

Chapter one

Introduction

1.1 Introduction

Breast cancer is the most frequently diagnosed cancer (23% of total cancer cases) and the leading cause of death (14% of deaths), in females, worldwide (Jemal A, Bray2011). According to the Globocan 2008 estimates, approximately 1.37 million women are diagnosed with breast cancer per year. In economically developing countries, it's the leading cause of cancer related deaths amongst women. In fact, in many of the developing countries especially in Africa, the institutions are significantly limited with regard to oncology care and resources (Abdel-Wahab M et2013)

Majority of the black patients presented with stage 3 and 4 disease. In higher income countries, such as the USA, the breast cancer mortality incidence has been decreasing by approximately 2% per year since 1990 with only about 15% of patients presenting with advanced stage disease(Murray EM.2003). This may be attributed to the earlier detection of breast cancer by the implementation of awareness and screening programs, easier access to diagnostic testing and timeouts implementation of effective treatment. In contrast, in low to middle income countries, approximately 60-80% of the patients present at more advanced stages. Adequate cancer registries in the developing countries, we are unable to accurately state what percentage of patients present with more advanced disease. The advanced presentation, as well as poorer access to care and limited treatment options, results in higher breast cancer.

Worldwide, the treatment of locally advanced breast cancer and metastatic breast cancer is an oncologic challenge. In developing countries, this is confounded by the situations mentioned previously. Protocols for the treatment of advanced breast cancer differ amongst institutions, based on the resources available to that country.(Anderson BO et 2010).

In the Radiation Isotopes Center of Khartoum , there is limited access to many of the chemotherapy agents and no access to the targeted agents used in advanced breast cancer. The rest of Sudan as well as other developing countries mirror this. In fact, other developing countries especially in Africa, are significantly limited with regard to oncology care and resource (Abdel-Wahab M, Bourque 2013). However, in countries, especially developing countries, where the screening programs are not as well established and access to medical care is not as efficient, many patients present with more advanced disease.

The issue that we face at our facility, and in many developing countries, is that we have limited access to modern chemotherapy regimens and no access to the required biological agents in the state sector. Therefore, if patients do not respond to the chemotherapy and/or the hormonal treatment, palliative radiotherapy remains the only option to treat complications of locally advanced disease (such as ulceration or bleeding).

Radiotherapy for symptom control is an important treatment option for breast cancer patients. Pain, neurological symptoms, symptoms of obstruction and compression, bleeding, or exulceration in advanced breast cancer can be effectively controlled. Dose fractionation and the type of radiotherapy must be tailored to each patient individually,

taking into account the patient's perspective, goals of treatment, and prognosis. In the case of limited life expectancy, irradiation should be performed with higher doses per fraction and a short overall treatment time. Selection of the individual palliative treatment concept including radiotherapy should be performed in a multidisciplinary and multi professional team.

Palliative radiotherapy is indicated to treat metastases that produce local symptoms or are expected to do so during the lifespan of the patient. Symptom relief is not only achieved by reduction of tumor size. Radiotherapy also has an anti-inflammatory, anti-secretory, anti-edematous, and analgesic effect, even at low doses. Local radiotherapy is efficient, safe, has few side effects, and is cost-effective. Metastatic breast cancer is a heterogeneous disease; the clinical course depends on several factors such as pattern of metastasis, tumor burden, interval between primary diagnosis and occurrence of metastasis as well as on biological tumor parameter

1.2 Definition of metastatic breast cancer (MBC):

According to the American Joint Committee on Cancer (AJCC) staging system, it includes Metastatic breast cancer is also classified as Stage4 breast cancer. The cancer has spread to other parts of the body. This usually includes the lungs, liver, bones or brain.(Cardoso F, Costa2014)

The spread of cancer usually happens through one or more of the following steps:

- Cancer cells invade nearby healthy cells. When the healthy cell is taken over, it too can replicate more abnormal cells.
- Cancer cells penetrate into the circulatory or lymph system. Cancer cells travel through the walls of nearby lymph vessels or blood vessels.

- Migration through circulation. Cancer cells are carried by the lymph system and the bloodstream to other parts of the body.
- Cancer cells lodge in capillaries. Cancer cells stop moving as they are lodged in capillaries at a distant location and divide and migrate into the surrounding tissue.
- New small tumors grow. Cancer cells form small tumors at the new location (called micro metastases.)

