"COMPARING 8GY VS 30 GY SCHEDULES OF PALLIATIVE RADIOTHERAPY IN THE TREATMENT OF PAINFUL SPINE METASTASIS"

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DEPARTMENT OF RADIOTHERAPY
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CHENNAI - 600 003

CERTIFICATE

This is to certify that the dissertation entitled, **"COMPARING 8GY VS 30 GY SCHEDULES OF PALLIATIVE RADIOTHERAPY IN THE TREATMENT OF PAINFUL SPINE METASTASIS"** submitted by DR.NARMADHA R, in partial fulfilment for the award of the degree of Doctor of Medicine in Radiotherapy by The Tamil Nadu Dr.M.G.R.Medical University, Chennai is a bonafide record of the work done by her in the department of radiotherapy Madras Medical College during the academic year 2014-17.

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CERTIFICATE OF THE GUIDE

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DECLARATION

I, Dr.NARMADHA.R solemnly declare that the dissertation titled **"COMPARING 8GY VS 30 GY SCHEDULES OF PALLIATIVE RADIOTHERAPY IN THE TREATMENT OF PAINFUL SPINE METASTASIS"** has been prepared by me and submitted to Tamil NaduDr.MGR Medical University, Chennai in partial fulfillment of the rules and regulations for the M.D degree examination in Radiotherapy.

Date: DR.NARMADHA.R

Place:

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CONTENTS

INTRODUCTION

INCIDENCE

Bone metastasis may be seen in 85% of patients dying due to cancer of breast ,prostate and lung .Bone metastasis is more common in breast and prostate cancer accounting for 70% of metastasis[1].Around 30-40% of bone metastasis is due to cancer of thyroid ,kidney and lung[2].Carcinomas of gastrointestinal tract gives rise to bone metastasis in 3-15% of patients.Less commonly lymphoma can cause bone destruction.

PROGNOSIS

Patients with bone metastasis ultimately has poor prognosis. Median survival inpatients with bone metastasis may vary from few months to several years depending on the primary tumour and presence or absence of metastasis to viscera. Those with metastatic disease to bone arising from lung may have a short overall survival of around 6 months ,whereas those with primary malignancy of breast or prostate may survive for several years. Overall survival depends on the primary site of malignancy and presence of visceral metastasis[3]. Survival is longer in skeletal only metastasis patients. Morbidity in patients with bone metastasis includes pain , hypercalcemia ,pathological fracture, spinal cord compression, neurologic deficits ,anxiety ,fatigue, insomnia and deterioration of quality of life.

SITE

Bone metastasis are the most common in axial skeleton. Metastases frequently occur in spine, pelvis and ribs. Lumbar spine is the most common site of bony metastasis. Proximal femur is the most common site in the appendicular skeleton.

Pain is the most common symptom in patients with bone metastasis. Radiotherapy plays a major role in effectively palliating painful bone metastasis. Radiotherapy provides partial response in around 80%-90% and complete response in 50% patients. These data are primarily from physician evaluation of patient. When patient evaluation of pain was used, pain improvement is seen in 80-90% and complete response in around 15-40% of the patients[4].

CLINICAL PRESENTATION

Metastatic bone disease related morbidity referred as Skeletal Related Events includes pain(that may need opioid, radiation or surgery) hypercalcemia , pathological fracture and compression of spinal cord .Pain is the most common symptom .Initially pain is either diffuse or well localised and worse at night. Eventually pain worsens with weight bearing activity. The development of functional pain may indicate the risk of fracture. Pathological fracture may be the first sign of bone metastasis. Pathological fractures are common in patients with primary malignancy of breast ,lung ,thyroid and kidney [2].

EVALUATION

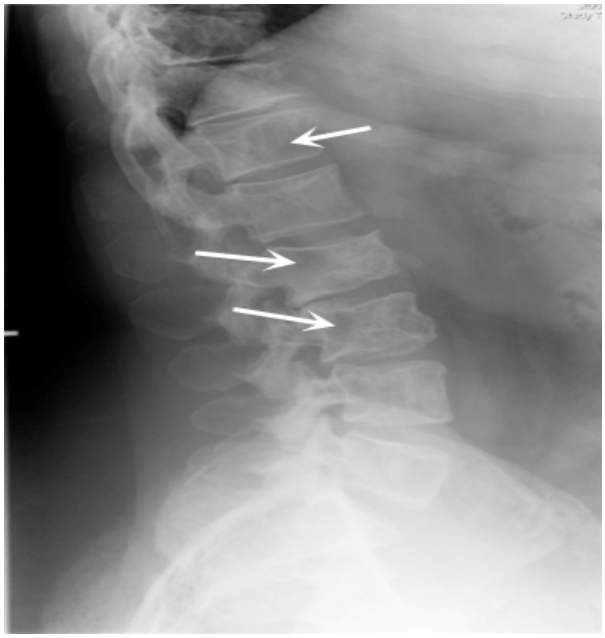
PHYSICAL EXAMINATION

Important steps to evaluate for bone metastasis initiates with physical examination of the entire skeletal system. Examination helps to take decision on the appropriate further imaging studies needed. Firm palpation often will reveals the painful area and point tenderness helps to directly identify the affected area of the bone.

Careful physical examination is important, as severe pain at one site may mask the pain at other areas .Neurological examination must be done in patients with spine metastasis to look for spinal cord compression or cauda equina syndrome[3].

PLAIN RADIOGRAPHY

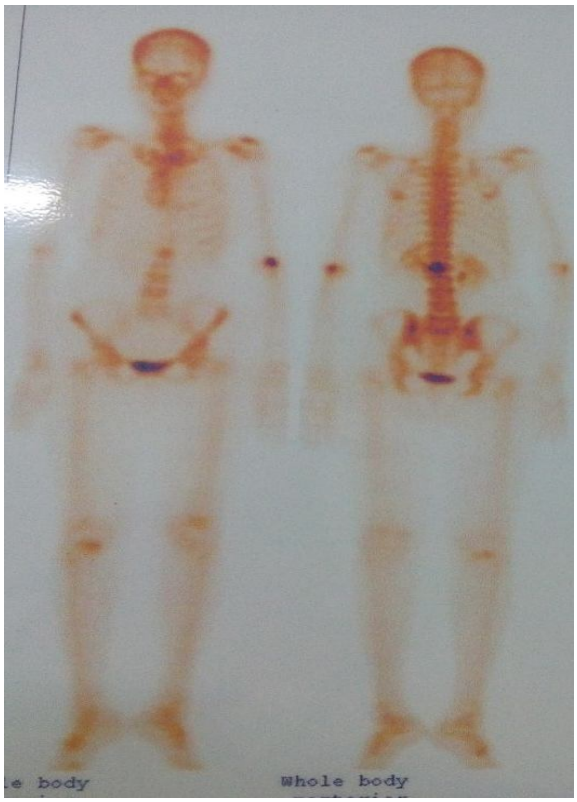
X-RAY SHOWING LUMBAR METASTASIS



Plain radiographs are the most appropriate first imaging evaluation done for symptomatic patients presenting with tenderness. The appearance of lesion on the x-ray depends on the primary tumour site and histology .Most metastatic lesion arising from lung or breast primary will appear osteolytic and those arising from prostate will appear osteoblastic . But most bone metastasis will have components of osteoblastic and lytic process. Advantage of X-rays are that they are easy to obtain and are inexpensive. Main disadvantage is small metastatic lesions are not seen .About 30 % to 50 % minerals in the bone should be destroyed to be apparent on x-rays. X-ray of spine metastasis shows classically the absence of pedicle-“winking owl sign”.

BONE SCAN

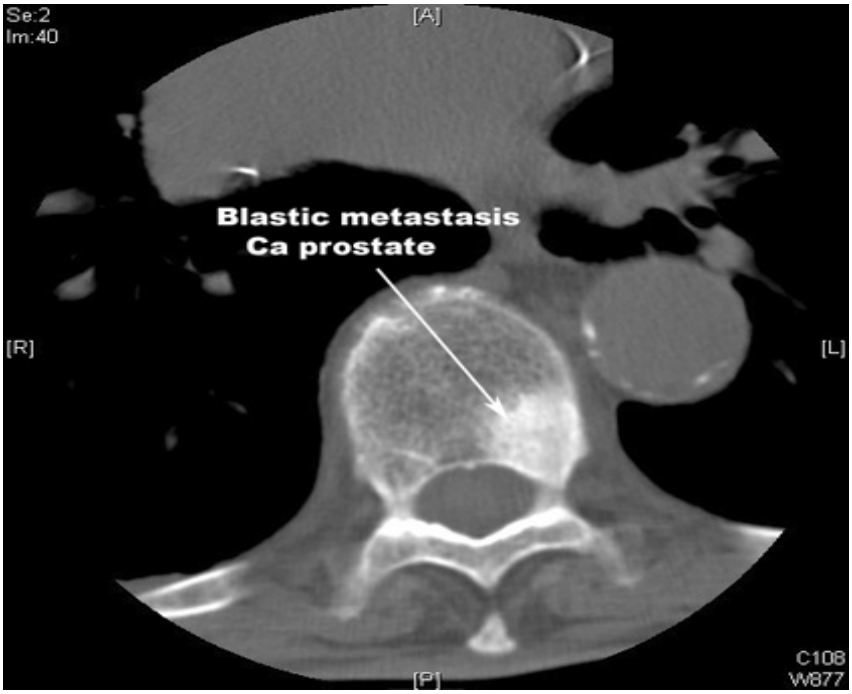
BONE SCAN SHOWING UPTAKE IN THE VERTEBRA



Technetium-99m bone scan is the best imaging for screening patients those are at risk of bone metastasis and to evaluate the extend of metastasis in the bone. It is an indicator of osteoblastic bone activity .Bone scans are not specific for metastasis and a confirmatory imaging is especially important in weight bearing bones. False positivity is seen in trauma, arthritis or Paget's disease of bone. False negativity may be seen in fast growing ,aggressive bone tumours if they are predominantly osteolytic.

CT-SCAN

CT SCAN SHOWING OSTEOBLASTIC METASTASIS



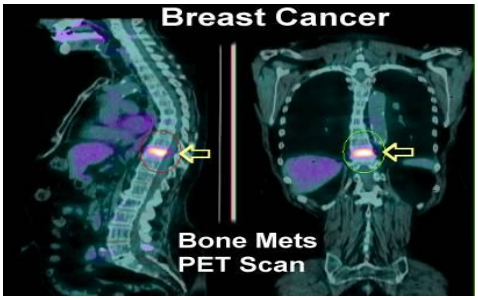
CT scans are more sensitive than X-rays and provides better localization of lesion within the bone .Considering the cost and time consumability ,CT scans may not be useful in screening of skeletal metastasis .CT scans may be used to define the extend of cortical involvement but are not superior for marrow involvement .CT scan helps to assess cortical destruction and the risk of pathological fracture[5].

MRI SCAN

MRI is superior to x-ray or Bone scan in assessing the red bone marrow involvement mainly for the spine. MRI is also used for evaluating the neurovascular structures .MRI is superior than bone scan to evaluate vertebral body lesions. It may also help to distinguish fracture of spine caused by malignancy and osteoporosis. MRI is more sensitive (91 to 100%) than bone scintigraphy (62 to 85%) for vertebral lesions[6].

PET SCAN

PET SCAN SHOWING UPTAKE IN DORSALSPINE



Positron Emission Tomography using 18-Fluorodeoxyglucose evaluates the areas of increased metabolic activity.PET scan is useful in detecting the osteolytic lesion but are less sensitive for osteoblastic lesions. The addition of CT to PET, as in most of modern PET-CT scanners, also reveals osteoblastic lesions that may not be metabolically active on FDG PET alone .

FDG PET outperformed bone scan for osteolytic, mixed, and CT-silent lesions. Studies have shown that PET scans are more sensitive than bone scan or whole body MRI in detecting bone metastasis.

THERAPEUTIC MODALITIES

PAIN MANAGEMENT

Following are the common measures done to palliate bone pain in patients with bone metastasis.

i) WHO PAIN LADDER

Commonly followed pain relief guideline is the World Health Organization . It comprises of 3 step of medication prescription based on the intensity of cancer pain[7] which is prescribed either " by the clock " or on demand.

WHO PAIN LADDER

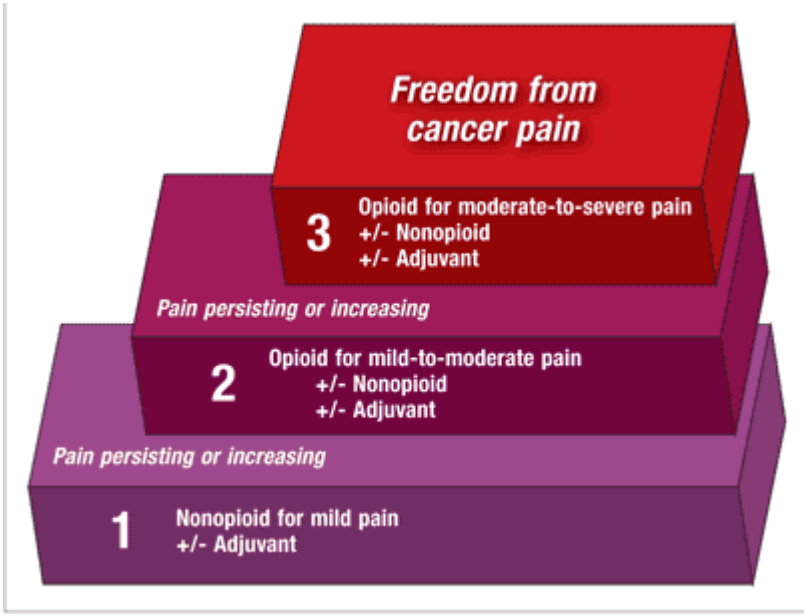


Figure 2. World Health Organization's Pain Relief Ladder. Source: Reference 5.

STEP 1

Step 1 consisting of non-opioids is used for mild pain. It includes

- Non Steroidal Anti-Inflammatory Drugs (NSAID) ,
- COX-2 inhibitors
- Acetaminophen
- Adjuvants
- Topical analgesic .

Adjuvants refer to "drugs that are not analgesics per se but can be used for this indication in special circumstances". Many anti-epileptics , anti-depressants (gabapentin, pregabalin ,amtriptyline)and steroids are used for neuropathic type of pain.

STEP 2

Step 2 includes weak opioids such as

- Hydrocodeine
- Codeine
- low-dose oxycodeine.
- tramadol .

These drugs have reduced side effects profile than pure opioids and has additional effect for neuropathic type of pain.

STEP 3

Step 3 consists of stronger opioids such as

- morphine
- Hydromorphine
- Fentanyl
- High-dose oxycodeine
- Meperidine, and
- Methadone.

For those having chronic pain, it is recommended to combine long acting and short acting drugs . The long-acting extended-release morphine is given in chronic baseline pain and short acting opioid with repetitive dose is used for acute onset pain.

Breakthrough pain defined as " abrupt, short-lived, and intense flare of pain in the setting of chronic stable pain managed with opioids". It is managed with oral transmucosal fentanyl citrate, sublingual fentanyl, intranasal fentanyl spray or fentanyl buccal soluble film with the rapid effect within 10 to 15 minutes of administration[8].

Ketamine, an *N* methyl D-aspartate (NMDA) receptor antagonist, is a less commonly used in treating intractable severe pain due to various cause. It is found to be effective even if megadoses of i.v, oral, or intrathecal opioids are proven to be ineffective or in case of opioid intolerance .

ii)BONE MODIFYING AGENTS

Bisphosphonates are pyrophosphates analogue which act by binding via higher affinity with the calcium phosphate & are potent agents that affects the resorption of bone. Bisphosphonates also induce apoptosis of tumour cells. Bisphosphonates reduce bone pain , malignant osteolysis, delays the onset and decrease the occurrence of Skeletal Related Events.

There are two types of bisphosphonates with different mechanism. The first type is non-nitrogen-containing bisphosphonates(clodronate) are metabolized into cytotoxic compounds by osteoclasts and the second type is nitrogen-containing bisphosphonates. This group includes zoledronic acid, pamidronate and ibandronate inhibiting the mevalonate pathway, leading to osteoclast apoptosis.

Both types of bisphosphonates may be administered for the prevention and treatment of SREs associated with bone metastases in cancer patients. Zolendronic acid is more potent than other drugs, in part due to inhibition of tumour adhesion to bone matrix. Zolendronic acid is contraindicated when creatinine clearance is less than 30 ml/min. Ibandronate can be safely administered in renal failure .

DENOSUMAB

Denosumab is monoclonal antibody that binds and neutralizes the RANK Ligand and so inhibits osteoclast function , bone resorption and local bone destruction. In bone metastasis, it produced superior results than Zoledronic acid in terms of prevention and delaying the development of SREs[9]. When compared to Zoledronic acid, it showed a significant delay in time for first Skeletal related event by about 17%[10].

iii)SURGICAL MANAGEMENT

The main goal of surgical approach is to prevent or to treat pathological fracture of bone, to relieve pain or to improve neurological function. Surgical techniques are minimally invasive ,Posterior approach decompressive surgery by doing a laminectomy & fixation of spine are the commonest procedure for spine. Fractures or at risk of fracture of long bones needs surgical intervention to improve the functional outcome and quality of life[11].

