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Oncology

A STUDY OF SINGLE FRACTION VERSUS MULTIPLE FRACTIONS OF RADIOTHERAPY FOR PAINFUL BONE METASTASIS

Dr.N.Rajya Lakshmi MDRT — Assistant Professor of Radiotherapy,Siddhartha Medical College,Vijayawada.

Dr.M.Panduranga Kumari* — MDRT,Assistant Professor of Radiotherapy,Kurnool Medical College,Kurnool.*Corresponding Author

ABSTRACT

Objectives : The purpose of this study is to compare single fraction Radiotherapy(8 gray) with multiple fractions Radiotherapy(30 gray in 10 fractions) in the treatment of painful bone metastases in terms of

1.Pain palliation(Verbal Rating Scale)
2.Functional Outcome(ECOG Performance Scale)
3.Analgesic Requirement
4.Duration of Overall Response

Materials and Methods:

In this study 40 patients with painful bone metastases from any primary, localised to single region that could be encompassed in single Radiotherapy field are included.All these metastases are radiologically verified.These 40 patients are randomly divided into two arms with 20 patients in each arm .Arm-A patients received 8 gray of radiotherapy in single fraction,Arm-B patients received 30 gray in 10 fractions at the rate of 3 gray per fraction.A single direct field or two parallel opposed fields are planned depending upon the site of metastases.

Two arms were compared in terms of efficacy of pain palliation(Verbal Rating Scale),Functional Outcome(ECOG Performance Status),Analgesic Requirement,Duration of Overall Response ,before RT ,immediately,1 week,4 weeks,8 weeks,12 weeks after RT.

Results:

Two arms are equal in terms of Pain palliation,Functional Outcome ,Analgesic Requirement,Duration of overall Response.But patients receiving 8 gray in Single fraction arm had lot of social,economic and emotional comfort as the duration of hospital stay is decreased.

Conclusion:

Our study highlights the utility of 8 gray in single fraction as an effective pain palliation method equally efficacious when compared to 30 gray in 10 fractions of fractionated radiotherapy regimen.The advantage of 8 gray in single fraction regimen is being less expensive,patient friendly and decreased duration of hospital stay.

KEYWORDS : Painful Bone Metastases,Gray,Fraction

INTRODUCTION

Bones are the third most common site of distant metastases after lung and liver in advanced cancer. Bone metastasis is usually detected after diagnosis of primary but in 10-15% of cases they are the first lesions to be detected.

About 50% of all cancer patients develop metastases in their life time and half of them develop skeletal metastases. Breast, prostate, and lung malignancies are the common causes of bone metastases. Other primaries include Bladder, kidney, uterus, melanoma, thyroid tumors. Most of the bone metastases are mixed variety but pure lytic lesions seen in myeloma and pure osteoblastic type are seen in prostate malignancy.

Bone metastases are usually multiple, solitary metastases are produced only in <10% of cases. Axial skeleton is the most common site of bone metastases. Metastatic bone disease is associated with skeletal complications that can cause considerable morbidity and mortality, including bone pain, impaired mobility, hypercalcemia, pathological fractures and spinal cord compression.

Current management of bone metastases includes Radiotherapy, chemotherapy, hormone therapy, surgery, radionuclide and supportive therapy either alone or in combination. In most of the cases the treatment intent is palliation, when treatment goals are pain relief, preservation of mobility, function and quality of life and if possible, prolongation of survival.

Radiotherapy is the most effective treatment of bone metastases. At least 75% of patients achieve pain relief following radiotherapy and half of them stay free from pain.

Different Fractionation regimens are in practice for pain palliation. The purpose of this study was to compare single fraction RT with multiple fraction RT in the palliative treatment of painful bone metastases. In Indian patients where metastatic disease constitute a significant proportion of our total cancer workload in RT departments, as >50% of the patients present in advanced stage disease and ultimately develop metastases**.** This study addresses a therapeutic question of considerable clinical significance.

AIMS AND OBJECTIVES

The purpose of this study is to compare single fraction Radiotherapy (8 Gray) with fractionated radiotherapy regimen (30 Gray in 10 fractions) in the treatment of painful bone metastases, in terms of

1) Pain palliation (verbal rating scale)
2) Functional outcome (ECOG performance status)
3) Analgesic requirement
4) Duration of response

REVIEW OF LITERATURE

Incidence:

Bone metastases are a frequent complication of cancer, occurring in up to 70 percent of patients with advanced breast or prostate cancer[1] and in approximately 15 to 30 percent of patients with carcinoma of the lung, colon, stomach, bladder, uterus, rectum, thyroid, or kidney. The exact incidence of bone metastasis is unknown, but it is estimated that >100,000 in the United States develop osseous metastases annually[2,3].

Anatomy:

The adult human skeleton has a total of 206 bones, excluding the sesamoid bones[4] The appendicular skeleton has 126 bones, axial skeleton 74 bones, and auditory ossicles six bones. Each bone constantly undergoes modeling during life to help it adapt to changing biomechanical forces, as well as remodeling to remove old, microdamaged bone and replace it with new, mechanically stronger bone to help preserve bone strength.

The four general categories of bones are:

- Long bones: clavicles, humeri, radii, ulnae, metacarpals, femurs, tibiae, fibulae, metatarsals, and phalanges.
- Short bones: carpal and tarsal bones, patellae, and sesamoid bones.

- Flat bones: skull, mandible, scapulae, sternum, and ribs.
- Irregular bones: vertebrae, sacrum, coccyx, and hyoid bone.

Flat bones form by membranous bone formation, whereas long bones are formed by a combination of endochondral and membranous bone formation.

The skeleton serves a variety of functions:
- Structural support for the rest of the body,
- Permits movement and locomotion by providing levers for the muscles,
- Protects vital internal organs and structures,
- Provides maintenance of mineral homeostasis and acid-base balance,
- Serves as a reservoir of growth factors and cytokines,
- Provides the environment for hematopoiesis within the marrow spaces[5].

The long bones are composed of a hollow shaft, or diaphysis; flared, cone-shaped metaphysis (below the growth plates); and rounded epiphyses (above the growth plates). The diaphysis is composed primarily of dense cortical bone, whereas the metaphysis and epiphysis are composed of trabecular meshwork bone surrounded by a relatively thin shell of dense cortical bone.

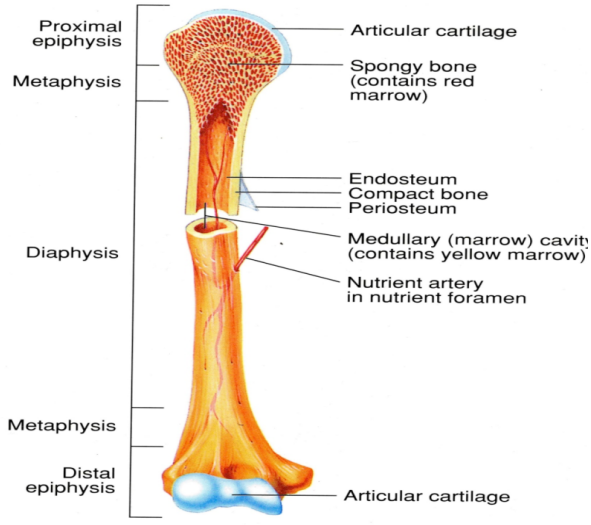

Figure 1: LONG BONE ANATOMY

The adult human skeleton is composed of 80% cortical bone and 20% trabecular bone overall[6]. Different bones and skeletal sites within bones have different ratios of cortical to trabecular bone. The vertebra is composed of cortical to trabecular bone in a ratio of 25:75. This ratio is 50:50 in the femoral head and 95:5 in the radial diaphysis.

Cortical bone is dense and solid and surrounds the marrow space, whereas trabecular bone is composed of a honeycomb-like network of trabecular plates and rods interspersed in the bone marrow compartment. Both cortical and trabecular bone are composed of osteons.

Cortical osteons are called Haversian systems. Haversian systems are cylindrical in shape, are approximately 400 mm long and 200 mm wide at their base, and form a branching network within the cortical bone[7]. The walls of Haversian systems are formed of concentric lamellae. Cortical bone is typically less metabolically active than trabecular bone, but this depends on the species. There are an estimated 21×10^6 cortical osteons in healthy human adults, with a total Haversian remodeling area of approximately 3.5 m^2. Cortical bone porosity is usually <5%, but this depends on the proportion of actively remodeling Haversian systems to inactive cortical osteons. Increased cortical remodeling causes an increase in cortical porosity and decrease in cortical bone mass. Healthy aging adults normally experience thinning of the cortex and increased cortical porosity.

Trabecular osteons are called packets. Trabecular bone is composed of plates and rods averaging 50 to 400 mm in thickness [6]. Trabecular osteons are semilunar in shape, normally approximately 35 mm thick, and composed of concentric lamellae. It is estimated that there are 14×10^6 trabecular osteons in healthy human adults, with a total trabecular area of approximately 7 m^2.

Cortical bone has an outer periosteal surface and inner endosteal surface. The periosteum is a fibrous connective tissue sheath that surrounds the outer cortical surface of bone, except at joints where bone is lined by articular cartilage, which contains blood vessels, nerve fibers, and osteoblasts and osteoclasts. The periosteum is tightly attached to the outer cortical surface of bone by thick collagenous fibers, called Sharpeys' fibers, which extend into underlying bone tissue. Periosteal surface activity is important for appositional growth and fracture repair. Bone formation typically exceeds bone resorption on the periosteal surface, so bones normally increase in diameter with aging. The endosteum is a membranous structure covering the inner surface of cortical bone, trabecular bone, and the blood vessel canals (Volkman's canals) present in bone. The endosteum is in contact with the bone marrow space, trabecular bone, and blood vessel canals and contains blood vessels, osteoblasts, and osteoclasts. The endosteal surface has a total area of approximately 0.5 m^2, with higher remodeling activity than the periosteal surface, likely as a result of greater biomechanical strain or greater cytokine exposure from the adjacent bone marrow compartment. Bone resorption typically exceeds bone formation on the endosteal surface, so the marrow space normally expands with aging.

Cortical bone and trabecular bone are normally formed in a lamellar pattern, in which collagen fibrils are laid down in alternating orientations [6]. Lamellar bone is best seen during microscopic examination with polarized light, during which the lamellar pattern is evident as a result of birefringence. The mechanism by which osteoblasts lay down collagen fibrils in a lamellar pattern is not known, but lamellar bone has significant strength as a result of the alternating orientations of collagen fibrils, similar to plywood. The normal lamellar pattern is absent in woven bone, in which the collagen fibrils are laid down in a disorganized manner. Woven bone is weaker than lamellar bone. Woven bone is normally produced during formation of primary bone and may also be seen in high bone turnover states such as osteitis fibrosa cystica, as a result of hyperparathyroidism, and Paget's disease or during high bone formation during early treatment with fluoride.

There are primarily three types of cells within mature bone: osteocytes, osteoblasts, 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[7]. These cells create an acidophilic environment that causes dissolution of the hydroxyapatite crystals and proteolysis of the bone matrix.

Bone Growth, Modeling, and Remodeling:

Bone undergoes longitudinal and radial growth, modeling, and remodeling during life. Longitudinal and radial growth during growth and development occurs during childhood and adolescence. Longitudinal growth occurs at the growth plates, where cartilage proliferates in the epiphyseal and metaphyseal areas of long bones, before subsequently undergoing mineralization to form primary new bone.

Modeling is the process by which bones change their overall shape in response to physiologic influences or mechanical forces, leading to gradual adjustment of the skeleton to the forces that it encounters. Bones may widen or change axis by removal or addition of bone to the appropriate surfaces by independent action of osteoblasts and

osteoclasts in response to biomechanical forces. Bones normally widen with aging in response to periosteal apposition of new bone and endosteal resorption of old bone. Wolff's law describes the observation that long bones change shape to accommodate stresses placed on them. During bone modeling, bone formation and resorption are not tightly coupled. Bone modeling is less frequent than remodeling in adults[8]. Modeling may be increased in hypoparathyroidism[9], renal osteodystrophy[10], or treatment with anabolic agents[11].

Bone remodeling is the process by which bone is renewed to maintain bone strength and mineral homeostasis. Remodeling involves continuous removal of discrete packets of old bone, replacement of these packets with newly synthesized proteinaceous matrix, and subsequent mineralization of the matrix to form new bone. The remodeling process resorbs old bone and forms new bone to prevent accumulation of bone microdamage. Remodeling begins before birth and continues until death. The bone remodeling unit is composed of a tightly coupled group of osteoclasts and osteoblasts that sequentially carry out resorption of old bone and formation of new bone. Bone remodeling increases in perimenopausal and early postmenopausal women and then slows with further aging, but continues at a faster rate than in premenopausal women. Bone remodeling is thought to increase mildly in aging men.

