UNIVERSITY OF KHARTOUM
Faculty of Medicine
Postgraduate Medical Studies Board

EVALUATION OF PALLIATIVE MANAGEMENT OF ADVANCED BREAST CANCER

By
Mohammed Abu Elgasim Ahmed
M.B.B.S (University of Khartoum)

A thesis Submitted in partial fulfillment for the requirements of the Degree of Clinical MD in Surgery, April, 2003

Supervisor
prof. El Rasheid Ahmed Abd Alla
MD, FRCSI
Professor of Surgery
U of K
أَلْهَوُذَ التَّعَالِيّ قَالَ:

«قَلِيَّاً إِلَّا أَلْلَهِ أَوْتَيْتُهُ وَمَا (الْعَظِيمِ) اِلَّهِ صَدِيقٌ»
Dedication

To

all patients with advanced cancer, especially to those who accepted to be part of this study, being so helpful inspite of much suffering and pain.

I wish for them enjoyable and better life
I would like to express my gratitude to my supervisor Prof. Elrasheed Ahmed Abdalla, Professor of Surgery, Faculty of Medicine, University of Khartoum, for his guidance and useful discussion. Also would like to extend my ample thank to Prof. Taha Ba’ashar for his invaluable advice in the assessment of psychological disturbances in breast cancer patients.

I would like to thank Dr. Amira Zino, who studied breast cancer 5 years ago for her sincere help.

I am grateful to Mr. Hassan Ali at Health Education Administration for the analysis of data and to the library staff at the National Centre for Researches.

Thanks to the nursing staff at E2 ward (KTH) and Chemotherapy Division (RICK), also to the technicians in Radiotherapy Unit and to the working staff in the Medical Records Unit at RICK for being helpful.

Last but not the least my thanks are due to Miss Widad A/ Magsoud for her tremendous effort in typing this work.
### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Meaning</th>
</tr>
</thead>
<tbody>
<tr>
<td>AJCC</td>
<td>American Joint Committee on Cancer</td>
</tr>
<tr>
<td>CMF</td>
<td>Cyclophosphamide, Methotrexate, 5-Fluoro-uracil</td>
</tr>
<tr>
<td>KI</td>
<td>Karnofsky index</td>
</tr>
<tr>
<td>KTH</td>
<td>Khartoum Teaching Hospital</td>
</tr>
<tr>
<td>LABC</td>
<td>Locally Advanced Breast Cancer</td>
</tr>
<tr>
<td>MBC</td>
<td>Metastatic Breast Cancer</td>
</tr>
<tr>
<td>QL</td>
<td>Quality of life</td>
</tr>
<tr>
<td>UICC</td>
<td>International Union Against Cancer</td>
</tr>
<tr>
<td>UICC</td>
<td></td>
</tr>
</tbody>
</table>
ABSTRACT

Introduction: Breast cancer in Sudan is the commonest female cancer, nevertheless only few researches considered this problem. Quality of life for patients with advanced cancer received little attention from medical community.

Objectives: To study quality of life (QL), palliation, symptoms control and satisfaction in patients with advanced breast cancer.

Design: A prospective cross sectional assessment in 90 patients selected randomly, inpatients and outpatients from KTH and RICK were included, in the period between March to September 2002.

Methods: Through direct interview, QL using KI and other domains were assessed at least 3 weeks following palliation.

Results: Initially the median KI was 6.8, following palliation it was 7.2, radiotherapy for painful bone metastases and aspiration for pleural effusion showed symptoms control in some 93% and 70% of cases respectively. Poor symptoms control was recognized in patients with lymphoedema and pathological fractures. Mood disturbances were identified in 41%. Doctor patient relationship in more than 20% needs correction. In 58% of patients, pain relief was partial, and in 16% was poor.
Discussion: Palliation was partially effective majority of patients emerged from poor zone, but not reaching good quality life. Pain was under treated, other symptoms showed variable control.

Conclusion: In this study the concept of QL was taken primary and oit, these results may be more useful, if compared with further studies using different scales of QL measurement, as this may help in the identification of a simple and precise method for evaluation in a highly subjective issue such as QL.
الطرح:

أكثر يشكل أنه إلا السودان في الثدي سرتان سرعان أجراّته التي البحث قلّة رغم دراسة المجتمع اقامة قلّاً امّاً للكسيدة، عند شيواه السرطانات لحيائة النوعية مرحلة في السرطان ذات الأبيضى.

الغرض:

المرضى لهؤلاء الحياة النوعية على المطفلة المعالجة أثر دراسة هذه أجرّت.

الرضا درجة تحليل لهذه إضافة المختلفة الأعراض على السيطرة في قدّرتها على واعتبار وعلاج الطبي على.

التصميم:

وصف مسقيلة دراسة هذه من تكون على عينة مقطعية تحليل عمل تتمّ لajaran 95 مريض حتى مارس ومن الثورة في العشائيب باختيار التأخر مرحلة في الثدي السرطان ومن ثمّ لعام سبتمبر 2002 بالأشعة العلاج ومركز التعلمي الخرطوم مستشفى في.

الطريقة:

نوعية في الموروث الأخرى واعمل مكتشفة مشرّعة باستعمال إجراء تتمّ للحياة الأقل على أسابيع ثالثة بفترات المعالجة تلقّم عقب المريض مع مبادرة مقابلة.

النتائج:

كان البداية باهنة الافسفكي للفحص 8.6% وأصبح 2.7% لوحظ المعالجة بعد الإشعاعي العلاج عقب العظم في الثانية الاستجابة ومجرد 65% 93% لأنّ الفحص من، على تعرض الكسور ذات المريض في الحبس درجة لدي ينفي اضطراّب على يدل ظهور 41% أو فيدراء يا كبيط في 55% أو تسع و20% لبيب 5 15.8% وثورة كلهَّ المحتوى أدّى دِّير عزة إذا.


ALKUĐAY: الذات حياة طبيعية

するのは مستعملاً في جزءًا فاعلية أثبتت المطلفة المعالجة متوسطة أخرى إلى ردية نوعية.

التحكيم جليًا تفاوتًا أظهر الآخرين الأعراض معظم في.

الخاتمة: ماتحة حاجة هناك أن كمًا بالترشيح، جدير هام النية أولية دراسة كنقطة الحياة نوعية السبل أسير على تحقق حتى بينهما المقارنة ثم مختلفة وسائل باستعمال متعددة دراسات لعمل الناحية من الوعر المجل هذا في القياسية وأدقه.

LIST OF FIGURES

Page

Fig. 1: Age distribution in patients with advanced breast cancer 36
Fig. 2: Sex distribution among patients

37

Fig. 3: Residence of patients

37

Fig. 4: Education levels of patients

38

Fig. 5: Financial status of patients

38

Fig. 6: Involved breast among patients

39

Fig. 7: Pattern of presentation among patients

39

Fig. 8: Pattern of locally advanced breast cancer

40

Fig. 9: Site of distant metastases

40

Fig. 10: Overall symptoms control

41

Fig. 11: Symptom control for painful bony metastases in 30 patients treated with the radiotherapy

41

LIST OF TABLES

Table 1: Using the Karnofsky index as indicator: The effect of
palliation on the functional aspect of Q.L. 42

**Table 2:** Hemoglobin concentration (g/dl) in 90 patients 43

**Table 3:** Amount of blood transfusion in pints (n=38) 43

**Table 4:** Investigations showing evidence of metastases (n=59) 44

**Table 5:** Complications of breast surgery in patients with locally advanced breast cancer (n=38) 44

**Table 6:** Chemo-therapeutic agents (n=67) 45

**Table 7:** Side effects of chemotherapy (n=67) 45

**Table 8:** Mood disturbances (were recognized in 37 patients) 46

**Table 9:** Follow up of doctors to their patients (inpatients group =38) 46

**Table 10:** Time spent with patients (n=90) 47

**Table 11:** This table shows the answer to the question: Do doctors discuss all problems you have? 47

**Table 12:** Patients were classified according to their knowledge about the diagnosis into 3 categories (n=90) 48

**Table 13:** Patients knowledge about the diagnosis and mood disturbances, the relation ship 48

**Table 14:** Sleep following palliative care (n=90) 49

**Table 15:** Mobility following palliative care (n=90) 49

**Table 16:** Appetite (n=90) 49
Table 17: Social interaction (n=90) 50

Table 18: Pain relief in 57 patients: Effects of non steroidal analgesics 50

Table 19: Patient satisfaction (n=90) 51

Table 20: Family satisfaction (88 co-patients) 51

Table 21: The relationship degree between patients and co-patients 52

Table 22: Psychological aspect in-patients will breast surgery (n=74) 52

Table 23: Symptom control in patients with locally advanced breast cancer, using two modes of therapy (n=49) 53

Table 24: Pattern of bone secondaries (n=34) 53

Table 25: Pattern of extaspinal secondaries: different sites (n=18) 54

Table 26: Symptom control in patients with dyspnea due to pleural effusion (n=10) 54

Table 27: Sites of distant metastases showing no symptoms 55
CONTENTS

Acknowledgment.................................................................................................................. I
Dedication ................................................................................................................................. II
Abbreviations ............................................................................................................................... III
Abstract ........................................................................................................................................ IV
Abstract (Arabic) ........................................................................................................................... VI
List of figures ............................................................................................................................... VIII
List of tables ................................................................................................................................. IX

CHAPTER ONE
INTRODUCTION ...................................................................................................................... 1
LITERATURE REVIEW .............................................................................................................. 6
OBJECTIVES .............................................................................................................................. 25

CHAPTER TWO
PATIENTS & METHODS ........................................................................................................ 26

CHAPTER THREE
RESULTS ......................................................................................................................................... 29

CHAPTER FOUR
DISCUSSION ............................................................................................................................. 57
CONCLUSION ............................................................................................................................. 67
REFERENCES .............................................................................................................................. 68
APPENDIX (Questionnaire)
INTRODUCTION

Breast cancer in all parts of the world, seems to be responsible for the highest proportions of all female cancer deaths. It’s the commonest cancer of females in developing world.

