Chapter Two

Literature Review

2.1 Metastatic Breast Cancer overview

Metastatic breast cancer is not a curable disease. Usually occurs several years after the early breast cancer. Breast cancer is the most common cancer among Sudanese women. According to the new statistics in Sudan 1400 breast cancers are diagnosed in the country each year and 1063 cases lead to death. Due to the higher risk of age group 35–65 years The decision on the therapy of invasive breast cancer depends on several factors such as cancer stage, tumor size and type, pathological and cytological status of the tumor, the patient's opinion, the presence or absence of estrogen and progesterone receptors in the cytoplasm of tumor cells and so on.

Breast cancer primarily metastasis bones, lungs, regional lymph nodes, the liver and brain(M. Hosseini et 2012). Approximately, 70% of patients with advanced breast cancer have bone metastasis. Bone is the most commonly observed site for distant metastases and is the location of 30%–40% of first tumor recurrence (M. Bendre, D2003). The women whose first recurrence occurs in skeleton have a better prognosis than those with visceral metastasis to the liver, lungs or brain. Most bone metastases can be successfully controlled for a long time(D.J. Slamon2001- L.J. Suva, R.J. 2009), . Brain metastasis has been observed in 10% of breast cancer patients with metastatic properties (M.E. Shaffrey, M 2004 -R.E. Coleman2009)

2.2 Epidemiology of Metastatic breast cancer.

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 mortality Due to lack of incidences. However, research at Radiation isotopes center of Khartoum, revealed that there may be other factors at play in developing countries, which may affect cancer survival. Factors such as patients' distrust of "western medicine" and the use of traditional medicine first, lack of understanding of the disease and allowing older, often conservative, family members to make treatment decisions are commonplace. There are also the financial implications, as patients cannot afford to lose working hours to come for investigations, chemotherapy and daily for radiotherapy.

Worldwide, the treatment of 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. In Sudan, despite the fact that we have the advantage of expert multidisciplinary teams, there is limited access to many of the chemotherapy agents and no access to the targeted agents used in advanced breast cancer. In fact, other developing countries especially in Africa, are significantly limited with regard to oncology care and resources.

2.3 Diagnosis of MBC

Metastatic Breast Cancer (MBC) is often found by a symptom—perhaps a recurring pain or cough, shortness of breath, lack of appetite, headaches or an injury. It is also possible to learn of metastases through routine scans.

1. Biopsy
2. Bone Scans
3. Chest X-Ray
4. CT/CAT Scan (Computerized Tomography or Computerized Axial Tomography)
5. Liver Scan
6. MRI (Magnetic Resonance Imaging)
7. PET Scan (Positron-Emission Tomography)
8. PET CT Scan

2.4 Treatment of MBC:

Metastatic breast cancer, also known as stage IV or advanced breast cancer is breast cancer that has spread to other organs in the body. Metastases from breast cancer may be found in lymph nodes in the armpit, or they can travel anywhere in the body. Common sites include distant organs like the lung, liver, bone and brain. Even after an original tumor is removed, microscopic tumor cells may remain in the body, which allows the cancer to return and spread.

Patients may initially be diagnosed with metastatic disease, or they may develop metastases months or years after their initial treatment. The risk of breast cancer

returning and metastasizing varies from person to person and depends greatly on the biology of the tumor and the stage at the time of the original diagnosis.

Treatment options for metastatic breast cancer

Treatment for metastatic breast cancer includes many of the same treatments as other stages of breast cancer:

1. Chemotherapy
2. Hormone therapy
3. Radiation therapy
4. Targeted therapy
5. Surgery

2.4.1 Surgery

Surgery to remove metastatic breast cancer isn't common, but a small study suggests that some women can benefit from surgery to remove breast cancer that has metastasized to the liver if the cancer has certain characteristics:

1. hormone-receptor-positive
2. responded to chemotherapy before surgery
3. didn't grow in the time between metastatic diagnosis and surgery

Breast surgery was believed to be palliative and performed only to relieve symptoms such as local bleeding, infection, or pain.

Palliative Surgery

• Laminectomy for spinal cord compression

• Orthopedic operations to prevent fractures

2.4.2 Chemotherapy

The systemic treatment of MBC includes endocrine therapy, chemotherapy and targeted biological agents. The choice of treatment depends on disease related factors such as hormone status, HER2 status, tumor burden and need for rapid disease control; as well as patient related factors such as biological age, menopausal status, co-morbidities, performance status, socio-economic and psychological factors, patient preference and therapies available.(Cardoso F, Murray EM et2003)

If patients are ER/PR positive, without extensive or symptomatic visceral involvement, endocrine therapy is the first choice of treatment. Types of endocrine therapies available are: selective oestrogen receptor modulators (Tamoxifen), oestrogen receptor down regulators (Fulvestrant), luteinising hormone-releasing hormone analogues (Goserelin), third generation aromatase inhibitors (Anastrozole, Letrozole, Exemestane), Progestins and anabolic steroids. Patients on long-term endocrine therapy may develop resistance (Dodwell D,et2006, Musgrove EA et 2009)Clinical studies have shown that mammalian target of rapamycin (mTOR) inhibitors enhances the efficacy of endocrine therapy.If patients are HER2 positive, the addition of Trastuzumab to endocrine treatment has shown to improve progression free survival

 (Kaufman B,et 2009)

Lapatinib is a second anti Her2 agent. Trials have looked at using Lapatinib in combination with Capecitabine in patients who progressed on Herceptin, Anthracyclines and Taxanes. It showed a progression free survival of 8.4 months versus 4.4 nths in the placebo arm.

Studies have also considered combining Lapatinib with Trastuzumab, if the patient progresses on Trastuzumab alone. If patients are ER positive with symptomatic or extensive visceral metastasis, ER negative or have progressed on hormonal treatment, chemotherapy is the treatment of choice.agents that may be used include Anthracyclines, Taxanes, Vinca Alkaloids, Capecitabine,Chemotherapy Fluorouracil, Methotrexate, Platinum agents, Mitomycin C and Gemcitabine. If the patient is HER2 positive, the chemotherapy may be used with the targeted agents as mentioned previously. Other targeted agents available are Pertuzumab, Palbociclib and Ado-Trastuzumab Emantasine (T-DM1).(Cardoso F, Harbeck N)

2.4.3 Radiotherapy:

Radiotherapy is the use of ionizing radiation in the treatment of disease. Ionizing radiation is so called because, when it interacts with matter, ions are created. The major types of radiation used for treatment are X-rays or gamma rays. Electromagnetic radiation with photons of energy greater than 10 electron volts can eject orbital electrons from the target atoms creating ions. The excess photon energy is transferred to kinetic energy of the ejected electron, which further interacts with other atoms losing energy. Ultimately all the photon energy is deposited in the target material and many ions are created. The energy of the X-ray or γ-ray photon determines the physical and biological characteristics of its interaction with the target material (in medicine the target material is the cell and tissues).