Mirel developed a system of scoring with the location of the bone lesion, pain, cortical destruction and radiologic appearance. Score more than 9 mandates prophylactic surgical fixation

TABLE SHOWING MIREL'S SCORING

Table 1. Mirels scoring system for assessing pathologic fracture risk in long bones.

Criterion	1	2	3
Lesion site	Upper limb	Lower limb	Peritrochanteric
Pain	Mild	Moderate	Functional
Lesion type	Blastic	Mixed	Lytic
Lesion size (as a proportion of the bone diameter)	Less than 1/3	1/3 to 2/3	More than 2/3

Adapted from Mirels H. Metastatic disease in long bones: a proposed scoring system for diagnosing impending pathologic fractures. Clin Orthop. 1989;249:256-64.

NOMS SYSTEM FOR SPINE METASTASIS:

. For spine metastasis, a new decision framework NOMS that takes into account 4 points in deciding the treatment has been developed. It includes 4 assessments:

Neurologic

Oncologic

Mechanical Instability

Systemic Disease

The advantage is that it includes newer technology and also the evidence based medicine . Considering the4 points, a multidisciplinary team will decide the appropriate management including surgery, radiotherapy , systemic treatment, or by combining these[12].

The Neurological findings to be included are

- Degree of spinal cord compression
- Myelopathy
- Functional radiculopathy.

The oncological aspect is predicated from existing evidence on toxicity and duration of response to available methods like radiation ,radiosurgery, immunotherapies ,hormonal therapy or chemotherapy.

Spinal instability is recently described for malignancy using Spinal Instability Neoplastic Score (SINS) . The recognition of spinal instability is important since unstable vertebra do not show response to irradiation /chemo and it mandates surgical interventions like Percutaneous Cement Augmentation /Pedicle screw/brace / an open surgical management.

Final result of NOMS includes the spread of malignancy, comorbidities along with the survival expected .These will influence the treatment option to be given including surgery ,irradiation and medical management.

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iv)RADIONUCLIDES

Calcium & phosphorus analogs tend to accumulate in the bone in the area of active turnover .Radioisotopes that emit beta rays or low energy gamma rays will allow local treatment at the site where it accumulates with minimal side effects.. Radionuclides are administered in single injection and can be combined with chemotherapy or radiation. Phosphorus-32 was the first used radioactive isotope in the treatment of bone metastasis .It produced pain relief but unacceptable bone marrow toxicity.

Strontium -89 (Sr) chemically similar to calcium is deposited preferentially in the region of active osteogenesis. It is a pure beta emitter of energy 1.4Mev and has a half-life of 50.6 days[13].

Samarium -153(Sm) primarily a beta emitter of energy 0.81 Mev and gamma rays of 103 Kev which can be used for imaging purpose. Sm-EDTMP(ethylene diamine tetra methylene phosphoric acid) will accumulate in the area of hydroxyappatite at active bone turnover .Physical half-life is 46.3hours but about half is eliminated within 8 hours of injection, shorter biological half-life[14].

Rhenium-186(Rh) emits medium energy of beta rays (1.07 Mev).It makes a stable bisphosphonate complex to hydroxyl ethylidene disphosphate. Maximum bone uptake is within three hours of i.v administration. Biological half-life is about 4.5-6 hours[15].

Radionuclides have the advantage of treating all the bony lesions simultaneously. Retention in metastatic area inside the bone is higher than in normal bone in the ratio of 10:1.Average time for response is 1-2 weeks and duration of action is 18 weeks .Retreatment is possible after 10-12 weeks for strontium 89 and 6-10weeks for samarium. Reversible myelosuppression especially thrombocytopenia is the main treatment related toxicity noted.

REVIEW OF LITERATURE

PATHOPHYSIOLOGY

NORMAL BONE

Mature bone is comprised of three cell types namely osteocytes ,osteoclast and osteoblast. The osteogenic cells will differentiate into osteoblast when there is mechanical or chemical stimulus for remodelling or repair. The osteoblastic cell builds bone by depositing collagen type I in the extracellular space .Inorganic hydroxyappatite complex of calcium and phosphorous are deposited within the matrix .The osteoblasts then matures into osteocytes to maintain the structure of bone.

The osteoclast are classical multinucleated giant cells originating from the pleuripotent hematopoietic bone cells [16] .osteoclast cells causes resorption of bone by creating an acidophilic environment which will dissolve the hydroxyappatite and proteolysis of matrix.

Normal bone is being constantly remodelled every 120 to 200 days .bone resorption first occurs for initial 20 to 40 days followed by new bone formation for next 100 to 150 days .Activation of osteoclastic cells are due to proteins related to tumour necrosis factor, receptor activator of nuclear factor-KB (RANK) ,RANK ligand and osteoprotegrin. RANK ligand is produced by osteoblast cells, stromal cells and T lymphocytes .

RANK-L attaches to RANK receptors present over the osteoclastic precursor cells and thereby promotes generation of osteoclast cells. Osteoprotegrin are decoy receptors of RANKL ,protects the bone by preventing the differentiation and activation of osteoclasts[16].The ratio of osteoprotegrin : RANKL produced by osteoblast will determine the extent of resorption.

MECHANISM OF BONE METASTASIS

Metastasis to bone occurs mainly via

1) Hematogenous

2)direct invasion

3)lymphatics

Batson's paraspinal venous plexus is an important route of metastasis to the axial bones .These longitudinal valveless plexus extend from sacrum to skull .Venous blood from breast ,thyroid ,lung ,kidney and prostate drain into this plexus causing predilection for axial skeletal metastasis. Presence of red marrow in the highly vascularised axial skeleton leads to preferential involvement[17].

Direct spread is less common and usually is due to direct infiltration from site of malignancy. Lymphatic spread is rare but spread from a metastatic node is not uncommon ,mainly to left side of spine.

THEORIES ON METASTASIS

Many theories are re-emerging regarding the explanation for selective metastatic nature of tumour cells[18].

"**TRADITIONAL METASTATIC MODEL"** –suggest that a select subpopulation of cancer cells acquire the metastatic capacity during the later stage of tumourigenesis[19].

"**DYNAMIC HETEROGENICITY THEORY"**-suggest that metastatic potential of cancer cells is mainly determine d by rate at which tumour variants with increased metastatic potential occur in the primary site[20].

" **CLONAL SELECTION THEORY"** - suggests that development of a primary tumour is consequence of series of multiple molecular or cellular changes resulting in a clonal selection .This process alters the phenotype of tumour cells allowing acquisition of tumour-specific characteristics, such as site specific metastasis[21].

"**STEM CELL THEORY"** proposes that site selective metastasis is due to activation of cancer stem cell compartment in a specific organ, like the breast[22].

Malignant cell may go to every organ equally but have preferential growth in certain organ (organ tropism).There are chemotactic factors that is released locally in the bone which attracts the malignant cell.

Following are the steps involved in metastasis of any malignancy to bone:

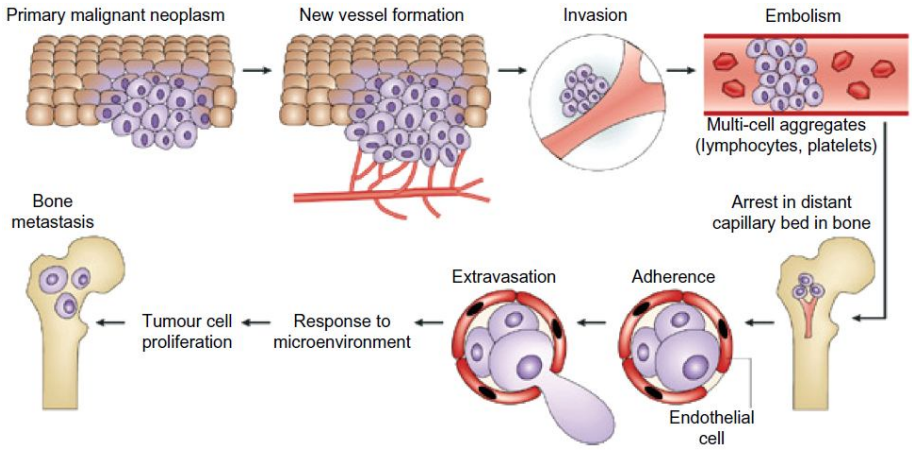
(Mareel et al 1991 and Choong 2003)

1)Growth at primary site

2)Detachment of tumour cells

3)Invasion of tissue stroma

4)Neoangiogenesis



5)Escape from tissue

6)Stays in circulation

7)Chemo attraction & arresting ("docking and locking") in marrow vessels.

8) Extravasation

9)Setting up of microenvironment

10)Stimulation of osteolytic and /or osteoblastic pathway

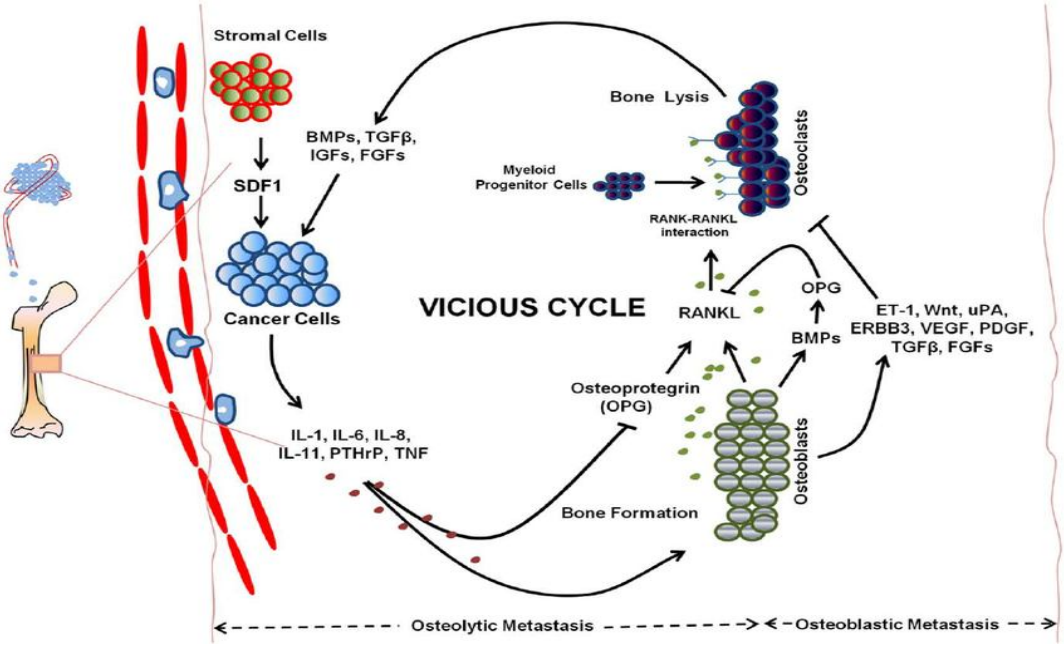
MECHANISM OF BONE METASTASIS

The bone microenvironment includes the cells of bone marrow like osteoblastic along with other cellular niches which provides microenvironment to support the stem cells .The balance between osteoclast and osteoblast maintains the bone milieu. Any disturbance to this changes the healthy bone to a metastatic microenvironment. Malignant cell have the ability to remain dormant for years before progressing into macro-metastasis.

Bone metastasis are generally classified as either osteolytic or osteoblastic based on the predominant radiologic appearance. Osteolytic type of bone metastasis are much more common .osteoclasts activated by the tumour cells are responsible for bone resorption causing pathologic fractures and hypercalcemia[23].

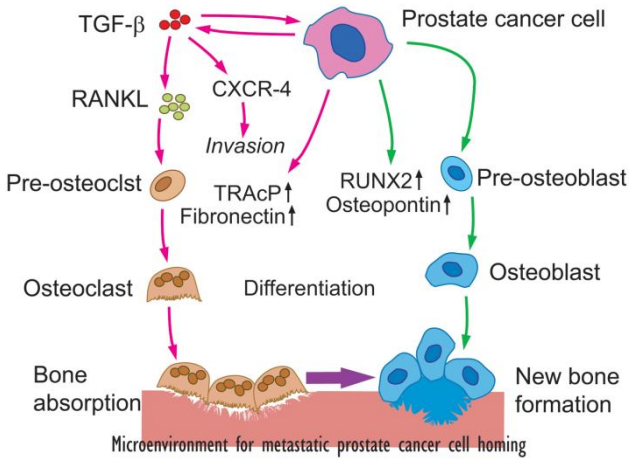
The cytokines and growth factors expressed by the tumour cells causes interaction with osteoblastic and osteoclasts and the balance of this determines the nature of lesion and their corresponding radiological appearance. Bone metastasis from breast and lung cancer are predominantly osteolytic. The osteoclastic activity has been related to the growth factors and cytokines released by tumour cells including IL-6,IL-11,PTHrP,TNF-□.

VICIOUS CYCLE OF BONE METASTASIS

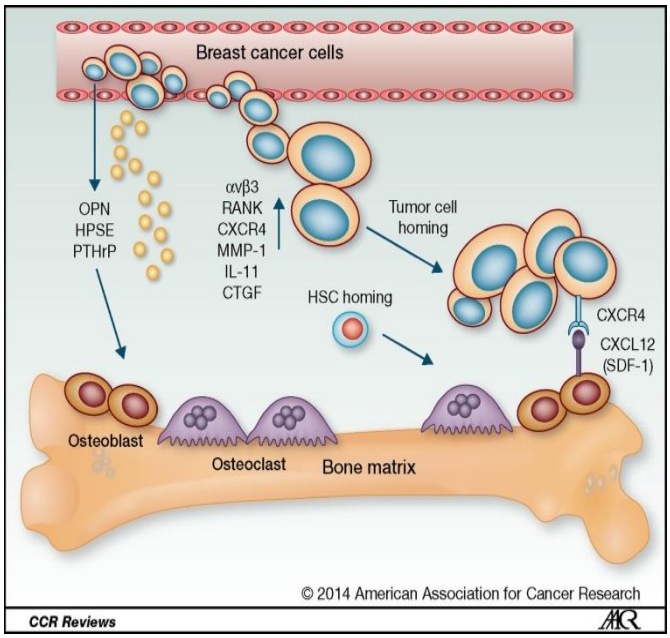


.Bone resorption will lead to release of bone derived growth factors that in turn will react with the tumour cell and set a vicious cycle. The osteoblastic activity is related to endothelin-1,insulin like growth factor.

OSTEOBLASTIC METASTASIS IN PROSTATE CANCER



OSTEOLYTIC METASTASIS IN BREAST CANCER



MECHANISM OF BONE PAIN

Pain arising from the bone metastasis is a neuro -chemical process different from pain mechanism like inflammation or neuropathy[24] .Adult bone is supplied by A-delta along with C fibres. Primary nociceptive afferents contain large number of receptors which will respond to noxious stimulus. Its unique than other types of sensation as these will respond to only one type stimulus. Receptors belonging to Vanilloid family (VR-1) will detect heat, acidity and lipid metabolites; purinergic receptors will react to ATP,ADP ;mechanically gated channels will respond to mechanical stimulus and number of receptors will respond to molecules of inflammation like cytokines , histamines, endothelins , growth factors(nerve) ,serotonin and prostaglandins.

Continuous stimulation of the receptors then produce a plastic change contributing to lowering of threshold and is known by the process of peripheral sensitization .It is the mechanism for hyperalgesia and allodynia which are hallmarks of neuropathic pain[7].

Tumours contain many type of cells including inflammatory ,immune cells like lymphocytes and macrophages attributing to acidosis and activation of sensitive ion channels. Tumour growth within the bone causes distension of nerve fibres and activates the mechanically sensitive channels and entrapment of nerves often leads to aberrant regenerations resulting in neuronal pathway.

Next mechanism seen in studies from animals is the wide neuro-chemical reorganization in spinal segments receiving signal from peripheral nerve fibre. They supply the bone containing the malignant cells, demonstrate amplification and perpetuates pain perception called "**central sensitization[25]**".

