EVALUATION OF 6GY SINGLE DOSE RADIOTHERAPY IN COMPARISON WITH 8GY SINGLE DOSE RADIOTHERAPY IN THE TREATMENT OF PAINFUL BONE METASTASES

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CERTIFICATE

This is to certify that **Dr.P.N. Sathiyamoorthy** has been a Post Graduate Student during the period May 2007 to March 2010 in the Department of Radiotherapy, Madras Medical College, Govt. General Hospital, Chennai.

This Dissertation titled "**Evaluation of 6Gy single dose radiotherapy in comparison with 8 Gy single dose radiotherapy in the treatment of painful bone metastases"** is a bonafied work done by him during the study period and is being submitted to the Tamil Nadu Dr.M.G.R. Medical University in partial fulfillment of the M.D Branch IX Radiotherapy Examination.

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CONTENTS

INTRODUCTION

Bone metastases often present as the first evidence of disseminated disease. The incidence of bone metastases varies significantly depending on the primary site, with breast and prostate cancer accounting for up to 70% of patients with metastatic disease .

Even though the ultimate prognosis is poor, a proportion of the patients may survive for several months or even years and will require active treatment because of symptoms related to their bone metastases. Pain, pathologic fractures, hypercalcemia, neurologic deficits, and immobility decrease the quality of remaining life for these patients. Associated depression and anxiety may further compromise the quality of survival.

Radiation therapy is considered as the treatment of choice for palliation of painful bone metastases for many years [1,2]. Its main aim is relief of bone pain, prevention of pathological bone fractures as well as its healing, with anticipated effect upon improving mobility, function, and quality of life.

Also, data from retrospective studies [3,4] and prospective randomized trials [5, 6] showed that single fraction treatments may be as effective as multifraction regimens. Since single fraction treatment may be advantageous for both patient and institution, various single dose fraction schedules have been investigated [2, 3, 7–13]. Yet, optimal single dose of RT required for pain relief is unknown, although one study showed that 8 Gy gives a higher probability of pain relief than 4 Gy [14].

Furthermore, a dose level in - between the 4 Gy and 8 Gy (namely, 6 Gy) also appeared to be effective in achieving pain relief [12], not very different from that achieved with 8 Gy. In order to define the “lowest” optimal single dose of RT in the treatment of patients with metastatic bone pain, we underwent a prospective randomized trial comparing two single-fraction regimens of RT exploring dose-response effect in this trial setting.

The reason for evaluating a lower dose than one already proven to be effective (8Gy) is two fold ; the possibility of reirradiation increases, in view of the late side effects, and there was an assumption that the acute effects would be less with a smaller dose.

EPIDEMIOLOGY

INCIDENCE

The exact incidence of bone metastases is difficult to determine. Autopsy studies have reported bone metastases in up to 85% of the patients dying of breast, lung and prostate primaries.[15,16] Most other primary tumors can metastasize to bone, including kidney, thyroid, endometrium, cervix, bladder, and gastrointestinal tract cancers, but these sites account for less than 20% of patients with bone metastases. [14,16] Radiologic studies lead to antemortem diagnosis of bone metastases in about 50% of patients with metastatic cancer originating in breast, prostate, and lung cancer, but only in 3% to 15% of patients with gastrointestinal tumors [15,16]. Some hematologic malignancies including myeloma and lymphoma can also cause significant pain and bone destruction.

SURVIVAL

The ultimate prognosis for patients with bone metastases is poor, with median survival typically measured in months rather than years. Overall survival depends on the primary site and the presence or absence of visceral metastases.

Patients with bone metastases from lung cancer have short median survival durations of 6 months. However, patients with bone metastases from breast or prostate primary sites may have significantly longer survival times. In patients with bone-only

metastatic prostate or breast cancer, median survivals of 2 to 4 years have been reported.[17,18.]

Whether the survival time is only a few months or extends to multiple years, these patients will often require active treatment because of pain, difficulty with ambulation and immobility, hypercalcemia, pathologic fractures, neurologic deficits, anxiety, depression, spinal cord or nerve root compression, and general deterioration of quality of life [19.]

SITES

The axial skeleton is the most common site of bone metastases, with metastases most frequently occurring in the spine, pelvis, and ribs. The lumbar spine is the single most frequent site of bone metastases [20]. In the appendicular skeleton, the proximal femurs are the most common site of metastatic disease, and humeral lesions also occur frequently. The acral sites (feet and hands) are rarely involved.

Certain skeletal sites are associated with specific areas of bone metastases. For example, scapular metastases are seen more frequently from renal primaries [21.] Involvement of the skull is more common with breast primaries. The distal appendicular skeleton (tibia, fibula) and acral sites (especially the hands) are more common with lung primaries, and involvement of the toes is seen more commonly with genitourinary primaries.

PATHOPHYSIOLOGY

NORMAL BONE

There are primarily three types of cells within mature bone : osteoblasts, osteocytes and osteoclasts. Osteoblasts originate from osteogenic cells, found in the periosteum or endosteum. The osteogenic cells differentiate into osteoblasts when there is a mechanical or chemical stimulus for remodeling or repair. The osteoblasts build bone by depositing collagen type I into the extracellular space. An inorganic complex of calcium and phosphate (hydroxyapatite) is laid down within this organic matrix to provide the strength and density of the bone.

The osteoblasts then mature into osteocytes, which maintain the bone structure. Osteoclasts are multinucleated giant cells that originate from pluripotent hematopoietic bone marrow cells and are adherent to the bone surface [22]. These cells create an acidophilic environment that causes dissolution of the hydroxyapatite crystals and proteolysis of the bone matrix.

The differentiation and activation of osteoclasts occurs because of the effects of a group of proteins that are related to tumor necrosis factor, including osteoprotegerin, receptor activator of nuclear factor-kB (RANK), and the RANK ligand (RANKL). Osteoblasts and stromal cells express RANKL and activated T cells may also release RANKL. The RANKL binds to the RANK receptor on osteoclast precursors, which then induces the formation of mature osteoclasts.

Osteoprotegerin is a decoy receptor for RANKL, and inhibits the differentiation and activation of osteoclasts [22]. The destruction of bone by osteolytic metastases is mediated by the osteoclasts, not by the tumor cells. However, the factors that activate the osteoclasts are likely produced by the tumor cells including RANKL, interleukin-1, interleukin-6, and macrophage inflammatory protein . The mechanisms for osteoblastic activation are not clearly delineated, but it appears that bone resorption occurs first even in osteoblastic metastases from prostate cancer [23].

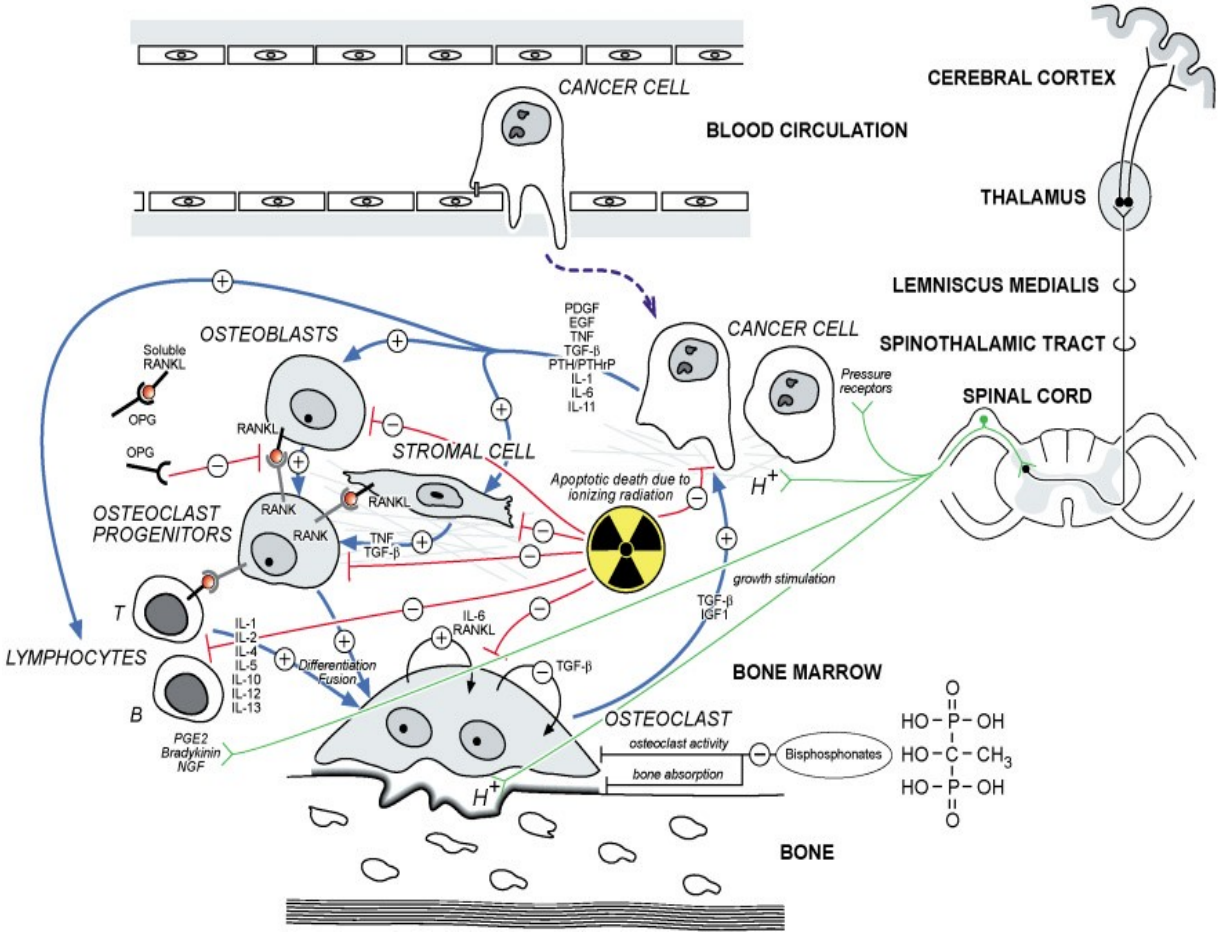
Normal bone is constantly being remodeled in a cycle lasting about 120 days (3 to 6 months). For the first 20 days of the cycle, the bone is resorbed by osteoclasts. The bone is then rebuilt by osteoblasts during the next 100 days.

METASTASES TO THE BONE

A metastases to the bone is a consequence of a cascade of events including (Mareel et al., 1991 and Choong, 2003).

1. progressive growth at the primary site,
2. tumor neo-vascularization,
3. detachment of tumor cells from the primary tumour,
4. invasion in the neighbouring tissues
5. intravasation into the blood stream,
6. survival in the circulation,
7. homing and arrest at the level of the bone marrow,
8. extravasation,
9. evasion of the host defence,
10. growth and stimulation of the osteoclast mediated bone resorption .

Fig. 1. The vicious circle of bone metastases.



The vicious circle of a developing bone metastases is represented by the thick blue arrows. Cancer cells inside the bone marrow produce a cascade of enzymes which – through stimulation of stromal cells, osteoblasts, lymphocytes and osteoclast progenitorcells – eventually stimulates osteoclasts to destroy the bone. At the right side of the figure, the physiological pain pathway is represented. Pain receptors capture different pain signals, which are transported via sensory neurons (in green) and the spinal cord to the thalamus and finally to cortical neurons. Radiation induces apoptotic death, not only of tumour cells (thereby reducing pressure) but also of all other cells in the cascade. Inhibitory effects of radiation are shown in red lines. The name of tissue is in bold capital print. (Adapted from Mundy, 2002 and Mareel and Leroy, 2003).

CANCER CELLS

The presence of large quantities of growth factors inside the actively proliferating bone marrow stimulates growth of metastatic tumour cells leading to a vicious cascade of events. Cancer cells - like inflammatory cells - release osteoclast activating factors, such as PTH and PTH releasing protein (PTHrP), Interleukin- 1(IL-1), IL-6, IL-11, Tumor Necrosis Factor (TNF), Transforming Growth Factor Beta (TGF-β), Epidermal Growth Factor (EGF), Platelet Derived Growth Factor (PDGF) and prostaglandins. All these molecules can trigger osteoblasts and stromal cells to stimulate the differentiation and fusion of osteoclast progenitor cells.

OSTEOCLASTS

Activated osteoclasts eventually cause the breakdown of the bone matrix. Osteoclasts are specialized cells that originate from monocyte precursor cells under the influence of RANKL, the ligand of the Receptor Activator of NF-κB (RANK) on the osteoclast precursor. The naturally occurring decoy receptor osteoprotegerin (OPG), a member of the TNF receptor family, inhibits the effect of RANKL on osteoclast differentiation. RANKL is produced by osteoblasts and stromal cells as a regulator of bone formation and destruction. Free floating soluble RANKL is also able to stimulate the osteoclast progenitors. OPG is now being proposed in clinical trials for the treatment of bone metastases through the capturing of the free floating RANKL molecules.

Amongst other functions RANKL will also induce lymphocyte development and can thus be involved in the inflammatory reaction in the immediate vicinity of metastatic tumor cells. Recently it was shown a that RANKL was produced by the osteoclasts thus suggesting an autocrine stimulating loop inside the osteoclast in both physiological and pathological conditions.

