EWINGS SARCOMA FAMILY OF TUMORS

BY

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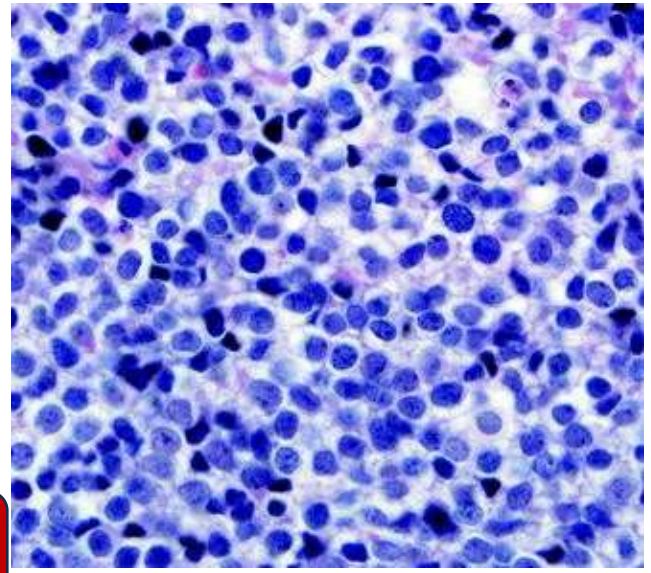
BLUE ROUND CELL TUMOR

RETINOBLASTOMA

MEDULLOBLASTOMA

SMALL CELL LUNG CANCER

WILMS TUMOR



NEUROBLASTOMA

EWINGS SARCOMA

HEPATOBLASTOMA

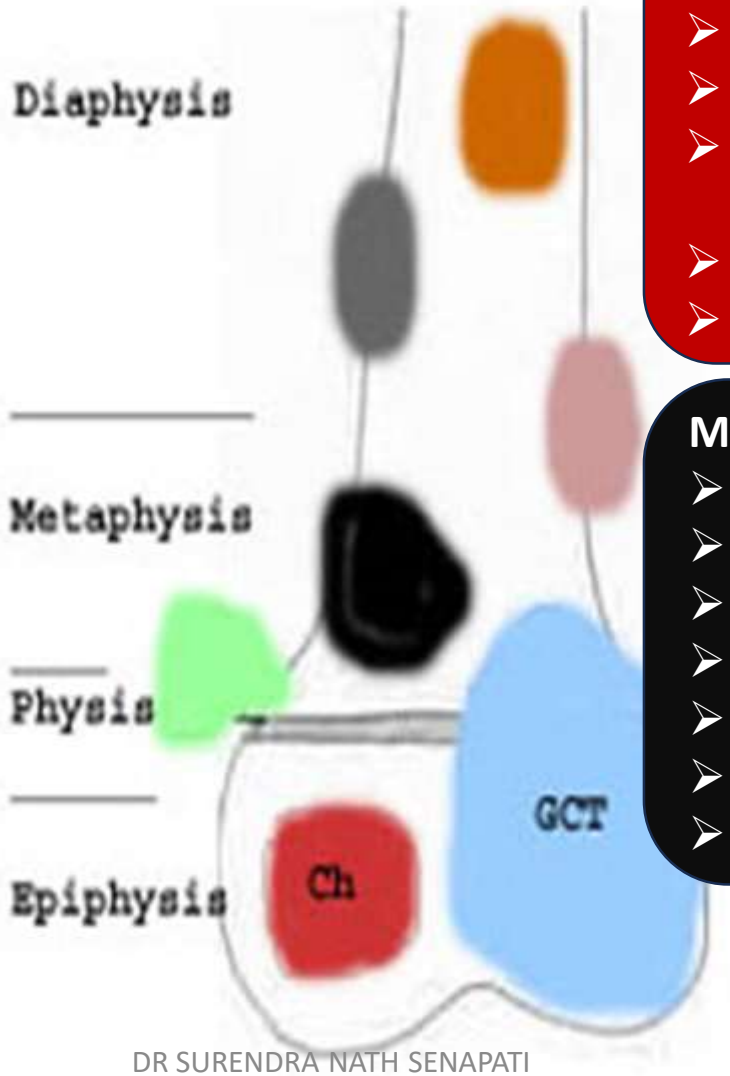
LYMPHOMA

ORIGIN OF DIFFERENT BONE TUMORS

DIAPHYSIS CORTEX
ADAMANTINOMA
OSTEOID OSTEOMA

METAPHYSIS CORTEX
NON OSSIFYING FIBROMA
OSTEOID OSTEOMA

EPIPHYSEAL LESIONS:
CHONDROBLASTOMA
- **GIANT CELL**
- **CHONDROMA**
- **CHONDROSARCOMA**



DIAPHYSIS MEDULLARY CAVITY
- EWINGS SARCOMA
- MULTIPLE MYELOMA
- LYMPHOMA

BENIGN
- FIBROUS DYSPLASIA
- ENCHONDROMA

METAPHYSIS MEDULLA
- **OSTEOSARCOMA**
- **CHONDROSARCOMA .FIBROSARCOMA**
- **OSTEOBLASTOMA, ENCHONDROMA,**
- **FIBROUS DYSPLASIA,**
- **SIMPLE BONE CYST,**
- **ANEURYSMAL BONE CYST**
- **GIANT CELL TUMOR**

PRIMORDIAL NEURAL STEM CELLS

EWINGS FAMILY OF TUMOR

ULTRASTRUCTURE

IHC

GENETICS

CLASSIC EWINGS SARCOMA

EXTRASKELETAL SOFT TISSUE EWINGS SARCOMA

ASKINS TUMOR

PNET OF BONE & SOFT TISSUE

SPECTRUM OF NEURAL DIFFERENTIATION

JAMES STEPHEN EWING
(1866-1943)

LEAST

EWING'S SARCOMA

EXTRA SKELETAL

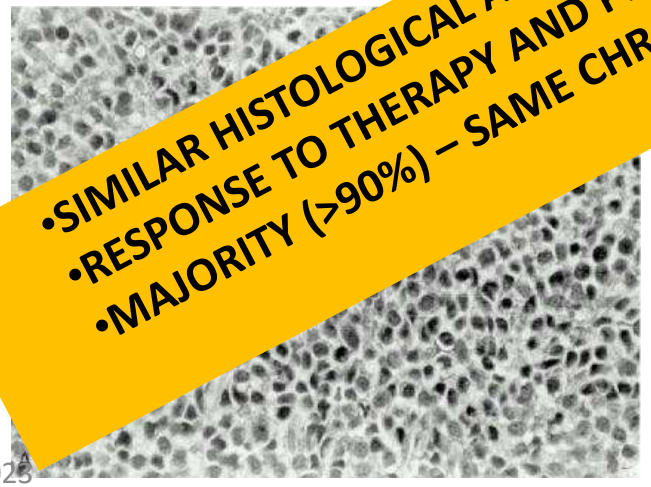
ATYPICAL

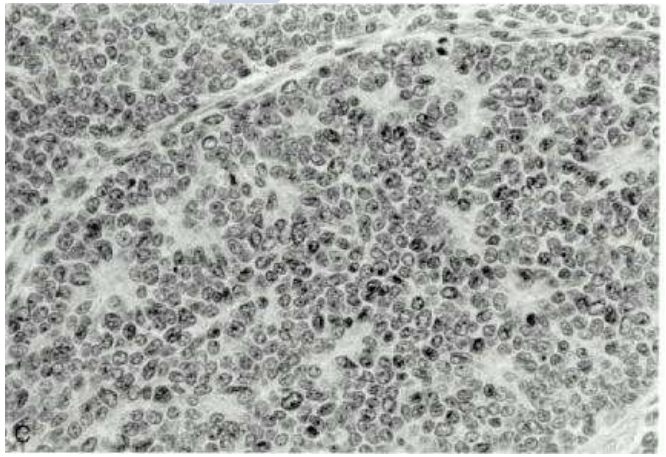
ROEPITHELIOMA

ASKIN TUMOUR

WELL

•SIMILAR HISTOLOGICAL APPEARANCE
•RESPONSE TO THERAPY AND PROGNOSIS
•MAJORITY (>90%) – SAME CHROMOSOMAL TRANSLOCATION T(11;22) (Q24;Q12),

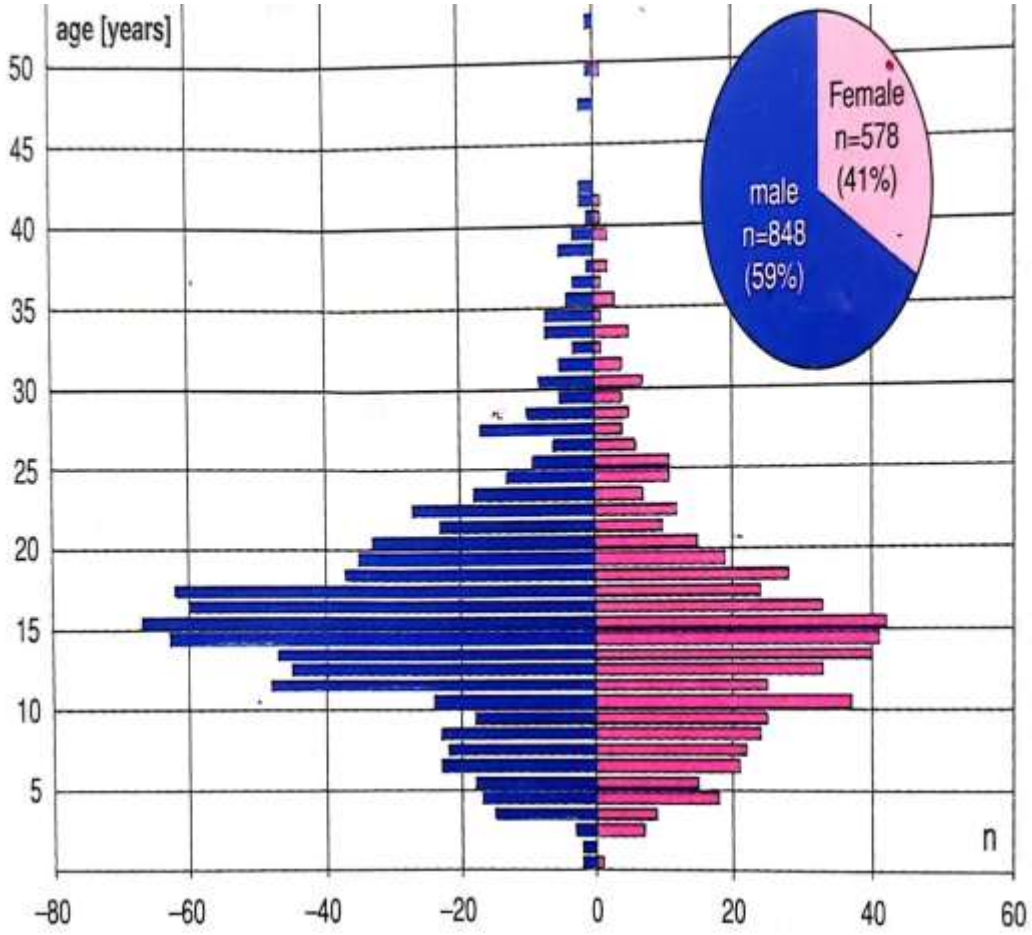


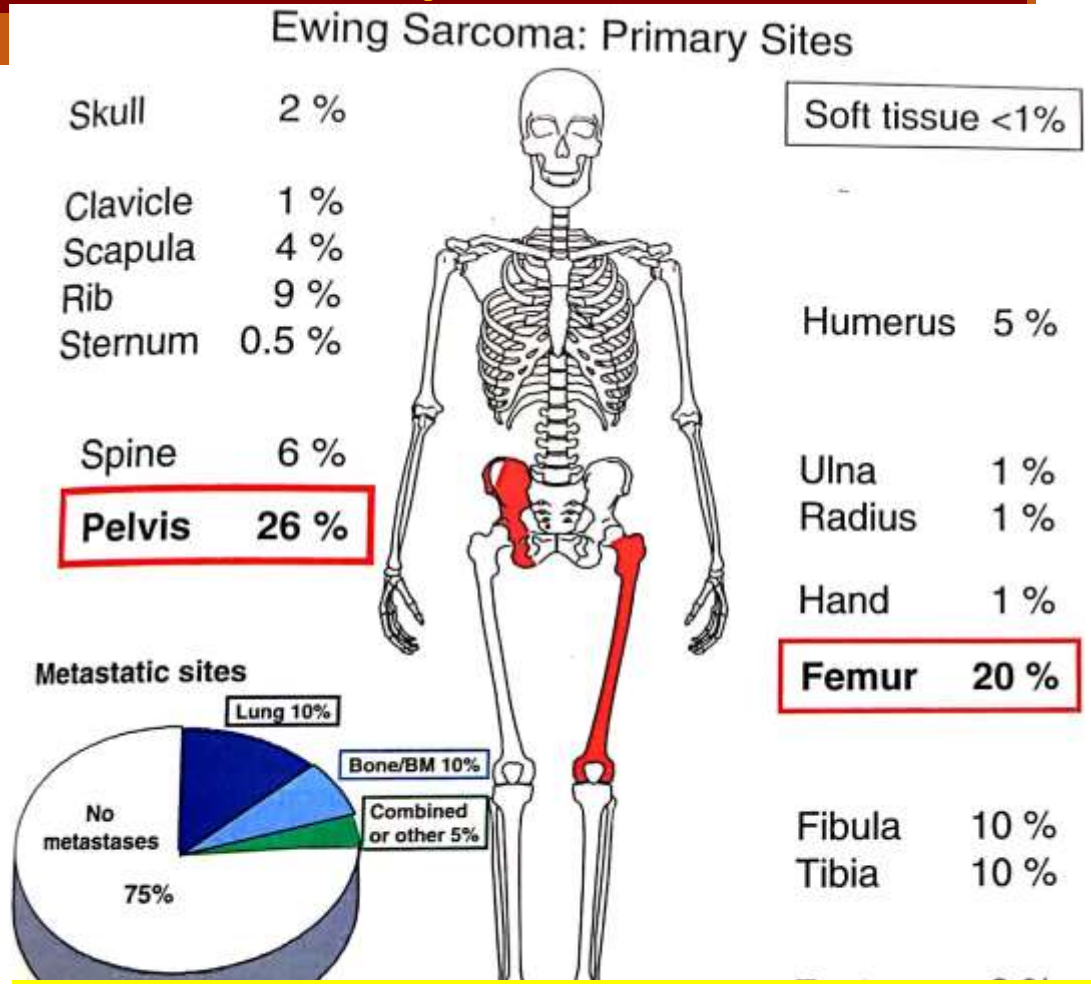


EWING'S SARCOMA

- **2ND MOST COMMON MALIGNANT BONE TUMOR IN CHILDHOOD.**
- **80% PTS YOUNGER THAN 20 YRS.CASES CONTINUED TO DIAGNOSED TILL THIRD DECADE (BUT DECREASED INCIDENCE)**
- **M:F=1.2:1.**
- **MOST COMMON IN CAUCASIAN THAN ASIANS**
- **ORIGIN: PRIMORDIAL NEURAL STEM CELL**
- **"SMALL ROUND BLUE CELL TUMORS OF CHILDHOOD"**
- **EWINGS SARCOMA FAMILY OF TUMORS(ESFT)**

