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## POSTSURGICAL MANAGEMENT OF PATIENTS WITH BREAST CANCER AT KENYATTA NATIONAL HOSPITAL

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### ABSTRACT

**Objective:** To assess post-surgical management of patients with breast cancer at the Kenyatta National Hospital.

**Design:** Retrospective analysis of patients treated for breast carcinoma at Kenyatta National Hospital between January 1989 and January 2000.

**Setting:** Kenyatta National Hospital.

**Subjects:** Three hundred and seventy-four patients who had surgery or biopsy for breast cancer at the Kenyatta National Hospital.

**Intervention:** Chemo-hormonal therapy and/or radiotherapy for adjuvant, metastatic, or palliative purposes.

**Results:** Twenty-two patients received adjuvant chemotherapy, and 21 patients received chemotherapy for metastatic disease. Forty-six patients received adjuvant radiotherapy and 53 had radiotherapy for palliative purposes. One hundred and twenty-six patients were given tamoxifen for adjuvant and metastatic purposes. The median duration of follow-up was 20 months.

**Conclusion:** Chemotherapy is grossly underutilized in the treatment of breast cancer at the Kenyatta National Hospital, and radiotherapy is also underutilized. Follow-up durations are dismal and if this is used as a surrogate measure for survival then survival durations for breast cancer patients are also dismal at the Kenyatta National Hospital.

### INTRODUCTION

The use of chemotherapy in the management of early stage breast cancer is an option considered more often today than in the past. In randomized trials chemotherapy reduced breast cancer recurrence by 35% and mortality by 27% in women under 50 years of age, as demonstrated by the Early Breast Cancer Trialists' Group (EBCTG)(1). This reduction was also significant amongst women aged 50-69 years, being 20% reduction in recurrence and 11% reduction in mortality. The beneficial effects of adjuvant multi-drug chemotherapy is seen regardless of nodal status, although absolute benefit of the effect is somewhat smaller among women with node-negative disease.

The EBCTG also demonstrated that the use of tamoxifen for five years as adjuvant therapy for early stage breast cancer was associated with a 47% decrease in disease recurrence and a 26% decrease in the risk of death in women whose tumours were oestrogen receptor (ER) positive or ER status unknown(2). For metastatic breast cancer (MBC) on the other hand polychemotherapy alone leads to median survivals of about 20 months and the addition of hormonal therapy does not alter this figure

significantly. For those whose tumours express Her-2 addition of Her-2 antibody (herceptin) to polychemotherapy has been shown to lead to median survivals of 25 months(3). Post-mastectomy radiotherapy on the other hand reduced local recurrence rate by a factor of 0.6 and could result in about 10% improvement in survival rate(4-6). Radiotherapy is also indicated for palliation especially of skeletal metastases.

Kenyatta National Hospital is a national referral hospital for Kenya and also the teaching hospital for the medical school of the University of Nairobi. It has a radiotherapy unit and also a haematology/medical oncology unit. We set out to review the treatment of breast cancer at the Kenyatta National Hospital and this report constitutes the non-surgical aspects of treatment.

### MATERIALS AND METHODS

Files of patients who underwent surgery or biopsy for breast cancer at the Kenyatta National Hospital between January 1989 and January 2000 inclusive were studied retrospectively. Information recorded down included sex, age at diagnosis, last menstrual period, histology, site of breast involved, disease stage at diagnosis. This latter was worked out indirectly in most cases

from information contained in the case notes and histology reports. Other information sought included type of surgery performed, date the patient went for radiotherapy and whether this was for adjuvant or palliative purposes, date the patient started chemotherapy and whether this was for neoadjuvant, adjuvant or for metastatic disease; the type of chemotherapy; the date the patient started tamoxifen and whether this was for adjuvant purposes or for metastatic disease; the last date of follow-up; the disease status at the last date of follow-up, reason for cessation of follow-up if indicated; if death was recorded, the date of death.

From the case notes attempts were made as much as possible to adopt the TNM staging system.

