ROLE OF RADIOTHERAPY IN RECURRENT AND METASTATIC BREAST CANCER

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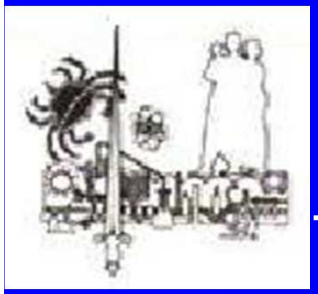
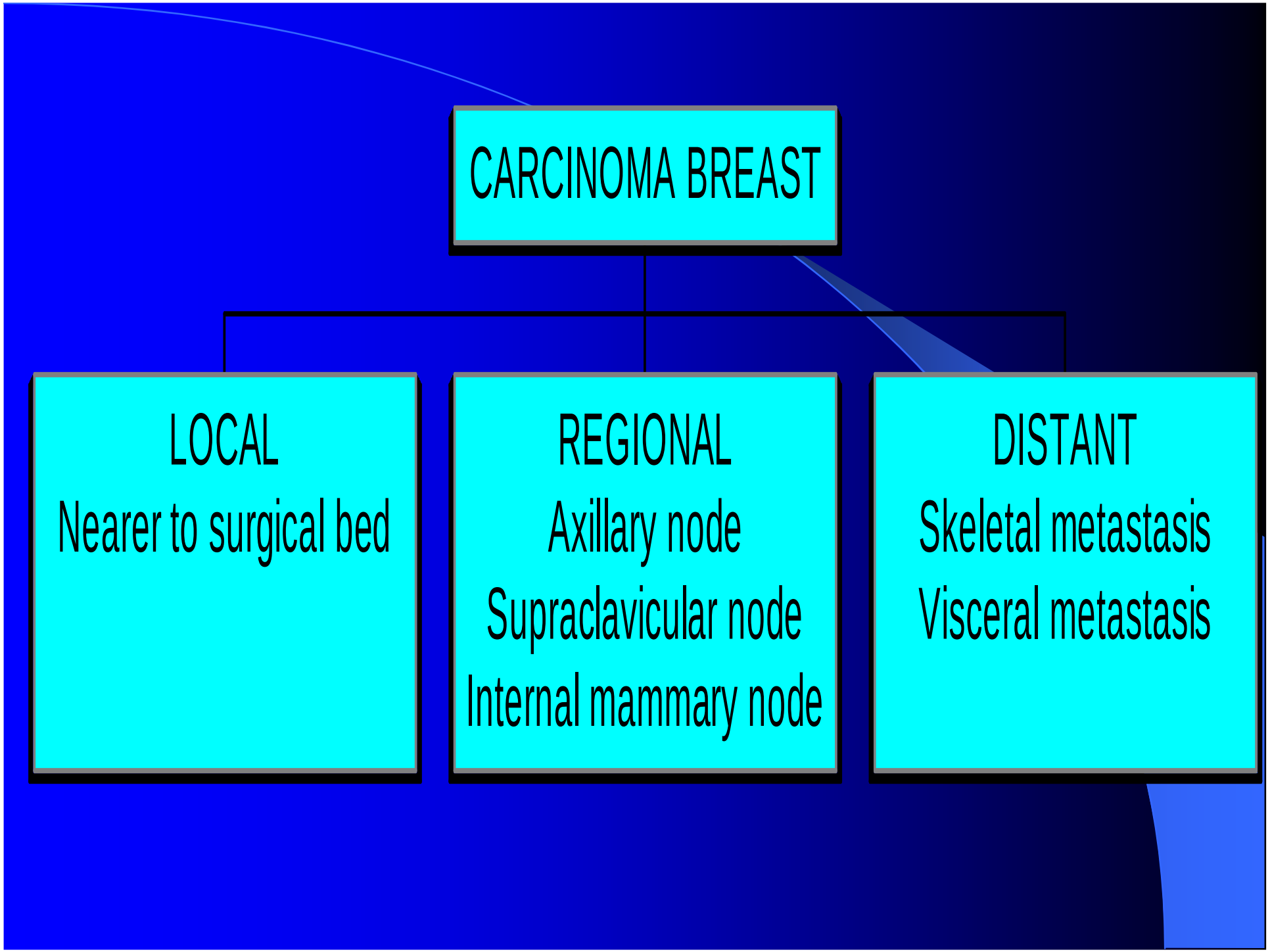


The Gujarat Cancer & Research Institute, Ahmedabad.

- Breast cancer must be considered as systemic disease
- 10% of breast cancer diagnoses as stage-IV
- Locally advanced breast cancers are at risk for both distant and locoregional failure


CARCINOMA BREAST
LOCAL
Nearer to surgical bed
REGIONAL
Axillary node
Supraclavicular node
Internal mammary node
DISTANT
Skeletal metastasis
Visceral metastasis

TUMOR SPREAD

Breast tumor grows

Travel along the duct

↓

Eventually breaking through basement membrane of the duct

↓

Invading adjacent lobules, ducts, facial strands and the mammary fat

↓

Spreading through the breast lymphatics and peripheral lymphatics

↓

Tumor grow through the wall of the blood vessels

- Halsted model – orderly progression to regional lymph nodes and from there to distant metastatic site.
- Keynes and Crile et.Al. –Systemic disease.
- Fisher –systemic process involving host-tumor interaction based on laboratory and clinical study.
- Hellman – Breast cancer is a heterogeneous disease that metastases are a function of tumor growth and progression factors even when detected as every small lesion.

Time-course Of Distant Metastasis

- The majority of the metastasis occur within 5 years after the diagnosis of the primary disease but it can be extent as long as 20-30 years after the initial diagnosis.
- The time to appearance of a metastatic disease is depend upon

-Initial primary tumor size
-Axillary status
-Hormonal receptor status

FACTORS RELATED WITH RECURRENCE

- Young age at diagnosis
- African American women
- Tumor > 2 c.m.
- Multicentric disease
- Extracapsular invasion
- Medial quadrant of breast
- Sentinal lymph-node metastasis >2m.m.
- Lymphatic-vascular invasion
- -ve hormonal receptor
- High fraction of cells in S-phase
- Thymidine labelling index
- High mitotic index
- Proliferating cell nuclear antigen
- Her-2/neu proto-oncogene
- Ki-67
- High EGFR
- P-53 tumor suppression gene mutation
- Serum markers such as CA 15-3 and CA 27-29

PROGNOSTIC FACTOR CATEGORISED BY THE COLLEGE OF AMERICAN PATHOLOGIST

CATOGARY-I	CATOGARY-II	CATEGORY-III
TUMOR SIZE	Her-2/neu EXPRESSION	TUMOR ANGIOGENESIS
LYMPHNODE STATUS	p-53 MUTATION	EGFR
MICROMETASTASIS	LYMPHATIC INVASION	TRANSFORMING GROWTH FACTOR
HISTOLOGIC GRADE	VASCULAR INVASION	Bcl-2
MITOTIC COUNT	DNA PLOIDY	CATHEPSIN-D OVEREXPRESSION
HORMONAL RECEPTOR		

COMMON SITES OF METASTASIS

- **REGIONAL FAILURE**

-AXILLARY NODES

-INTENAL MAMMARY NODES

-SUPRACLAVICULAR NODES

- **DISTANT METASTASIS**

-SKELETAL

-VISCERAL(lung, liver, brain, adrenal gland,orbit, skin, ovary, stomach, any region of the body)

Haagensen's autopsy series on the detectable metastasis at the various sites

- Lung -70%
- Liver - 65%
- Bone - 70%
- Adrenal gland - 50%
- Brain - 20%

Other sites 10-20% such as

- Ovaries
- Heart
- Peritoneum
- Skin
- Lymph nodes

DIAGNOSTIC TESTS FOR DETECTING METASTASIS

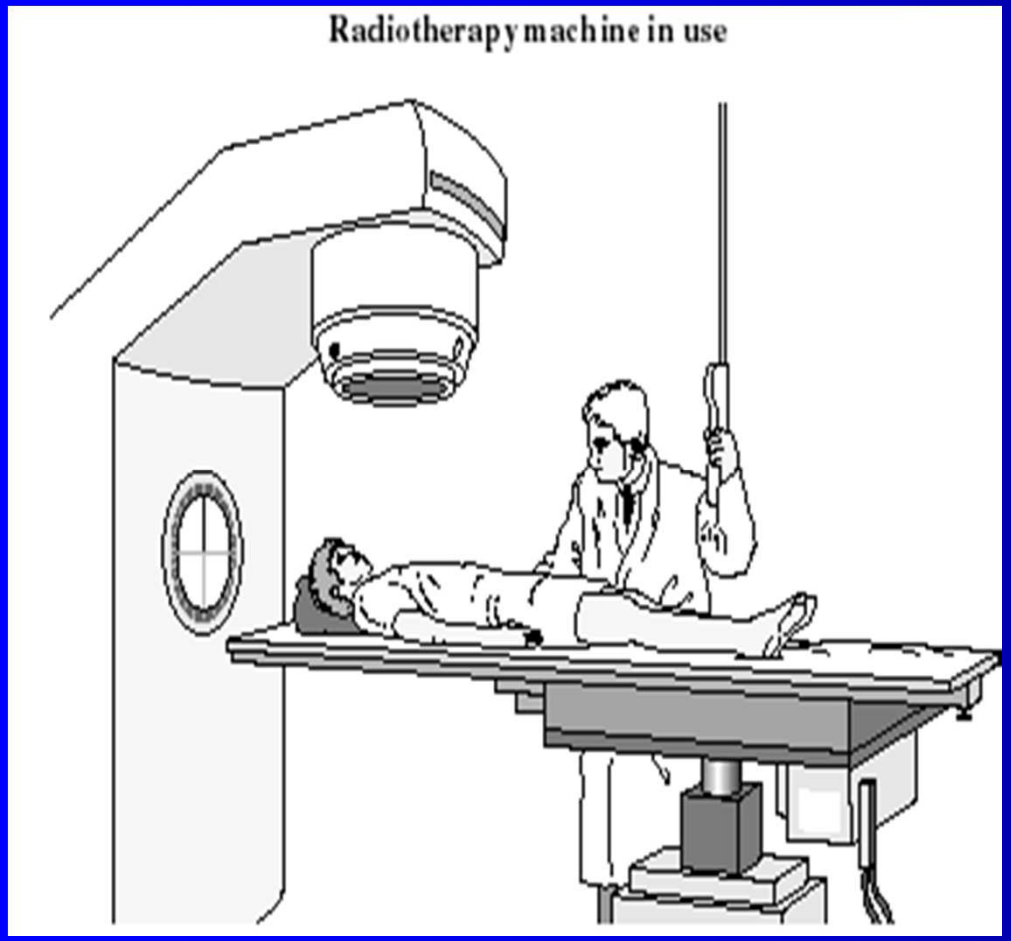
- X-ray Chest
- Ultrasonography of Abdomen and Pelvis
- Computerised Tomography of Chest, Abdomen, Pelvis, Brain
- PET-CT scan
- Haemogram
- Renal Function Tests
- Liver Function Test(assessing physiologic function

TREATMENT GOAL FOR METASTATIC BREAST CANCER

- To palliate symptoms
- Arrest tumor growth to prevent symptoms due to increasing pressure
- To improve quality of life
- To prolong survival

Prompt supportive measures should be offered according to an individual needs.

TREATMENT MODALITIES



Types of treatment modality depend upon

- Site and extent of metastatic disease
- Hormone receptor status
- Disease –free interval
- Age of patient
- Menopausal status

- **LOCAL CONTROL BY**

RADIOTHERAPY

SURGERY

- **SYSTEMIC CONTROL BY**

HORMONAL THERAPY

- Hormone receptor +ve patient with no life threatening condition

CHEMOTHERAPY

- Hormone receptor –ve
- Symptomatic visceral disease
- Life-threatening condition

TARGETED THERAPY

Complete remission can be achieved in 5-15%

LOCAL RECURRENCE

LOCATION

- Close to the site of the original tumor
- Tumor cells aggregates close to the surgical bed

FACTORS RELATED WITH LOCAL RECURRENCE

- **Age < 40 years**
- **Tumor > 3 c.m. size**
- **Multicentric disease**
- **Positive surgical margin**
- **Extensive intraductal component**
- **LCIS component**
- **Peritumoral lymphatic infiltration**
- **Grade-3 disease**
- **>3 positive axillary lymph node**
- **ER/PR –ve**
- **BRCA 1-2**
- **P-53 overexpression**

LOCAL RECURRENCE AFTER CONSERVATIVE BREAST SURGERY

- Salvage mastectomy with or without post-operative radiotherapy
- Second breast conserving surgery with interstitial brachytherapy

CHEST WALL RECURRENCE FOLLOWING MRM

RADIOTHERAPY

is treatment of choice

- To control bleeding
- To control discharge
- Reduces ulceration
- To decrease bulk of tumor

CHEMOTHERAPY

- Loco-regional relapse with distant metastasis
- Previously irradiated patient
- Palliation with radiotherapy unsatisfactory