Stage	TNM Classifications
Stage 0:	in situ breast cancer - Tis, N0, M0
Stage I:	T1, N0, M0
Stage IIa:	T0-1, N1, M0, or T2, N0, M0
Stage IIb:	T2, N1, M0, or T3, N0, M0
Stage IIIa:	T0-2, N2, M0, or T3, N1-2, M0
Stage IIIb:	T4, N (any), M0, or T(any), N3, M0
Stage IV:	T(any), N(any), M1

Table 1-1 Breast Cancer Stage

1.3 Treatment guideline of metastatic breast cancer :

Metastatic breast cancer (MBC) is incurable, but still treatable, especially if there are limited metastases. The intent of treatment is palliative, providing symptomatic relief

and optimization of the length and quality of life. Median survival is approximately 18 to 24 months in these patients, though in some circumstances, for example with bone metastasis, the life expectancy may be longer. If the patient has a good performance status and has locally advanced disease as well, local palliation could optimize their quality and length of life.(Cardoso F, Harbeck2012)

1.4 Palliative care:

Palliative care is defined by the WHO (World Health Organization)as the active total care of patients whose disease is not responsive to curative treatment .The goals of the treatment in the palliative care phase are mainly to control the symptoms, to enhance the quality of life, and to optimize the patient's limited remaining time. For palliative treatment of cancer patients, anti-cancer treatments such as radiotherapy, chemotherapy, molecular targeted therapy and hormonal therapy can help in achieving these goals.

1.4.1 Palliative Radiotherapy Overview

About 34–50% of patients receiving radiotherapy are of palliative intent (Janjan N,2008). Similar to other clinical domains, the practice of palliative radiotherapy is always guided by basic ethical principles and available clinical evidence. It requires sophisticated assessment to balance the potential benefits and burdens to the patients with respect to patient's autonomy and expectations, and consideration of logistical factors Palliative radiotherapy is mainly indicated to relieve various local symptoms in cancer patients; to prevent debilitation such as spinal cord compression and

pathological fracture; and to achieve durable loco regional control (Wong K2004) (table 1). The effectiveness has been confirmed by cumulative clinical evidence. For metastatic bone pain, palliative radiotherapy can achieve an overall pain response rate of 59–62%, and a complete pain response rate of 32–34%.

For multiple brain metastases, the overall response rate to external irradiation is around 60% with 30–40% achieving marked neurological improvement.

<p>Pain relief: Metastatic bone pain Painful lymphadenopathy Pain due to soft tissue infiltration by cancers Neuropathic pain due to nerve compression and infiltration</p> <p>Rescue of neurological deficit Spinal cord compression Brain metastases</p> <p>Relief of pressure symptoms Thoracic tumours: SVCO Upper airway obstruction Dysphagia Collapse of lung Reduced the increased intracranial pressure secondary to brain metastases Retroperitoneal tumours Relief of hydronephrosis Pelvic tumours Relief of hydronephrosis Urinary retention Intestinal obstruction</p> <p>Control of fungation and ulceration of metastatic or primary skin cancers</p> <p>Haemostasis: Haemoptysis Bleeding rectal or gynaecological cancers Bleeding skin cancers</p> <p>Prophylaxis of impending symptoms Prevention of spinal cord compression Prevention of pathological fracture Prevention of pending pressure symptoms</p> <p>Durable control of advanced locoregional disease beyond cure.</p>
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Table 1-2 Indication of palliative radiotherapy

1.4.2 Principle of Palliative Radiotherapy:

The intention of giving radiotherapy for palliation of symptoms is improvement in quality of life by decreasing or eradicating symptoms. This will not be achieved if the treatment itself induces a lot of side effects. Also, patients with metastatic cancer have a reduced life span, this may only be months, and therefore the treatment itself should not consume a major portion of the patients remaining lifespan. The major benefit of radiotherapy is the speed with which symptom improvement develops and the certainty of response. Sufficient radiation dose must be given to ensure that the symptom response will last for the rest of the patient's life. Too low a dose means retreatment at some later time is needed. Hence guiding principles are:

1. Accurate anatomical localization of the symptomatic tumor deposit.
2. Simple treatment techniques and field arrangements
3. Short hypo fractionated treatment regimes.
4. Moderate dose treatment to achieve a good predictable response and to keep treatment toxicity to a minimum.
5. Consider the patient's overall life expectancy when determining the treatment aims and the treatment duration.