STROMAL CELLS

Other mechanisms that are involved in this tumour-host microevironment involve the TGF-β and TNF produced by stromal cells. This particular pathway was recently documented to be essential in the development of bone lesions in rheumatoid arthritis . TGF-β promotes the production of PTHrP produced by bone cells and tumour cells that, in its turn, stimulates bone turnover by enhancing the osteolytic action of the osteoclasts . TGF-β can, on the other side, also promote apoptosis of osteoclasts thereby reducing osteolysis. Recently it was shown that stromal cells - derived from normal bone marrow - produce monocyte chemotactic proteins (MCPs) that are involved in the bone marrow homing of multiple myeloma cell lines.

INFLAMMATORY CELLS

Prostaglandins - produced by the attracted inflammatory cells - are present in the bone metastases micro-environment and induce further inflammation. Inflammation is a critical element in tumour progression. The tumour microenvironment is largely orchestrated by inflammatory cells .

Those inflammatory cells are responsible for the acute effects of inflammation, frequently resulting in pain. Synthesis and release of inflammatory cytokines mediate the effects. Cytokines can be defined as proteins produced by a cell in response to a variety of stimuli . They are secreted by producer cells and then influence the behaviour of target cells. Many classes of cytokines are known: growth factors, lymphokines, colony stimulating factors, transforming growth factors, TNFs, interferons. It is important to realize that cytokines can be directly produced by the tumour cells, but are often produced in larger amounts by the inflammatory cells that are attracted by the tumour cells.

The cytokines produced by the tumour cells usually aim at survival and proliferation of the tumour, while the cytokines produced by the inflammatory cells may help the organism to fight against the cancer cells, resulting in an inflammatory reaction which frequently causes pain. This inflammatory reaction is a very complex system, with many synergistic and counteracting cytokines being present at the same moment. Moreover, many cytokines have overlapping biological effects. The synthesis and presence of cytokines will result in the production of other cytokines, with again different functions and effects, creating a complex network.

Blocking one pathway can force a cell to use another one as a kind of escape route, to eventually obtain the same effect, but via a previously unused and seemingly redundant mechanism . TGF-β is produced by cancer cells and can act as a growth factor for certain cells, but can also block the mitogenic effects of EGF, PDGF, fibroblast growth factor (FGF) and insulin . Cancer cells losing the TGF- β receptor will lose at

least one survival limiting factor. But, while inhibiting growth, TGF-β at the same time stimulates osteoclasts and thereby helps the cancer cells to invade into the bone. Moreover, e.g. in colon cancer cells, TGF- β may transform fibroblasts into myofibroblasts which will secrete other factors that promote invasiveness of the cancer cells .

Although cancer cells are self and should not evoke an immune response, they are often surrounded by large amounts of inflammatory cells. In some cases these inflammatory cells may even make up more than 50 % of the tumour cellular volume. This also explains the clinical experience that anti-inflammatory drugs, like steroids or non-steroidal anti-inflammatory compounds can give a (temporary) decrease in tumour volume. Even routine antibiotics may reduce tumour volume, of course only in cases of infected tumours that are heavily loaded by inflammatory cells.

THE PREDILECTION OF CERTAIN TUMOR SITES TO METASTASIZE TO BONE

The apparent predilection of some tumors for certain sites in bone has been ascribed to the anatomic relationship between venous drainage of the primary site and the blood supply of bones that are common sites of metastases.[25,26,27,29] However, most metastatic sites cannot be predicted from anatomic considerations alone. A number of animal tumors show preference for metastases to one or two specific organs, which might be explained by organ tropism.[15]

Possible mechanisms include the following [28] :

1. Tumor cells disseminate equally to all organs, but preferentially grow in specific organs (organ-specific growth may be stimulated by local growth factors or hormones present in the bone or bone marrow);

2. Circulating tumor cells may adhere preferentially to the endothelial luminal surface only in specific bones, which may be mediated through organ-specific endothelial determinants such as glycoproteins. The endothelial cells of marrow sinusoids lack a basement membrane, but have gaps between them that make the wall more penetrable by tumor cells than other vascular elements [29] ;

3. Circulating tumor cells may respond to factors diffusing locally out of the bone, which act chemotactically to attract the cells. Degradation products of normal bone resorption are chemotactic for tumor cells in vitro .[25 ,30]

These chemotactic substances comprise connective tissue elements from bone such as type I collagen and collagen fragments, and their presdence could also explain, at least partially, the localization of tumor cells in bone in vivo. [25] If this mechanism contributes to localization of metastases to specific sites in bone, these sites must release more of the chemotactic substances than other sites.

The proteins Nm-23 and Awd may be important to the metastatic process in general, but current data are too preliminary to speculate about their possible role in bone metastases.[31]

Metastases in bone are found almost invariably in the red marrow, and the bones most frequently involved are those with a high proportion of red marrow [32], more than 80% of bone metastases are found in the axial skeleton. The spine, pelvis, and ribs are often the earliest sites of metastases, whereas the skull, femora, humeri scapulae, and sternum are involved later. Different types of primary tumors do not show a significant difference in their distribution to different bones, except that cancers of the prostate bladder, cervix uteri, and rectum tend to involve the bones of the pelvis. [33] Solitary bone metastases are rare except for patients with renal cell carcinoma or neuroblastoma in which 5% to 10% of the patients may have a single site of bony involvement. [32,33] Bone metastases are usually wide spread by the time of their first clinical manifestion.

Bone metastases have local effects resulting in increased bone destruction (osteolysis), increased bone formation (osteosclerosis), or both. [25, 34] Osteolytic metastases are the predominant types of lesions in most cancers, but a sclerotic appearance is seen in the majority of metastases from prostate cancer, in about 10% of metastases from breast cancer, and more rarely in those derived from other cancers. Microscopically, there are no qualitative differences between lytic and sclerotic metastases. In the majority of skeletal metastases, new bone formation develops simultaneously with bone destruction, and the radiologic appearance merely reflects the process that predominates. [25,32,34,35]

A minority of patients may have diffuse involvement of the marrow without radiographic abnormalities. Unbalanced remodeling of bone with excessive resorption and minimal new bone formation appears to be the usual feature of multiple myeloma. [36]

PAIN DUE TO BONE METASTASES

The relationship between bone invasion and bone pain is unclear. Patients may have multiple bone lesions without related bone pain. Conversely, patients may have considerable pain without radiologic evidence of bone metastases, or there may be dissociation between the perceived location of the pain and the sites of known bone lesions.[37]

Mechanisms that may cause pain from bone metastases include the following [38,39]:

(1) stimulation of nerve endings in the endosteum resulting from release of chemical agents from the destroyed bone tissue such as prostaglandins, bradykinin, substance P, or histamine;

(2) stretching of periosteum by increasing size of the tumor;

(3) fractures; and

(4) tumor growth into surrounding nerves and tissues.

Few of these mechanisms are supported by definitive data. Stimulation of nerve endings in the endosteum by chemical agents released from the destroyed bone tissue is probably the main mechanism of bone pain from small metastases; as metastases enlarge, stretching of the periosteum probably contributes to pain.

Pain from bone metastases is frequently the first symptom for which the patients will seek advice . Pain is a complex experience that is based on the transduction of a noxious environmental stimulus in the periphery of the body and that is modulated

by cognitive and emotional processing by the cortical neurons of the brain. The subjective nature of pain has hampered the development of randomised trials considerably and has recently lead to initiatives to promote a universal language when reporting the palliative antalgic effects of any form of therapy for bone metastases .

In general there are two types of pain in patients with bone metastases. The first type is a continuous pain and is usually described as a dull aching pain that increases in severity over time. A second type of bone cancer pain is movement-evoked, breakthrough or episodic and is more acute in nature .

The pain from bone metastases can be explained by direct stimulation of afferent pain nerve fibres that are stimulated by mechanical injury or by a multitude of factors present in the complex microenvironment of bone metastases. Local tissue acidosis is a hallmark physiologic response to injury and inflammation and the degree of pain is correlated with the magnitude of acidification. A number of acid-sensing ion channels (ASIC3/VR1) are found on sensory neurons (Julius and Basbaum, 2001).

Stimulus	**Representative receptor/moleculartargets**
Nerve Growth Factor (NGF)	Transmembrane receptor Kinase A (TrkA)
Bradykinin receptor	Bradykinin (G-protein coupled) membrane
Serotonin	5-Hydroxy Tryptamine receptor (5-HT3)
Adenosine tri phosphate (ATP)	ATP gated ion channel (P2X3)
H+	Acid-sensing ion channel (ASIC3)
	Vanilloid receptor (VR1)
Lipids	Prostaglandin E2 (PGE2), VR1
Pressure	Degenerin family of ion channels (DEG/ENaC)

CLINICAL PRESENTATION

The morbidity associated with metastatic bone disease, often referred to as skeletal-related events or SREs, includes pain that may require opiates, the need for radiotherapy and/or surgery, hypercalcemia, pathologic fractures, and spinal cord compression.

PAIN

The most common symptom is pain. Pain may initially be either a well-localized focus of pain or a diffuse ache, typically worse at night and often not relieved by lying flat. Pain from extremity lesions tends to be well defined, in contrast to spine and pelvic sites, which produce vague, diffuse symptoms. Eventually the pain worsens with weight-bearing activity. Initially, pain results from the physical presence of tumor in the bone, with the release of inflammatory mediators, neuropeptides, and cytokines, as well as elevation of the intraosseous pressure due to tumor mass effect, and causes irritation of intraosseous and per-iosteal nerve endings.

Functional pain is caused by the mechanical weakness of the bone that can no longer support the normal stresses of daily activities. Mechanical pain is more typically associated with the focal bone loss within lytic lesions; however, radiographically blastic lesions may also weaken the bone through associated areas of osteolysis that are sufficient to compromise structural integrity. The development of functional pain may be a marker for bone at risk for fracture.

HYPERCALCEMIA

Hypercalcemia of malignancy is the most common metabolic complication of malignancy. In breast carcinoma, hypercalcaemia traditionally occurred in around 10% to 20% of patients.[40] However; the incidence has fallen markedly over the past two decades through the increasingly widespread use of bisphosphonates to prevent skeletal complications.

Hypercalcemia is mediated by up to three mechanisms in metastatic bone disease. Excessive osteolysis may release more calcium than the kidney can cope with. Advanced metastatic disease with severe bone destruction at multiple sites is the more frequent cause of this complication. In addition, tumors, particularly of squamous cell histology, may secrete parathyroid hormone-related protein (PTHrP) that will both mobilize skeletal calcium and stimulate the kidney to reabsorb calcium inappropriately. With a decrease in activity because of pain, disuse osteolysis will exacerbate the hypercalcemia.

With mild degrees of hypercalcemia, patients are often asymptomatic but, as the level of calcium rises, patients become progressively dehydrated and may develop fatigue, lethargy, nausea, vomiting, anorexia, and disorientation. Rehydration and initiation of bisphosphonate therapy will restore calcium levels to normal and repeated treatments may prevent recurrent episodes.

PATHOLOGIC FRACTURES

Pathologic fractures may be the first sign of metastatic bone disease. In breast carcinoma, as many as 35% of patients with bone disease experience a fracture. Breast, lung, renal, and thyroid cancer have been the most common cancers with pathologic fracture, but even in endocrine resistant prostate cancer, where osteoblastic metastases are typical, annual fracture rates in excess of 20% may be seen.

EVALUATION

PHYSICAL EXAMINATION

The physical examination is an important step in evaluating a patient with bone metastases. It may help make decisions regarding appropriate subsequent imaging studies. Firm palpation will often elicit the specific area of pain, with 'point tenderness' often pointing directly to the affected area in the bone. It is important to carefully evaluate the entire skeletal system with examination, as intense pain at one site often masks subjective reports of pain at other sites. A careful physical examination may reveal hidden pain in other locations. A thorough neurologic examination is also important, especially in patients with spinal metastases, to carefully evaluate for the possibility of spinal cord, cauda equina, or nerve root compression.

PLAIN RADIOGRAPHS

For symptomatic patients with point tenderness, plain radiographs are typically the most appropriate first imaging study. Such radiographs are easy to obtain and inexpensive. The appearance of bone metastases on x-rays varies depending on the primary site and histology. Most bone metastases from lung cancer and breast cancer appear osteolytic, whereas most from prostate cancer appear osteoblastic . However, nearly all bone metastases have components of both osteolytic and osteoblastic processes. The primary disadvantage of plain radiographs is that small lesions are rarely seen. Approximately 30% to 50% of the bone mineral content must be lost before the lesion will be apparent on x-rays.

NUCLEAR MEDICINE BONE SCAN

Technetium-99 m bone scintigraphy is the best method for screening patients at risk for bone metastases and is useful to evaluate the extent of metastatic disease in the bone. Bone scintigraphy is an indicator of osteoblastic activity. Because multiple myeloma is frequently purely osteolytic, bone scans are less useful for evaluating extent of disease in myeloma.

Bone scintigraphy is not specific for metastatic disease, and positive findings must often be confirmed using other imaging studies. A confirmatory study is especially important in a weight-bearing bone such as the proximal femur. False-positive readings may be seen in areas of arthritis, trauma, or Paget's disease. In addition, the osteoblastic activity in healing bone after treatment may give the appearance of

progressive disease. False-negative readings may occur in fast-growing, highly aggressive tumors, especially if these are mainly osteolytic.

CT SCANS

Computed tomography scans are more sensitive than plain radiographs, and may be better able to localize the lesion within the bone. However, CT scans are more expensive, more time-consuming, and may not be useful as a screening tool for skeletal metastases. The CT may be useful in defining the extent of cortical destruction and helping to assess the risk of a pathologic fracture . In addition, the CT scan may be used to guide needle biopsies to obtain a tissue diagnosis. CT scans have limited usefulness in detecting marrow involvement, but are much better than plain radiographs at evaluating soft tissue extension of disease.