According to data from 1988 to 1990 US women the life risk for being diagnosed with breast cancer is 12.2%, or 1 in 8, and the lifetime risk for being dying from breast cancer is 3.6%, or 1 in 28.

In the period between January 1954 to December 1961, two hundred and sixty cases were reported in Sudan, accounting for 21.9% of all female cancers. The same report\(^{(1)}\) mentioned high rate of breast Sarcoma (16 case out of 260), attributing this to the great majority of very advanced, often ulcerating, malignant conditions.

In a retrospective study\(^{(2)}\) in 4 years period (between Jan. 1981 to Dec. 1984) in Radiation and Isotope Center, Khartoum (RICK), total number of patients was 546 accounting for 42% of all female malignancies.

For Breast cancer in Sudan only a few researches were done, although, it seems there’s an increase number of cases. The table below obtained from Statistics and Medical Registration Section at RICK, showing new cases of breast cancer referred from allover Sudan during the last decade.
<table>
<thead>
<tr>
<th>Year</th>
<th>New patients</th>
<th>% from total female cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>2002</td>
<td>575</td>
<td>32.1</td>
</tr>
<tr>
<td>2001</td>
<td>596</td>
<td>35.4</td>
</tr>
<tr>
<td>2000</td>
<td>500</td>
<td>36.3</td>
</tr>
<tr>
<td>1999</td>
<td>455</td>
<td>35.2</td>
</tr>
<tr>
<td>1998</td>
<td>502</td>
<td>23.7 %</td>
</tr>
<tr>
<td>1996</td>
<td>314</td>
<td>22 %</td>
</tr>
<tr>
<td>1994</td>
<td>255</td>
<td>15.5 %</td>
</tr>
<tr>
<td>1993</td>
<td>162</td>
<td>36.2 %</td>
</tr>
<tr>
<td>1992</td>
<td>292</td>
<td>24.4 %</td>
</tr>
<tr>
<td>1991</td>
<td>165</td>
<td>17.7 %</td>
</tr>
<tr>
<td>1990</td>
<td>200</td>
<td>23.2 %</td>
</tr>
<tr>
<td>1989</td>
<td>203</td>
<td>-</td>
</tr>
</tbody>
</table>

*Number of patients from allover the country referred to RICK.*

In an epidemiological study in 1998, Gaalein, Shaigia and Mahas were found to be tribes with higher frequencies, Nuba and Rizigat are the commonest tribes in the West. Suggesting genetic or environmental factors.
One manifestation of this disease in Sudan is advanced stage at presentation as shown is the study done in 1986, stage 3 and 4 relative frequencies were 34.2 and 10% respectively.\(^{(2)}\)

Breast cancer is a heterogeneous group of diseases, not only one disease; it has different biological behaviours, bizarre outcome. It is a field of many researches, some of them are promising, but still no substantial improvement in overall survival during the last years. Many studies in developed world are directed towards early stages of the disease, comparing different modalities of treatment options which are so numerous, aiming to improve local disease control as well as disease free overall survival. On the other hand, the situation of breast cancer in Sudan is different in many aspects, and there are many difficulties faced in managing those with advanced disease.

The efficacy of palliation, and planning for it is of a paramount importance in achieving a good quality of life.

To a large extent psychological, physical, social, and other parameters of quality of life, are difficult to measure quantitatively. There are many scales developed to facilitate measurement, none of them was tested in Sudanese patients with breast cancer. They have been originally prepared and tested is western communities. In this study a simple scale, extensively used in cancer patients, measuring functional status,
Karnofsky performance index (KI). It was one of the earliest attempts to evaluate quality of life after an intervention. Karnofsky and Burchenal (1948) recognized that the outcome of treatment of cancer with chemotherapeutic drugs should be judged not only by objective measurements such as dimensions of the tumor, but also by the wellbeing of the patient, they put forward a 10 – point scale, graded from worst (score 1) to best (score 10):

1. Moribund; fatal processes progressing rapidly.
2. Very ill; admission to hospital for treatment needed.
3. Severely disabled; spend a lot of time in hospital.
4. Disabled; needs special care most of the time.
5. Needs a lot of assistance and frequent medical care.
6. Needs occasional help but can usually cope.
7. Can care for self but can’t carry on normal activities.
8. Has some symptoms ad normal activity is an effort.
9. Has minor symptoms can carry on normal activities.
10. Has no complaint.

Patient’s understanding of the disease is dictated by what she knows about it, and may be by a previous experience of some body else got the disease, and died horribly of it. This is reflected seriously on patient’s attitude and emotional status, it needs appreciation and
awareness from doctor’s side. As well as better explanation based on a sound doctor-patient relationship.

Pain control in patients with advanced cancer is usually difficult, usually the degree of pain as disabling chronic and irritating symptom is under evaluated and under treated.

Poor results in studies covering advanced cancers in terms of survival is understandable, but poor palliation is both serious and inhumane, and by no means acceptable. It’s interesting to mention here, in this country, doctors tend to hide the real diagnosis from patients, and probably find difficulty when faced by a patient who insists to discuss it; because it’s unusual situation for them, and it needs special capabilities to be able to communicate with the patient about cancer diagnosis without hurting him so much, or destroying any hope for life he has. But most of our patients like not to be told that they have a killing disease, and they usually tend not to ask or seek such information. This makes the doctor’s approach more difficult, since many of the patients may have wrong ideas that might increase their worries unnecessarily, yet very difficult to be shown frankly or discussed overtly. When a patient refuses surgery, one way used to convince her, is to tell her about how bad her condition will be, and how her breast is going to fungate into an offensive wound.
Acceptance of mastectomy through a fearful approach as such, has a devastating effect on patient’s psychological well being, especially if local recurrence occurs.

I think this terrible way should never be used or considered valuable, but keeping patient informed about necessary facts is essential; since patient’s contribution in treatment planning and decision making is always regarded as the best.

**LITERATURE REVIEW**

**Advanced breast cancer:**

Advanced breast cancer may be defined as cancer for which no prospect of cure can be offered by local treatment.

Breast cancer may be advanced by virtue of local progression or because of wide spread dissemination. Dissemination may occur either through lymphatic channels or via blood stream.

Extensive lymphatic permeation may cause disease in the supraclavicular fossa, internal mammary nodes, and subsequently in the intra-thoracic and intra-abdominal nodes. Spread by the blood stream may occur to any part of the body, though breast cancer has a predilection for bones, liver, lungs and brain.
The distribution of metastases is not entirely random; oestrogen receptor-positive tumours metastasize more often to bone.\(^{(4)}\) Locally advanced breast cancer, by definition stage III, is usually easy to diagnose.\(^{(5,6)}\)

- Skin: fixation, Peaud’orange, overlying erythema, oedema and arm lymphoedema, satellite nodules, retraction of the breast.
- Solid attachment to underlying muscles.
- Hard, slightly irregular, matted and fixed axillary nodes, or larger than 2cm.
- According to UICC, the staging system of TNM, which was published is 1987.\(^{(7)}\) It considers supraclavicular metastasis as stage IV. Tumor fixation and ulceration, fixed nodal involvement were grave signs and carry poor prognosis.\(^{(8)}\)

According to data\(^{(9)}\) obtained from more than 50,000 patients in 1989, five years survival for stage III ranges from 42 - 51\% and for stage IV is 10 - 13 \%.