PRIMARY AFFERENTS

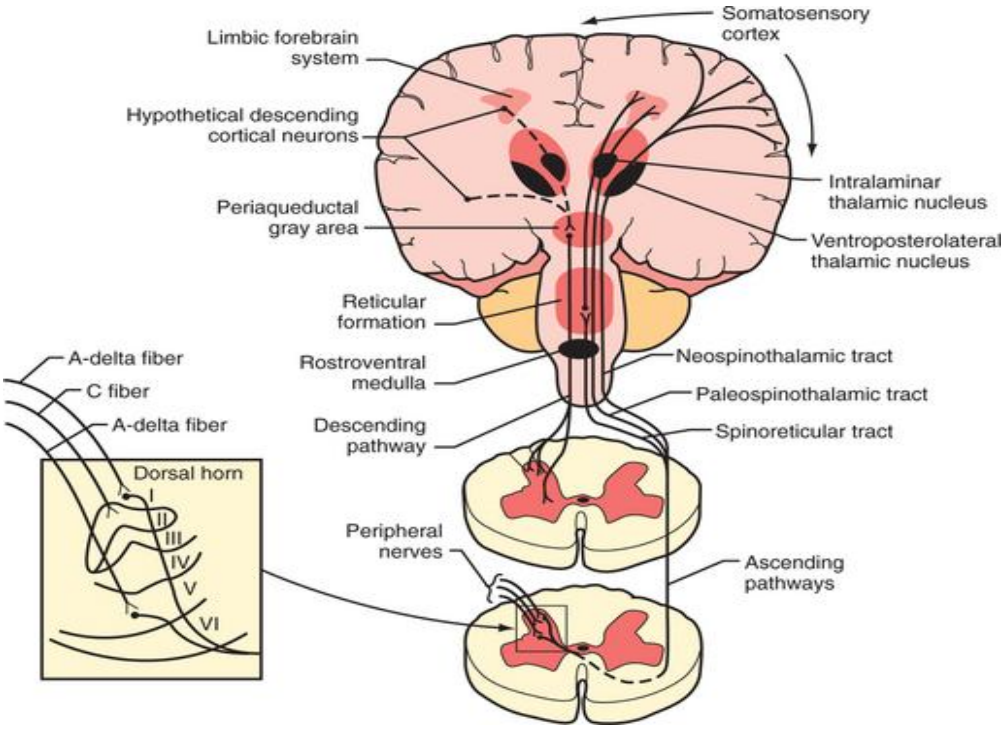
Previously metastatic pain was thought to arise from vascular blockage, neuronal compression or bone injury or due to instable bone. In these studies they did not look into the basic process of stimulation of nociceptive receptors, signalling and sensitisation. Peripheral nerves send the non-noxious stimuli through Ab fibres and noxious stimuli through Ad and C fibres to dorsal horn of the spinal cord.

Then it undergoes various modulation(both excitatory and inhibitory)and are relayed to brain . Now the concept is the periosteum along with bone is innervated .Ad fibres express neuropeptide Y, vasoactive intestinal peptide and neuropeptidergic C fibres expressing Calcitonin gene related peptide (CGRP), vallinoid receptor (VR1) and sympathetic neurones (SNS)[26-31]. Neuropeptides like, glutamate VIP ,CGRP and substance P are involved in metabolism of bone.

Several data showed the metastatic bone environment causing complex remodeling of neurons ,which is felt as pain by the humans . Also tumor is not supplied by nerves and the process happens within Periosteum outside the matrix.

Bone periosteum produce chemicals like CGRP and substance P which are secreted by neurons in dorsal root ganglion, fifth nerve ganglion , and vagal ganglion. These neurons will react to any form of stimuli like nociceptive, heat, or other visceral stimuli and known to be peptidergics .CGRP and Substance P neurons are seen within bone(including marrow and periosteum) .In preclinical models, sarcomas ,cancer arising from prostate gland and mammary gland are found to produce sprout of ectopic neuronal fibers and neuroma like structure within bone periosteal layer[32].The fibers supplying metastasis containing bone are more dense with reorganization.

BONE PAIN PATHWAY



NEUROTROPHINS

Neurotrophins are proteins that is important for regulation of cell survival, development and functioning of sensory and sympathetic neurons and are responsible for generating pain & its maintanence . Neurotrophins are usually produced by most adult tissues in a very low quantity. They are produced in large amount during inflammation or injury ,especially nerve growth factor.

The nerve growth factor , brain-derived neurotrophic Factor & neurotrophin3 are group of chemicals and their receptors include

Tropomyosin -Related Kinase (TrK) A, B & C[33] .On binding to their receptors, nerve growth factor will lead to modulation of functions of chemicals produced from nociceptive receptors resulting in increased nociception. The chemicals may be molecules like neuro-filaments ,neurotransmitter like substance P, channels , and receptors . Brain derived neurotrophic factor modulates the NMDA receptor at cord level and Dorsal root ganglion. Increase in brain derived neurotrophic factor in descending pain modulating regions of medulla suggests that BDNF is involved in metastatic pain.

OSTEOCLAST ACTIVATION

Osteoclasts are multi-nucleated cells that will cause resorption of bones .Their formation and activation require Macrophage Colony Stimulating Factor , interaction between Receptor Activator for Nuclear factor k B (RANK) on osteoclast precursor cells and the RANK ligand secreted by osteoblasts & acidic microenvironment.

The RANK- RANKL binding is necessary to maintain balance between osteoclast activation and osteoblast. The osteoblastic cell release Osteoprotegrin that will bind to and sequester RANK ligand thereby prevents the activation of osteoclastic cell. Tumour cells and immune cells (T cells) produce RANK ligand ,so can sequester osteoprotegrin. The acidity also facilitates osteoclast mediated bone resorption thereby contributing to bone destruction[34,35].

ACID SENSING ION CHANNELS:

Malignancy comprise a wide variety of cells essential for functioning of the bone-tumor environment. Other than cancerous cells , stem cell, , immune cells, pro inflammatory cell, tumour- associated fibroblast , tumour stromal progenitor cell and pericytes . Cells involved in inflammation leads to production of malignant cells and consist of macrophages , mast cell, neutrophil and lymphocyte. These cells secrete chemical mediators along with protons that will produce an acid microenvironment.

Cancer cells produce a reverse pH with high pH within the cell and a low pH outside the cell .This reverse gradient favours growth factor nondependent cellular proliferation, evades cell death, migration of tumour cells , metastasis and reprograms the energy producing metabolic pathway [36].

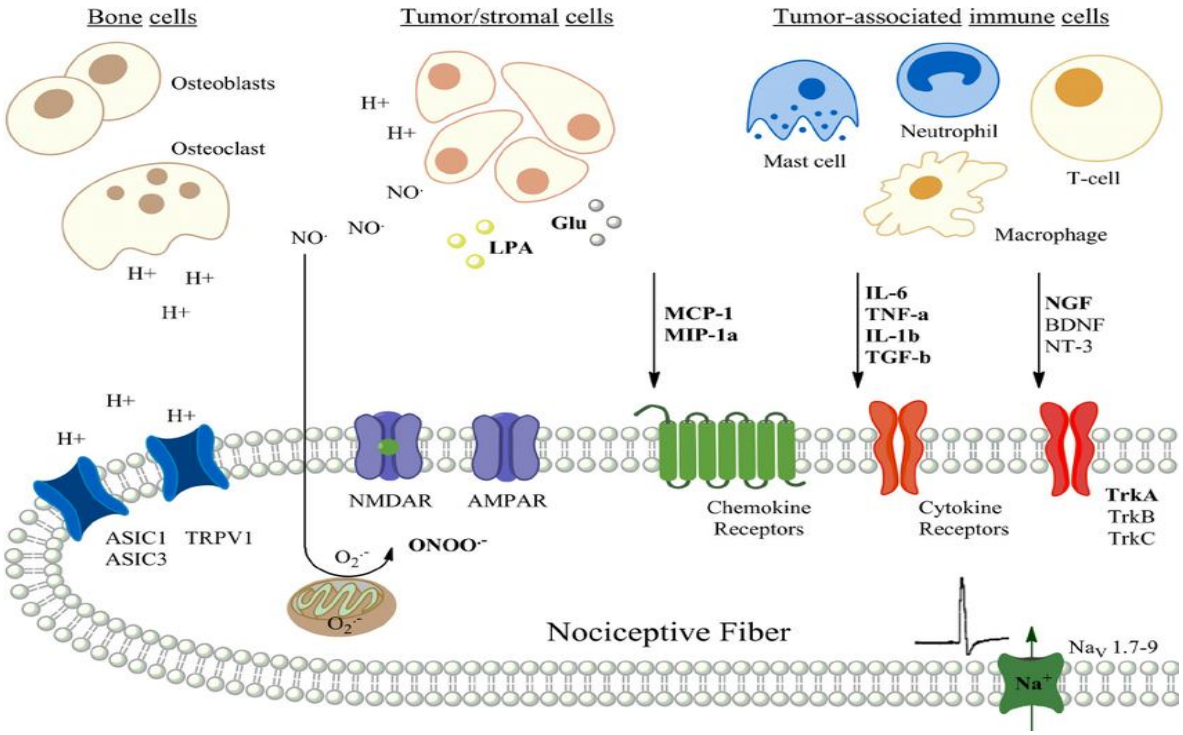
Increased proliferation along with low blood supply to the center of tumour will result in low oxygen concentration .To adapt for the low oxygen concentration, up-regulation of glucose transporter like GLUT 1, and the enzymes involved in glycolysis takes place. The up-regulation of glycolytic process results in increased acid production.

When the pH outside the cell increases, there is increase in mineralization of precursors of osteoblast and genetic transcription of osteoblasts along with elevation of osteopontin level *in vitro* .

Decrease in extracellular pH will reduce the osteoblast induced synthesis of collagen and the action of alkaline phosphatase . Osteoclast mediates the resorption by releasing protease and this generates protons . Protons will cause effective sensitization of nerve fibers .

ASICs(acid sensing ion channels) are epithelial sodium channel family constituting ion channels and has 7 types of channels. The ion-channels are sensitive to low pH outside the cell[37]. The channels are found widely in the neurons and by osteoblasts and osteoclasts.ASIC3 is unique as it a sustained signal contributing to non-adapting nature of pain arising from wide range of acidity. When ASIC 3 is modulated ,this result in generation along with maintanence of pain from acute inflammation and chronic neuropathy. Since these channels are found only in the bones and nerves , drug modulations warrants research in pain due to metastasis to bone. The sensory nerves in the bone expose Transient Receptor Potential channels, Vanilloid sub-family1 (TRPV 1) .These channels are stimulated by low pH ,capsaicin, heat greater than 43 °C, voltage variation, and vanilloids.

ACID SENSING ION CHANNELS IN THE BONE



TRPV 1 channel is found in astrocytes , perivascular structures, and neurons like Dorsal root ganglion ,C fibers & Aδ nerve fiber. Lysophosphatidic acid released by tumour & platelet stimulates TRPV channels .It is found to favor the tumour spread to bone by increasing the release of Interleukins-6 and Interleukins-8[38] .

INFLAMMATORY MEDIATORS

Tumours that invade and grow in bone medulla stimulate the afferent nerves .They also cause alteration of the osteoblast/osteoclast balance and also stimulate active inflammation to take place.

Cancerous cells secrete variety of interleukins like interleukin 1 &6,growth factors like Nerve Growth Factor, chemokines , cytokines including tumour necrosis factor , prostanoids and endothelin .The chemical molecules will decrease the pH to less than 5 in the bone and cause direct sensitization of the nerve fibres.

The cells of immune system release proteins helpful in cell to cell interaction called cytokines . The main 2 types namely the cytokines and chemokines play a main role in pain due to inflammation and neuropathy. Chemical mediators of inflammation like Tumour necrosis factor alpha, Interleukins-6, and Tissue growth factor -β stimulates osteoclast production. cytokines are responsible for tumor cell development ,metastasis ,osteoclastogenesis and can cause modulation of pain both central and peripheral nervous system.

Prostanoids derived from cell membrane arachidonic acid in the presence of enzyme cyclooxygenase are proinflammatory .They are released from immune and tumour cells. They stimulate the prostanoid receptor found in peripheral afferents ,inducing pain[39].

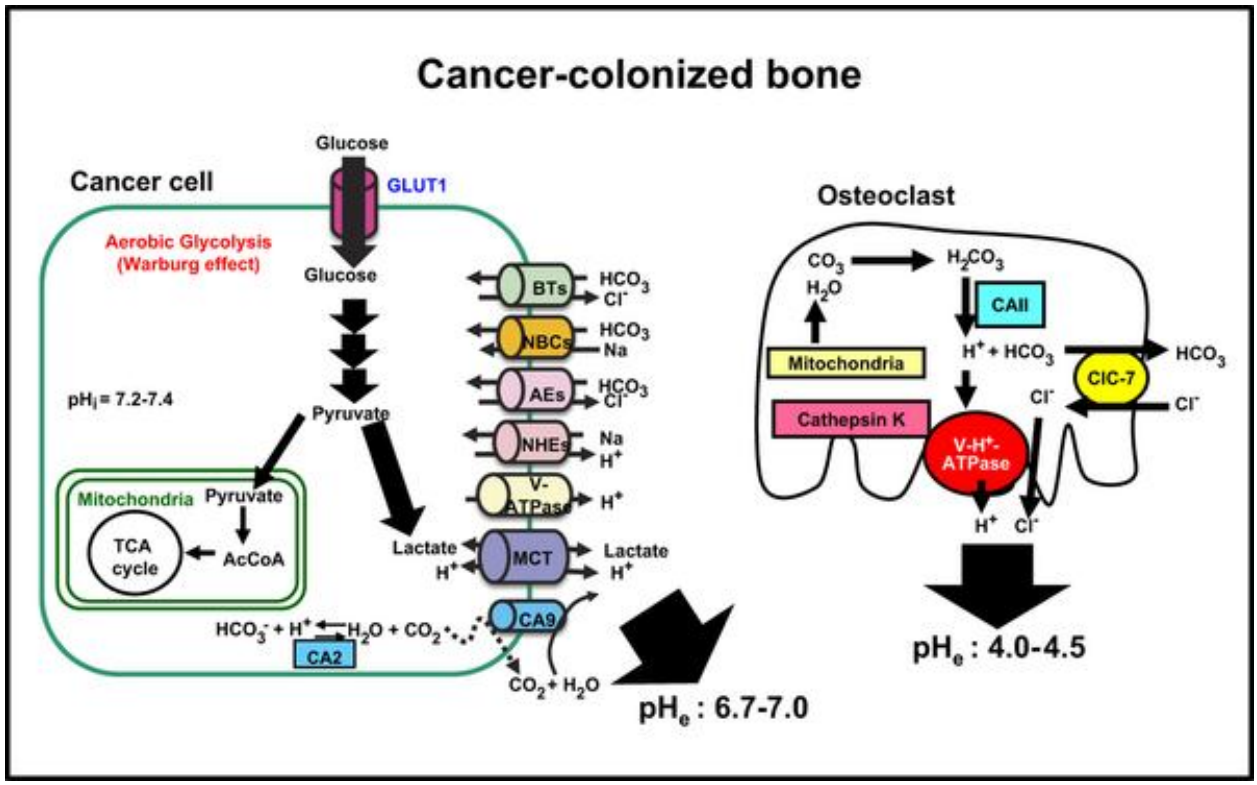
Endothelins produce nociceptive stimuli through Endothelin receptor , involve in tumour transduction, angiogenesis and endothelial growth.

OXIDATION INDUCED STRESS:

Oxidation induced stress is an important hallmark representing cancer burden .Oxidative stress is found to have a significant place in many type of pain like those arising from inflammation and neuropathy .Oxidation induced stress arises in tumor containing bone environment from the cancer & tumor stromal cells which produce stress and stimulate nerve fibers .

Pro nociception is due to stress-induced increased release of glutamate from cancerous cell. Glutamate mediated neurotransmission is responsible for many type of pain other than cancer-induced[40] .