MRI SANS

Magnetic resonance imaging is better than plain radiography or nuclear medicine bone scintigraphy at assessing the involvement of trabecular bone (red marrow), especially in the vertebral bodies. The findings are typically best seen on T1 contrast-enhanced images and short tau inversion recovery (STIR) images. Metastatic prostate cancer is visible as high-intensity lesions on the STIR images, and is visible prior to its appearance on bone scintigraphy . In addition, MRI scans are useful in determining the involvement of neurovascular structures. MRI scans are not useful as a screening tool for bone metastases. However, MRI scans may be more sensitive than bone scintigraphy in the vertebral body region . The sensitivity of MRI scanning has been reported as 91% to 100%, compared with 62% to 85% for bone scintigraphy . In addition, MRI images

can help distinguish whether a vertebral body compression fracture is from malignancy or from osteoporosis.

PET SCAN

Positron emission tomography scanning evaluates areas of increased metabolic activity, most commonly using the 18-fluorodeoxyglucose (FDG) isotope. These scans are useful in detecting osteolytic bone metastases, but are less sensitive for osteoblastic metastases. In addition, precise determination of the location of lesions is difficult with PET scans, but the use of simultaneous CT scans allows for much better localization of the abnormal FDG uptake . PET scans may be useful as a whole-body screening tool . Comparative studies have shown PET scans to be more sensitive than Tc-99 m scintigraphy or whole-body MRI scans in detecting bone metastases . There may be limitations in the sensitivity of PET scanning in certain areas such as the skull, where the intense physiologic uptake from the adjacent brain parenchyma may obscure small skull metastases.

THERAPEUTIC MODALITIES

Optimal management requires a multidisciplinary team. Medical treatment, radiation therapy, surgery, and bone targeted treatment with the bisphosphonates are combined depending on the biology of the disease, extent of the skeletal involvement, and the life expectancy of the patient.

PAIN MANAGEMENT

The majority of patients with bone metastases will experience pain during their disease course, and pain control can significantly improve their quality of life. Pain management may be achieved either by debulking disease using cytotoxic therapy or by symptomatic control with pharmacologic interventions. The use of a validated pain scale, gives the patient an opportunity to describe the severity of pain and the interference of pain with function in a manner that can be understood both by the patient and the physician . This also allows for comparisons of pain levels over time, to better assess the effectiveness of treatments.

WHO ANALGESIC LADDER

Pain control can be achieved in the majority of patients using the World Health Organization analgesic ladder.

- **Step I** uses nonopioid analgesics such as acetaminophen or non steroidal anti-inflammatory drugs;
- **step II** uses weak opioids such as codeine;
- **step III** uses strong opioids such as morphine.

These medications are increased as necessary until the patient is free of pain. Typically, the medications are given on a routine schedule (‘by the clock’) rather than waiting until a certain level of pain (‘on demand’).Using this schedule, 70% to 76% of patients will have good pain relief . Adjuvant medications such as gabapentin or amitriptyline may be added for neuropathic pain. Antianxiety or antidepressant medications may also be of benefit in selected patients.

RADIATION THERAPY

EFFECTS OF IRRADIATION ON BONE METASTASES

The main goal of palliative radiation treatment is the relief of pain or dysfunction caused by the bone metastases. For most patients who achieve pain relief after irradiation this lasts for two-thirds of their remaining life (Perez et al., 2004). **Adequate management of this group of patients is important for a number of reasons**:

- Bone pain secondary to metastases is the most common pain syndrome requiring palliative treatment in cancer patients;
- Patients with predominant bone metastases have longer duration of survival than patients with predominantly visceral metastases;
- Complications of bone metastases are common and produce high morbidity.

It is a common misconception that ionizing radiation will result in a decrease in normal ossification. External beam irradiation produces ossification in 65% to 85% of lytic metastases in unfractured bone. Some of the ossification may occur by heterotopic ossification within the lesion, however, in most cases, there is formation of mature organized bone in the healed lesion, seemingly by direct osteogenesis .

Radiation therapy has been reported to be effective in palliating painful bone metastases, with partial pain relief seen in 80% to 90% of patients, and complete pain relief in 50% of patients . These data are primarily from studies using physician

evaluation of pain. When patient evaluation of pain is used, pain improvement is seen in 60% to 80% of patients and complete pain relief is seen in 15% to 40% of patients .

The response to treatment depends on a large number of factors, including sex, primary site and histology, performance status, type of lesion (osteolytic vs. osteoblastic), location of the metastases, weight-bearing vs. non-weight-bearing site, extent of disease, number of painful sites, marital status, level of pain prior to treatment.

The effectiveness of the treatment also depends on the goal:

- palliation of pain,
- prevention of pathologic fracture,
- avoidance of future treatments,
- local control of the disease.

The doses required and volumes treated may be quite different for each of these goals.

When radiation travels through a living cell, it can damage the reproductive material in the cell directly and indirectly. Direct damage includes base deletions and single and double strand breaks in the DNA chain. Indirect damage occurs when radiation interacts with water molecules in the cell, releasing toxic free radicals. Repair of the damage is possible both in normal cells and cancer cells. Cancer cells have less capacity to repair damaged DNA, and hence a therapeutic ratio can be exploited.

Radiation can be delivered by an external beam of radiation directed at the site of interest, or in the form of radionuclide given intravenously as an inorganic soluble compound.

MECHANISM

Although treatment by external irradiation is successful in most patients the exact mechanism of action is unknown *(Hoskin, 2003).*

The doses used - though less than a radical course of radiotherapy - will cause high levels of tumour cell kill. There will therefore be a substantial reduction in the number of viable tumour cells within the radiation field and in due course this will result in shrinkage of the tumour bulk. Once the tumour cells are removed from the bone, osteoblastic repair will partially restore the integrity of the bone. Certain features of the response - like pain diminishing after a few sessions - suggest that tumour shrinkage itself is unlikely to account for the early period of pain relief seen.

The absence of a dose response relationship suggests that tumour shrinkage may not be that important since tumour shrinkage would not be expected with some of the very low single doses - down to **4 Gy** - which have been shown to cause pain relief. Furthermore there appears to be no obvious relationship between the radiosensitivity of the primary tumour and the response on pain. The striking clinical observation that some patients experience symptom relief within 24 hrs after the irradiation leads to the hypothesis that early reacting and very sensitive cells and the molecules they produce are involved in this answer.

Obvious candidate cells are the inflammatory cells that are largely present in the bone metastases micro-environment. Reduction by ionizing radiation of the inflammatory cells inhibits the release of chemical pain mediators and is probably responsible for the rapid reaction seen in some patients *(Mercadante, 1997)*.

Other candidate cells are the osteoclasts. Osteoclastic activity is an early and important response to tumour cell invasion. Recently it has been demonstrated that urinary markers of bone resorption (and thus osteoclastic activity) and pain relief after radiation treatment were correlated *(Hoskin et al., 2000)*.

Doses of **5 Gy** given to metatarsal bones of embryonic mice resulted in a selective elimination of the precursor cells for osteoclast formation *(Scheven et al., 1986)*. A clear dose-response relationship between the dose of ionizing radiation and the decrease in osteoclast number in vitro was observed *(Tsay et al., 1995)*. The calculated life span of the osteoclast in this study was 9 to 10 days. In a further investigation by the same group *(Tsay et al., 1999)* they showed that in the first weeks after exposure to moderate doses of ionizing radiation the number of osteoclasts did not diminish.

Other studies have shown that the influx of osteoclast precursor cells in vivo is effectively suppressed by ionizing radiation *(Comas, 1970)*. The resorbing activity of the osteoclast is less radiosensitive but can be inhibited, in a dose dependent way, by a dose of at least 5 Gy, as was established by morphometric and biochemical methods in a mouse embryo model *(Scheven et al., 1985)*.

Another indirect hint to the importance of the effect of ionizing radiation on the inflammatory cell / osteoclasts comes from work done with cyclooxygenase-2 (COX-

2) selective inhibitors. In a mouse model it was shown that the chronic administration of a COX-2 inhibitor attenuated the pain, reduced the tumour burden, osteoclastogenesis and bone destruction by more than 50% *(Sabino et al., 2002).* In the control mice the increased bone resorption was explained largely by the sarcoma-induced osteoclast proliferation and hypertrophy.

The COX-2 inhibitor reduced this proliferation and hypertrophy. Prostaglandins (particularly PGE2) modulate the osteoclast function and by reducing the production of PGs there is a reduction in proliferation and hypertrophy of the osteoclasts. Besides the analgesic effect of ionizing radiation and bisphosphonates a secondary goal is the re-ossification of the osteolytic lesion.

THE DOSE, TARGET VOLUME AND FRACTIONATION

The target volume for primary irradiation of a bone metastases is defined by the anatomical borders of the bone marrow compartments inside the bone. The margins are adjusted for motion uncertainty depending on the site of the bone metastases.

All of the studies were randomized but blinding was often impossible. Radiotherapy, in these trials produced complete pain relief at one month in 25% of the patients. A relief of at least 50% at one month was achieved in 41% of patients. Analyzing the various fractionation schedules there were no significant overall differences found. All trials taken together showed that half of the patients who achieved complete relief took four weeks to achieve it.

With 43 different fractionation schedules, it was impossible to obtain the strength of evidence needed to show if there is a difference in efficiency between a single

fraction and multiple fractions radiation treatment for pain relief. Hypo fractionated schedules result in somewhat more acute toxicity. The whole of the available evidence suggests however that an increase in the number of fractions does not translate in an increase of the therapeutic benefit.

RESULTS OF PUBLISHED CONTROLLED CLINICAL TRIALS ON DOSE AND FRACTIONATION FOR THE PALLIATION OF PAINFUL BONE METASTASES
(UPDATE JAN 2004)

Reference	Comparison	Number of patients Randomized	Primary endpoint p-value
Tong 1982	A: 20 Gy in 5 fractions vs B: 40.5 Gy in 15 fractions	266	n.s.
Madsen 1983	A: 20 Gy in 2 fractions vs B: 24 Gy in 6 fractions	57	n.s.
Price 1986	A: 8 Gy in 1 fraction vs B: 30 Gy in 10 fractions	288	n.s.
Okawa 1988	A: 20 Gy in 10 fractions vs B: 22.5 Gy in 5 fractions vs C: 30 Gy in 15 fractions	80	n.s.
Hirokawa 1988	A: 25 Gy in 5 fractions vs B: 30 Gy in 10 fractions	128	n.s.
Cole 1989	A: 8 Gy in 1 fraction vs B: 24 Gy in 6 fractions	29	n.s.
Reference	**Comparison**	**Number of patients Randomized**	**Primary endpoint p-value**
Kagei 1990	A: Single fraction vs B: multiple fractions	27	n.s.
Hoskin 1992	A: 4 Gy in 1 fraction vs B: 8 Gy in 1 fraction	270	n.s.
Porter 1993	A: < 10 Gy in 1 fraction vs B: 20 Gy in 5 fractions vs C: 30 Gy in 10 fractions	125	n.s.
Rasmusson 1995	A: 15 Gy in 3 fractions vs B: 30 Gy in 10 fractions	217	n.s.
Niewald 1996	A: 20 Gy in 5 fractions vs B: 30 Gy in 15 fractions	97	n.s.
Gaze 1997	A: 10 Gy in 1 fraction vs B: 22.5 Gy in 5 fractions	265	n.s.

The **RTOG trial 97-14** is an example of a large and recently reported trial that had as objectives:

1. to determine whether 8 Gy in a single fraction provides equivalent pain relief compared to 30 Gy in 10 fractions for patients with painful bone metastases,
2. to determine the duration of pain relief,
3. to determine the effect on quality of life measures;
4. to determine the incidence of pathologic fracture and
5. to determine cost-effectiveness of therapies in terms of cost/quality adjusted life years.

Preliminary results *(Hartsell et al., 2003)* were presented in abstract form at the ASTRO meeting 2003 and confirm the data from the other trials: there was no difference in pain relief when comparing both treatment regimens.

We can conclude that single fraction radiation treatment compared to multiple-fraction radiation treatment provides equal palliation and quality of life and based on a Dutch study *(Van den Hout et al., 2003)* single fraction treatment has a lower medical and societal cost. Therefore single fraction radiation treatment is the treatment of choice for cancer patients with painful, uncomplicated bone metastases.

In an effort to investigate the place and **role of single fraction RT** in the treatment of painful bone metastases, researchers from the Royal Marsden Hospital, Sutton, UK conducted three consecutive studies.

In their first study [6,] single dose of 8 Gy was found to be as effective as multifraction regimen consisting of ten daily fractions of 3 Gy, considered by many as "standard" regimen for treating bone metastases: no difference was found in CR rate, speed of onset or duration of pain relief between the two regimens. Thus, for the first time, it was shown that single fraction RT can be considered effective and safe option in palliation of bone metastases. Since no effect of histology was found in that study [6] and single doses lower than 8 Gy could have also been effective as the one investigated. Two additional studies investigated the efficacy of a single fraction RT in palliation of bone metastases in last decade.

REIRRADIATION

As effective systemic treatment and better supportive care result in improved survival, certain subsets of patients with bone metastases have longer life expectancies than before. An increasing number of patients outlive the duration of the benefits of initial palliative radiotherapy for symptomatic bone metastases, requiring reirradiation of the previously treated sites. Additionally, some patients fail to respond initially but may benefit from reirradiation. Among the radiation trials comparing single versus multiple

fractionation schemes, reirradiation rates varied from 11% to 42% following single-fraction and 0% to 24% following multiple-fraction schedules.