EWING SARCOMA: DISTRIBUTION BY SITE, AGE AND SEX

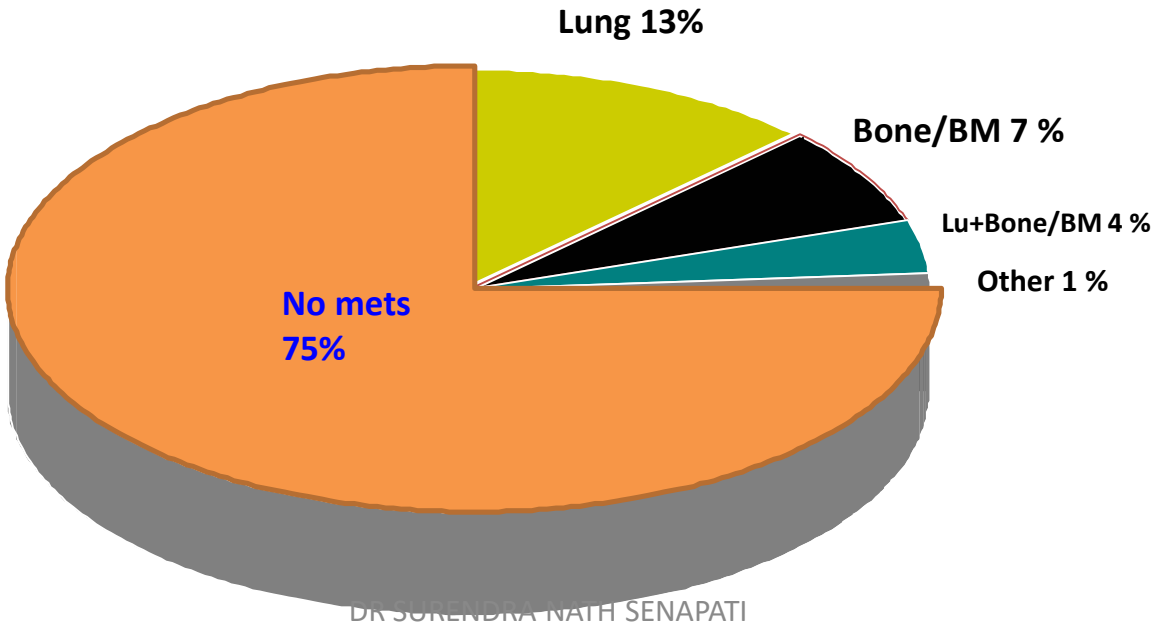




- MORE COMMON IN DIAPHYSIS OR METADIAPHYSIS
- EXTREMITIES (51%)
- CENTRAL AXIS (49%): PELVIS, CHEST WALL, SPINE, HEAD & NECK

DISSEMINATION

- DIRECT EXTENSION INTO ADJACENT BONE OR SOFT TISSUE.
- METASTASES GENERALLY SPREAD THROUGH BLOODSTREAM
- 25% PRESENT WITH METASTATIC DISEASE
  - LUNGS (38%)
  - BONE (31%)
  - BONE MARROW (11%)
- **NEARLY ALL PTS. HAVE MICROMETASTASIS AT DIAGNOSIS, SO ALL NEED CHEMOTHERAPY.**



The 11;22 Translocation And The Family of Ewing's Sarcomas

- **Reciprocal translocation t(11;22)(q24;q12)**
- **Found consistently in bone and soft tissue Ewings, PNET, Askin tumors**
- **Unifying diagnostic criterion for Ewing's family of tumors**
- ***EWS* (RNA binding protein) fused to *FLI-1* or *ERG* (transcription factors of the ETS family)**
- **Translocation results in a tumor-associated fusion gene**
  - **Fusion transcript present in > 95% of tumors of Ewings family**

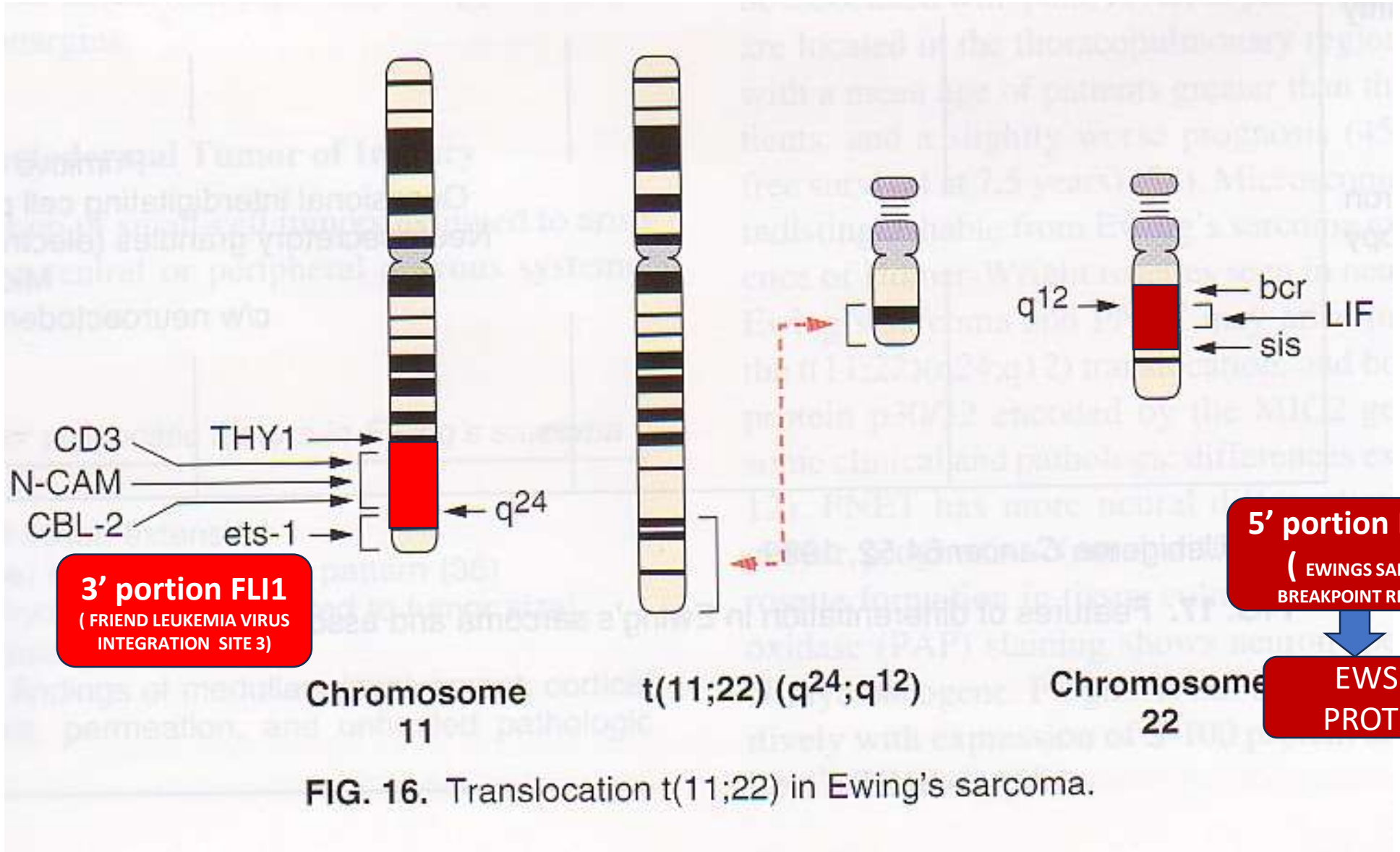
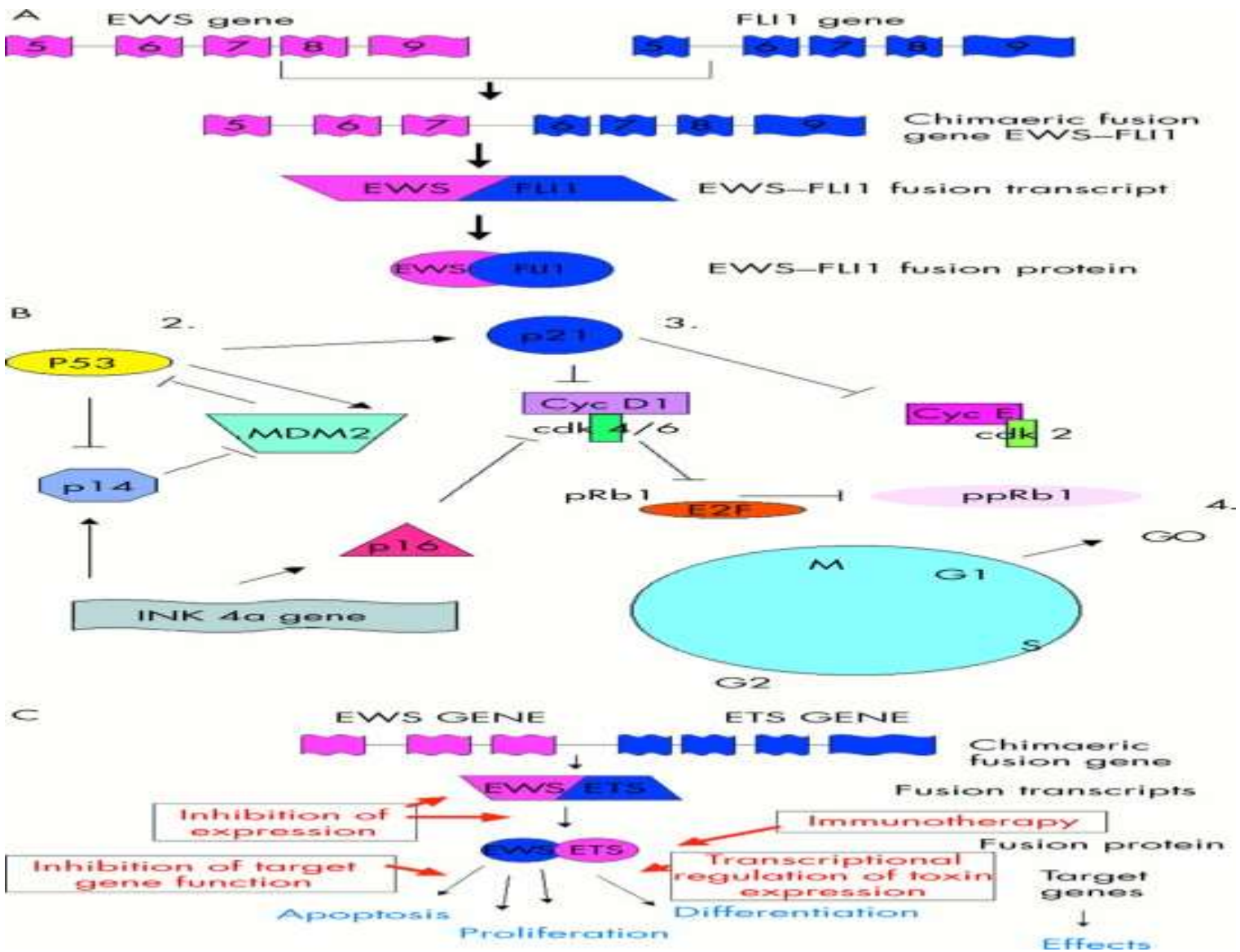


FIG. 16. Translocation t(11;22) in Ewing’s sarcoma.

DIAGRAMMATICAL REPRESENTATION OF THE T(11;22) (Q24;Q12) TRANSLOCATION RESULTING IN THE GENERATION OF THE EWS–FLI1 TYPE 1 FUSION TRANSCRIPT.



S A Burchill J Clin Pathol 2003;56:96-102

CYTOGENETICS

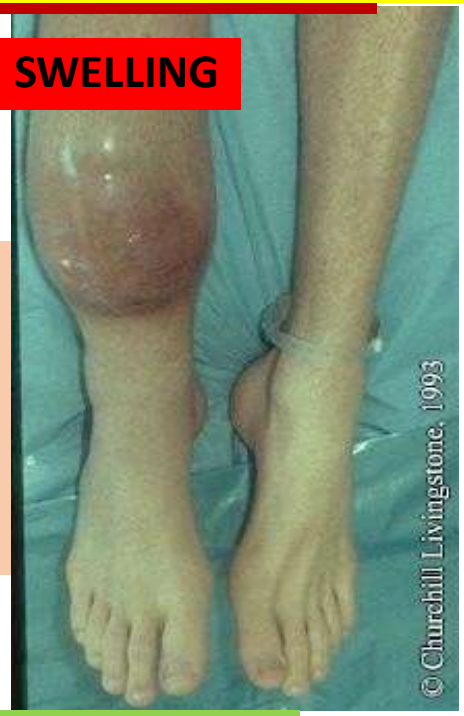
- EWING'S SARCOMA ARE ASSOCIATED WITH CHROMOSOMAL TRANSLOCATION BETWEEN THE EWS GENE AND GENE OF ETS FAMILY OF TRANSCRIPTION FACTORS.