Patients with LABC have poor prognosis, and survival if not offered a systemic therapy. The debate is concerned with the sequence in which these modalities should be used.\(^{(10,11,12)}\)

Metastatic breast cancer commonly follow a slow and indolent course when compared with other solid tumour metastasis, patients with
bony metastases may survive along time with their disease in contrast to patients with visceral metastases; who have a median survival of six months. Although most women with metastatic cancer will eventually succumb to the disease, chemotherapy, hormonal therapy, radiotherapy, and limited surgery are all effective treatment modalities for palliation, improvement in quality of life, and prolongation of life.\textsuperscript{(13)}

Patients with LABC at presentation or with local recurrence should be fully evaluated for evidence of systemic disease. The protocol should include:

(a) FNA or core biopsy for diagnosis.
(b) A full blood count with examination of the film; leucoerythroblastic features are not uncommon.
(c) Liver function tests to include alkaline phosphatase.
(d) Calcium levels, many patients with hypercalcaemia are asymptomatic.
(e) Liver ultrasound.
(f) Chest radiograph.
(g) Isotope bone scan.

Other tests may be indicated for symptoms or as a follow-up to the first round of tests. Most metastatic disease will be demonstrated by these tests but any new symptom in a patient with previous diagnosis of
breast cancer demands consideration of the possibility of metastatic disease. It’s not unknown for the first recurrence of breast cancer to occur 30 years after the primary treatment.

**Palliation:**

Palliative care is a rapidly advancing branch of medicine and as adopted by WHO palliation is defined as “the active, total care of a person whose condition is not responsive to curative treatment”.

The concept of palliative care embraces optimal symptom control and quality of life as well as appropriate rehabilitation, and is no longer regarded as a negative lack-of-treatment.

The palliative management of advanced breast cancer is complex and the options for both local and systemic treatment are extensive, therefore, a clear view of the objectives of treatment is necessary.

- **Cure:** is an unrealistic expectation in advanced breast cancer.
- **Survival:** a good response to systemic treatment may result in increased survival but such gains should be weighed against treatment side effects. Effective local treatment may alleviate symptoms without altering the progress of the underlying disease process, sometimes there may be survival benefits.
- **Symptom control:** regardless of the situation in which the disease has become apparent, the patient should be fully evaluated and life
threatening or function threatening conditions identified and controlled. Adequate relief of pain, anxiety, insomnia, nausea, side effects of treatment, and other metastatic manifestation is necessary.

Presentation with an offensive breast cancer is not uncommon in Sudanese patients. It is caused by polyamines formed in the center of the necrotic mass, polyamines are reactive and adhere to almost any thing with which they come in contact including skin, or clothing, leaving a residual nauseating odour in the room. When visitors leave, the smell stays on their clothing and skin; as a result, patients refrain from contact with other. Patients themselves often don’t notice the odour but recognize other’s response to it.

A part from surgical treatment to breast, local control measures include the following.(17)

(a) Frequent dressing with highly absorbent, non-adhesive material.
(b) Sliver nitrate 1% solution soaked in large gauze pads.
(c) Maggots these are worms in the necrotic tissue and it actually debride the wound. For its removal diethyl ether applied to the surface and deep into the wound.
(d) Isolate in private room, an outward facing fan is placed to blow air out of the window, the offensive mass should be kept covered.
(e) Room deodorizers.
(f) Meteronidazole 250-500mg t.i.d, particularly if anaerobic bacterial infection is present.

**Neoadjuvant chemotherapy:**

Still in developed countries 10-20% of all breast cancer patients have stage III at presentation of which 25 – 30% are inoperable. In Sudan a series of 546 patients between Jan 1981 to Dec 1984, advanced breast cancer account for 42%.

The lack of efficacy in using a combination of the two local treatment modalities, surgery and radiotherapy, confirmed the fact stage III Breast cancer is a systemic disease.

Neoadjuvant chemotherapy is delivered before removal of primary tumour. It has several theoretical advantages; the presence of a palpable or radiologically measurable mass permits response to be assessed as a direct *in vivo* measure of the sensitivity of the tumor cells to the particular drugs used, early detection of a resistant tumor will enable the oncologist to discontinue a worthless therapy, thus avoiding unnecessary toxicity, or to change to a potentially more effective regimen. Also, the earlier the disease is treated, the less likely it is that resistant tumor clones will have emerged spontaneously.

Finally, preoperative chemotherapy has been shown to reduce primary tumour size (down grading), thus allowing an increased rate of
breast conserving surgery\textsuperscript{(20)} and increased resectability rate for tumours have been inoperable.

In two trials\textsuperscript{(20, 21)} comparing neoadjuvant chemotherapy to adjuvant one, a significant advantage in terms of disease-free and overall survival was found in neoadjuvant group, in other two trials\textsuperscript{(22, 23)} equivalent results in disease-free and overall survival were obtained.

Three to six cycles of induction chemotherapy results in high objective response rate, this enables local treatment measures to achieve better tumor control. However, overall survival is only marginally affected.\textsuperscript{(24, 25)}

The Disease free survival and overall survival were significantly better in patients treated with more intensive chemotherapy.\textsuperscript{(26)}

The current recommendations for patients with inoperable or inflammatory cancer are treatment with maximum doses of systemic therapy in an attempt at the aggressive eradication of micro metastases prior to local therapy. Doxorubicin containing regimen is suggested for the best response. For operable cancer stage III A no firm guidelines exist, the biggest problem with these patients is early relapse, and death from metastatic disease. Because of these consideration, the first step in treatment for most patients is combination chemotherapy,\textsuperscript{(27)} followed by
surgery and radiotherapy to decrease relapse. The role of adjuvant hormonal therapy in this group of patients is still under investigation.

**Metastatic cancer:**

Patients with metastases has a median survival of two years, 5 years survival is only 10%. Treatment in this setting is purely palliative. Systemic therapy achieved improvement in survival, but was never curative arms of systemic therapy were chemotherapy and hormonal therapy.

About 40-80% of patients with advanced disease with receptors positive tumors will benefit from hormonal therapy, (i.e. positive oestrogen and progesterone status carries a good prognosis).

Tamoxifen, non steroidal anti oestrogen, is tumorstatic agent, cancer cells are not destroyed; but arrested. It should be used for extended period, 5 years. Regardless to oestrogen receptor status, patients with metastases may have response to tamoxfen.

Axillary nodal involvement of more them 4 lymph nodes proves to be a marker for the metastatic potential of a tumor.

**Bone metastases:**

Bone is first site for metastases in 26%, as many as 74% will eventually have it. Usually patients present with pain and at late stage with pathological fractures. Breast secondaries to bone are usually of
osteolytic type, but to lesser degree osteoblastic or mixed. Sites in order of frequency are: spine, pelvis, ribs, skull, and proximal long bones. Bone scan can show asymptomatic lesions.

If more than 50% of the cortex is eroded over more than 2 cm then it’s considered that the long bones are liable to imminent pathological fracture; under these circumstances it is best to stabilize the bone before it breaks. Even where a fracture has already occurred, stabilization and radiotherapy will relieve pain and stop the progression of tumor growth, allowing patients to remain mobile and may even allow the fracture to heal.

The exact mechanism by which radiotherapy relieves pain isn’t known, but is postulated to result from tumor shrinkage, that relieves periosteal tension and from direct inhibition of specific humoral factors, such as, prostaglandin’s. Response to radiotherapy is excellent with complete response rates ranging from 50 - 60% and overall response rate of 70-90%. Surgical stabilization is indicated before radiotherapy, since it interferes with normal bone healing. The management of isolated, slow growing metastases is excision, aiming to improve survival, the defect is reconstructed by cemented megaprosthesi.

Hormonal and chemotherapy may also prove to be useful in management of bone metastasis. Sternal metastases should be treated
promptly, since; if left untreated, the thoracic cage is unstable, leading to amid dorsal vertebral fracture.

**Malignant pleural effusions:**

Breast and lung cancer are responsible for the majority of malignant pleural effusion. The diagnosis of a malignant pleural effusion signifies limited survival for most patients. During their final months, dyspnea is the most common symptom and requires palliation. A decision relating to palliation and the modality of therapy should be based on total assessment of the patient and not a single variable. Local treatment remains the most common and effective palliation. Assessing the response to therapeutic thoracentesis determines the degree of relief of dyspnea and the time course of recurrence. Lack of a beneficial effect suggests the patient may have a trapped lung, atelectasis, lymphangitic carcinomatosis, or tumor embolism. Short- term chest tube drainage has variable results and is not recommended. Chemical pleurodesis through a standard chest tube or small- bore catheter is a commonly used and effective treatment. Talc slurry consistently produces the highest success rates, followed by the tetracyclines and bleomycin. Although acute respiratory failure has been reported following talc pleurodesis, these episodes represent a very small percentage of the total reported cases of talc poudrage and slurry pleurodesis. Whether acute reported failure is directly related to talc in the
absence of other risk factors remains unclear. Other possible causes for acute respiratory failure following pleurodesis include reexpansion pulmonary edema, excessive premeditation, severe comorbid disease, and sepsis from unsterile talc or poor chest tube technique. Factors that need to be considered before recommending chemical pleurodesis include response to therapeutic thoracentesis, general health of the patient, performance status, pleural space elastance, the primary malignancy, and pleural fluid pH. Chronic indwelling catheters have been shown to be effective alternation to chemical pleurodesis. Pleuroperitoneal shunting can provide palliation to patients with a trapped lung, a malignant chylothorax, or others who have failed pleurodesis. Parietal pleurectomy should be reserved only for patients who have failed chemical pleurodesis or have a trapped lung with an expected survival >6 months. To provide the highest quality of life for patients with malignant pleural effusions, the least invasive, morbid and costly therapy should be used. Success of the initial procedure is important, as repeat procedure are associated with additional hospitalization, patient discomfort, and increased expense; therefore, the selection of patients for palliation and the modality utilized is critical to avoiding further hardship to the patient.(29)

**Cerebral metastases:**
The commonest primary sites for cerebral metastases include melanoma, bronchus and breast.\footnote{30}

Brain metastases are important in brain cancer (15%), metastases may be either single or multiple and diagnostically may be difficult to distinguish from primary brain tumour.