There are at least three scenarios of 'failure' where reirradiation may be considered. Response to reirradiation may be different for each of these scenarios:

- No pain relief or pain progression after initial radiotherapy,
- Partial response with initial radiotherapy and the hope to achieve further pain reduction with more radiotherapy, and
- Partial or complete response with initial radiotherapy but subsequent recurrence of pain.

In summary, available data support the reirradiation of sites of metastatic bone pain following initial irradiation, particularly where this follows an initial period of response. There is also limited evidence that a proportion of nonresponders would respond to reirradiation. However, there remains a small group of patients who appear to be nonresponsive to any amount of palliative radiotherapy. Although the data do support the clinical practice of reirradiation, the preferred dose fractionation at time of reirradiation is unknown. A phase III international randomized trial of single versus multiple fractions for reirradiation of painful bone metastases is ongoing and will help address the practical questions facing radiation oncologists when providing palliative radiation services.

HEMIBODY RADIATION THERAPY

Hemibody irradiation (HBI), or wide-field radiation therapy, refers to the technique of treating a large portion of the body with external-beam irradiation. Although the term hemibody irradiation is used, typically the field does not cover half of the body, but more accurately treats about one third of the body. The treatment has been used for palliation of symptoms and as an adjuvant to prevent the development of new bone metastases. The treatment for palliation of pain is most useful in patients who have diffuse, widespread bone metastases.

The treatment volumes have been divided into upper, middle, and lower HBI. The fields for upper HBI cover the thorax and abdomen from the neck to the top of the iliac crests. For midbody HBI, the fields include the abdomen and pelvis from the diaphragm to the ischial tuberosities, and for lower HBI treatment, the field borders are from the top of the pelvis to the inferior portion of the femurs.

RTOG 78-10 was a dose-searching prospective protocol evaluating the maximum tolerated dose (MTD) for single-dose HBI [40]. The MTD for middle and lower hemibody treatment was 8 Gy. The MTD for the upper HBI was 6 Gy if the lung dose was uncorrected and 7 Gy if lung corrections were used.

LITERATURE REVIEW

Most of the studies using high-dose single fraction RT in the treatment of painful bone metastases in the last three decades with a total of more than 1500 patients are given .

STUDIES USING SINGLE -FRACTION RT

AUTHOR(REF)	YEAR	RT DOSE(Gy)	OVER ALL RESPONSE RATE(%)
Vargha *et al.*	1969	18	90
Penn *et al.*	1976	15	89
Hendricksen *et al.*	1976	9	88
Jensen andRoesdahl *et al.*	1976	7.5	85
Price *et al.*	1986	8	73
Barak *et al.*	1987	6 8 10	71
Price *et al.*	1988	4	43
Karstens *et al.*	1989	4	45
Hoskin *et al.*	1992	4 8	44 69
Uppelschoten *et al.*	1995	6	88
Jeremic *et al.*	1998	4	59
		6	73
		8	78
Metin Guden *et al.*	2002	6	88.7

If we exclude the two initial studies that used extremely high single doses of 18 Gy and 15 Gy, respectively (and produced overall response rates not very different from those obtainable with 6–10 Gy), all other used single fractions in the range 4–10 Gy. Although different means of evaluation of patients response to treatment have been used, overall response rates seem to follow the pattern as we have observed it during current study.

STUDIES USING SINGLE FRACTION 6Gy RT IN PAINFUL BONE METASTASES

Barak et al [12] in 1987 reported on a study that evaluated the efficacy of high single doses (6,8, and 10 Gy, respectively) of radiation on pain relief. Among the 94 evaluable patients, 12 (13%) patients received 6 Gy, 66 (70%) received 8 Gy, and 16 (17%) patients received 10 Gy. Response to radiation was 71% which lasted up to 6 months in 37% patients and up to 12 months in 21% patients in 6Gy arm. Most patients who achieved pain relief did so in the first week post-RT. There were no differences in pain relief among the patients with different metastatic sites treated or with different histologies.

Uppelschoten et al [41] in 1995 reported on the use of a single fraction RT of 6 Gy in palliation of bone metastases in 170 patients. Pain relief was achieved in 88% patients with CR observed in 39% patients. The pain relief was observed in the first week post-RT in 58% patients.

Jeremic et al [42] in 1998 reported on a study that evaluated the efficacy of high single doses (4,6, and 8 Gy, respectively) of radiation on pain relief. Among the 327 evaluable patients, 109 patients received 4 Gy, 108 received 8 Gy, and 110 patients received 8 Gy. Response to radiation was 59 % in 4Gy arm, 73% in 6Gy arm and 78% in 8Gy arm. The pain was observed in the first week post-RT in 19.6% patients.

Metin Guden et al [43] in 2002 reported on the use of a single fraction RT of 6 Gy in palliation of bone metastases in 62 patients. Pain relief was achieved in 88.7% patients with CR observed in 37.1% patients. The pain relief was observed in the first week post-RT in 53% patients.

Of additional importance is the fact that series using single fraction of 6 Gy produced overall response rates of approximately 70–75% [as high as 88% in a series of Uppelschoten et al and 88.7% in Metin Guden et al]. Since single fraction RT of 6 Gy did not produce results inferior to that obtained with 8 Gy, further studies are needed to get more informations regarding optimal single fraction RT in the treatment of painful bone metastases.

There are no sufficient data to support a clear statement concerning dose-response relationship and response duration beyond 3 months for single fraction RT in the treatment of painful bone metastases.

AIM OF THE STUDY

The present study aims at comparing pain relief obtained with (trial arm) 6Gy single fraction radiotherapy against 8Gy single fraction radiotherapy (control arm) in painful bone metastases.

The study also aims at comparing the Toxicity , Infield Events involved with the above two therapeutic protocols.

MATERIALS AND METHODS

STUDY PERIOD : From July 2008 up to June 2009

ELIGIBITY CRITERIA: sixty patients with painful bone metastases who satisfied the following eligibility criteria were included in this study.

1. Age > 18 years.
2. Genders: Both Male and Females
3. Performance status: ECOG 0 – 3.
4. Histological or cytological diagnosis of malignancy associated with radiological evidence of painful bone metastases from any primary tumor site.
5. If patients with two sites of pain requiring separate treatment are to be entered, the same randomized treatment option will be used for both sites, but response at each site will be scored and analyzed separately.
6. Anticipated remaining life of at least 12 weeks (3 months) .
7. Pain due to bone metastases.
8. Evaluable pain history.
9. Informed consent

EXCLUSION CRITERIA :

1. Primary histology myeloma .
2. Sites of previous RT or previous radioisotope treatment.
3. Bisphosphonate treatment.
4. Previous surgical intervention at the same locus.
5. Complicated bone metastases (pathological fractures, metastatic spinal cord compression) conditions or circumstances, which may interfere with treatment or follow-up.

ARMS OF THE TRIALS:

ARM 1: **TRIAL ARM : 6 Gy single fraction; mandate first treatment** ,if moderate or severe pain persists or recurs (as measured by categorical pain scale or VAS greater than 50 mm), **>4 weeks after initial RT,** retreat with 6 Gy single fraction; **second retreatment** is optional if moderate or severe pain recurs (as measured by categorical pain scale or VAS greater than 50 mm),

ARM 2 :CONTROL ARM : 8 Gy single fraction; mandate first treatment if moderate or severe pain persists or recurs (as measured by categorical pain scale or VAS greater than 50 mm), **>4 weeks after initial RT,** retreat with 8 Gy single fraction; **second retreatment** is optional if moderate or severe pain recurs (as measured by categorical pain scale or VAS greater than 50 mm),

PRETREATMENT WORK - UP

1. Complete clinical examination.
2. Complete blood counts including Hemoglobin assay.
3. Biochemical investigations to assess renal function.
4. Histopathological documentation.
5. Chest X-ray.
6. Skeletal survey / Bone scan.

RADIOTHERAPY DETAILS:

The radiation is given by Telecobalt machine (Theratron Phoenix).

Direct fields are used to treat vertebral column and parallel opposed fields are used to treat pelvis, hip, and long bones. Doses are specified at 5 cm depth for spine fields and to the midplane when parallel opposed fields are used. Rib metastases are treated with one direct field, dose specification on the dose maximum.

When treating lower thoracic or lumbar-sacral or pelvic/hip field, inevitably a varying volume of gastrointestinal tract was included in the treatment volume. Measures were taken to prevent acute side effects such as nausea and vomiting or radiation-induced enteritis by placing adequate blocking and administering appropriate medication (e.g. antiemetics).

Tumor doses of 6Gy, 8Gy are given in a single fraction to patients in the two treatment groups.

RADIOBIOLOGICAL COMPARISON

RELATIVE EFFECTIVENESS (RE)

It denotes the relative effectiveness per unit dose for fractionated beam therapy

RE = 1+ d/ (α/β) d- Dose per fraction, α damage (irrepairable), β damage (repairable).

High α/β - characteristic of cell with little repair capability

e.g. tumour cells [from 5 - 20 Gy]

Low α/β - characteristic of cell with high repair potential

e.g.late responding normal tissue [1-4 Gy]

CALCULATION OF RELATIVE EFFECTIVENESS:

Early reacting tissue (α/β = 10 Gy,)

Late reacting tissue (α/β = 3 Gy)

RELATIVE EFFECTIVENESS (RE) FOR 8 GY

- Early reacting tissue **(REe) = 1+ 8/ 10 = 1.8**
- Late reacting tissue **(RE l) = 1+ 8/3 = 3.6**

RELATIVE EFFECTIVENESS (REF) FOR 6 GY

- Early reacting tissue **(REe) = 1+ 6/ 10 = 1.6**
- Late reacting tissue **(RE l) = 1+ 6/3 = 3.0**

BIOLOGICAL EFFECTIVE DOSE :

BED is the product of the total dose and the relative effectiveness.

BED = Nd [1+d/(α/β)] N – Number of fraction , d- Dose per fraction

CALCULATION OF BED

BIOLOGICAL EFFECTIVE DOSE FOR 8 GY

- BED for Early reacting tissue = 8 x 1.8 = 14.4Gy
- BED for late reacting tissue = 8 x 3.6 = 28.8 Gy

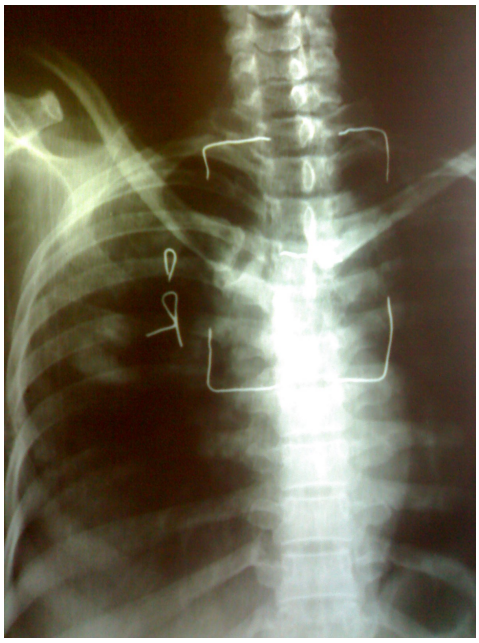
BIOLOGICAL EFFECTIVE DOSE FOR 6 GY

- BED for Early reacting tissue = 6 x 1.6 = 9.6Gy
- BED for late reacting tissue = 6 x 3 = 18 Gy

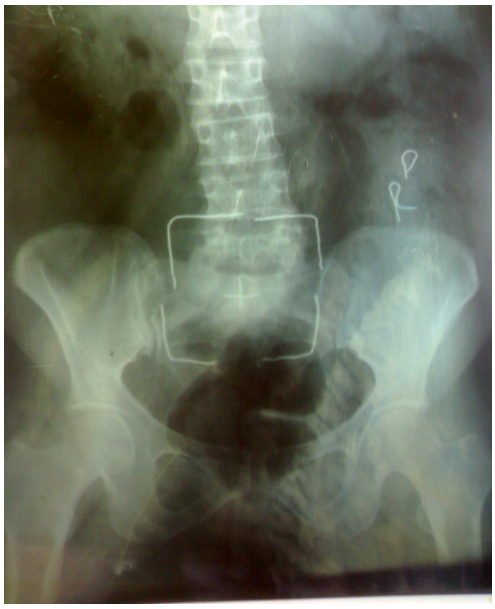
BED	8Gy - SINGLE #	6Gy - SINGLE #
Early reacting tissue	14.4 Gy	9.6 Gy
Late reacting tissue	28.8 Gy	18 Gy

TREATMENT VERIFICATION : X – ray simulation.

D2,D3,D4 VERTIBRAL METASTSES



L5 VERTIBRAL METASTSES



PAIN ASSESSMENT

On the day of treatment planning or performing the irradiation, responsible radiation oncologist met the patient accompanied by at least one family member/relative judged to be the person that would spend most of the time with the patient and the pain chart was explained. The initial pretreatment assessment was made by the patient at this stage. Followed by pain assessment performed **weekly** i.e. 1,2,4, weeks after completion of radiation and again on **eighth week** after radiation.

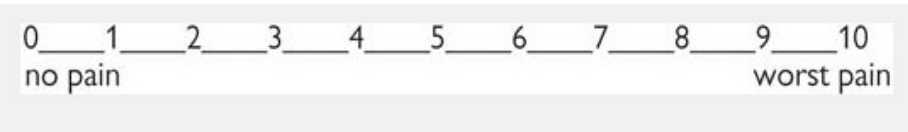
PAIN SCALE

Visual analogue scales (VAS)

The VAS is an unmarked line with extremes marked as no pain and worst pain. Patients are asked to mark the point in the line that describes their pain.

