## Please state any conflicts of interest

The authors have no conflict of Interest.

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## Competing interests

The author(s) declare that they have no competing interests.

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