The characteristic symptoms are those of raised intracranial pressure, and will usually produce headache, nausea, vomiting and drowsiness, focal neurological damage and convulsions.

The diagnosis is usually suggested by isotope or CT brain scanning; which may show a single or multiple abnormal areas of increased uptake of isotope on atypically spherical lesion, often with obvious contrast enhancement on CT-scanning. Although local oedema is often present, this usually less than that seen with high-grade primary brain tumours, MR scanning can also be informative. Treatment with dexamethasone, often at high dosage 6 mg every 6 hours orally, IV, or IM is often valuable to produce rapid reduction of intracranial pressure and relief of cerebral edema, dexamethasone exerts its effect rapidly and can be quickly reduced in dosage. An effective palliative tool is radiotherapy, whole brain and meninges irradiation.

In study\footnote{31} of 162 breast cancer patients with brain metastases, 145 patients were treated with irradiation (60 cobalt or 6 MV) of whole
brain, 10 patients underwent surgery and 17 received symptomatic treatment only (corticosteroid). Survival was 82 weeks for surgical patients, 26 weeks for radiotherapy, 5 weeks for steroid. The study revealed that according to Karnofsky index, solitary metastases is a significant prognostic factors.

Carcinomatous meningitis from breast carcinoma is an aggressive metastatic complication with a poor prognosis,\(^{(32)}\) in analysis of 35 patients the authors\(^{(33)}\) suggest that patients with a poor KP (Kornofsky performance status) \(<7\) should be treated symptomatically and these with a good KP \(\geq 7\) should receive more aggressive treatment. The overall median survival was only 77 days.

**Lung metastases:**

Metastatic lung lesions are most often peripheral, are detected by chest radiograph, and are asymptomatic \(85\%\) of the time, resection of metastases by wedge resection with at least a 1cm tumour-free margin can result in long-term survival benefit. The best results occur for removal of small (less than 3 cm) solitary lesions, but long-term survival for patients with multiple resected metastases can be achieved. It is associated with radiographic changes similar to lung metastases. Survival rate following resection of metastases of breast cancer to lung is \(12 – 27\%\).\(^{(34)}\)

**Liver metastases:**
Symptoms or clinical signs suggesting metastatic disease in the liver are usually late occurrences. Consequently, findings such as ascites, jaundice, right upper quadrant pain, elevation of liver function values are associated with poor prognosis in collected series of resected liver metastases, there are few 5-year survivors, unlike the condition of colorectal metastases to the liver, where, in most reported series, the 5-year survival rate ranges from 25 to 40%.

In one series, resection of liver secondaries in 22 patients of breast cancer, has resulted in 5-year survival in only two patients.\(^{(35)}\)

**Psychosocial aspects:**

The diagnosis of cancer tends to reflect premorbid mechanisms of coping and interacting.\(^{(36)}\)

Common losses experienced:

(a) Loss of health and physical integrity.

(b) Loss of self-esteem.

(c) Loss of religious convictions (what did I do wrong to deserve this?)

(d) Separation from family members especially children.

(e) Changes in sexual activities.

Common reactions:

(a) Hostility and anger.
(b) Anxiety: which worsen sensation of pain.

(c) Entitlement: patients seek special attention as a compensation for losses.

(d) Depression: is appropriate if it isn’t severe.

(e) Psychosis.

Patients and their partners must be informed that sexual activities are not harmful and that cancer is not contagious. Many patients lose interest in sex and may require psychosexual support.

**Management of cancer pain:**

The vast majority of patients with advanced cancer (as many as 90%), and as many as 60% of patients with any stage of disease experience pain of significant degree. However, cancer pain frequently is undertreated for a multitude of reasons and fears that are largely unfounded. Effective management of cancer pain is achieved best with a multidisciplinary approach including pain specialists, Oncologists, nurses, pharmacists, physiatrists, physical and occupational therapists, psychologists, psychiatrists, primary care physicians, social workers and surgeons. Open line of communication is of paramount importance to the successful management of cancer pain. Cancer pain may be due to direct tumour involvement of bone, nerves, viscera, blood vessels, and can be postoperative, post radiotherapy, or post chemotherapy.
Narcotic use should follow the basic principles of cancer pain management, beginning with an agent that has the potential to provide relief; individualization of the agent, route, dose, and schedule; titration to efficacy; provision of relief for breakthrough pain (sudden onset pain). Side effects should be anticipated and treated.

Change from one route of administration to another should be done with equianalgesic doses, and the oral route should be used whenever possible. Various adjuncts to pain management can be used, it include steroids, antidepressant, anxiolytics, and neuroleptics, as well as neuroablative, neurostimulatory, and anaesthetic procedures.\(^{28, 38}\)

*The WHO has designed a three-step approach:*

(a) NSAID if there’s inflammatory component to the pain.

(b) If not fully controlled, opioids or non-opioids are used alone or combined with adjuvant drugs.

(c) Morphine, adjuvant are employed as needed.

About 50% of physicians in a recent multi-center study gave their cancer patients insufficient analgesics for pain control\(^{39}\) the reason for this is fear of patient addiction.

In patients with advanced cancer who have a good pain response to NSAIDs but who continue to have problem with peptic ulcers, omperazole 20 mg may be considered for longer-term use than usual.
COX-2 inhibitors, a new generation of NSAIDs, associated with much less GI irritation and bleeding, these agents may to be useful in cancer.

**Nutrition:**

Preoperative and postoperative chemotherapy and radiation therapy can adversely affect nutritional status.

Nutrition plays a key role is the recovery and rehabilitation of cancer patients. Adequate protein, calories, and essential micronutrient help maintain a reasonable quality of life for these patients. Cancer cachexia is a syndrome of progressive involuntary weight loss and intractable anorexia.\(^{(40)}\)

Cancer cachexia and significant weight loss is much observed in visceral malignancy than in breast cancer.

Metabolic abnormalities is cachexia:

a- Carbohydrates: insulin resistance, glucose intolerance; increased gluconeogenesis, Cori’s cycle activity, glucose turn over.

b- Fats: decreased lipoprotein lipase increased fatty acid mobilization and turnover, serum lipid levels, and glycerol turnover.

c- Proteins: decreased skeletal muscle anabolism; increased skeletal muscle catabolism and protein turnover.

**Nutritional requirements:**
The healthy person requires 2000 to 2700 (25 cal/kg) calories per day distributed as follows: 15% protein (1g/kg), 50% carbohydrate (3g/kg), and 35% fat (1g/kg). To achieve a positive nitrogen balance and sustain weight, cachectic patients require hyperalimentation with 2700 to 4000 calories and twice the recommended daily allowance of aminoacids and essential nutrients.

Nutritional therapy doesn’t prolong survival if the tumour cannot be controlled, but it often provides psychological palliation, especially when active cancer treatment is not helpful.

In one study using the Healthy Eating Index (HEI) in breast cancer patient was found to be a mean total score of 67.2, most often diets were evaluated as there that (need improvement) being low in energy and dietary variety, the same study concluded poorer diet may be outcome of depression.\(^{(41)}\)

**Lymphoedema:**

It’s a common and troublesome problem, cosmetic deformity, physical discomfort of the upper extremity, disability recurrent episodes of cellulitis and lymphangitis are expected. It’s a permanent disability requiring daily attention, breast cancer patients are more distressed by their appearance with lymphoedema than by mastectomy. The incidence
of lymphoedema is greatly increased when combined surgery and radiotherapy used in the axilla.\(^{(42)}\)

A report from the Royal Marsden noted that, with careful volumetric measurements, 25.5\% of the breast cancer patients returning follow up over a 6-month period had more than 200 ml volume increase in the arm after axillary treatment.\(^{(43)}\)

Careful arm measurement to detect earliest lymphoedema, a difference in circumference of more than 2 cm between the arms, if the other limb is normal has a clinical significance, arm elevation, properly fitted compression garments, and in severe cases intermittent compression devices, manual lymph drainage and exercise regimen should be initiated as soon as possible to arrest this process.

American Cancer Society precautions listed in 1979 for lymphoedema patients to avoid arm swelling or infection include:

\textbf{a-} Avoid injection, vaccination, blood pressure monitoring in the ipsilateral arm.