Categorical numerical rating scales (NRS) -- 11 point scale

The NRS is similar to the VAS but uses numbers or gradations that indicate the severity of the pain experience.



Categorical verbal rating scales (VRS) -- 4 point scale

A VRS involves a sequence of words describing different intensity levels of pain such as: 0- None, 1-3 Mild, 4-7 Moderate, 8-10 Severe.

FOLLOW UP PERIOD : minimum 6 month.

The primary endpoint is clinically significant pain relief in the first six months of follow-up evaluated with the IAEA (International Atomic Energy Agency) pain measurement score measuring pain severity and pain frequency.

The pain score is obtained by multiplying pain severity by pain frequency.

Pain severity is classified as 0 (none), 1 (mild), 2 (moderate) and 3 (severe).

Pain frequency is classified as 0 (none), 1 (occasional = less than daily), 2(intermittent= at least once daily) and 3 (constant).

Analgesic use is recorded before and after treatment**.**

The narcotic score is obtained by multiplying drug severity by drug frequency.

Drug severity is classified as 0 (none given), 1 (analgesic), 2 (mild narcotic)and 3 (strong narcotic).

Drug frequency is classified as 0 (none given), 1 (less than once daily), 2 (once daily) and 3 (twice or more daily).

RESPONSE ASSESSMENT:

Complete response (CR) is defined as a pain score of 0.

Partial response (PR) is defined as a reduction of score >2 or a >50% reduction of the pre-treatment pain score. Response is classified as positive if no increase in analgesic use was evident.

Stable disease (SD) is defined by an unaltered pain score

Progressive disease (PD) by an increase in the score >2 or a >50% increase in the pre-treatment pain score.

TOXICITY ASSESSMENT:

Radiotherapy Oocology Group (RTOG) Toxicity Criteria **.**

Upper GI – RTOG acute morbidity scoring criteria

Grade	Change
0	No change
1	Anorexia with 5% weight loss from base line. Nausea, abdominal pain not requiring medication.
2	Anorexia with 15% weight loss from base line. Nausea, abdominal pain,vomiting requiring medication.
3	Anorexia with >15% weight loss from base line requiring NG tube or parenteral support. Severe abdominal pain despite medication. Haematemesis, melena or abdominal distention

4	Ileus, sub-acute obstruction, perforation, GIT bleeding requiring transfusion. Abdominal pain requiring tube decompression or bowel diversion.

Lower GI including pelvis - RTOG acute morbidity scoring criteria

Grade	**Change**
0	No change
1	Increased frequency or change in bowel habits, rectal discomfort not requiring medication.
2	Diarrhea requiring para-sympatholytic drug. Mucous discharge, rectal / abdominal pain requiring medication.
3	Diarrhea requiring paraenteral support, mucous or bloody discharge requiring sanitary pads.
4	Acute / subacute obstruction, fistulae or perforation, GIT bleeding Requiring transfusion. Abdominal pain, tenesmus requiring tube decompression or bowel diversion.

RESULTS

Out of the 1802 Cancer patients treated between July- 2008 and June- 2009 in our Radio therapy dept, 85 (4.7%) presented with bone metastases. A total of 60 patients with single and multiple bone metastases who met the eligibility criteria entered into this study at the time they developed their first painful bone metastases. Any subsequent metastases and its treatment was not included in the study and every effort was made to distinguish the pain that first occurred from that of any subsequent metastatic site, even in the cases of pain recurrence at the original site in the presence of painful second or any other additional metastatic bone site.

PATIENTS CHARACTERISTIC

1. NUMBER OF CASES

Arms	Number of cases
6Gy ARM (TRIAL ARM)	30
8Gy ARM (CONTROL ARM)	30

2.AGE DISTRIBUTION

In this study in trial arm (6Gy) we enrolled patients between 21-70 years of age. The median age of the patients in 6Gy arm was 53 years and most (40%) of the patients were in the 5^{th} decade of life. In control arm (8Gy) we enrolled patients between 31-70 years of age. The median age of the patients in 6Gy arm was 55 years and most (46%) of the patients were in the 5^{th} decade of life.

Age Group(Years)	6Gy Arm	8Gy Arm
21 - 30	1(3%)	-
31 - 40	3(10%)	3(10%)
41 - 50	6(20%)	7(23%)
51 - 60	12(40%)	14(46%)
61 - 70	8 (26%)	6(20%)

3. SEX DISTRIBUTION

SEX	6Gy Arm	8Gy Arm
Male	11(37%)	9 (30%)
Female	19(63%)	21(70%)

In both arms female patients are more than male patients. Male : female ratio is 1:1.7 in 6Gy arm and 1:2.3 in 8Gy arm.

4.PRIMARY TUMOR SITES

In this study bone metastases predominatly from carcinoma breast(>50%) and lung cancer(>26%) in both arms.

SITE	6Gy Arm	8Gy Arm
BREAST	17 (57%)	16 (54%)
LUNG	8 (26%)	9 (30%)
PROSTATE	2 (7%)	3 (10%)
PNET	2 (7%)	1(3%)
KIDNEY	1 (3%)	--
THYROID	--	1(3%)

5.METASTATIC BONE SITES

SITE	6Gy ARM	8Gy ARM
CERVICAL SPINE	1	1
DORSAL SPINE	17	18
L-S SPINE	13	12
PELVIS/HIP	1	3
FEMUR	4	3
HUMERUS	3	2
METATARSAL	1	-
STERNUM	1	-

In both study groups dorsal spine and lumbo - scaral spine are more commonly involved**.**

6.INITIAL PAIN SCORE

PAIN SCORE	6Gy ARM	8Gy ARM
MILD	5 (17%)	5(17%)
MODERATE	13 (43%)	11(37%)
SEVERE	12 (40%)	14(46%)

In this study we included 13% of the patients had mild pain and 83% of patients in each group had moderate to severe pain, a finding consistent with the reports in the literature.

7. INITIAL ANALGESIC REQUIRMENT

ANALGESIC DRUGS	6Gy ARM	8Gy ARM
ANALGESIC (NSAID)	5 (17%)	4(13%)
MILD NARCOTIC	23 (76%)	24 (80%)
STRONG NARCOTIC	2 (7%)	2 (7%)

In this study the trial (6Gy) arm 17% of patients on NSAID drugs, 76% of patients on mild narcotic drugs i.e. Tramadol and 7% on strong narcotic drug i.e. Morphine. In control (8Gy) arm 13% of patients on NSAID drugs, 80% of patients on mild narcotic drugs i.e. Tramadol and 7% on strong narcotic drug i.e. Morphine before strating the radiotherapy treatment.

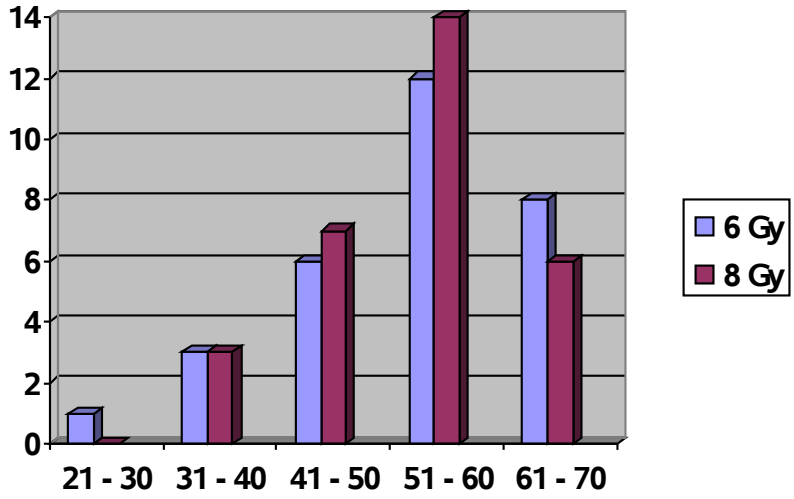
There were no differences among the two treatment groups in any of these characteristics. No difference was found among the two treatment groups regarding initial pain score and the use of analgesics.

8.TREATMENT FIELDS

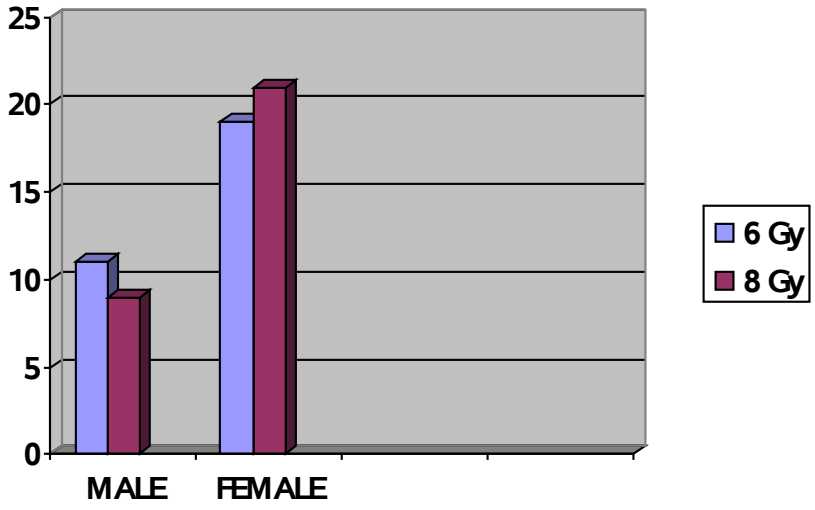
NO. OF FIELDS	6Gy ARM	8Gy ARM
ONE	12(40%)	10(33%)
TWO	15(50%)	17(67%)
THREE	3(10%)	3(10%)

In trial arm (6Gy) 50% of patients were treated with two fields and 40% with one fields. In control arm 67% of patients were treated with two fields and 33% with one fields. 10% of the patients were treated with three fields in both arms.

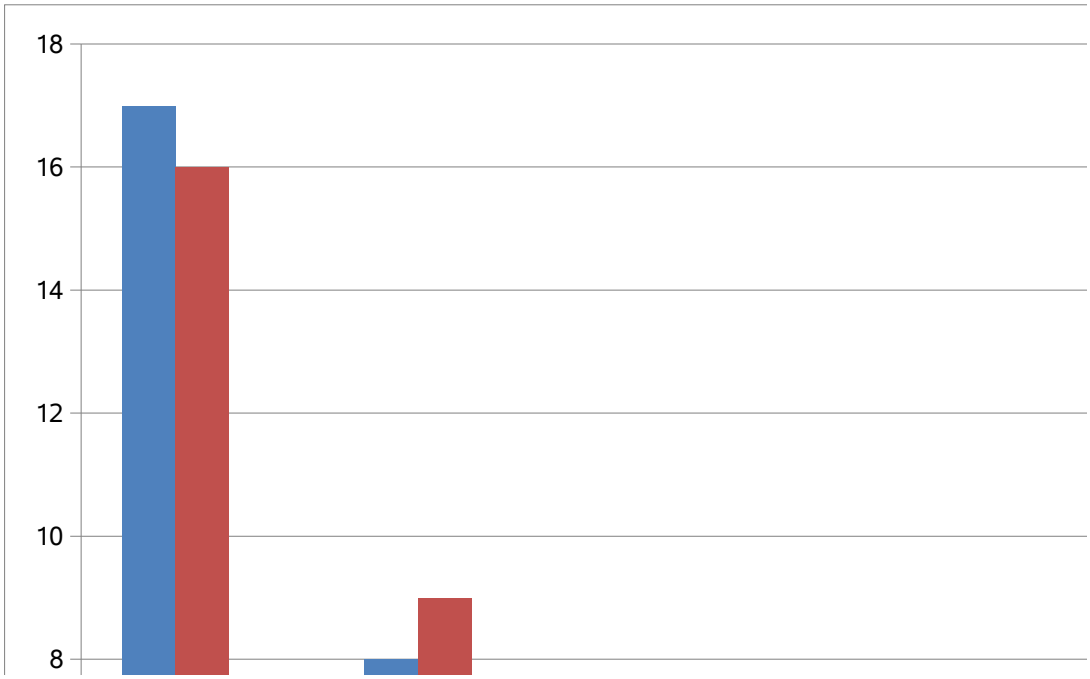
AGE DISTRIBUTION (YEARS)