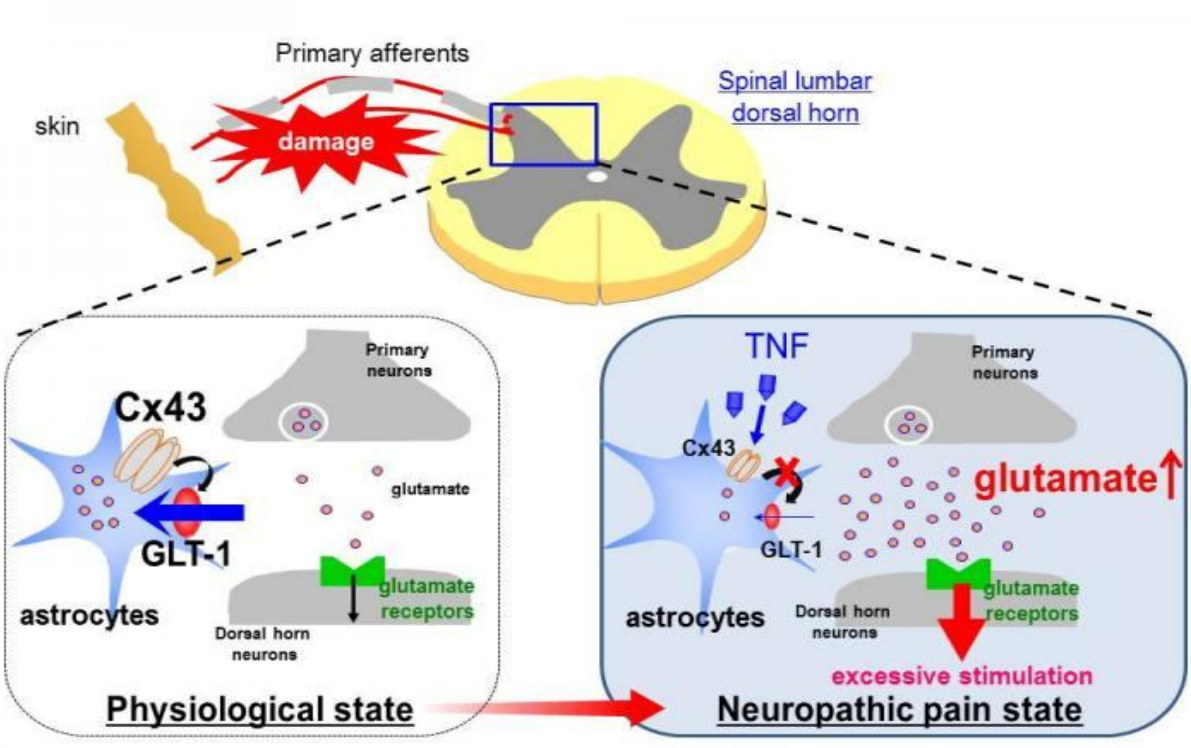
ANAEROBIC METABOLISM IN HYPOXIC TUMOUR



Warburg effect i.e, cancerous cell depend on the anaerobic glycolytic pathway for production of ATP within the low glucose and oxygen conditions. This cause excessive generation of reactive oxygen species[41] .

Several receptors including NMDA ,mGluR 1 & 5 are found in the peripheral nerve fibers. .Through the receptors, glutamate can produce signals and hence leads to sustained nociception state. Bone- tumor cell release glutamate that can stimulate osteoclast production and modulate the function of osteoblasts.

GLUTAMENERGIC TRANSMISSION IN PAIN PATHWAY



Tumor burden also causes oxidation-induced stress in the metastatic bony environment .Stimulation of the constitutively active nitric oxide synthase generates both Nitric Oxide and the reactive product peroxynitrite -ONOO-.Nitric oxide is produced from cancer cells and their associated stroma. Because Nitric Oxide diffuses easily, nerve fibers supplying the tumour containing bone environment are at more risk . When NMDA receptors are exposed to nitrogenous products ,it elevates their sensitivity to glutamate.

CANCER INDUCED CENTRAL SENSITIZATION

Studies have reported that the spinal cord receiving input from metastatic bone show neuro-chemical changes . The modifications are concurrent change of dynorphin , galanin, ATF3, substance p , GFAP in astrocytes, expression of Fos and microglia .An increase in dynorphin in the spinal cord also occurs in neuropathic pain and persistent inflammation .The increase in GFAP labelling in dorsal horn was likely due to hypertrophy of astrocytes and correlated with the extent of bone destruction. Activation of glial cells in the spinal cord may contribute to development or maintenance of persistent pain by releasing algesic substances that excite nociceptive dorsal horn neurons[42] .

In vivo studies reveal In normal animals, the proportions of wide dynamic range (WDR) to nociceptive-specific neurons in this lamina lie at 26% WDR to 74% nociceptive specific. Conversely, with the establishment of cancer pain from a breast cancer model, this ratio shifts to 47% WDR to 53% nociceptive. This phenotypic shift of the superficial dorsal horn population was accompanied by a WDR hyper excitability to mechanical, thermal, and electrical stimuli in the superficial and deep dorsal horn. This observation strongly correlates with the development of behavioural signs of pain.

MECHANISM OF PAIN RELIEF AFTER RADIATION

TARGET CELLS FOR EXTERNAL BEAM RADIATION TO BONE:

Hoskin et al ,2003 stated although external irradiation is successful in most patients with painful bone metastasis, the exact mechanism of action is unknown. Radiation dose given even though lower than the definitive schedule of irradiation causes high quantity of cell killing. Therefore this results in substantially low quantity of viable cancerous cell in irradiated field With due course, it causes tumour shrinkage. When the cancerous cells disappear , the osteoblasts will start the repair process and restores the bone strength .

While the above said mechanism occurs without doubt ,other thing to be known is if this is the sole possibility for radiation induced analgesic action. There are particular aspects of response such as pain diminishing within some sessions - suggesting tumour shrinkage by itself is not the answer for earlier relief of pain .

There is no dose -response relation for irradiation given to bone metastasis. This is due to the fact that tumour size reduction might not be the mechanism as tumour size reduction is not expected with very low dose such as single 4Gy shown relief from bone pain .Also there seems no obvious relation pain relief and sensitivity of primary malignancy to irradiation .

Mercadante et al, 1997 observed that obvious finding of some patients get symptom relief even within one day of irradiation has lead to hypothesis that the early reacting and very sensitive cells and molecules they produce are involved in this answer. Obviously candidate cells are the inflammatory cells present in large proportion in the metastatic bone micro-environment. Reduction of the inflammatory cells by ionizing radiation inhibits the release of chemical mediators and is probably responsible for the rapid reaction seen in some patients.

Another potential cells is the osteoclasts. Hoskin et al in 2000 stated "Osteoclastic cell activity is an early and important response to tumour cell invasion of bone. It was demonstrated that the urinary markers of bone resorption and pain relief after radiation treatment correlated.

Scheven et al 1986 observed that a dose of about 5 Gy given to metatarsal bones of the embryonic mice resulted in selective elimination of the precursor cells for osteoclast formation .

Tsay et al., 1995 described a clear dose-response relationship between the dose of ionizing radiation and decrease in osteoclast number in vitro was observed (The calculated life span of osteoclast in the study was 9 to 10 days. Tsay et al., 1999 with further observation reported In the first weeks after exposure to moderate doses of ionizing radiation, the number of osteoclasts did not diminish.

Many studies along with Comas et al ,1970 showed the influx of osteoclast precursor cells in vivo was effectively suppressed by ionizing radiation. The resorbing activity of osteoclast was less radiosensitive but can be inhibited in a dose dependent way, by a dose of at least 5 Gy.

The authors hypothesized two mechanisms would explain this change in resorbing activity:

(1) interference with enzymatic processes involved in resorption of cartilage matrix and mineral or

(2) alterations in mobility of the osteoclast.

RADIOTHERAPY FOR BONE METASTASIS

Radiation therapy oncology group (RTOG) 74-02 was the first randomized trial to evaluate the different radiation dose and fractionation schedules. This trial recruited 1016 patients and compared various dose of radiotherapy in palliating patients with bone metastasis.

Radiotherapy dose range was 1500cGy given in 5 fractions to 3000cGy given in 10 fraction for patients with multiple metastasis and 2000cGy given in 5 fraction to 4050cGy given in 15 fraction for single metastasis. The pain assessment done by physician was described as " having no pain or mild ,moderate or severe pain". The overall response was 89% and complete response in 53% and 30 % had partial relief of pain.

Among various schedules used, there was no statistically significant difference in relief of pain. Patients who had more severe pain showed statistically less response than those with lower initial pain score Later it was reanalysed for improvement including narcotic score and the incidence of reirradiation to the same site .It was concluded that number of radiation fractions used correlated with reirradiation given, complete relief prior to retreatment.

Two large randomised trials have compared the single dose radiation to long course radiation in patients with bone metastasis.

The multicentric Dutch trial was done to evaluate patients who had bone metastasis from solid tumour. patients were randomised from march 1996 to September 1998 by 17 radiotherapy institutes of Netherland[43]. Patients with painful metastasis area need to be treated in a target volume. previous irradiated patients ,those with spinal cord compression and pathological fracture were excluded. Patients with cervical spine metastasis were excluded as there was a belief that high dose fraction might cause Radiation Myelopathy. Patients with primary malignancy of melanoma and renal cell carcinoma was also excluded due to difference in their biologic behaviour.

Of the 17 institutions participated,8 institutions included those with favourable prognosis including breast primary females with no visceral metastasis on complete remission after systemic therapy and Prostate cancer patients having KPS 60% or above who were not given prior hormonal treatment .They were separately randomized to answer questions to find if patients with prolonged survival also benefitted from single fraction radiotherapy . In order to evaluate if the randomized patients were representing ,those who had pain at metastatic site are taken for registration.

Patients were then randomized to either single fractionation of 8Gy or to 2400cGy given through six fraction. There was nil restriction/ guidelines given regarding radiation technique. Primary site ,baseline pain score performance status ,site of metastasis and those who need systemic therapy were recorded.

First questionnaire at randomisation was filled by patients themselves without the treating physician's interference. A 11-point pain scale for assessing maximum painful experience over the past week was scored between 0 and 10(Worst).Also they had to note the medications taken for relief. Medications were divided into Phase I including NSAID and non-opioid ,Phase II including mild opioid and Phase III using strong opioid according to WHO pain ladder. Quality of life was assessed by Rotterdam Symptom Checklist.

The first 12 week review questionnaire of self assessment of painful treated area ,medication usage ,QOL along with side effect was assessed weekly upto 12 weeks. Response after radiation was defined as decrease in initial score by atleast 2 points .complete response was considered when pain score was lowered to 0 or 1 independent of medication. A subsequent increase of score to initial or higher score was progression. Time to respond and time to progression was calculated from randomization date and date of progression respectively.

Total of 4084 patients was taken for registration to study in 17 institutions of Netherland and 1171 patients were eligible for the inclusion criteria and were randomized for either 4Gy * six fractions(n=586) or 8Gy * one fraction(n=585) . The reason for not randomizing includes - consent not there(22 %), pain score less than two (8 %),not solid malignancies (1 %) , not single treatable area (24%),fractures needed surgery(8%),cervical metastasis(6%), cord compression(13%),already irradiated (8%),

renal cell cancer (6%),favourable diagnosis (3%) in some institutions. The median survival was 30 weeks period. No significant difference was found among the 2 arms (P= 0.24) .The median overall survival was 28 weeks in 24Gy arm and 33 weeks in 8Gy arm.

Difference for primary tumour site with survival of 69weeks was seen in Breast malignancy,40 week in Prostate patients,13 week in Lung primary & others with 16 weeks survival.

Pain reduction was clearly shown in first four-six weeks. No significant difference between two arms and mean difference of pain score between the arms was < half-a- score. The response evaluation stated that confidence interval of difference in response was within a 10% margin . At end of one year, the difference reduced to 1% and the margin was 6%.This result meant that two schedules can be safely considered equivalent.

There was no significant difference in the time to progression among the two arm ,all the patients of both the group or within the favourable groups. The time for pain progression in 24 Gy arm was 24 weeks and in 8Gy arm ,the median was 20 weeks. Overall response rate was 71% and 35 % had complete response and progression in 49% of responders. There was no significant difference between the two arms regarding response rates. Also no indication that the effect was related to tumour type or site of metastasis.

Retreatment was given in 188 patients indicating majority of patients had acceptable pain response. There was a statistically significant difference with 25% retreated in 8Gy arm and 7% retreated in 24Gy arm. In logistic regression analysis ,the results showed that the retreatment depends on pain score preceding treatment. Higher initial score patients had high chance of retreatment($p<0.0001$). It also showed that pain alone was not the reason for retreatment as chances for retreatment still depended on treatment schedules($p<0.0001$) with pain eliminated out.

Time to retreatment was earlier in single 8Gy arm ($p<0.0001$) compared to 24Gy arm, with an average of about 14 weeks for 8Gy arm and 23 weeks for 24Gy arm. The preceding score was 7.52 in 24Gy arm and 6.82 in 8Gy arm suggesting that higher score was awaited in 24 Gy arm before retreatment was decided upon.

The difference in spinal cord compression was not significant between the two arms .More fractures were observed in 8Gy arm (4%) compared to 24Gy arm (2%).Time for occurrence was 21 weeks in 8Gy arm and 17 weeks in 24Gy arm. There was no significant difference in the quality of life between both the groups.

Occurrence of toxicities including nausea, vomiting ,itching, tiredness and painful skin was assessed in first 4 weeks. There was no significant difference between the two groups. One patient had small bowel ileus in 24Gy arm and radiation enteritis in 8Gy arm.

Global analysis of the study indicated the equality of single fraction to multifractionated treatment for painful bony metastasis but with more retreatments in 8Gy arm. This was observed in those patients with long survival. General conclusion was that single fraction which is more convenient for patients and economic to treating radiotherapy unit, is preferred for patients with painful metastasis though higher the chance of retreatment.

Another large phase 3 RCT done by RTOG comparing single dose and longer course schedules for palliating painful bone metastasis was RTOG 9714 done in United States .It was done to assess the effectiveness of various radiotherapy regimens in more homogenous study population using more sensitive tools for evaluation. Measuring physical , social ,psychological aspect of quality of life along with pain was done. “Functional Assessment of the Cancer Therapy”, Self assessment Brief Pain Inventory to evaluate the site ,severity ,duration , relief and interference with routine activities was used.

Mild pain -score of 1-4

Moderate pain- score of 5-6

Severe pain score 7-10.

Primary objective was to determine if 8Gy given in single dose has equivalent pain relief & narcotic relief as 30Gy given in 10 fractions to painful bone metastasis. This study recruited patients with primary cancers of breast and prostate alone for homogenous population having long survival to assess the duration of relief & fracture .

Eligible patients include

- Age more than equal to 18 years .
- Histology proven tumours of Breast or Prostate
- Radiologic proof showing metastases
- Pain at metastatic site
- KPS atleast 40
- Life expectancy of atleast three months.

Pain score was assessed using " Brief Pain Inventory with a score of atleast five on the scale from0-10 or less than five but taking medications with oral morphine equivalent dose of 60mg or more". Eligible sites were categorised into weight bearing and others.

Those with upto 3different painful areas of bone metastasis are included in the study. Those on bisphosphonates / any systemic treatment were included if there was not introduced within 30 days of entering the study. Informed consent for study was obtained prior to randomization.

Patients were excluded if pathological fracture or impending fracture or prior radiation was given to the same site or undergone surgery .Neurological or radiological proof of compression of cord /Cauda Equina were ineligible .Prior to randomization ,information that were required included History ,clinical examination ,KPS score ,radiological documentation of metastasis done within eight weeks period & who were able to complete the brief pain inventoryI, ,Health Utilities Index III and FACT assessment.

Study population was assigned to either groups in a random way :8Gy delivered in one fraction or 30 Gy given in 10 fraction for two weeks .Treatment was allocated with permuted block design and was well balanced within institutions. Patient stratification was done by pain score, no. of painful site(single or many),region (weight bearing or not) and whether on bisphosphonates .

Simulation of the treatment fields were required prior to radiation. Radiation treatment volume included radiological abnormality with atleast 2 cm margin, but treating the full bone was not required.

RESULTS

Between 1998 and 2001, 949 patients totally were enrolled in this study .898 patients were eligible included 455 n 8Gy arm and 443 in 30Gy arm. Patient characteristics were balanced in both the groups. Cervical spine metastasis was treated in 5.2%(n=47),thoracic spine in 19.4%(n=174) and lumbar spine in 26.6%(n=239) .Patient compliance was excellent in completing score and QOL questionnaire. FACT & Health Utilities III was finished in 98% of study population.

Median survival in 8-Gy armwas9.1 months and in 30-Gy arm was 9.5months(p=.820).at one year follow up, overall survival in 8-Gy arm was 41% and in 30-Gy arm was 42% and 2 year survival in both the arm was 22%.Patients in both the arm tolerated treatment well ,but acute toxicities were high in 30Gy (grade 2-4,70 events ,17%)compare to patients in 8-Gy arm(42

events,10%,P=0.002). Gastro intestinal toxicity accounted for 50% of all acute toxicities. In 30-Gy arm two patients had grade 4 acute toxicities(vomiting and neutropenia) .Two Patients in each arm had grade 3 late toxicities. No grade 4 late toxicity was reported. Late toxicity of grade 2 or more was 4% in both the arms. Those with toxicities were followed up for 7.6 months.

At the time of randomization 845 patients completed Brief Pain inventory. At 3 months 573 patients completed Brief Pain inventory. Missing BPI at the end of three months included dead, not found, refusal or too sick ,late form or intuitional error. 93 out of 573(17%) achieved a complete response and 280 patients(49%)achieved partial response and overall response rate was 66%.About 10%(55) had pain progression. Three month Brief Pain inventory assessment in 8-Gy arm was available in 288 patients and in 30-Gy arm for 285 patients. A partial response rate in 8-Gy arm was 50% and 48% in 30-Gy arm. Complete response was 15 %(44) in 8-Gy arm and 18% (51) in 30-Gy arm (P=.6).For patients with single painful site, complete response was 18% for 8 Gy & 21% in 30 Gy. Partial response - 52 %(85) in 8-Gy arm and 51% (79) in 30-Gy arm among 165 patients and 156 patients respectively. At the end of three months about 33% no longer required narcotics. At the end of three months, response was the same in the two arm after stratifying for number of treatment sites, weight bearing sites, pre-treatment score or if the patients got bisphosphonate.