RADIOTHERAPY TECHNIQUE

- Parallel opposed pair of tangential field

- Direct electron beam field with 6-8 Mev

With 2 c.m. margin all around

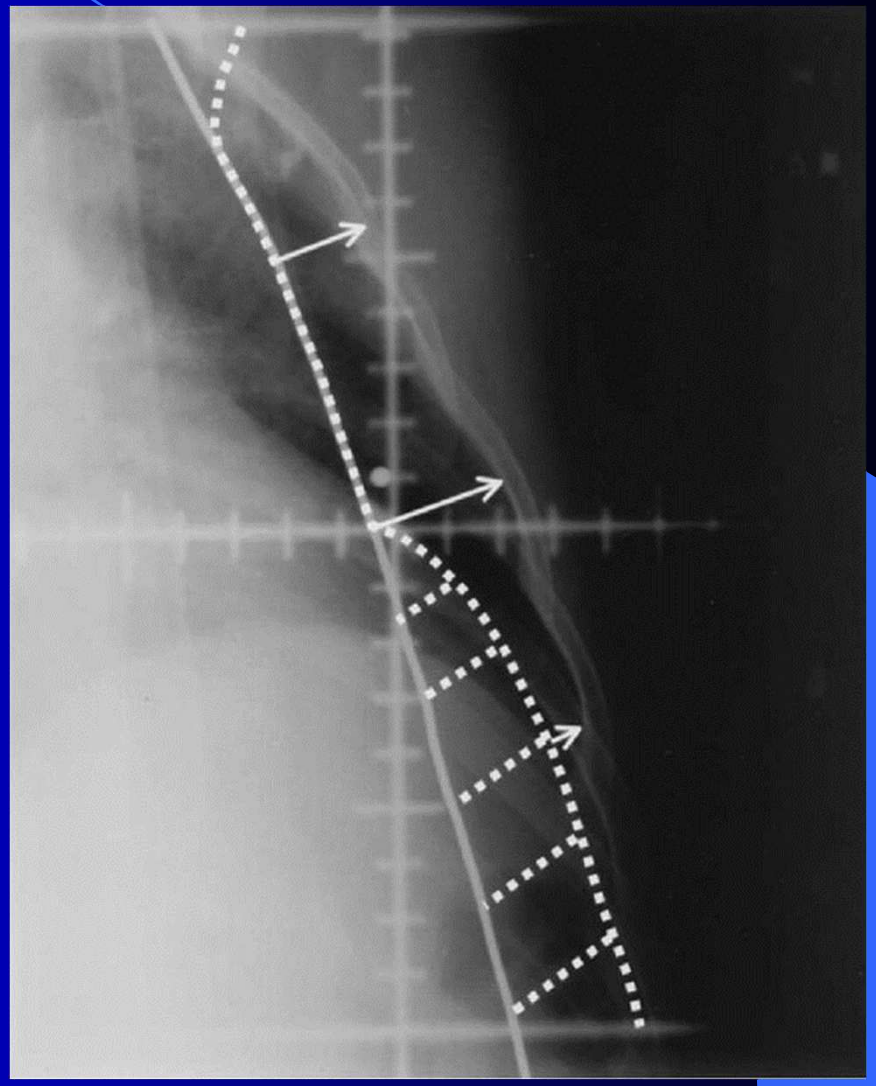
DOSE-FRACTIONATION SCHEDUALS

- 30 Gy in 10 Fr

- 20 Gy in 5 Fr

TANGENTIAL FIELD

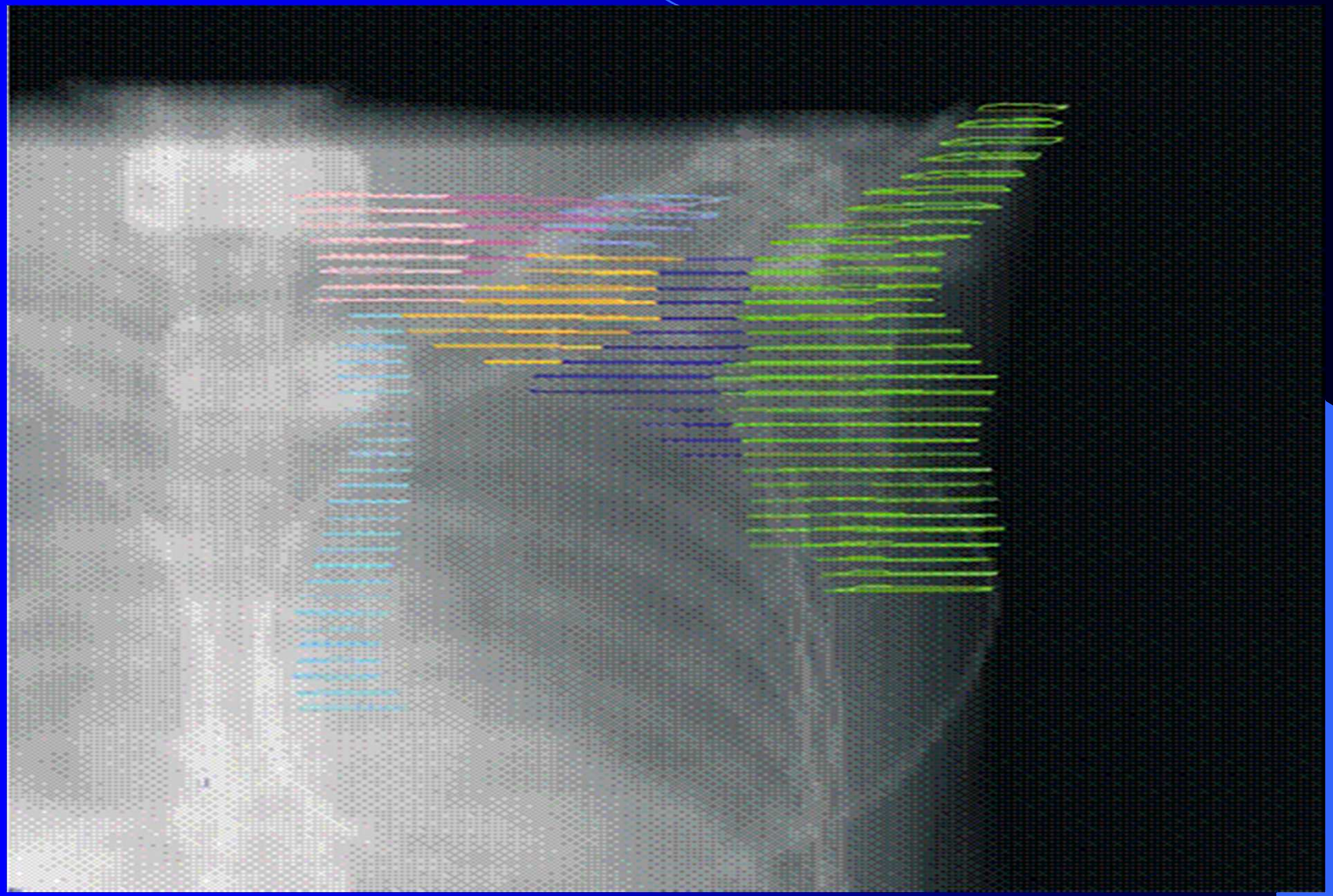
SIMULATOR FILM OF TANGENTIAL FIELD



ELECTRON APPLIANCES

REGIONAL FAILURE

DRAINING LYMPHATIC AREAS



FACTORS RELATED WITH AXILLARY NODE

- Age < 60 year
- Tumor > 1 c.m.
- Outer quadrant location
- Infiltrating ductal histologic type
- M.D./P.D. nuclear grade
- Presence of lymphatic-vascular invasion
- Aneuploidy
- High fraction of cells in S-phase

FACTORS RELATED WITH SUPRACLAVICULAR NODE

- Age < 40 year
- Tumor size > 3 c.m.
- High histologic grade
- Angiolymphatic invasion
- > 4 positive L-I & II axillary lymph node
- Gross extranodal extension of axillary node
- Negative estrogen receptor
- DNA synthetic fraction > 4%

Supraclavicular node failure < 1%in prophylactically treated nodes

FACTORS RELATED WITH INTERNAL MAMMARY NODE

- Age < 40 year
- Tumor > 2 c.m.
- Inner quadrant tumor
- Positive axillary node

Clinical parasternal recurrences appear more slowly than axillary and supraclavicular recurrences ; the delay probably due to the size of tumor necessary before it can be palpated between the costal cartilages as parasternal mass

RADIATION TECHNIQUE

- Single field on cobalt with bolus

Or

- Single field with electron depend upon depth of tumor

With 2 c.m. margin all around

RADIATION DOSE

- **30 GY / 10 #**
- **20 GY / 5 #**
- **Additional dose should be delivered through reduced field to the site of residual palpable disease**

SYSTEMIC FAILURE

- The systemic spread of the disease is common in breast carcinoma with high metastatic potential
- It is considered as an ominous sign but expected lifetime is still good and every effort should be made
- Treatment of metastatic breast cancer generally focuses on relieving symptoms and extending woman’s lifetime

FACTORS RELATED WITH SYSTEMIC FAILURE

- Larger local tumor size
- Higher histologic grade
- >3axillary lymph node metastasis
- Negative hormone receptor tumor

Micrometastasis was detected in 30.6% of patient.

It was an independent predictor of poor outcome.

SKELETAL METASTASIS

- Bone metastasisis seen in almost 33% of breast cancer cases clinically where as in autopsy series as high as 70%.
- Bone as a preffered site of metastasis due to high blood flow in areas of red marrow.(breast drains principally by azygos venous system communicating with Batson's paravertebral plexus)
- Most patient with breast cancer have predominantly osteolytic lesion but atleast 15-20% have predominantly osteobastic lesion
- Bone metastasis due to breast cancer patient are still alive for 5 years after discovery

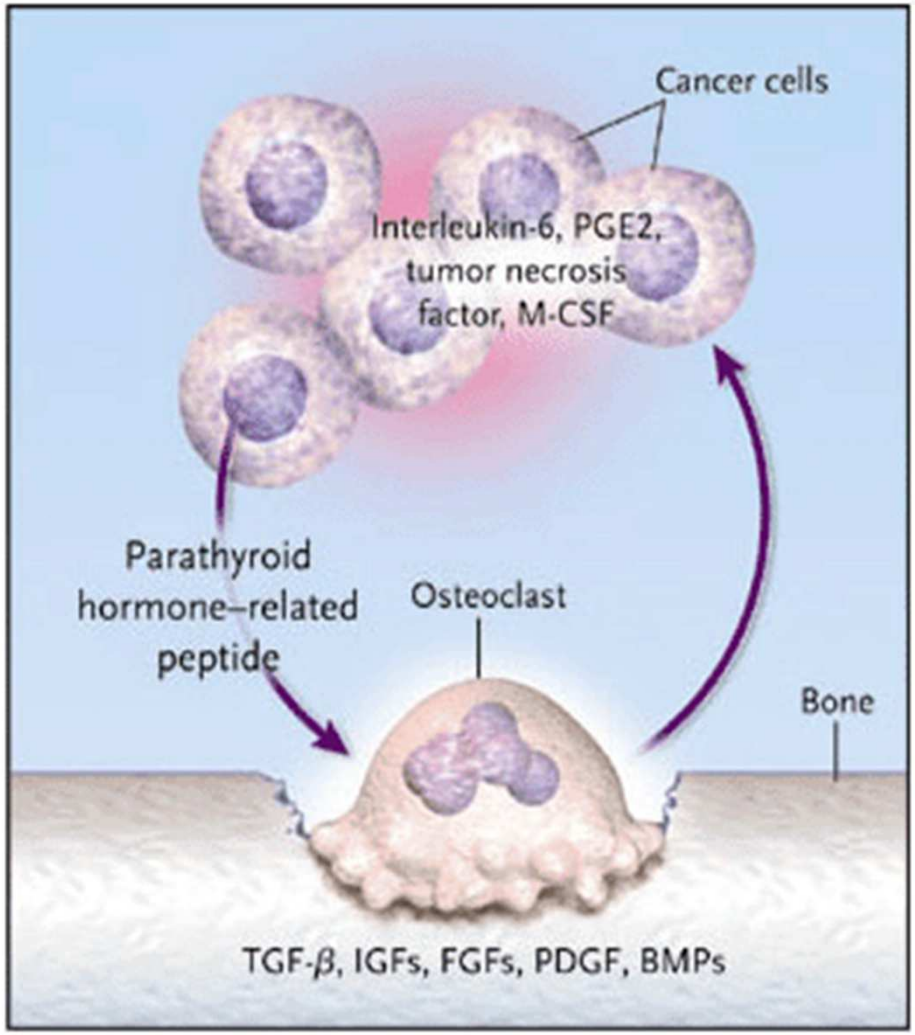
SKELETAL METASTASIS

- Tumor cells in bone
- Production of parathyroid hormone related peptide
- Activates osteoblasts and osteoclasts in bone
- Osteoclast