The remodeling cycle is composed of four sequential phases:
- Activation
- Resorption,
- Reversal,
- Formation.

Activation: Recruitment and activation of mononuclear monocyte-macrophage osteoclast precursors from the circulation[12], lifting of the endosteum that contains the lining cells off the bone surface, and fusion of multiple mononuclear cells to form multinucleated preosteoclasts. Preosteoclasts bind to bone matrix via interactions between integrin receptors in their cell membranes and RGD (arginine, glycine, and asparagine) containing peptides in matrix proteins, to form annular sealing zones around bone-resorbing compartments beneath multinucleated osteoclasts.

Osteoclasts mediated bone resorption takes only approximately 2 to 4 week during each remodeling cycle. Osteoclast formation,activation and resorption are regulated by the ratio of receptor activator of NF–κβ ligand (RANKL) to osteoprotogerin (OPG),Interleukin-1(IL-1) and,Interleukin-6(IL-6),colony-stimulating factor(CSF), parathyroidhormone,

1,25–dihydroxy vitaminD,and calcitonin[13,14]. Regulation of osteoclastogenesis by receptor activator of NF–κβ ligand (RANKL) and osteoprotegerin (OPG) : colony-stimulating factor 1 (CSF-1) normally stimulates osteoclast recruitment. Two forms of RANKL are produced by osteoblasts precursors to stimulate osteoclast recruitement and activation. The membrane bound form directly interacts with membrane bound RANK molecules on adjacent osteoclast precursors.OPG acts as a decoy receptor to prevent RANKL or RANKL from interacting with RANK. The ratio between RANKL and OPG produced by osteoblasts and osteoblast precursors controls RANKL-stimulated osteoclastogenesis.

Resorption: Resorbing osteoclasts secrete hydrogen ions via H+-ATPase proton pumps and chloride channels in their cell membranes into the resorbing compartment to lower the pH within the bone-resorbing compartment to as low as 4.5, which helps mobilize bone mineral15. Resorbing osteoclasts secrete tartrate-resistant acid phosphatase, cathepsin K, matrix metalloproteinase 9, and gelatinase from cytoplasmic lysosomes[16] to digest the organic matrix, resulting in formation of saucer-shaped Howship's lacunae on the surface of trabecular bone and Haversian canals in cortical bone. The resorption phase is completed by mononuclear cells after the multinucleated osteoclasts undergo apoptosis[17,18].

Reversal phase: Bone resorption transitions to bone formation. At the completion of bone resorption, resorption cavities contain a variety of mononuclear cells, including monocytes, osteocytes released from bone matrix, and preosteoblasts recruited to begin new bone formation. The coupling signals linking the end of bone resorption to the beginning of bone formation are as yet unknown. Proposed coupling signal candidates include bone matrix derived factors such as TGF-β, IGF-1(Insulin Like Growth Factor-1), IGF-2 (Insulin Like Growth Factor-2), bone morphogenetic proteins, PDGF, or fibroblast growth factor[19-21]. TGF-β concentration in bone matrix correlates with histomorphometric indices of bone turnover and with serum osteocalcin and bone-specific alkaline phosphatase. TGF-β released from bone matrix decreases osteoclast resorption by inhibiting RANKL production by osteoblasts. The reversal phase has also been proposed to be mediated by the strain gradient in the lacunae[22,23]. As osteoclasts resorb cortical bone in a cutting cone, strain is reduced in front and increased behind, and in Howship's lacunae, strain is highest at the base and less in surrounding bone at the edges of the lacunae. The strain gradient may lead to sequential activation of osteoclasts and osteoblasts, with osteoclasts activated by reduced strain and osteoblasts by increased strain. The osteoclast itself has also been proposed to play a role during reversal[24].

Bone Formation: It takes approximately 4 to 6 months to complete. Osteoblasts synthesize new collagenous organic matrix and regulate mineralization of matrix by releasing small, membrane-bound matrix vesicles that concentrate calcium and phosphate and enzymatically destroy mineralization inhibitors such as pyrophosphate or proteoglycans[25]. Osteoblasts surrounded by and buried within matrix become osteocytes with an extensive canalicular network connecting them to bone surface lining cells, osteoblasts, and other osteocytes, maintained by gap junctions between the cytoplasmic processes extending from the osteocytes[26]. The osteocyte network within bone serves as a functional syncytium. At the completion of bone formation, approximately 50 to 70% of osteoblasts undergo apoptosis, with the balance becoming osteocytes or bone-lining cells. Bone-lining cells may regulate influx and efflux of mineral ions into and out of bone extracellular fluid, thereby serving as a blood-bone barrier, but retain the ability to redifferentiate into osteoblasts upon exposure to parathyroid hormone or mechanical forces[27]. Bone-lining cells within the endosteum lift off the surface of bone before bone resorption to form discrete bone remodeling compartments with a specialized microenvironment[28]. In patients with multiple myeloma, lining cells may be induced to express tartrate-resistant acid phosphatase and other classical osteoclast markers.

The end result of each bone remodeling cycle is production of a new osteon. The remodeling process is essentially the same in cortical and trabecular bone, with bone remodeling units in trabecular bone equivalent to cortical bone remodeling units divided in half longitudinally[29]. Bone balance is the difference between the old bone resorbed and new bone formed. Periosteal bone balance is mildly positive, whereas endosteal and trabecular bone balances are mildly negative, leading to cortical and trabecular thinning with aging. These relative changes occur with endosteal resorption outstripping periosteal formation.

The main recognized functions of bone remodeling include preservation of bone mechanical strength by replacing older, microdamaged bone with newer, healthier bone and calcium and phosphate homeostasis. The relatively low adult cortical bone turnover rate of 2 to 3% per year is adequate to maintain biomechanical strength of bone. The rate of trabecular bone turnover is higher, more than required for maintenance of mechanical strength, indicating that trabecular bone turnover is more important for mineral metabolism. Increased demand for calcium or phosphorus may require increased bone remodeling units, but, in many cases, this demand may be met by increased activity of existing osteoclasts. Increased demand for skeletal calcium and phosphorus is met partially by osteoclastic resorption and partly by nonosteoclastic calcium influx and efflux. Ongoing bone remodeling activity ensures a continuous supply of newly formed bone that has relatively low mineral content and is able to exchange ions more easily with the extracellular fluid. Bone remodeling units seem to be mostly randomly distributed throughout the skeleton but may be triggered by microcrack formation or osteocyte apoptosis. The bone remodeling space represents the sum of all of the active bone remodeling units in the skeleton at a given time.

Pathophysiology of Bone Metastases:

Bone metastases are often described as either osteolytic or osteoblastic, but these are different representations of abnormalities in the normal bone-remodeling process. Breast and lung cancers more commonly cause osteolytic appearing lesions, and lesions caused by prostate and thyroid cancers more often have an osteoblastic appearance. However, only myeloma is associated with purely

osteolytic lesions[7]. Most other tumors have a combination of osteolytic and osteoblastic components.

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-κ (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[7]. 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 1. The mechanisms for osteoblastic activation are not clearly delineated, but it appears that bone resorption occurs first even in osteoblastic metastases from prostate cancer[30].

Metastases to the bone most often occur in the red marrow, which is found in highest concentration in the axial skeleton. This most often occurs by hematogenous spread, but may occur by direct extension as well. Involvement of adjacent bone by direct extension (e.g., mandibular involvement from an oral cavity cancer) does not necessarily imply that there is a higher likelihood of distant bone metastases, and its management is very different from that of bone metastases from hematogenous spread. The predilection of certain tumor sites to metastasize to bone may be related to local growth factors in the bone such as transforming growth factor-β, insulin-like growth factors I and II, fibroblastic growth factors, or platelet-derived growth factors, preferential adherence to endothelial surfaces in certain bones by cell adhesion molecules, or chemotactic attraction from bone cells by osteocalcin or type I collagen[7,31,32]. The relatively high proportion of hematogenous metastasis to bone compared with other sites in the body cannot simply be explained by blood flow, which is more than 30 times greater in lung than in red bone marrow[33].

Cancers Producing Bone Metastases:

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[1]. Bone metastases may be found in up to 85% of patients dying from breast, prostate, or lung cancer. Other primary sites with a propensity for bone metastases include thyroid, melanoma, and kidney. On the other hand, gastrointestinal sites of primary malignancy give rise to bone metastasis in only 3% to 15% of patients with metastatic disease[31]. Some hematologic malignancies including myeloma and lymphoma can also cause significant pain and bone destruction[34].

The axial skeleton is the most common site of bone metastasis, with metastasis most frequently occurring in the spine, pelvis, and ribs. The lumbar spine is the single most frequent site of bone metastasis[35,36,37,38]. 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 primaries39. 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.

Table: 1 TYPES OF BONE METASTASES IN DIFFERENT CANCERS

LUNG		
	Carcinoma	Lytic metastasis
	Carcinoid	Sclerotic metastasis
BREAST	Carcinoma	Lytic or Mixed
GENITO URINARY		
	Renal cell carcinoma	Lytic, expansile
	Wilms'Tumor	Lytic metastasis
	Bladder	Lytic, occasionally sclerotic
	Prostate	Sclerotic
REPRODUCTIVE ORGANS	Cervix	Lytic or Mixed
	Uterus	Lytic
	Ovary	Lytic
	Testis	Lytic, Occasionally Sclerotic
THYROID		
	Follicular Carcinoma	Lytic, Expansile
	Medullary carcinoma	Lytic Occasionally sclerotic
GI TRACT		
	Stomach	Sclerotic or mixed
	Colon	Lytic, occasionally sclerotic
	Rectum	Lytic
ADRENAL		
	Pheochromocytoma	Lytic expansile
	Carcinoma	Lytic
	Neuroblastoma	Lytic,occasionally sclerotic
SKIN		
	Squamous cell carcinoma	Lytic
	Melanoma	Lytic Expansile.

Sites of Skeletal Involvement by Malignant Disease:

Tumor cells commonly metastasize to the most heavily vascularized parts of the skeleton, particularly the red bone marrow of the axial skeleton and the proximal ends of the long bones, the ribs, and the vertebral column. Although metastases to the appendicular skeleton occur less frequently, they are found occasionally in patients with melanoma and renal cancer. Galasko[40,41] has reviewed in detail the distribution of skeletal metastases from various solid tumors. A major determinant of the site of skeletal metastasis is blood flow. Because prostate carcinoma frequently metastasizes to the vertebral column, it was suggested 50 years ago that access occurs through the vertebral venous plexus (Batson's plexus). Batson's plexus is a low-pressure, high-volume system of vertebral veins, which can communicate with the intercostal veins, and runs up the spine; this has been suggested as the reason that prostate tumor cells metastasize so readily to the spine. This plexus has extensive intercommunications that apparently function independently of other major venous systems such as the pulmonary, caval, and portal systems[42]. It has been studied by the injection of dye into the dorsal vein of the penis in cadavers and experimental animals[42]. Although a number of researchers have agreed that this system may be important for the spread of tumor cells to the axial skeleton[40,41,43-45] have questioned its importance.

Steps Involved in Tumor Cell Metastasis:

Although it is clear that the bone microenvironment is an extremely fertile soil for the growth of breast, prostate, and lung carcinomas, it has also been proven clinically and experimentally that not all cancer cells form metastatic colonies in bone as readily as others. For example, cancers of the endometrium, urothelium, and head and neck cause bone metastases less frequently than breast or prostate carcinomas. This suggests that carcinomas such as breast and prostate possess certain intrinsic properties that facilitate development of bone metastases. These properties probably include the following:

- Production of proteolytic enzymes necessary for detachment from the primary site, invasion into surrounding soft tissues, intravasation, extravasation, and bone matrix degradation, .
- Expression or loss of cell adhesion molecules (CAM) essential for detachment from the primary site and for accumulation at the metastatic site.
- Migratory activity in order to circulate, and

- Enhanced capacity to escape from host immune surveillance in order to survive

Not all of these properties, however, are specific for bone metastasis. All metastatic cancer cells presumably need to acquire these common properties when they metastasize to any distant organ site, such as lungs, liver, brain, or bone. Thus, in addition to these general properties, there must be additional properties of breast and prostate carcinoma cells that specifically facilitate the formation of a bone metastasis. The attachment of tumor cells to other cells and to extracellular structures is critical to the metastatic process. Cell adhesion molecules such as laminin and E-cadherin play key roles in several important events involved in cancer cell invasion and metastasis. Cell adhesion molecules mediate not only cell-to-cell but also cell-to-substratum communications. For example, CAMs mediate cancer cell adhesion to normal host cells and to extracellular matrix, thereby regulating tumor cell invasiveness and proliferation[46].
Secretion of Proteolytic Enzymes:

Tumor cells produce proteolytic enzymes to degrade basement membranes and traverse the sinusoids and capillaries through which they travel to enter the tissue stroma. This migration process may involve direct production of proteolytic enzymes by tumor cells, such as type-IV collagenase, or even production of proteolytic enzymes by host cells.