\textbf{b-} Avoid puncturing the skin.

\textbf{c-} Avoid lifting heavy objects.

\textbf{d-} Don’t shave or use deodorant under the affected arm until permission is granted from the surgeon.
Quality of life (QL):

QL evaluation has gained increasing attention within the oncology community over the past two decades. The breadth of quality of life research in women with breast cancer has expanded substantially during this time.

Descriptive QL studies, using several means and instruments in patients undergoing active treatment can identify the impact breast cancer treatment has on a patient life. Thus help in decisions of initiating or continuing such treatment.

QL assessment now is incorporated in many clinical trials providing a patient-rated assessment of treatment and complement the traditional end points in clinical trials.

In one study\(^{(44)}\) comparing the QL of women with different cancer sites, and to examine the agreement between patient-self reported QL and QL ratings provided by clinicians and significant others, 248 patients with gynaecologic and breast cancer, for all women, global QL and emotional functioning were mostly affected during or after treatment. There were no statistically significant differences in QL among different cancer sites. QL scores of health providers and relatives were generally in close agreement with those of patients. In studies of quality of life in
breast-cancer significant impairment of body image and sexuality was observed in patients underwent mastectomy in particular.\(^{(45)}\)

**OBJECTIVES**

1- To study the quality of life in patients with advanced breast cancer.

2- To assess the efficacy of different palliative procedures used for symptoms control.

3- To identify the degree of patients satisfaction with doctor and treatment.
PATIENTS AND METHODS

This is a prospective study, probably the first study in Sudan designed to address the issue of quality of life in patients with advanced breast cancer receiving palliative care.

Random selection of 90 patients with either stage III or IV breast carcinoma, according to TNM classification.

Patients were interviewed at two hospitals, Khartoum Teaching Hospital (KTH) and Radiation and Isotopes Centre, Khartoum (RICK), study period from March to September 2002. Full explanation to the patients about the study and verbal consents from them to be enrolled in it were obtained through direct interview; informations regarding patient’s demographic data, the disease, palliative procedures, and adjuvant treatments was collected in a specially designed data sheet (Appendix).

Complete filling of data in the questionnaire sheet was at least three weeks following surgery, or after completion of radiotherapy, or during chemotherapy cycles.
Informations were entered into a computer system for analysis using EPI-6 software.

In this study, assessment of quality of life was done in a cross-sectional pattern (i.e., patients were not assessed longitudinally several times, but only one time following palliation); for this reason, results in this study reflect the early effects of palliation.

Since the quality of life is a highly subjective issue, assessment was done by the author for all patients to minimize interobserver error.

The domains of quality of life are derived from the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire. Breast Cancer (EORTC-QLQ-BR23), which includes physical, functional, social psychological, body image, sexual enjoyment, symptom control and financial aspects, these items were assessed precisely during the interview. To measure functional aspect of quality of life, a universal index was used, the Karnofsky index. Measurement was done before and after palliation. Karnofsky defined poor performance status as \( \leq 7 \).

In this study, age of the patients was taken as they or their relatives state it, but when inappropriate age is given, then estimation was used. For levels of education, high education were university graduates, low education were illiterate.
Financial status of patients who sought support for treatment expenses were classified as low. Moderate status for those who paid for the treatment, but still complaining for cost. High status for patients who have no problems at all.

Various psychological disturbances are seen in cancer patients, in this study, the commonest two, depressions and anxiety were studied in details using the following guidelines for diagnosis.

The presence of psychological symptoms of anxiety such as fear, apprehensions and irritability and any one of somatic symptoms such as palpation, pain, tremors, dizziness insomnia, poor concentration or G1 disturbances was adequate to label the patient as having anxiety.

For depression, psychological symptoms of minor depression such as loss of pleasure in life, interest in oneself or other, and low self-esteem, and any one of somatic symptoms which are fatigue, sleep disturbance, headache, anorexia, pains, weight changes, reduced lipido and poor concentration are enough to label the patient as having minor depressive episode.

For social life mood disturbances and satisfaction both patients and their relatives were inquired.
RESULTS

Ninety patients with advanced breast cancer were studied, an average age of the patients was 47.3 (SD 13.6) years, the youngest was 24, the oldest was 75. The third and fourth decades showed increased frequencies, 33(36.6%) and 20(22.3%) patients respectively (Fig. 1).

There were three males with breast cancer representing 3.3% of the study group (Fig. 2).
Patients residence, either rural or urban, was 59(65.6%) for the former and 31(34.3%) for the later (Fig. 3).

Low education level and low financial status were recognized in 74(82.2%) and 52(57.8%) patients respectively (Fig. 4 and 5).

Total number of patients seen in KTH was 16(17.8%), while it was 74 (82.2%) in RICK.

Average duration since initial diagnosis was 21.1 (SD 28.2) months ranges from 1 to 168 months. The average duration of metastatic symptom was 2.9, (SD 2.2) months ranged from 1 to 12 months, highest frequency in 17 patients who had symptoms of metastases for 2 month.
Bilaterality of breast cancer was seen in 5 (5.5%) patients, left and right cases were 51 (56.7%) and 34 (37.8%) respectively (Fig. 6).

LABC was diagnosed in 31 (34.4%) patients, MBC in 41 (45.6%) (Fig. 7).

Patients metastatic cases as follows: bone 22, supraclavicular LN 3, liver 3, pleura 2, brain 2, liver and bone 2, bone and lung 2, liver and pleura 3, pleura and bone 1, brain and bone 1. There were 18 (20%) patients with both LABC and MBC, in this group metastatic cases as follows: pleura 7, bone 5, lung and supraclavicular LN 4, liver 1, liver and bone 1.

Skin fixation, fungation, and ulceration were the pattern of presentation in LABC
patients in 38(77.6%), 31(63.3%) and 28(57.1%) patients respectively (Fig. 8).

Bone was the commonest site for distant metastases; in 34(57.6%) patients with metastases bone was involved (Fig. 9).

Breast surgery had been done for 74(82.2%) patients, hormonal therapy was used in 72(80%) patients, while chemotherapy and radiotherapy for 67(74.4%) and 46(51.1%) respectively.

Using KI to assess functional aspect of QL, the average KI in 90 patients with advanced breast cancer was 6.88 (SD 1.81) initially but raised to 7.2 (SD 1.71) following introduction of palliation. No change in KI following palliation for metastases involving liver, lung and bony
metastases presenting with pathological fracture.

Improvement in KI from 5.8 to 7.1 for patients with pleural effusion (Table 1).

Average haemoglobin concentration was 9.4 (SD 1.421) g/dl, 54.4% of patients had Hb below 10 g.dl (Table 2). Only 38(42.2%) patients received blood transfusion with an average of 2.31 (SD 1.51) pints per patient, 65.8% of patients received two pints (Table 3).

CXR and abdominal ultrasound were done to all patients yielding positive results in 20% and 11% respectively. On the other hand, skeletal surveys were done only for 15 patients and bone scan for 25 patients, both tests
showed high positivity rate 88% and 93% respectively (Table 4).

Out of 49 patients with LABC only 38 patients underwent palliative surgery, toilet mastectomy in 21 patients, simple mastectomy in the rest, while 11 patients received neoadjuvant chemotherapy.

No major vascular and brachial plexus injuries, or massive lymph-oedema in those patients. The rate of postoperative infection was 13.2% (Table 5).

Among the 67 patients treated with chemotherapy, CMF regimen was used in 43(64%) patients, followed by doxorubicin containing regimen in almost 20(29.9%) patients. The commonest side effect was
gastrointestinal disturbances seen in 44 (65%) patients receiving those drugs (Tables 6 and 7).

Mood disturbances were recognized in 37 (41%) patients (Table 8). The informant was the patient himself in 31 (83.4%) of cases or his relatives in 27 (73%) of cases.

Twelve (31%) patients claimed of not being seen daily by their treating doctors (Table 9).

Nineteen (21.1%) declared that time spent with them was short (Table 10).

Sixteen (17.8%) patients thought of not being able to discuss all problems they had with their treating doctors (Table 11).
Almost half of the patients know the diagnosis and/or willing to discuss it, while 42.2% either don’t know or deny it (Table 12).

Patients who know the diagnosis were found to have had a higher rate of mood disturbances (P = 0.0007) (Table 13).

Problems in sleep, mobility and appetite were recognized in 24(26.7%), 37(41%), 34(37.8%) patients respectively (Tables 14, 15 and 16).

Social interaction was found to be normal in 69(76.7%) patients (Table 17).

Pain control in 57 patients using analgesic (NSAIDs) was only partial relief in more than half of the cases (Table 18).
Strikingly none of the 90 patients was found, at present or past, to be using morphine.

Complications regarding radiotherapy were minimal; erythema, pigmentation and subcutaneous fibrosis was seen in only 4(8.7%) patients.

Patients and family complete dissatisfaction was recognized in 4.4% and 3.4% respectively (Tables 19 and 20). Co-patients were sisters and daughters in 25.8% and 22.5% respectively, spouse was co-patients in only 12.4% and cases (Table 21).