  -destroy bone matrix

  -releasing embeded growth factor

- Further stimulates tumor cells



- Osteolytic lesion can cause

  -severe pain

  -pathological fracture

  -life threatening hypercalcemia

  -spinal cord compression

  -other nerve compression syndrome

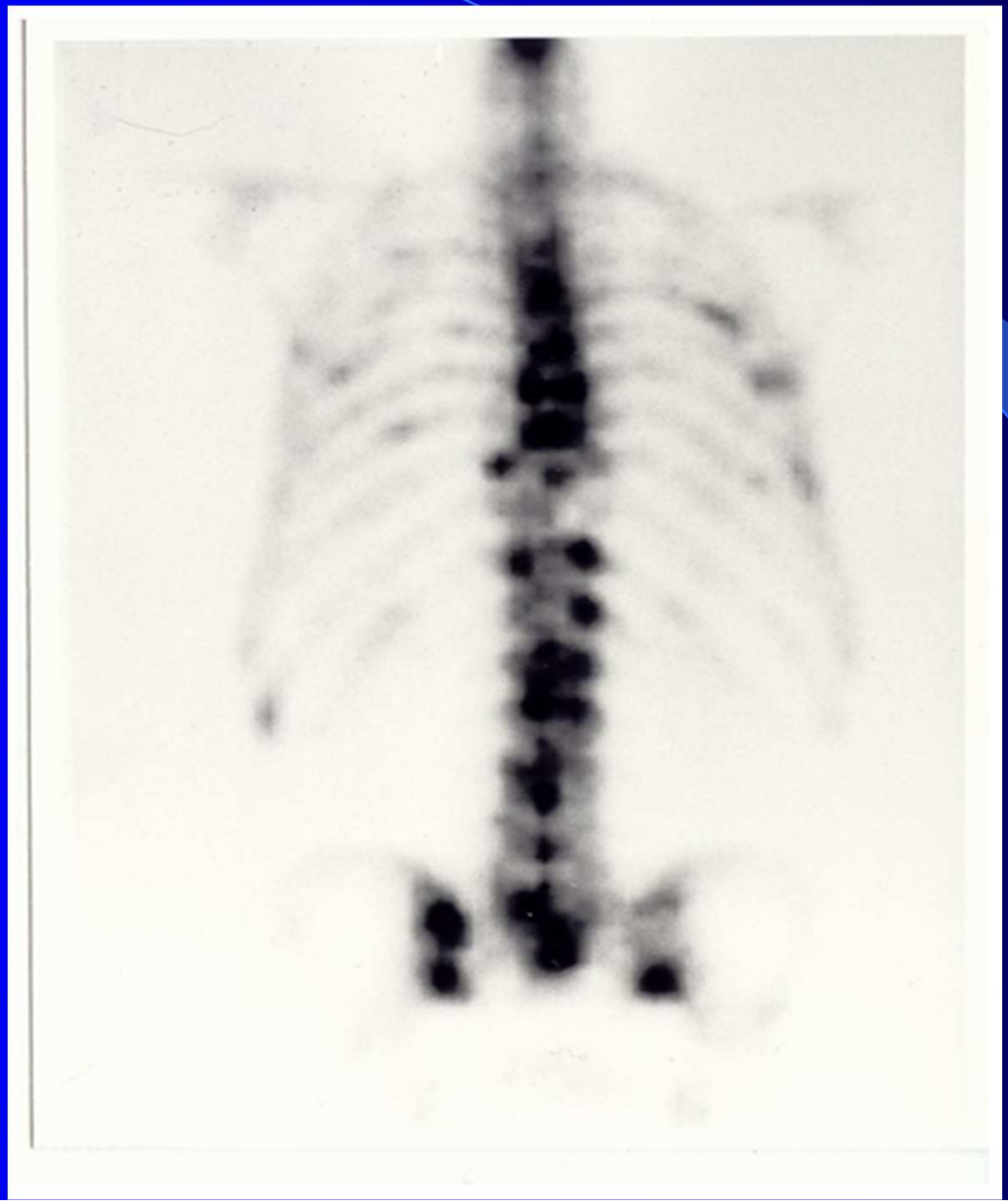
COMMON SITES

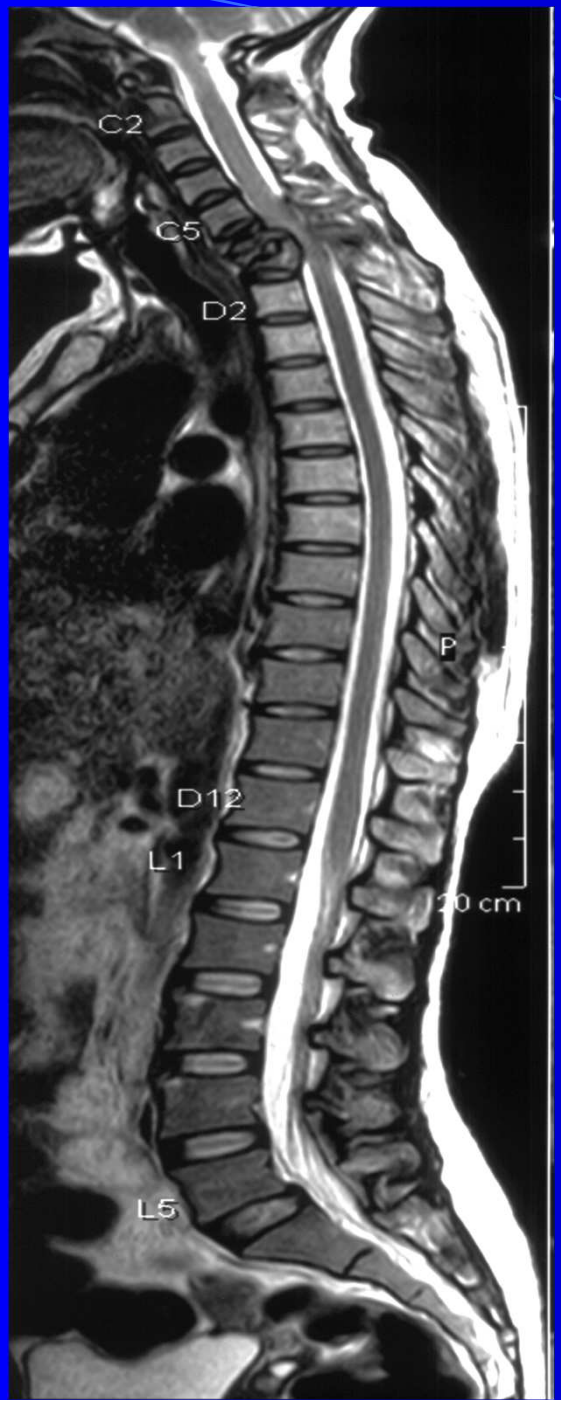
- SPINE
- PELVIS
- FEMUR
- HUMERUS

INVESTIGATION

- X-RAYS
- RADIO-OPAQUE ISOTOPE SCAN
- CT-SCAN
- MRI

MULTIPLE BONE METASTASIS




C2
C5
D2
P
D12
L1
20 cm
L5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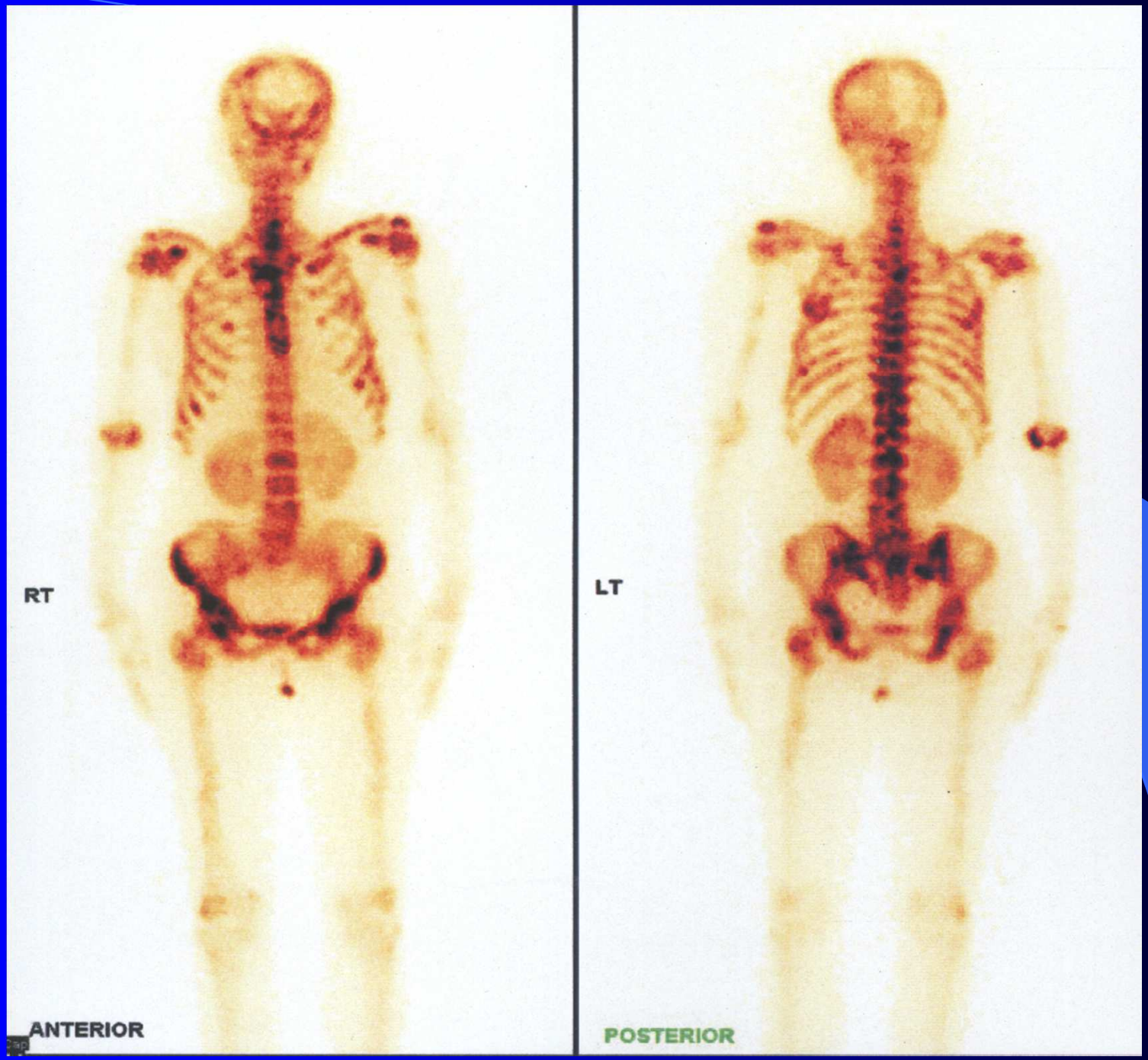

RT
ANTERIOR
LT
POSTERIOR

TREATMENT

Depend upon

- Patient's general status
- Site of metastatic lesion
- Pathological fracture

RT indicated for long term management for localised bony metastasis

- To relieve bone pain(60-80%)
- Prevention of fracture at critical site
- Recalcification process in the destroyed bone matrix
- Improves morbidity

TYPES OF TREATMENT

- Restoration of musculoskeletal stability
- Various types of internal fixation
- Immobilization casts
- Rehabilitation
- radiotherapy

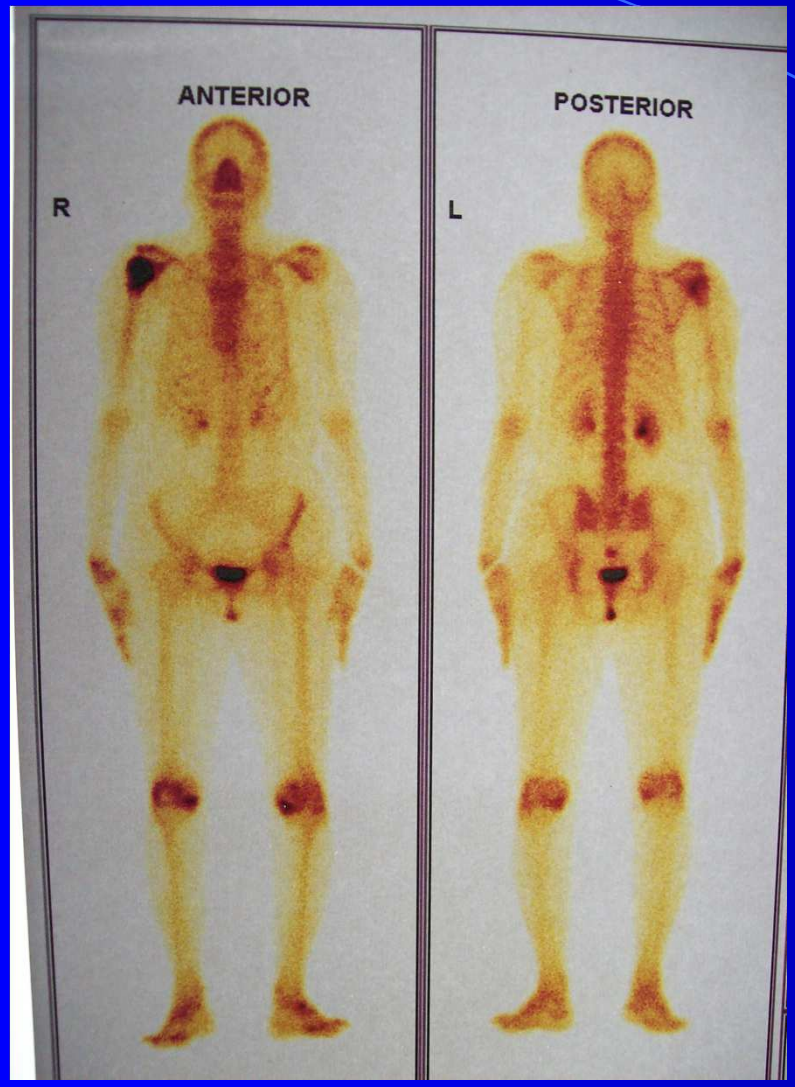
RADIOTHERAPY PORTAL

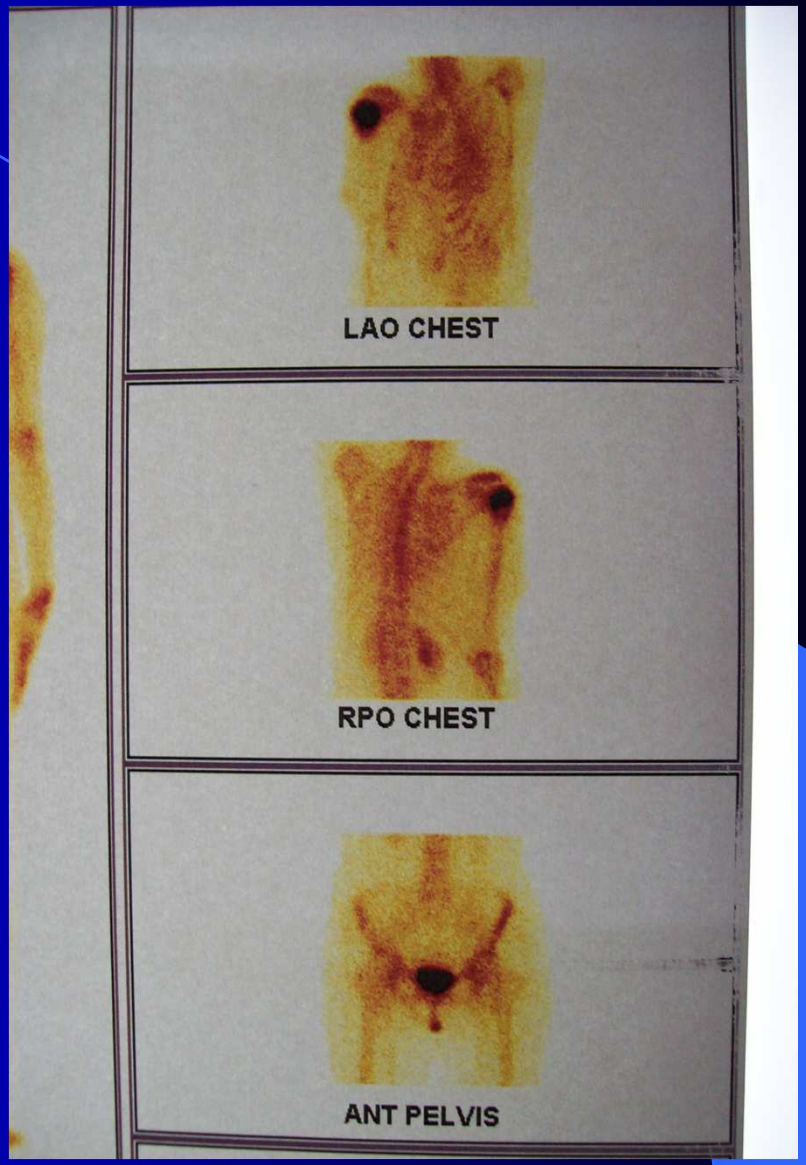
- Single or parallel opposed fields with 2 c.m. margin