Photons of ionizing radiation interact with matter and lose their energy in 3 ways:

1. Photo electric effect

2. Compton scattering

3. Pair production

One or other of these processes predominate at different photon energies. The net effect of all ionizing photon interactions is deposition of energy in the target tissue and the production of energetic electrons and ions. When this occurs in human tissue cells die.

Dividing the radiation dose into more, smaller fractions of treatment will reduce the severity of acute effects but will not alter the late effects. The total dose given is more important for determining late effects although fraction size is also important. When using radiotherapy for palliative treatment, the late effects are usually not a great concern as the patient's survival is short and they do not live long enough to manifest these effects. However, late effects do need to be considered if retreatment of an area previously irradiated is contemplated or when treating a patient who has a metastatic cancer that is compatible with a long survival e.g. myeloma, thyroid cancer, and some breast and prostate cancer. The radiation dose which produces an acceptably low probability of late tissue damage is called the Tolerance Dose. The tolerance dose is different for different tissues, with quite a dose range from the most sensitive to the most resistant tissue. The tissue with the lowest tolerance dose, which is in the path of the radiation beam, is obviously the dose limiting tissue for a particular course of treatment.

2.5 Radiotherapy for the Treatment of MBC

Palliative radiation therapy for metastatic breast cancer can generally be performed with simple techniques and simple technology.

The radiation treatment process is complex and consists of multiple steps. These are broadly summarized in a simplified form in Figure 3. The steps are not always

necessarily in the same order not are all the steps always needed. The latter is especially true for palliative radiation therapy where CT scanning and target volume delineation are not always required, particularly when a large fields are used to treat systemic disease or pain
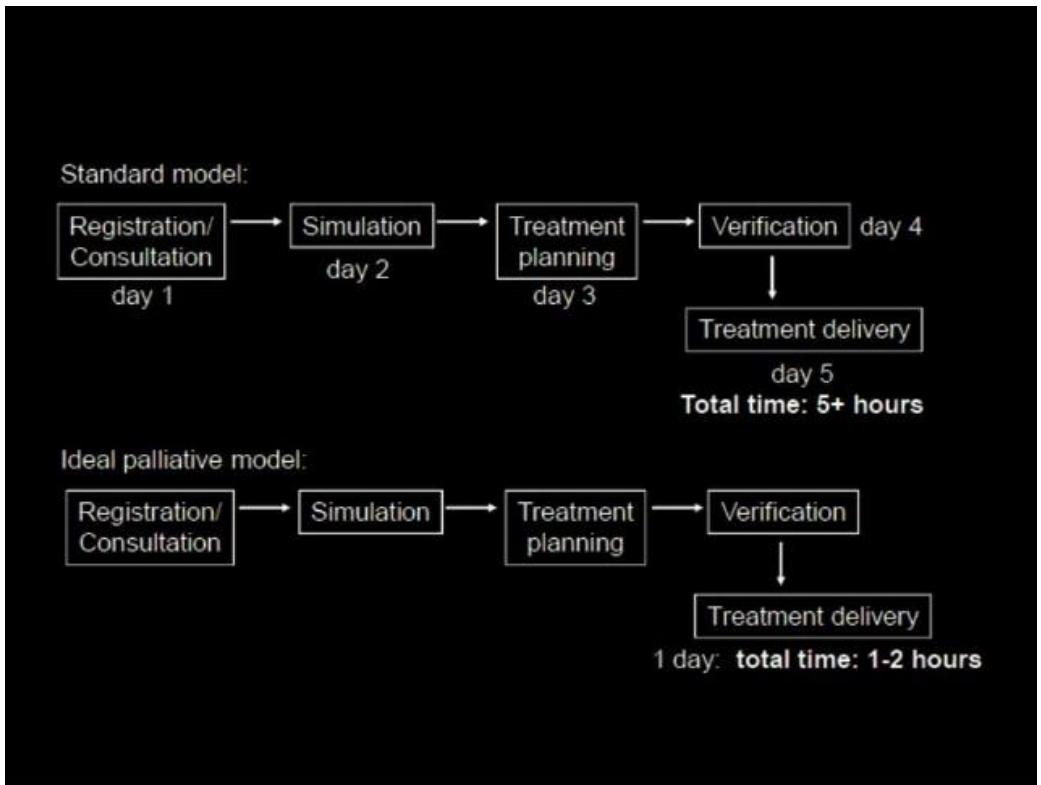

Figure 2-1 Schematic block diagram demonstrating the multiple steps in the radiation treatment process.

2.5.1 The Role of Palliative Radiotherapy in metastatic breast cancer MBC

1. Bone Pain and Bone Metastasis

The skeleton is one of the commonest sites for metastatic cancer of any type. Whilst cancer in the bones is not usually directly life threatening it is frequently a source of pain which is a major debility. On occasions the more disabling complication of pathological fracture, spinal cord compression and hypocalcaemia may also occur. Local irradiation of one or more painful bone deposits is associated with a high probability of pain relief. This graph plots probability of pain relief related to time for one clinical trial of palliative irradiation of painful bone metastasis where a multifraction treatment regime was compared with a single fraction. It demonstrates that the onset of pain relief may take 2-3 weeks to occur. It also shows that a single fraction of 8Gy is as effective as 30Gy in 10 fractions for achieving pain relief. (Roslyn D et2006)

However, other studies show that longer term pain relief, greater tumor shrinkage, and thus, fewer episodes of retreatment are achieved by a multifraction treatment program. Hence the choice of dose and fraction number needs to be tailored to the patient's general condition, expected survival and convenience of access. While single dose treatment may be adequate for pain relief, when tumor shrinkage is the goal this may not be adequate. For example, in spinal cord compression, where extension of soft tissue tumor from the vertebral bone into the spinal canal causing the spinal cord to be compressed and neurological impairment, or in a weight bearing bone, where sufficient bone destruction has occurred to reduce the mechanical strength of the bone. In these situations significant tumor shrinkage is required to relieve symptoms.

So, short course fractionated treatment is preferred either 30Gy in 10 factions or 20Gyin 5 fractions at 5 fractions per weeks.

2. Cerebral Metastases

Brain metastases are a major cause of symptoms and neurological disability. In general, patients present with multiple tumor deposits in the brain in the setting of widespread metastatic disease elsewhere. However as systemic chemotherapy improves, and as the brain is a sanctuary site for chemotherapy, brain metastases may be seen as the first site of metastatic disease. The median survival for patients with brain metastases varies from 1 month to several years depending on the primary cancer. Survival is related to the extent of neurological deficit at diagnosis and the extent of metastatic disease outside the brain.

Corticosteroids can palliate brain metastasis symptoms in a proportion of cases but the beneficial effect diminishes with time. Palliative cerebral irradiation, because it kills the tumor and causes tumor shrinkage, consolidates and improves on the steroid response and maintains the response for a prolonged time.