RESULTS

Files for 374 patients (1 man and 373 women) were available for study. The age range at diagnosis was 17-75 years with a median age of 44 years and a mean age of 47 years. For 250 patients it was possible to derive TNM staging (Table 1). Eighty five patients out of 250 (34%) had diagnoses when the disease was already metastatic. Only 26/250 patients (10.4%) had presumably node negative disease at diagnosis.

One hundred and forty two patients received radiotherapy, or chemotherapy, or both, for adjuvant, metastatic and palliative purposes, or both (Table 2).

Twenty patients received adjuvant chemotherapy and 21 patients received chemotherapy for metastatic disease. Forty six patients received adjuvant radiotherapy and 53 received radiotherapy for palliative purposes. Only 5 out of 48 patients (10.4%) who had a diagnosis when the disease was metastatic had chemotherapy soon after the primary treatment was given, being mainly radiotherapy and in some cases even surgery. In 9 out 48 cases (18.8%) with clear metastatic disease chemotherapy was delayed and given after disease progression following palliative radiotherapy. Cyclophosphamide (C), methotrexate (M), and 5-fluorouracil (F) (CMF)-based chemotherapy was given to 17 patients for adjuvant purposes and 11 patients for metastatic purposes, while cyclophosphamide (C), doxorubicin (A), and 5-fluorouracil (F) (CAF), or CAF-like combinations were given to three patients for adjuvant purposes and to four patients with metastatic disease.

Tamoxifen was given to 126 patients, 73 of whom were pre-menopausal and 53 who were postmenopausal (Table 3). In all cases the number of courses of chemotherapy or duration of tamoxifen use was impossible to derive. The use of tamoxifen whether in pre-menopausal or postmenopausal women did not correlate with duration of follow-up ( $\chi^2 = 16.75, 0.05 < p < 0.1$ ).

Table 1

Stage at diagnosis according to TNM system

Stage at Diagnosis	T1/T2 N0M0 or NXMX	T1/T2 N1-N3 M0 or MX	T3-T4 N0M0 or NX MX	T3-T4 N1-N3 M0/MX	Any TMI	Total
Number	26	50	30	59	85	250

Table 2

Chemo-radiotherapy against disease stage at diagnosis (7)

	T1-T2 N0-N3 M0	T1-T2 N0-N3 M1	T3 N0-N3 M0	T3 N0-N3 M1	T4 N0-N3 M0 or MxMx	T4 N0-N3 M1	Total
RT Adjv.	21	-	11	8	3	3	46
RT Met	7	1	5	6	2	32	53
CMF Adjv	8	1	4	2	1	1	17
CMF Met	3	1	2	2	1	2	11
CAF + like adjv	2	-	-	1	-	-	3
CAF + like Met	1	-	-	-	-	3	4
Others adjv	1	1	-	-	-	-	2
Others met	-	-	2	1	-	3	6
Total	43	4	24	20	7	44	142

RTAdj = Adjuvant Radiotherapy

RTMet = Palliative Radiotherapy.

CMFAdj = Adjuvant cyclophosphamide, methotrexate, 5-Fluorouracil.

CAF + like Adj = Adjuvant cyclophosphamide, adriamycin and 5-fluorouracil (CAF) or CAF-like combinations.

CAF +like Met = CAF or CAF-like combinations in the metastatic setting.

Others Adj = Adjuvant treatment with other chemotherapy combinations than CMF, CAF, or CAF-like.

Others Met = Other combination chemotherapies as above, in the metastatic setting.

**Table 3**  
Follow-up durations according to menopausal status and the use of Tamoxifen (Percentages are in brackets)

	Premenopausal plus tamoxifen	Premenopausal minus tamoxifen	Postmenopausal plus tamoxifen	Postmenopausal minus tamoxifen	Total
Follow-up ↓ (months)					
<12	38 (52.1)	51 (54.3)	33 (62.3)	17 (47.2)	139 (54.3)
12-23.9	15 (20.5)	17 (18.1)	10 (18.9)	6 (16.7)	48 (18.8)
24-35.9	7 (9.6)	8 (8.5)	1 (1.9)	9 (25)	25 (9.8)
36-59.9	8 (11.0)	9 (9.6)	4 (7.5)	2 (5.6)	23 (9.0)
60-119.9	5 (6.8)	7 (7.4)	5 (9.4)	2 (5.6)	19 (7.4)
120+	–	2 (2.1)	–	–	2 (0.8)
Total	73	94	53	36	256