RADIATION DOSE

- 30GY/10FR
- 20GY/5FR
- 8GY/single fraction
- LHBI 8GY/2FR

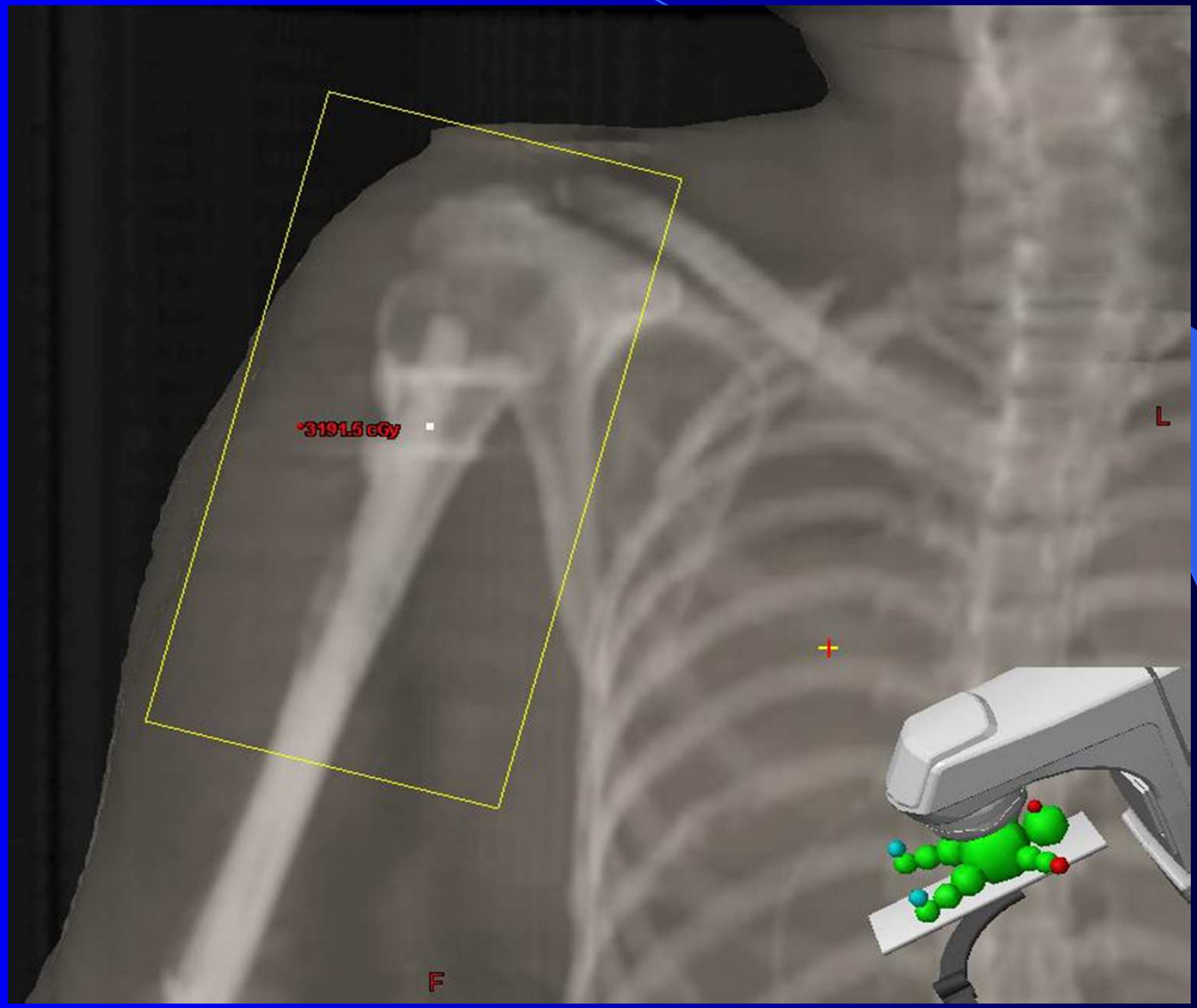
FRACTURE OF HUMERUS

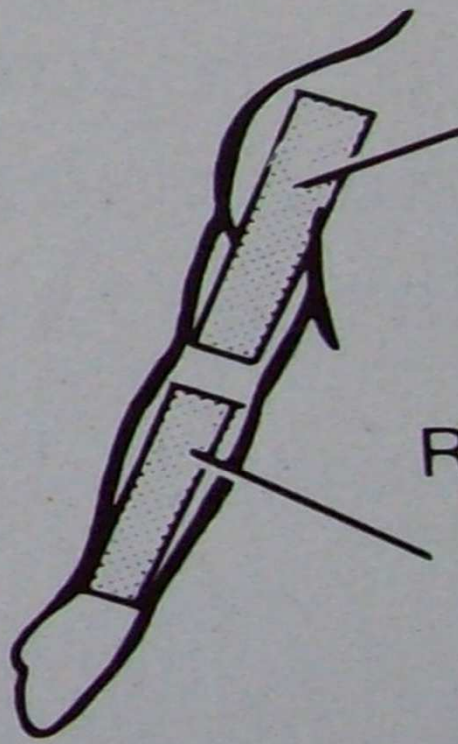

ANTERIOR
POSTERIOR
R
L


LAO CHEST
RPO CHEST
ANT PELVIS

BONE UNION

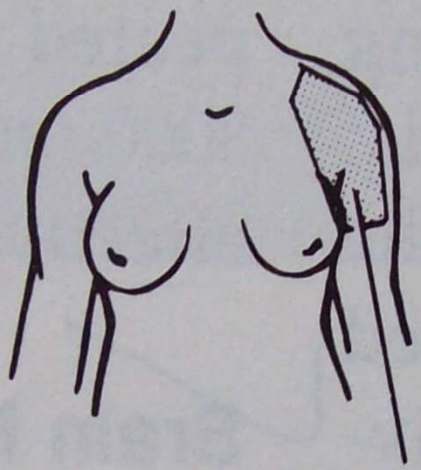
ROLE OF RT TO SHOULDER





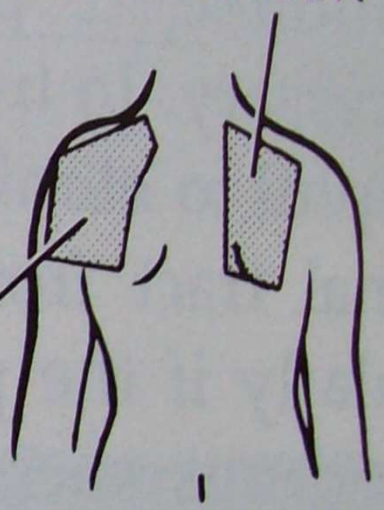
HUMERUS
2000 RADS TD
1 WEEK

RADIUS OR ULNA
2000 RADS TD
1 WEEK



SCAPULA AND
HUMERUS
2000 RADS TD
1 WEEK

SCAPULA
2000 RADS TD
1 WEEK



RIBS

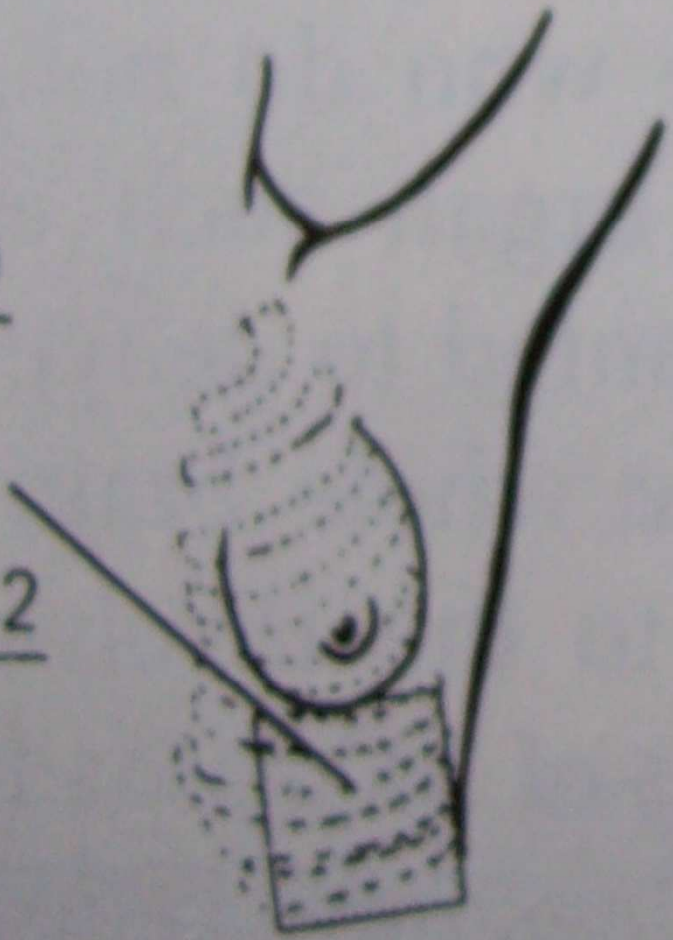
3000 RADS GD

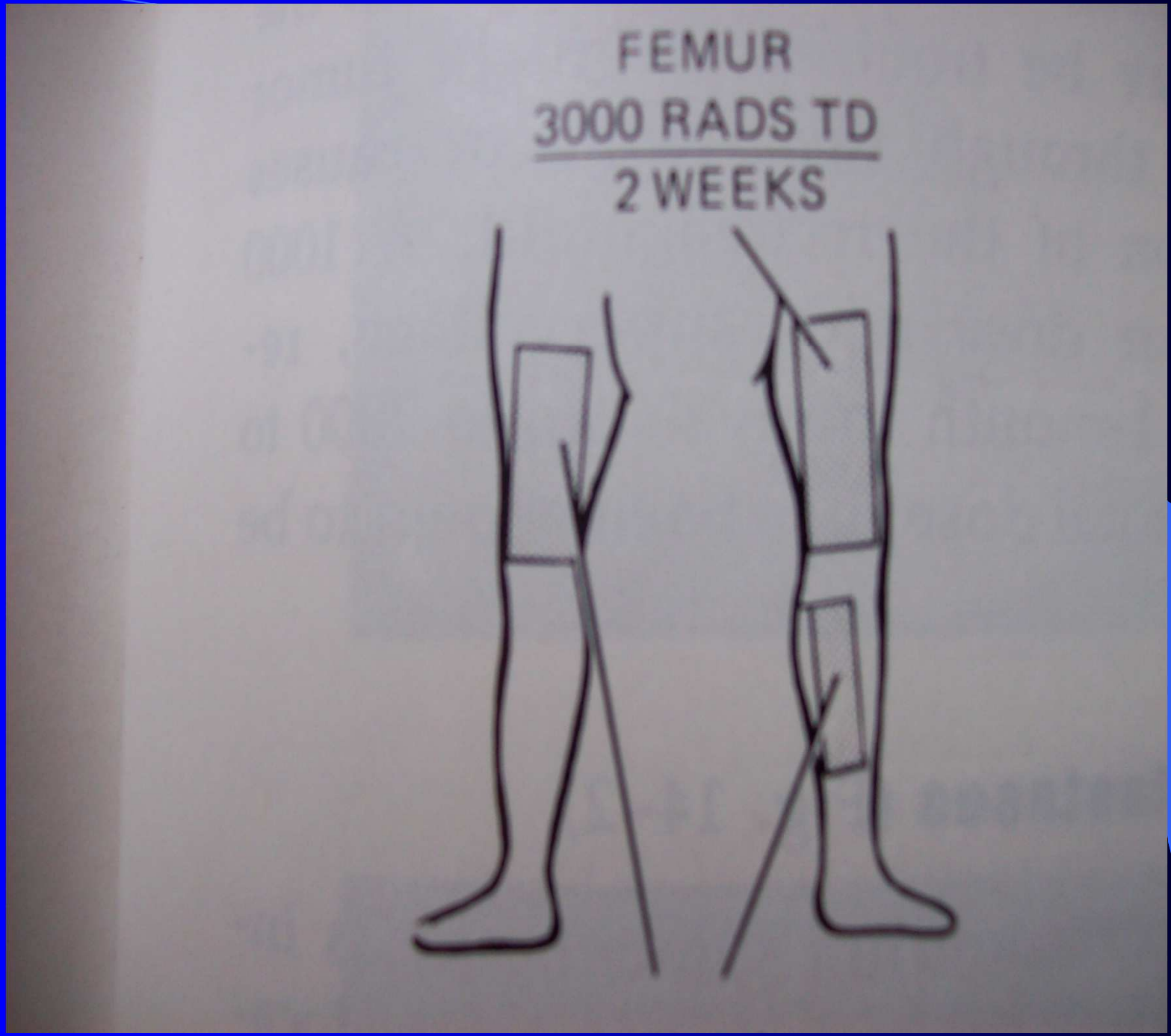
1 WEEK

or

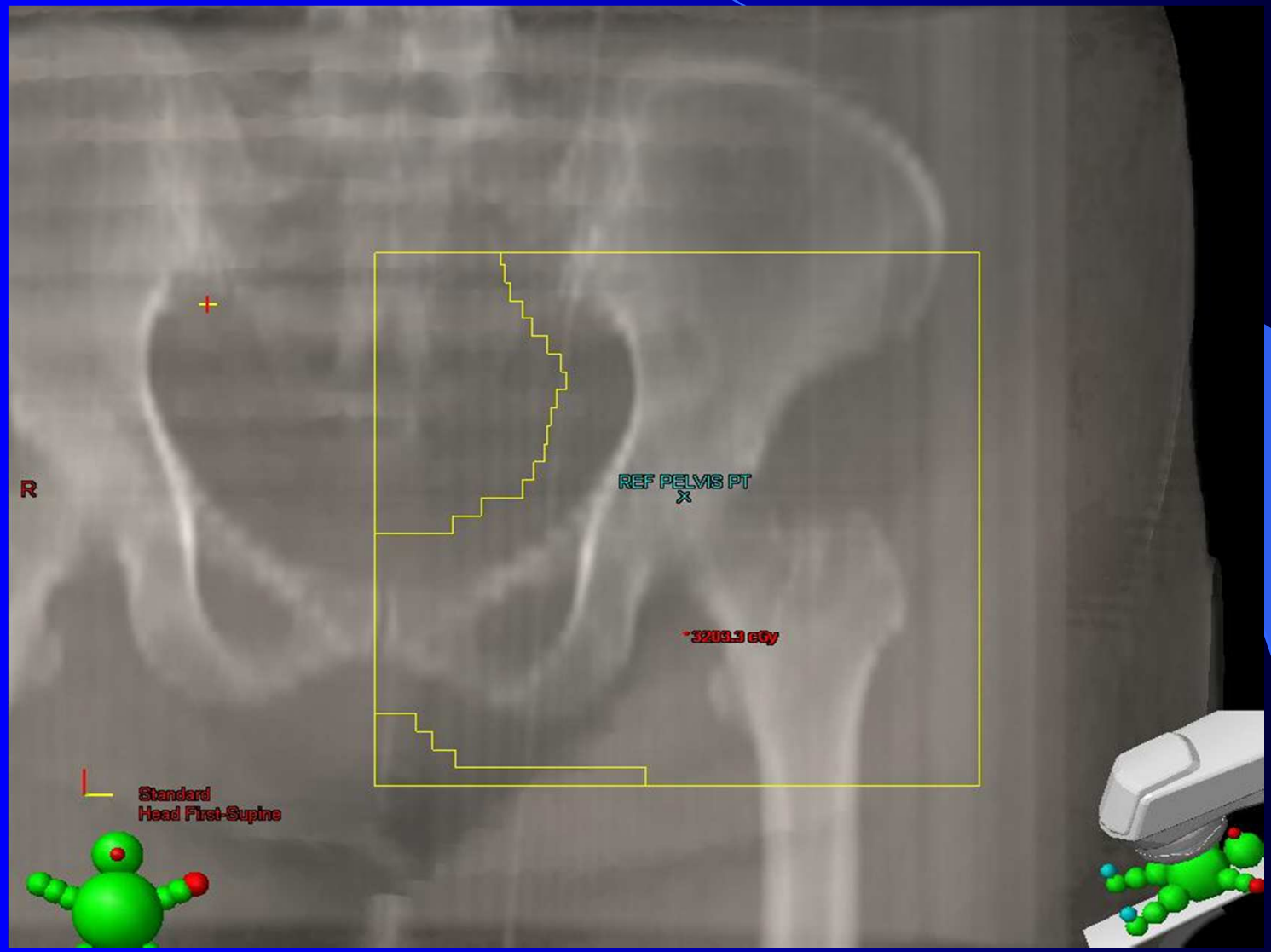
800 RADS GD x 2

2 DAYS




FEMUR
3000 RADS TD
2 WEEKS

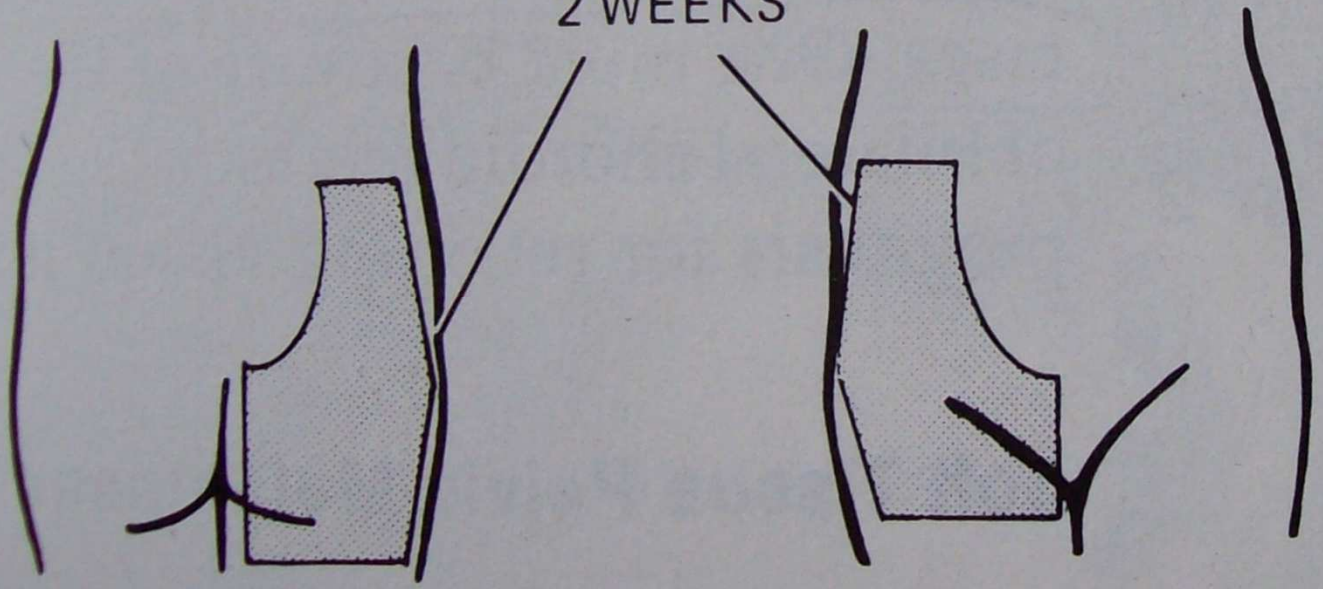
ROLE OF RT TO HEMIPELVIS



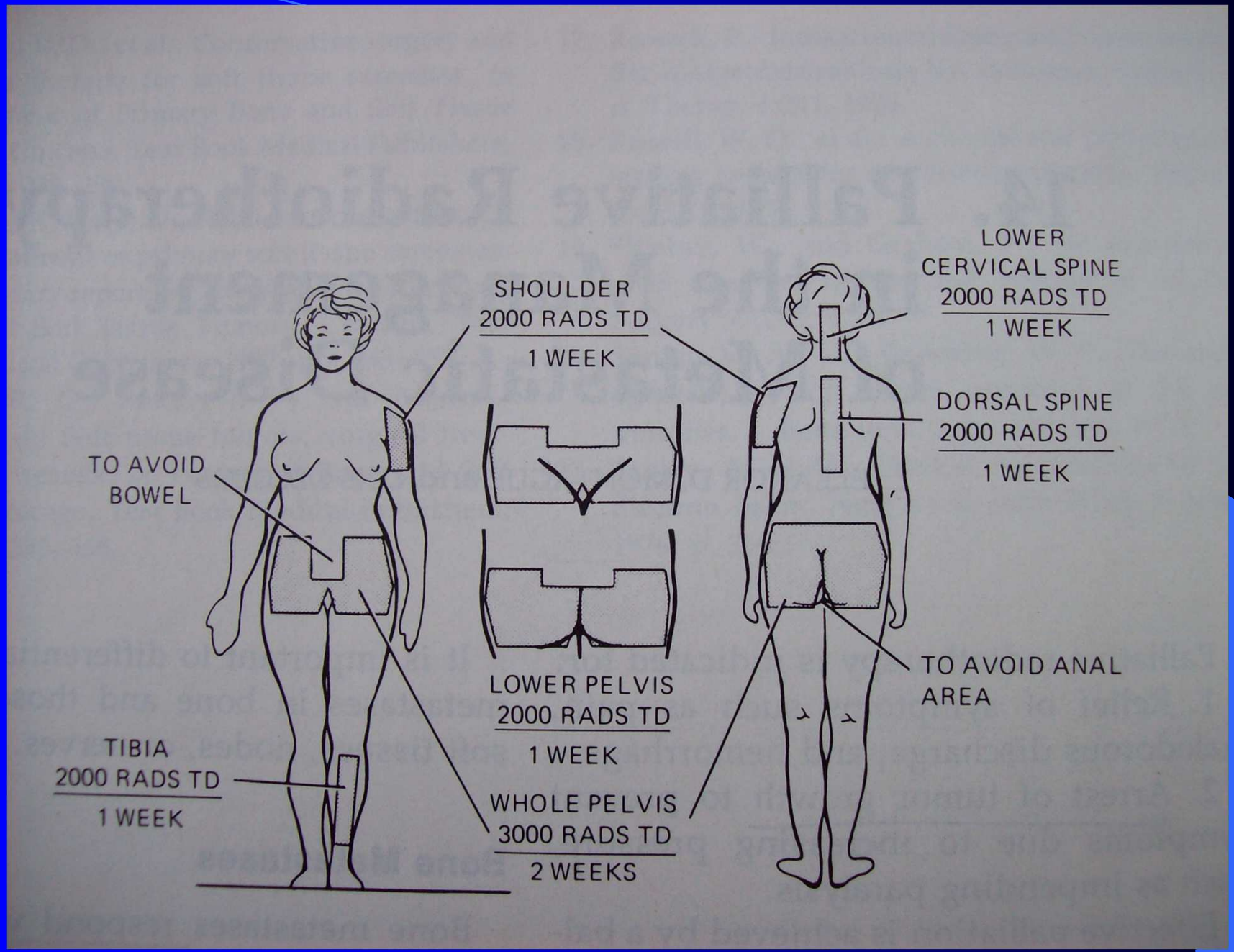
HEMIPELVIS OR HIPJOINT

3000 RADS TD

2 WEEKS



MULTIPLE BONE METASTASIS IN PELVIS


LOWER
CERVICAL SPINE
2000 RADS TD
1 WEEK
SHOULDER
2000 RADS TD
1 WEEK
DORSAL SPINE
2000 RADS TD
1 WEEK
TO AVOID
BOWEL
TO AVOID ANAL
AREA
LOWER PELVIS
2000 RADS TD
1 WEEK
TIBIA
2000 RADS TD
1 WEEK
WHOLE PELVIS
3000 RADS TD
2 WEEKS

IMPENDING PATHOLOGICAL FRACTURE

- A typical metastatic lesion of a long bone destroys a segment of medullary structures and corresponding cortical bone
- The cortical defects can not bear the normal torsional and weight bearing forces.
- Treated with prophylactic internal fixation followed by external beam radiotherapy to inhibit tumor growth and prevent fracture.

SPINAL CORD COMPRESSION

SITE

- Extradural
- Rarely intradural
- Metastasis to spinal cord and cauda equina (5-10%)
- Epidural cord compression (adenocarcinoma)
- Thoracic spine most frequent site

PRESENTATION

- Pain
- Weakness
- Sensory loss
- Sphincter disturbances
- Radicular or reffered pain
- Various neurological deficits

INVESTIGATION

- X-ray spine (vertebral collapse)
- Bone scan
- CT scan
- MRI

TREATMENT

- High dose steroid with localized external beam radiotherapy