Response rate was the same at the end of three months ,when the international consensus for Complete Response was used ("score of zero with stable or reducing analgesic intake").CR was seen in 10 % (n=25) of 8-Gy arm & 12 % (n=31) in 30Gy .

There was a 5% of patients in 8-Gy arm and 4% of patients in 30-Gy arm had pathologic fracture with in the treatment field. Adjacent to treatment site ,fracture was seen in around 3 - 4 % . Decision to re-treat was made by the physician . There was a significant difference in the reirradiation rate in two arms .Patients in 8Gy arm had 18 %retreatment rate and 9% in 30Gy arm. Majority of the reirradiation occurred within 9 months of first radiation. At the end of 3 months, pain & narcotic relief ,fracture incidence was the same in two arms.

Koswig and Budach in 1999 randomized patients(n=107) to either 30Gy or 8Gy .Overall response rate was 79% in 8Gy and 82% in 30Gy arm ,with complete response in 31% of 8Gy arm and 33% in 30Gy arm .No significant difference was noted in respect to pain response .They reported significant higher rate of remineralisation in 30 Gy arm at 6 months .Remineralisation of lytic lesion appears dose-dependent and fractionated schedule appears advantageous.

The United Kingdom Bone Pain Trial Working Party randomised patients(n=765) with painful bone metastasis to either 8 Gy in one day or 20 Gy given in 5 fraction or 30 Gy given in 10 fraction. The time for first response, , complete relief and time for progression in pain was same in 12 months follow up. Retreatment rates were twice in 8Gy arm compared to multifractionated radiotherapy.

There was no difference in GI toxicity , compression of cord or fracture. The study concluded that single 8Gy was safe and effective as multifractionated radiation in palliation of bone metastasis atleast for 12 months.

Results of many randomized trials during the last 25 years that compared short course low total dose schedules to long course high dose schedules were concluded as follows:

- Single 8Gy radiation treatment provides similar relief of pain as like long treatment schedules (30Gy or 20Gy)
- Response rate was lower when scoring was done by patients instead of physicians.
- Reirradiation rates were high after short course by a factor of 2-3
- Response rates were better for those with low initial pain score.
- There is no consistent dose-response relation for palliating bone metastasis.

REIRRADIATION:

Results from various studies comparing single and multifractionated regimens showed reirradiation rate from 11-42% after single fraction and 0-24% after multifractionated treatment. Response after reirradiation may vary after each situation:1)No response or progression after initial radiation 2)Partial response after initial radiation and expected further pain relief after more radiation 3)Recurrence of pain after initial response to radiation.

Dutch Bone metastasis study group demonstrated the effectiveness of reirradiation for painful bone metastasis .Among those patients who not responded to radiation were reirradiated. About 66 % of patient who initially received single 8Gy responded to retreatment versus 33 % of patients who received prior multifractionated radiation.

It was also shown that multi-fraction long- course radiotherapy results in better re-calcification and fewer recurrences of spinal cord compression within the irradiated spinal region . In case of recurrence, Nieder et al. reviewed that re-irradiation of the spinal cord to a cumulative biological equivalent dose (BED) of 130 to 135 Gy2 was safe when the initial dose did not exceed 90 Gy2(alpha /beta of 2).

Therefore, for patients with spinal cord compression or who are at risk of spinal cord compression, a more protracted initial course of radiotherapy is recommended in order to avoid unsalvageable recurrence and complicated calculation during retreatment in patients with good performance status.

It is also generally recommended to consider re-irradiation after at least 4 weeks in patients not responding to initial radiation and definitely at the time when pain recurs. When organs at risk are in-field of re-treatment portal, tissue tolerance has to be taken into consideration. However, as the time for recovery is still unknown, exact tolerance of organs at risk during retreatment is uncertain and more studies are warranted in this aspect[44].

Aims and Objectives :

To compare the pain relief at the end of 3 months in patients treated with two different fractionation schedules of single 8Gy fraction versus multiple fractionated 30Gy for painful spine metastasis .

Objectives:

1)To compare the acute toxicities in the two arms

2) To assess the requirement of reirradiation in the two arms within 3 months of initial treatment

MATERIALS AND METHODS

Study Centre

Study was done at the department of Radiotherapy, Rajiv Gandhi Government General hospital & Madras Medical college located at Chennai.

Study Design:

The study is double arm prospective one comparing 8Gy in one fraction and 30 Gy in ten fraction as control arm in 1:1 randomisation for patients with painful spine metastasis.

Study Population

Study population includes patients presenting with painful spine metastasis with known biopsy proven primary tumour elsewhere. Patients were eligible if they had biopsy proven malignancy and radiological evidence of spine metastasis with pain

Sample size :30 patients in each arm

Study period: one year

INCLUSION CRITERIA

- Biopsy proven malignancy of any primary site
- painful spine metastasis
- Radiological evidence of spine secondaries
- age -18 to 75 years
- ECOG -1 and 2
- Single field of maximum length upto 15 cm
- No previous irradiation to index site
- life expectancy of more than 3 months

EXCLUSION CRITERIA

1)Primary bone tumour

2)No radiological evidence of bone metastasis

3) ECOG 3 and 4

4)Previous irradiation of the same spine

5)Life expectancy of < 3 months

6)Established pathological fracture

7)Prior surgical fixation

8)Introduction of systemic therapy started within 30 days prior to RT

PRETREATMENT ASSESSMENT

INFORMATION REQUIRED

1.Discharge summary of previous consultation (haematological, imaging , histopathology reports and treatment given)

2.Drug history

3.Ortho spine surgery opinion details where relevant

4.CT or MRI or bone scan –reports and film

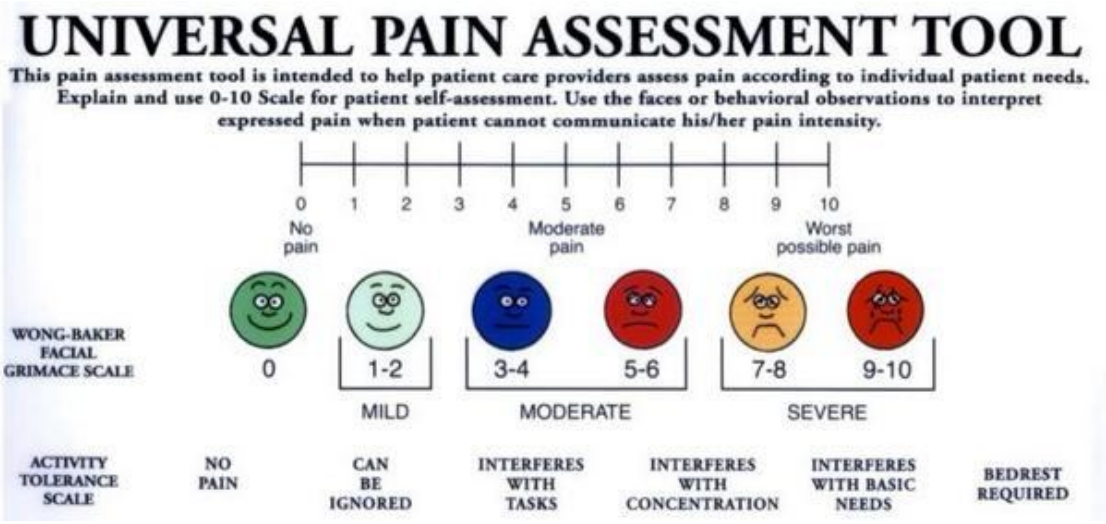
5. Site and severity of pain

6.Staging investigation of primary disease

PERFORMANCE STATUS-ECOG SCORE

ECOG	Description
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 selfcare. Totally confined to bed or chair

PAIN ASSESSMENT



Universal pain assessment tool is made use of to evaluate the intensity of pain. It scores from 0 to 10,with 0 being no pain and 10 being the worst score possible. This tool combines Wong Baker Facial grimace scale and activity tolerance scale and helps to effectively assess the pain more effectively.

WHO PAIN LADDER

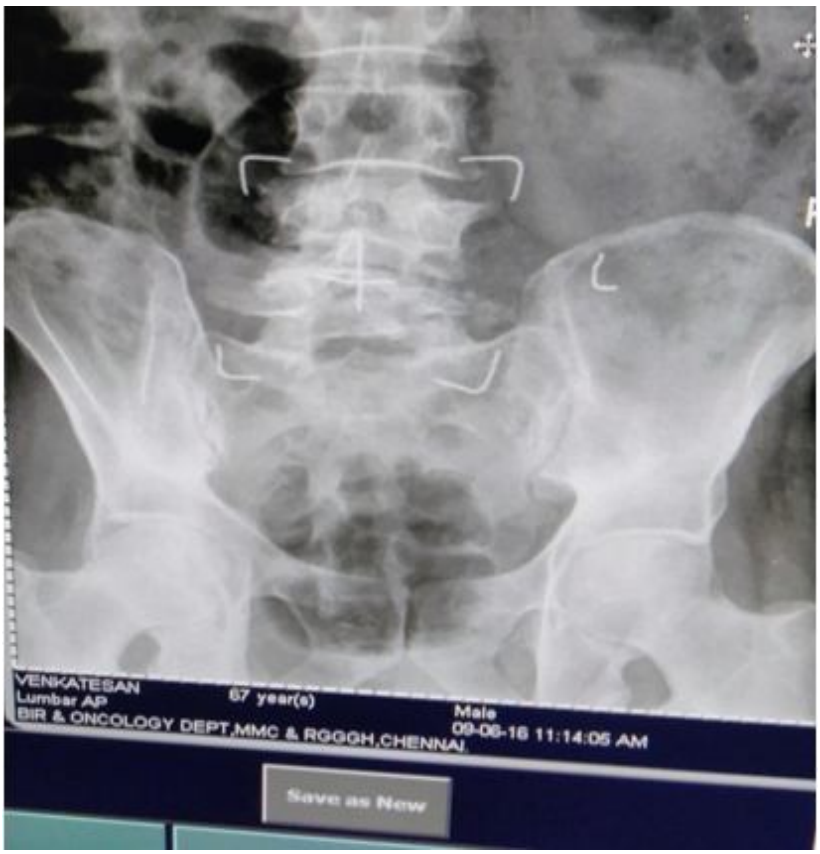
STEP	DRUGS
1	Paracetamol, NSAIDS± Adjuvants
2	Weak opioids+ step 1 drugs (codeine, dihydrocodeine, tramadol)
3	Strong opioids+ step 1 drugs(morphine, dimorphine ,fentanyl)

Adjuvants: steroids ,tricyclic antidepressants, anti convulsants

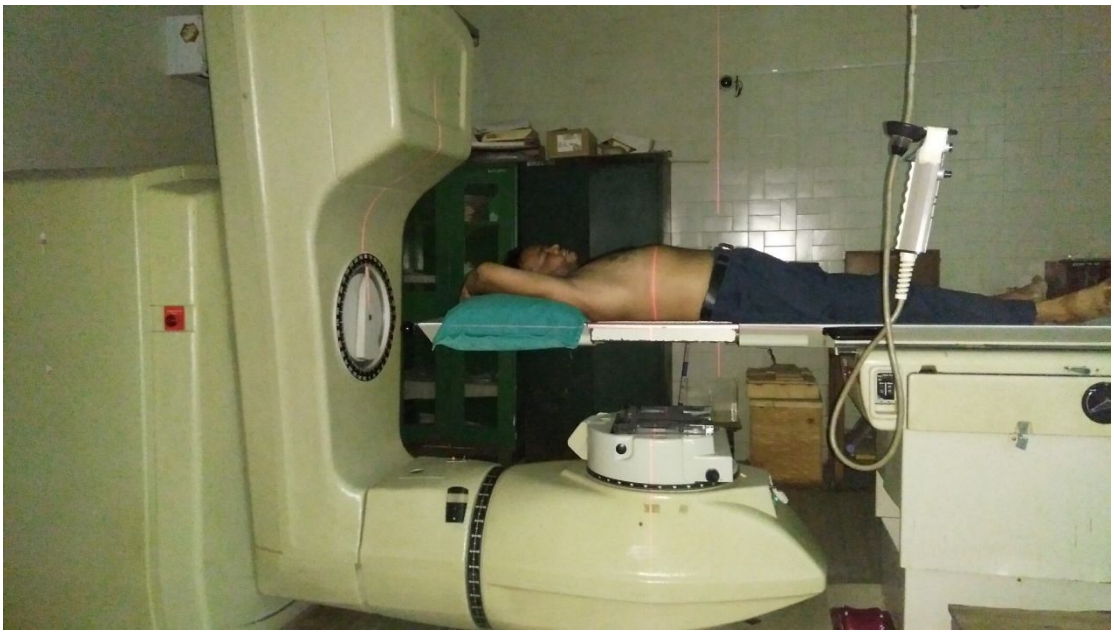
TREATMENT PROTOCOL

Patients included for this study were assessed for pain and those with pain more than 5 and metastatic lesion in the vertebrae that is treatable in single field (within 15cm) were planned for radiation. Treatment fields were defined following X-ray simulation of the involved region. Margin included one vertebrae above and below the involved spines and the lateral margin would encompass the transverse process of the vertebrae on either side.

X-RAY SIMULATION OF LUMBAR FIELD



TREATMENT POSITION WITH GANTRY ROTATION



Inj.Dexamethasone 16 mg was given prior to initiation of radiation and tapered with time course. Patients were treated using Theratron phoenix (cobalt 60) with single PA portal either directly or with gantry rotation .As per the institutional protocol ,all patients were given I.V zolendronic acid 4mg every 28 days.

BIOLOGICALLY EFFECTIVE DOSE:

BED	8Gy in 1 #	30 Gy in 10 #
Tumour (□/□=10)	14.4	39
Spinal cord (□/□=2) (□/□=3)	40 29.3	75 60

GASTROINTESTINAL TOXICITY-CTCAE

Gastrointestinal toxicity was assessed using common toxicity criteria for adverse events.

Table 1. National Cancer Institute Common Terminology Criteria for Adverse Events: Gastrointestinal Toxicity

ADVERSE EVENT	GRADE 1 (MILD)	GRADE 2 (MODERATE)	GRADE 3 (SEVERE)	GRADE 4 (LIFE THREATENING OR DISABLING)	GRADE 5 (DEATH)
Constipation	Occasional or intermittent symptoms; occasional use of stool softeners, laxatives, dietary modification, or enema	Persistent symptoms with regular use of laxatives or enemas indicated	Symptoms interfering with activities of daily living; obstipation with manual evacuation indicated	Life-threatening consequences (e.g., obstruction, toxic megacolon)	Death
Diarrhea	Increase of < 4 stools per day over baseline; mild increase in ostomy output compared to baseline	Increase of 4–6 stools per 24 hours over baseline; IV fluids indicated < 24 hours; moderate increase in ostomy output compared to baseline; not interfering with activities of daily living	Increase of 7 stools per 24 hours over baseline; incontinence; IV fluids 24 hours; hospitalization; severe increase in ostomy output compared to baseline; interfering with activities of daily living	Life-threatening consequences (e.g., hemodynamic collapse)	Death
Nausea	Loss of appetite without alteration in eating habits	Oral intake decreased without significant weight loss, dehydration or malnutrition; IV fluids indicated < 24 hours	Inadequate oral caloric or fluid intake; IV fluids, tube feedings, or total parenteral nutrition indicated 24 hours	Life-threatening consequences	Death
Vomiting	1 episode in 24 hours	2–5 episodes in 24 hours; IV fluids indicated < 24 hours	6 episodes in 24 hours; IV fluids or total parenteral nutrition indicated 24 hours	Life-threatening consequences	Death

Note. Based on information from National Cancer Institute, 2006.

RESPONSE ASSESSMENT:

Response to bone pain after radiation is assessed using the following criteria at various intervals including week 1 week 4 and week 12 after radiation.

PAIN RESPONSE ASSESSMENT SCALE

RESPONSE	CRITERIA
Complete Response	having no pain at 3 months after radiation therapy
Partial Response	pain score that was at least two points lower than the initial score
Stable Response	one-point change in pain score in either direction
Progression	pain score that was at least two points higher than the initial score

STATISTICAL EVALUATION

Data was entered in Microsoft Excel and analysis was done using SPSS software with Mann-Whitney U test.