Cell Motility:
Tumor cells may migrate from the vasculature toward bone surfaces in response to a number of chemotactic factors. Bone matrix itself contains multiple factors with chemotactic potential for tumor cells, and these are potentially available locally as a consequence of bone remodeling and bone resorption. These include fragments of type-I collagen, which have been shown to cause unidirectional migration of tumor cells[47], and fragments of the bone protein osteocalcin, which may also cause chemotaxis of tumor cells and monocytes[48]. The conditioned media harvested from resorbing or remodeling bones contain chemotactic activity that stimulates the unidirectional migration of rat and human tumor cells [49,50] .The nature of the factor responsible has not been identified, but potential candidates transforming growth factor-β (TGF-β) and platelet-derived growth factor (PDGF), both of which are present in abundant amounts in bone[51] and released during bone resorption, may play an important role.

Mechanism of Osteolytic Bone Metastasis:
Tumor cells in breast cancer produce factors that directly or indirectly induce the formation of osteoclasts. In turn, bone resorption by osteoclasts releases growth factors from the bone matrix that stimulate tumor growth and bone destruction[52].This reciprocal interaction between breast-cancer cells and the bone microenvironment results in a vicious circle that increases both bone destruction and the tumor burden.

Tumor cells, in particular breast-cancer cells, secrete parathyroid hormone–related peptide as the primary stimulator of osteoclastogenesis. In addition, tumorcells produce other factors that increase the formationof osteoclasts, including interleukin-6, prostaglandin E2(PGE2), tumor necrosis factor, and macrophage colony stimulating factor (M-CSF). These factors increase the expression of receptor activator of nuclear factor-*k* β ligand (RANKL), which directly acts on osteoclast precursors to induce the formation of osteoclasts and boneresorption. The process of bone resorption releases factors such as transforming growth factor-β (TGF-β), insulin-like growth factors (IGFs), fibroblast growth factors(FGFs), platelet-derived growth factor (PDGF), and bone morphogenetic proteins (BMPs), which increase the production of parathyroid hormone–related peptide by tumor cells as well as growth factors that increase tumor growth. This symbiotic relationship between bone destruction and tumor growth further increases bone destruction and tumor growth.

Bone is an abundant source of inactive growth factors, which are activated during the bone-resorptive process[53] and which can then stimulate the growth of breast-cancer cells. Parathyroid hormone–related peptide is probably the factor produced by breast-cancer cells and most solid tumors that stimulates the formation of osteoclasts[54,55]. Both parathyroid hormone–related peptide and parathyroid hormone bind the same receptor (PTHR1) and induce the expression of RANKL on marrow stromal cells. Parathyroid hormone is the main peptide regulator of calcium homeostasis, and parathyroid hormone–related peptide has biologic effects on bone similar to those of parathyroid hormone[56]. In the amino acid sequences of parathyroid hormone and parathyroid hormone–related peptide, 8 of the first 13 amino acids are identical, and both peptides have similar three-dimensional structures[56]

The production of parathyroid hormone–related peptide is increased in metastases of breast cancer to bone. Only 50 percent of primary breast cancers express parathyroid hormone–related peptide,whereas 92 percent of metastases of breast cancer to bone produce the peptide[57].However, it is unclear whether this difference results from induction of the peptide in the bone microenvironment or whether tumors that produce the peptide are more likely to metastasize to bone. When breast-cancer cells from patients are injected into nude mice and metastasize to bone, they increase the production of parathyroid hormone–related peptide[54].The peptide induces the formation of osteoclasts and bone resorption, which releases transforming growth factor-β. Transforming growth factor -β, in turn, further increases production of the peptide by the breast-cancer cells[58].An antibody against parathyroid hormone–related peptide is being evaluated in patients with bone metastases from breast cancer.

In the vicious circle of breast-cancer metastases, bone destruction increases local calcium levels, which promotes tumor growth and the production of parathyroid hormone–related peptide[59]. Breast-cancer cells also produce, or induce, interleukin- 6, prostaglandin E2, macrophage colony-stimulating factor, interleukin-1, and tumor necrosis factor α[60,61] which may also play an important role in the induction of osteoclast formation by breastcancer metastases. Prostaglandin E2 can increase the expression of RANKL and directly enhance the effects of RANKL on the formation of osteoclasts[61]. Together, these data suggest that parathyroid hormone– related peptide is a major mediator of osteolytic bone destruction by breast cancer and other solid tumors.

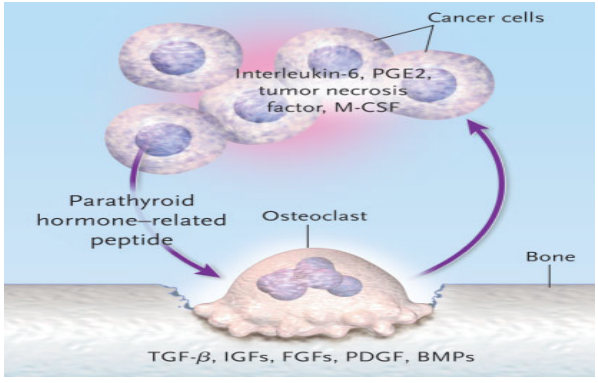

Figure 2: THE VICIOUS CIRCLE OF OSTEOLYTIC METASTASIS

Mechanism of Osteoblastic Bone metastases:
The mechanisms of osteoblastic metastasis and the factors involved are unknown. Endothelin-1 has been implicated in osteoblastic metastasis from breast cancer[62]. It stimulates the formation of bone and the proliferation of osteoblasts in bone organ cultures[63], and serum endothelin-1 levels are increased in patients with osteoblastic metastasis from prostate cancer[64]. Furthermore, in an animal model of osteoblastic metastasis, treatment with a selective endothelin-1A–receptor antagonist decreased both osteoblastic metastasis and the tumor burden[62]. The antagonist had no effect on the growth of the tumor at orthotopic sites. These results suggest that blocking osteoblast-inducing activity by tumors may decrease tumor growth and osteoblast activity and suggest that a vicious circle may also be involved in osteoblastic metastasis in which tumors induce osteoblast activity and thus the subsequent release from the osteoblasts of growth factors that increase tumor growth. In addition to endothelin-1,

platelet-derived growth factor65, a polypeptide produced by osteoblasts in the bone microenvironment, urokinase[66,67], and prostate-specific antigen (PSA)[68] may also be involved.

Symptoms:
- Intractable pain
- Pathological fracture
- Spinal cord compression
- Hypercalcemia

Bone Pain: Bone pain is a severe problem in patients with bone metastases

Mechanism of Bone Pain:
Possible mechanisms include mechanical instability, irritation of periosteal stretch receptors, tumor-directed osteoclast-mediated osteolysis, tumor cells themselves, or tumor-induced nerve injury, production of nerve growth factor or stimulation of other cytokine receptors[1,3,69,70]. Mechanisms of pain may be multifactorial, a combination of therapies may be superior to any one therapy alone[69].

Pathologic Fractures:
Pathologic fractures occurring spontaneously or following trivial injury are frequent in patients with metastatic bone disease, particularly in those with osteolytic lesions. They occur most frequently in the vertebral bodies and the proximal ends of long bones, which are common sites of metastasis.

Nerve Compression Syndromes:
Spinal cord compression may occur when tumors invade and impinge directly on the spinal cord but results more frequently because severe destructive osteolytic lesions lead to fracture and fragility of one or more vertebral bodies. In such cases, compression of the cord occurs as a result of the subsequent deformity. Nerve compression syndromes also occur occasionally in patients with osteoblastic lesions because of bony overgrowths that impinge directly on nerves or narrow foramina or canals.

Hypercalcemia:
Hypercalcemia occurs frequently in patients with metastatic bone disease, particularly in patients with osteolytic lesions. Approximately 30% of patients with breast carcinoma develop hypercalcemia at some time, usually late in the course of the disease[71]. Myeloma also causes hypercalcemia in approximately one third of patients, also usually later in the disease as the tumor burden increases[72]. The frequency of hypercalcemia may decrease with more widespread use of bisphosphonates. Hypercalcemia is almost always due primarily to an increase in bone resorption, which is caused in turn by the production of bone-active agents by the tumor cells that stimulate osteoclastic bone resorption.

Evaluation:
History-
The most common symptom of bone metastases is slowly progressive, insidious pain that is fairly well localized. The pain may be worse at night. Pain from the femur or acetabulum may worsen with weight bearing or ambulation. In contrast, pain from the inferior ischium or sacrum may be worse with sitting but less bothersome with ambulation. Although the pain is frequently localized, pain may radiate to other areas. This is most frequently seen with pain in the lower back, pelvis or hips that may radiate down the legs. Pain that radiates does not necessarily indicate nerve impingement because radicular pain can also be caused by spasm of muscles that originate or insert near the area of disease (e.g., pain in the hip radiating to the knee).

Physical Examination-
The physical examination is an important step in evaluating a patient with bone metastases. Firm palpation will often elicit the specific area of pain, with a point tenderness often pointing directly to the affected area in the bone. A thorough neurologic examination is also important, especially in patients with spinal metastases, to carefully evaluate for the possibility of spinal cord, cauda equine, or nerve root compression.

Plain Radiographs-
For symptomatic patients with point tenderness, plain radiographs are typically the most appropriate first imaging study. 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

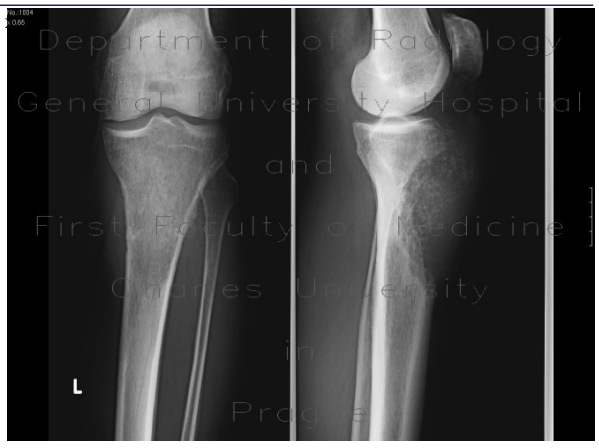

Figure 3: PLAIN RADIOGRAPHS SHOWING OSTEOLYTIC BONE METASTASES

Computed Tomography-
Computed tomography (CT) 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 metastasis. 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.

Magnetic Resonance Imaging-
Magnetic resonance imaging (MRI) 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 images can help distinguish whether a vertebral body compression fracture is from malignancy or from osteoporosis.

Technetium-99 m MDP Bone Scintigraphy-
It is the best method for screening patients at risk for bone metastasis 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.

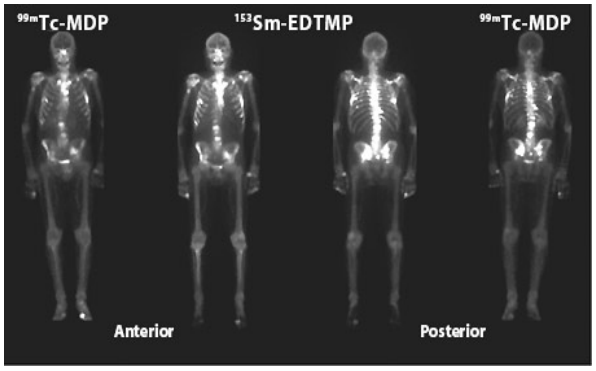

Figure 4: TECHNETIUM-99 M MDP BONE SCINTIGRAPHY

Positron Emission Tomography-

Positron emission tomography (PET) scanning evaluates areas of increased metabolic activity, most commonly using the 18-fluorodeoxyglucose (FDG). 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 MDP 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.

Fluoride 18 Bone Scan is more sensitive than Tc-99 m MDP scintigraphy in detecting osteoblastic metastasis and as Fluoride 18 is a positron emitting agent can obtain higher resolution of modern day PET cameras.Due to simultaneous coregistration with CT leads to proper localization and increased specificity as well as increased sensitivity as some lytic lesions missed on Fluoride bone scan can be seen on CT.

Treatment:

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.