- Neurological decompression spinal stabilization procedures should be followed by radiotherapy

RADIATION TECHNIQUE

- Direct single posterior field
- Oblique wedge field

The portal should include at least one vertebra above and below the involved site

RADIATION DOSE

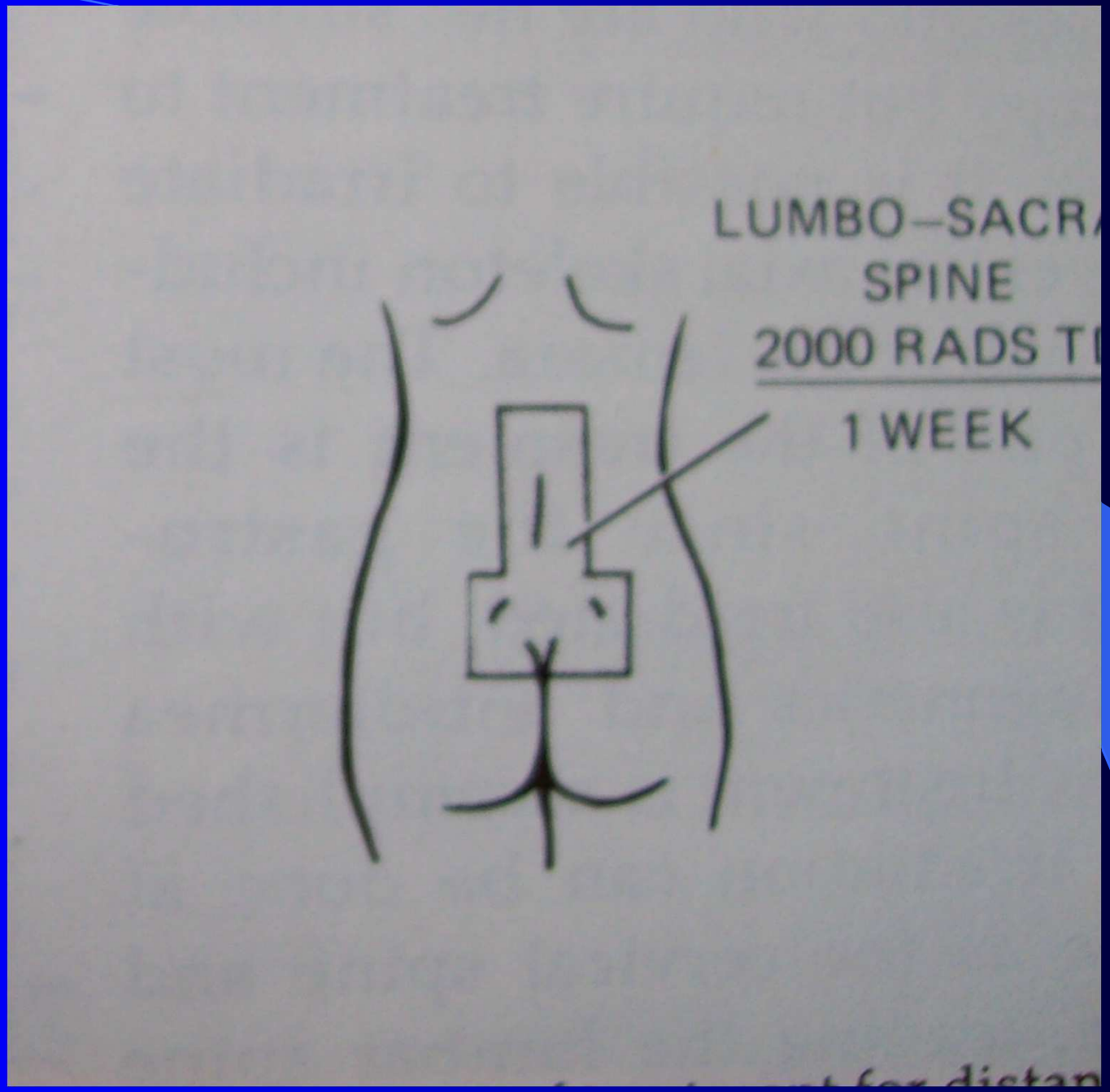
- 30GY /10FR
- 20GY /5FR
- 8GY/FR

The dose is calculated at a depth of

(cervical 3 c.m.

dorsal 4 c.m.

lumber 5 c.m.)


LUMBO–SACR
SPINE
2000 RADS T
1 WEEK

STRONTIUM-89

- Sr-89 is an analog of calcium and concentrates in osteoblastic bone carcinoma lesion.
- After intravenous injection of ionic Sr-89 it is cleared rapidly from the blood; approximately 50% of injected activity is deposited in bone and remain for as long as 100 days.
- The standard dose is 40-60 micro ci(1.48-2.22MBq)per kg body weight given intravenously.

BIPHOSPHONATES

- Biphosphonates should be used in bony metastatic disease
- To prevent progression of lytic disease.
- To delay skeletal related events.
- To decrease pain
- -Zoledronic acid (4mg by 15 min. infusion)
- -Pamidronate(90mg by 2 hr. infusion)

VISCERAL METASTASIS

CNS METASTASIS

- It is considered as late metastasis of systemic disease
- CNS(brain, cranial nerve, leptomeninges, spinal cord) sanctuary site for metastasis
- Clinically symptomatic metastasis to CNS is 10-15% but occult metastasis is common
- Patient with Her-2 positive breast tumor have been reported to develop CNS metastasis at higher rates

TREATMENT

- Whole brain radiotherapy (to kill the cells and shrink the tumors so decreases pain)
- SRS boost (to improve functional autonomy)
- Neurosurgery
- Judicious use of corticosteroids(reduces peritumoral oedema and provide symptomatic relief

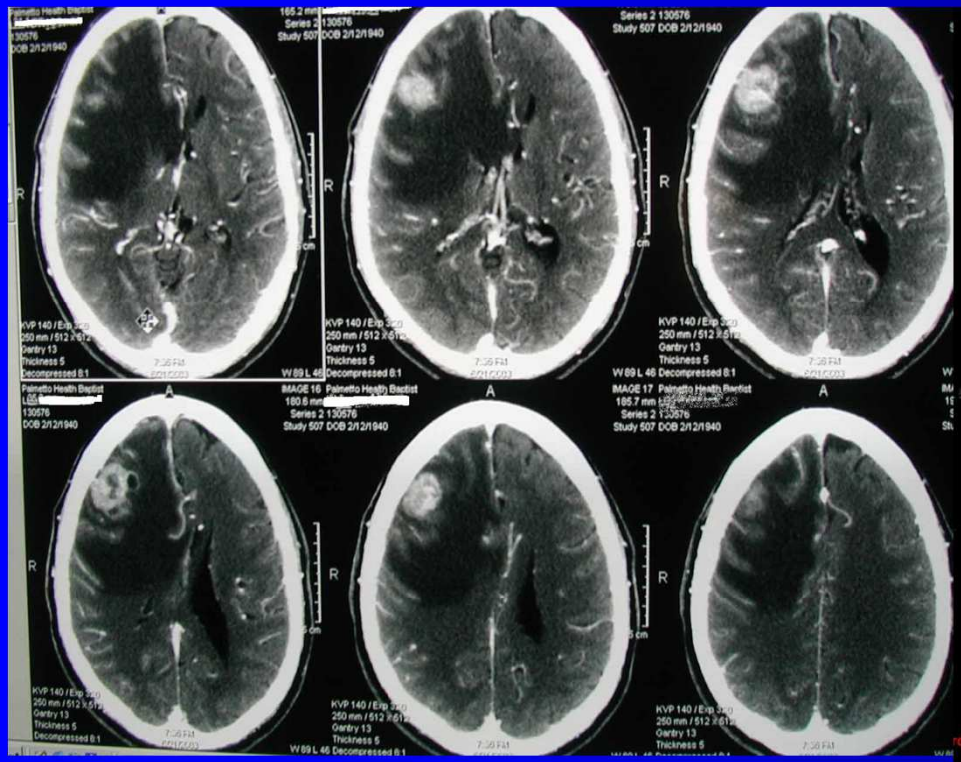
BRAIN METASTASIS

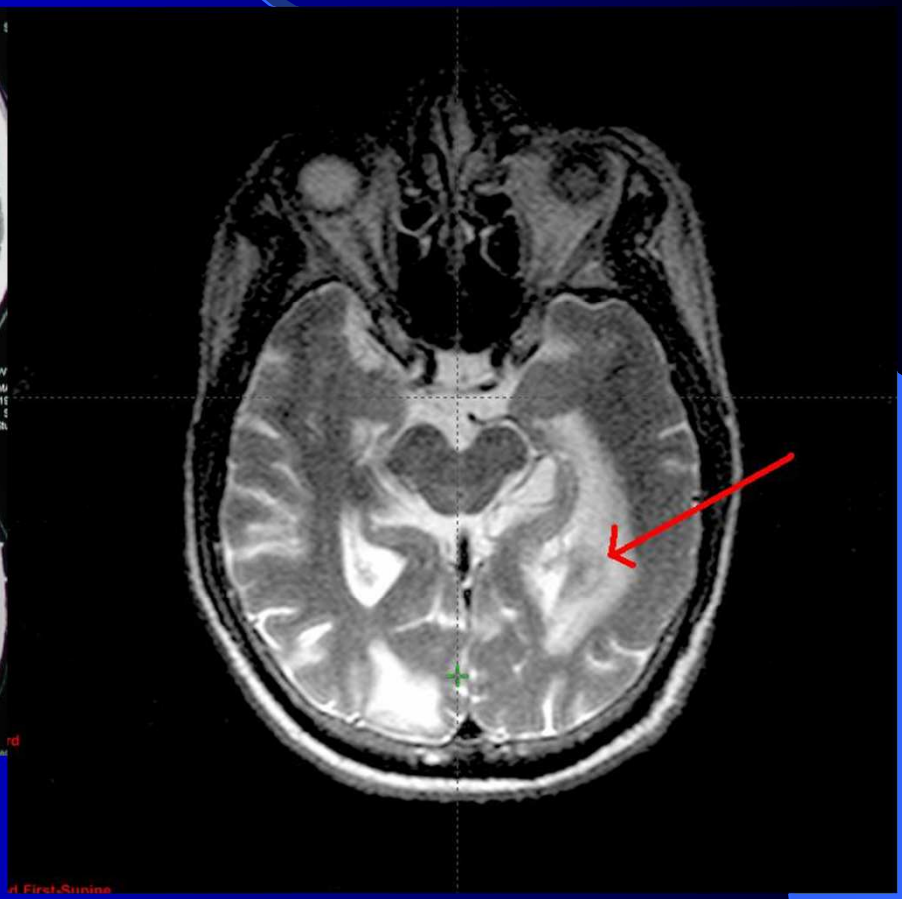
- Breast cancer is the second most common cause of metastasis to the brain after lung cancer
- Median time to development of the brain secondaries is about 1-1.5 years.