OBSERVATION AND RESULTS

AGE DISTRIBUTION

	Frequency	Percent
Less than 50 years	25	41.7
51 to 60 years	27	45.0
more than 61 years	8	13.3
Total	60	100.0

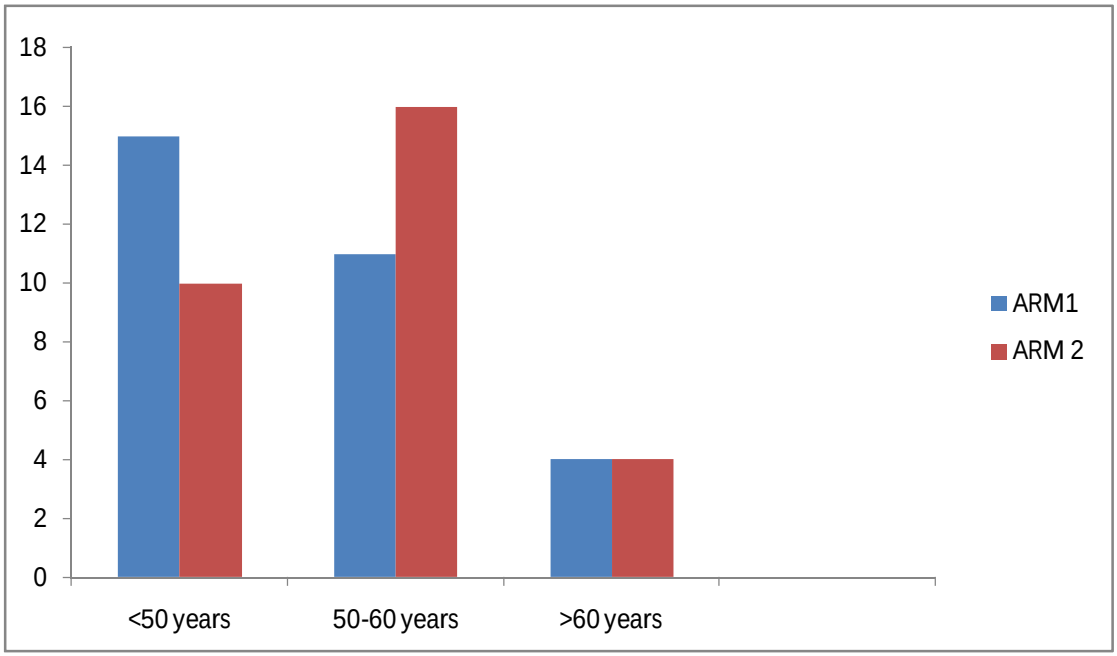
Majority of the patients belong to age group of 50-60 years .41% of patients were less than 50 years and 45 % were between 50-60 years of age.

AGE DISTRIBUTION IN ARM 1 AND ARM 2

AGE	ARM1		ARM 2	
	COUNT	PERCENT	COUNT	PERCENT
<50 YEARS	15	50	10	33.3
50-60 YEARS	11	36.7	16	53.3
>60 YEARS	4	13.3	4	13.3

Minimum age of patient included was 23 years in arm 1and 18 years of age in arm 2.Maximum age of patient included in arm 1 was 72 years and 73 years of age in arm 2.50% of patients in arm 1 were less than 50 years of age and 53.3 % of patients in arm 2 were between 50-60 years of age.

AGE DISTRIBUTION IN ARM1 AND ARM 2

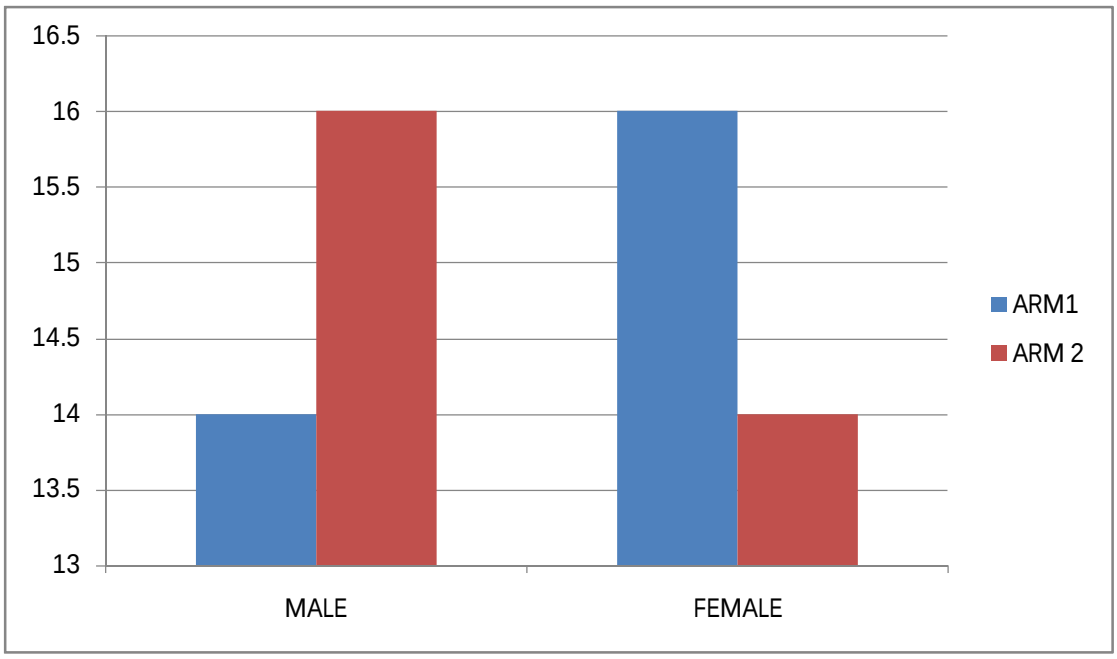


SEX DISTRIBUTION

GENDER	ARM 1		ARM 2	
	COUNT	PERCENT	COUNT	PERCENT
MALE	14	46.7	16	53.3
FEMALE	16	53.3	14	46.7

- Male patients in arm1 was 14(46.7%) and in arm 2 was 16(53.3%).
- Female patients in arm1 was 16 (53.3%) and 14 in arm 2(46.7%)

GENDER DISTRIBUTION



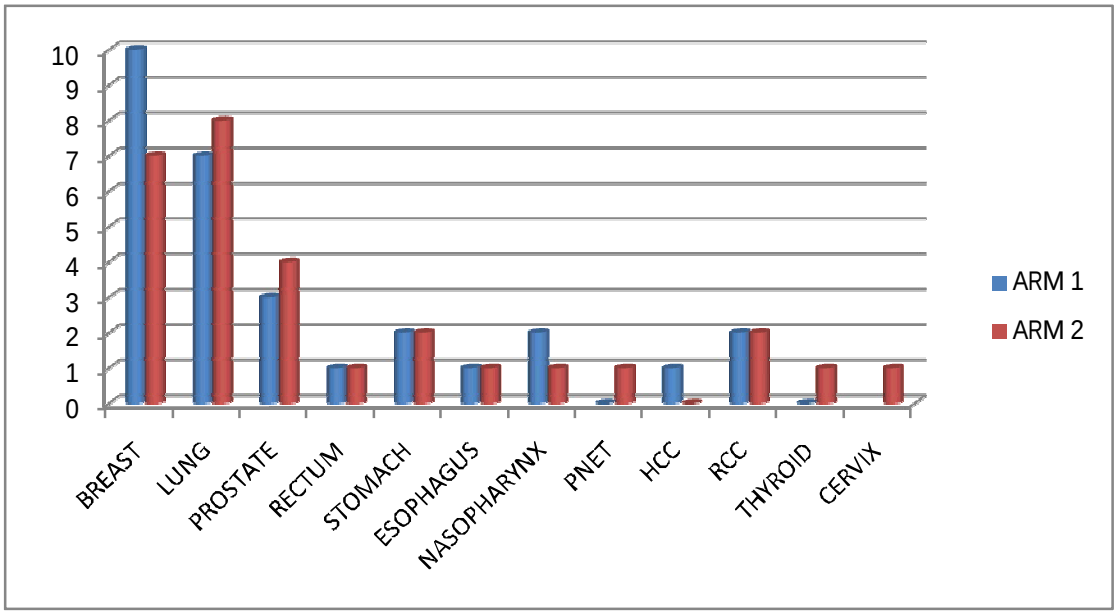
PRIMARY SITE

Breast was the primary site of malignancy in 33.3% in 8Gy arm and 23.3% in 30Gy arm .Lung cancer was primary site in 23.3 % in arm 1 and 26.7% in arm 2.Prostate cancer patients in arm 1 were 10% of patients and 13.3 %patients in arm 2.Other malignancies included were those arising from nasopharynx , cervix, esophagus, rectum, stomach, hepatocellular, kidney, thyroid, pancreas and primitive neuro-ectodermal tumour.

PRIMARY SITE IN ARM 1 AND ARM 2

PRIMARY	ARM 1 COUNT	ARM 1 PERCENT	ARM 2 COUNT	ARM 2 PERCENT
Breast	10	33.3	7	23.3
Cervix	0	0	1	3.3
Esophagus	1	3.3	1	3.3
Hepatocellular	1	3.3	0	0
Lung	7	23.3	8	26.7
Nasopharynx	2	6.7	1	3.3
Pancreas	1	3.3	1	3.3
PNET	0	0	1	3.3
Prostate	3	10	4	13.3
RCC	2	6.7	2	6.7
Rectum	1	3.3	1	3.3
Stomach	2	6.7	2	6.7
Thyroid	0	0	1	3.3

PRIMARY SITE IN ARM 1 AND ARM 2



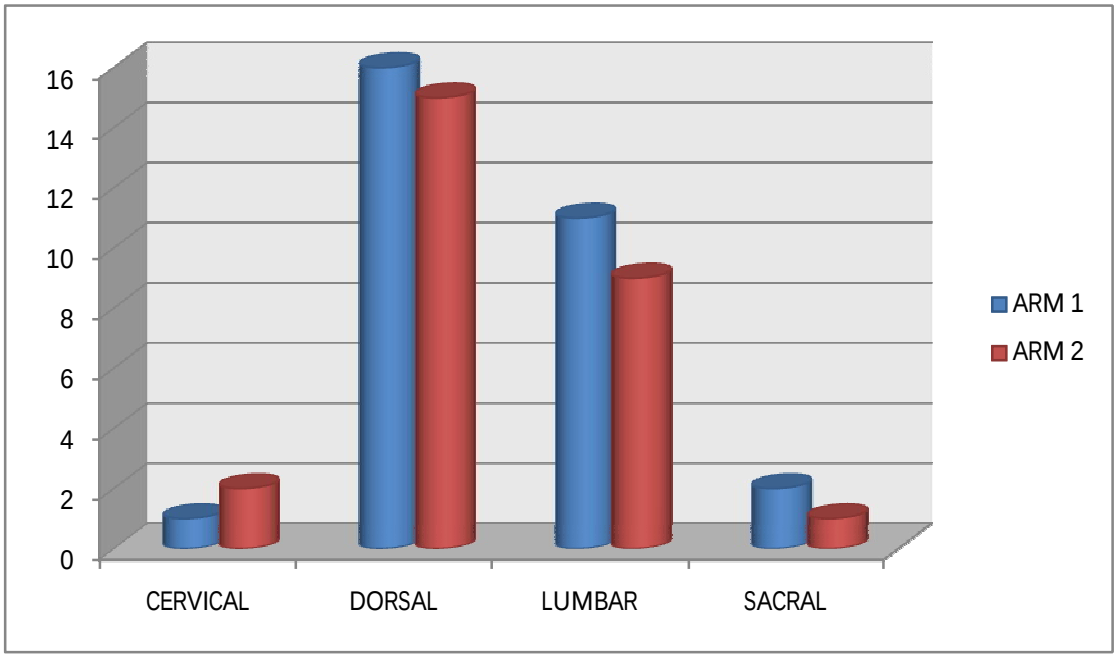
SPINE LEVEL

- Dorsal spine metastasis was found in 16 patients of 8Gy arm and in 15 patients of 30Gy arm.
- Lumbar spine metastasis was seen in 11 patients in8Gy arm and in 12 patients in 30Gy arm .
- Cervical spine metastasis was seen in one patient of 8Gy arm and in 2 patients in 30Gy arm .
- sacral metastasis was seen in 2 patients in 8Gy arm and 1 patient in 30Gy arm .

DISTRIBUTION OF SPINE METASTASIS

SPINE	ARM 1 COUNT	ARM 1 PERCENT	ARM2 COUNT	ARM2 PERCENT
CERVICAL	1	3.3	2	6.7
DORSAL	16	53.3	15	50
LUMBAR	11	36.7	12	40
SACRAL	2	6.7	1	3.3

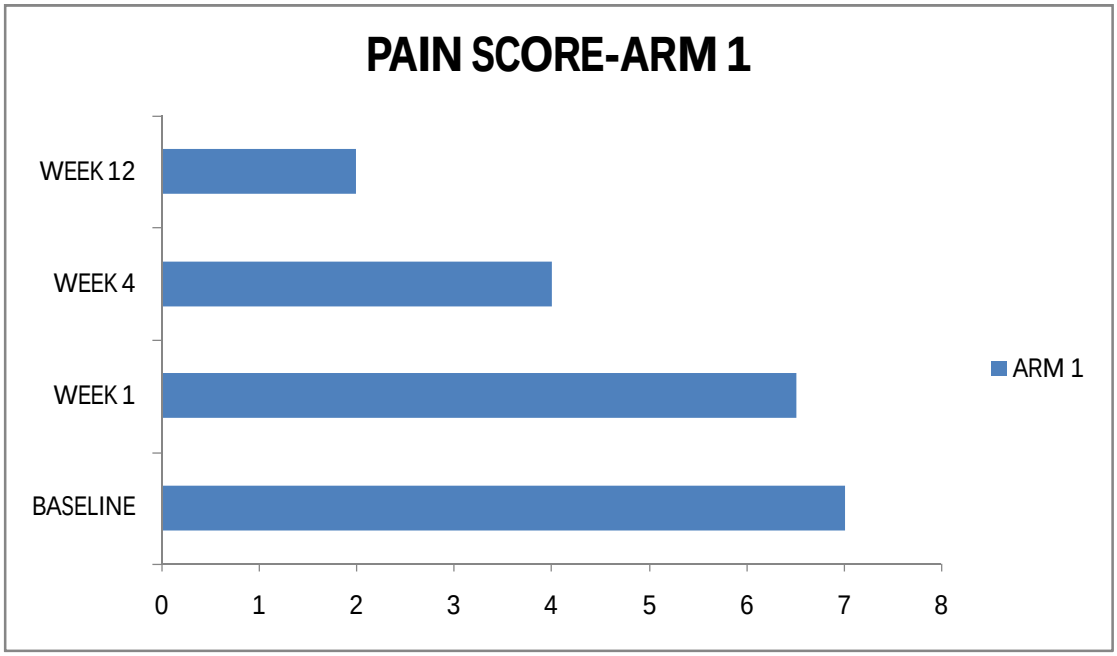
SPINE LEVEL IN ARM 1 AND ARM 2

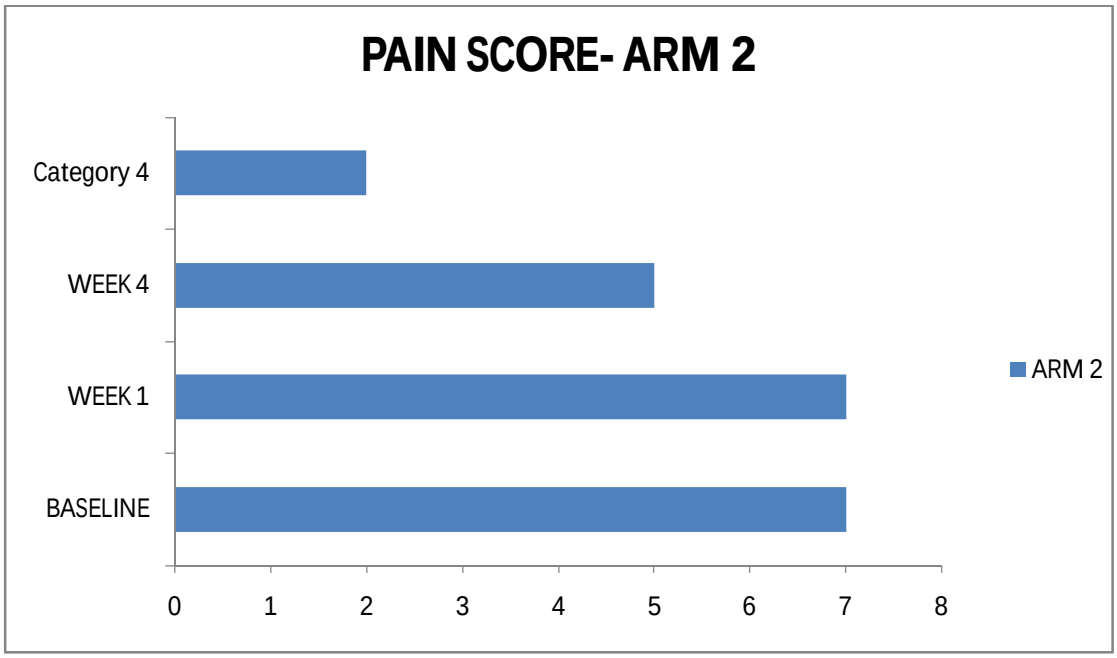


COMPARISON OF PAIN SCORE AT DIFFERENT TIME INTERVAL-ARM1 AND ARM 2

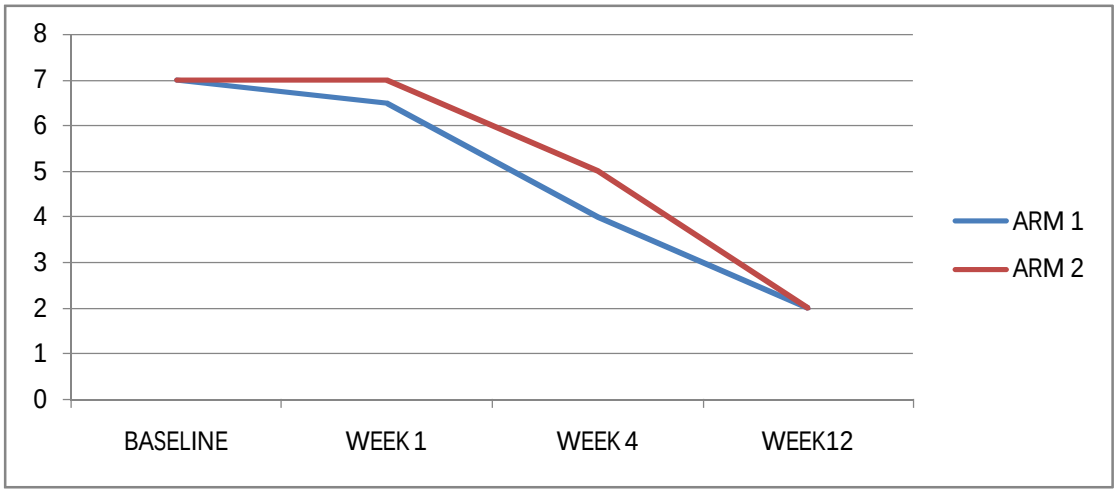
FOLLOW UP AT	MEDIAN PAIN SCORE ARM 1	MEDIAN PAIN SCORE ARM 2	P VALUE
PRESENTATION	7	7	.337
WEEK1	6.5	7	.597
WEEK 4	4	5	.191
WEEK 12	2	2	.962
P VALUE	.000	.000	

- No difference in pain score noted between 8Gy and 30Gy arm through out the follow up period.
- Significant pain reduction noted in patients of both the treatment schedules.