Palliative brain irradiation is aimed at maintaining and improving neurological function and performance status until death occurs from some other metastases at another site. Again the treatment program can be tailored to the patient's general condition and expected survival. For whole brain treatments most use 5 or 10 fractions but a single dose can be used.

2.5.2 Radiotherapy Planning and Treatment :

2.5.2.1 Patient data acquasion

A planning field was performed on patients either on conventional Hustise simulator using the imaging protocol according to the metastatic site. Patients were scanned in the treatment position and asked to breathe normally or on simple treatment couch using manual anatomical land mark to draw the field size of radiation field depended on patient previous images

2.5.2.2 Treatment Planning

The patients in the study and all patients were planned using Pinnical3 TPS produced by the physics team in the RICK hospital. the recent report by the International Atomic Energy Agency that describes the requirements for setting up a new facility (IAEA,2008)Thus, consideration should be given for the acquisition of appropriate diagnostic equipment required for defining the target volume. Patient immobilization devices are particularly important for treating patients this is an important consideration since the treatment should not create any morbidity or additional suffering for the patient. Patient external contouring devices may also be needed to determine dose delivery with some accuracy.

.Treatment planning of MBC in spinal cord compression

It occurs in three sites:

Thoracic spine   60%

Lumbosacral spine   30%

Cervical spine   10%

22

Immobilization:

Body cushion with comfortable prone head rest

Field Arrangement:

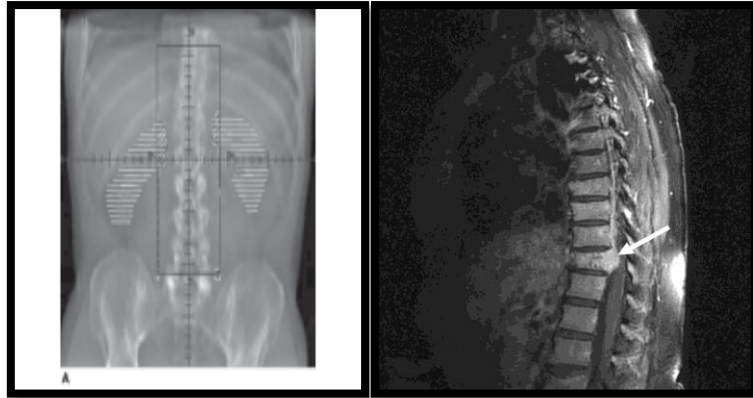Prescribe at 5-8cm depending on particular level in cord (cervical – lumbar)

Figure 2-2 Field Arrangement in MSC

Field arrangement:

1- Laterally

1 cm margin beyond the pedicle to cover the spinal cord and meninges along the nerve root up to the spiral ganglia

2-caudal

1cm below the termination of the sac L5-S3

Technique

1. SSD

2. gantry angle =0

3. IMP point is length and depth of spinal cord

Dose:

Treat extradural disease – visualize on MRI + 2 vertebral bodies

1. 8Gy / 1fraction

2. 20 Gy / 5fraction / 5 days
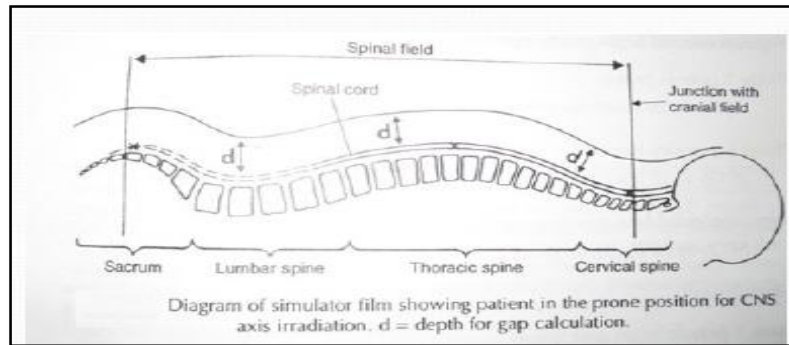
3. 30 Gy / 10 fraction / 2 weeks

Figure 2-3 patient position in spinal cord compression field in MSCC

Treatment planning of in whole brain irradiation

This is a diverse group; consideration must be given to the following:

1. Single or multiple metastases

2. Performance status

3. Histology of disease (and options for systemic therapy)

4. Control of disease outside the CNS

Single metastases

In those with a single cerebral metastasis, good performance status and control of disease outside the CNS consider neurosurgery or stereotactic radio-surgery. Otherwise use WBRT as below.

Multiple metastases

For patients with a good performance status WBRT is indicated with 20 Gy in 5 fractions (there is no evidence that 30Gy in 10 fractions is superior).

For patients with a poor performance status radiotherapy may be in appropriate, if however radiotherapy is deemed appropriate use 12 Gy in 2 fractions.

Radiotherapy techniques

1. Clinical markup (250 kV)

2. Simulation

3. CT simulation

Immobilization

Thermoplastic shell (not if clinical markup), head band or sand bags]

Field Arrangement

Treatment volume

1. CTV = Whole brain

2. PTV = CTV + 1 cm

3. Practically this is defined by 'Reids' base line - supra-orbital ridge to tragus or external audiorymeatus.

4. Normal field size 15 x 20 cm (ensure complete coverage of skull to avoid patchy hair loss)

5. Normal separation 15 cm (required for clinical markup).

Treatment technique

1. Beam energy.1.25 6, 8 MV photons (or 250 kV)

2. Supine

3. Neck straight

4. Head rest

5. Lateral opposed fields

Retreatment

Patients who relapse after WBRT and who had a good clinical, symptomatic and radiological response to their initial treatment and who are expected to have a reasonable survival can be retreated:
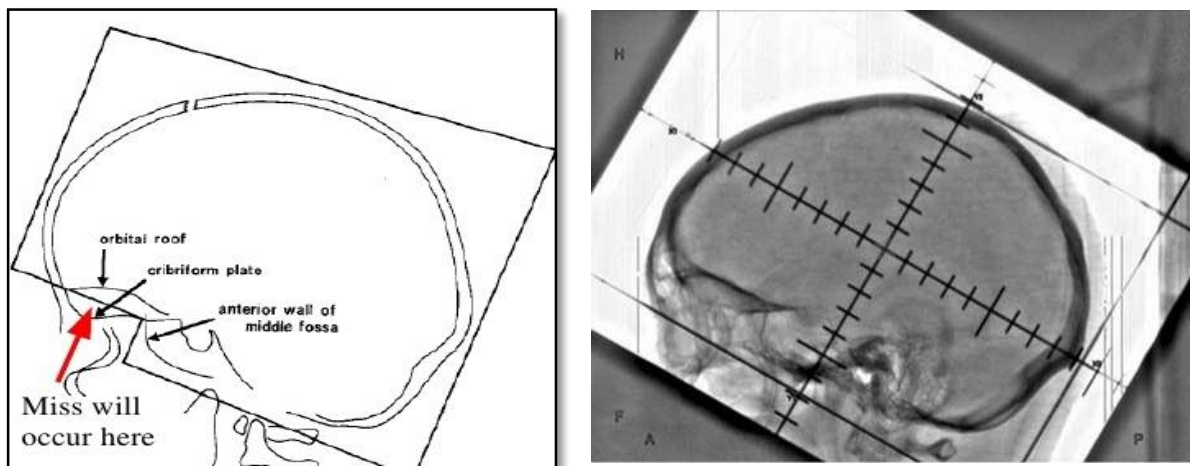
Dose:

20 Gy in 10 in over two weeks.

Figure 2-4 field arrangement for WBRT

Radiotherapy treatment of bone irradiation:

Indications for Radiotherapy :

1. Bone metastases presenting with pain not adequately controlled by analgesia

2. Bone metastases causing mass effect

3. Inoperable impending / existing pathological fracture

4. Pathological fracture following surgical fixation

High Risk of Pathological Fracture:

If the cortex of the bone is eroded in relation to an osteocytes metastasis in a limb, surgical stabilization should be considered to prevent fracture. Postoperative radiotherapy should then be given.

Suggested X-ray parameters indicating high risk of fracture are:

a. > 50% cortical destruction

b. > 3cm maximum diameter

c. 3cm axial cortical involvement

d. Multi-focal lytic disease

Metastatic Pain at several sites:

Wide field or hemi body irradiation can be considered in this situation. Single fraction regimens appear to offer good symptom relief with acceptable toxicity.

Re-Irradiation:

This may be indicated for recurrent symptoms at any site and needs to be assessed individually with an assessment of previous radiation doses, response to previous irradiation (degree and length), prognosis and local radiation tissue tolerance.

Immobilization

1. Head / C-Spine

2. Thermoplastic Shell

3. Extremities: may benefit from Body foam

Orientation, Set-up, Wax / Bolus

Indicated by the treatment site with the use of adequate foam pads or pillows to optimize both patient comfort and treatment reproducibility.

Site	Patient position
Head	Supine, prone for posterior lesions, head rest
Spine:	Prone if patient able (otherwise supine), head rest
Pelvis	Supine
Extremities	Treatment site to be positioned away from normal tissue
Scapula	Supine unless mark-up on-set
Ribs	Dependent on site of rib metastasis to be treated
Sternum	Supine

Table 2-1 patient position according to tumor site in bone metastatic

Localization:

Conventional Simulation, Virtual Simulation via CT or clinical mark-upon-set (with subsequent confirmation of localization by simulation, if necessary).

Clinical examination may aid localization of tender areas, marked with wire for external beam or pen for orthovoltage therapy.

Areas particularly amenable to mark on set

1. Superficial scalp
2. Scapula
3. Ribs
4. Sternum

Target Definition:

The GTV = The volume of metastatic disease, as determined by diagnostic imaging and clinical examination

The CTV = The GTV + surrounding bone at risk of microscopic involvement

The PTV = The CTV with a margin dependent on the treatment site Field borders should cover the area of metastatic involvement (the CTV)with a 1-3cm margin while making anatomical considerations to aid future matching of fields and to avoid treatment of normal tissues. For post-operative treatment, the field should include metalwork with a 12cmmargin.

Field Borders& Arrangement:

site	Field	Field Arrangement
Head	For whole skull treatment, refer to Radiotherapy Clinical Protocol for Brain Metastases, Whole Brain Radiotherapy. For mark-up on-set, a 1-2cm margin on the GTV should suffice, with the field size and shape chosen using the choice of applicators available ± lead shielding.	Usually parallel opposed fields unless mark-up on-set of a skull lesion
Spine	The affected vertebrae with 1-2 vertebrae above (superior field border) and below (inferior field border), unless matching with previous fields. The lateral field borders: 2cm lateral to vertebral body edge, or 1 - 2cm lateral to Para vertebral extension whichever is most lateral. Where the lower lumbar spine is treated, the sacrum may also be included in a 'Spade' shaped field. The SIJs are included with a 1 -2cm margin, for the	Where the T-Spine is not included and the patient is able to have the shoulders sufficiently caudal to be out of the field, a parallel opposed pair of lateral fields may be used to minimizemicrosites. Otherwise, a single posterior field.

	lateral field border.	
	For C-Spine lesions treated with a parallel opposed lateral pair, the field should include the spinous processes with a 1 -2cm margin posterior to spinous process and 1-2cm anterior to the anterior aspect of the vertebral body.	A single posterior field
Pelvis	Lower pelvic fields follow anatomical division of the pelvis into quadrants, unless the field border traverses disease. For lesions involving the proximal femur, the lesser trochanter is included with a 1-2cm margin inferiorly	A parallel opposed pair, anterior and posterior
Extremities	The field should include the GTV with a 1-3cm margin in the super-inferior direction and a 1.5-2cm margin laterally. As stated above, metalwork should be covered with a 12cm margin(unless ,by doing so, field length is unacceptably long).A corridor of normal tissue should remain Out of the field to reduce the risk Of lymphedema.	A parallel opposed pair, anterior and posterior

Scapula	For parallel opposed fields the arm should be abducted to minimize the volume of lung in the field. For mark-up on- set, field borders are determined as above for head fields.	Either single posterior field or parallel opposed pair if the shoulder is to be included in the field
Ribs	As for mark-up on-set for head fields.	Usually a single applied field
Sternum	Field borders include a 1-2cm margin on the GTV.	A single anterior / applied field

Table 2-2 Field border and Arrangement in bone metastatic

Prescription, Energy and Modality:

1- 6Gy/1 fraction Upper hemi body irradiation

2- 8Gy/1 fraction: Standard dose for palliation of painful bone metastic

3- 20Gy/5fraction: May be considered instead of single fraction for pat with a very good performance   status with:

   • Inoperable impending pathological fracture

   • Established pathological fracture

   • Prior surgical fixation

   • Re irradiation of bone metastases

   • Large field size with a significant volume of normal tissue

4- 30Gy/10 fraction: May be considered for patients with a good performance status and good prognosis (e.g. solitary bone metastasis from breast carcinoma)

5- 25Gy/5fraction: Radio biologically equivalent to 30Gy in 10#. May be considered for patients with a good performance status and good prognosis with a tumor with a high fraction sensitivity / low a/ß ratio (e.g. solitary bone metastasis from renal cell or melanoma)

2.5.2.3 Dose specification and beam characteristic

There are a number of ways of describing the characteristics of a radiation beam usein radiation therapy. In this section we will expand on the following characteristics that have an impact on the clinical quality of a radiation treatment:

• Beam penetration (energy)

• Scattering conditions and dose uniformity

• Beam edge sharpness (penumbra)