1.4.3 Role of Palliative Radiotherapy (PRT) :

The main indications are: pain relief (particularly bone pain), control of hemorrhage, fumigation and ulceration, dyspnea, blockage of hollow viscera, and the shrinkage of

any tumors causing problems by virtue of space occupancy. In addition, it has an important role in the palliation of three oncological emergencies: superior vena cava obstruction, spinal cord compression, and raised intracranial pressure due to cerebral metastases. More pragmatic fractionation schedules are being developed that are compatible with good results in terms of palliative end points, giving shorter courses with fewer hospital attendances for patient and family comfort and convenience. More clinical research and evaluation of palliative radiotherapy are required..

1.4.4 Regime of Palliative Radiotherapy (PRT):

There are various palliative breast radiotherapy regimes prescribed for local control of disease.

In RICK we use a variety of regimes: a single fraction of 8Gray (Gy), fractioned treatment of 20Gy at 4Gy per fraction for 5 fractions or 10 fractions in two weeks

The treatment plan depends on the resources available at the facility, patient ECOG performance status and disease factors.

1.4.5 Symptoms Improvement ratio (SIR):

Using the information gathered from the literature, we discussed various approaches for describing the clinical benefits of palliative radiotherapy. Our goal was a method that would be both simple to understand and of practical value to referring physicians and their patients. It also had to be consistent with the goals of palliative care. To describe the symptomatic improvement or clinically significant responses achieved with palliative radiotherapy, we suggest the symptom improvement ratio (SIR) concept.

1.5 The Problem of the study

Radiotherapy for symptom control is an important treatment option for breast cancer patients. Pain, neurological symptoms, symptoms of obstruction and compression, bleeding, or exulceration in advanced breast cancer can be effectively controlled. Dose fractionation and the type of radiotherapy must be tailored to each patient individually, taking into account the patient's perspective, goals of treatment, and prognosis. In the case of limited life expectancy, irradiation should be performed with higher doses per fraction and a short overall treatment time. Selection of the individual palliative treatment concept including radiotherapy should be performed in a multidisciplinary and multi professional team. In RICK we didn't have palliative radiotherapy protocol (PRP) .lack of knowledge about potential benefits of palliative radiotherapy in RICK .symptoms improvement not fallow.

1.6 Objectives:

1.6.1 Main objectives

Study of radiation therapy treatment effect of palliative metastatic breast cancer using concept symptoms improvement ratio

1.6.2 Specific objectives:

- 1- guidelines use of radiotherapy for symptom control in metastatic breast cancer
- 2- Main objective is a method that would be both simple to understand clinical benefits of palliative radiotherapy and of practical value to referring radiotherapist and their patients. It also had to be consistent with the goals of palliative care.

- 3- To define the accuracy of dose and volume calculations that are essential for palliative radiotherapy treatment
- 4- To describe the symptomatic improvement or clinically significant responses achieved with palliative radiotherapy

1.6 Significance of the study:

This is will be improve the palliative radiotherapy program. And reduce the fractionation of patient by use unique flexible palliative radiotherapy regimes. Also the study will show the patients response of radiotherapy treatment. Which will help to choose suitable regime and suitable radiotherapy machine.

1.7 Overview of the study:

The thesis included in chapters One – Five meet various aspects of this objectives:

Chapter One introduction of local and metastatic advance, the treatment guide line of MBC breast, palliative care in MBC, describes the palliative radiotherapy program for metastatic breast cancer that has been designed to treat the patient with breast palliative radiotherapy describes the different types of palliative radiotherapy and the possible side effects.

Chapter Two is concerned with the MBC, diagnosis and treatment of MBC also in historic perspective, in palliative radiotherapy: the Role of Radiotherapy in Palliative Care, the Basic Principle with (Radiation Physics, Radiobiology, and Fractionation of Radiation Dose.....)The Role of Palliative Radiotherapy in Practice. In this chapter the concept of palliative radiotherapy is also introduced and shown a principle and tool of it.

Chapter Three focuses at one of the major challenges in thesis: the assessment of patient pre and post radiotherapy session using different method of questionnaire and scale to different symptoms, calculation of dose in both in linear and Cobelt-60 machine for palliative cases .in clued the (Radiation Treatment Process, Radiation Therapy Equipment, Radiation Beam Characteristics, Machine Characteristics) also we describe the different radiotherapy regimes in MBC.

Chapter Four the result of palliative radiotherapy programmer include primary and secondary end point in (pain response, quality of life, toxicity ...) For all cases also the dose distribution in both linear and cobalt -60

Chapter Five: Discusses the data (discussion), Analysis recommendation, Conclusions and References.