Translocation	Genes	Chromosome	Percent
t(11;22)(q24;q12)	Ews FLI1	22 11	**85%**
t(21;22)(q22;q12)	Ews Erg	22 21	**10-15%**
t(7;22)(p22;q12)	Ews Etv1	22 7	**1-5%**
t(17;22)(q12;q12)	Ews E1af	22 17	
t(2;22)(q33;q12)	Ews Fev	22 2	

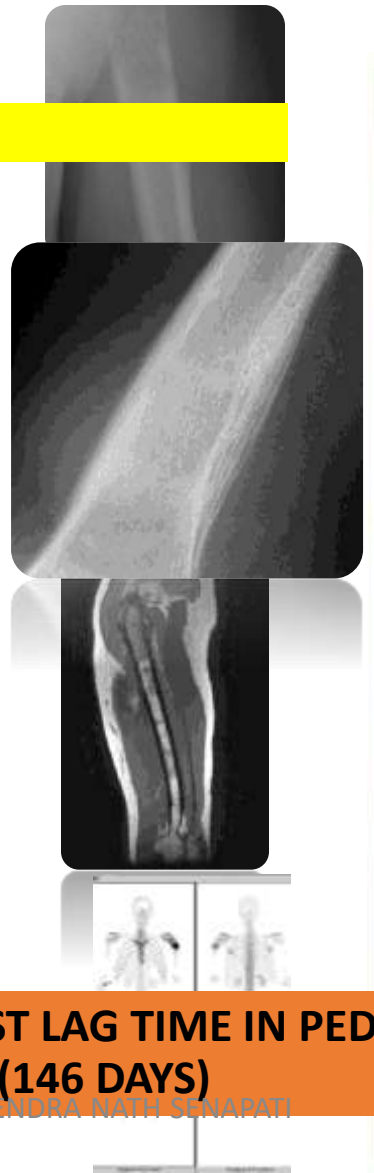
CLINICAL PRESENTATION

1.PAIN EARLIEST SYMPTOM, INTERMITTENT

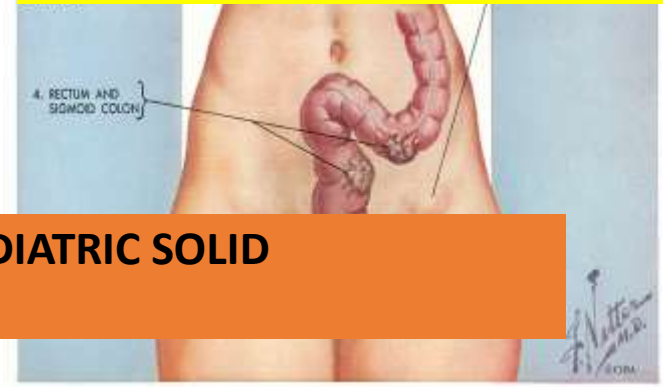
SWELLING



2. OCCAIONALLY,REMITTENT FEVER, MILD ANEMIA, LEUKOCYTOSIS, AND AN ELEVATED SEDIMENTATION RATE.



20% to 30% of the patients with ETB have overt metastases at the time of diagnosis. For EOE, 13% have overt metastases at diagnosis

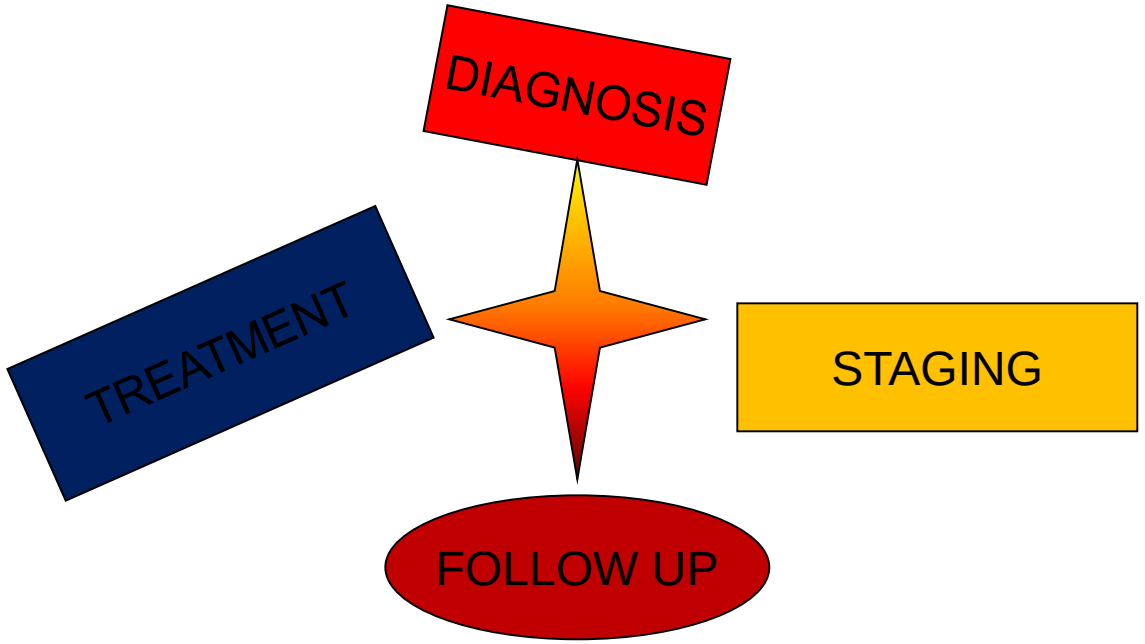


INCREASED SERUM LACTIC DEHYDROGENASE LEVELS AND WEIGHT LOSS

➢**LONGEST LAG TIME IN PEDIATRIC SOLID TUMOUR(146 DAYS)**

RARELY, DOES A PATIENT PRESENT WITH PATH.#

MANAGEMENT OF CANCER

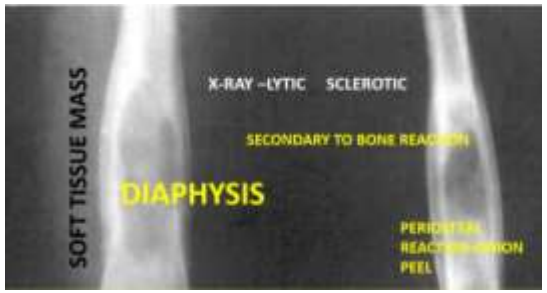


DIAGNOSIS

- CLINICAL
- BIOCHEMICAL
- RADIOLOGICAL
- ENDOSCOPY
- IMMUNOHISTOCHEMISTRY,CYTOGENETICS
- GRAPHICAL
- THERAPEUTIC

FINAL DIAGNOSIS:-EWING'S SARCOMA OF LEFT FEMUR

ANATOMICAL :- LEFT FEMUR



PATHOLOGICAL :- EWINGS SARCOMA

- SMALL,BLUE ROUND CELL
- MONOMORPHOUS APPEARANCE
- SCANTY CYTOPLASM

  HIGH NUCLEAR CYTOPLASMIC RATIO
- HOMER-WRIGHT ROSETTES
- MYC-2 POSITIVE
- t(11;22) (q24;q12)

DIAGNOSTIC WORK UP

	PRIMARY	STAGING
HISTORY & PHYSICAL EXAMINATION		
HISTO-PATHOLOGY	-BIOPSY -GENETICS -IHC	-BONE MARROW
IMAGING	-X-RAY -CT SCAN -MRI	-CT THORAX -BONE SCAN -PET SCAN
THERAPY	- RENAL – RFT - CARDIAC – 2D-ECHO	

CONFIRMATION OF DIAGNOSIS:

BIOPSY AND HISTOPATHOLOGIC EXAMINATION (CORE NEEDLE / OPEN BIOPSY)

CYTOGENETICS AND IHC

EVALUATION

BIOPSY

OPEN BIOPSY(preferably from soft tissue mass ,ONCOLOGY CENTRE,INITIAL SURGERY CAN BE PLANNED

HISTOPATHOLOGY:-SMALL BLUE ROUND CELL TUMOR.
IHC:-NSE,VIMENTIN,S-100,HBA-71,MYC

SEROLOGY:-LDH

B/L ILIAC FOR BMA AND BX.

- **EVALUATION FOR PRIMARY:-**
  - **CT,MRI,PET**
- **EVALUATION FOR METASTASIS:-**
  - **CT LUNGS,TC-99M BONE SCAN,PET**

BIOPSY APPROACH

DEPENDS UPON LOCATION,SIZE,SOFT TISSUE ELEMENT,AGE

INCISSIONAL

COMMONLY USED

DEPENDS ON LOCATION,NEUROVASCULAR BUNDLE

EXCISSIONAL

RARELY USED

NEEDLE(CLOSED)

SOFT TISSUE ELEMENT

SITE;- CAN EXCISED AT TIME OF RESECTION

OPEN

IN CHILDREN,OT PROCEDURE

LONGITUDINAL INCISSION

MOST SUPERFICIAL & PERIPHERAL PART OF TUMOR TO BE BIOPSIED

NOT VIOLATED CORTEX:-TREPHINE BX

FINE NEEDLE

ACCURACY:->80%

INSUFFICIENT MATTERIAL

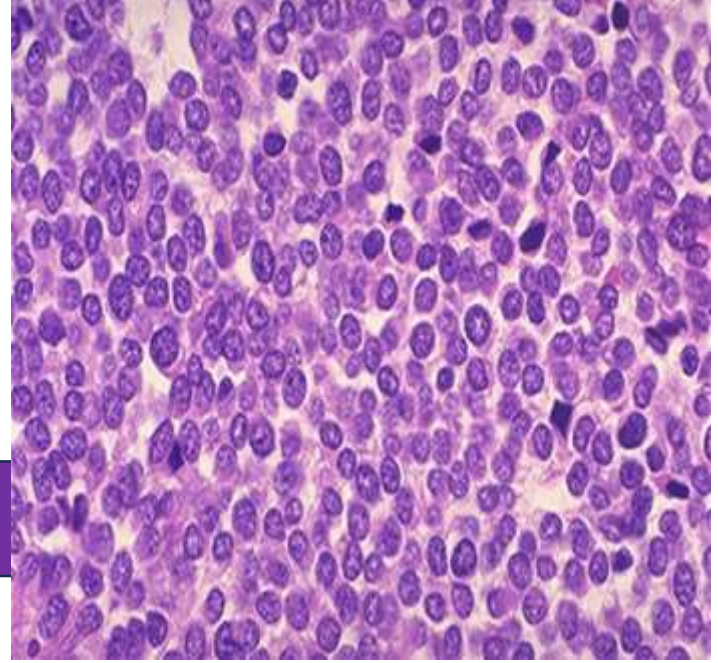
CORE

MAINTAIN ARCHITECTURE OF TISSUE

ACCURACY:->95%

SUFFICIENT MATTERIAL

TRIAGING OF SPECIMEN



BIOPSY

TISSUE

TRIAGING

IMPRINT FOR FISH

HP,IHC IN 10% NEUTRAL BUFFERS FORMALIN

SMALL ROUND CELL,HIGH N/C RATIO HOMER-WRIGHT PSEUDO ROSETTES

CD99:-STRONG +VE DIFFUSE MEMBRANE STAING:-95 TO 100% Mab:-O13,HBA71 PNET:-NSE,S-100.Leu-7

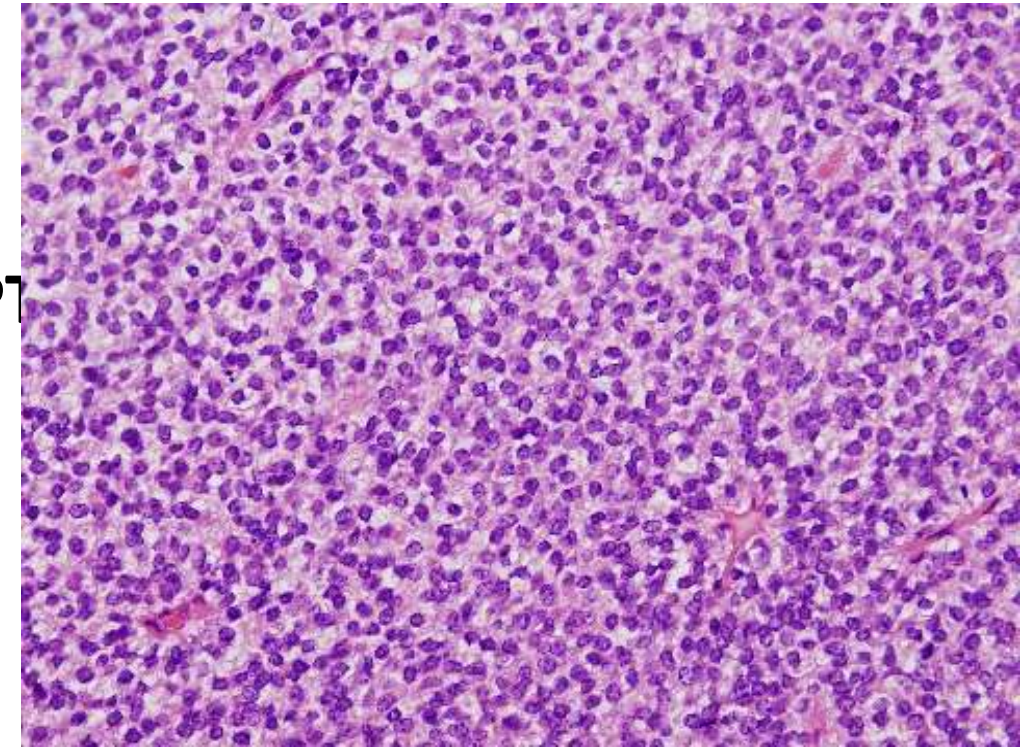
-70,RT-PCR

Translocation t(11:22)(q24:q22) t(21:22)(q24:q12)

IN GLUTARALDEHYDE FOR ULTRASTRUCTURAL STUDY

TISSUE CULTURE FOR CYTOGENETICS (karyo typing) AND FLOW CYTOMETRY(dna ploidy)

HISTOPATHOLOGY REPORT



- TYPE OF SPECIMEN WITH GROSS DESCRIPT
- EXTENT OF TUMOUR
- GRADE OF TUMOUR
- MARGINS OF RESECTION
- PERCENTAGE NECROSIS OF TUMOR
- EVIDENCE OF ANGIOLYMPHATIC INVASION, PNI, LYMPH NODE INVASION

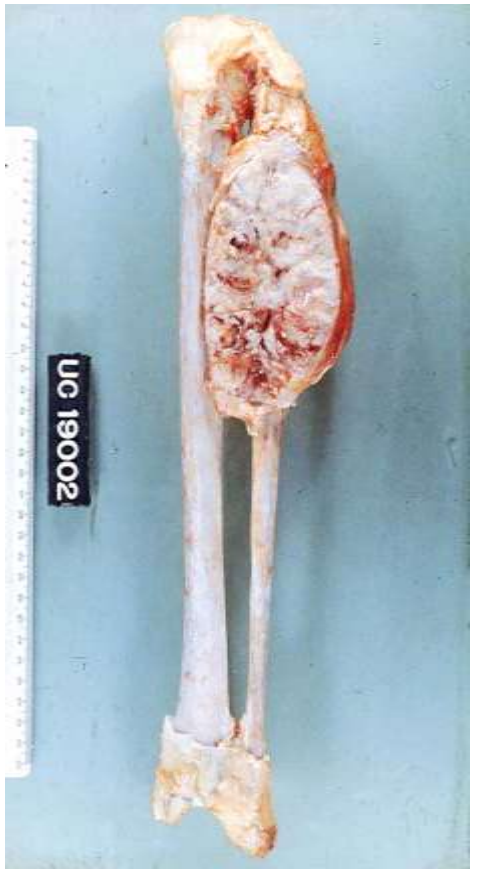
PATHOLOGY

GROSS:-

- **GRAY WHITE TUMOR WITH NECROSIS,HEMORRHAGE**
- **GLISTENING MOIST APPEARANCE**
- **GROWTH IN MEDULLARY CAVITY OF BONE**
- **EARLY INVN OF PERIOSTEAL SOFT TISSUE**

MICROSCOPIC:-

- **SMALL,BLUE ROUND CELL**
- **MONOMORPHOUS APPEARANCE**
- **SCANTY CYTOPLASM,HIGH NUCLEAR CYTOPLASMIC RATIO**
- **SOME TIME HOMER-WRIGHT ROSETTES**
- **ULTRASTUCTURE HELPFUL TO IDENTIFY NEUROECTODERMAL DIFFERENTIATION**



EWINGS Vs PNET

EWINGS	PNET
POORLY DIFFERENTIATED	HIGHLY DIFFERENTIATED
PSEUDOROSETTES ON LIGHT MICROSCOPE	NO PSEUDOROSETTES
DO NOT TYPICALLY STAIN POSITIVE FOR NEURAL MARKERS	IHC STAIN FOR NSE,SYNAPTOPHYSIN,S-100,CD 57
EXPRESS 1 NEURAL MARKER	EXPRESS >2 NEURAL MARKERS