• Contour and in homogeneity corrections

• Dose to bone *versus* soft tissue

Beam penetration (energy): Beam penetration, or beam quality, from a patient's treatment perspective is best described by percentage depth doses. Any energy in the megavoltage range has a relatively low surface dose and builds up quickly to a maximum dose. This "skin sparing" is the great advantage of megavoltage radiation treatments and is provided by any beam with energy of cobalt-60 (equivalent to 1.25 MeV) or higher. The depth of maximum dose increases with increasing energy and the remainder of the depth dose curve is also higher with higher energies. Generally, when

only one to four beams are used to treat a tumor at a depth, the higher energies tend to provide more uniform dose distributions with lower doses outside of the target regions. Figure 2 is an example of central ray dose profiles for a parallel-opposed treatment technique. As the number of fields increases the difference between the normal tissue doses outside of the target region decreases. In many of the developing countries, where poor nutrition is often the norm, the older patient population tends to be small and therefore the need for higher energy radiations decreases and cobalt-60 is quite adequate to treat a majority of patients

Central Ray Dose Profiles for Parallel Opposed Beams

SSD = 100 cm
Field size: 25 x 25 cm²
Patient thickness = 25 cm

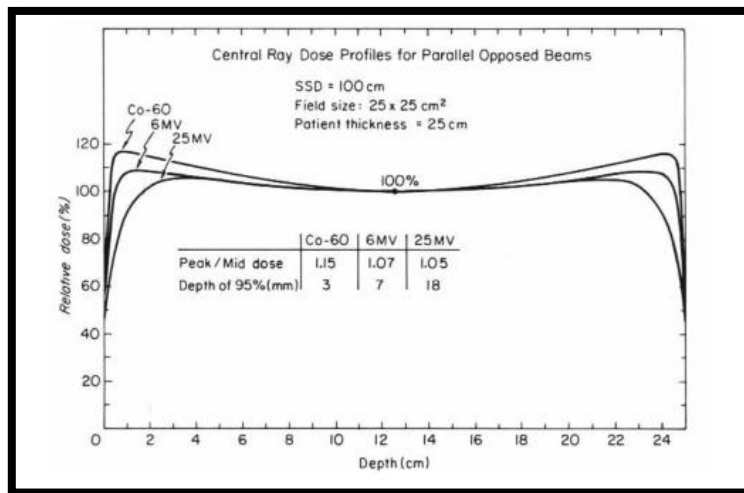|	Co-60	6MV	25MV
Peak / Mid dose	1.15	1.07	1.05
Depth of 95% (mm)	3	7	18

Figure 2-5 Central ray dose profiles for parallel-opposed beams with energies of cobalt-60, 6 MV and 25MV for a large patient with thickness of 25 cm and alarge field size of 25 × 25 cm2. The inset shows the ratios of maximum to mid-plane dose as well as the depth at which the dose near the surface reaches 95%

Scattering conditions / dose uniformity:

For small fields the scattering conditions or the dose uniformity is minor but for larger fields scattering condition can be reduced with flattening filters, compensators, and clever treatment planning.

Beam edge sharpness (penumbra):

The beam edge sharpness (penumbra) varies from 90% to 10% from the center of the beam to its edge for a specific field size. The penumbra also depends on the treated area density. Figure 3 show this variation in water with density 1.00 gm/cc and lung with density 0.20 gm/cc for a field size $5 \times 5cm2$, The equivalent dose is shown at a distance 10 cm for Co-60 and 4 MV linacs. For Cobalt-60, the surface to axis distance (SAD) is 80 cm.

Contour / in homogeneity corrections: Electronic disequilibrium is observed for high energy photon beams in the lung because of larger penumbral effects and possible reduced dose on central axis.

Dose to bone versus soft tissue: Tissue/bone (or tissue/prosthesis) interface effects cover a larger volume in higher energy photon beam. There is a small difference in dose to bone for MV energies with small fields and a large difference for large fields.

2.6. Radiobiology and fractionated radiotherapy

Cells die after being irradiated mainly due to damage to their DNA with the consequent loss of the ability to divide. DNA may be damaged either by direct ionization or indirectly by chemical interaction with the free radicals formed by ionization of water (most of the cell content). Induction of double strand breaks in DNA is the dominant

mechanism of cell killing by X-rays or γ-rays. Breaks in the DNA and mis repair of the damage to DNA, result in the cell dying when it next attempts to divide. Ionization produced by radiation is distributed randomly in cells; consequently cell death follows random probability statistics.

The typical single dose-cell survival curve has an initial shoulder and then becomes exponential at higher doses. The dose levels used in clinical practice are on the shoulder part of the curve.

The equation SF = e − (ad + ßd2) describes this curve. Where, SF is the surviving fraction of cells, a + ß are constants and d is radiation dose.

When multiple doses of radiation are given the effective survival curve is an exponential curve with a shallower slope. The fraction of cells surviving depends on, the size of each dose fraction, and a/ß ratio. The a/ß ratio is known to be different for different types of tissue. (Slowly proliferating cells ~ 3, compared to rapidly proliferating cells ~ 10) The calculation of multifraction treatment programmed which use different sized dose per fraction, to result in equivalent cell survival can be made using the a/ß ratio.
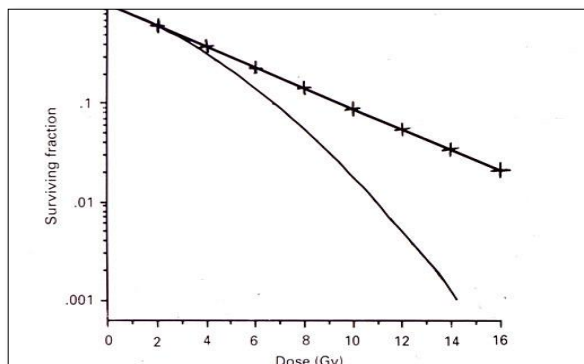

Figure 2-6 Effective Cell Survival Curve from multiple doses of radiation

Tissue Response to Radiotherapy

At the tissue level the response to irradiation reflects the cell survival and the regenerative capacity of the tissue stem cells. Since the death of irradiated cells is apparent when they attempt to divide, the observed effects of radiation on tissue are largely determined by the frequency of the cell division within that tissue. As, cancer cells are generally divided more rapidly than normal tissue cells, and cancer cells cannot repair and recover from ionizing radiation to the same degree as normal cells, more cancer cells are killed off than normal cells.

Fractionation of Radiation Dose.

Fractionation or dividing the total radiation dose into a number of smaller doses exploits the differences between the normal tissue and the cancer tissue response to radiotherapy.