Despite increasing understanding about the effective treatment of pain, patients with pain from bone metastases frequently have inadequate pain management. Barriers to pain treatment include physician underestimation of the patient's pain and reluctance by the patient to report pain73. There is a significant discrepancy between the physician estimate of pain and the pain level reported by the patient[74].

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 nonsteroidal 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 relief75,76.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.

The opioid-based pain medications frequently cause constipation and may cause nausea. Patients using opioid medications should routinely be administered a fiber medication with or without a stool softener to minimize constipation. Other side effects of the opioid analgesics may include sedation, mental status changes, and mood changes.

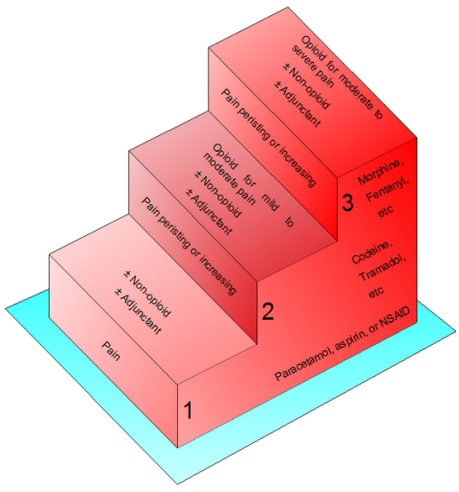

Figure 5: WHO ANALGESIC LADDER

Surgical Management-

Surgical management of bone metastases is performed primarily to prevent or treat pathologic fractures. The goals of surgical intervention are to prevent or relieve pain, improve motor function, and to improve overall quality of life. Treatment techniques are simpler and more effective when the procedure is performed prophylactically for an impending fracture rather than following the occurrence of a pathologic fracture. The risk of pathologic fracture depends on multiple factors including location and extent of the lesion; whether the lesion is osteolytic, osteoblastic or mixed; and the primary cancer site.

The femur accounts for 65% of pathologic fractures requiring surgical intervention77. The size of the bone metastasis is an important predictor of risk of fracture, especially with regard to the extent of cortical destruction. In series using plain radiographs, lesions ≥2.5 cm in the cortex of the femur were significantly more likely to fracture78. The proportion of cortical destruction is important as well. The risk of pathologic fracture of the femur begins to significantly increase when there is destruction of >50% of the cortex; the risk of fracture is 80% when >75% of the cortex is destroyed79. The location within the bone is important as well. An experimental model has shown that the greatest reduction in strength of the femur occurs with lesions in the inferior and medial aspect of the femoral neck, and posterior lesions have the least impact80.

A scoring system was proposed by Mirels81 that had a 12-point scale based on the location of the lesion, pain, extent of cortical destruction, and radiographic appearance (Table 2). The risk of fracture was 15% for a score of 8 and 33% for a score of 9. He proposed that prophylactic fixation was indicated for a score of ≥9.

Table :2 MIRELS' SCORING SYSTEM OF PREDICTION OF PATHOLOGIC FRACTURE RISK

Score	Pain	Location	Cortical Destruction	Radiographic Appearance
1	Mild	Upper limb	<1/3	Blastic
2	Moderate	Lower limb	1/3-2/3	Mixed
3	Severe	Peritrochanteric	>2/3	Lytic

A score is assigned for each of the four categories, and the sum of those scores is used to estimate the risk of pathologic fracture.

The decision to proceed with surgery should be based on a number of factors, which include but are not limited to the estimated risk of pathologic fracture. For patients with a very limited life span, surgery may not be indicated even if the risk of pathologic fracture is relatively high[77]. Clinical prediction of survival may be more accurate than relying on specific parameters such as diagnosis (primary site), performance status, number of bone metastases, presence of visceral metastases, and hemoglobin level[82].Fractures of the femoral neck can be managed either by total hip arthroplasty (which replaces both the femoral head and acetabulum) or by a proximal femoral endoprosthesis alone[77]. Fractures of the intertrochanteric area may be managed by open reduction and internal fixation without the use of a prosthesis. This may allow for better long-term gait because of preservation of the hip flexor and adductor strength77. Lytic disease that extends below the intertrochanteric area is treated with a long intramedullary rod that provides stability throughout the length of the femur . If there is significant destruction of the greater trochanter and femoral neck or head in addition to subtrochanteric involvement, a prosthetic replacement would be more appropriate than a reconstruction nail83. Fractures of the distal femur may be managed either with a plate and compression screw or with an intracondylar nail and screws augmented by intramedullary methylmethacrylate cement. The latter method may reduce the risk of late failure of the repair, especially in patients receiving postoperative radiation therapy[77].

Interventional Techniques:

Vertebroplasty is an effective method of palliating pain from vertebral body metastases, even in patients who have received prior radiotherapy[84]. Most patients experience pain relief within 48 hours. The procedure involves percutaneous injection of methylmethacrylate under CT or fluoroscopic guidance. Retropulsion of bone , epidural tumor, or collapse of the bone to less than one-third of its original

height are relative contradictions to percutaneous vertebroplasty because of the risk of the extrusion of the cement into the spinal canal, potentially causing neurologic complications. In some patients with epidural tumor, percutaneous vertebroplasty can be performed safely and effectively with a relatively low risk of serious complications[85,86].

Kyphoplasty involves percutaneous placement of a balloon-like device into symptomatic spinal metastasis(most commonly into a fractured or compressed vertebral body[87]. The balloon is then inflated to restore the height of the vertebral body, and methylmethacrylate is subsequently injected into this cavity. This procedure may provide significant relief of pain and improve overall functioning, especially in patients with mechanical instability of the vertebral body88.Kyphoplasty may be a better option than vertebroplasty in patients with vertebral wall deficiency[88].

An ablative procedure is frequently coupled with vertebropalsty or kyphoplasty.Radiofrequency ablation(RFA) may be used to ablate the tumor but is most effective for tumors that are osteolytic or mixed osteolytic and blastic. The RFA may not be as effective in tumors that are primarily sclerotic, Cryoablation may be used for larger lesions or those that are sclerotic. For both of these procedures, special attention to cord and nerve a temperature is required to minimize the risk of complications.

Neuroablative Techniques:
Common nerves that are neurolyzed include intercostal nerves (for thoracotomy pain), maxillary and mandibular nerves (for postherpetic neuralgia), and median branch nerves (for back pain) . Cryoanalgesia techniques involve the application of subzero temperatures to induce wallerian degeneration of neurons, but allowing normal regrowth of axons. Radiofrequency techniques apply heat to nerves to cause damage. Chemical neurolysis can be achieved with phenol or alcohol preparations.

Neuroaxial Techniques:
Both semipermanent epidural systems and permanent intrathecal delivery systems can be used to deliver local anesthetic and opiate medications in low concentrations to appropriate spinal cord root levels. The benefits of these methods include the use of local anesthetics in concentrations that are not toxic but can provide analgesia at the spinal cord level.

Systemic Treatment:
The pathophysiology of bone metastasis involves hematogenous dissemination and most patients with bone metastasis suffer from multiple synchronous sites of disease. Systemic chemotherapy may offer palliative benefit if symptoms are diffuse or constitutional, and disease is widespread.

Measurement of response to systemic therapy has generally been with the same criteria used for solid metastatic tumors: a measurable radiographic change. This works well for lung and liver metastasis, but not as well for bone metastasis. For bone metastases, the definition of a complete response is complete disappearance of all lesions on radiographs for at least 4 weeks. This is unlikely to occur even if all tumor cells are eradicated. A partial response requires some recalcification of lytic lesions, which may not be evident for 6 months or more89. PET scans may be more accurate at assessing response in a timely manner, but are too expensive to be used as a routine follow-up evaluation for bone metastases. Markers of bone resorption may be a good way to detect response to therapy, but are not clinically available at this time.

A number of hormonal therapies are available in the management of metastatic prostate and breast cancer. In properly selected patients, hormonal therapy has the potential for providing excellent palliation of metastatic disease with limited morbidity.

The bisphosphonates are pyrophosphate analogs that bind to calcium phosphate with high affinity and are potent agents affecting bone resorption[90]. There is emerging evidence that the bisphosphonates also induce apoptosis in cancer cells91. Clodronate is a first-generation, non-nitrogen-containing bisphosphonate. Clodronate has a high affinity for bone mineral and is subsequently taken up into activated osteoclasts during bone resorption, thereby ensuring high concentrations within osteoclasts92. The nitrogen-containing bisphosphonates inhibit the key enzyme farnesyldiphosphonate synthase in the mevalonate pathway[93]. This prevents the action of several additional enzymes required for bone resorption. The bisphosphonates include pamidronate, alendronate, ibandronate, risedronate, and zoledronic acid. Zoledronate is much more potent than the other bisphosphonates, in part because it also inhibits tumor cell adhesion to the extracellular matrix.

Complications of supportive therapy with bisphosphonates include osteoradionecrosis (particularly of the jaw) and renal insufficiency[94]. The mechanism of bisphosphonate-induced osteoradionecrosis is not known. Risk factors include the intravenous use of pamidronate and zoledronic acid, duration of treatment of 36 months or longer, older age in patients with multiple myeloma, and need for periodontal procedures[95].

Another form of systemic therapy is the use of agents that target the RANK pathway. Denosumab is a human monclonal antibody specific for RANK ligand. The antibody binds to RANKL and thus inhibits formation, activation,maturation,survival of osteoclasts[96]. Denosumab was superior to zoledronic acid in delaying or preventing the time to skeletal events.

Radiation Therapy:
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 versus. osteoblastic), location of the metastases, weight-bearing vs. non-weight-bearing site, extent of disease, number of painful sites, marital status, and 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, or local control of the disease. The doses required and volumes treated may be quite different for each of these goals.

There have been multiple randomized prospective trials in the past 25 years comparing shorter-course, lower total-dose treatment to the more standard longer course, higher-dose treatment. Several conclusions are clear from these studies:

- Single dose treatments of 8 Gy provide similar pain relief to longer treatment regimens (30 Gy in 10 fractions or 20 to 24 Gy in five to eight treatments).
- The retreatment rates are higher after short course treatment, by a factor of 2 to 3
- Response rates are lower when scored by the patient instead of by the treating physician.
- Response rates are better when the initial pain scores are lower, that is, when the patients are treated for moderate pain rather than severe pain.
- There is no consistent dose response relationship for palliation of bone metastases.

The lack of a dose-response relationship suggests that the mechanism of initial pain relief is not a reduction in tumor burden, but more likely a change in the local environment that has caused activation of bone resorption by osteoclasts. This helps to explain the seeming paradox of similar pain improvement with single-dose treatment compared with higher total-dose, longer-course treatment.

This mechanism of pain relief may also help to explain the higher rates of retreatment after single-dose 8-Gy treatment as there will be less cell kill with this dose compared with 30 Gy in 10 fractions. Thus, for patients with a longer life span, there is a greater opportunity for regrowth of the tumor, which may again impact the local milieu, causing osteoclast activation.

For patients with a poor performance status, difficulty making multiple

trips for treatment, extensive nonosseous metastases, and/or a short life expectancy, the most appropriate treatment is a single fraction of 8 Gy. For patients with a longer life expectancy, bone-only metastases, and good performance status, a longer course of treatment (30 Gy in 10 fractions) may be more appropriate to minimize the risk of retreatment. For selected patients with a solitary bone metastasis (oligometastasis), an even higher dose of treatment may be indicated, although this must be tempered by potential weakening of surrounding normal bone.

The single large fraction treatment may be more likely to cause a flare reaction, with a temporary increase in pain at the site of the metastases . The risk of this side effect may be diminished by the use of anti-inflammatory medications, either corticosteroids or nonsteroidal anti-inflammatory medications. Although the risk of significant acute toxicity has been low in the randomized trials, another potential concern is the risk of nausea or emesis if a significant portion of the stomach is within the treatment field (e.g., with a field covering the lower thoracic spine). It may be beneficial to give prophylactic antiemetics 1 to 2 hours prior to the treatment to minimize the possibility of this side effect.The use of bisphosphonates with external-beam radiotherapy may further improve the outcome in terms of both pain and bone healing.

HEMI BODY IRRADIATION:

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. The toxicities from each of the fields depend on the critical structures included. The most problematic of these is the risk of radiation pneumonitis with upper HBI. This is the dose-limiting toxicity for upper HBI, and dose-inhomogeneity corrections for the lung are necessary to minimize the risk of fatal pneumonitis. A lower total dose can be given to the upper hemibody fields compared with the middle or lower hemibody areas.