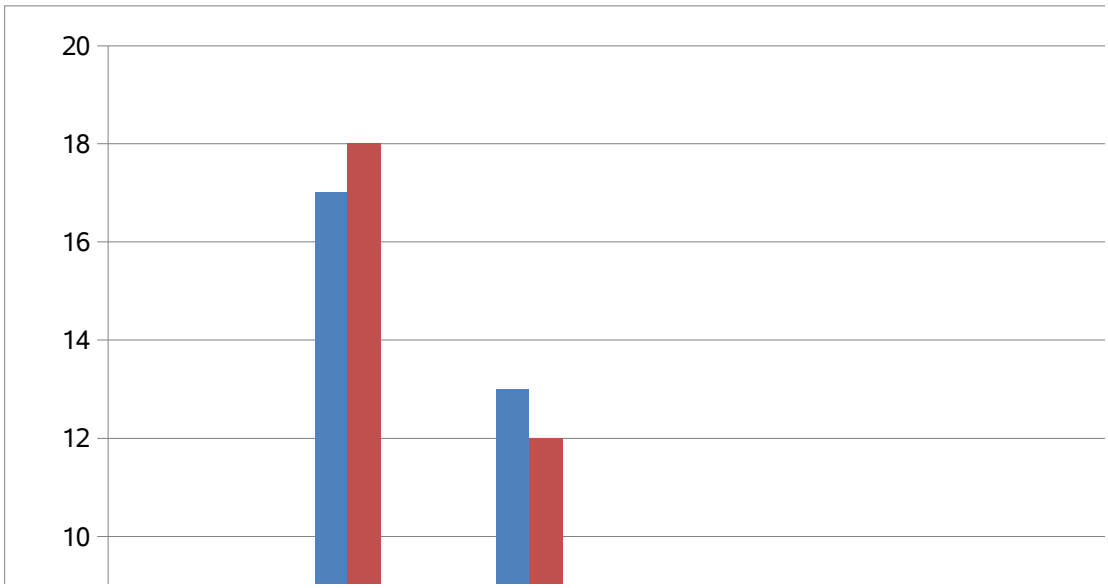
SEX DISTRIBUTION



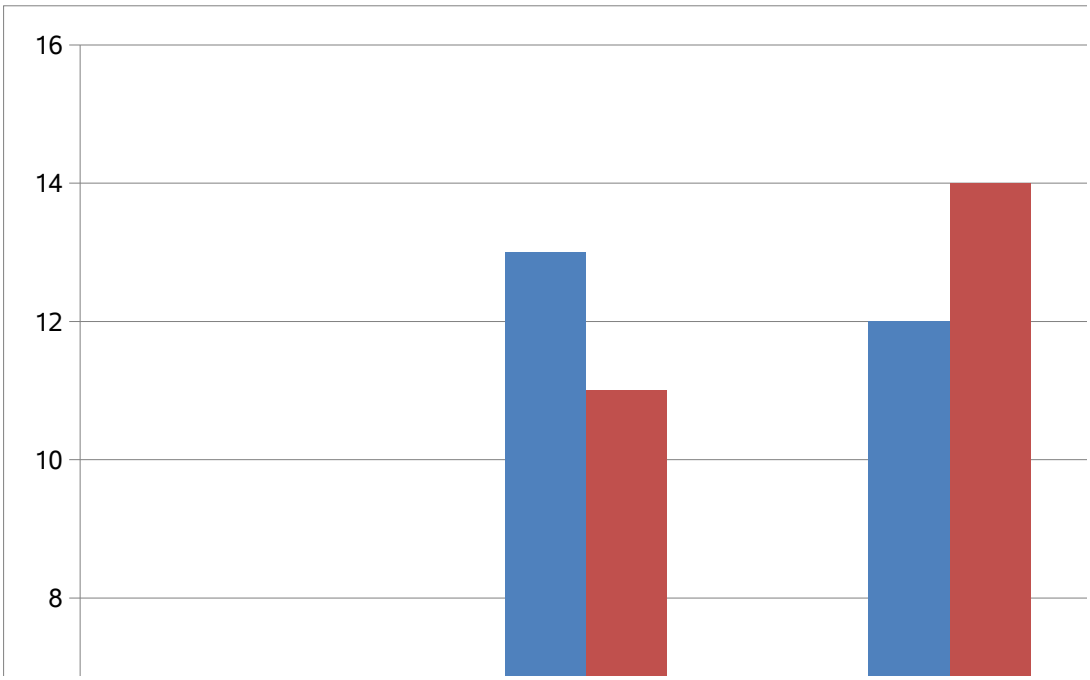
PRIMARY TUMOR SITES



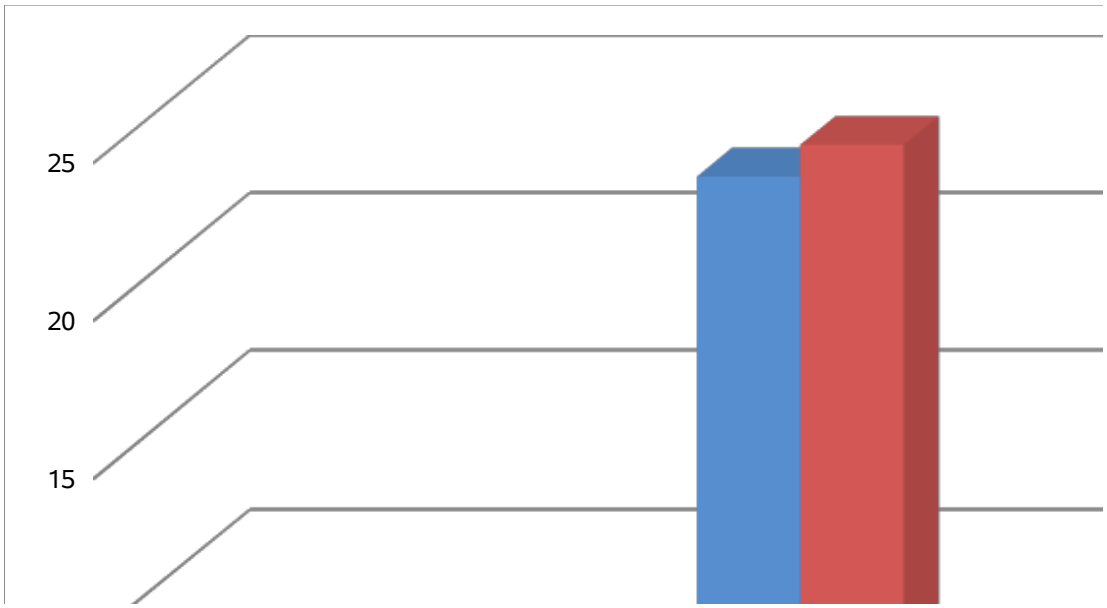
METASTATIC BONE SITES



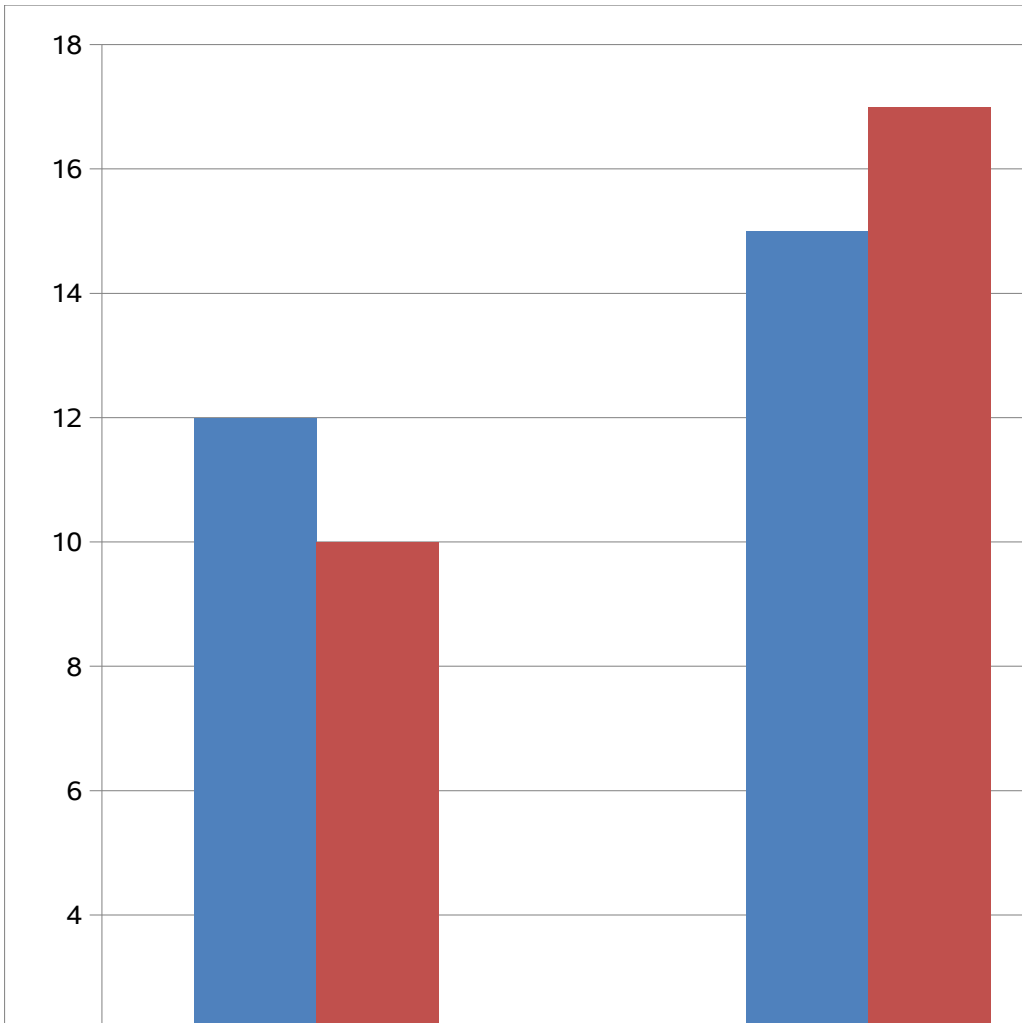
INITIAL PAIN SCORE



INITIAL ANALGESIC REQUIRMENT



TREATMENT FIELDS



CLINICAL RESPONSE ASSESSMENT

Although our initial aim was to monitor treatment response for at least 24 weeks and as long as possible thereafter, due to the fact that many patients died after 8 weeks from their RT, we used response that occurred up to 8 weeks post-RT to evaluate

treatment response, since all 60 patients survived that period and fully returned for study evaluation.

9.RESPONSE ASSESSMENT OF 6Gy ARM

RESPONSE	WEEK 1	WEEK2	WEEK 4	WEEK 8
PARTIAL RESPONSE	1	2	4	9 (30%)
COMPLETE RESPONSE	0	3	8	13 (43.3%)
OVER ALL RESPONSE	1	5	12	22 (73.3%)

The analysis of clinical response at the end of the 8th week revealed the following:

a. PARTIAL CLINICAL RESPONSE – In this arm a total of 9 patients attained partial clinical response i.e. 30% of all trial patients.
b. COMPLETE CLINICAL RESPONSE – A total of 13 patients attained complete clinical response i.e. 43.3% of all trial patients.
c. OVER ALL CLINICAL RESPONSE -- In this arm a total of 22 patients attained overall clinical response i.e.73.3% of all trial patients.

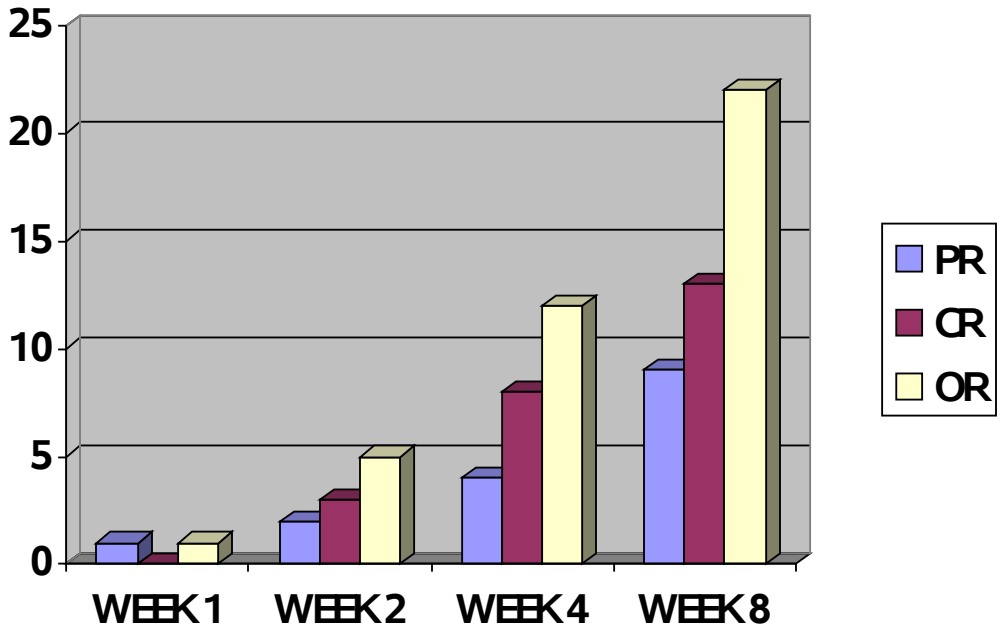
10.RESPONSE ASSESSMENT OF 8Gy ARM

RESPONSE	WEEK 1	WEEK 2	WEEK 4	WEEK 8
PARTIAL RESPONSE	1	3	4	9 (30%)
COMPLETE RESPONSE	0	3	9	14 (46.6%)
OVER ALL RESPONSE	1	6	13	23 (76.6%)

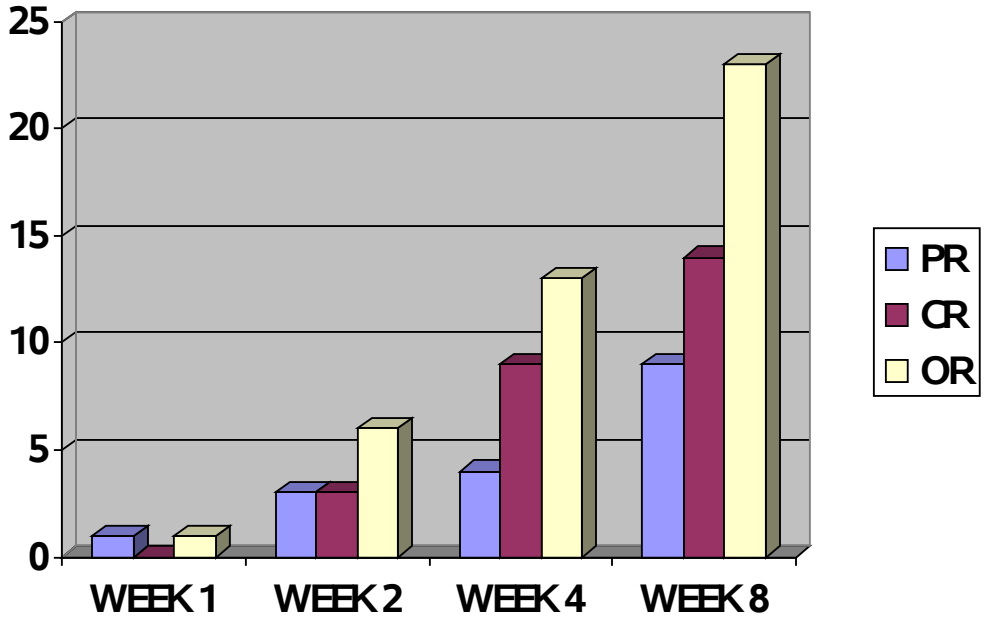
The analysis of clinical response at the end of the 8th week revealed the following:

a. PARTIAL CLINICAL RESPONSE – In this arm a total of 9 patients attained partial clinical response i.e. 30% of all trial patients.
b. COMPLETE CLINICAL RESPONSE – A total of 14 patients attained complete clinical response i.e. 46.6% of all trial patients.
c. OVER ALL CLINICAL RESPONSE -- In this arm a total of 2 patients attained overall clinical response i.e.76.6% of all trial patients.