Thirty-three patients were assessed in the region of sexuality, 6(18%) of them had problems, and 27 out of 49 patients (55%) want to have cosmetic substitute after being told.
about that (Table 22). Overall symptom control was good in 49 (59.7%) of cases (Fig. 10).

Although symptom control in patients with LABC treated by surgery was better than in those treated by neoadjuvant chemotherapy, it was statistically insignificant (P = 0.1432) (Table 23).

Massive lymph-oedema was seen in 6 (6.6%) patients, 3 of them had also local recurrences, 5 patients had previously received surgery and radiotherapy. Patients were in the range of poor quality of life (KI < 7) none of the patients showed improvement or received any form of palliation for the massive arm swelling.
Liver metastases in 10(16.9%) patients, 6 were symptomatic for it, ascites was seen in one patient. Four patients were asymptomatic.

Three patients had pleural effusion in addition to liver metastases, two of them were asymptomatic for that. Two patients had also LABC treated with toilet mastectomy.

Chemotherapy (the course contains steroid) was given to 9 patients.

In three (50%) patients with liver secondaries, good control was achieved.

Bone secondaries in 34(57.6%) patients, the commonest single site was the spine accounting for 27(47%) of all bone secondaries (Table 24). The commonest extraspinal
secondaries were located in limbs and pelvis (Table 25).

Good symptoms control using radiotherapy for painful bone metastases was seen in 19(63%) patients, only 2(6.7%) patients had persistent pain (Fig. 11)

Pathological fractures was seen 4 patients none of them was operated for internal fixation, all were bed ridden with poor KI, palliated only for pain using analgesics and radiotherapy.

Malignant pleural effusion in 13(23%) patients, it was symptomatic in 10 patients.

Palliation with pleural aspiration, and in 7 patient’s pleuraodesis was also performed using either oxytetracyline 1gram or blcomycin
30 mg intrapleural injection following aspiration.

Good symptoms control was detected in 4(40%) patients, poor symptoms control in three (30%) patients (Table 26).

Nodular lung opacities in 6(10.2%) patients with high possibility of being lung secondaries, no CT or tissue diagnosis was obtained from those patients.

All patients were asymptomatic for their lesions, except two patients having cough for a short duration, five patients were on chemotherapy.

Brain metastases in 3(5.1%) patients, mode of presentation was convulsion in 2 patients, paralysis and blindness in the third.
All patients received steroids, two received brain radiotherapy. Paraplegia and blindness in one patient showed no change. Improvement of convulsions was moderate in one patient and good in the other.

Asymptomatic metastases was seen in two third of patients with lung secondaries and one fifth of patients with pleural effusion.
Table 1: Using the Karnofsky index as indicator: The effect of palliation on the functional aspect of Q.L.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Karnofsky index before palliation</th>
<th>Karnofsky index after palliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locally advanced breast cancer</td>
<td>8.04</td>
<td>8.02</td>
</tr>
<tr>
<td>Bone metastases</td>
<td>6.23</td>
<td>6.26</td>
</tr>
<tr>
<td>Pleura metastases</td>
<td>5.80</td>
<td>7.10</td>
</tr>
<tr>
<td>Brain metastases</td>
<td>4.75</td>
<td>6.00</td>
</tr>
<tr>
<td>Lung metastases</td>
<td>7.33</td>
<td>7.33</td>
</tr>
<tr>
<td>Symptomless metastases</td>
<td>8.80</td>
<td>8.80</td>
</tr>
<tr>
<td>Liver metastases</td>
<td>5.66</td>
<td>5.66</td>
</tr>
<tr>
<td>Pathological fractures</td>
<td>5.83</td>
<td>5.83</td>
</tr>
</tbody>
</table>
Table 2: Hemoglobin concentration (g/dl) in 90 patients

<table>
<thead>
<tr>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 –</td>
<td>4</td>
</tr>
<tr>
<td>6 –</td>
<td>2</td>
</tr>
<tr>
<td>7 –</td>
<td>4</td>
</tr>
<tr>
<td>8 –</td>
<td>28</td>
</tr>
<tr>
<td>9 –</td>
<td>11</td>
</tr>
<tr>
<td>≥ 10</td>
<td>41</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>90</strong></td>
</tr>
</tbody>
</table>
Table 3: Amount of blood transfusion in pints (n=38).

<table>
<thead>
<tr>
<th>No. of pints</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6</td>
<td>15.8 %</td>
</tr>
<tr>
<td>2</td>
<td>25</td>
<td>65.8 %</td>
</tr>
<tr>
<td>≥3</td>
<td>7</td>
<td>18.4 %</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>38</strong></td>
<td><strong>100 %</strong></td>
</tr>
</tbody>
</table>

Table 4: Investigations showing evidence of metastases (n=59)
<table>
<thead>
<tr>
<th>Indicator</th>
<th>Frequency</th>
<th>Positively</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest x-ray</td>
<td>90</td>
<td>19</td>
<td>20 %</td>
</tr>
<tr>
<td>Abdominal ultrasound</td>
<td>90</td>
<td>10</td>
<td>11.1 %</td>
</tr>
<tr>
<td>Skeletal survey</td>
<td>15</td>
<td>14</td>
<td>93.3 %</td>
</tr>
<tr>
<td>Bone scan</td>
<td>25</td>
<td>22</td>
<td>88 %</td>
</tr>
<tr>
<td>CT brain</td>
<td>3</td>
<td>3</td>
<td>100 %</td>
</tr>
<tr>
<td>CT abdomen/chest</td>
<td>0</td>
<td>0</td>
<td>0 %</td>
</tr>
</tbody>
</table>

**Table 5: Complications of breast surgery in patients with locally advanced breast cancer (n= 38)**

<table>
<thead>
<tr>
<th>Complication</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Upper limb paraesthesia</td>
<td>8</td>
<td>21.1 %</td>
</tr>
<tr>
<td>Infection</td>
<td>5</td>
<td>13.2 %</td>
</tr>
<tr>
<td>Skin defect (failure of primary closure)</td>
<td>4</td>
<td>10.5 %</td>
</tr>
<tr>
<td>Heamatoma /seroma</td>
<td>3</td>
<td>7.9 %</td>
</tr>
<tr>
<td>-------------------</td>
<td>---</td>
<td>-------</td>
</tr>
</tbody>
</table>

**Table 6: Chemo-therapeutic agents (n=67)**

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CMF</strong></td>
<td>43</td>
<td>64.2 %</td>
</tr>
<tr>
<td>Doxorubicin</td>
<td>20</td>
<td>29.9 %</td>
</tr>
<tr>
<td><strong>Taxol</strong></td>
<td>4</td>
<td>6 %</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>67</td>
<td>100 %</td>
</tr>
</tbody>
</table>

**Table 7: Side effects of chemotherapy (n= 67)**

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Bone marrow depression</strong></td>
<td>11</td>
<td>16.4 %</td>
</tr>
<tr>
<td>Alopecia</td>
<td>27</td>
<td>40.3 %</td>
</tr>
<tr>
<td>GI disturbances</td>
<td>44</td>
<td>65.7 %</td>
</tr>
<tr>
<td>Others</td>
<td>7</td>
<td>10.7 %</td>
</tr>
</tbody>
</table>
Table 8: Mood disturbances (were recognized in 37 patients)

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Depression</td>
<td>32</td>
<td>86.5 %</td>
</tr>
<tr>
<td>Anxiety</td>
<td>24</td>
<td>64.9 %</td>
</tr>
<tr>
<td>Psychosis</td>
<td>2</td>
<td>5.4 %</td>
</tr>
</tbody>
</table>

Table 9: Follow up of doctors to their patients

(inpatients group =38).
<table>
<thead>
<tr>
<th>Visits per days</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily</td>
<td>26</td>
<td>68.4 %</td>
</tr>
<tr>
<td>Every other day</td>
<td>3</td>
<td>7.9 %</td>
</tr>
<tr>
<td>&gt; 2 days</td>
<td>9</td>
<td>23.7 %</td>
</tr>
<tr>
<td>Total</td>
<td>38</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Table 10: Time spent with patients (n=90)
Table 11: This table shows the answer to the question:

Do doctors discuss all problems you have?

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Yes</strong></td>
<td>74</td>
<td>82.2 %</td>
</tr>
<tr>
<td><strong>No</strong></td>
<td>16</td>
<td>17.8 %</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>90</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>
Table 12: Patients were classified according to their knowledge about the diagnosis into 3 categories (n=90).

<table>
<thead>
<tr>
<th>Know the diagnosis</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Know the diagnosis</td>
<td>45</td>
<td>50 %</td>
</tr>
<tr>
<td>Do not know or deny</td>
<td>38</td>
<td>42.2 %</td>
</tr>
<tr>
<td>Not assessed</td>
<td>7</td>
<td>7.8 %</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100.0 %</td>
</tr>
</tbody>
</table>

Table 13: Patients knowledge about the diagnosis and mood disturbances, the relationship.