PAIN SCORE-ARM 1
WEEK 12
WEEK 4
WEEK 1
BASELINE
0
1
2
3
4
5
6
7
8
ARM 1


PAIN SCORE- ARM 2
Category 4
WEEK 4
WEEK 1
BASELINE
0
1
2
3
4
5
6
7
8
ARM 2

PAIN SCORE AT DIFFERENT INTERVALS IN ARM 1 AND ARM2



COMPARISON OF PAIN SCORE BASED ON AGE IN ARM 1

PERIOD	AGE	MEDIAN SCORE	P VALUE
Baseline	<50 years 51-60years >60 years	7 7 7.5	.777
Week 1	<50 years 51-60 years >60 years	7 6 5	.848
Week 4	<50 years 51-60 years >60years	4 5 4	.635
Week 12	<50years 51-60 years >60years	2 2 2	.625

COMPARISON OF PAIN SCORE BASED ON AGE IN ARM 2

PERIOD	AGE	MEDIAN SCORE	P VALUE
Baseline	<50years 51-60 years >60years	7 7 6.5	.807
Week 1	<50years 51-60 years >60years	6.5 7 6	.743
Week 4	<50years 51-60 years >60years	4.5 5 5.5	.504
Week 12	<50years 51-60 years >60years	3.5 2 3.5	.885

- No difference in pain relief noted in both the arm in respect to age of the patient throughout the study period.

COMPARISON OF PAIN SCORE BASED ON SEX IN ARM 1

PERIOD	SEX	MEDIAN SCORE	P VALUE
Baseline	Male Female	7 7	.035
Week 1	Male Female	7 6	.316
Week 4	Male Female	5 4	.210
Week12	Male Female	3 2	.036

- No difference in pain response seen between male and female patients of the two arm throughout the study period.

COMPARISON OF PAIN SCORE BASED ON SEX IN ARM 2

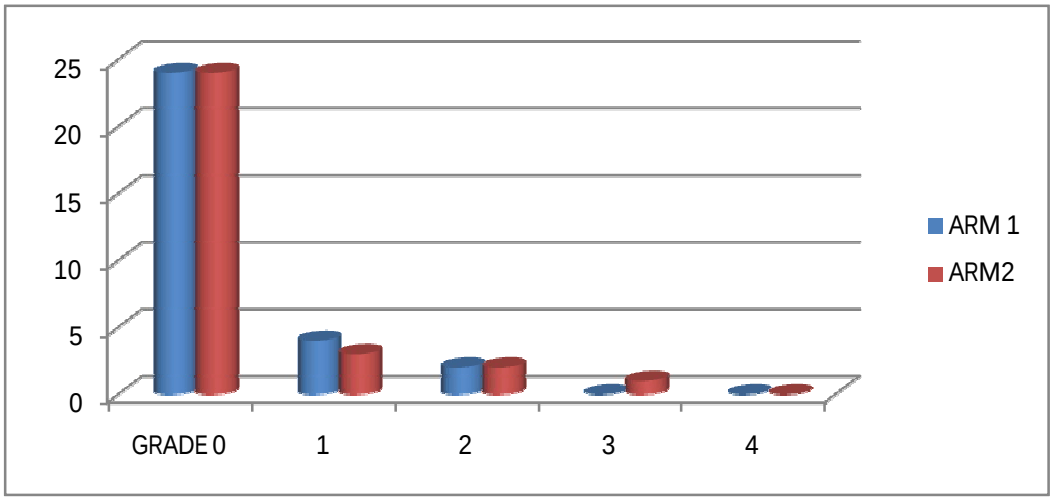
PERIOD	SEX	MEDIAN SCORE	P VALUE
Baseline	Male female	7 8	.230
Week 1	Male female	6 7	.442
Week 4	Male female	5 6	.623
Week 12	Male female	2 4	.153

No difference in pain relief noted in respect to gender in both the treatment schedule throughout the follow up period.

GASTROINTESTIAL TOXICITY

G.I TOXICITY GRADE	ARM 1	ARM 2
GRADE 0	24	24
GRADE 1	4	3
GRADE 2	2	2
GRADE 3	0	1
GRADE 4	0	0

G.I TOXICITY IN ARM 1 AND ARM 2

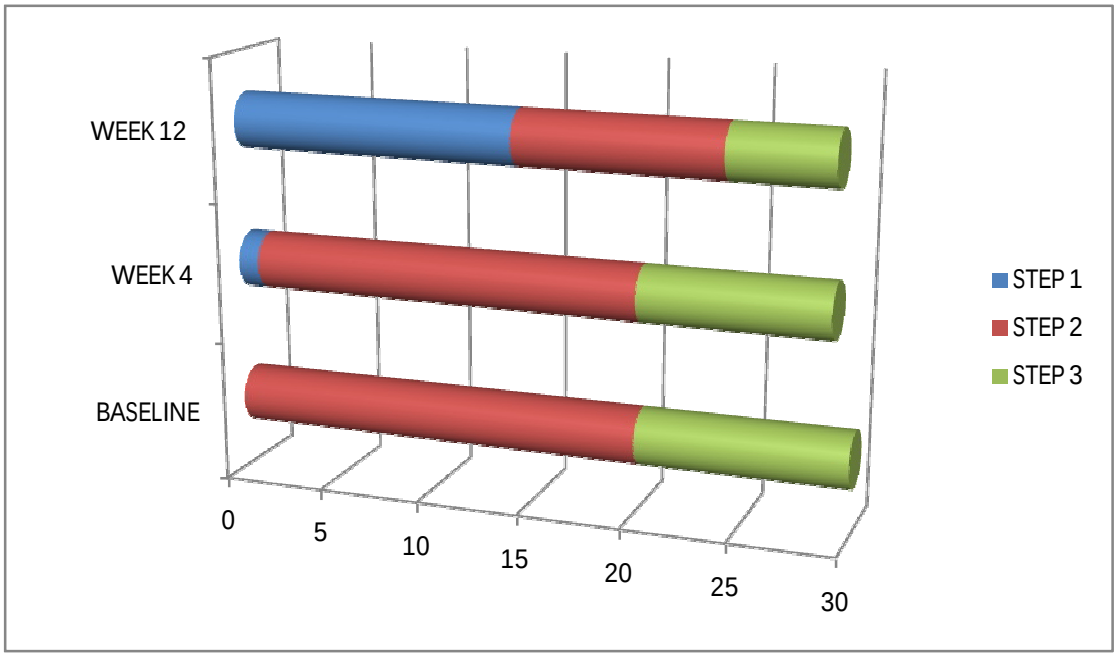


- Majority of the patient in both the arm had no gastro intestinal toxicity. In 8Gy arm,4 patients had grade 1 toxicity and 3 patients in 30Gy arm had grade 1 toxicity.
- None had grade 4 toxicity in either arm.

WHO PAIN LADDER OF MEDICATION -ARM 1

PERIOD	STEP 1	STEP2	STEP 3
PRESENTATION	0	20	10
MONTH 1	1	19	9
MONTH 3	14	10	5

WHO PAIN LADDER OF MEDICATION -ARM 1

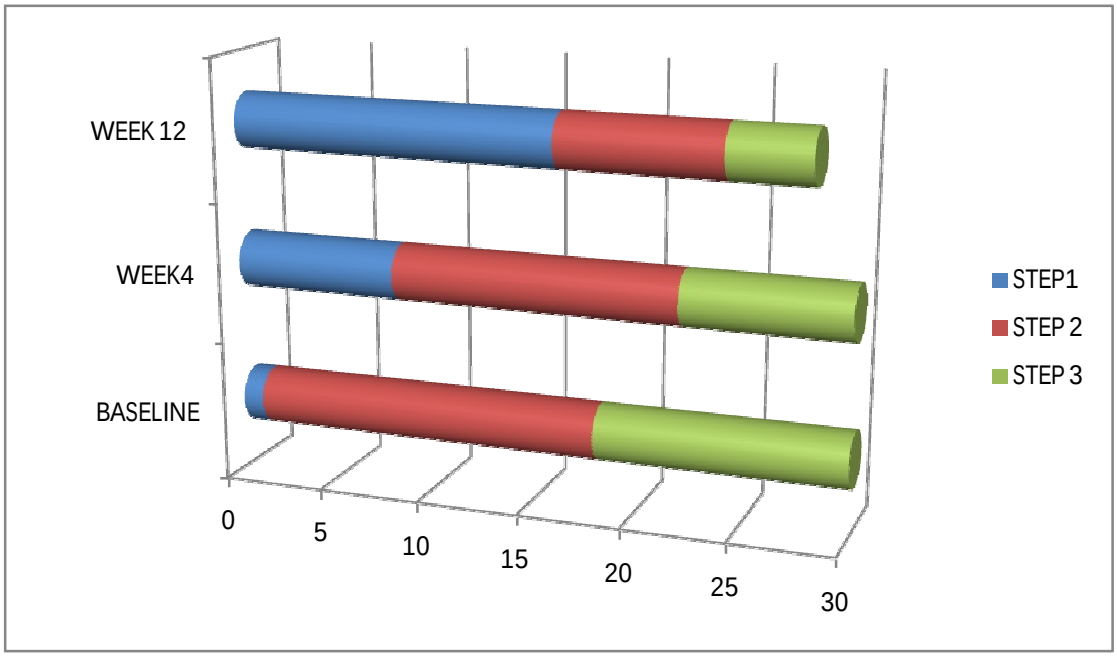


During initial presentation ,majority of patients in arm 1 were on step 2 WHO analgesics(n=20).At the end of 3 months, majority of patients stepped down to step 1 medications(n=14).

WHO PAIN LADDER OF MEDICATION -ARM 2

PERIOD	STEP 1	STEP2	STEP 3
PRESENTATION	1	17	12
MONTH 1	8	14	8
MONTH 3	16	8	4

WHO PAIN LADDER OF MEDICATION -ARM 2

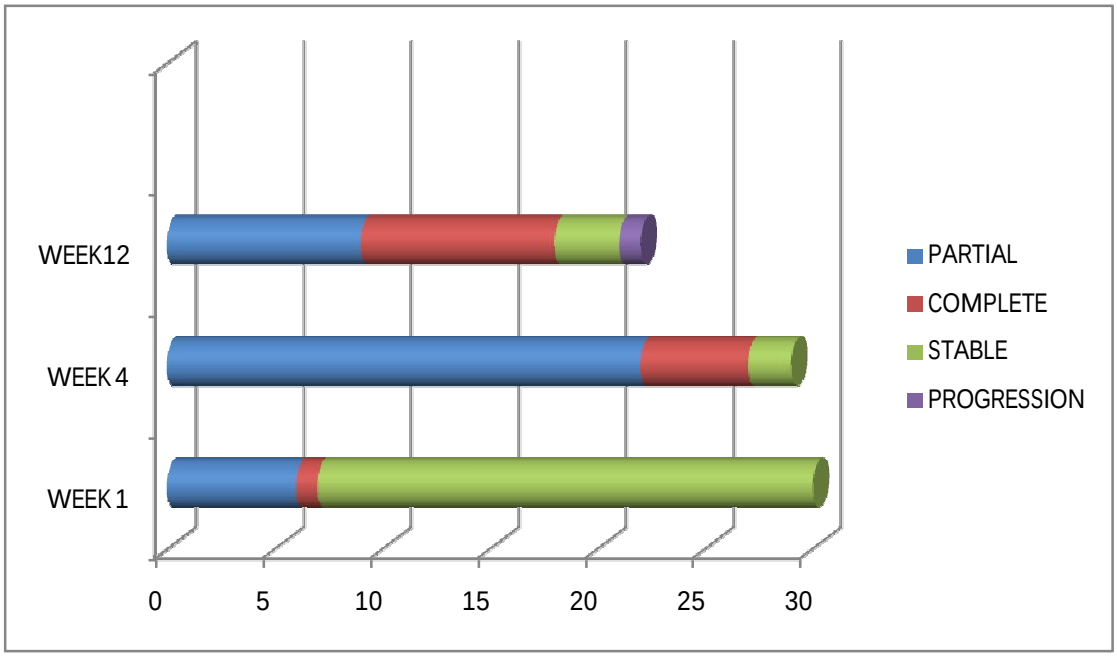


In arm 2,majority of patients were on step 2 WHO analgesics during initial presentation(n=17).At the end of 3 months ,most of the patients were in step 1 medication (n=16).

PAIN RESPONSE IN ARM 1

RESPONSE	WEEK 1	WEEK 4	WEEK 12
PARTIAL RESPONSE	6	22	9
COMPLETE RESPONSE	1	5	16
OVERALL RESPONSE	7	27	25
STABLE DISEASE	23	2	3
PROGRESSION			1

PAIN RESPONSE IN ARM 1

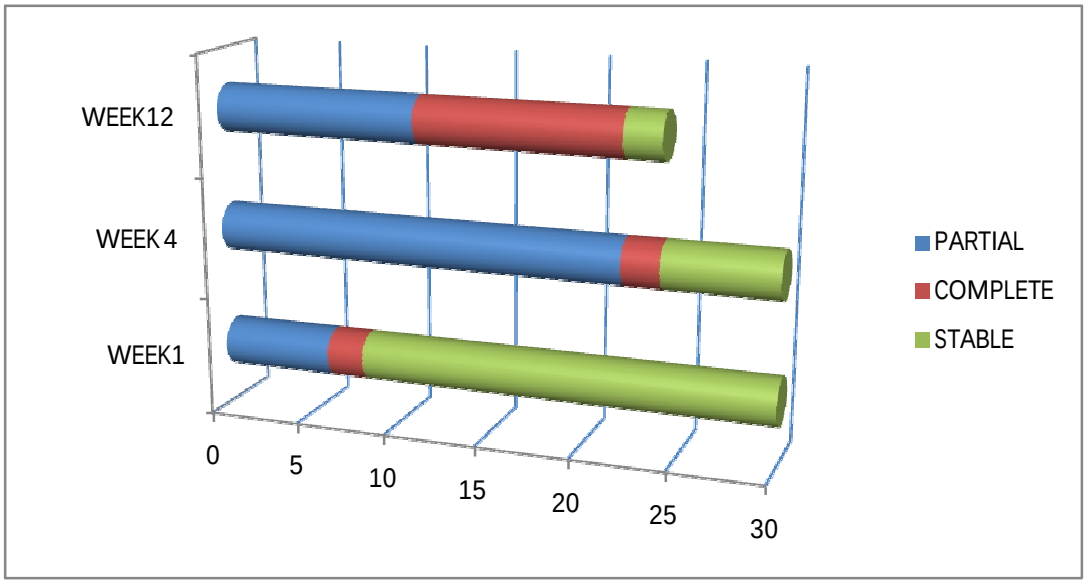


- Complete response in arm 1 at the end of 3 months was 53%(n=16) and Partial response was 30%(n=9) .
- Overall response rate in arm 1 at 3 months was 83.3%
- One patient was retreated with 30Gy for persistent pain at the end of three months.