$\chi^2 = 16.75, 0.05 < p < 0.1.$

**Table 4**  
Follow-up durations according to disease stage at diagnosis (204 cases evaluable) (Percentages are in brackets)

Stage →	T1-T2 NOM0/MX	T1-T2 N1-N3 M0/MX	T3-T4 N1-N3 M0/MX	T3-T4 N2-N3 M1	Total
Duration ↓ (Months)					
<12	5 (26.3)	23 (45.1)	37 (56.1)	49 (72.1)	114
12-23.9	4 (21.1)	13 (25.5)	11 (16.7)	11 (16.2)	39
24-35.9	3 (15.8)	6 (11.8)	7 (10.6)	3 (4.4)	19
36-59.9	4 (21.1)	3 (5.9)	7 (10.6)	3 (4.4)	17
60-119.9	2 (10.5)	5 (9.8)	(6.1)	2 (3.0)	13
120	1 (5.3)	1 (2.0)	–	–	2
Total	19 (100)	51 (100)	66 (100)	68 (100)	204

**Table 5**  
Follow-up for metastatic disease according to the size of the primary tumour (68 cases evaluable)

T Stage	T1	T2	T3	T4
Follow-up > 60 months	5.3%	2%	0%	0%
Follow-up > 24 months	36.8%	17.6%	16.7%	7.4%

**Table 6**  
Follow-up against post surgical treatment given (Percentage are in brackets)

Treatment →	Radiotherapy	Chemotherapy	Radiotherapy + Chemotherapy	None	Total
Follow-Up ↓ (Months)					
< 60	69 (95.8)	14 (82.4)	21 (72.4)	89 (98.9)	193 (92.9)
60+	3 (4.2)	3 (17.6)	8 (27.6)	1 (1.1)	15 (7.2)
Total	72	17	29	90	208

For those who had no adjuvant treatment, follow-up for less than 60 months or 6 months and above was statistically different ( $\chi^2 = 31.46, p < 0.001$ ).

**Table 7**

*Menopausal status against duration of follow-up (339 cases evaluable) (Percentages are in brackets)*

Menopausal status →	premenopausal	postmenopausal	Status undetermined	Total
Follow-up ↓ (months)				
<60	164 (19.1)	105 (93)	45 (93.8)	314 (92.6)
60+	14 (7.9)	8 (7)	3 (6.2)	25 (7.4)
Total	178 (100)	113	48	339

The median duration of follow-up was 20 months. The duration of follow-up for 36 months and above was longer for patients whose diseases were diagnosed earlier than those with advanced disease, but the difference was not statistically significant (Table 4). The majority of patients who had no adjuvant treatment were followed up for less than 12 months. Those who had radiotherapy alone, chemotherapy alone, or radio-chemotherapy were followed up for significantly longer durations (Table 6) ( $\chi^2 = 31.46, p < 0.001$ ).

One hundred and seventy out of 286 patients (59.4%) were lost to follow-up while 89 (31.1%) were transferred to their local hospitals after surgery (Table 7).

**DISCUSSION**

The age range and median age for patients in this series were similar to findings in our earlier study based at the radiotherapy department (Othieno-Abinya, Babu and Onyango - unpublished data). They were also similar to findings in an earlier study by Bjegaard and Kung'u(7). This is important to note because breast cancer age of occurrence in any given population has an important bearing on screening.

Even though male breast cancer is known to be commoner in black men than in other races it was recorded in only one patient out of 374 (0.3%). An overview analysis by the EBCTG has demonstrated the importance of systemic adjuvant therapy for women with early breast cancer. Randomized trials have shown that combination chemotherapy reduces breast cancer recurrence by up to 35% with 27% reduction in mortality among women aged less than 50 years(1). Even among women aged 50-69 years the benefits are significant with 20% reduction in recurrence and 11% reduction in mortality.