RTOG 78-10 was a dose-searching prospective protocol evaluating the maximum tolerated dose (MTD) for single-dose HBI[97] . 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. Improvement in pain was noted in 80% of patients with breast cancer and 90% of patients with prostate cancer. Overall, the response rate in terms of pain relief was 73%, with complete relief of symptoms seen in 19%. Pain relief was seen relatively rapidly, with 50% of responses occurring within 2 days and 95% of responses within 2 weeks. The subsequent study RTOG 82-06 evaluated the use of HBI in addition to local radiotherapy to determine if the HBI would prevent the development of new sites of disease[98]. All of the patients received involved field irradiation to one or more painful sites, and half of the patients were randomly assigned to receive single-dose HBI as well. The median time to progression was 6.3 months in the local treatment only group compared with 12.6 months for those receiving HBI. Fewer patients receiving HBI required additional treatment. The incidence of severe hematologic toxicity was low and transitory, but was seen only in the group receiving HBI.

The doses per fraction have ranged from 2.5 to 4 Gy to a total of 8 to 20 Gy. The maximum tolerated dose on the RTOG 88-08 study was 17.5 Gy in seven fractions. On the International Atomic Energy Agency study, 3 Gy twice daily for 2 days (12 Gy total) or 3 Gy daily for 5 days (15 Gy total) was more effective than 4 Gy daily for 2 days.

The primary toxicities were hematologic and gastrointestinal. The rationale for these doses was to decrease the acute toxicity. However, each of these regimens requires multiple treatments during several days, and the acute toxicities are not appreciably different than the single-dose treatment. With the use of appropriate antiemetic premedications and with cytokines to aid in hematologic recovery, there does not appear to be any appreciable benefit to the fractionated HBI compared with the single dose.

Premedication with antiemetics and anti-inflammatory medications will significantly reduce the acute side effects of treatment. Prior to the development of the 5-HT3 receptor antagonists, nausea was a significant side effect of treatment, even with pre- and posttreatment using steroids, prochlorperazine, and intravenous hydration. With the use of ondansetron, granisetron, or other 5-HT3(Serotonin) receptor antagonists, the incidence of acute nausea and emesis has been minimized and HBI is well tolerated[99]. A typical premedication regimen consists of dexamethasone, 8 to 16 mg, and ondansetron, 8 to 16 mg, 1 hour before treatment with HBI[100] .

Figure 6: LINEAR ACCELERATOR

Radiopharmaceuticals:

The concept of radiopharmaceutical treatment is compelling[101]. Calcium (and to a lesser extent phosphorous) analogs will preferentially accumulate in bone, especially in areas of active bone turnover. A radioactive isotope that is a β-emitter or low energy β-source will allow localized treatment in the areas in which the radiopharmaceutical accumulates, thus minimizing side effects and giving an excellent therapeutic ratio. The radiopharmaceuticals are given in a single injection that is easily administered. The treatment can be combined with other modalities, including chemotherapy or external-beam radiation therapy.

The first radiopharmaceutical used for treatment of bone metastases was phosphorous-32 (P-32). Treatment with P-32 for diffuse bone metastases was successful in giving subjective pain relief, but with unacceptable bone marrow toxicity. Other radioisotopes have been used for the palliation of diffuse osseous metastases, with a better therapeutic ratio than P-32. Strontium-89 (Sr-89) is chemically similar to calcium, and is deposited in the bone matrix, preferentially in sites of active osteogenesis. Sr-89 is a pure β-emitter with an energy of 1.4 MeV and a half-life of 50.6 days[102]. Samarium-153 (Sm-153) is primarily a β-emitter, but also has a component of gamma emission, which is useful for imaging purposes. The Sm-153 ethylene diamine tetra methylene phosphoric acid (EDTMP) is concentrated in areas of high bone turnover, accumulating in areas of hydroxyapatite. The physical half-life of Sr-153 is 46.3 hours, but the biologic half-life is much shorter because about half of the compound is excreted in the urine within 8 hours of injection[103]. These two isotopes have been evaluated in multiple prospective trials. There are other newer isotopes that are being evaluated including rhenium-186, rhenium-188, and tin-117 m. All of these isotopes accumulate in areas of osteoblastic activity, especially in areas of increased uptake on bone scintigraphy; for this reason, most of the patients entered on prospective trials have metastatic prostate cancer.

Strontium-89: Strontium-89 (Sr-89) is chemically similar to calcium, and is deposited in the bone matrix, preferentially in sites of active osteogenesis. Sr-89 is a pure Î²-emitter with energy of 1.4 MeV and a half-life of 50.6 days[102].Strontium-89 treatment is cost effective.

Samarium-153: Samarium-153 (Sm-153) is primarily a β-emitter, but also has a component of gamma emission, which is useful for imaging purposes.The Sm-153 ethylene diamine tetra methylene phosphoric

acid (EDTMP) is concentrated in areas of high bone turnover, accumulating in areas of hydroxyapatite. The physical half-life of Sr-153 is 46.3 hours, but the biologic half-life is much shorter because about half of the compound is excreted in the urine within 8 hours of injection103.

Samarium-153 is chelated with ethylene diamine tetra-methylene phosphoric acid to form Sm-153 EDTMP, a compound that is preferentially taken up in newly formed bone.The unbound remainder of the drug is rapidly cleared via urinary excretion. Doses above 2.5 mCi/kg are associated with neutropenia.

Patient Selection:
Radiopharmaceuticals, specifically Sr-89 and Sm-153, are effective in providing pain relief for patients with diffuse osseous metastases. This is primarily true for metastases that have an osteoblastic component. In general, if a Tc-99 m nuclear medicine bone scan shows localized areas of increased uptake, then radiopharmaceutical treatment is likely to be of benefit. An advantage of radioisotope treatment is that it can be combined with other modalities, such as external-beam radiation therapy or chemotherapy. Because the targets of treatment are similar, treatment with bisphosphonates should not be given simultaneously with radioisotopes as this may reduce the efficacy of both medications. Relative contraindications to therapy would be impaired renal or hepatic function, or inadequate hematologic reserve.

Complementary Therapies :
Several complementary medicine modalities such as hypnosis, massage, music therapy, mind-body exercises , and dietary supplementation have been shown to reduce anxiety and chronic pain. Acupuncture is perhaps the most extensively studied method for pain control. Acupuncture relieves both acute (e.g., postoperative dental pain) and chronic (e.g., headache, osteoarthritis) pain . Acupuncture appears effective against cancer-related pain Palliative radiation therapy is of significant benefit to patients with painful bone metastasis, with most patients experiencing relief in the magnitude of pain following treatment. Response rates to palliative radiation therapy for localized sites of pain are consistently higher than response rates from palliative systemic therapy, and palliative external-beam radiation therapy remains the mainstay of treatment for clinically localized painful bone metastasis. Providing shorter, single fraction palliative treatment schedules (i.e., 800 cGy X one fraction) for properly selected patients with bone metastasis can help better integrate palliative radiation therapy into the multidisciplinary management of patients with metastatic cancer and offer equivalent palliation compared with longer courses of palliative radiation therapy. Systemic targeted therapies including Sm-153 and Sr-89 offer yet another means to target painful sites of blastic bone metastasis without limiting our ability to use localized external-beam radiation therapy and systemic chemotherapy.

MATERIALS AND METHODS

Type of Study:
Prospective study (randomized selection of patients)

Place of Study:
Department of Radiotherapy,
MNJ Institute of Oncology,
Red Hills, Hyderabad, Andhra Pradesh.

Study period:
November 2011 to October 2013

Patients:
Total 40 patients and were randomised into two arms, each arm contain 20 patients.

Mean age of the patient is 44.5 years.
Male patients are16 and remaining 24 patients are females.
Patients are followed for 12 weeks.
Reviews: Immediately after radiotherapy, after 1 week, 4weeks, 8weeks and 12 weeks.

Inclusion Criteria:
The study includes patients with painful bone metastases from any primary, localized to a single region that could be encompassed in a single radiation field. All metastases were radiologically verified and histopathologically confirmed primary.

Exclusion Criteria:
1) Previous radiotherapy to the region concerned,
2) Presence of any co-morbid condition to which the patient's symptoms can be attributed. Eg: (osteoporosis)

Positioning and Technique:
For spinal metastases treatment was prescribed in prone position. For long bones and pelvic bones metastases treatment was prescribed in supine position.

The Target volumes were based on clinical and radiological judgment. Fields were planned to include known skeletal manifestation with an additional 2-3 cm margin. For spinal lesion the fields included at least one vertebral body above and below the painful vertebrae, a single direct field prescribed at particular depth is used for treatment delivery.

For cervical vertebral lesions dose was prescribed at 4 cm depth For thoracic and lumbar vertebrae at 5cm depth For long bone and pelvic lesions, mid plane prescribed doses were delivered by two opposing fields

Equipment used to deliver Radiation:
High Energy Linear accelerator
Cobalt 60

Therapeutic Radiotherapy Regimen Schedule:
ARM A: 8 Gray in single fraction.
ARM B: 30 Gray in ten fractions.

Patients with bone metastases are allocated to each arm randomly. Informed consent was obtained from all the patients before they underwent clinical evaluation including a detailed history, physical examination, baseline laboratory investigations and imaging studies.

Evaluation of baseline pain, analgesic consumption and performance status were recorded on the first day of treatment. At the same time, the scoring system was explained to the patient.

Patient Evaluation Criteria:
Pain palliation response was defined as improvement in pain score with respect to the pretreatment value. It was evaluated by verbal rating scale

Verbal rating scale: Is a 5 point pain scale from 0-4
0- No pain
1- Mild Pain
2- Moderate pain
3- Severe Pain
4- Incapacitating pain

Functional Outcome:
Table: 3 ECOG Performance Status

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Analgesic Requirement:
0- Not requiring any analgesics
1- Simple analgesics(NSAIDs)
2- Mild Narcotics (codeine, tramadol)
3- Strong narcotics(Morphine, Fentanyl)
4- High dose narcotics Inadequate

Duration of Response: Defined as the time from initial response of

pain relief to the return of pain to its baseline value or more.

Follow Up Evaluation:
Patients were followed up immediately after treatment, 1week after treatment on phone and then monthly follow up visit to the hospital for three months. At each follow up, assessment of pain score, performance status and analgesic requirements were noted.

Response Definitions: The extent of pain relief was the main indicator for effective palliation.

Overall Response: Defined as improvement in pain score by at least one point with respect to the pretreatment value.

Complete Response: Defined as achieving a pain score of 0 at any point during follow-up.

Time for Onset of Response: Day when patient reported improvement in pain score by at least one point.

Duration of Response: Defined as time from initial response till return of pain to its base line value.

Duration of Complete Response: was calculated from date of complete pain relief to the date of increase in pain score above zero.

RESULTS:
In this study total 40 patients were randomized into two arms, each arm contain 20 patients. Mean age of the patient is 44.5 years.

TABLE: 4 AGE DISTRIBUTION

AGE	ARM- A NO.OF PATIENTS	ARM- A % OF PATIENTS	ARM- B NO.OF PATIENTS	ARM- B % OF PATIENTS
10- 19 YEARS	1	5	1	5
20- 29 YEARS	3	15	1	5
30- 39 YEARS	3	15	3	15
40- 49 YEARS	6	30	7	35
50- 59 YEARS	6	30	2	10
60- 69 YEARS	1	5	5	25
70- 79 YEARS	0	0	1	5

Male patients are 16 and remaining 24 patients are females. Patients were randomized into two arms, Arm – A containing 13 female patients (65%),7 male patients (35%) received RT of 8 gray in single fraction. Arm – B containing 11 female patients (55%), 9 male patients (45%) received RT of 30 gray in 10 fractions.

Bone metastases from different primary sites were included. In Arm-A, 9 cases are breast carcinomas,3 are lung primaries,3 cases are Metastases of unknown origin(MUO),1 is from carcinoma nasopharynx,2 cases are from cervical carcinomas,1 case is carcinoma Penis,1 case is bone secondaries from Renal Cell Carcinoma.These 20 patient received 8 gray of radiation in single fraction.Pain score ,functional status(ECOG Performance status),Analgesic Requirement are assessed before RT,immediate post RT,1 week Post RT,4 weeks Post RT,8weeks Post RT,12 weeks Post RT.Duration of Response is assessed.

In Arm-B 7 cases are from Carcinoma Breast,2 cases are from Carcinoma Lung,3 cases are from Prostate Carcinoma,2 cases are from Metastases of Unknown Origin(MUO),1 case is from Nasopharyngeal Carcinoma,1 case is from Parotid carcinoma,1 case is from Carcinoma Oesophagus,1 case is from Medulloblastoma,1case is from Ewings Sarcoma,1 case is from Non-Hodgkins Lymphoma. These 20 patient received 30 gray of radiation in 10 fractions.Pain score ,functional status(ECOG Performance status),Analgesic Requirement are assessed before RT,immediate post RT,1 week Post RT,4 weeks Post RT,8weeks Post RT,12 weeks Post RT.Duration of Response is assessed.