HISTOPATHOLOGY GRADE

Tumor Differentiation	Mitotic Count	Tumor Necrosis
Sarcoma closely resembling normal adult mesenchymal tissue (eg, low-grade leiomyosarcoma (1 point)	0-9 mitoses per 10 high-power fields (HPF) (1 point)	No necrosis (0 points)
Sarcomas for which histologic typing is certain (eg, myxoid/round cell liposarcoma) (2 points)	10-19 mitoses per 10 HPF (2 points)	< 50% tumor necrosis (1 point)
Embryonal and undifferentiated sarcomas, sarcomas of doubtful type, synovial sarcomas, soft tissue osteosarcoma, Ewing sarcoma/primative neuroectodermal tumor (PNET) of soft tissue (3 points)	≥20 mitoses per 10 HPF (3 points)	≥50% tumor necrosis (2 points)

The scores for these variables are added to calculate THE **FOLLOWING G VALUES:**

GX - GRADE CANNOT BE ASSESSED
G1 - TOTAL SCORE OF 2 OR 3
G2 - TOTAL SCORE OF 4 OR 5
G3 - TOTAL SCORE OF 6 OR HIGHER

POST CT RESPONSE EVALUATION

RESPONSE TO CHEMOTHERAPY

Huvos Grading System

Grade	Necrosis %	5 yr EFS %	Responders %
I	<50	0	19
II	50 -90	37	22
III	90-99	84	18
IV	100	84	42

POG-CCG (Modified Huvos System)

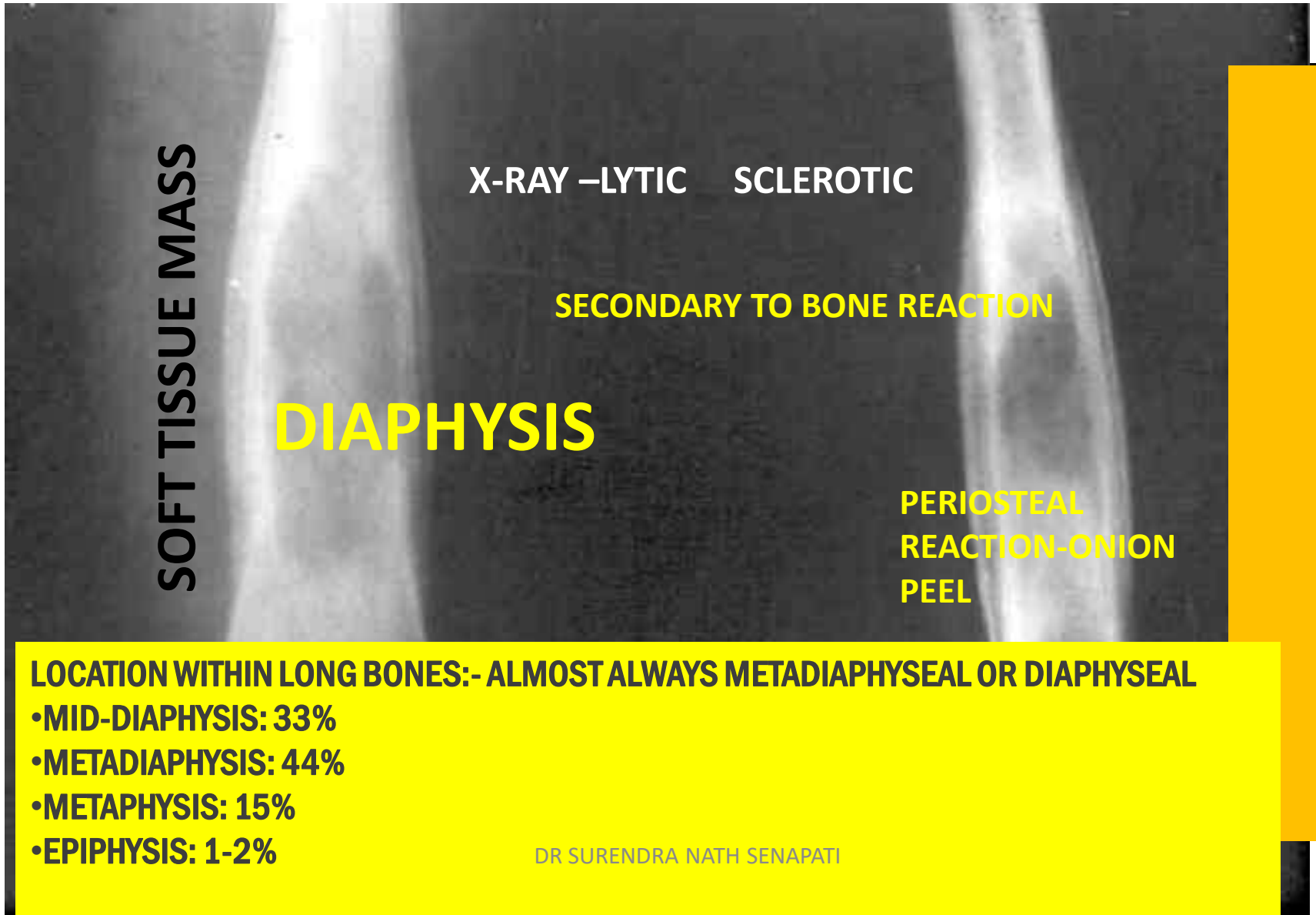
Grade	Necrosis (%)	OS – 3 yrs (%)
I	0	30
II	A – 1 to 10 B – 11 to 90	30
III	91-99	49
IV	100	73

IHC MARKER	*PNET	EWING'S SARCOMA	LYMPHOMA	MESENCHYMAL CHONDROSARCOMA	RHABDOMYOSARCOMA
NSE	+		-	-	-
S-100	+	-	-	+	-
CK	-	-	-	+	-
DESMIN	-	-	-	-	+
CD45	-	-	+	-	-
SYNAP/CHROMA	+	-	-	-	-
MIC-2	+	+	-	-	-
PAS		+	-		
RETICULIN		-	+		

IMAGING

- **PLAIN FILM:-**
  - **MOTTLED OR MOTH EATEN LESION**
  - **LYTIC Vs BLASTIC**
  - **ONION SKIN APPEARANCE**
- **MRI:-**
  - **EXTENT OF BONE MARROW INV.**
  - **SOFT TISSUE INV**
- **CT SCAN:-BONE DESTRUCTION**
- **BONE SCAN**
- **BONE MARROW BIOPSY**
- **PET-CT**

IMAGING :- PLAIN X-RAY



- LYTIC OR MIXED LYTIC-SCLEROTIC AREAS PRESEN
- MULTI-LAYERED SUBPERIOSTEAL REACTION (ONION SKINNING)
- LIFTING OF PERIOTEUM (CODMAN'S TRIANGLE)

LOCATION WITHIN LONG BONES:- ALMOST ALWAYS METADIAPHYSEAL OR DIAPHYSEAL

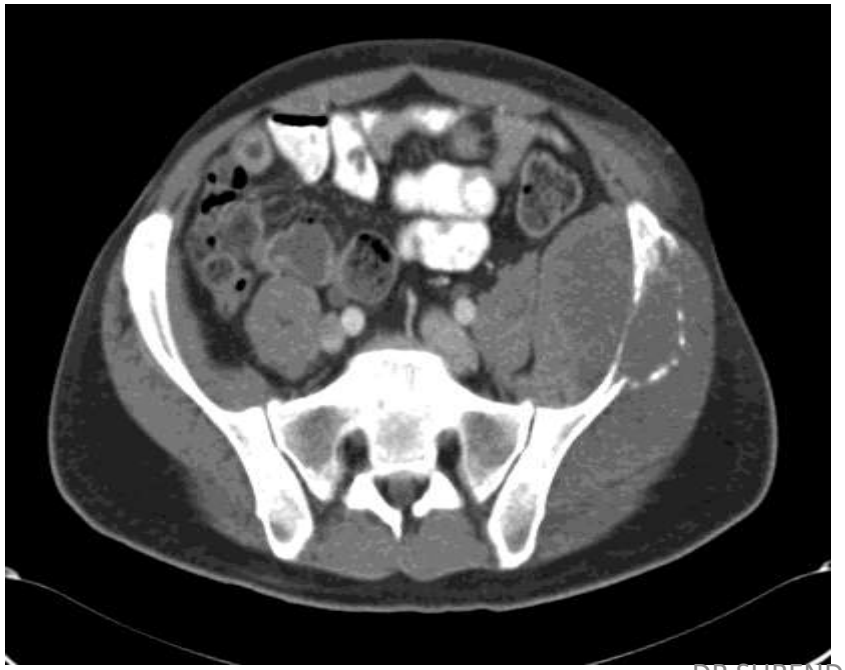
- **MID-DIAPHYSIS: 33%**
- **METADIAPHYSIS: 44%**
- **METAPHYSIS: 15%**
- **EPIPHYSIS: 1-2%**

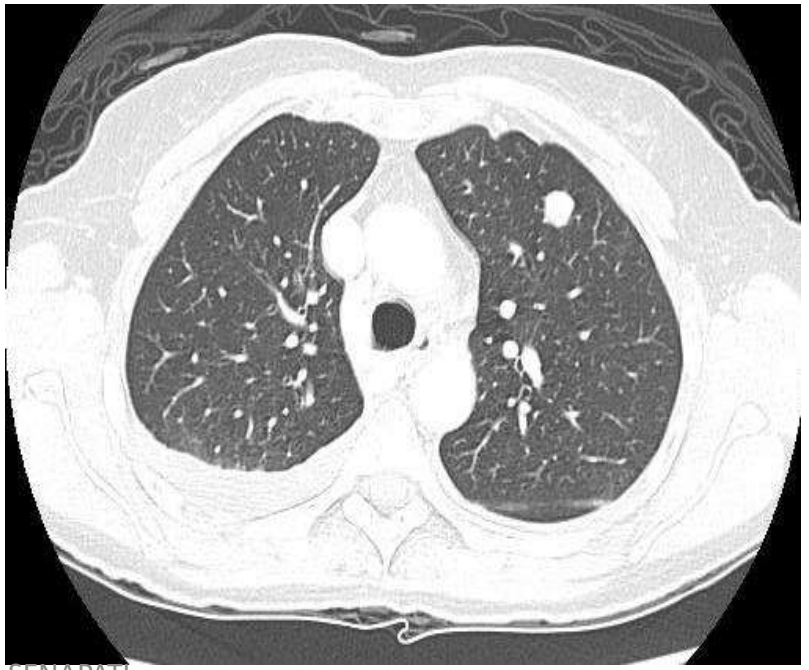
CT SCAN:

BONE DESTRUCTION BEST SEEN

CHEST METASTASIS

RESPONSE EVALUATION.

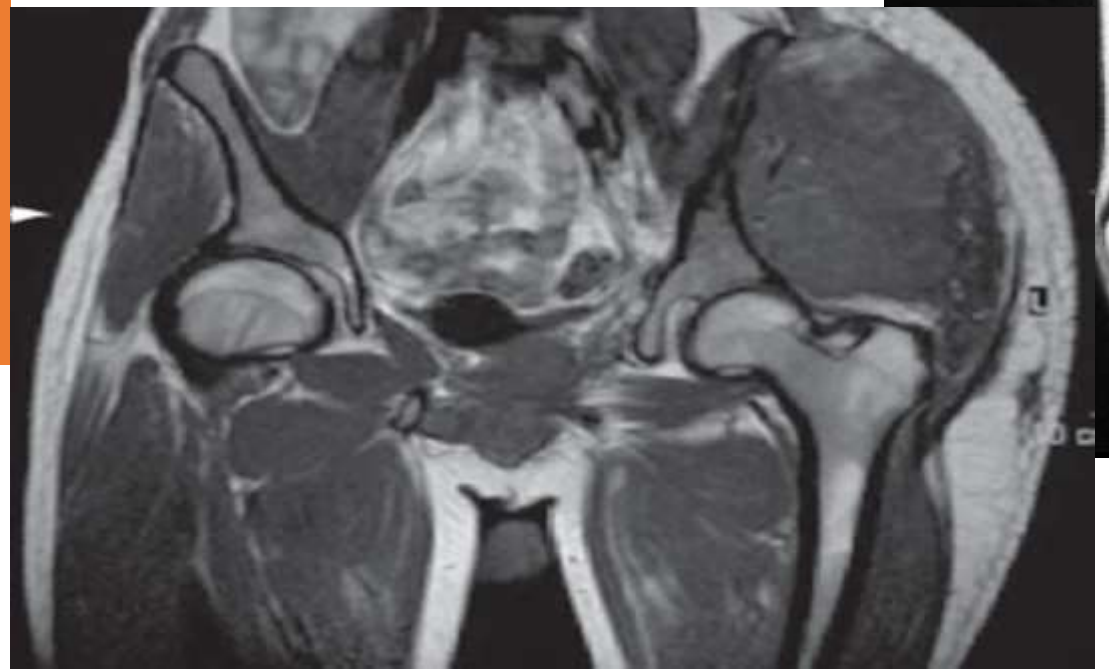


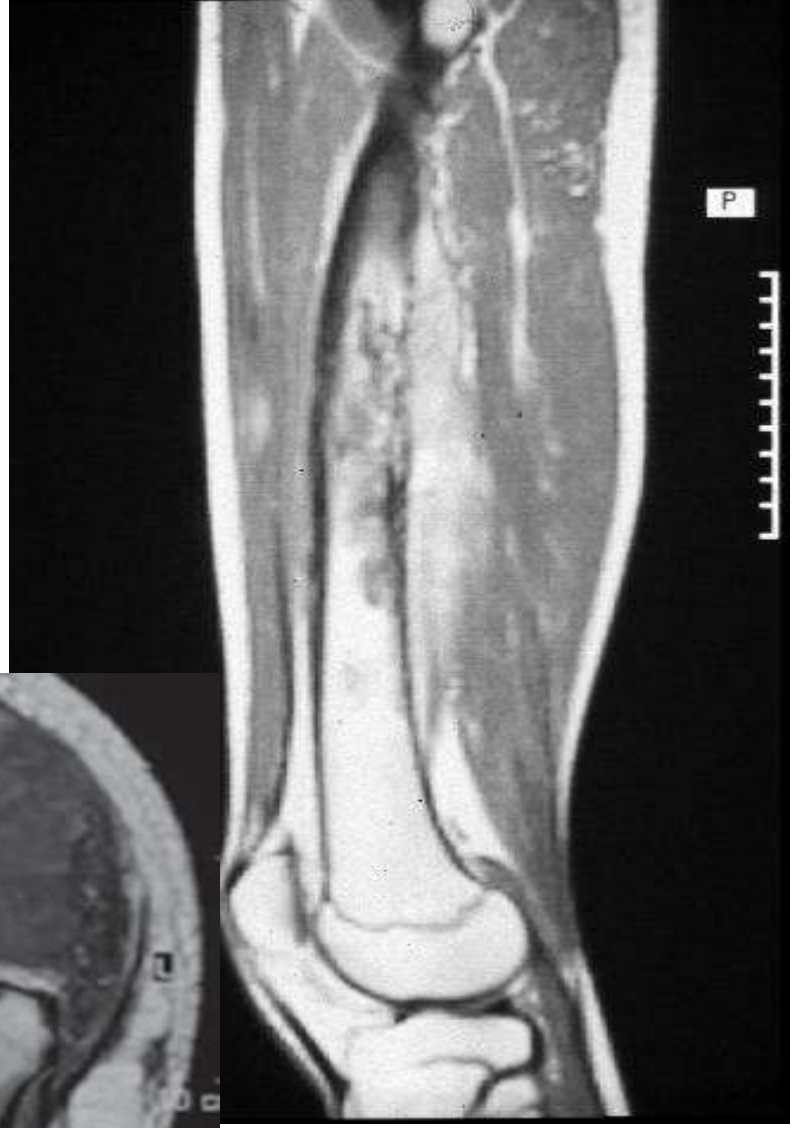


MRI:

- **EXTRA-OSSEOUS(T2) AND INTRAMEDULLARY(T1) EXTENT OF LESION**

- **INTRA-MEDULLARY EXTENT**
- **SOFT TISSUE EXTENSION**
- **SKIP LESIONS**
- **RELATION ADJACENT STRUCTURES, VESSELS , NERVES**
- **MULTI-PLANAR**
- **RESPONSE EVALUATION**





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Medicine (Baltimore). 2018 Nov; 97(48): e13457.
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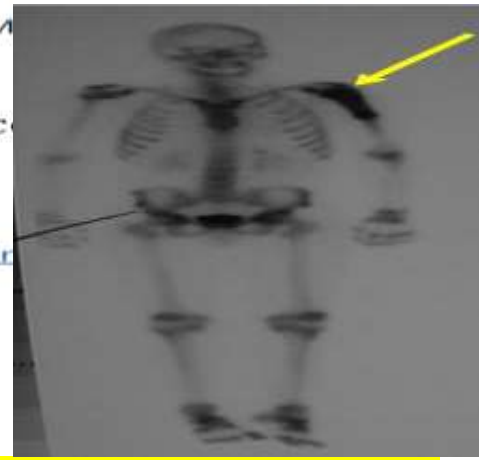
Effectiveness of ^{18}F-FDG PET/CT in the diagnosis, staging and recurrence of Ewing sarcoma family of tumors

A meta-analysis of 23 studies

Tao Huang, MS,[a] Feng Li, BS,[b] Zexing Yan, MD,[c] Yupeng Ma, MS,[a] Fei Xiong, MD,[d] Xia Cai, BS,[b] Qin Fanxiao Liu, MD,[d,f,*] and Jinlei Dong, PhD[f,*]

Monitoring Editor: Tamer Hassan.

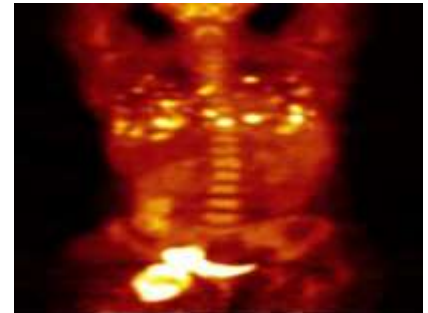


^{18}F-FDG PET AND PET/CT, WITH EXTREMELY HIGH ACCURACY, COULD BE CONSIDERED VALUABLE METHODS FOR DETECTING METASTASIS AND POST-OPERATIONAL RECURRENCE, WHICH MIGHT HAVE A PROFOUND IMPACT ON THE DEVELOPMENT OF TREATMENT PROTOCOLS FOR ESFT.

PET IS SUPERIOR TO BONE SCINTIGRAPHY/WHOLE BODY MRI IN THE DETECTION OF BONE METASTASES OF EWING TUMOURS.

FOR THE DEPICTION OF SMALL LESIONS, MAINLY REPRESENTED BY PULMONARY METASTASES, PET IS LESS SENSITIVE THAN HELICAL COMPUTED TOMOGRAPHY

Gyorke T et al Nucl Med Commun. 2006 Jan;27(1):17-24



METASTATIC WORK UP

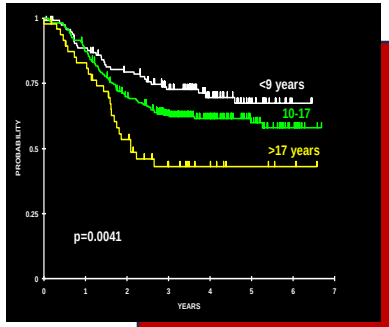
- INCIDENCE OF METASTASIS:-25%
- COMMON SITES:-LUNG,BONE,BONE MARROW
- BONE MARROW INV:-< 10%
- BONE MARROW INV:-POOR PROGNOSIS(SAMPLE TO BE COLLECTED FROM POSTERIOR ILLIAC CREST)

STAGING INVESTIGATIONS AT DIAGNOSIS

Investigation	Primary tumor site	Staging for metastases
Radiograph in two planes, whole bone with adjacent joints	++	At suspicious sites
MRI and/or CT, affected bone(s) and adjacent joints	++	At suspicious sites
Biopsy: material for histology and molecular biology	++	At suspicious sites
Thoracic CT (lung window)		++
Bone-marrow biopsy and aspirates: microscopy (molecular biology still investigational)		++
Whole body 99 m-technetium bone scan	++	++
FDG-PET	±	±

CT, computed tomography; FDG-PET, fluorine-18 fluorodeoxyglucose positron emission tomography; MRI, magnetic resonance imaging; ++, mandatory; ±, indicated, if available.

PROGNOSTIC FACTORS

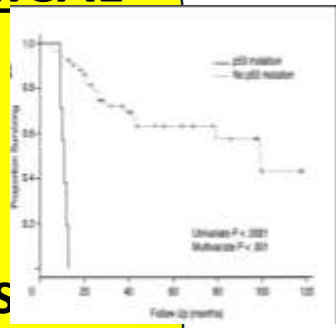


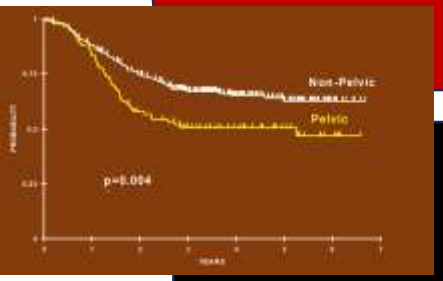
PATIENT FACTORS

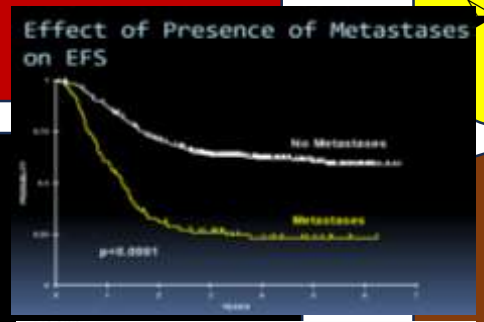
- YOUNGER AGE:- BETTER PROGNOSIS
- FEMALE CHILD:- BETTER PROGNOSIS

PATHOLOGICAL AND BIOCHEMICAL FACTORS

- LDH:- INCREASE-POOR PROGNOSIS
- TYPE-1:-EWS-FL1 TRANSCRIPT-BETTER PROGNOSIS
- HIGH TELOMERASE:-POOR PROGNOSIS
- TP-53 MUTATION:-POOR PROGNOSIS
- DEGREE OF NEURAL DIFFERENTIATION:- NO IMPACT







TUMOR FACTORS

- SITE:- DISTAL EXTREMITY>CENTRAL LESION>PROXIMAL EXTREMITY
- SIZE:-1/PROGNOSIS(>200ml)
- METASTASIS:-POOR PROGNOSIS

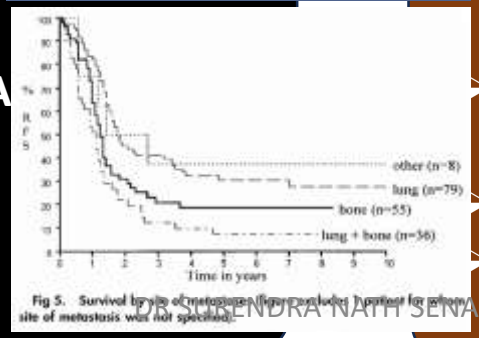


Fig 5. Survival by site of metastases (bone excludes lung/not for whom site of metastasis was not specified).

TREATMENT FACTORS

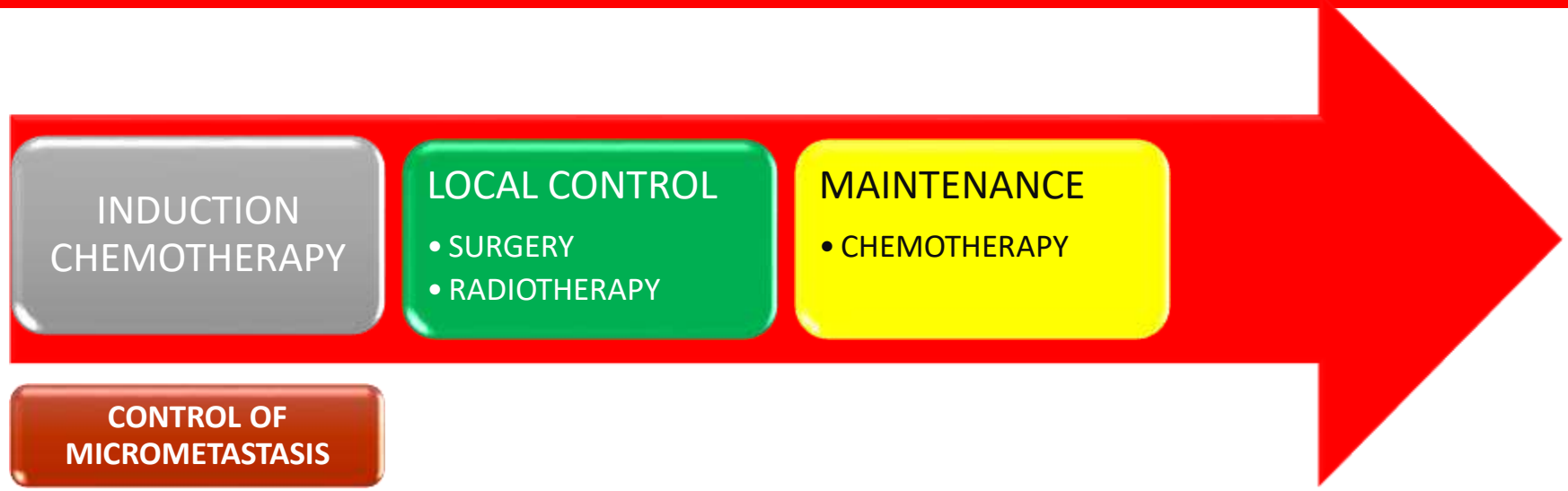
- RESPONSE TO TREATMENT:-CR-BETTER PROGNOSIS
- EXTENT OF EXCISSION
- EXTENT OF NECROSIS

Prognostic Factors in Ewing's Tumor of Bone: Analysis of 975 Patients From the European Intergroup Cooperative Ewing's Sarcoma Study Group
JCO Sep 17, 2000:3108-3114

PROGNOSTIC FACTORS

Disease factors	Favorable prognosis	Unfavorable prognosis
Site	Distal extremity (tibia, fibula, radius, ulna, hands, feet)	Central lesions (especially pelvic bones) less favorable: proximal extremity (humerus, femur), ribs
Size	<8 cm in greatest diameter or <200 mL estimated volume	Larger tumors
Age	<10 yrs	>10 yrs
Soft tissue extension	Absence of radiographically identifiable soft tissue extension	Presence of soft tissue extension by radiograph or significant extension by computed tomography
Molecular factors	Unaltered p53 mutation and p16/p14ARF	p53 mutation and p16/p14ARF homozygous deletion
Extent of disease	Localized	Metastatic
Site of Metastasis	Lung	Bone / bone marrow Both Lung and Bone
Response to CT	Responsive	Unresponsive

STANDARD TREATMENT PROTOCOL



•EVALUATION OF EFFECTIVENESS OF THE REGIMEN.
•DECREASES THE VOLUME OF LOCAL THERAPY FOR SURGERY OR RT.
•SOME BONE HEALING OCCURS DURING CT, DIMINISH THE RISK OF PATHOLOGICAL FRACTURE

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NCCN Guidelines Version 1.2024
Ewing Sarcoma

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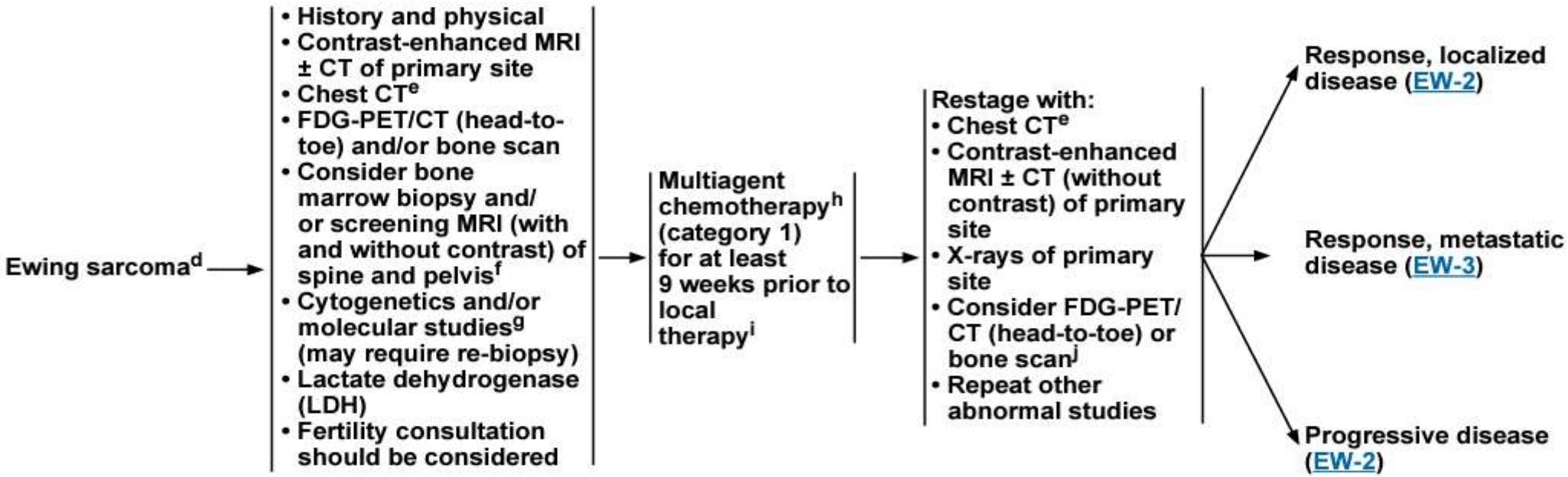

[a] Multidisciplinary Team (TEAM-1).
[b] Principles of Bone Cancer Management (BONE-A).
[c] Ewing sarcoma can be treated using this algorithm, including primitive neuroectodermal tumor of bone, Askin tumor, and extraosseous Ewing sarcoma.
[d] Consider CGP or other fusion panel for Ewing sarcoma to identify translocations if pathologic workup of targeted polymerase chain reaction (PCR), fluorescence in situ hybridization (FISH), or cytogenetics is negative.
[e] Chest CT can be performed with or without contrast as clinically indicated. Non-contrast CT is recommended for restaging.
[f] Campbell KM, et al. Pediatr Blood Cancer 2021;68:e28807.
[g] Ninety percent of Ewing sarcoma will have one of four specific cytogenetic translocations. For patients with Ewing-like sarcoma (eg, *CIC::DUX4, BCOR::CCNB3*) an alternate treatment paradigm can be considered. For those who are negative, additional molecular testing is recommended.