<table>
<thead>
<tr>
<th></th>
<th>Abnormal mood</th>
<th>Normal mood</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient know</td>
<td>26</td>
<td>19</td>
<td>45 (54.2 %)</td>
</tr>
<tr>
<td>Patients don’t know</td>
<td>8</td>
<td>30</td>
<td>38 (45.8 %)</td>
</tr>
<tr>
<td>Total</td>
<td>34 (41 %)</td>
<td>49 (59 %)</td>
<td>83 (100 %)</td>
</tr>
</tbody>
</table>

*P. 0.0007*
Table 14: Sleep following palliative care (n=90).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate</td>
<td>66 73.3 %</td>
</tr>
<tr>
<td>Inadequate</td>
<td>24  26.7 %</td>
</tr>
<tr>
<td>Total</td>
<td>90  100.0 %</td>
</tr>
</tbody>
</table>

Table 15: Mobility following palliative care (n=90)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mobile</td>
<td>53  58.9 %</td>
</tr>
<tr>
<td>Limited</td>
<td>23  25.6 %</td>
</tr>
<tr>
<td>Bedridden</td>
<td>14  15.6 %</td>
</tr>
<tr>
<td>Total</td>
<td>90  100 %</td>
</tr>
</tbody>
</table>
Table 16: Appetite (n=90)

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>56</td>
<td>62.2 %</td>
</tr>
<tr>
<td>Abnormal</td>
<td>34</td>
<td>37.8 %</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Table 17: Social interaction (n=90)

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>69</td>
<td>76.7 %</td>
</tr>
<tr>
<td>Abnormal</td>
<td>19</td>
<td>21.1 %</td>
</tr>
<tr>
<td>Not assessed</td>
<td>2</td>
<td>2.2 %</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>100 %</td>
</tr>
</tbody>
</table>

Table 18: Pain relief in 57 patients: Effects of non steroidal analgesics
<table>
<thead>
<tr>
<th>Complete</th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>15</td>
<td>26.3%</td>
</tr>
<tr>
<td>Partial</td>
<td>33</td>
<td>57.9%</td>
</tr>
<tr>
<td>Non</td>
<td>9</td>
<td>15.8%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>57</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

Table 19: Patient satisfaction (n=90).

<table>
<thead>
<tr>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Full</strong></td>
<td>67.7%</td>
</tr>
<tr>
<td>Partial</td>
<td>25.6%</td>
</tr>
<tr>
<td>Non</td>
<td>4.4%</td>
</tr>
<tr>
<td>Not assessed</td>
<td>2.2%</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>
### Table 20: Family satisfaction (88 co-patients).

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full</td>
<td>72</td>
<td>80 %</td>
</tr>
<tr>
<td>Partial</td>
<td>13</td>
<td>14.4 %</td>
</tr>
<tr>
<td>Non</td>
<td>3</td>
<td>3.4 %</td>
</tr>
<tr>
<td>Not assessed</td>
<td>2</td>
<td>2.2 %</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>90</strong></td>
<td><strong>100 %</strong></td>
</tr>
</tbody>
</table>

### Table 21: The relationship degree between patients and co-patients

<table>
<thead>
<tr>
<th></th>
<th>Frequent</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Spouse</strong></td>
<td>11</td>
<td>12.4 %</td>
</tr>
<tr>
<td>Parent</td>
<td>5</td>
<td>5.6 %</td>
</tr>
<tr>
<td>Son</td>
<td>15</td>
<td>16.9 %</td>
</tr>
<tr>
<td><strong>Daughter</strong></td>
<td>20</td>
<td>22.5 %</td>
</tr>
<tr>
<td>Brother</td>
<td>8</td>
<td>9 %</td>
</tr>
<tr>
<td>Sister</td>
<td>23</td>
<td>25.8 %</td>
</tr>
</tbody>
</table>
Table 22: Psychological aspect in patients treated by breast surgery (n=74)

<table>
<thead>
<tr>
<th>Item</th>
<th>Frequency</th>
<th>Total No. of patients assessed</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fully accepted surgery</td>
<td>59</td>
<td>74</td>
<td>79.7 %</td>
</tr>
<tr>
<td>Body image disturbance</td>
<td>21</td>
<td>43</td>
<td>48.8 %</td>
</tr>
<tr>
<td>Psycho – sexual problem</td>
<td>6</td>
<td>33</td>
<td>18.2 %</td>
</tr>
<tr>
<td>Asks for cosmetic substitute</td>
<td>27</td>
<td>49</td>
<td>55.1 %</td>
</tr>
</tbody>
</table>

Table 23: Symptom control in patients with locally advanced breast cancer, using two modes of therapy (n=49).

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>Systemic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Good</td>
<td>29 (76.3 %)</td>
<td>5 (45.4 %)</td>
</tr>
<tr>
<td>Moderate</td>
<td>5 (13.2 %)</td>
<td>3 (27.3 %)</td>
</tr>
<tr>
<td>Poor</td>
<td>4 (10.5 %)</td>
<td>3 (27.3 %)</td>
</tr>
<tr>
<td>Total</td>
<td>38 (100 %)</td>
<td>11 (100 %)</td>
</tr>
</tbody>
</table>

*P. 0.1432*
Table 24: Pattern of bone secondaries (n= 34)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spinal</td>
<td>16</td>
</tr>
<tr>
<td>Extraspinal</td>
<td>7</td>
</tr>
<tr>
<td>Spinal + extraspinal</td>
<td>11</td>
</tr>
<tr>
<td>Total</td>
<td>34</td>
</tr>
</tbody>
</table>

Table 25: Pattern of extaspinal secondaries: different sites (n=18)

<table>
<thead>
<tr>
<th>Frequency</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limbs</td>
<td>7</td>
</tr>
<tr>
<td>Pelvis</td>
<td>4</td>
</tr>
<tr>
<td>Sternum / ribs</td>
<td>1</td>
</tr>
<tr>
<td>Frequency</td>
<td></td>
</tr>
<tr>
<td>-----------------</td>
<td>---</td>
</tr>
<tr>
<td>Good</td>
<td>4</td>
</tr>
<tr>
<td>Moderate</td>
<td>3</td>
</tr>
<tr>
<td>Poor</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>10</td>
</tr>
</tbody>
</table>

Table 26: Symptom control in patients with dyspnea due to pleural effusion (n=10).

Table 27: Sites of
distant metastases showing no symptoms

<table>
<thead>
<tr>
<th></th>
<th>Frequency</th>
<th>A symptomatic</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pleura</td>
<td>13</td>
<td>3</td>
<td>23.1 %</td>
</tr>
<tr>
<td>Liver</td>
<td>10</td>
<td>4</td>
<td>40 %</td>
</tr>
<tr>
<td>Lung</td>
<td>6</td>
<td>4</td>
<td>66.7 %</td>
</tr>
<tr>
<td>Supraclavicular</td>
<td>7</td>
<td>7</td>
<td>100 %</td>
</tr>
<tr>
<td>Bone</td>
<td>34</td>
<td>3</td>
<td>8.8 %</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>70</strong></td>
<td><strong>21</strong></td>
<td><strong>30 %</strong></td>
</tr>
</tbody>
</table>
DISCUSSION

The average age of the 90 patients with advanced cancer of the breast contributed into this study was 47.3 years, similar to other series where all stages of cancer were included. Elnaeem (1987) reported an average of 47.9 in a series of 546 patients, Hidayatalla (1974) and Saad (1984) reported an average age of 48.8 and 48.2 years respectively.\(^2\)

There were two peaks of age showing higher frequencies of breast cancer, from 31 to 40 and from 41 to 50, particularly the former. This might indicate a tendency of aggressive or rapidly progressive form of the disease in younger Sudanese females. It’s interesting to mention here two important points that might also explain the above finding, the first is absence of birth certificates for many patients, and the second is
the tendency for some women to give a younger age. These two points add to uncertainty concerning the actual age of patients, i.e. it was doubtful whether all patients classified in these categories gave their real age.

Regarding the age and breast cancer the investigators in Danish Epidemiology Science Centre,\(^{(46)}\) evaluated data on 10,356 premenopausal women younger than 50 who had breast cancer diagnosed between Jan. 1978 and July 1996. Compared with older patients, patients aged younger than 35 at diagnosis were at high risk of being node positive (P=0.02), and grade I was significantly lower (P<0.001). Multivariate and grade I was significantly lower (P<0.001). Multivariate analysis showed that, women younger than 35 years had the worst prognosis.

Therefore, the formentioned hypothesis needs critical evaluation and further studies.

Male cancer (3.3%) was higher than reported in western series (1%). Male presentation reported by Elnaeem was 4.4%, Hidayatalla and Saad reported 6.25% and 2.5% respectively. Therefore, this result strengthens the findings that the prevalence of cancer of the breast in Sudanese males is higher than the prevalence reported in literature.