In Arm-A initially before starting RT one patient had a pain score of 2,eleven patients had pain score of 3,eight patients had a pain score of 4,no patient had a pain score of 1,mean score of 3.35 . In Arm-B initially before starting RT one patient had pain score of 2 ,twelve patients had pain score of 3,seven patients had a pain score of 4,no patient had a pain score of 1,mean score of 3.30, p-value = 0.786

TABLE 5: PAIN SCORES BEFORE RADIOTHERAPY

PAIN SCORE BEFORE RT	NO.OF PATIENTS IN ARM-A	PERCENTAGE OF PATIENTS IN ARM-A	NO.OF PATIENTS IN ARM-B	PERCENTAGE OF PATIENTS IN ARM-B
0	0	0	0	0
1	0	0	0	0
2	1	5	1	5
3	11	55	12	60
4	8	40	7	35

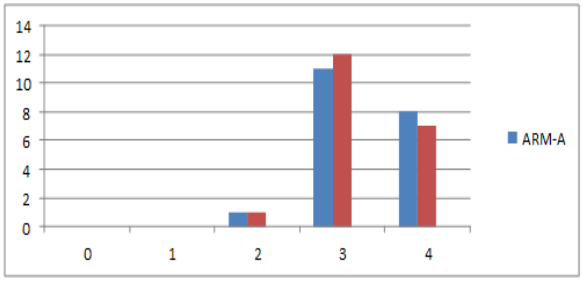

CHART 1: PAIN SCORES BEFORE RADIOTHERAPY

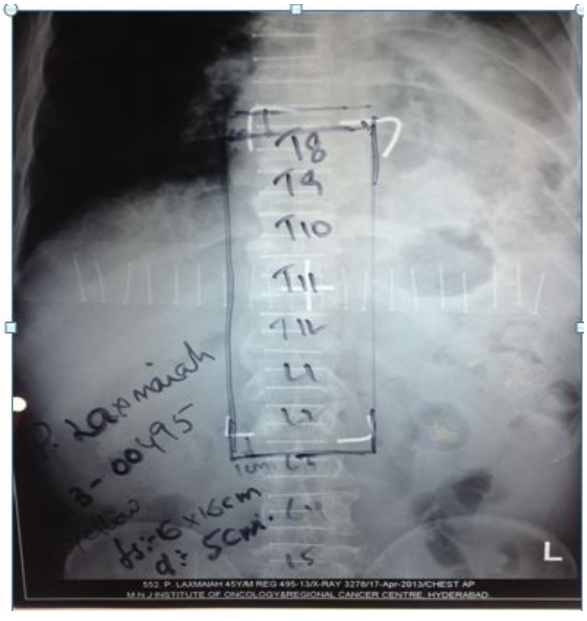

Figure 7: PLANNING X-RAY

Immediately after RT in Arm-A one patient had a pain score of 2,eleven patients had pain score of 3,eight patients had a pain score of 4,no patient had a pain score of 1,mean score of 3.350.In Arm-B, Immediately after RT one patient had pain score 2, twelve patients had pain score of 3,seven patients had a pain score of 4,mean sore of 3.30, p-value=0.786

In Arm – A,One week post RT no patient had pain score 0,seven patients had pain score 1,eight patients had pain score 2,five patients had pain score 3,no patients had pain score 4,mean score of 1.9.In Arm - B One week post RT no patient had pain score 0,seven patients had pain score 1,nine patients had pain score 2,four patients had pain score

3,no patients had pain score 4,mean score of 1.85, p-value=0.838

In Arm-A, 4 weeks post RT five patients had pain score 0, seven patients had pain score 1, four patients had pain score 2, four patients had pain score 3,no patients had pain score 4 mean score of 1.350.In Arm-B, One month post RT four patients had pain score 0,eight patients had pain score 1,four patients had pain score 2, four patients had pain score 3,no patient had pain score 4,mean score of 1.40, p-value=0.883

In Arm-A,8 weeks post RT four patients had a pain score of 0, three patients had a pain score of 1, eight patients had a pain score of 2, four patients had a pain score of 3, one patient had a pain score of 4,mean score of 1.75.In Arm-B, Two months post RT four patients had a pain score of 0, four patients had a pain score of 1, seven patients had a pain score of 2, five patients had a pain score of 3, no patient had a pain score of 4,mean score of 1.65, p-value=0.781

In Arm-A,12 weeks post RT RT four patients had a pain score of 0, three patients had a pain score of 1, eight patients had a pain score of 2, four patients had a pain score of 3, one patient had a pain score of 4,mean score of 1.75.In Arm-B,12 weeks post RT RT four patients had a pain score of 0, four patients had a pain score of 1, seven patients had a pain score of 2, four patients had a pain score of 3, one patient had a pain score of 4,mean score of 1.70, p-value=0.893

TABLE 6: PAIN SCORE 12 WEEKS POST RT

PAIN SCORE 12 WEEKS POST RT	NO.OF PATIENTS IN ARM-A	PERCENTAGE OF PATIENTS IN ARM-A	NO.OF PATIENTS IN ARM-B	PERCENTAGE OF PATIENTS IN ARM-B
0	4	20	4	20
1	3	15	4	20
2	8	40	7	35
3	4	20	4	20
4	1	5	1	5

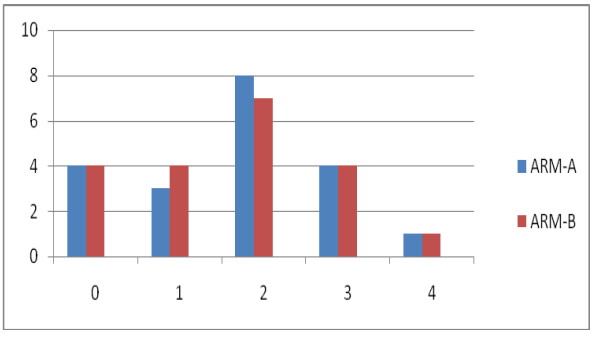

CHART 2: PAIN SCORE 12 WEEKS POST RT

ECOG performance status initially in Arm-A is two in 6 patients,three in 8 patients ,four in 6 patients mean score of 3.0.In Arm-B, ECOG performance status initially in Arm – B is two in 5patients,three in 9 patients ,four in 6 patients,mean score of 3.05, p-value = 0.840

TABLE 7: ECOG PERFORMANCE STATUS BEFORE RT

ECOG PERFORMANCE STATUS BEFORE RT	NO. OF PATIENTS IN ARM-A	PERCENTAGE OF PATIENTS IN ARM-A	NO. OF PATIENTS IN ARM-B	PERCENTAGE OF PATIENTS IN ARM-B
0	0	0	0	0
1	0	0	0	0
2	6	30	5	25
3	8	40	9	45
4	6	30	6	30

In Arm-A,immediate after RT two in 6 patients,three in 8 patients,four in 6 patients,mean score of 3.000.In Arm-B, Immediate after RT two in 5 patients,three in 9 patients,four in 6 patients,mean score of 3.050, pvalue = 0.840

In Arm-A,1 week after RT ,one for 4 patients,two for 12 patients,three for 2 patients,four for 2 patients,mean score of 2.100.In Arm-B, 1 week after RT ,one for 4 patients,two for 11 patients,three for 3 patients,four for 2 patients,mean score of 2.150, p-value = 0.856

In Arm-A,4 weeks after RT zero for 2 patients,one for 6 patients,two for 11 patients,three for 1 patients ,mean score of 1.550. In Arm-B, 1 month after RT zero for 2patients,one for 6 patients,two for 10 patients,three for 2 patients,mean score of 1.6, p-value=0.843

In Arm-A, 8 weeks after RT zero for 2patients,one for 5 patients,two for 11 patients,three for 2 patients, mean score of 1.65.In Arm-B, 8weeks after RT zero for 2patients,one for 5 patients,two for 10 patients,three for 3,mean score of 1.700, p-value=0.852

In Arm-A, 12 weeks after RT zero for 2patients,one for 6 patients,two for 10 patients,three for 2 patients,mean score of 1.600.In Arm-B, 12 weeks after RT zero for 2patients,one for 6 patients,two for 9 patients,three for 3 patients,mean score of 1.650, p-value = 0.853

TABLE 8: ECOG PERFORMANCE STATUS 12 WEEKS POST RT

ECOG PERFORMANCE STATUS 12 WEEKS POST RT	NO. OF PATIENTS ARM-A	PERCENTAGE OF PATIENTS ARM-A	NO. OF PATIENTS ARM-B	PERCENTAGE OF PATIENTS ARM-B
0	2	10	2	10
1	6	30	6	30
2	10	50	9	45
3	2	10	3	15
4	0	0	0	0

Analgesic requirement in Arm-A initially was two in 7 patients, three in 13 patients,mean score of 2.700.Analgesic requirement in Arm-B initially was , two in 6 patients,three in 14 patients, mean score of 2.650, p-value = 0.744

TABLE 9: ANALGESIC REQUIREMENT BEFORE RT

ANALGESIC REQUIREMENT BEFORE RT	NO. OF PATIENTS ARM-A	PERCENTAGE OF PATIENTS ARM-A	NO. OF PATIENTS ARM-B	PERCENTAGE OF PATIENTS ARM-B
0	0	0	0	0
1	0	0	0	0
2	7	35	6	30
3	13	65	14	70
4	0	0	0	0

In Arm-A,Analgesic requirement immediately after RT two in 6patients,three in 14 patients , mean score of 2.700.In Arm-B, Immediately after RT two in 7 patients,three in 13 patients ,mean score of 2.65, p-value = 0.744

In Arm-A,1 week after RT ,one in 9 patients,two in 7 patients,three in 4 patients ,mean score of 1.750.In Arm-B, 1 week after RT ,one in 10 patients,two in 7 patients,three in 3 patients,mean score of 1.650, p-value = 0.682

In Arm-A, 4 weeks after RT zero in 4 patients,one in 8 patients,two in 6 patients,three in 2 patients mean score of 1.3. In Arm-B, 4 weeks after RT zero in 4 patients,one in 8 patients,two in 6 patients,three in 1 patients,four in 1 patient,mean score of1.35, p-value=0.873

In Arm-A, 8 weeks after RT zero in 4 patients,one in 4 patients,two in 9 patients,three in 3 patients,mean score of 1.55. In Arm-B, 8 weeks after RT zero in 4 patients,one in 4 patients,two in 9 patients,three in 2 patients,four in 1 patient, mean score of 1.60, p-value = 0.881

In Arm-A,12 weeks after RT zero in 4 patients,one in 5 patients,two

in 8 patients,three in 3 patients, mean score of 1.550.In Arm-B, 12 weeks after RT zero in 4 patients,one in 5 patients,two in 8 patients,three in 2 patients,four in 1 patient, mean score of 1.550, p-value = 0.881

TABLE 10: ANALGESIC REQUIREMENT 12 WEEKS POST RT

ANALGESIC REQUIREMENT 12 WEEKS POST RT	NO. OF PATIENTS ARM-A	PERCENTAGE OF PATIENTS ARM-A	NO. OF PATIENTS ARM-B	PERCENTAGE OF PATIENTS ARM-B
0	4	20	4	20
1	5	25	5	25
2	8	40	8	40
3	3	15	2	10
4	0	0	1	5

Duration of response in Arm _ A 1 month in 5 patients,3months in 12 patients,no response in 3 patients.In Arm _ B duration of response 1 month in 5 patients,3 months in 12 patients,no response in 3 patients, p-value = 1.000

TABLE 11: DURATION OF RESPONSE

DURATION OF RESPONSE IN ARM-A IN MONTHS	NO.OF PATIENTS IN ARM-A	PERCENTAGE OF PATIENTS IN ARM-B	NO.OF PATIENTS IN ARM-B	PERCENTAGE OF PATIENTS IN ARM-B
0	3	15	3	15
1	5	25	5	25
2	0	0	0	0
3	12	60	12	60

There is no significant difference in between two arms in terms of pain control,functional outcome,analgesic requirement and duration of response.