SITE

- Supratentorial cerebrum
- Cerebellum
- Leptomeningeal carcinometosis
- Extradural deposits in vertebral column

BRAIN METASTASIS





BRAIN METASTASIS

PRESENTATION

- Headache
- Impaired higher function
- Cranial nerve palsies
- Loss of motor function

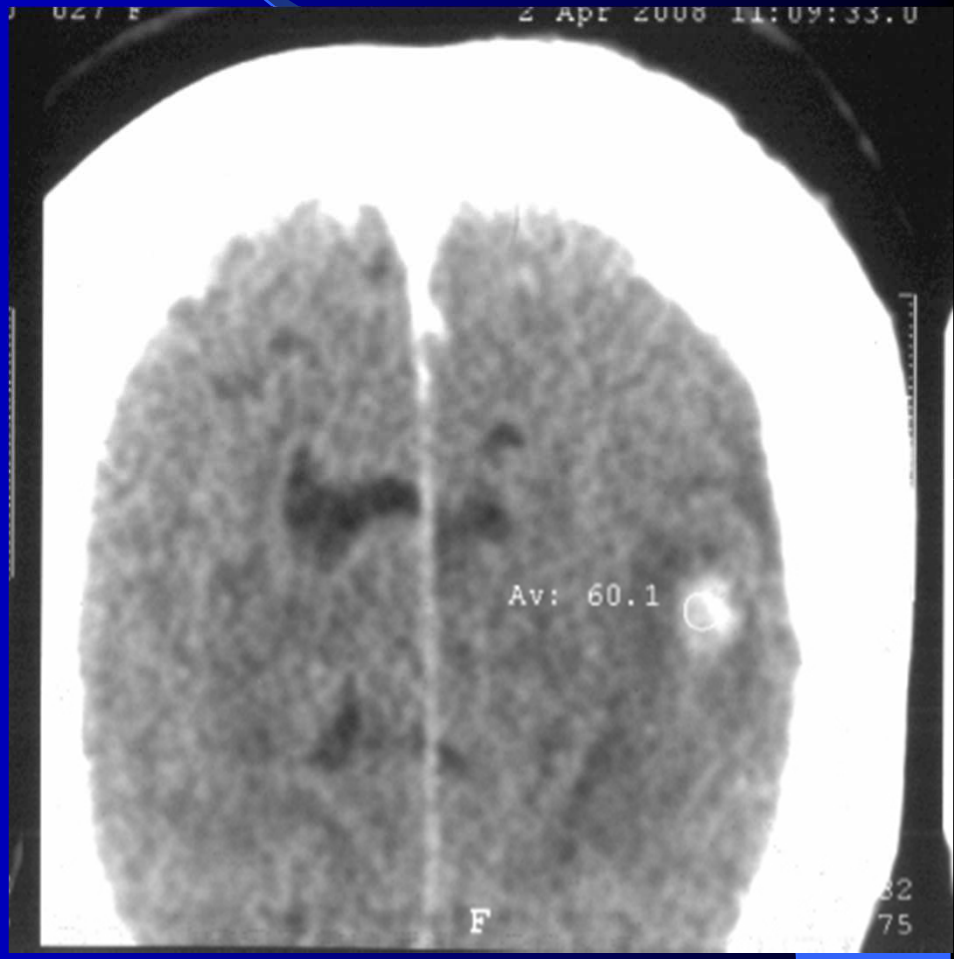
INVESTIGATION

- CT scan of brain
- MRI brain

MANAGEMENT OF BRAIN METASTASIS

- Judicious use of steroids
- Mannitol
- Anticonvulsants
- Antiemetic therapy

BRAIN METASTASIS



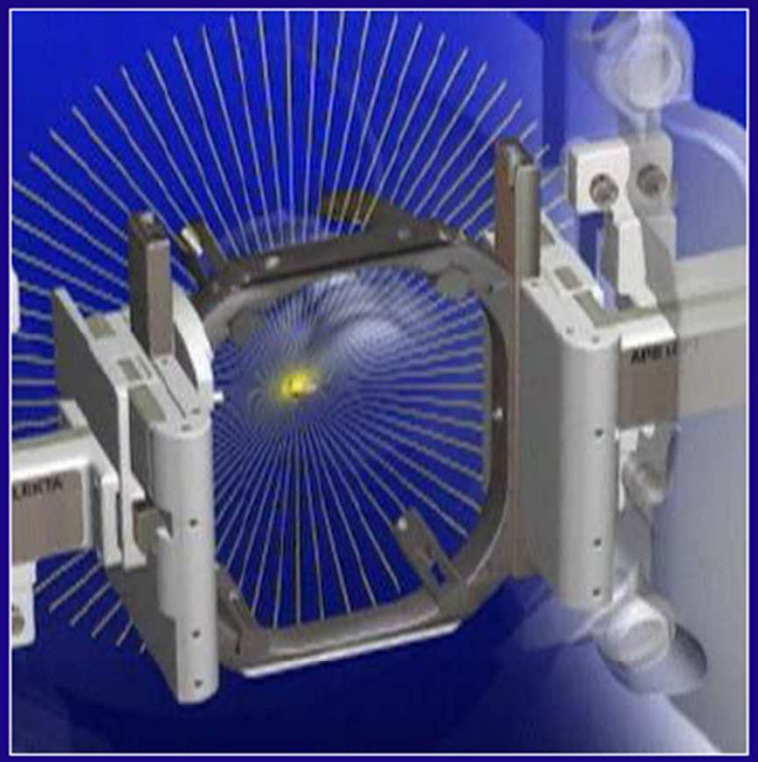
MANEGEMENT OF SOLITARY METASTASIS

- Surgical resection only after PET-CT scan with post operative radiotherapy
- Whole brain radiotherapy (30GY/10#)with boost by SRS

Role of SRS in Solitary Brain Metastasis

- Stereotactic radio surgery (SRS)
- Palliative radiotherapy – 30 Gy / 10 # followed by SRS boost
- Single fraction (12-15 GY)

Stereotactic Radiosurgery



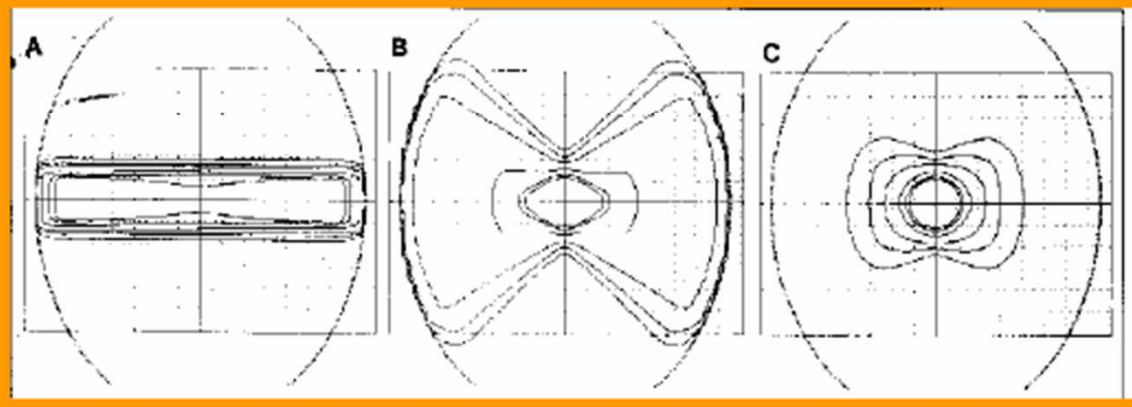
The delivery of a single, high dose of irradiation to a small and critically located intracranial volume, sparing normal structure

INDICATION

- Small target volume(<3 c.m.)
- Sharply defined target
- High conformity
- Sensitive structures excluded from the target

Co-planar .vs. Non-coplanar beams

- tolerance of normal tissue depends upon both the dose and volume of the tissue irradiated
- normal tissue irradiation can be minimized through stereotactic definition of target and sharply focused, multiple, non-coplanar beams



A. Parallel opposed beams

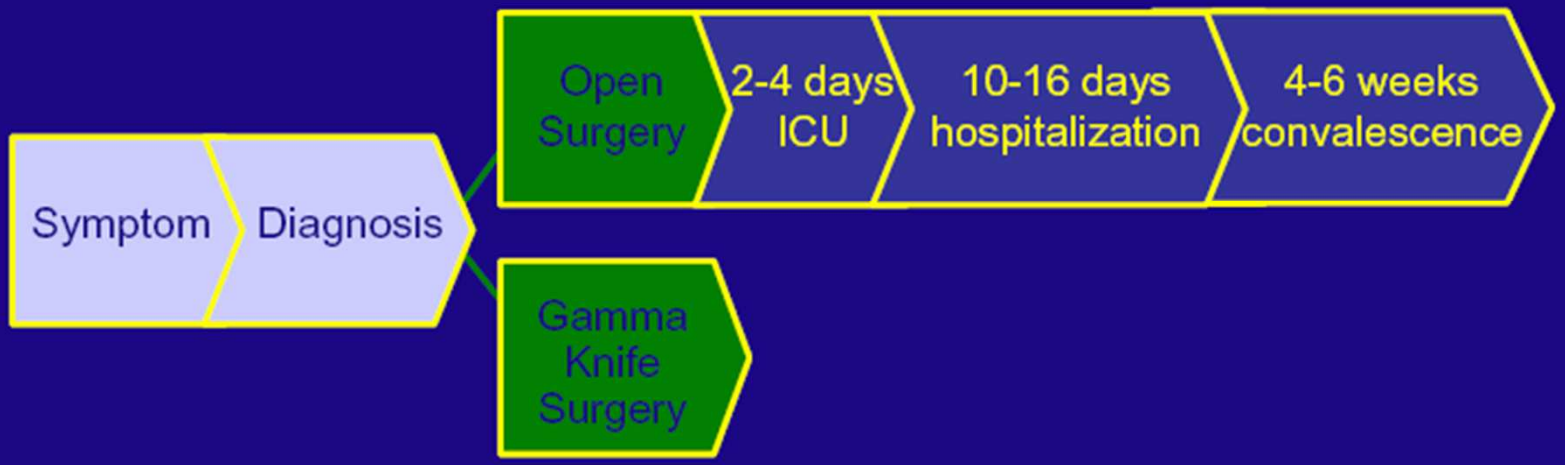
B. Coplanar arcs (bilateral 100°)

C. Non-coplanar beams

Advantages

- Enhances clinical outcome
- Improves quality of life
- Time factor

The Time Factor

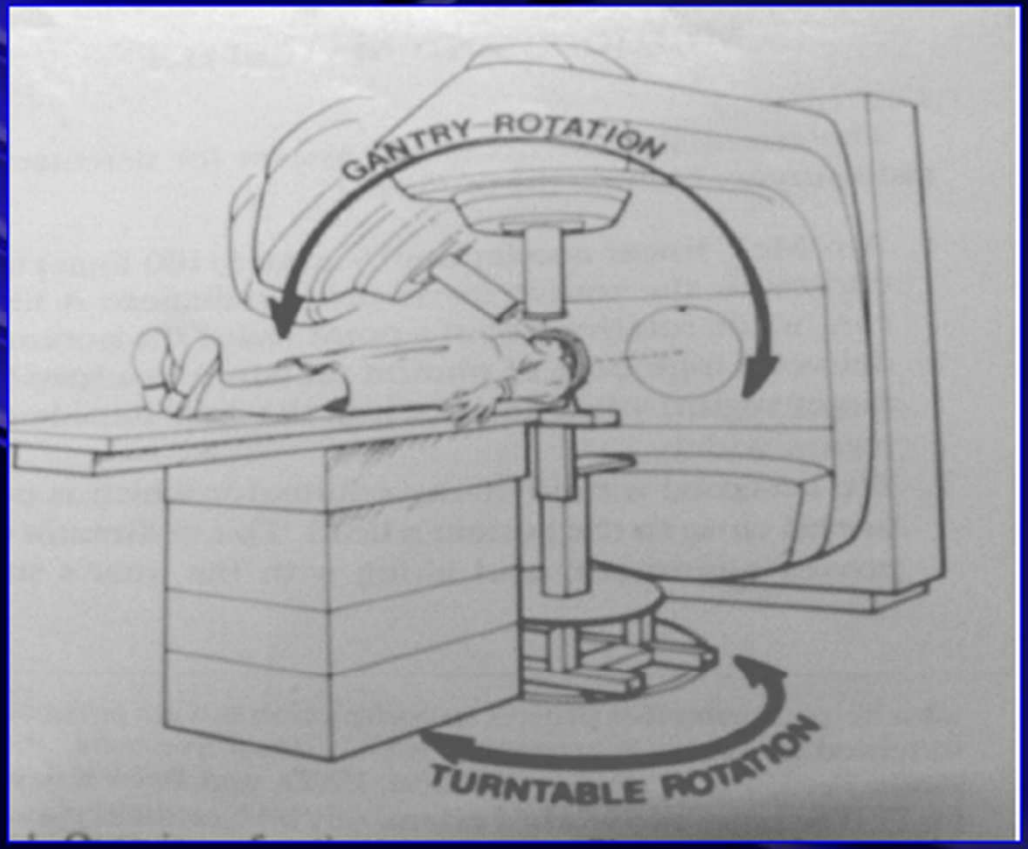


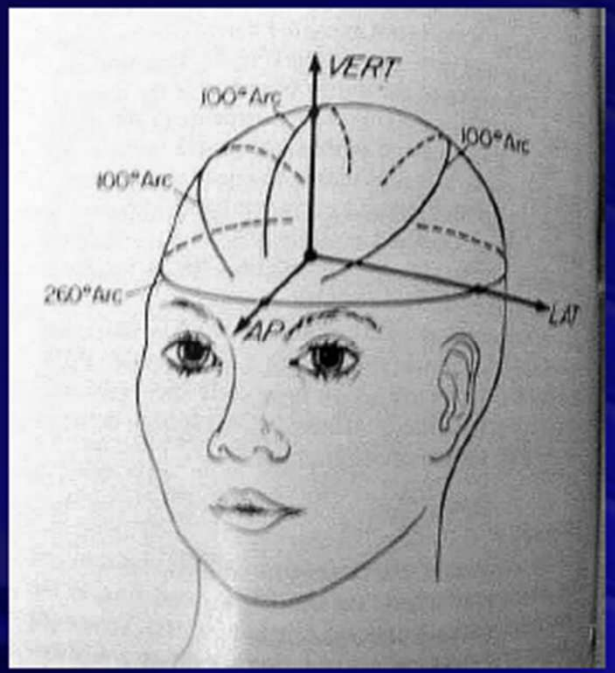
Quality of Life

- Minimally invasive
- Less trauma
- Faster recovery
- Minimal hospitalization
- Fewer complications
- Documented efficacy