Only 22 out of 374 patients in our study (5.9%) received adjuvant chemotherapy. The most likely reason for this apparent gross omission is the shortage of cytotoxic drugs at the public institution that makes surgeons get used to the idea that there is no need to refer patients for post surgical adjuvant therapy. Even if patients are seen by medical oncologists and are given prescriptions to source these drugs by themselves cost remains a problem for the general Kenyan public.

*Could there have been any other reasons negating the use of adjuvant chemotherapy to such a magnitude?*

Adjuvant systemic therapy may be considered unnecessary among patients whose prognosis is considered so favourable that they cannot benefit significantly from such treatment. Women with node-negative breast cancers less than 1 cm in diameter and histologic grade 1 are reported to have the same survival likelihood as age-matched women without breast cancer(8,9). This is a group that is mainly detected by mammographic screening(10), a facility that is not used routinely in our population. Furthermore out of 250 patients regarded as barely evaluable for stage, only 76 patients in our series were considered to have been diagnosed early with T1 and T2 tumours, yet some of them already had metastases, not only to regional lymph nodes but also to distant sites. Fifty of them were clearly node-positive and for the remaining 26 a good number were classified as NXMX. Adjuvant chemotherapy could therefore not have been largely ignored because of apparent good prognosis.

Another group of cases may be excluded from getting adjuvant chemotherapy because adjuvant chemotherapy is considered ineffective, either in general terms or in reference to a specific chemotherapy. But, it is also known that the beneficial effect of adjuvant multidrug chemotherapy is seen regardless of nodal status although the absolute benefit of the effect is somewhat smaller among women with node-negative disease. Chemotherapy was not largely ignored in these patients because of the perceived lack of benefit.

The one group of women in whom systemic therapy would not be administered because it would not be effective is hormonal therapy for women whose tumours lack hormone receptors(2). The use of tamoxifen for five years for early-stage breast cancer is associated with a 47% decrease in disease recurrence and a 26% decrease in the risk of death in women whose tumours are oestrogen receptor-positive or those whose oestrogen receptor (ER) status are unknown according to some observations(2). Unfortunately hormone receptor determination facilities have only been set up recently at the Nairobi Hospital. The cost of performing this at the equivalent of 64 US dollars is still considered by patients and physicians as unaffordable in many cases. Consideration is hardly given to the fact

that the cost of taking tamoxifen at 20 mg daily for one month is 14.6 US dollars, and the current recommendation is that it be taken for a total of five years. It is therefore more prudent to know that a patient is not likely to benefit from taking tamoxifen for five years if their cancers are hormone receptor negative, side effects set aside.

Postmenopausal women are generally considered tamoxifen responsive and premenopausal women tamoxifen resistant. Seventy three out of 178 premenopausal (41%) received tamoxifen and 53 out of 113 post menopausal women (47%) also received tamoxifen in this series, indicating lack of discrimination in the use of tamoxifen.

Another example of a situation where treatment may prove ineffective is using herceptin (trastuzumab) in tumours with low levels of her-2 expression(11). Assays for her-2 expression on the other hand have been set up at the Nairobi Hospital even more recently, and none of our patients had them done. None of them was treated with herceptin which is still considered experimental in the adjuvant setting, though established in treatment of metastatic disease.

Even women with very low risks of breast cancer recurrence would need adjuvant systemic therapy, as long as the agent chosen for use has very low risks of toxicity. Tamoxifen would be considered as such an agent, but only in hormone receptor positive tumours.

When considering adjuvant chemotherapy it is now established that among women with node-positive disease, anthracycline containing combinations (CAF) or CAF-like) are superior to CMF in terms of decreasing the risks of recurrence and death(1). Seventeen of our patients received CMF for adjuvant purposes, and only three received CAF and CAF like adjuvant therapy. Apart from physician preference CAF and CAF-like combinations are also considered costly for patients in public hospitals in Kenya. On average doxorubicin/cyclophosphamide combination costs the equivalent of 256 US dollars per course of treatment if 5-HT3 receptor blocking agents are included to prevent nausea and vomiting. The cytotoxic drugs alone cost less than half of that. The standard Bonadonna CMF which gives cyclophosphamide 100 mg/m<sup>2</sup> orally daily on days 1 to 14 inclusive, methotrexate 40 mg/m<sup>2</sup> intravenously on days 1 and 8, and 5-fluorouracil 600 mg/m<sup>2</sup> intravenously on days 1 and 8, on a 28 day cycle costs about 64 US dollars per course. Unfortunately it is unusual that the standard Bonadonna CMF is the one given by most oncologists the World over.