TABLE 12: ANOVA FOR PAIN SCORE

Source of Variations	df	Sum of Squares	Mean Squares	F Ratio	Probability	η^2	$\eta\rho^2$	ω^2
Time	5	151.6208	30.32417	36.1134	1E-06	0.441662	0.441952	0.297873
ARM	1	0.104167	0.101667	0.124053	0.725005	0.000303	0.000544	-0.00214
Time*ARM	5	0.120833	0.024167	0.02878	0.999597	0.000352	0.000631	-0.01187
Error (B)	228	191.45	0.839693					
Total	239	343.2958	1.436384					

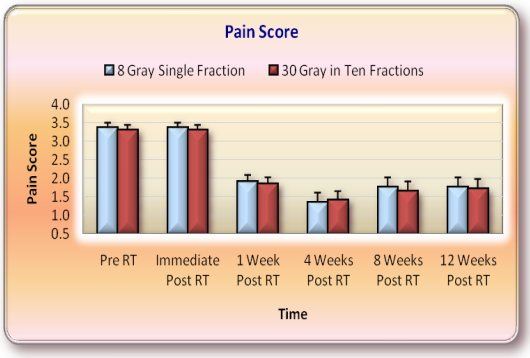

CHART 3:ANOVA FOR PAIN SCORE

TABLE 13: ANOVA FOR DURATION OF RESPONSE

Source of Variations	df	Sum of Squares	Mean Squares	F Ratio	Probability	η^2	$\eta\rho^2$	ω^2
Between Groups	1.000	0.000	0.000	0.000	1.000	0.000	0.000	-0.026
Within Groups	38.000	57.900	1.524	0.000	1.000	0.000	0.000	0.000
Total	39.000	57.900	1.485					

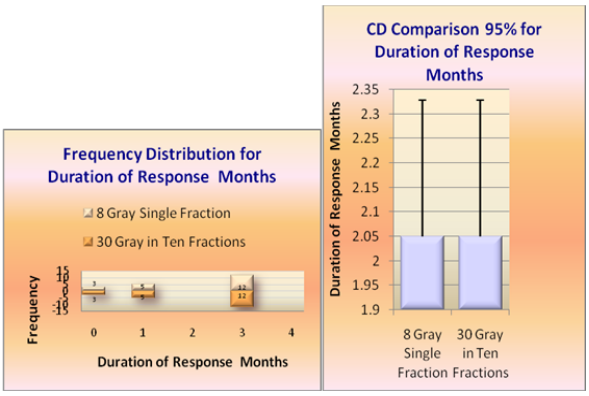

CHART 4: ANOVA FOR DURATION OF RESPONSE

TABLE 14: ANOVA SUMMARY

		Pain Score	ECOG Performance	Analgesic Requirement
Time	5.00	30.32	18.88	14.54
ARM	1.00	0.10	0.15	0.00
Time*ARM	5.00	0.02	0.00	0.04
Error (B)	228.00	0.84	0.67	0.70
Total	239.00	1.44	1.03	0.98
General Mean	-9.00	2.22	2.17	1.91
C.V.	-9.00	41.26	37.55	43.84
C.D. 95%	-9.00			
Ai.- Aj. (Time)	-9.00	0.40	0.36	0.37
Bi.- Bj. (ARM)	-9.00	0.23	0.21	0.21
AiBi-AiBj	-9.00	0.57	0.51	0.52
AiBi-AjBi	-9.00	0.57	0.51	0.52

DISCUSSION

Current management of bone metastases includes Radiotherapy, chemotherapy, hormone therapy, surgery, radionuclide and supportive therapy either alone or in combination. In most of the cases the treatment intent is palliation, when treatment goals are pain relief, function and quality of life and if possible, prolongation of survival.

Radiotherapy is the most effective treatment of bone metastases. At least 75% of patients achieve pain relief following radiotherapy and half of them stay free from pain.

Different Fractionation regimens are in practice for pain palliation. The purpose of this study was to compare 8 gray in single fraction RT with 30 gray in 10 fractions of multiple fraction RT in the palliative treatment of painful bone metastases. In Indian patients where metastatic disease constitute a significant proportion of our total cancer workload in RT departments, as >50% of the patients present in advanced stage disease and ultimately develop metastases**.** This study addresses a therapeutic question of considerable clinical significance.

Average pain score before RT is 3.35 in Arm-A,3.30 in Arm-B. Patients were followed for 12 weeks. Pain relief, ECOG performance

status, analgesic requirement are assessed Immediately after radiotherapy, after 1 week, 4weeks, 8weeks and 12 weeks. Duration of pain relief was also assessed.

There is no statistically significant difference between the two arms in terms of pain relief(p-value=0.725),functional outcome(p-value=0.6358) Analgesic requirement(p-value=0.9387) ,Duration of response between the two arms(p-value=1.000). Pain score was highest during initial phase and immediately after RT,there after Pain score decreased lowest is at 1 month post RT on average.functional outcome measured in terms of ECOG performance status was better at 1 month Post RT.Analgesic Requirement was lowest at 1 month Post RT.To sum up the results the response is best at 1 month Post RT in both single fraction and multiple fractions arm and increasing thereafter.

Many studies were conducted to study the efficacy of different fractionation regimens in palliation of bone metastases.

In 1982, the Radiation Therapy Oncology Group (RTOG) for the first time reported that short-course RT schedules were as effective as longer-treatment programs in achieving pain relief from bone metastases in their trial RTOG 7402 .Randomised patients with solitary lesions to receive 40.5 gray in 15 fractions or 20 gray in 5 fractions .patients with multiole metastases were randomized to receive 30 gray in 10 fractions or 15 gray in 5 fractions, 20 gray in 5 fractions,25 gray in 5 fractions by blocing the spinal cord after 20 gray.Outcome is 90 % with pain relief and 54 % with complete pain relief.No difference in pain relief between different radiotherapy regimens.No difference in promptness of pain relief among different regimens,except there was an association between the dose and promptness for complete pain relief,fastest in 15 gray arm,slowest in 25 gray arm.No difference in duration of response.Conclusion is no difference among the regimens[104]. However, their trial was criticized for many of its shortcomings such as the inclusion of a heterogeneous group of primary cancer sites, the use of physician assessment of pain, and the fact that narcotic relief and the incidence of radiation therapy re-treatment were not taken into consideration.

RTOG 9714 (1998 – 2008) :Randomised 898 patients of prostate or breast cancer.Weight bearing areas are included with life expectancy >3 months,KPS >=40.Arm - A received 8 gray in single fraction versus Arm – B 30 gray in 10 fractions.Primary outcome pain relief at 3 months.Outcome:3month complete pain relief 15 % in Arm- A vs 18 % in Arm – B (p=0.6);Partialpain relief 50 % in Arm – A vs 48 % in Arm – B (p=0.6);Stable in 26 % in Arm – A vs 24 % in Arm – B (NS);Progressive 9 % in Arm – A vs 10 % in Arm- B (NS).Comparable narcotic relief.Retreatment rate 18 % in Arm _A vs 9 % in Arm –B(p<0.001).Acute toxicity rate 10 % in Arm – A vs17 % (p= 0.002) in Arm - B,Late toxicities rare (4%) in both the arms.

Conclusion: 8 gray in single fraction and 30 gray in 10 fractions arms are equivalent in terms of pain relief and narcotic relief.8 gray in single fraction arm had less acute toxicities but higher retreatment rates than 30 gray in 10 fractions arm105.

EUROPEAN STUDIES. In 1999, the Dutch Bone Metastasis Study group evaluated 8 Gy in 1 fraction versus 24 Gy in 6 fractions in 1171 patients with bone metastases[106]. No statistically significant differences were found in pain response, treatment side effects, and quality of life between these two schedules106.

Norway prospective randomized multicenter trial[107], 376 patients were randomized to single-fraction (8 Gy x 1) or multiple-fraction (3 Gy x 10) radiotherapy. Both groups experienced similar pain relief within the first 4 months, and this was maintained throughout the 28-week follow-up. No differences were found for fatigue and global quality of life. Survival was similar in both groups, with median survival of 8-9 months.

In another European randomized clinical trial comparing these two palliative radiotherapy regimens in painful bone metastases[108], a total of 160 patients were assigned to receive a single 8-Gy fraction or 30 Gy in 10 fractions. This trial also showed that a single-fraction regimen of 8 Gy was as safe and effective as a multi-fraction regimen of 30 Gy for painful bone metastases in terms of pain relief. However, the authors also found that the re-treatment rate of 8-Gy arm was much higher than that of 30-Gy arm (28% vs 2%).

A fourth European study compared the efficacies of 8 Gy in 1 and 5 Gy in 4 in a total of 241 patients[109]. The two groups did not differ with respect to age, sex, primary tumor, metastasis localization, analgesic consumption (type and dose), performance status, prior systemic treatment, degree of pain, and quality of life. The degree of pain relief did not differ between the two treatment groups. Neither was there any significant difference in the duration of pain relief, the number of new painful sites, and the need for reirradiation; the toxicity was minor.

The Bone Trial Working Party Study (BTWPG) reported another large scale trial, which compared 8 Gy in a single fraction versus 20 Gy in 5 fractions or 30 Gy in 10 fractions in 765 patients[110]. There were no significant differences in the time to first improvement in pain, time to complete pain relief, or time to the first increase in pain at any time up to 12 months from randomisation; furthermore, the class of analgesic used and the adverse events also showed no significant differences. According to the authors, a single fraction of 8 Gy was as safe and effective as a multi-fraction regimen for the palliation of metastatic bone pain for at least 12 months. Furthermore, the greater convenience and lower cost made 8 Gy single fraction the treatment of choice for the majority of patients. However, similar with the RTOG9714 trial, retreatment was twice as common after 8 Gy than after multi-fraction radiotherapy.

In Iran, the most common clinical RT fractionation schedule for bone metastases is 30 Gy in 10 fractions, which is quite similar with that in the United States. In 2008, Amouzegar–Hashemi et al. performed a randomized clinical trial to compare responses to 8Gy in a single fraction or 30 Gy in 10 fractions among Iranian patients[111], in which 58 patients were enrolled for the evaluation of pain one month after treatment. The results showed that these two schemes showed no significant difference in pain relief. The overall response rate was 71%, similar to results obtained from western countries.

Cochrane Review, 2004:"Paliiation of metastatic bone pain:single fraction versus multifraction radiotherapy – a systemic review of the randomized trials."[112].Pooled meta-analysis .11 trials,345 patients.Any primary site,but mainly prostate,breast and lung.

Pain Response : Single fraction60 % vs multifraction 59% (NS).Complete response34 % vs 32 % (NS).Single fraction higher re-treatment 21 %vs 7%(SS).

Pathological Fracture: Single fraction 3 % vs 1.5%.

Conclusion: Single fraction as effective as multiple fractions at relieving pain. Higher re-treatment and higher rate of pathologic fracture in the single fraction arm.

University of Toronto,2007-"Palliative Radiotherapy Trials for Bone metastases:A Systematic Review."[113] Single – fraction versus multiple fraction RT.Conclusion is Overall response and complete response same in single fraction(8/1) and multifraction treatments. Retreatment rate higher with single fraction.

Obviously, most of these prospective randomized trials showed no significant difference between the short-course or long-course schemes in terms of pain control and adverse effects. Some of the trials showed that 8 Gy in one fraction scheme had a higher retreatment rate than the multi-fraction schemes. To compare the need for re-irradiation in patients randomised to single-fraction radiotherapy (8 Gy x 1) or multiple-fraction therapy (3 Gy x 10), Sande et al[114]. conducted a long-term follow-up in cancer patients receiving radiotherapy for bone metastases. Patients in this study were followed up until death, and the result showed that patients in the single-fraction arm received significantly more re-irradiations as compared to the multiple-fraction arm (27% vs 9%, p=0.002).

The Dutch Bone Metastasis Study Group did a societal cost– utility analysis on their randomized, controlled trial[115] and found that, compared with the multiple-fraction radiotherapy, single-fraction radiotherapy provides equal palliation and quality of life and has much lower medical and societal costs.

In conclusion, randomized trials from different areas in the world have demonstrated that single-fraction radiation therapy is sufficient to achieve palliation of painful bone metastases with optimized convenience for both patients and caregivers. A single dose of 8 Gy seems to become the standard treatment. It is also notable, however,

patients receiving short-course radiotherapy may receive remarkably more re-irradiations. Therefore, the RT scheme should be tailored for each patient after cautious considerations.

CONCLUSIONS :

In this prospective randomized study 40 patients are randomized into two arms.Arm-A received 8 gray of RT in single fractions,Arm-B received 30 gray in 10 fractions.Conclusions of this study are:

1.8 gray in single fraction arm has similar pain relief compared to 30 gray in 10 fractions arm except for time gain.

2. 8 gray in single fraction arm has similar functional outcome (ECOG Performance status) compared to 30 gray in 10 fractions arm except for time gain.