RESPONSE ASSESSMENT OF 6Gy ARM



RESPONSE ASSESSMENT OF 8Gy ARM



Although we scored response at 12 and 24 weeks post-RT, we found it impossible to present meaningfully. Both CR and overall response rates rose sharply at 12 (and 24) weeks post-RT, and were 95–100% for overall response rates at 24 weeks post-RT which were due to the death of many patients after 8 weeks post-RT, especially non-responders.

DURATION OF RESPONSE IN RESPONDERS:

We analyzed mean duration of response in responders in both treatment groups. We found that the trial arm(6Gy) patients have 21.3 mean weeks of pain free periods. The control arm(8Gy) patients have 25.1 mean weeks of pain free periods.

11. DURATION OF RESPONSE IN RESPONDERS

ARMS	N	MEAN(WEEKS)	SD	P value
6Gy ARM	22	21.3	8.6	
8Gy ARM	23	25.1	10.2	0.18

No difference was found between the two treatment groups regarding the duration of response in responders whose mean values ranged from 21 to 25 weeks.

TIME TO THE FIRST OCCURRENCE OF ANY PAIN RELIEF:

We also analyzed the first occurrence of any pain relief in responders in both treatment groups. We found that the trial arm(6Gy) patients have any pain relief at 4.36 weeks(mean). The control arm (8Gy) patients have any pain relief at 4.22 mean weeks .

12.TIME TO THE FIRST OCCURRENCE OF ANY PAIN RELIEF

ARMS	N	MEAN(WEEKS)	SD	P value
6Gy ARM	22	4.36	1.9	
8Gy ARM	23	4.22	1.9	0.80

However, when using time to the first occurrence of any pain relief as an endpoint, no difference between 6Gy arm and 8Gy arm.

INFLUENCE OF HISTOLOGY ON RESPONSE

In order to investigate influence of histology on response, we evaluated response to treatment according to various histologies. There was no difference between the various groups of patients, except that patients having tumors considered such as breast, and prostate, tended to have higher overall response rates than those having tumors of the lung, kidney, or PNET, but the difference was not significant. Due to a small patient numbers in different subgroups compared, any further analysis would be meaningless.

13.OVERALL RESPONSE AT 8 WEEKS ACCORDING TO HISTOLOGY

PRIMARY TUMOR SITES

SITE	BOTH ARMS	6Gy ARM	8Gy ARM
BREAST	26 /33 (78%)	13 /17 (76%)	13/ I6 (81%)
LUNG	11 /17 (64.7%)	5 /8 (62.5%)	6/9 (66.6%)
PROSTATE	4 /5 (80%)	2/2 (100%)	2/ 3 (66.6%)
PNET	2 /3 (66.6%)	1 /2 (50%)	1 /1 (100%)
KIDNEY	1 /1 (100%)	1 /1 (100%)	--
THYROID	1/1 (100%)	-	1 /1 (100%)

INFLUENCE OF METASTATIC SITE ON RESPONSE

We also analyzed the influence of metastatic bone site in overall response rate at 8 weeks. It revealed metastatic site had no influence on the overall response rate up to 8 weeks post-RT and patients with different metastatic sites treated did not have different response rates.

14.OVERALL RESPONSE AT 8 WEEKS ACCORDING TO METASTATIC BONE SITES

SITE	BOTH ARMS	6Gy ARM	8Gy ARM
CERVICAL SPINE	2 /2 (100%)	1 /1 (100%)	1 /1 (100%)
DORSAL SPINE	27 /35 (77%)	13 /17 (76.4%)	14 /18 (77.7%)
L-S SPINE	18 /25 (72%)	9/ 13 (69%)	9 /12 (75%)
PELVIS / HIP	3 /4 (75%)	1/1 (100%)	2/3 (66.6%)
FEMUR	5/7 (71.4%)	3 /4 (75%)	2/3 (66.6%)
HUMERUS	4/5 (80%)	2/3 (66.6%)	2/2 (100%)
METATARSAL	1 /1 (100%)	1/1 (100%)	-
STERNUM	1/1 (100%)	1 /1 (100%)	-

RETREATMENT

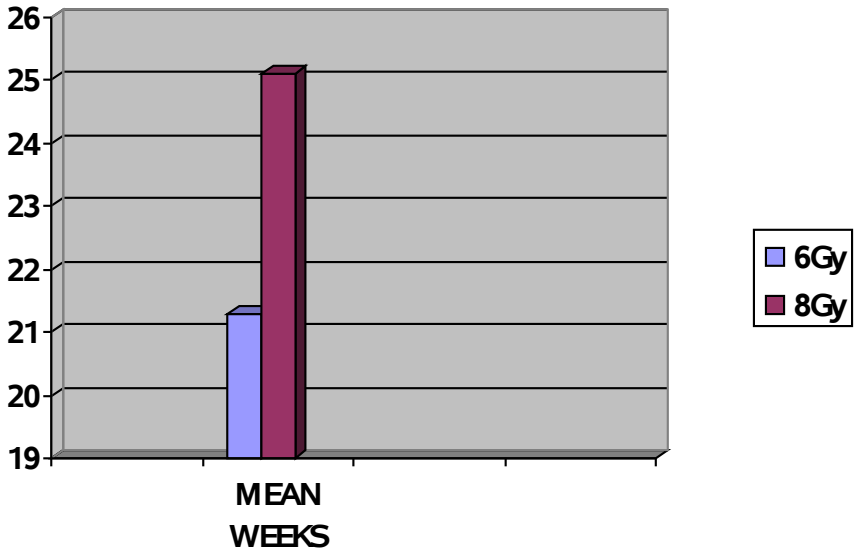
In trial arm two patient one with PNET and another with lung cancer were retreated with 6Gy at the end of 9 week, who were non responders after first treatment. In control arm two patient one with breast and another with lung cancer were retreated with 8 Gy at the end of 9 week, who were non responders after first treatment. The metastatic site was in dorsal spine in all four patients.

There was no difference in incidence of retreatment by RT during the study period among the two treatment groups, occurring in 2/30 (6.6%), and 2/30 (6.6%) patients in the, 6Gy arm and 8Gy arm. respectively (p= 0.5).

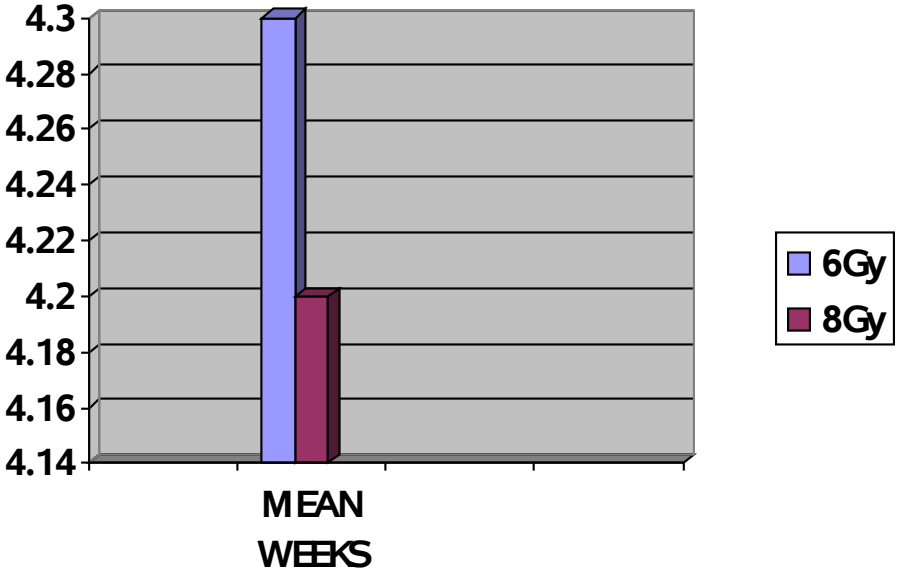
TOXICITY

No pathological fractures or spinal cord compressions were seen in this patient population during the 8 weeks post-RT. Nausea and vomiting grade 1 and 2 occurred , in 5/30 (16.6%) patients in 6Gy arm, and in 6/30 (20%) patients in 8Gy arm (p =0.38). Diarrhea grade 1 and 2 occurred in 3/30 (10%) patients in 6Gy arm and in 5/30 (16.6%) patients in 8Gy arm (p =0.21). There were no other acute gastrointestinal toxicity. No effect of field size on the incidence of toxicity was found.

DURATION OF RESPONSE IN RESPONDERS



TIME TO THE FIRST OCCURRENCE OF ANY PAIN RELIEF



DISCUSSION

Bone metastases are observed in approximately 50% of patients with cancer. Metastatic disease to the bone is a common cause of pain and other significant symptoms that are detrimental to quality of life. Radiotherapy is considered as the treatment of choice. Its main aim is relief of bone pain, prevention of pathological fracture as well as its healing, with anticipated effect upon improving mobility, function, and quality of life.

Our primary aim was to attempt to define the **optimal lowest single fraction RT** in painful bone metastatic patient population.

Target cells of radiotherapy in painful bone metastases are **inflammatory cells** and **osteoclasts.** By giving very low single dose i.e. **4Gy** shown to cause pain relif, without showing any tumour shrinkage. Here obvious target cells are the inflammatory cells that are largely present in the bone metastases micro-environment. Reduction by ionizing radiation of the inflammatory cells inhibits the release of chemical pain mediators and is probably responsible for the rapid reaction seen in some patients *(Mercadante, 1997).*

Other target cells are the osteoclasts. Osteoclastic activity is an early and important response to tumour cell invasion. Recently it has been demonstrated that urinary markers of bone resorption (and thus osteoclastic activity) and pain relief after radiation treatment were correlated *(Hoskin et al., 2000*).

Doses of **5 Gy** given to metatarsal bones of embryonic mice resulted in a selective elimination of the precursor cells for osteoclast formation (*Scheven et al., 1986)*. A clear dose-response relationship between the dose of ionizing radiation and the decrease in osteoclast number in vitro was observed (*Tsay et al., 1995*). The calculated life span of the osteoclast in this study was 9 to 10 days. In a further investigation by the same group (*Tsay et al., 1999*) they showed that in the first weeks after exposure to moderate doses of ionizing radiation the number of osteoclasts did not diminish.

Other studies have shown that the influx of osteoclast precursor cells in vivo is effectively suppressed by ionizing radiation (*Comas, 1970*). The resorbing activity of the osteoclast is less radiosensitive but can be inhibited, in a dose dependent way, by a dose of at least 5 Gy, as was established by morphometric and biochemical methods in a mouse embryo model (*Scheven et al., 1985*).

Here we studied two higher (6 and 8 Gy, respectively) single fractions radiotherapy to painful bone metastases. Results of this study show that two higher single fractions achieved better results in terms of CR, and significantly better in terms of overall response rates.

CLINICAL RESPONSE ASSESSMENT

The analysis of clinical response at the end of the 8th week revealed the following

COMPLETE CLINICAL RESPONSE :

A total of 13/30 patients attained complete clinical response i.e. 43.3% of all trial patients. In control arm 14 / 30 patients attained complete clinical response i.e. 46.6%. The **p-value is 0.5** significant, thereby indicates both study groups have equivalent complete response.

CR RATE

ARM	Week 1	Week 2	Week 4	Week 8
6 Gy ARM	0	3/30	8/30	13/30 (43.3%)
8Gy ARM	0	3/30	9/30	14/30 (46.6%)
P-value	0.5	0.5	0.44	0.5

PARTIAL CLINICAL RESPONSE:

A total of 9/30 patients attained parital clinical response i.e. 30% of all trial patients. In control arm 9 / 30 patients attained partial clinical response i.e. 30%.

The **p-value is 0.5** significant, thereby indicates both study groups have equivalent partial response.