Fractionation exploits the 4 R's of radiotherapy:

1. Repair of sub lethal damage in normal cells

2. Repopulation of normal cells

3. Redistribution of cancer cells to more sensitive phases of the cell cycle

4. Reoxygenation of hypoxic areas in the cancer

Fractionation of the radiation dose aids the repair and recovery of the normal tissue and increases the radiation sensitivity of the cancer cells. Over a multi fraction course of irradiation these differences add up, to minimize normal tissue effects and increase cancer cell kill. Fractionation is also important for normal tissue effects. The faster turning over normal tissues like mucosa, skin and bone marrow are responsible for the

observed acute effects of radiation. These are the effects seen during or soon after the irradiation is given. The acute effects of radiation are a manifestation of the death of rapidly dividing normal cells, and always recover after treatment (for the usual doses used in treatment).

The more slowly dividing normal cells show the effects of radiation much later, e.g. kidney, bone, fibro vascular tissue. The late effects of radiation are a manifestation of depletion of the functional parenchyma cells of a tissue. Late effects are the dose limiting effects in radiotherapy.

2.7. Techniques in palliative radiotherapy:

IAEA-TECDOC-1549, Criteria for Palliation of Bone Metastasis — Clinical Applications, is a guide for researchers and practitioners, summarizing recommendations and practices (IAEA-TECDOC-. 1549, (2007) Criteria for simulation are not formalized in palliative radiotherapy. In keeping with the goals of palliation, however, simulation and palliative radiotherapy techniques should be simplified to maximize the patient's comfort. Simulation or portal imaging is beneficial when treating spinal cord compression or vertebral metastases to ensure coverage of involved vertebral bodies. Treatment planning performed after simulation accounts for body shape, and ensures adequate dosimetric

coverage, including the anterior aspect of the vertebral body. Simulation and/or imaging are important when palliative radiotherapy fields must account for prior radiotherapy portals, particularly over the spinal cord and other critical structures.

While simulation is usually a standard of care in high income and most middle income countries, it is not always mandatory, especially for the treatment of long bones, like the femur and hummers. During emergent initiation of radiotherapy, for all income level nations, port films have long been acceptable .The site and volume of tumor involvement are the most important considerations in the development of a palliative radiation treatment plan because of

the radiation tolerance of adjacent normal tissues to treatment. Unlike the comprehensive radiation treatment portals used in curative therapy, palliative radiation generally only encompasses the tumor volume critical to symptoms. Radiation treatment planning must minimize possible toxicities, and account for prior courses of radiation. Toxicities are reduced by limiting the volume irradiated, and through the application of dosimetric principles that reduce integral dose.

2.8 . Fractionation in palliative radiotherapy:

In contrast to the low daily radiation doses [1.8 to 2 Gy) given with each treatment during conventional radiation schedules to total radiation doses of 50 Gy to 60 Gy over 5 to 6 weeks, hypo fractionation with short overall treatment duration and larger daily radiation fractions is recommended in most palliative radiotherapy applications. Because of normal tissue tolerance to radiation, the total radiation dose that can be administered is low when high doses of radiation are given with each daily fraction. Hypofractionated radiation schedules can range from 2.5 Gy per fraction administered over 3 weeks for a total radiation dose of 35 Gy to a single 8 Gy dose of radiation   (*KAASA, S., et al.,2006 ,JANJAN, N.A.,2009)*

Survival is determined by the location and number of sites of metastatic disease rather than the number of radiation fractions used for a localized area of disease. Overall survival rates for a single fraction of radiation are equivalent to a course of palliative radiation with multiple fractions.

A single 8 Gy fraction is generally administered in most European countries and Canada for uncomplicated bone metastases given the equivalent outcomes in a wide range of randomized clinical trials. A single large radiation fraction is as effective in relieving pain as other radiation schedules that have more treatments .Retreatment with the same dose is possible if time between fractions is not too short, usually not N shorter than one week.

There are five reasons why a shorter radiation schedule is advantageous for patients with a poor prognosis..

First, it is easier for patients with a poor performance status to complete therapy. Second, response and survival rates are equal for single and multifraction therapy at three months because median survival is less than six months among patients with a poor prognosis and averages around 24 months among patients with metastatic disease *(CHOW, E., LUTZ, S., BEYENE, J2003 CHOW, E., HARRIS, K., FAN, G 2007)*.

This is an important consideration when the number of weeks of survival is evaluated relative to the number of weeks spent receiving palliative treatment. Third, the option of retreatment after a single fraction of radiation may also provide benefit to patients with good prognostic factors as a means to periodically reduce tumor burden and control symptoms in non-critical anatomic sites. Fourth, a single fraction of radiation is more cost effective. The cost of radiation therapy is reduced by 41% with the use of a single fraction of radiation therapy when compared to a ten fraction course of palliative radiation. In addition, the cost of radiation therapy is less expensive than the continued cost of analgesics (MACKLIS, R.M et 1998).

An analysis of the Dutch prospective study also showed cost benefit for a single fraction of radiation when compared to multiple radiation fractions, even when retreatment was included in the single fraction arm [173]. Fifth, a single dose makes most efficient use of resources and allows more patients to be treated.

Metastatic cancer is often treated as a chronic disease and treatment is given to prevent or relieve symptoms of the disease. Re-irradiation for persistent or recurrent pain is often precluded when higher radiation doses are administered, but re-irradiation is possible after a single fraction of radiation .

For patients with metastatic disease, time is critical. The time under radiation needs to be considered as the opportunity cost of palliative treatment (SCOPE STEERING COMMITTEE 2002). If the median survival of a patient with bone metastases is six months (180 days), the patient

will spend 0.6% of the remaining survival time under radiation treatment when a single fraction of radiation is given. If 10 radiation fractions are given, 8% of the remaining survival time and if 20 fractions are prescribed 16% of the remaining survival time will be consumed by radiation therapy. Even if retreatment with a second single fraction is required, the patient will only spend about 1% of the survival time under radiation therapy. For lung cancer patients with a three month survival time, 1% of the remaining time is spent with a single fraction of radiation as compared to 16% if 10 fractions are given, or 30% if 20 fractions are prescribed.

Acute radiation toxicities are linked to the dose per fraction, total dose, and the area and volume of tissue irradiated. If mucosal surfaces like the respiratory tract, gastrointestinal tract and bladder can be excluded from the radiation portals, acute radiation side effects can be significantly reduced whether a single or multiple fractions are prescribed. A more protracted course of radiation is still used for patients with good prognostic factors who require treatment over the spine and other critical sites (WU, J.S., et 2003)

For most patients who receive palliative radiation for pain, however, a single fraction of radiation provides an efficient and effective therapeutic option. Single fraction radiotherapy for uncomplicated bone metastases provides benefit in every respect. From the patient's perspective, a single fraction of palliative radiotherapy effectively relieves symptoms without a prolonged course of therapy that can incur discomfort, and consume valuable time during a limited life expectancy. From the caregiver's perspective, a single fraction of radiotherapy eliminates additional efforts of care, and reduces potential pain associated with transportation to and from the radiotherapy Centre over approximately two weeks. From the societal perspective, a single fraction of radiotherapy is cost effective and meets the criteria of 'Quality Adjusted life years' (QUALYS) .