For metastatic breast cancer (MBC), a key component of evaluating the patient once more is the determination of the tumour's hormone receptor (oestrogen receptor [ER] and progesterone receptor [PR] status, and Her-2 status). These were not performed for our patients for reasons already given. Attempts should be made to address this locally because breast cancer is one solid tumour in which treatment decisions ideally should now be based on knowledge of biologic features of the malignancy, and results of ER, PR, and Her-2 assays should guide treatment

decisions for most patients with metastatic disease. Chemotherapy was given to only twenty one women with MBC in our series, despite the knowledge of the fact that in women with breast cancer insensitive to hormones, or those who have failed hormonal treatment for MBC chemotherapy offers disease control and palliative benefits, and can relieve symptoms and improve quality of life(12,13). Achievement of complete remission with chemotherapy is a favourable prognostic factor for women with MBC(14). In such a situation there is no evidence for superiority of one chemotherapy protocol over another, or of polychemotherapy over single agent sequential therapy(15). CAF or CAF-like combination was given to only four women with MBC in this series. Again the reasons could be economic, physician preference, or outright lack of awareness of the benefits derived from them.

Even though taxanes (paclitaxel and docetaxel) have been demonstrated to have considerable activity in anthracycline resistant breast cancer (16), none was used in our series. Single agent docetaxel at 75 mg/m<sup>2</sup> and paclitaxel at 175 mg/m<sup>2</sup> would cost 1026 and 1700 US dollars respectively in Nairobi, and that is out of reach of our general patient population. Herceptin is now gaining importance as a treatment in the 30% to 40% of women with MBC who have Her-2 positive tumours, stressing the fact that Her-2 determination should be carried out routinely on newly diagnosed breast cancer tissues. None of our patients were treated with herceptin because at the time of treatment for most of them herceptin was not yet in clinical use and for the few who were treated later, there were no facilities for Her-2 testing locally, and even the drug cost is as high as for the taxanes, making it out of reach of patients in public hospitals.

For almost two decades tamoxifen has been the gold standard for first-line hormone therapy of hormone sensitive MBC(18). It was generously utilised in our patients both in the pre-menopausal and postmenopausal settings. Despite the availability of facilities for hormone receptor testing in Nairobi many physicians still have the misconception that it costs their patients less if they take tamoxifen regardless of hormone receptor status than having to go through the assays.

Aromatase inhibitors have activity in post-menopausal women with breast cancer, and have been used widely in second-line therapy(19), and now even in first line therapy as is the case with anastrozole and letrozole, which are as effective as tamoxifen in this setting. None of our patients were put on aromatase inhibitors. Cost may have been an overriding factor, as a month's dose of anastrozole at 1 mg daily costs 192 US dollars in Nairobi. Lack of physician awareness could also have contributed.

In the pre-menopausal setting it appears that combined hormonal therapy with tamoxifen and ovarian ablation achieved by using gonadotrophin releasing hormone (GnRH) analogs may be superior to the latter alone(20,21). Unfortunately a month's dose of depot buserelin or goserelin costs about 192 US dollars in Nairobi, understandably none of these agents was available for

patients in this series. Ovarian ablation by surgical means or by irradiation of the ovaries is commonly practiced at the KNH but no information on this aspect was gathered in our study. Tamoxifen has been used for over three decades and most experience has been accumulated with it. Endometrial carcinogenesis is rare but its a real long term complication. A variety of pure antioestrogens and selective oestrogen receptor modulators (SERMS) are currently undergoing clinical trials. Hopefully their lack of partial oestrogenic agonist activities in various tissues that are found in tamoxifen and raloxifene will be of clinical advantage. So far they have not found any advantage over anastrozole(22,23).