RESPONSE IN ARM 2

RESPONSE	WEEK 1	WEEK 4	WEEK 12
PARTIAL RESPONSE	6	22	11
COMPLETE RESPONSE	2	2	15
OVERALL RESPONSE	8	4	26
STABLE DISEASE	22	6	2

PAIN RESPONSE IN ARM 2



- Complete response in arm 2 at the end of 3 months was seen in 50%(n=15) and partial response was seen in 36.6%(n=11)
- Overall response was 86.6% in arm2 at 3 months.

RESPONSE BASED ON HISTOLOGY

BREAST

			FINAL_RESPONSE		Total	
			NO	YES		TEST
Arm	8 Gy	Count	0	9	9	FISHER'S EXACT P VALUE – 0.438
	30 Gy	Count	1	6	7	

PROSTATE

		FINAL_RESPONSE	Total
		YES	
Arm	8 Gy Count	3	3
	30 Gy Count	4	4

LUNG CANCER

		FINAL_RESPONSE		Total
		NO	YES	
Arm	8 Gy count	1	6	7
	30 Gy Count	1	7	8

NASOPHARYNX

		FINAL_RESPONSE		Total
		NO	YES	
Arm	8 Gy Count	1	1	2
	30 Gy	0	1	1

ESOPHAGEAL CANCER

			FINAL_RESPONSE		Total
			NO	YES	
Arm	8 Gy	count	0	1	1
	30 Gy	Count	1	0	1

STOMACH CANCER

			FINAL_RESPONSE		Total
			NO	YES	
	8 Gy arm	Count	1	1	2
	30 Gy arm	Count	0	2	2

In order to evaluate the influence of histology on pain response, we evaluated the response according to various histologies. There was statistically significant difference between various group of patients except that patients with breast ,prostate had high response .Because of few patients in different subgroups ,any further analysis would be difficult.

DISCUSSION

The purpose of this study is to find if treatment schedule of 8Gy given by one fraction was as effective as 30Gy given in 10 fraction with respect to pain relief at the end of 3 months in patients in spine metastasis .The distribution of patients in two arms of the study was well balanced with respect to age ,sex ,site of metastasis and pain score at the time of presentation. All patients included in the study showed good compliance and responded willingly to questions when contacted over telephone for following up .

Pain relief compared at the end of 3 months after irradiation showed that majority of patients in both the arm had either complete or partial response .Overall response was 83.3 % in single fraction 8Gy arm and 86.6% in fractionated 30Gy arm which had no statistically significant difference .There was no statistical difference in terms of acute toxicity between the two arm. One patient was retreated in the single 8Gy arm for persistent pain at 3 months.

When patients were sub-grouped based on age ,the highest median pain score at initial presentation was seen in greater than 60 years in arm1 .In contrast, patients in arm 2 who were less than 60years of age had the highest median pain score. On statistical analysis this observation was found to be not significant.

Gender based analysis showed that initial median pain score was same among males and females in arm 1 and slightly higher in arm 2 which was not statistically significant. Analysis based on the severity of pain revealed patients in both the arm had moderate to severe pain .Analysis on the use of medications showed no statistical difference since majority of patient in both the arm were on step 2 analgesics at the time of presentation and majority stepped down to step 1 medications at 3 months after irradiation .

Acute gastrointestinal toxicity was mild in both the arm and had no statistical difference .One patient in arm 2 had grade 3 toxicity(nausea and vomiting) .No skeletal events like pathological fracture of spine or spinal cord compression was found in both the arm during the 3 month follow up period.

CONCLUSION

The conclusion from this prospective study comparing single fraction 8Gy with multifractionated 30Gy is that single fraction radiation schedule provides similar pain relief in patients with spine metastasis when assessed at three month follow up. This is in concurrence with the multiple randomized trials and meta-analysis done in the past 25 years.

The observation in this study suggest that single fraction radiation schedule would be adequate in palliative setting as long the end point is pain relief for bone metastasis. This short course treatment schedules provides convenience for patients with painful metastasis who need not be positioned for radiation over 2 weeks. It also gives convenience for the care givers due to short hospital stay. Despite the results from various randomised trials done comparing the efficacy of single fraction with long course high dose regimens around the world, it is still less practised.

In developing countries where the demand exceeds the availability of health care resources, balance must be made in an attempt to cure the good prognostic early stage patients and in palliating those with pain. In high volume centres, short radiation schedules for palliation provides opportunity to treat more patients in the same treatment time.

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INFORMATION TO PARTICIPANTS

Title: "**COMPARING 8GY VS 30 GY SCHEDULES OF PALLIATIVE RADIOTHERAPY IN THE TREATMENT OF SPINE METASTASIS "**

Name of Participant:
Name of the Principal(co – investigator) :DR.R.NARMADHA
Name of the institution : Department of radiotherapy, RGGGH, MMC.

You are invited to take part in this research/ study/procedures/tests. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

What is the purpose of research?

Bone metastasis is a common manifestation of malignancy often presenting as the first evidence of dissemination. It develops in up to 70% of patients with prostate cancer and breast cancer, and remaining from those with cancers of the lung, bladder, and thyroid. Metastasis can occur in any bone, though they are more common in sites containing red bone marrow.Approximately70%ofbone metastasis occur in the axial skeleton more frequently occurring in spine pelvis and ribs. If patients have skeletal metastases only, their average survival is longer. With prolongation in survival ,pain ,pathological fractures, hypercalcemia, neurological deficits and immobility decreases the quality of remaining life . Associated depression and anxiety may further compromise the quality of survival. **Radiotherapy is considered as the treatment of choice** for palliation of painful bone metastasis with partial pain relief seen 80% to 90% and complete pain relief in 50% of patients.

We want to compare the effectiveness of two different fractionation schedules routinely used to treat patients with spine metastasis .We have obtained permission from the Institutional Ethics Committee.

The study design

Double arm prospective study

Study Procedures

The study involves patients with painful spine metastasis with a biopsy proven primary malignancy of any site. Baseline pain assessment score is evaluated .palliative radiotherapy is planned and executed as per the allotted arm after verifying the fields with X-ray simulation. Every month when you come for the routine follow up, the study physician will examine you and evaluate the pain assessment score. In case of persistent or progressive pain ,X-ray will be taken to assess the disease status and considered for retreatment.

In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document.

You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, Institutional Ethics Committee and any person or agency required by law like the Drug Controller General of India to view your data, if required.

The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. You will be taken care of and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment/discontinuing of procedures etc.

Signature of Investigator Signature of Participant

Date Date

INFORMED CONSENT FORM

TITLE OF THE STUDY **"COMPARING 8GY VS 30 GY SCHEDULES OF PALLIATIVE RADIOTHERAPY IN THE TREATMENT OF PAINFUL SPINE METASTASIS "**

NAME OF THE PARTICIPANT:

NAME OF THE PRINCIPAL (Co – Investigator) : **DR.R.NARMADHA**

NAME OF THE INSTITUTION: MADRAS MEDICAL COLLEGE

_____ have read the information in this form (or it has been read to me). I was free to ask any questions and they have been answered. I am over 18 years of age and, exercising my free power of choice, hereby give my consent to be included as a participant in **COMPARING 8GY VS 30 GY SCHEDULES OF PALLIATIVE RADIOTHERAPY IN THE TREATMENT OF PAINFUL SPINE METASTASIS ”**”

1. I have read and understood this consent form and the information provided to me.
2. I have had the consent document explained to me.
3. I have been explained about the nature of the study.
4. I have been explained about my rights and responsibilities by the investigator.
5. I have been informed the investigator of all the treatments I am taking or have taken in the past 12 months including any native (alternative) treatment.
6. I have been advised about the risks associated with my participation in this study.*****
7. I agree to cooperate with the investigator and I will inform him/her immediately if I suffer unusual symptoms. *****
8. I have not participated in any research study within the past 12month(s). *****
9. I agree to under go complete blood count, renal and liver function test, chest x ray, CT scan of the head and neck
10. I am aware of the fact that I can opt out of the study at any time without having to give any reason and this will not affect my future treatment in this hospital. *****
11. I am also aware that the investigator may terminate my participation in the study at any time, for any reason, without my consent. *****
12. I hereby give permission to the investigators to release the information obtained from me as result of participation in this study to the sponsors, regulatory authorities, Govt. agencies, and IEC. I understand that they are publicly presented.
13. I have understand that my identity will be kept confidential if my data are publicly presented
14. I have had my questions answered to my satisfaction.
15. I have decided to be in the research study.

I am aware that if I have any question during this study, I should contact the investigator. By signing this consent form I attest that the information given in this document has been clearly explained to me and understood by me, I will be given a copy of this consent document

Name and signature / thumb impression of the participant (or legal representative if participant incompetent)
Name _____ Signature_____ Date_____
Name and Signature of impartial witness (required for illiterate patients):
Name _____ Signature_____ Date_____
Address and contact number of the impartial witness:

Name and Signature of the investigator or his representative obtaining consent Name _____ Signature_____ Date_____

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr. Narmadha.R.
Postgraduate in M.D.(Radiotherapy)
Madras Medical College
Chennai 600 003

Dear Dr. Narmadha.R.,

The Institutional Ethics Committee has considered your request and approved your study titled **"COMPARING 8Gy VERSUS 30Gy SCHEDULES OF PALLIATIVE RADIOTHERAPY IN THE TREATMENT OF PAINFUL SPINE METASTASIS" No.26102015.**

The following members of Ethics Committee were present in the meeting held on **06.10.2015** conducted at Madras Medical College, Chennai-3.

1. Prof.C.Rajendran, M.D.,	:Chairperson
2. Prof.R.Vimala, M.D., Dean, MMC, Ch-3	:Deputy Chairperson
3. Prof.Sudha Seshayyan, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.B.Vasanthi, M.D., Professor Pharmacology, MMC	: Member
5. Prof.A. Rajendran, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Saraswathy, M.D., Director, Inst. of Pathology, MMC	: Member
7. Prof.Srinivasagalu, Director, Inst.of Inter Med. MMC	: Member
8. Tmt. J. Rajalakshmi, JAO, MMC	: Lay Person
9. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
10. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

Member Secretary, Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

ஆராய்ச்சி தகவல் தாள்

ஆராய்ச்சியின் பெயர்

முதுகெலும்புக்கு பரவியுள்ள புற்றுநோய்க்கு கொடுக்கப்படும் இருவேறு கதிர்வீச்சு சிகிச்சை முறைகளை பற்றிய ஆராய்ச்சி.

ஆராய்சிச பெயர்

பங்கேற்பாளர் பெயர்

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் புற்று நோயாளிகளிடம் கதிர்வீச்சு சிகிச்சைப் பற்றிய ஆராய்ச்சி.

முதுகெலும்புக்கு பரவியுள்ள புற்றுநோய்க்கு கொடுக்கப்படும் இருவேறு கதிர்வீச்சு சிகிச்சை முறைகளை பற்றிய ஆராய்ச்சி.

இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். இதனால் தங்கள் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சியின் போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

இந்த சிறப்பு பரிசோதனைகளின் முடிவுகளையும் நோயின் தன்மை பற்றியும் ஆராய்ச்சியின் முடிவின் போது தங்களுக்கு அறிவிப்போம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர்

கையொப்பம்

தேதி

ஆராய்ச்சி ஒப்புதல் கடிதம்

பெயர் : தேதி :

வயது : உள் புற நோயாளி எண் :

பால் : ஆராய்ச்சி சேர்க்கை எண் :

சென்னை இராஜீவ்காந்தி அரசு பொது மருத்துவமனைக்கு வரும் புற்றுநோய் நோயாளிகளிடம் கதிர்வீச்சு சிகிச்சை பற்றிய ஆராய்ச்சி.

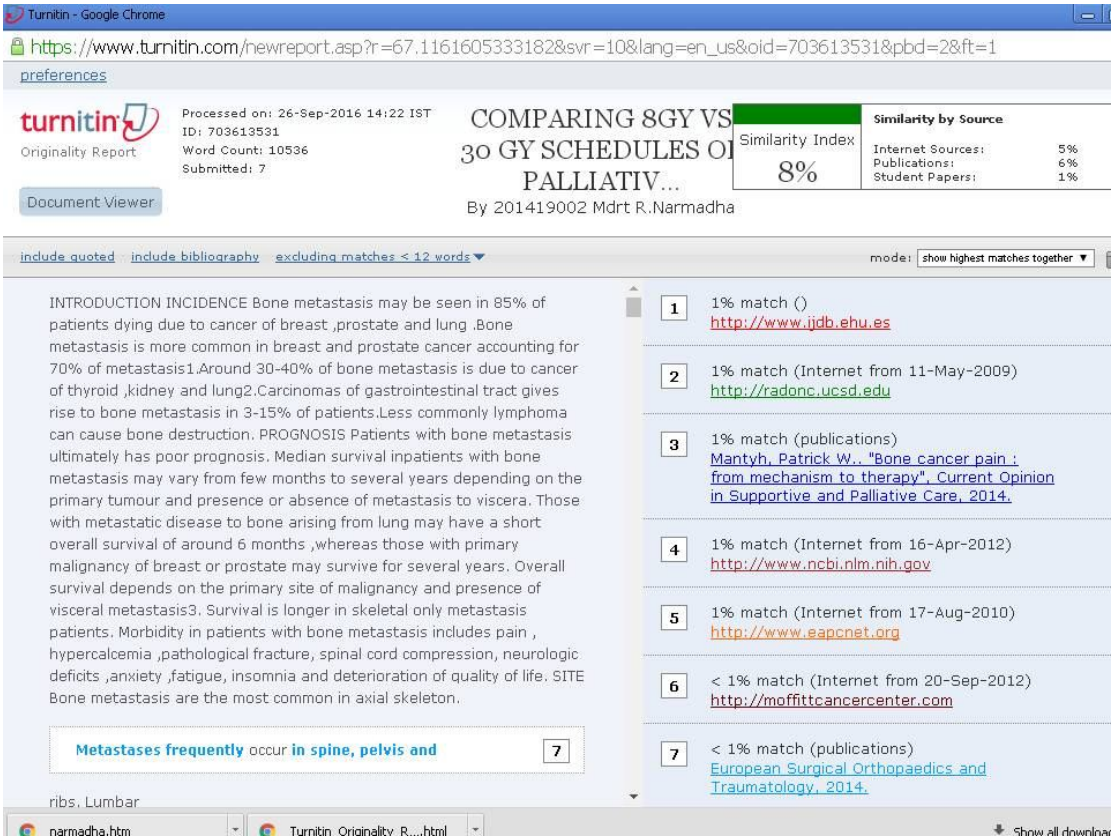
முதுகெலும்புக்கு பரவியுள்ள புற்றுநோய்க்கு கொடுக்கப்படும் இருவேறு கதிர்வீச்சு சிகிச்சை முறைகளை பற்றிய ஆராய்ச்சி.

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க விரும்புகிறீர்களா. இந்த ஆராய்ச்சியில் தீவிர கதிர்வீச்சு சிகிச்சை அளித்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களின் நோயின் ஆய்வறிக்கையோ சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதை தெரிவித்துக் கொள்கிறோம்.

முடிவுகளை அல்லது மருந்துகளை வெளியிடும் போதோ அல்லது ஆராய்ச்சயின் போதோ தங்களின் பெயரையோ அல்லது அடையாளங்களையோ வெளியிடமாட்டோம் என்பதையும் தெரிவித்துக் கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் பங்கேற்பாளர் கையொப்பம்

தேதி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INTRODUCTION INCIDENCE Bone metastasis may be seen in 85% of patients dying due to cancer of breast ,prostate and lung .Bone metastasis is more common in breast and prostate cancer accounting for 70% of metastasis1.Around 30-40% of bone metastasis is due to cancer of thyroid ,kidney and lung2.Carcinomas of gastrointestinal tract gives rise to bone metastasis in 3-15% of patients.Less commonly lymphoma can cause bone destruction. PROGNOSIS Patients with bone metastasis ultimately has poor prognosis. Median survival inpatients with bone metastasis may vary from few months to several years depending on the primary tumour and presence or absence of metastasis to viscera. Those with metastatic disease to bone arising from lung may have a short overall survival of around 6 months ,whereas those with primary malignancy of breast or prostate may survive for several years. Overall survival depends on the primary site of malignancy and presence of visceral metastasis3. Survival is longer in skeletal only metastasis patients. Morbidity in patients with bone metastasis includes pain , hypercalcemia ,pathological fracture, spinal cord compression, neurologic deficits ,anxiety ,fatigue, insomnia and deterioration of quality of life. SITE Bone metastasis are the most common in axial skeleton.
Metastases frequently occur in spine, pelvis and 7
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