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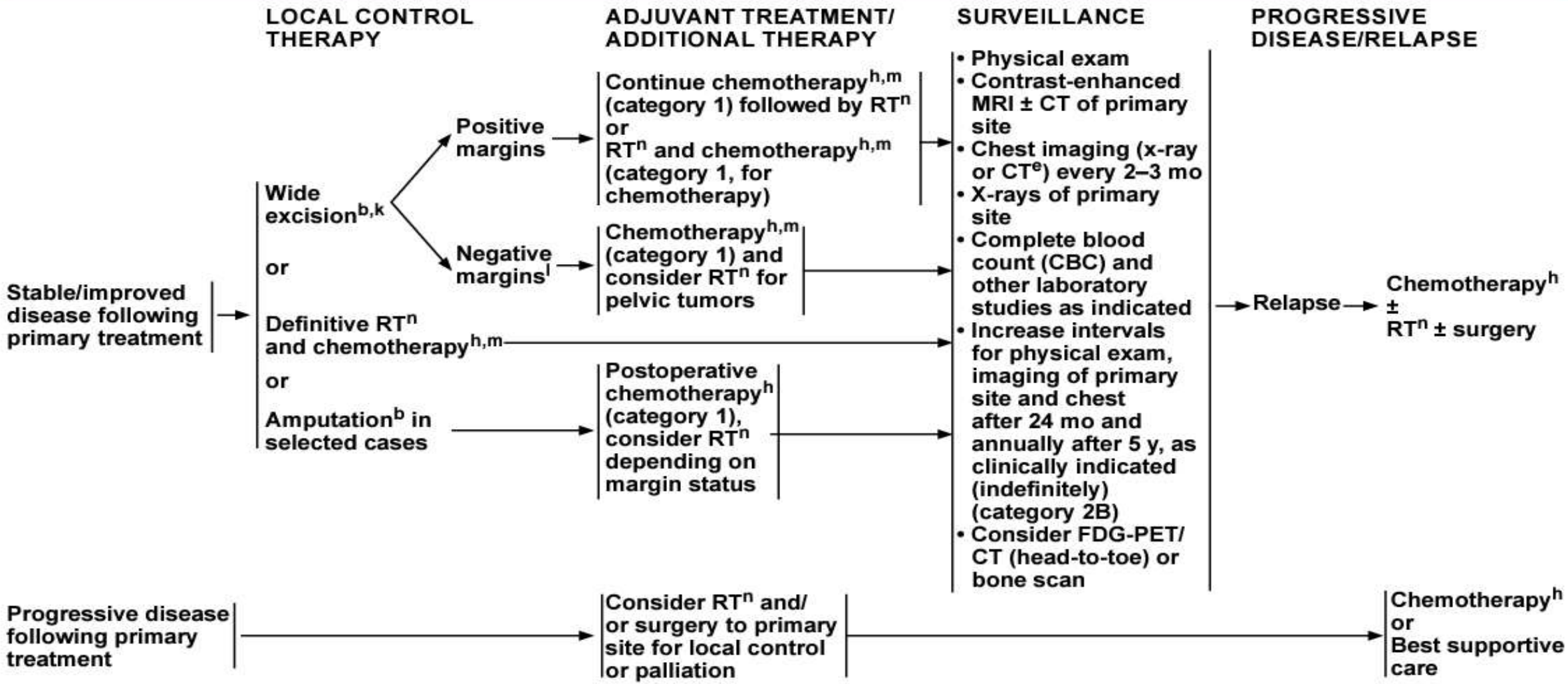
Ewing Sarcoma



[b] Principles of Bone Cancer Management (BONE-A).
[h] Bone Cancer Systemic Therapy Agents (BONE-B).
[e] Chest CT can be performed with or without contrast as clinically indicated. Non-contrast CT is recommended for restaging.
[k] Consider preoperative RT for marginally resectable lesions.
[l] RT may be considered for close margins.

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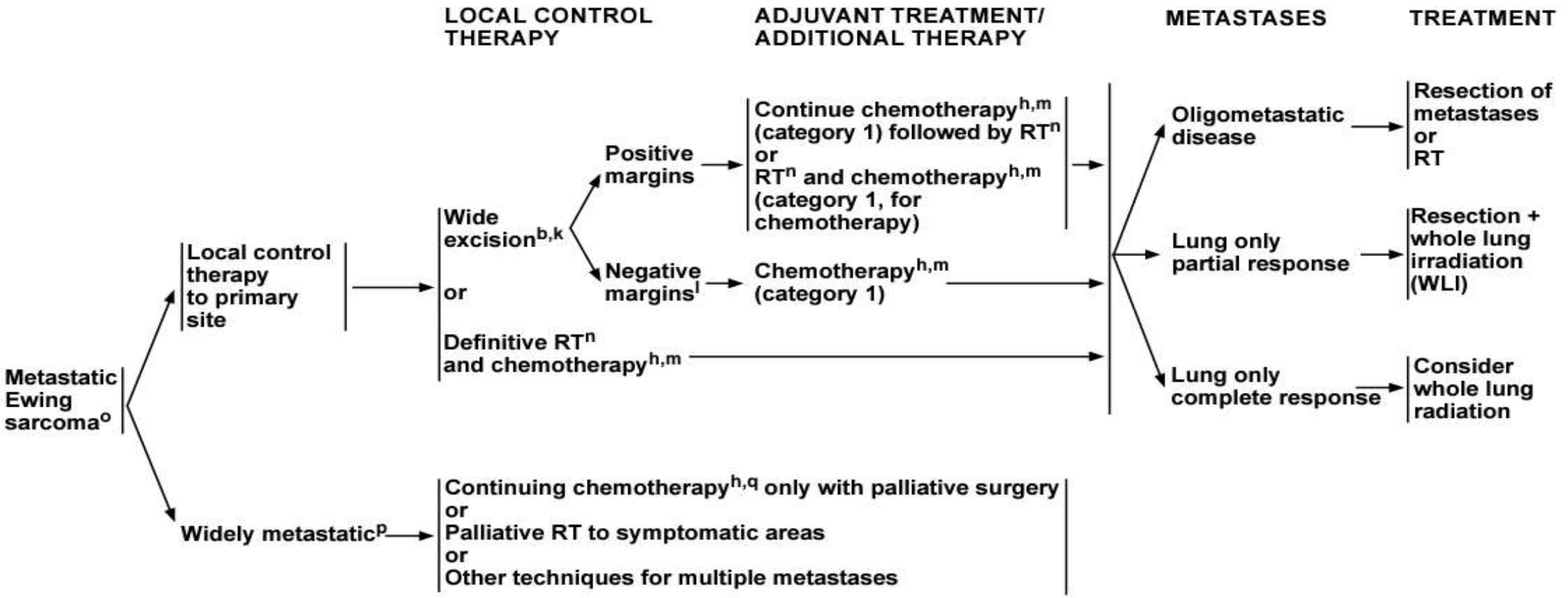


[b] Principles of Bone Cancer Management (BONE-A).
[h] Bone Cancer Systemic Therapy Agents (BONE-B).
[k] Consider preoperative RT for marginally resectable lesions.
[l] RT may be considered for close margins.
[m] There is category 1 evidence for between 28 and 49 weeks of chemotherapy depending on the chemotherapy and dosing schedule used.

NEOADJUVANT CHEMOTHERAPY

- CHEMOTHERAPY IS GIVEN IN TWO PHASES :
  - INDUCTION CHEMOTHERAPY
  - MAINTENANCE CHEMOTHERAPY

- EFFECTIVE CHEMOTHERAPY HAS IMPROVED LOCAL CONTROL RATES ACHIEVED WITH RADIATION TO 85-90%
- ADVANTAGE OF THIS APPROACH:
  - EVALUATION OF EFFECTIVENESS OF THE REGIMEN.
  - DECREASES THE VOLUME OF LOCAL THERAPY FOR SURGERY OR RT.
  - SOME BONE HEALING OCCURS DURING CT, DIMINISH THE RISK OF PATHOLOGICAL FRACTURE.

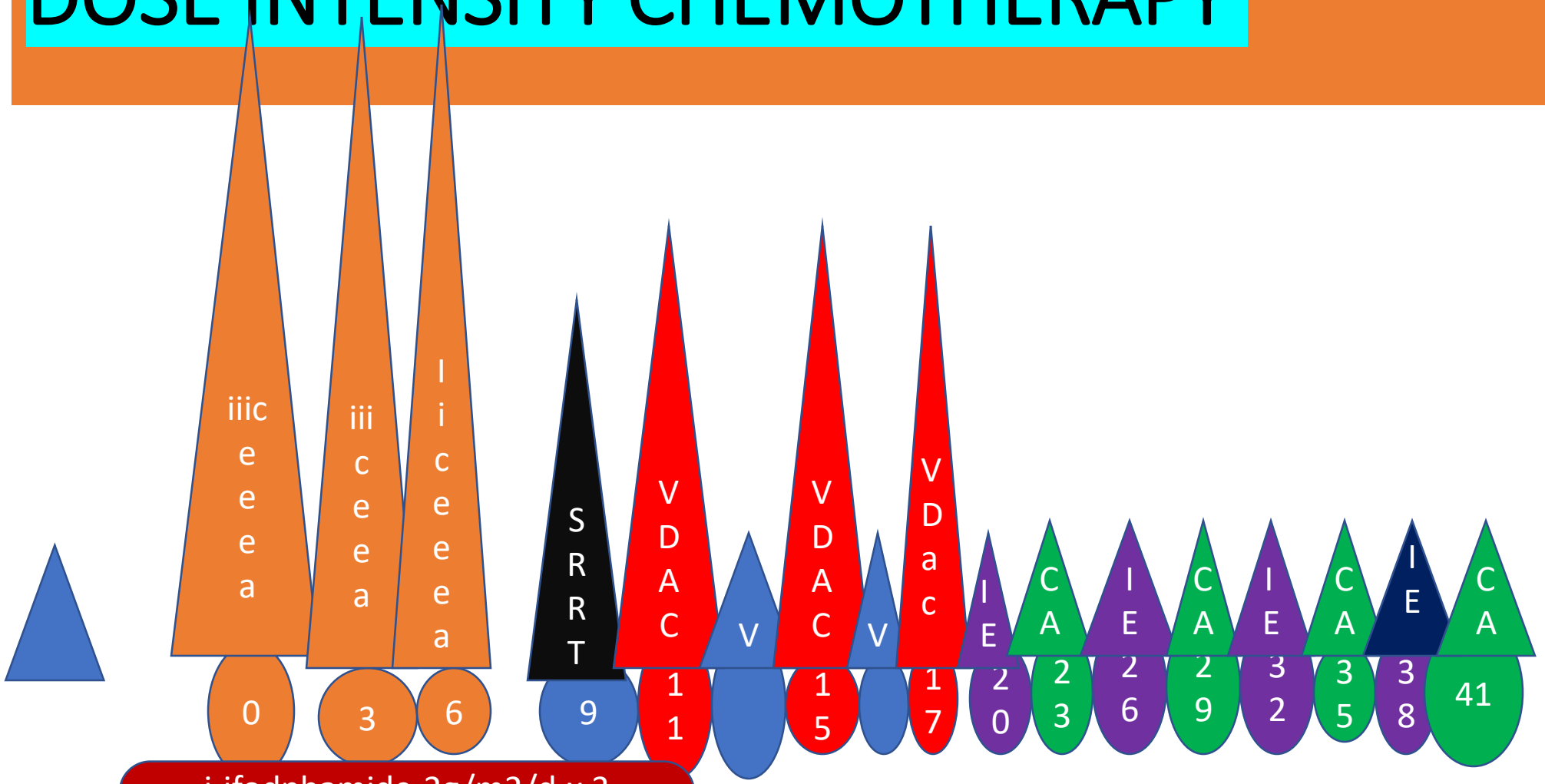
Table 3. Treatment results in selected clinical studies of localized Ewing's sarcoma

Study	Reference	Schedule	Patients	5-year EFS	*p* value[a]	Comme
IESS studies						
IESS-I (1973–1978)	Nesbit et al. [68]	VAC	342	24%		VAC v
		VAC + WLI		44%		
		VACD				
IESS-II (1978–1982)	Burgert et al. [69]	VACD				Value of aggressive cytoreduction
First POG–CCG INT-0091 (198				%	.005	Value of combination IE in localized disease, no benefit in metastatic disease
		+IE	198	69%		
Second CCG (1995-	[98]	VCD + IE 48 weeks	492	75% (3 yrs)	.57	No benefit of dose-time compression
		VCD + IE 30		76% (3 yrs)		

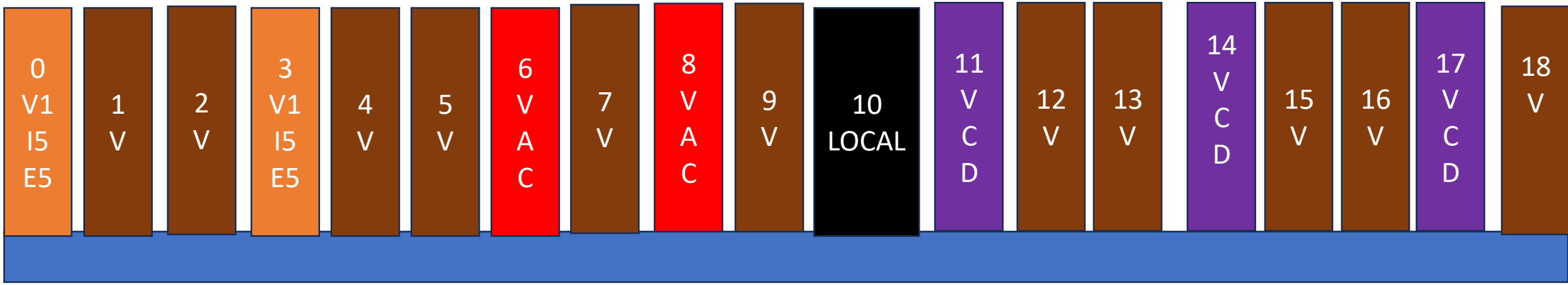
- **IESS-1AND IESS-2 SHOWED 4 DRUG REGIMEN VACD IS SUPERIOR TO 3 DRUG VAC IN TERMS OF RFS AND OS.**
- **POG-COG,INT-OO91:ADDING IE IMPROVED 5-YEAR OS (61→72%) FOR LOCALIZED DISEASE, BUT NOT FOR METASTATIC DISEASE (25%).**