Health resources can be optimized with single fraction radiotherapy since ten patients benefit from a single fraction of palliative radiotherapy instead of one patient being treated with ten fractions of palliative radiotherapy.

2.9 Evidence of hypo fraction and once weekly radiotherapy in MBC:

A randomized clinical trial was undertaken in 1986, with the aim to test the hypothesis that hypo fractionation is as effective as the standard 2Gy per fraction and offered reduced cost to patients and the health facilities.(Yarnold J,et 2005) The primary endpoint was the late effect of healthy tissue and secondary endpoints were tumor recurrence and palpable fibrosis. This trial generated reliable estimates for a/ß for late change in breast (3.6Gy) and late change in breast appearance (3.1Gy). It did not generate reliable estimates for a /ß for tumor control. This trial was used as a basis for the UK Standardization of Radiotherapy Trail (START trial) (Trialists' Group et 2008)

Similar randomized phase three trial in 20013132These a/ß ratios were confirmed by a The START A Trial studied women with early breast cancer who received adjuvant radiotherapy post breast conserving surgery or mastectomy.(Yarnold J,et 2005)

The patients were either randomized to 50Gy in 25 fractions or 41.6Gy in 13 fractions or 39Gy in 13 fractions. Treatment duration in all three arms was 5 weeks. The data was consistent with the hypothesis that breast cancer and dose limiting normal tissue respond similarly to change inradiotherapy fraction size. The adjusted estimates of the a/ß ratio for tumor control was 4.6Gy and for late change in breast appearance was 3.4Gy. The START B trial ran concurrently with the START A trial. It compared 40Gy in 15 fractions of 2.67Gy per fraction in 3 weeks to the control group of 50Gy in 25 fractions 2Gy in 5 weeks. The results were consistent with the START A trial that hypo-fractionation, over a reduced treatment time (accelerated therapy), produced the same rate of loco-regional relapse and late adverse effects as the standard 50Gy treatment. The hypo fractionated regimes tested in the START trials are now standard

practice in most institutions. The risk of hypo fractionation is the effects on the late responding tissue. The larger the fraction, the greater the expected late effect will be. Results of studies on the long-term side effects of hypo fractionated radiotherapy for breast cancer show comparable results for the risk of local recurrence and cosmetic outcome.(Whelan TJet 2010, Havilland JS et2013)

In 1987, Rostom et al, investigated using once weekly hypo fractionated radiotherapy (6.5Gy weekly for 6 fractions) as definitive or adjuvant treatment in elderly patients. Of the 84 participants, 18 had undergone a mastectomy. This study demonstrated that the hypo fractionated regime was well tolerated. There were less acute side effects than conventional radiotherapy (50Gy) and only 1 of the 66 patients who had an intact breast developed late fibrosis of the breast.35

Maher et al published a retrospective review, evaluating ER positive elderly women who were unfit for surgery or norm fractionated radiotherapy, in 1995.25 the patients had received Tamoxifen 20mg daily, as well as once weekly radiotherapy of 6.5Gy for 5 fractions to the involved breast and 2 fractions to the tumor bed. The majority of the patients were stage 1 and 2. This study showed that at 36 months, the overall survival was 87%, the disease specific survival was 88% and the local control rate was 86%. Ten percent of the patients had WHO grade 2 skin reactions and 3% had WHO grade 3 skin reactions. There was late fibrosis of the breast in 39% of the patients, but late tissue damage was accepted as adverse squeal in the patients. No pneumonitis or rib fractures were reported. These patients were however treated in the lateral decubitus position, which would reduce dose to lung and ribs.

Courdi et al performed a similar study in 2006 with the same dose fractionation.26 A third of these patients had T3 and T4 tumors. Their local control rate was similar at 85%. They had grade

1 and grade 2 skin reactions in 20% and 9% of the patients respectively. No grade 3 skin reactions were reported. There was late fibrosis in the breast of 49% of the patients, majority being grade 1 and grade 2. The progression free survival at 5 years was 78%.

In 2005, Orthalan *et al* studied the same hypo fractionate regime at the same institution as Courdi.27 They, however, reviewed those patients who received the radiotherapy in the postoperative setting. Seventy six percent of the patients received adjuvant hormones as well. More than 85% of the patients tolerated the treatment. The outcomes showed a 5- and 10- year disease free survival of 80% and 71.5% respectively and an overall survival of 71.6% and 46.5%. The local relapse rate was 2.3%. WHO grade 1 and 2 skin effects were seen in 26% of patients, with no grade 3 effects. Late effects was comparable to those seen in patients receiving 42.5Gy in 16 fractions.33

Kirova *et al* compared adjuvant hypo-fractionated radiotherapy to norm fractionated radiotherapy in the post-operative setting.28 Patients either received 50Gy in 25 fractions or 6.5Gy once weekly for five fractions. The outcomes were very similar to the above trial, except that there was a higher rate of late effects (33%) in the hypofractionated regimen. Thus also affirming that once-weekly ultra hypo fractionated radiotherapy is an acceptable alternative to norm fractionated radiotherapy.

This graph plots probability of pain relief related to time for one clinical trial of palliative irradiation of painful bone metastasis where a multifraction treatment regime was compared with a single fraction. It demonstrates that the onset of pain relief may take 2-3 weeks to occur. It also shows that a single fraction of 8Gy is as effective as 30Gy in 10 fractions for achieving pain relief.
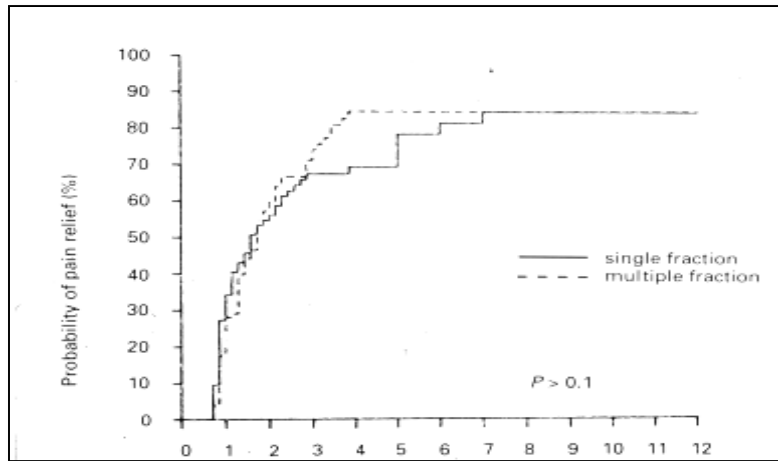
Figure 2-7 Probability of pain relief related to Time

However, other studies show that longer term pain relief, greater tumor shrinkage, and thus, fewer episodes of retreatment are achieved by a multifraction treatment program. Hence the choice of dose and fraction number needs to be tailored to the patient's general condition, expected survival and convenience of access. While single dose treatment may be adequate for pain relief, when tumor shrinkage is the goal this may not be adequate. For example, in spinal cord compression, where extension of soft tissue tumor from the vertebral bone into the spinal canal causing the spinal cord to be compressed and neurological impairment, or in a weight bearing bone, where sufficient bone destruction has occurred to reduce the mechanical strength of the bone. In these situations significant tumor shrinkage is required to relieve symptoms. So, short course fractionated treatment is preferred either 30Gy in 10 factions or 20Gyin 5 fractions at 5 fractions per weeks

2.10 Different between radiotherapy modalities:

Photon beams (electromagnetic wave) and particle beams (particle) are the two mode of radiation. In particle beam therapy, heavy particle and proton are used; and in conventional radiation therapy, X-ray and gamma ray are used for cancer treatment.