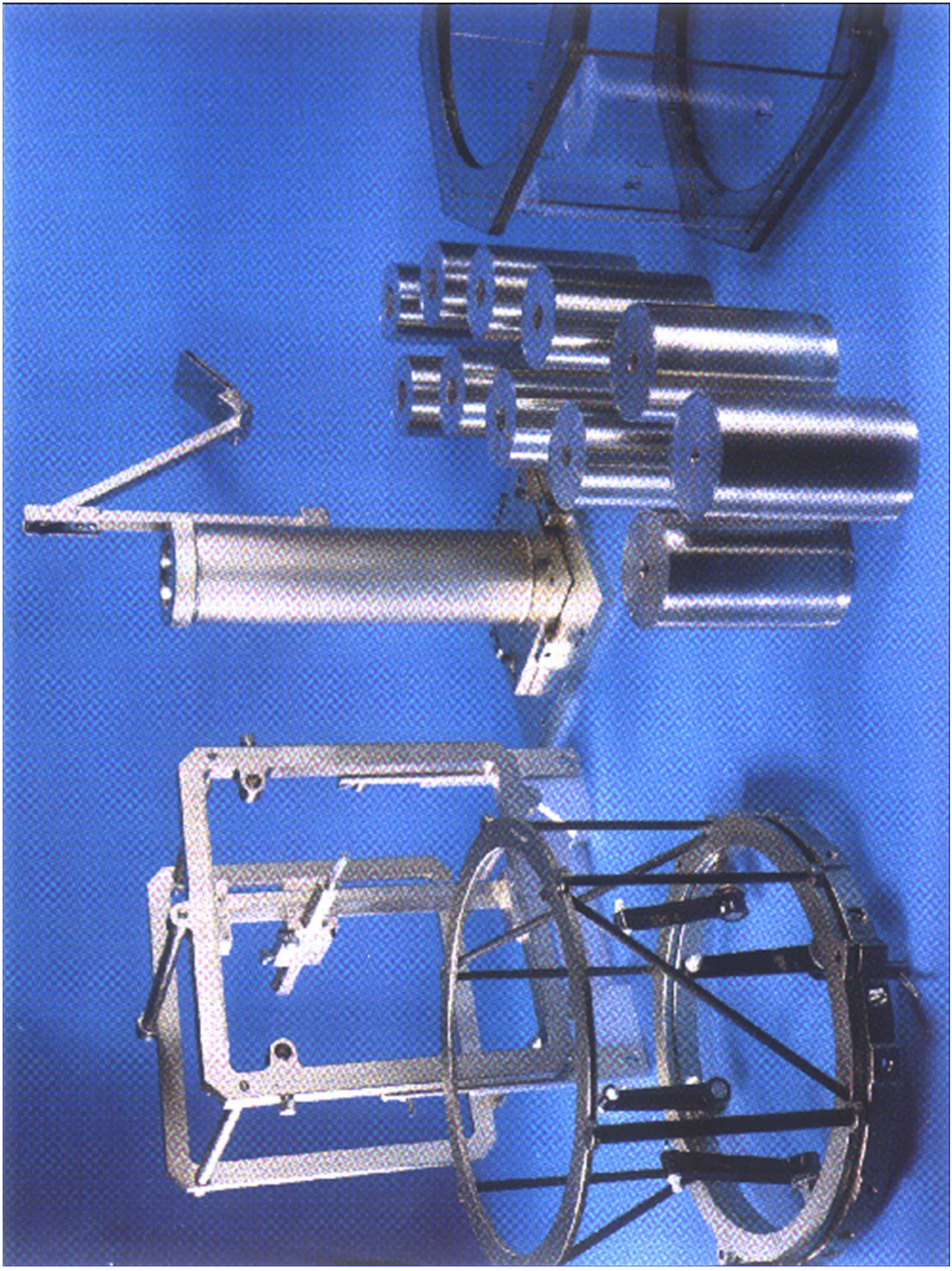
Gamma Knife

LA based Radiosurgery





Lutz IJROBP 1988; 14: 373-81

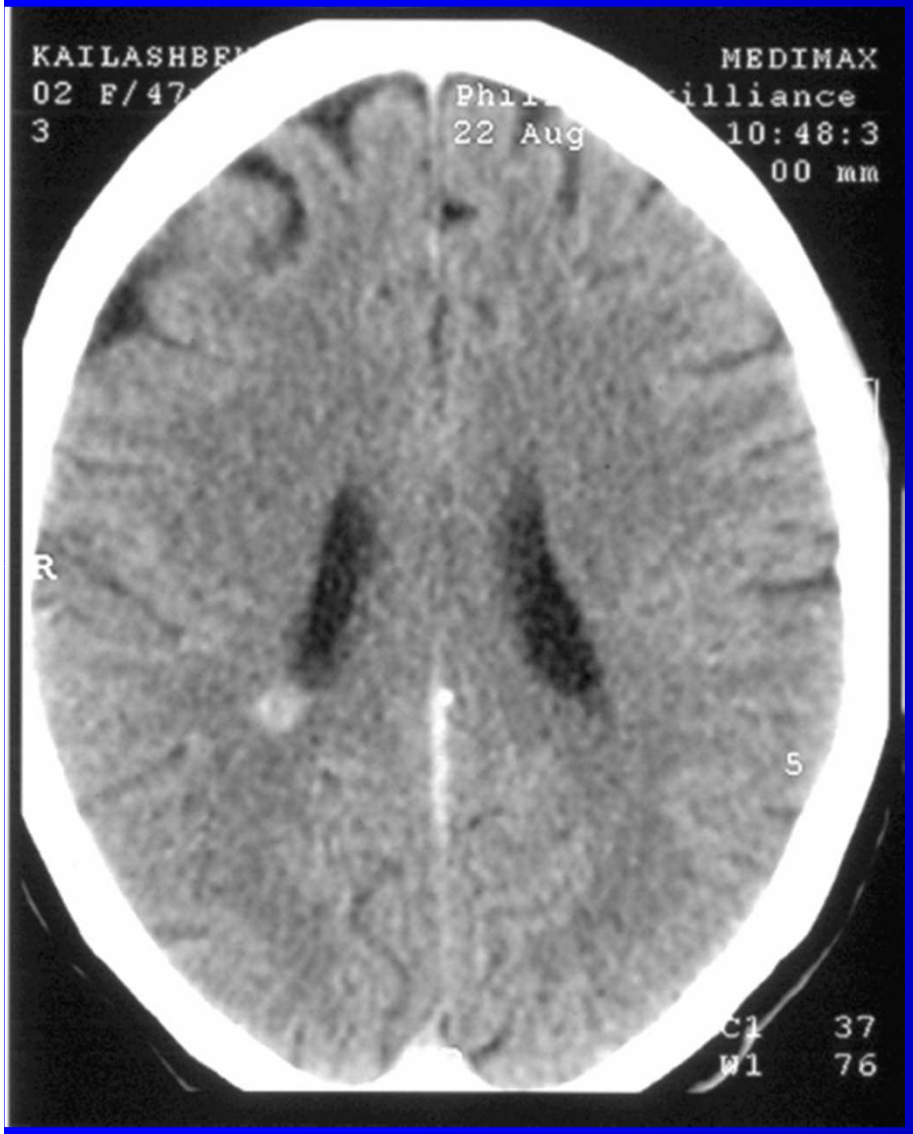


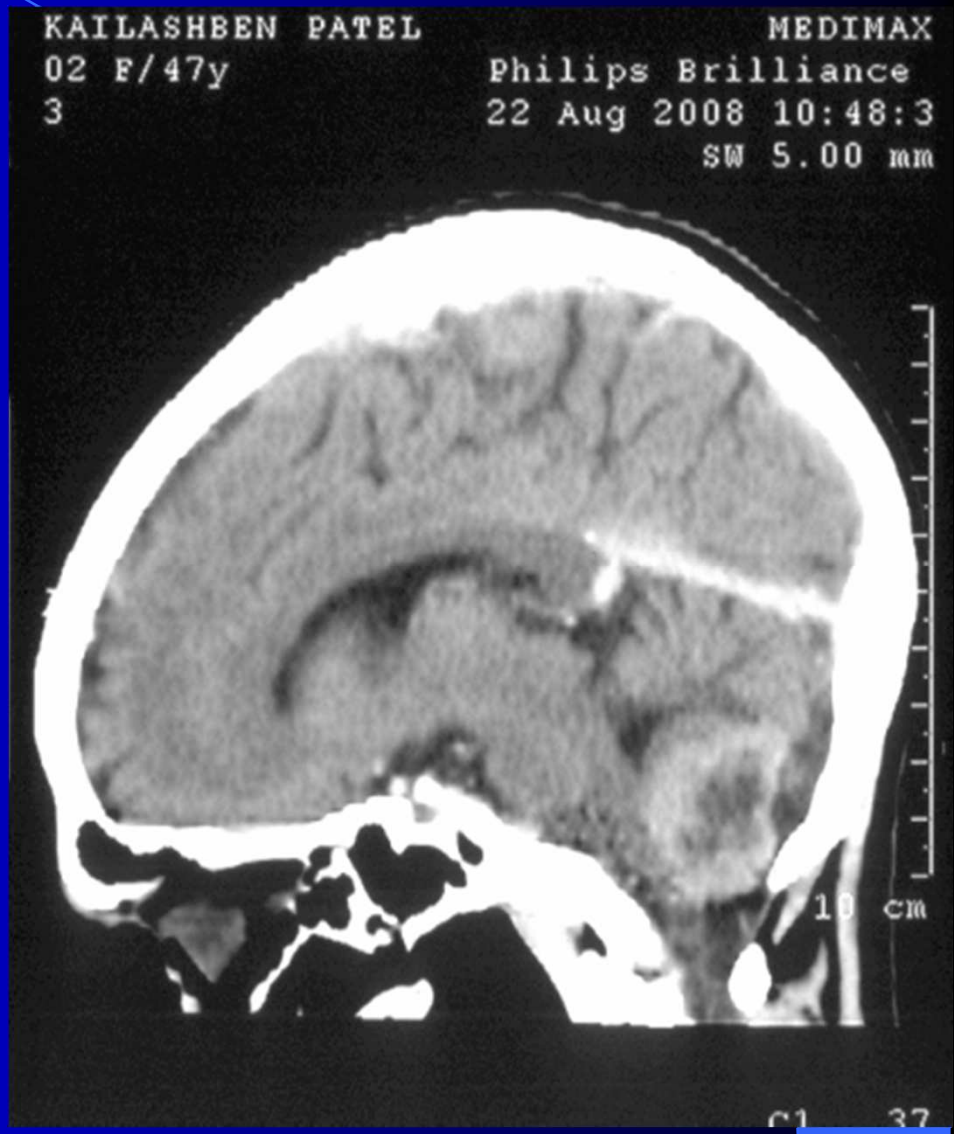
PROCEDURE OF SRS

RADIATION DELIVERY THROUGH SRS

MULTIPLE BRAIN METASTASIS

MULTIPLE BRAIN METASTASIS





MANAGEMENT OF MULTIPLEMETASTSIS

- Whole brain radiotherapy (30 GY/10 FR)
  With or without TEMOZOLAMIDE

METASTASIS WITH SIGNIFICANT MASS EFFECT

- Produces consequent hydrocephalus or herniation
- Requires urgent surgical intervention

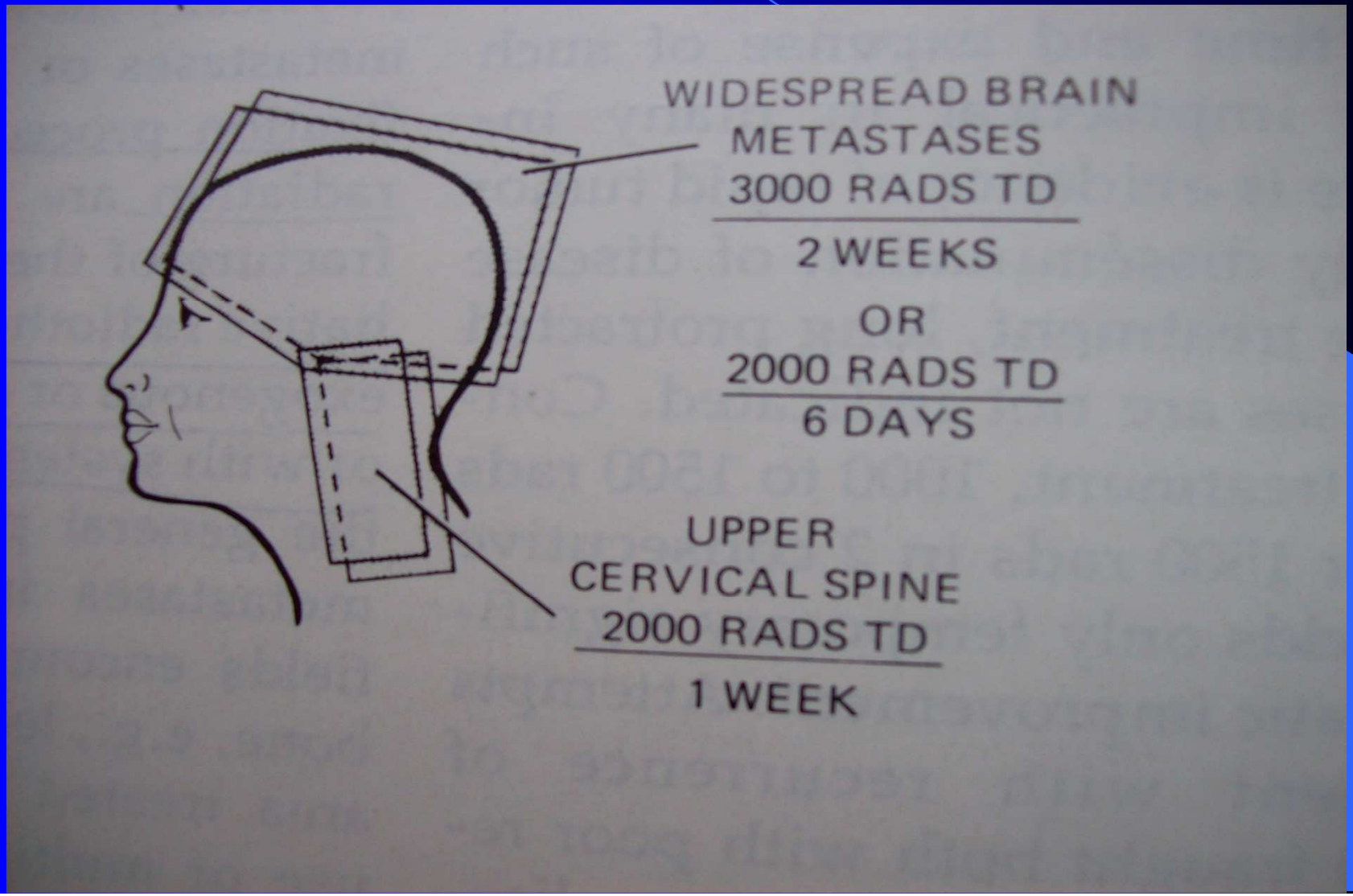
PORTALS OF RADIOTHERAPY

- Radiotherapy plays a major role in brain secondaries and in leptomeningeal carcinometosis

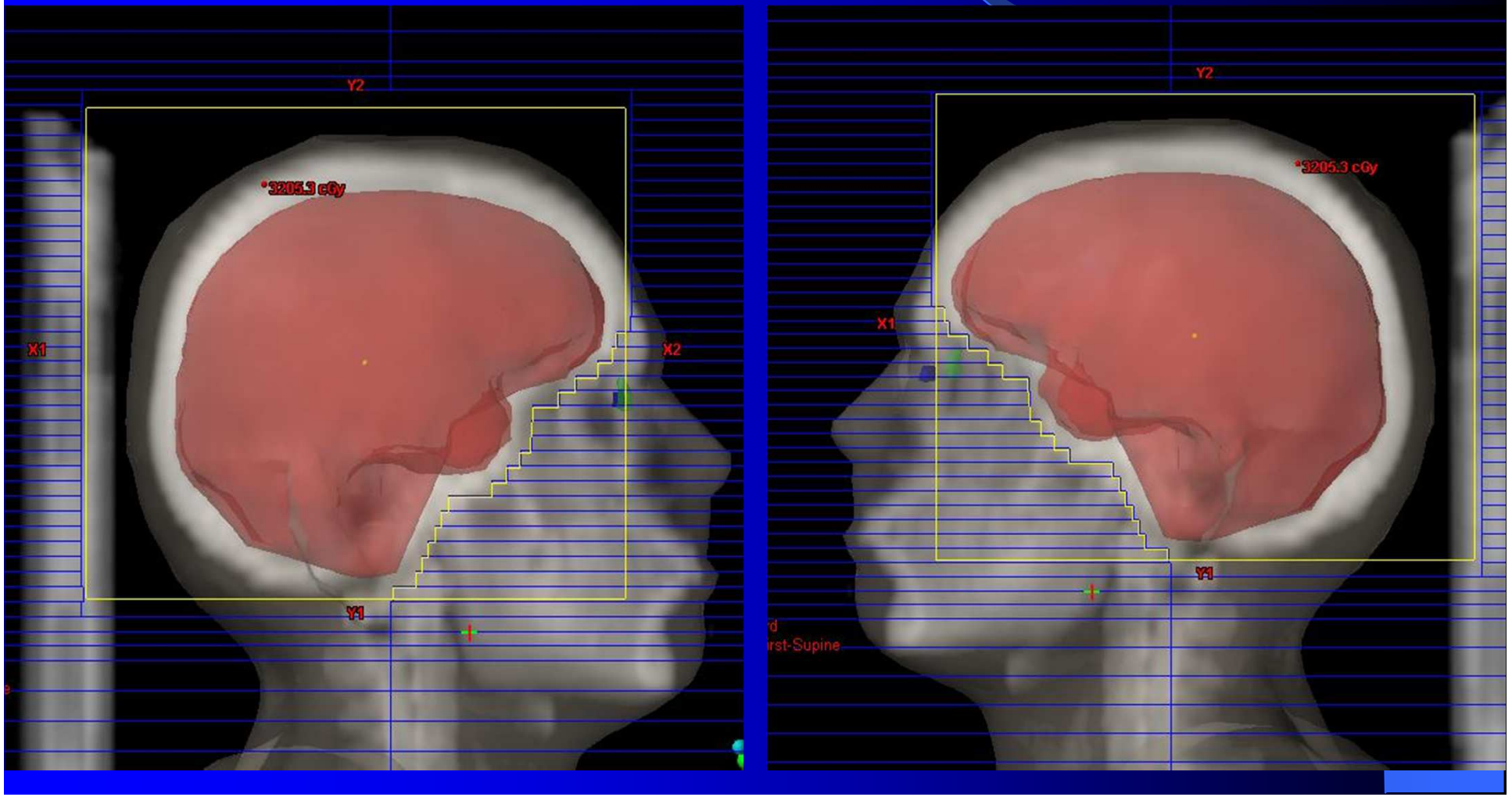
- Radiation portal should cover the entire cranium and basal meninges

  (two lateral step-ladder / German helmet) fields or slanting field.