Study	Reference	Schedule	Patients	5-year EFS	*p* value[a]	Comments
CESS studies						
CESS-81 (1981–1985)	Jürgens et al. [67]	VACD	93	<100 ml, 80%; ≥100 ml 31% (both 3 yrs)		Tumor volume (< or ≥100 ml) and histological response are prognostic factors
				Viable tumor <10%, 79%; >10%, 31% (both 3 yrs)		
CESS-86 (1986–1991)	Paulussen et al. [73]	<100 ml (SR): VACD	301	52% (10 yrs)		Intensive treatment with I for high-risk patients. Tumor volume (< or ≥200 ml) and histologic response as prognostic factor
		≥100 ml (HR): VAID		51% (10 yrs)		.
EICESS studies (CESS + UKCCSG)						
EICESS-92 [1992–1999]	EICESS group, personal communication,	SR: VAID vs. VACD	155	68% vs. 61%	.8406	Stage, histologic response, type of local therapy as prognostic factors; randomized comparisons not significant
	May 2004	HR: VAID vs. EVAID	326	51% vs. 61%	.2141	

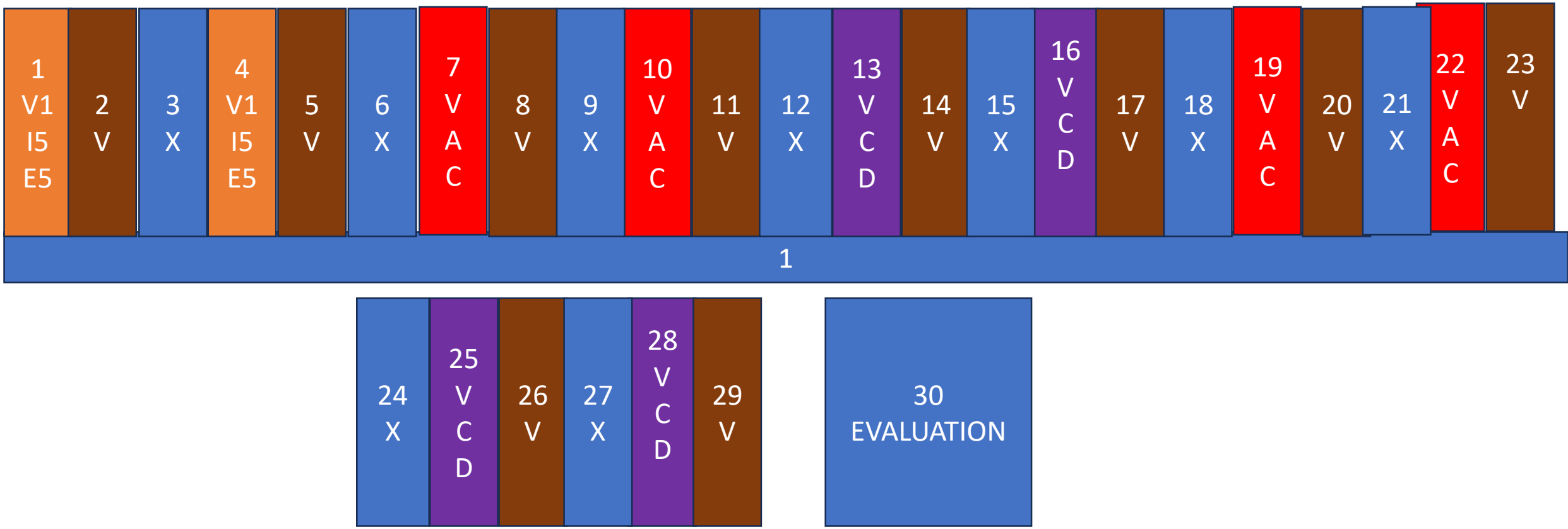
DOSE INTENSITY CHEMOTHERAPY



EFT 2001 PROTOCOL
INDUCTION AND LOCAL THERAPY



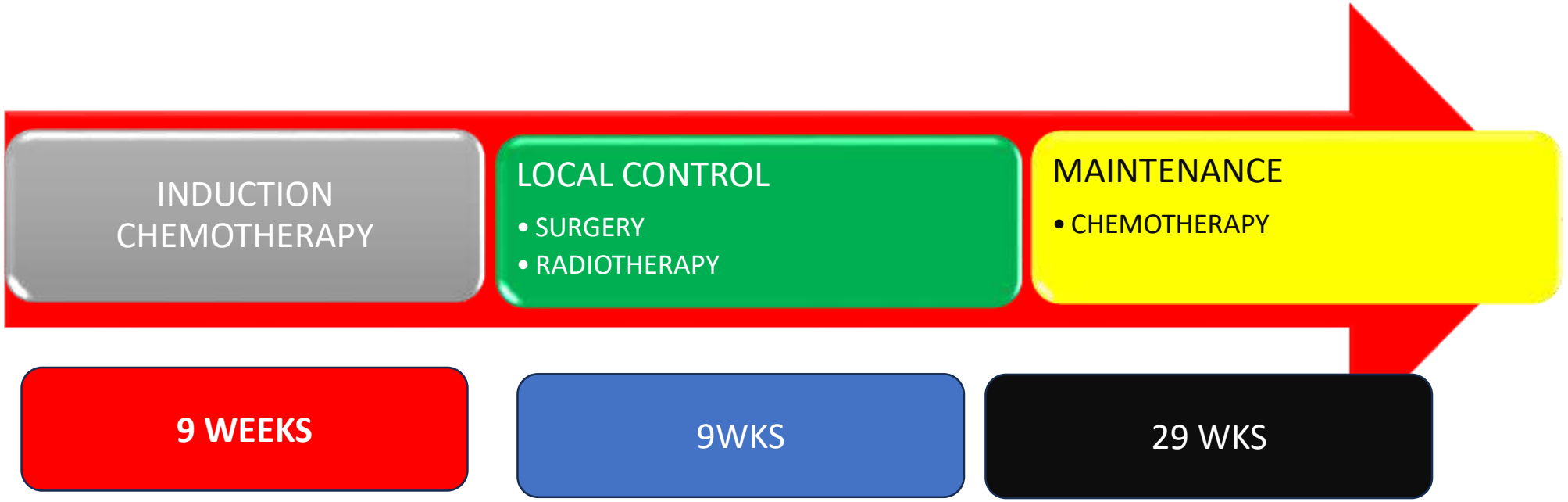
EFT 2001 PROTOCOL MAINTENANCE



CHEMOTHERAPY PROTOCOL EFT 2001

DRUG	DOSE RATE	ROUTE
V=VINCRISTINE	1.5MG/M^2	SLOW IV PUSH OVER 1 MINUTE
I=IFOSFAMIDE	2GM/M^2	500ML NS OVER 1 HOUR
M=MESNA	400MG2	IV PUSH AT 0,3,6 & 9 HOURS OF IFOSTAMIDE START
E=ETOPSODE	100MG/M^2	IN 250 ML NS OVER 1 HOUR
A=ADRIAMYCIN	60MG/M^2	IN 500ML NS OVER 6 HOURS
C=CYCLOPHOSPHAMIDE	600MG/M2	IN 200ML NS OVER 30 MINIUTES
D=DACTINOMYCIN	1GM/M^2	SLOW IV PUSH
G-CSF	5µG/KG/DAY	FOR 10-14 DAYS
X=NO DRUG		
ALL STAGE IV PATIENTS RECEIVED TAMOXIFEN 40MG/M2 DAILY FOR 2 YEARS.		

STANDARD TREATMENT PROTOCOL- DURATION



LOCAL TREATMENT

SURGERY

- EXCISSION
- RECONSTURCTION

- SURGEY Vs RADIATION NO RANDOMIZE TRIAL
- BETTER LOCAL WITH SURGERY
- TREATMENT IS INDIVISUALIZED DEPENDS UPON
  - SITE AND SIZE OF TUMOR
  - ADJ.ANATOMICAL STRUCTURE
  - AGE
  - INDIVIDUAL PREFFERENCE

RADIATION

- DEFINITIVE RT
- PRE OP RADIATION
- POST OP.RADIATION

LOCAL THERAPY

- **RT IN EWINGS SARCOMA: CESS-86 TRIAL**

177 Pts Local ds	Definitive RT	Sx	PORT
%of Pts	25%	22%	53%
Local control	86%	100%	95%
EFS 10yrs	0.50	0.63	0.50
Distant mets	26%	29%	16%

STANDARD TREATMENT PROTOCOL

Induction Chemotherapy

LOCAL CONTROL

- ***SURGERY***
- ***RADIOTHERAPY***

Maintenance

- Chemo

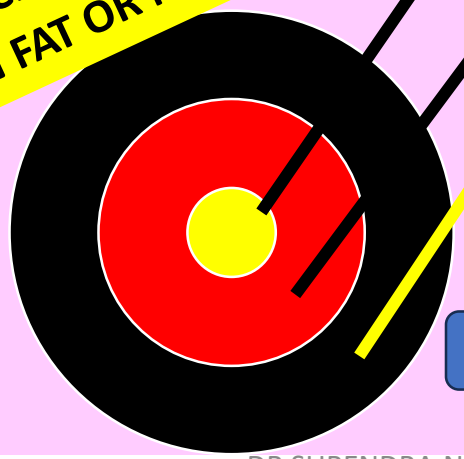
SURGERY (DEPENDS ON LO

CURATIVE SURGERY REQUIRES WIDE LOCAL EXCISION AND NEGATIVE MARGIN
BONY MARGINS OF AT LEAST 1 CM, WITH A 2 TO 5 CM MARGIN RECOMMEND.
SOFT TISSUE AT LEAST 5MM IN FAT OR MUSCLE , WITH 2MM THROUGH FASCIAL PLANES.

ENNEKING CLASSIFICATION OF SURGICAL INTERVENTION

Intralesional resection	Tumor opened during surgery, or surgical field contaminated, or microscopic or macroscopic residual disease
Marginal resection	Tumor removed *en bloc*; however pseudocapsule of
Wide resection	Tumor compartment
Radical resection	ment is removed *en bloc*, for ance amputation in lower leg tumor

From Enneking WF, Spanier SS, Goodman MA. A system for the surgical staging of musculoskeletal sarcoma. Clin Orthop 1980;153:106–120.



INTRALESIONAL(Mi+Ma)

MARGINAL(Mi+P.C)

WIDE EXCISSION

RADICAL RESECTION

RECONSTRUCTION

- DEPENDS UPON LOCATION,AGE,TYPE OF ADJ TREATMENT
- AUTOLOGOUS BONE GRAFT:- FIBULA,PELVIC BONE
- STRUCTURAL BONE ALLOGRAFT
- METALLIC ENDOPROSTHESIS
- ALLOGRAFT-PROSTHETIC COMPOSIT
- ARTHRODESIS

SURGERY

- **DEPENDS ON LOCATION AND EXTENT**
- **TYPE :-EXCISSION AND RECONSTRUCTION**
- **EXCISSION**
  - **INTRALESIONAL RESECTION**
  - **MARGINAL RESECTION**
  - **WIDE RESECTION**
  - **RADICAL RESECTION**
- **RECONSTRUCTION(DEPENDS ON LOCATION,AGE,TYPE OF ADJ,TREATMENT)**
  - **AUTOLOGOUS BONE GRAFT**
  - **STRUCTURAL BONE ALLOGRAFT**
  - **METALLIC ENDOPROSTHESIS**
  - **ALLOGRAFT-PROSTHETIC COMPOSIT**
  - **ARTHRODESIS:-DURABLE**
- **VASCULARISED AUTOGRAFT SHOULD BE AVOIDED IF PLANNING POST OP RADIATION**
- **RESECTION WITHOUT RECONSTRUCTION:-PROXIMAL FIBULA,CLAVICLE,SCAPULLA,ILLIUM,RIB**
- **PERIACETABULAR LESION,AXIAL SKELETON LESION :-AVOID SURGERY**

STANDARD TREATMENT PROTOCOL

Radiotherapy can, in combination with chemotherapy, achieve local control, but complete surgery when feasible has to be regarded as the first choice of local therapy.

RADIATION

PRE OP RADIATION

- TO STERILIZE THE TUMOR COMPARTMENT BEFORE SURGERY
- REDUCE THE RISK O… DISSEMINATIO… SURGERY
- WHE… …CTED MARGIN IS ESPE…

ADV- LOCAL … ROL IMPROVE (LOCAL RECURRENCE WITH PRE-OP RT <5%(EI-CESS-92 : SCHUCK ET AL – IJROBP-1998 & 2003)

DIS – NO BENEFIT IN THOSE WITH WIDE RESECTION

EFFECT OF NACT ASSESSMENT IS LOST

- LARGE …
- …SITE-TUMORS WHERE …ON IS IMPOSSIBLE (FOR …LL, FACE, VERTEBRA, OR PELVIC PRIMARY)WHERE ONLY AN INTRA-LESIONAL RESECTION IS ACHIEVABLE
- PATIENT WITH POOR SURGICAL RISK
- PATIENT REFUSING SURGERY
- FAILURE – 26% WITH RT. SURGERY ± RT – 4 TO 10% (FISS-INT – 001
- PELVIS – RT VS SURGERY – SIMILAR LOCAL CONTROL

POST OP RADIATION

- INTRALESIONAL RESECTION
- MARGINAL RESECTION
- FOR GROSS OR MICROSCOPIC POSITIVE MARGIN
- WIDE RESECTION WITH POOR HISTOLOGICAL RESPONSE TO NEOADJUVANTCHEMO THERAPY (>10% VIABLE TUMOR CELLS IN THE SPECIMEN

BASED ON CESS-81, CESS-86, EICESS-92 STUDIES : SCHUCK ET AL,IJROBP-1998 & 2003

VOLUME,DOSE ,FRACTIONATION SCHEDULE

- PATIENT MAY BE TREATED IN SUPINE ,PRONE, OR LATERAL POSITION SITE DEPENDENT.
- 6MV OF ENERGY USE
- FIELD SHOULD NOT CROSS JOINTS UNLESS ESSENTIAL.
- ENTIRE MEDULLARY CAVITY NEED NOT BE INCLUDED IN THE RT PORTAL.
- TRY AND SPARE A STRIP(1-2CM) OF NORMAL TISSUE FOR LYMPH DRAINAGE(20–30 GY USUALLY CAN BE GIVEN TO ENTIRE CIRCUMFERENCE OF AN EXTREMITY, DOESN'T CAUSE LYMPHEDEMA)
- AVOID GROWTH PLATE(MORE THAN 20 GY CAN PREMATURELY CLOSE EPIPHYSIS)
- FOR RIB PRIMARY ,WITH PLEURAL EFFUSION, RT TO HEMITHORAX
- MINIMUM DOSE SHOULD BE > 40 GY(MICROSCOPIC DISEASE -45 GY,MACROSCOPIC RESIDUAL- 55.8GY)
  - DEFINITIVE RT – 55-60 GY
  - PRE/POST OP RT– 45-55 GY
- # - CONV – 1.8 TO 2 GY
  - HYPER # - NO IMPROVEMENT OF LOCAL CONTROL, BUT ↑ TOXICITIES
- NO NEED OF TOTAL COMPARTMENTAL IRRADIATION
- VOL. -SAFETY MARGIN
- - TUMOUR EXTENSION ON MRI + LONGITUDINAL MARGIN – 2-3 CM, LATERAL MARGIN – 2CM
- - AXIAL TUMOUR – 2CM MARGIN
- SCAR, CONTAMINATED SITE
- LUNG MET. – WHOLE LUNG RT 12-20 GY, NO PROPHYLACTIC PULM. RT
- PALLIATIVE RT TO RELIEVE BONE PAIN & NEUROLOGICAL COMPLICATION