PR RATE

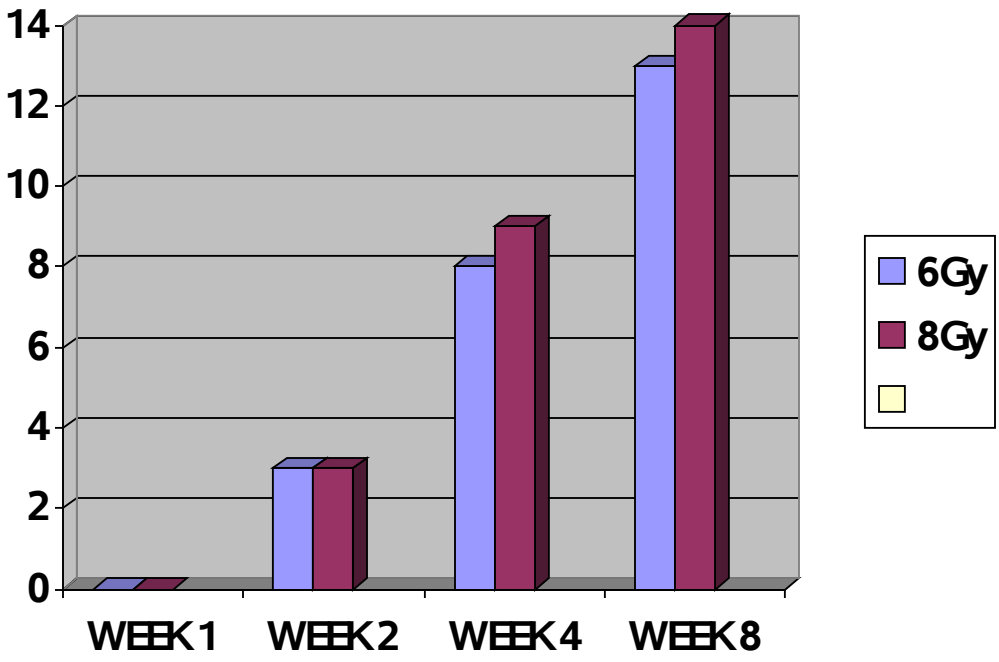
ARM	Week 1	Week 2	Week 4	Week 8
6 Gy ARM	1/30	2/30	3/30	9/30 (30%)
8Gy ARM	1/30	3/30	4/30	9/30 (30%)
P-value	0.5	0.45	0.44	0.5

OVERALL RESPONSE RATE

A total of 22/30 patients attained clinical response i.e.73. 3% in trial patients. In control arm 23 / 30 patients attained clinical response i.e. 76.6%. The **p-value 0.40** in overall response rate is significant.

ARM	Week 1	Week 2	Week 4	Week 8
6 Gy ARM	1/30	5/30	11/30	22/30 (73.3%)
8Gy ARM	1/30	6/30	13/30	23/30 (76.6%)
P-value	0.5	0.44	0.25	0.4000

CR RATE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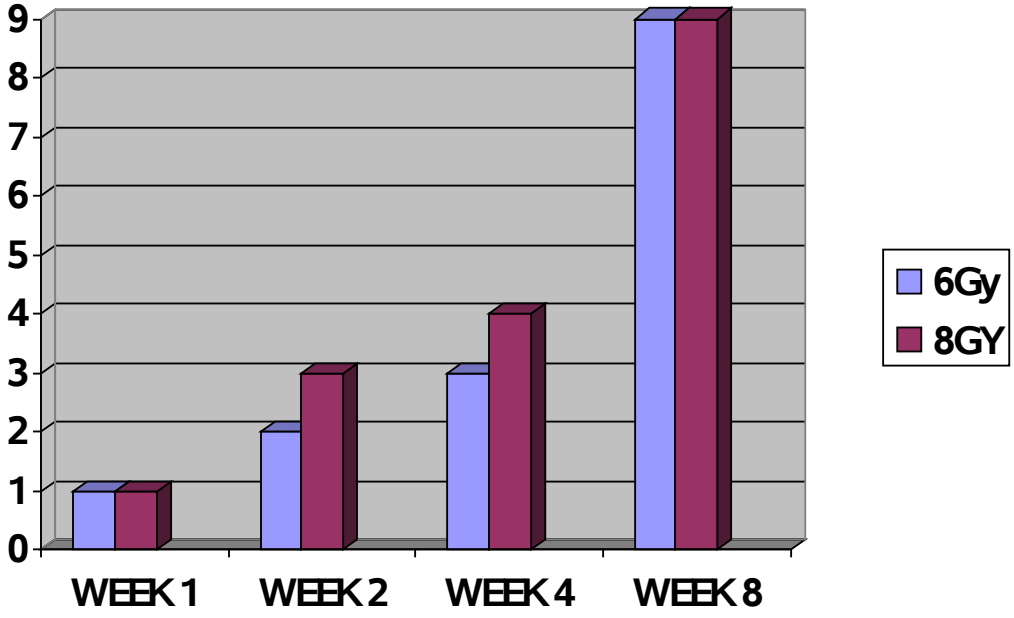
PR RATE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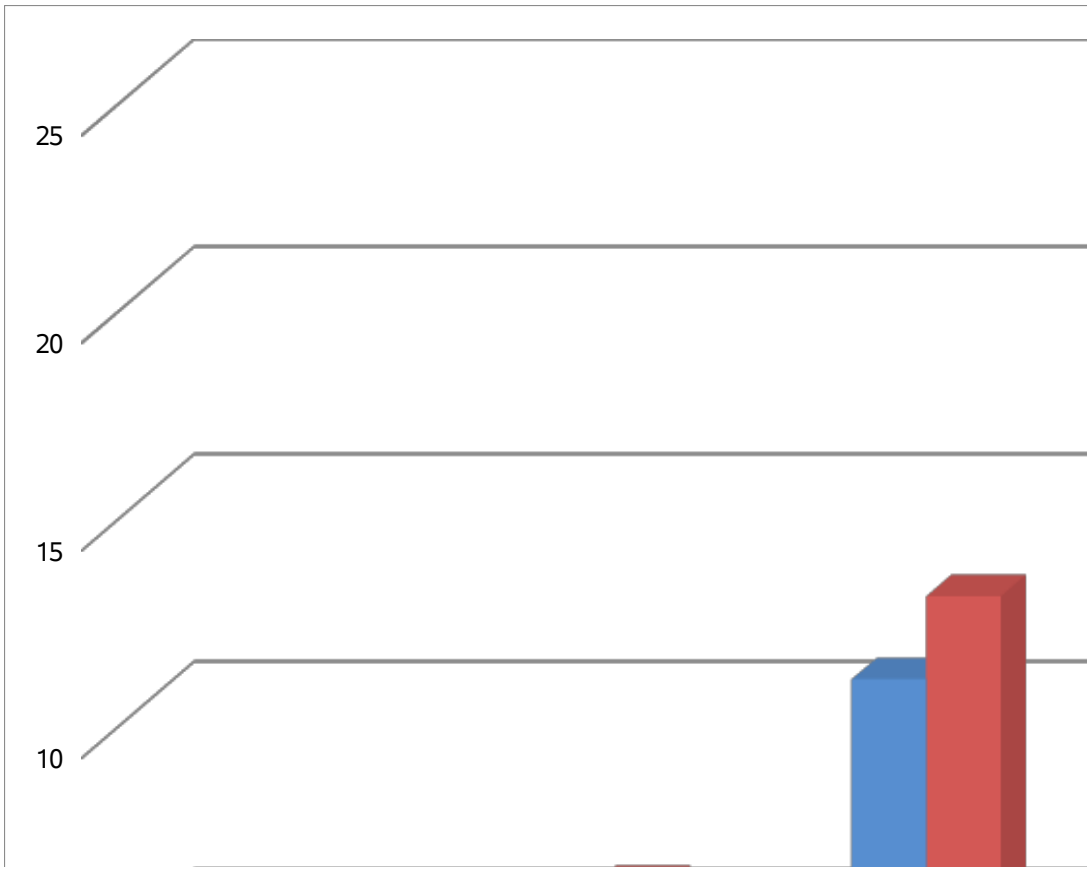
OVERALL RESPONSE RATE



DURATION OF RESPONSE IN RESPONDERS:

We analyzed mean duration of response in responders in both treatment groups. We found that the trial arm(6Gy) patients have 21.3 mean weeks of pain free periods. The control arm(8Gy) patients have 25.1 mean weeks of pain free periods. The **p-value 0.18** is significant.

TIME TO THE FIRST OCCURRENCE OF ANY PAIN RELIEF:

We also analyzed the first occurrence of any pain relief in responders in both treatment groups. We found that the trial arm(6Gy) patients have any pain relief at 4.36 weeks(mean). The control arm(8Gy) patients have any pain relief at 4.22 mean weeks. The **p-value 0.8** is significant.

RETREATMENT

The retreatment rate were 2/30 (6.6%), and 2/30 (6.6%) patients in the, 6Gy arm and 8Gy arm. respectively (p= 0.5).

TOXICITY

Nausea and vomiting grade 1 and 2 occurred, in 5/30 (16.6%) patients in 6Gy arm, and in 6/30 (20%) patients in 8Gy arm (p =0.38). Diarrhea grade 1 and 2 occurred in 3/30 (10%) patients in 6Gy arm and in 5/30 (16.6%) patients in 8Gy arm (p =0.21).

So, the speed of onset of pain relief, response duration , retreatment rate, and toxicity there is no difference between 6Gy arm and 8Gy arm . Also we could not find any influence of histology or metastatic site on pain relief between the two treatment groups, which may have some implications for future studies.

ANALYSIS OF SINGLE FRACTION 6Gy RADIOTHERAPY PROTOCOLS

The radiation dose was chosen taking into account the various protocols tried out by the various studies like Barak et al [12,] Uppelschoten et al [41], Jermic et al [42], and Metin Guden et al [43].

AUTHOR(REF)	YEAR	RT DOSE(Gy)	OVER ALL RESPONSE RATE(%)
Barak *et al.*	1987	6	**71**
Uppelschoten *et al.*	1995	6	88
Jeremic *et al.*	1998	4	59
		6	**73**
		8	**78**
Metin Guden *et al.*	2002	6	88.7
CURRENT STUDY		6 8	**73.3** **76.6**

From this table overall response rate for single fraction 6Gy radiotherapy was ranges from 71 – 88%. The Uppelschoten *et al* study and Metin Guden *et al.* study gave Highest response rate i.e. 88%. Our current study gives compareable overall response rate for 6Gy and 8Gy single fraction radiotherapy i.e. 73.3% and 76.6%.

Since single fraction RT of 6 Gy did not produce results inferior to that obtained with 8 Gy, further studies are needed to get more informations regarding optimal single fraction RT in the treatment of painful bone metastases.

CONCLUSION

The following conclusions can been drawn from this prospective trial which compared 6Gy single fraction radiotherapy with already proven 8Gy single fraction radiotherapy in the treatment of painful bone metastases.

The 6Gy single fraction radiotherapy produces similar , time to the first occurrence of any pain relief, duration of response in responders, complete response rate, overall response rate, retreatment rate and toxicity with 8Gy single fraction radiotherapy in the treatment of painful bone metastases.

We conclude that single fraction 6Gy radiotherapy is good option in palliation of painful bone metastases.

The impact of this single fraction on long term survival as well as the long term morbidity are to be analyzed in future with larger sample size. This task would certainly not be easy to achieve, unless performed in a prospective randomized multi-institutional cooperative group trial that will enable sufficient number of patients for any analysis needed with that aim. Having a world wide problem of bone metastases in mind, extremely big population of cancer patients would be eligible for the study of that type. It may now be the time for undertaking such trial that may help get some answers regarding "optimum low dose single fraction RT" in the treatment of painful bone metastases.

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ANNEXURE I

28

INSTITUTIONAL ETHICAL COMMITTEE
GOVERNMENT GENERAL HOSPITAL & MADRAS MEDICAL COLLEGE,
CHENNAI-600 003.

Telephone 044-2530 5000
Fax : 044 – 25305115

K.Dis.No.006859/P & D3/Ethics/Dean/GGH/09 Dated:23-03-2009

Title of the work "Evaluation – 6 Gy single dose radiotherapy in comparison with 8 Gy single dose radiotherapy in the treatment of painful bone metastasis"

Principal Investigator Dr. P.N. Sathiyamoorthy
II year M.D (Radiotherapy) post graduate student

Department Radiotherapy. MMC & Govt Ch.3.

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting which is held on 31st March at 2 P.M in Government General Hospital, Deans, Chamber, Chennai-3.

The members of the Committee, the Secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The principal investigator and their term are directed to adhere the guidelines given below:

1. You should get detailed informed consent from the patients/participants and maintain confidentiality.
2. You should carry out the work without detrimental to regular activities as well as without extra expenditure to the Institution or Government.
3. You should inform the IEC in case of any change of study procedure, site and investigation or guide.
4. You should not deviate form the area of the work for which I applied for ethical clearance.
5. You should inform the IEC immediately, in case of any adverse events or serious adverse reactions.
6. You should abide to the rules and regulations of the institution(s)
7. You should complete the work within the specific period and if any extension of time is required, you should apply for permission again and do the work.
8. You should submit the summary of the work to the ethical committee on completion of the work.
9. You should not claim funds from the Institution while doing the work or on completion.
10. You should understand that the members of IEC have the right to monitor the work with prior intimation.

SECRETARY
IEC, GGH, CHENNAI

CHAIRMAN
IEC, GGH, CHENNAI

For DEAN
GGH &MMC, CHENNAI

DM 30-03 (3)