PALLIATIVE CRANIAL RT

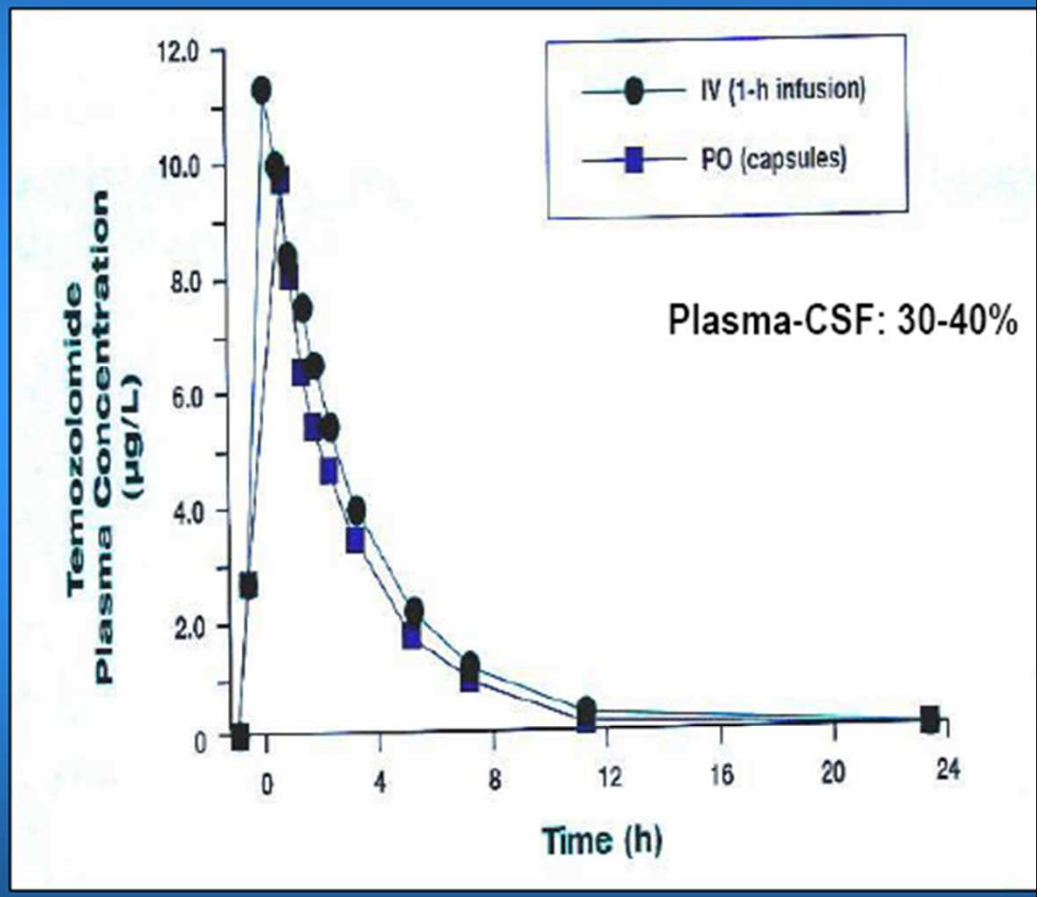


PALLIATIVE CRANIAL WHOLE BRAIN RT



Temozolomide (TMZ)

- Oral administration
- excellent concentration in CNS
- encouraging antitumour activity
- favourable toxicity profile
- synergism with radiotherapy and other agents



RADIOTHERAPY WITH TEMOZOLAMIDE

Outcome versus Toxicity

Toxicity

Local Control

Survival

What can improve the outcome Without increase in complications

CARCINOMATOUS MENINGITIS

- CM is the disseminated form of malignancy due to spread of malignant cells into cerebrospinal path involving intracranial meninges and meninges around the nerve roots of the spinal axis.

- Presented with severe backache, headache, vomiting, and neck rigidity.

TREATMENT

- Medical decompression
- Craniospinal irradiation (25-30GY in 15FR)
- Intrathecal chemotherapy

CHOROIDAL METASTASIS

- Incidence-10-40%
- Metastatize to intraocular structure than eyelids or orbit
- Two-third of the ophthalmic metastasis from BC involves the globe and choroid is more commonly involved.
- Substantial number of patients will show bilateral metastasis

PRESENTATION

INTRACHOROIDAL METASTASIS

- Distorted vision
- Diplopia
- Sudden blindness due to retinal detachment

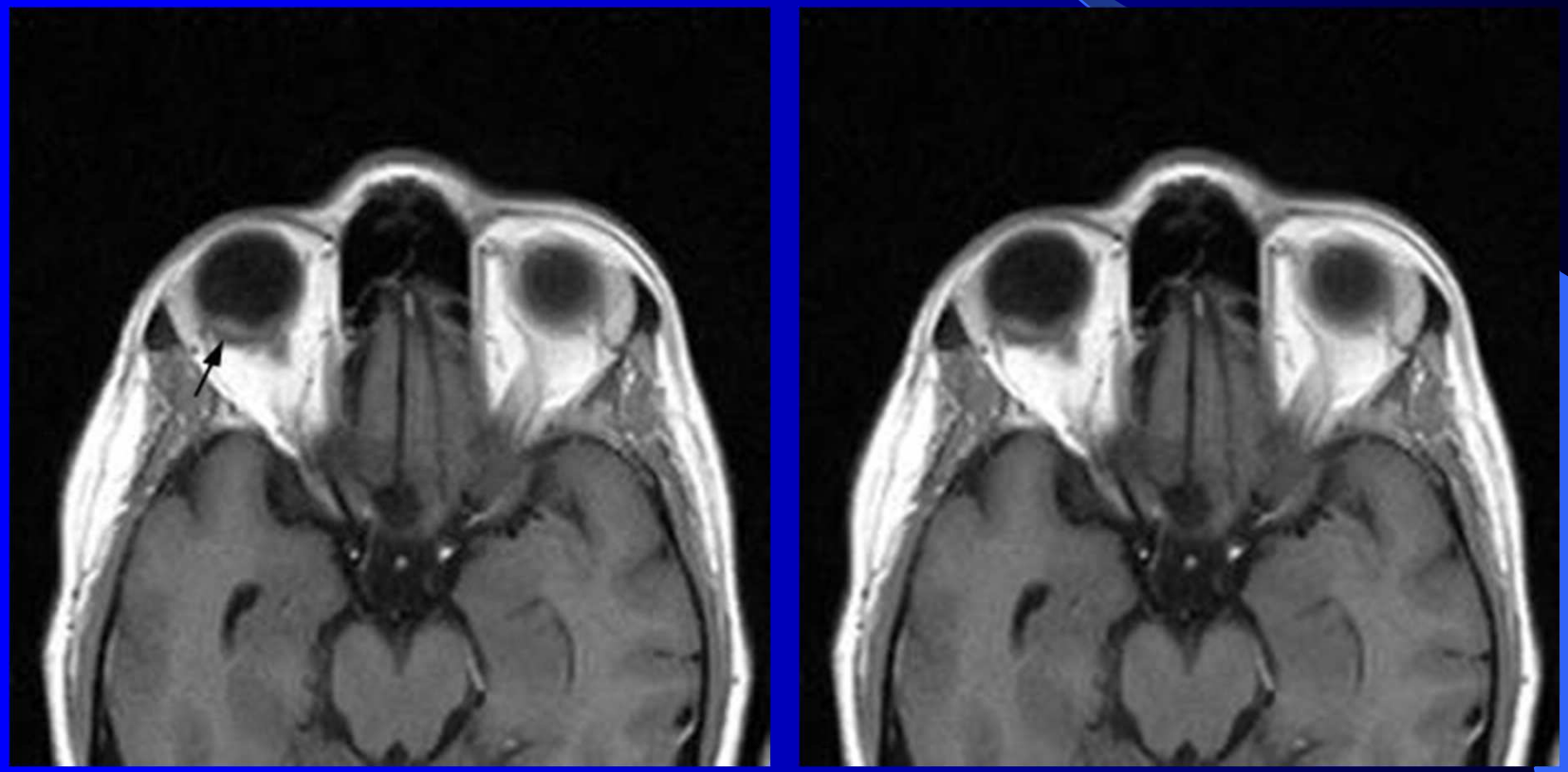
ORBITAL METASTASIS

- Proptosis
- Periorbital swelling
- Palpable mass
- Lid lag

INVESTIGATION

- Ophthalmic examination
- Ultrasonography of eye (B-scan)
- CT scan
- MRI of orbit
- Fluorescent angiography
- FNAC

CHOROIDAL METASTASIS

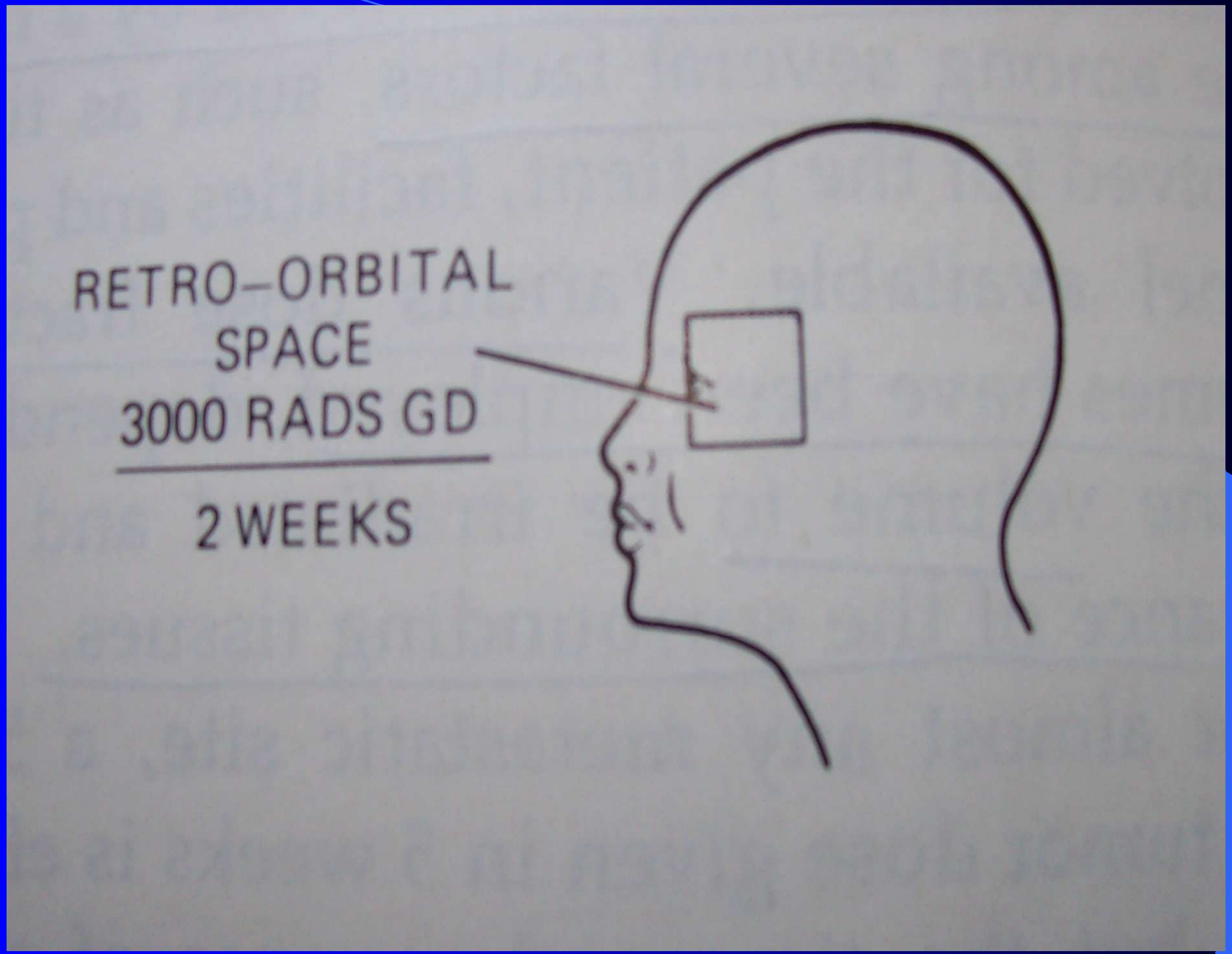


TREATMENT

- Radiotherapy 30GY / 10 FR over 2 weeks by lateral portal and calculated at 2.5 c.m. depth.
- Anterolateral wedge fields used in case of orbital metastasis with eyelid extension.
- Prognosis following early radiotherapy is generally good.

RETINAL METASTASES
CAUSING
VISUAL IMPAIRMENT
4000 RADS TD

4 WEEKS


RETRO–ORBITAL
SPACE
3000 RADS GD
2 WEEKS

BRACHIAL PLEXOPATHY

- < 3% of cases.
- Pain due to involvement of lower trunk (C7, C8, D1) and upper plexus(C5, C6)
- Atrophy of muscles
- Sensory changes
- Motor loss
- Horner’syndrome (50%) ominous sign
- Investigated by CT scan and MRI

TREATMENT

- Radiotherapy is the treatment of choice. 30GY/10FR over 2weeks.
- Radiotherapy portal includes lower neck and supraclavicular areas extending medially to cover C5-D1 nerve roots.
- Systemic chemotherapy if general status is good.
- Steroid with other analgesics.

SKIN METASTASIS

LIVER METASTASIS

- Ominous sign
- Presented with anorexia, malaise, weight loss, biliary obstruction, hepatic pain (due to capsular infiltration or haemorrhage)
- Treated with chemotherapy and / or radiofrequency ablation.

PULMONARY METASTASIS

- Systemic chemotherapy
- Excision if feasible and solitary nodule

PLEURAL EFFUSION

- Pleural drainage
- Sclerotherapy
- Intrapleural administration of Bleomycin

PERICARDIAL METASTASIS

- Malignant pericardial effusion and cardiac tamponade
- Investigated by CxR ,ECG, echocardiogram USG-guided aspirate
- Bleomycin installed as asclerosant.

OVARIAN ABLATION

- Premenopausal Patients
- ER / PR +ve
- Surgical Oopherectomy Vs. Ovarian Ablation
- Small Pelvic field RT(Inferior border is 1 c.m. below the top of pubic symphysis)
- Dose : 12 – 15 Gy in 5 #
- Response is slow (2-3 months),50-55%in ER+ve and 5-10%in ER-ve


THANK YOU