Considering the basic features such as beam energy, depth-dose value, available wide range field size, dose rate, beam penumbra, radiation source replacement and spent source disposal as mentioning in table 3, a Cobalt 60 therapy unit is inferior to 6MVX-ray linear accelerator. However, a Cobalt 60 therapy unit offers, compared with6MV X-ray linear accelerator, more reliability, less need for a good power supply system, less need for skilled persons for maintenance as shown in table 2-3.(Yin W .Cheb B et2008) The initial capital cost and after-installation maintenance cost in 5 years running time of a Cobalt 60 therapy unit are less than that of a 6MV X – ray linear accelerator Though in 10 years running time both costs are almost equal due to the cobalt 60source must be replaced every 5-7 years, the lifespan of a modern 6MV-X ray linear Accelerator is getting shorter and shorter as the modern advanced technology change sever faster than before.(Yin W, Chen B et 2008)

Items Unit	Energy (MeV)	Source Diameter (mm)	D_{max} (cm)	Dose rate (cGy/min)	PDD at 10cm	Minimum Field Size (cm)	Penumbra (mm)	Source Replacement (wave guide)
Co-60	1.33 1.17	~ 20	0.5	≤ 200	55%	≥ 5 × 5	≥ 10	~ Every 7 years
6MV Linac	6MV X-ray	~ 2 × 3	1.5	~ 600	67%	0.5×0.5	≤ 7	Depends on patient load ~ 2-3 years (1500 HT hrs)

Table 2-3 Main features' comparison of Cobalt-60 and 6MV Linacs.

LINAC	Cobalt 60 machine
Continuing progress in technology, design & utility	New machines have improved beam capabilities.
6MV – adequate penetration to treat very vast majority of tumors	Does not give ideal depth dose, but adequate for palliative therapy.
Platform that allows for advanced curative treatment.	Primarily used for palliative treatment.
Upgradeable for advanced treatment modalities to improve the accuracy & quality of treatment.	Continuously depleting sources mean longer treatment times – compromised treatment efficiency & quality. Cumbersome exchange & disposal of sources
Standard of external beam therapy in Developed Countries.	

Table 2-4:   Comparison of new LINAC and Cobalt 60 machine

The beam characteristics of the Co-60, and 6 MV photon beams that will be compared, with emphasis on palliative care, are:

a)Surface Dose

b)Dose Build-up depth

c)Penetration – Depth Dose at 5cm and 10cm

d)Beam Flatness & Symmetry

e)Stability of Dose-rates

The differences are small when multiple beams are used, even though the single beam characteristics show a slight advantage for use of the 6MV beams.

The differences in the surface dose and build-up region, between Co-60 and 6 MV beams, show an advantage in using the Co-60 beams in treating Breast and Head & Neck cancers. Good skin sparing is achieved and adequate dose is delivered to the superficial tissues, which are part of the clinical target volumes.
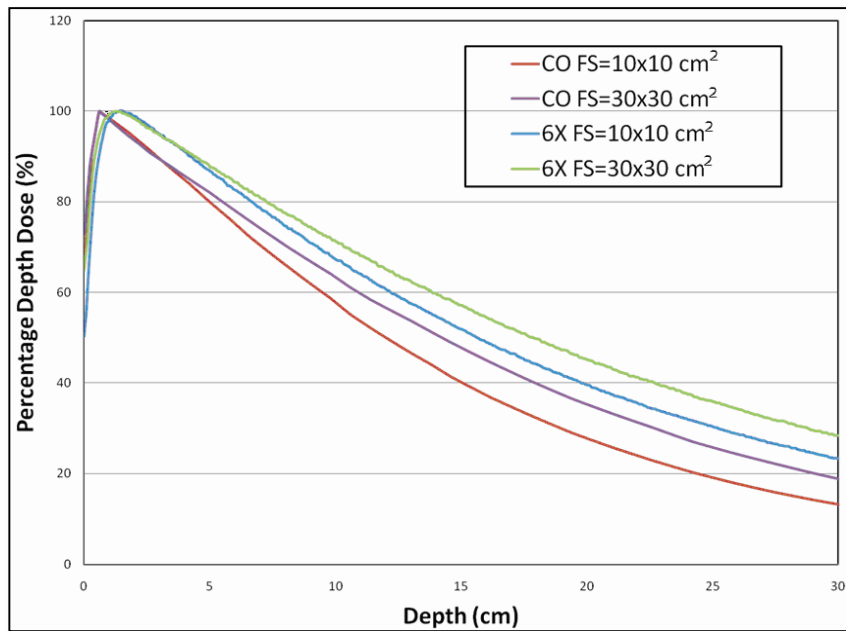

Figure 2-8Co6vs.6 MV Photon Beam Percentage Depth Dose

Most palliative treatments are delivered with two parallel opposed beams, for a total dose of 30Gy in 10 fractions. When treating thin body sections, about 10cm thick, theCo-60 beams are preferable to ensure adequate dose delivery even at shallow depths.

The build-up zone of higher energy beams can be a disadvantage (N.Suntharalingam2007)

Choice of either Cobalt-60 or Linacs depends on infrastructure, resources availability, professional staff availability, radiation safety regulatory control (decommissioning source disposal control) and type of institution (palliative care center vs palliative plus radical care

center). A comparison between Cobalt and Linacs sources according to these parameters for three different environments is shown in table 2-5

Environment	Poor		Moderate		Excellent	
	Cobalt	Linac	Cobalt	Linac	Cobalt	Linac
Infrastructure	N	N	Y	N	Y	Y
Resources	N	N	Y	N	Y	Y
Professional Staff	N	N	Y	N	Y	Y
Radiation Safety	N	N	Y	N	Y	Y
Type of centre						
Palliative only	N	N	Y	N	Y	Y
Palliative and Curative therapy	N	N	Y	N	Y	Y

Table 2-5 compression between cobalt and linear in different environmental