Rural residence might be a contributing factor to late presentation, as two thirds of patients were rural inhabitants, where lack
of knowledge, awareness and health education, delay in seeking medical advice, or failure to continue adjuvant therapy in RICK are predominant.

Illiteracy (82.2%) might be a significant factor contributing to presentation with advanced disease.

The ability to pay for treatment expenses was taken as an independent factor to measure the financial status, in some cases it mightn’t reflect the actual financial status of the patient; since treatment expenses may be paid by a relative or a neighbour.

Management of breast cancer is a costly procedure starting from investigations, histological examination, expenses for surgical treatment, drugs, and adjuvant therapy. The current treatment expenses is reduced to half at RICK (15,000 SD for radiotherapy, 7000 SD for one CMF cycle, 35,500 SD for one dose of taxol-the patients usually needs 6 cycles).

In addition to this patient’s transportation and occasionally delayed management can add to the cost unnecessarily.

The majority (52 patients) sought help to pay for treatment expenses from support organization inside or outside hospital, and probably there might be some patients who stopped their treatment plan following surgery for financial reasons. Breast cancer is an economic problem causing much suffering to patients who came from poorer families.
Many reports found an increased incidence of the left breast cancer than the right, Elnaeem\(^{(2)}\) reported a ratio of 52: 47, it is puzzling in the study to find a higher ratio of 56: 37, also there was a higher rate of disease bilaterality (5.5%).

The collective review by Wanebo and associates, revealed an overall incidence of bilaterality in 3.7% among 22, 563 cases. With 29% being synchronous and 71% metachronous.\(^{(47)}\) We think it was expected to have a higher rate of bilateral disease in our patients because they have late disease.

It is recognizable the relatively short duration before presentation with metastases (2.9 months). Breast cancer is a painless condition in majority of cases of early disease but becomes painful with progressive and advanced disease.

Pretreatment evaluation in patients with advanced breast cancer was inadequate, there was a high yield of positivity of bone scanning and skeletal survey, this means these investigations are utilized only in symptomatic patients with high clinical suspicion. Their use before starting management is recommended,\(^{(48)}\) since patients with stage III cancer are at a higher risk of metastases (in many series more than 20%).

In surgery for LABC, a high rate of infection (13.2%) may be explained by the presence of ulcer or necrosis. The aim of surgery was
locoregional control of the disease, toilet and occasionally simple mastectomy was performed for operable LABC. Surgery showed better symptom control than neoadjuvant chemotherapy, possibly due to its early effect, but this difference between the two modes of treatment was statistically insignificant.

Though in many breast cancer patients in many breast cancer centers the use of neoadjuvant chemotherapy is becoming the first choice for LABC, most of our patients were treated surgically as first line of management. Treatment strategies are evolving in this area, therefore, further studies are needed.

Although all patients on chemotherapy have received antiemetic drugs, gastrointestinal disturbances was the commonest side effect of this treatment. Further studies are needed to identify whether the doses prescribed are inadequate or patients didn’t take them.

Alopecia and bone marrow suppression were also recognized in a considerable proportion of patients.

Unlike chemotherapy the complications of radiotherapy were much less, five out of the six patients who had massive lymphoedema had received radiotherapy following surgery, this might strongly suggest that such combined treatment is the cause.
Bone was found to be the commonest site for metastases of breast cancer, in 57.6% of patients with metastatic disease. This finding is comparable to results of a large retrospective study\(^{49}\) of 718 patients with metastatic disease, skeletal secondaries were reported in 51% of cases. Our results are also consistent with Albashir\(^{50}\) in both studies spine, limbs and pelvis are frequently involves in this order. Albashir found spine was involved in 43% whereas in this study it was 47%.

Radiotherapy for bone secondaries was an effective palliative tool, and had achieved good symptom control in 63% and moderate control in 30%, while Albashir reported an overall response of 56%, however, many series in literature concluded: radiotherapy should be considered as palliation modality of choice.

Unfortunately none of the four patients of pathological fracture treated with internal fixation, also none of the patients received prophylactic fixation. It is essential to mention that such surgery has an invaluable effect on QL to those patients and it is recommended for every patient with life expectancy more than two months. Probably lack of facilities and excessive workload in Orthopaedic Department could explain such malmanagement.

Assessment of symptom control for patients with pleural effusion, done two- to three weeks following aspiration, it was found that
good to moderate control of dyspnea and cough in two thirds of patients. Pleurodesis had been done in more than half of the patients, assessing its effect is bay and the scope of this study, since it needs longer follow-up. In one retrospective study\(^{(51)}\) in 25 patients with pleural effusion secondary to breast cancer treated with aspiration followed by pleurodesis, the response was assessed at 30 days by CXR and clinical examination, 18 patients out of the 25(72%) gained complete or partial response. In another study\(^{(52)}\) pleurodesis offered good control with recurrence in only two patients out of 29.

Half of patients with symptomatic liver secondaries showed relief of pain followed systemic chemotherapy, the effect is probably related to the steroid added to the regimens. Some series\(^{(53,54)}\) for metastatic liver disease of breast cancer, showed a better response to intraarterial infusion chemotherapy over systemic chemotherapy and improved median survival from 5 to 27 months, such facilities are not available in RICK.

**Page 63**

Overall results proves beyond doubt that palliation was valuable and changes QL to a better one but it was inadequate to reach a good QL.

Mood disturbances were fairly common in this group of patients, 37(41%), majority of patients had both depressed and anxious mood, it is
essential to mention, according to these results the contribution of psychological workers is needed in those patients.

According to patients, 12(30%) of the 8 inpatients claimed that they were not seen by their treating doctors daily. If this is true, it may be explained partially by negative attitude from the doctor towards his incurable or terminally ill patients, a doctor who feels helpless to alleviate the many problems those patients had or who his confronted with intolerably, psychologically unstable patient might choose to avoid seeing them daily.

Those patients need to be seen daily, and adequate time to discuss all problems they have is equally important. Almost a fifth of patients weren’t properly served regarding time and full discussion.

Knowledge of diagnosis was found to be associated with mood disturbances i.e., patients who knows the diagnosis are the group with highly rate of mood disturbances. (Test of significance was highly positive). But there are many confounding factors shading this relationship, such as the age of patient, educational level, social and cultural factors, religious altitude, pre morbid personality, and what the patient knows about malignancy itself. These factors need to be critically analyzed before reaching any conclusion. Studies in this area might help us to adopt the most convenient approach regarding patient’s knowledge
of diagnosis of cancer, and whether frank discussion of the diagnosis is valuable or not.

Sleep and appetite problems were so common following palliation, further longitudinal studies (assessing at different intervals) are needed to clarify palliation itself has contributed to these problems.

Complete bed ridden patients (15%) always had bad KI, patients with treatable causes, like pathological fracture, none of them had internal fixation, which was regarded as major surgery for high risk patient who is not going to live long.

Aggression, withdrawal, antisocial behavior and other abnormal social interactions were found in almost one fifth of all cases, it was larger than expected. The help of social and psychological workers shouldn’t be under-evaluated.

It is widely spread using NSAIDs for pain management, no patient regardless to severity or nature of pain found to use morphine. Pain was under-treated in our patients, which a similar to many other series.

Co- patients were sister and daughter in more than 40%, with poor contribution of spouse 11%. Husband should share with his wife in planning for management and follow-up.
Smaller number of patients was assessed regarding body image disturbance and sexuality, large proportion of patient have problems.

Only 55% of those who were given full idea about mammoplasty want to have the procedure, plastic procedures are not contraindicated in incurable breast cancer patients.

Dissatisfaction [towards doctors and treatment] among patients and families was less than 5%, probably this wasn’t due to a perfect management, rather than to a response shift phenomena in our patients this phenomenon is defined as a change in the meaning of self evolution of QL as a result of changes in their internal standards, value, or conceptualization of QL. In other words, patients may have lowered their internal standard, altered their values and changed their ideas about what constitutes a good QL to accommodate deteriorating function.

CONCLUSION
Quality of life in Sudanese patients with advanced breast cancer emerged from the poor zone following palliation. But still not achieving progress to the good zone.

Practically surgery is still the commonest mode of therapy used in patients with LABC. Although it had better symptom control than neoadjuvant chemotherapy in the early period (1 month), the difference was statistically insignificant between the two.

Pain is under treated in the majority of patients.

Two fifths of patients had mood disturbances, one fifth had social problems, quarter of patients had sleep problems, a third had poor appetite, two fifths had mobility problems, and in a fifth of patients doctor-patient relationship needs to be corrected.

Radiotherapy for painful bone metastases and aspiration for malignant pleural effusion were effectively palliative procedures with good symptom control.

Patients with massive lymphoedema and pathological fractures were poorly palliated.

Although most of our patients showed satisfaction with a treatment and doctor, this can merely be a reflection of poor expectation they had.
REFERENCES


9- American Joint Commission on Cancer staging Manual, 5\textsuperscript{th} ed. Philadelphia: LippinCott Raven; 1997. P.