The median follow-up for patients in this study was 20 months but no significant difference was seen between those who had early breast cancer and those who had advanced disease. Disease staging derived on retrospective studies are commonly flawed and could reflect lack of clear difference between "early" and "advanced" disease. The follow-up duration in this study was shorter than 30 months obtained in an earlier study based at the radiotherapy department in the same hospital (Othieno-Abinya, Babu, and Onyango - unpublished data). It is possible that once patients had had surgery and were referred for radiotherapy they continued being followed up in the latter department.

The local recurrence rate after mastectomy in breast cancer patients varies significantly in reported series, ranging from 2% to over 50%. In 1958 Ralson Paterson and colleagues in Manchester demonstrated that radiotherapy was able to reduce significantly the amount of local recurrences thereby preventing patients from dying from symptoms of uncontrolled local disease(24). A reduction of the local recurrence rate by a factor of 0.6, by post-mastectomy radiotherapy has now been demonstrated. Furthermore improvement in local control can lead to about 10% improvement in survival(4-6). This implies that distant metastases may arise from recurrent local disease, stressing the need for adequate local treatment. Recht(25) has shown that local recurrence rate in T3 tumours or those who have at least four positive axillary lymph nodes varies between 14 and 46% despite receiving adjuvant chemotherapy. On the other hand physicians are advised to bear in mind the balance between the gain in local control and survival, and the disadvantages of radiotherapy. The consensus is that loco-regional recurrence rate of 20% at 10 years or more justifies postoperative radiotherapy. This degree of high risk for local recurrence obtains in microscopically incomplete resection, T3N0 tumours with unfavourable histologic signs or positive nodes, and for patients with four or more positive lymph nodes. Post-mastectomy irradiation of the chest wall and axilla should be considered separately since the recurrence rate in the axilla is much lower than on the chest wall. As for the optimal time interval between breast conserving surgery and radiotherapy in breast cancer there is no clear consensus. In post-mastectomy cases where both adjuvant chemotherapy and radiotherapy are indicated

the consensus is that chemotherapy be given to completion followed by radiotherapy. On the other hand most retrospective studies in breast conserving therapy suggest that the interval between surgery and radiotherapy should probably not exceed six weeks because more recurrences have been experienced if intervals were longer(26). Breast conserving surgery was hardly offered to any of our patients with early disease. It is notable however that 46 patients in this study were given radiotherapy for adjuvant purposes and 53 for palliative purposes. This was a lot more than those given chemotherapy, and the simple reason is the perceived high cost of chemotherapy as compared to radiotherapy. Loco-regional radiotherapy of breast cancer for adjuvant purposes costs 256 US dollars in the same institution.

Whereas adjuvant chemotherapy targets systemic micrometastases and hence the positive impact on survival, combination of radiotherapy and systemic therapy in breast cancer has led to improved loco-regional control compared to radiotherapy alone(27,28). On the other hand adjuvant chemotherapy on its own is not able to reduce significantly the loco-regional recurrence rate in high risk breast cancer patients. This therefore requires a combination of both modalities.

Sequencing of adjuvant chemo-radiotherapy after breast conserving surgery is now the controversial point, which one comes first. While major trials are still underway to address this issue it would appear prudent to give sandwich chemo-radiotherapy. Two courses of chemotherapy are given followed by loco-regional radiotherapy to completion then 4-6 courses of chemotherapy(29-31). Since the use of chemotherapy in this series was negligible, sequencing considerations were not important.

One hundred and seventy out of 286 patients (59.4%) were lost to follow-up and 89 (31.1%) were transferred soon after surgery, making it difficult to compare strictly the duration of follow-up against survival determinants such as adjuvant treatment and stage of disease at diagnosis.

## CONCLUSION

Chemotherapy for breast cancer is grossly under-utilised at the Kenyatta National Hospital, and even adjuvant radiotherapy is under-utilised. Tamoxifen on the other hand is over-utilised, especially in the pre-menopausal setting. Follow-up durations for these patients are dismal, suggesting and/or reflecting under-treatment. A breast clinic was recently set up in this institution and hopefully some of the issues raised will be looked into.

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