3. 8 gray in single fraction arm has similar Analgesic requirement compared to 30 gray in 10 fractions arm except for time gain.

4.Duration of response is also similar between the two arms.

5.To sum up 8 gray in single fraction arm is similar to 30 gray in 10 fractions arm,but single fraction will be suitable for patients with poor Performance status and and with decreased life expectancy. Duration of hospital stay can be reduced in patients receiving single fraction and it is also cost effective.

SUMMARY

In this study total 40 patients were randomised into two arms, each arm containing 20 patients. Mean age of the patient is 44.5 years. Male patients are16 and remaining 24 patients are females. Patients were randomized into two arms, Arm-A containing 13 female patients (65%),7 male patients (35%) received RT of 8 gray in single fraction .Arm-B containing 11 female patients(55%),9male patients (45%) received RT of 30 gray in 10 fractions.Average pain score before RT is 3.35 in Arm-A,3.30 in Arm-B.Patients were followed for 12 weeks. Pain relief, ECOG performance status, analgesic requirement are assessed Immediately after radiotherapy, after 1 week, 4weeks, 8weeks and 12 weeks. Duration of pain relief was also assessed.

There is no satistically significant difference between the two arms in terms of pain relief(p-value=0.725),functional outcome(p-value=0.6358)Analgesic requirement(p-value=0.9387),Duration of response between the two arms(p-value=1.000). Pain score was highest during initial phase and immediately after RT,there after Pain score decreased lowest is at 1 month post RT on average.functional outcome measured in terms of ECOG performance status was better at 1 month Post RT.Analgesic Requirement was lowest at 1 month Post RT.To sum up the results the response is best at 1 month Post RT in both single fraction and multiple fractions arms.

ANNEXURES

MNJIO & RCC, HYDERABAD.
DEPT.OF RADIATION ONCOLOGY

Telephone: FAX:

PROFORMA

NAME-
AGE-
SEX-
OCCUPATION-
COMPLETE ADDRESS-
TELEPHONE NUMBER-
IP/OP NUMBER-
RT NUMBER-
HISTORY-
PRESENTING COMPLAINTS-

SITE OF PAINFUL BONE METASTASES-
OTHER SITES OF METASTASES-
SITE OF PRIMARY MALIGNANCY-

PRESCRIBED RADIOTHERAPY REGIMEN

ARM A/B

PAINSCORE: 0-NOPAIN, 1-MILD PAIN, 2-MODERATE PAIN, 3-SEVERE PAIN, 4-INCAPACITATING PAIN

Site of metastases	Before RT	Immediate after RT	1 week after RT	4 weeks after RT	weeks afterRT	12 weeksafter RT

FUNCTIONAL OUTCOME:

ECOG PERFORMANCE SCALE:

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

Site	Before RT	Immediate after RT	1 week after RT	4 weeks after RT	8 weeks after RT	12 weeks after RT

Analgesic Requirement: 0- Not requiring any analgesics, 1- Simple analgesics (aspirin, ibuprofen), 2- Mild narcotics (codeine, Tramadol), 3- Strong narcotics- (Morphine, Fentanyl), 4- High dose narcotics inadequate

Site	Before RT	Immediate after RT	1 week after RT	4 weeks after RT	8 weeks after RT	12 weeks after RT

Key to Master Chart :

1. S.NO - Serial Number
2. RT NO - Registration number
3. Y - Years
4. M - Male
5. F - Female
6. Rt - Right
7. Lt - Left
8. V - Vertebrae
9. NP - Nasopharynx
10. MUO - Metastases of Unknown Origin
11. RCC - Renal Cell Carcinoma
12. Non Hodgkins Lymphoma
13. P - Prior to Radiotherapy
14. I - Immediately after Radiotherapy
15. 1wk - 1 week after Radiotherapy
16. 4w - 4 weeks after Radiotherapy

17. 8w - 8 weeks after Radiotherapy
18. 12w - 12 weeks after Radiotherapy
19. C - Cervical
20. T - Thoracic
21. L - Lumbar
22. V - Vertebrae

LIST OF ABBREVIATIONS

1. ANOVA	Analysis Of Variables
2. C	Carpal
3.C Gy	Centi Gray
4. ECOG	European Cooperative Oncology Group
5. FGF	Fibroblast Growth Factor
6. Gy	Gray
7. H+ ATP	Proton Adenosine Triphosphate
8. M	Metacarpal
9. m2	Square Meter
10.m ci/kg	Milli Curie per Kilogram
11.MDP	Methylene Di Phosphate
12.MeV	Mega Electron Volt
13.mm	Milli Meter
14.MUO	Metastases of Unknown Origin
15.NFκβ	Nuclear Factor Kappa Beta
16.NHL	Non Hodgkins Lymphoma
17.NSAIDS	Non Steroidal Anti Inflammatory Drugs
18.OPG	Osteoprotogerin
19.P	Phalange
20.PDGF	Platelet Derived Growth Factor
21.PET	Positron Emission Tomogram
22.PTH	Parathyroid Hormone
23.PTHR	Parathyroid Hormone Receptor
24.p-value	Probability Value
25.RANK	Receptor Activated Nuclear Factor Kappa
26.RANKL	Receptor Activated Nuclear Factor Kappa Ligand
27.RTOG	Radiation Therapy Oncology Group
28.Tc 99	Technicium 99
29.TGF-β	Transforming Growth Factor Beta
30.TRAP	Tartarate Resistant Acid Phosphatase
31. WHO	World Health Organisation

MASTER CHART ARM-A

						PAIN SCORE-VERBAL RATING SCALE						ECOG PERFORMANCE STATUS						ANALGESIC REQUIREMENT						DURATION OF RESPONSE
Arm S.No	RT No	Age	Sex	Site	Primary	P	I	1wk	4W	8W	12W	P	I	1wk	4w	8w	12w	P	I	1wk	4w	8w	12w	
A1	7183/98	60Y	F	Lt Humerus	B/L Breast	4	4	2	0	0	0	3	3	2	0	0	0	3	3	2	0	0	0	3 months
A2	4388/05	38Y	F	T9-T10 V	Rt Breast	4	4	2	0	0	0	4	4	2	0	0	0	3	3	2	0	0	0	3 months
A3	1109/06	35Y	F	Rt Hemipelvis	Rt Breast	3	3	1	1	1	1	3	3	2	1	1	1	2	2	1	1	1	1	3 months
A4	4547/11	14Y	F	T5-T7 V	NP	4	4	2	2	2	2	4	4	3	2	2	2	3	3	1	1	1	1	3 months
A5	1159/11	25Y	M	Rt Hemipelvis	Rt Lung	4	4	1	1	4	4	4	4	2	2	3	3	3	3	1	1	2	2	1 month
A6	8817/11	48Y	F	T3-T4 V	MUO	3	3	2	2	2	2	4	4	4	3	3	3	3	3	3	2	2	2	3 months
A7	884/12	50Y	M	T6-T9 V	MUO	3	3	1	1	3	3	2	2	1	1	2	2	2	2	1	1	2	2	1 month
A8	1399/12	40Y	F	T5-T6 V	Rt breast	3	3	1	1	3	3	3	3	2	2	2	2	3	3	1	1	2	2	1 month
A9	1660/12	27Y	F	L2-L4 V	Lt breast	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	No Response
A10	1994/12	45Y	M	T11-L3 V	RCC	3	3	2	1	2	2	3	3	2	2	2	2	3	3	2	2	3	3	1 month
A11	2701/12	50Y	F	L2-L4 V	Cervix	3	3	1	1	1	1	3	3	2	2	1	1	3	3	1	1	1	1	3 months
A12	3074/12	32Y	F	T11-L3 V	Lt Breast	3	3	3	3	3	3	2	2	2	2	2	2	3	3	3	3	3	3	No Response
A13	3149/12	50Y	F	L2-L4 V	Cervix	3	3	3	3	3	3	2	2	2	2	2	2	3	3	3	2	2	2	No Response
A14	6002/12	45Y	M	Lt Humerus	Penis	4	4	1	0	2	2	4	4	1	1	2	2	3	3	1	1	2	2	1 month
A15	6287/12	53Y	F	T9-T11 V	Lt breast	3	3	2	1	1	1	3	3	2	1	1	1	2	2	1	1	1	1	3 months
A16	6439/12	48Y	M	C6-T4 V	Lt Lung	3	3	1	0	0	0	2	2	1	1	1	1	2	2	1	0	0	0	3 months
A17	59/13	24Y	F	L4-L5 V	Lt breast	4	4	3	3	2	2	3	3	3	2	2	2	3	3	3	2	2	2	3 months
A18	495/13	45Y	M	T9-L1 V	Rt lung	3	3	2	0	0	0	2	2	1	1	1	1	2	2	2	0	0	0	3 months
A19	4295/13	50Y	F	T1-T5 V	Rt Breast	4	4	3	3	2	2	4	4	4	2	2	2	3	3	2	2	2	1	3 months
A20	5654/13	58Y	M	T11 V	MUO	4	4	3	2	2	2	3	3	2	2	2	1	3	3	2	2	2	2	3 months

MASTER CHART ARM-B

						PAIN SCORE-VERBAL RATING SCALE						ECOG PERFORMANCE STATUS						ANALGESIC REQUIREMENT						DURATION OF RESPONSE
Arm S.No	RT No	Age	Sex	Site	Primary	P	I	1wk	4W	8W	12W	P	I	1wk	4w	8w	12w	P	I	1wk	4w	8w	12w	
B1	7046/11	64Y	M	T8-T9 V	Prostate	3	3	2	1	2	2	3	3	2	2	2	2	3	3	2	2	3	3	1month
B2	102/12	40Y	F	T4-T7 V	Lt Breast	3	3	1	1	1	1	3	3	2	2	1	1	3	3	1	1	1	1	3 months
B3	1303/12	30Y	M	T8-T12V	Rt Parotid	4	4	2	0	0	0	3	3	2	0	0	0	3	3	1	0	0	0	3 months
B4	5447/12	60Y	M	Pelvis	Prostate	3	3	3	3	3	3	3	3	3	3	3	3	2	2	2	3	3	3	No Response
B5	7135/12	55Y	F	C5-C6 V	Rt Breast	4	4	2	0	0	0	4	4	2	0	0	0	3	3	2	0	0	0	3 months
B6	7677/12	40Y	F	L1-L4 V	MUO	3	3	3	3	3	3	2	2	2	2	2	2	3	3	3	4	4	4	No Response
B7	8166/12	45Y	F	L4 Vertebra	Rt Breast	3	3	1	1	1	1	3	3	2	1	1	1	2	2	1	1	1	1	3 months
B8	8206/12	12Y	F	Pelvis	Medulloblastoma	4	4	1	1	2	2	4	4	1	1	2	2	3	3	1	1	2	2	1 month
B9	739/13	20Y	M	C7 V	Ewings sarcoma	4	4	2	2	1	1	4	4	3	2	2	2	3	3	1	1	1	1	3 months
B10	882/13	16Y	M	Pelvis	Prostate	3	3	2	1	1	1	3	3	2	1	1	1	2	2	1	1	1	1	3 months
B11	1940/13	30Y	F	C2-C3 V	NP	4	4	1	1	3	4	4	4	2	2	3	3	3	3	1	1	2	2	1 month
B12	2038/13	60Y	M	T11-T12 V	Lt Lung	3	3	1	0	0	0	2	2	1	1	1	1	2	2	1	0	0	0	3 months
B13	2051/13	60Y	F	Lt Hip	NHL	3	3	2	2	2	2	4	4	4	3	3	3	3	3	3	2	2	2	3 months
B14	2517/13	45Y	M	T2 V	Rt Lung	4	4	3	3	2	2	3	3	3	2	2	2	3	3	3	2	2	2	3 months
B15	2528/13	70Y	M	T5-T9 V	MUO	3	3	1	1	3	3	2	2	1	1	2	2	2	2	1	1	2	2	1 month
B16	3224/13	40Y	M	T9 V	Oesophagus	3	3	2	0	0	0	2	2	1	1	1	1	2	2	2	0	0	0	3 months
B17	3411/13	50Y	F	T8-T10 V	Lt Breast	3	3	1	1	3	3	3	3	2	2	2	2	3	3	1	1	2	2	1 month
B18	3640/13	40Y	F	T11-L3 V	Lt Breast	4	4	3	3	2	2	4	4	4	2	2	2	3	3	2	2	2	1	3 months
B19	5051/13	40Y	F	T8-T10 V	Lt Breast	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	No Response
B20	5130/13	35Y	F	Lt Humerus	Lt Breast	3	3	2	2	2	2	3	3	2	2	2	1	3	3	2	2	2	2	3 months

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