POST OPERATIVE

- ***PTV***: **PHASE I-** PRE CHEMO VOL + 2-3 CM. MARGIN

  PHASE II-POST SX SITE OF RESID.DIS.+2CM

SURGICAL MARGINS	RT DOSE NECROSIS 100%	RT DOSE NECROS.<100 %
Negative	NO RT	45 Gy
Close Marginal	45 Gy/25#/5wks	45 Gy+5.4Gy
R1	45 Gy	45 Gy+5.4Gy
R2	45 Gy+5.4Gy	45 Gy+10.8Gy

Borderline/Un-Resectable

- ***PTV***: **Phase I-** Pre Chemo Vol + 3cm. Margin

  Phase II-Post Sx site of Resid.Dis.+2cm

Response after Induction	**Phase I**	**Phase II**
Complete	45Gy/25#/5wks	No BOOST
>50% Regression	45Gy/25#/5wks	10.8Gy/6#/1wk
<50% Regression	45Gy/25#/5wks	14.4Gy/8#/1.5 wk

POG 8346

- **Purpose:** To determine if ***INVOLVED FIELD RADIATION (IF) IS EQUIVALENT TO STANDARD WHOLE BONE RADIATION (SF)*** in localtumor control; to establish patterns of failure following treatment; and to determine response, event-free survival(EFS), and overall survival rates from multidisciplinary therapy in Ewing's sarcoma.
- **RESULTS** AND **CONCLUSIONS**
- There ***WAS NO DIFFERENCE IN LOCAL CONTROL*** between those randomized to SF vs. IF.
- Adequate IF radiotherapy requires treatment to appropriate volumes as defined by MRI imaging and full radiation doses.

- ***AS MOST FAILURES IN EWING'S SARCOMA ARE SYSTEMIC, IMPROVED EFS REQUIRES MORE EFFECTIVE SYSTEMIC CHEMOTHERAPY.***

HYPERFRACTIONATION

- In CESS 86, dunst j et al ijrobp 1995 vol 32 pp 919-30

	Std RT	HFRT
5 yr EFS	53%	58%
5 yr LC	76%	86%
5 yr OAS	63%	65%

ROLE OF LUNG BATH IN PULMONARY METS

- **SURVIVAL ANALYSIS OF 171 PATIENTS FROM THE EICESS STUDIES.** PAULUSSEN M, ET AL ANN ONCOL. 1998 MAR;9(3):275-81.
- **WLI IMPROVED OUTCOME IN CASE OF ISOLATED PULMONARY INVOLVEMENT (0.40 VS. 0.19, P < 0.05). IN PM-PTS WITH COMBINED PULMONARY/SKELETAL METASTASES, INTENSIFICATION BY MEGATHERAPY AND/OR WLI IMPROVED EFS FROM 0.00 TO 0.27 (P = 0.0001).**
- **RT TARGET VOLUME : B/L LUNG. NO CARDIAC SHIELD. *DOSE 12.6 GY/7#, 1.6 GY/#***

SIDE EFFECTS

- FUNCTIONAL RESULTS : OF ALL THE PATIENT'S TREATED WITH RT
  - 60 % HAVE GOOD FUNCTIONAL ACTIVITY
  - 20 % HAVE MILD MORBIDITIES
  - 20 % HAVE SIGNIFICANT MORBIDITIES
- RISK FOR POST TREATMENT FRACTURES
- LYMPHEDEMA
- DERMATITIS; RECALL REACTION MAY OCCUR WITH DOXORUBICIN, DACTINOMYCIN.
- ADRIAMYCIN CARDIOMYOPATHY.
- IFOSPHAMIDE RENAL TOXICITY.
-

SECOND MALIGNANCY AFTER RADIATION

- SECOND MALIGNANCY AFTER RT
  - CUMULATIVE RISK AT 15YRS = 6 – 6.7%
- ***(CESS-81 & CESS-86; IJROBP:1997; 39)***
  - NO SECONDARY SARCOMAS SEEN AT DOSES <48 GY
- ***(KUTTERCH ET AL; JCO:1996, 14)***
  - RISK INCREASED BY ANTHRACYCLINE AND ALKYLATING AGENT CHEMOTHERAPY
  - OSTEOSARCOMA MOST COMMON.
  - LEUKEMIA CAN ALSO OCCUR.

ON SUMMARY

TABLE IV. Summary of Recommendations on Post-Operative RT

Indications	Gross or microscopic positive margins
	Clear margins but poor histopathological response to chemotherapy (necrosis <90% is the suggested minimum threshold, but <95–99% may be used based on institutional practice)
Timing	Within 6–8 weeks of surgery (though there is no evidence to suggest that a further delay leads to inferior outcomes)
Dose	45 Gy to the pre-chemotherapy volume
	10.8 Gy boost to areas of gross tumor residual
Fractionation	Standard daily fractionation of 1.8 Gy per fraction
	Hyperfractionated RT (with equivalent total dose) may be used to reduce long term side effects
Target volume	Initial phase (45 Gy): pre-chemotherapy tumor volume on MRI with 1.5–2 cm margins. Appropriate modifications should be made in tumors expanding into cavities or the lung
	Boost phase (10.8 Gy): post-operative gross residual disease with 1.5–2 cm margins

SECOND MOST COMMON CHILDHOOD PRIMARY BONE TUMOR.

ES FAMILY:- ES,ESES,PNET,ASKIN

ARISES FROM META DIAPHYSIS

AGE:-SECOND DECADE,M:F=1.2:1

COMMONEST SITE:- FEMUR,PELVIS

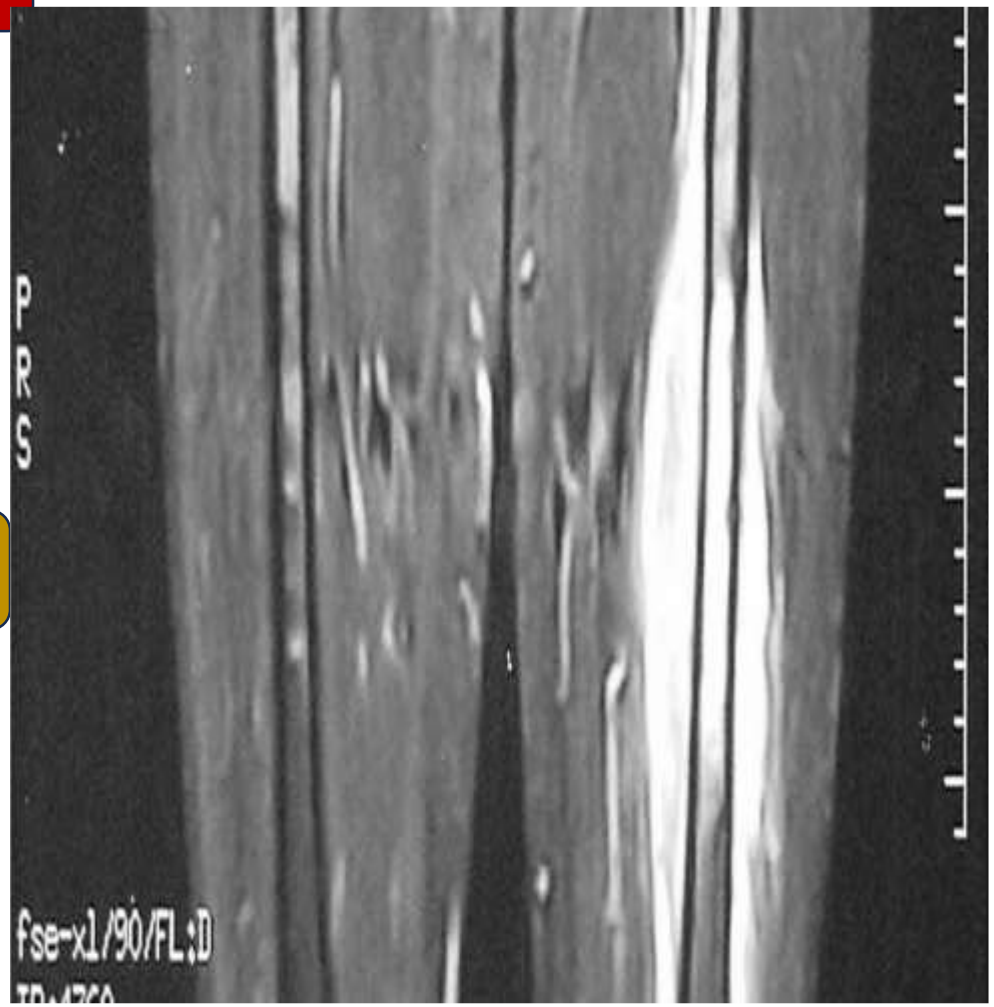
METASTASIS:-255(LUNG COMMON)

t(11;22) (q24;q12)

C/F;- PAIN,SWELLING,CONSTITUTIONAL SYMPTOMS

DIAGNOSIS; OPEN BIOPSY,IHC,GENETICS,MRI,CT,LDH,BONE MARROW

Lytic lesion with onion peel appearance on X-Ray



CORE / OPEN BIOPSY

SMALL / ROUND CEL, HOMER WRIGHT PSEUDOROSETTE

CD 99 +VE ,95-100% DIFFUSE MEMBRANE STAINING

GRADING BASED ON TUMOR DIFFERENTIATION, MITOTIC COUNT, NECROSIS (GI-2-3,G2-4-5, G3-6/MORE

CT NECROSIS – HUVOS –I<50, II-50-90%, III-90-99%, IV-100%
POG-1-0, IIA-1-10, B-11-90, III-91-99, IV-100

PNET-NSE, S.100, SYNA,MIC-2
E-S- MIC 2+, PAS+
LYMPHOMA-CD45+Ve, RETICULIN +Ve
RHABDO-DESMIN

METSDIAPHYSIS, SOFT TISSUE → ONION PEEL

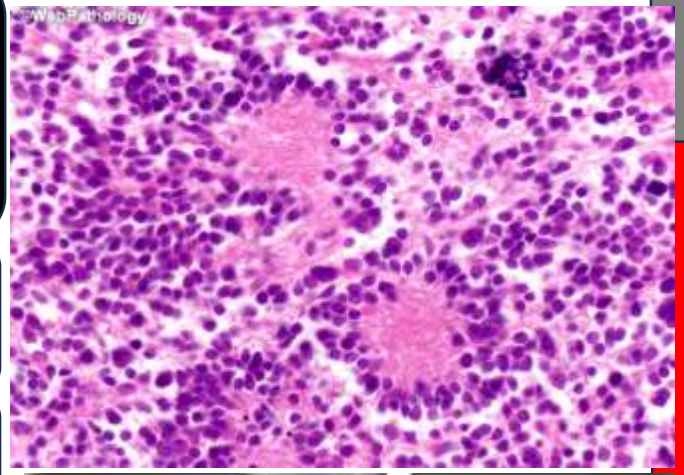
MRI T1 → MEDULLARY CAVITY, T2 EXTRA OSSEUS

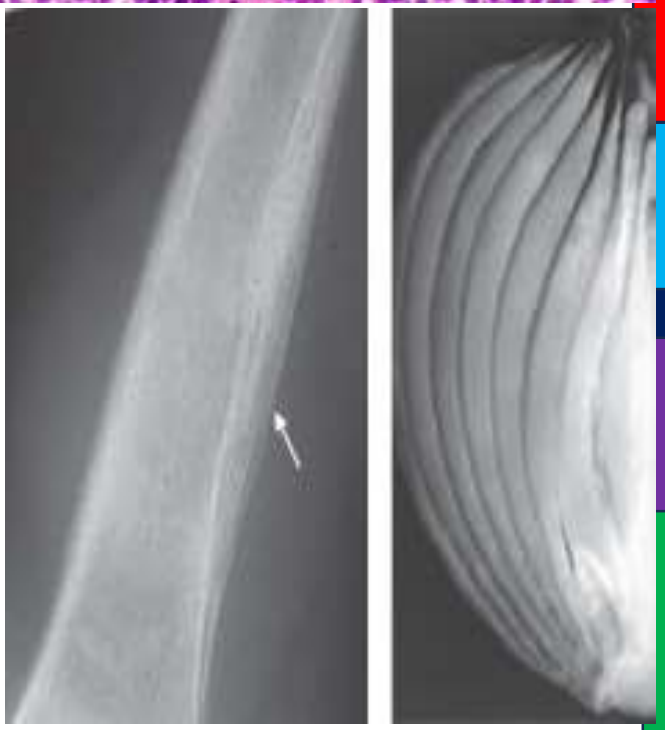
PET-DIST. BONY MET, PULM – HELICAL CT

PROGNOSIS –ASSES SITE, SIZE, SITE OF MET. , LDH, TELOMERASE, RESPONSE TO CT, EXTENT OF SUGERY

TREATMENT – INDUCTION, LOCAL RX, MAINTENANCE

CT PROTOCOL-DOSE INTENSITY CT / EFT PROTOCOL
VCR ,IFO, ETO, CYC, ADRIA, DACTI





INDUCTION -90 WKS, LOCAL 9 TO 18 WKS, MAINTENANCE-29 WKS

SX- EXCISION, RECONSTRUCTION
EXCISION-INTRALESIONAL, MARGINAL, WIDE RESECTION, RADICAL RESECTION
RECONSTRUCTION-AUTOLOGUS, ALLOGRAFT, METALLIC
BONY MARGIN-1CM, SOFT TISSUE-5MM, FASCIAL PLANE-2MM

DEFINITIVE RT- UNFAVOURABLE SITE, POOR SURGICAL RISK, REFUSES SRUGERY

PRE-OP RT – NARROW RESECTED MARGIN

POST RT- INTRALESIONAL/MARGINAL RESECTION, +VE MARGIN, POOR HP REPORT

SHOULD NOT CROSS JOINT
DO NOT GIVE RT TO ENTIRE MEDULLARY CAVITY, SPARE A STRIP – 1-2 CM
AVOID GROWTH PLATE

DOSE
DEFINATIVE-55-60GY, POST OP RT-45-55GY, LUNG MET-12.6GY/7#


THANK
YOU