Osteosarcoma : An Overview

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Osteosarcoma

- Osteo =Bone or Osteoid tissue
- Sarcoma +Malignant tumour of connective tissue



Osteosarcoma

- > Definition
- > Meaning of osteosarcoma
- > What is osteosarcoma ?
- > Microscopic appearance
- > Epidemiology
- > Skeletal distribution
- > Clinical presentation
- > Evaluation
- Plain X-Ray
- Classification
- > Treatment
- > Chemotherapy
- Conclusion

Epidemiology & Risk Factors

- Most common malignant bone tumour of children & adolescents
- Bimodal age : early adolescents & after 65 years
- Male : Female 1.2 : 1
- Etiology : unknown but relationship with rapid bone growth as peak at adolescent age (growth spurt time) when increase in bone length as metaphysis of distal femur, proximal tibia and proximal humer
- Risk factors:
 - Radiation in childhood >10 yrs back
 - Chemotherapy Alkylating agents
 - Benign bone lesion as Paget's, ch. Osteomylitis, osteochondroma

Osteosarcoma

Primary malignant tumours of bone are rare and constitutes only 0.2 % of all cancer

Osteosarcoma	-	35%
Chondrosarcoma	_	30%
Ewings sarcoma	-	15%
Othes	-	20%

Osteosarcoma is highly malignant tumour arising from primitive mesenchymal bone forming cell.



Osteosarcoma

Malignant tumor characterized by production of osteoid by malignant cells.

composed of sarcomatous stroma & malignant osteoblasts that directly form tumor osteoid , although fibrous or cartilagenous elements coexists or predominate.

arises in the *metaphysis of long bone* where normally growth is more active.

Bone tumours as per cell of origin

Bone-forming tumors

(malignant)

- > Osteosarcoma
- Central (medullary)
- Peripheral (surface)
- Paraosteal
- Periosteal
- High grade surface

Marrow tumors (malignant)

- Ewing's sarcoma
- Neuroectodermal tumour
- Malignant lymphoma of bone (Primary/secondary)
- Myeloma

Cartilage-forming tumors

(malignant)

> Chondrosarcoma

- Differentiated chondrosarcoma
- Juxta-cortical chondrosarcoma
- Mesenchymal chondrosarcoma
- Clear cell chondrosarcoma

Vascular tumors (malignant)

- Angiosarcoma
- Malignant haemangio pericytoma

Other tumors (malignant)

- Chordoma
- Adamantinoma

Classic High Grade Osteosarcoma

- These aggressive, high-grade tumors begin in an intramedullary location, but may break through the cortex and form a soft-tissue mass.
- The histologic hallmark malignant osteoblastic spindle cells producing osteoid, presence of woven bone with malignant appearing stromal cells
- subtypes -
- osteoblastic,
- chondroblastic
- o fibroblastic



STAGING OF OSTEOSARCOMA

Stage	Grade	Site	Metastases	
Enneking Staging System				
IA	Low	Intracompartmental	None	
IB	Low	Extracompartmental	None	
IIA	High	Intracompartmental	None	
IIB	High	Extracompartmental	None	
Ш	Any	Any	Present	
Stage	Grade	Local extent (cm)	Metastases	
AJCC Staging System ^a				
IA	Low	≤8	None	
IB	Low	>8 or discontinuous	None	
IIA	High	≤8	None	
IIB	High	>8	None	
III	High	Discontinuous	None	
IVA	Any	Any	Pulmonary metastases	
IVB	Any	Any	Other metastases	

^aUsed with the permission of the American Joint Committee on Cancer, Chicago, Illinois. The original source for this material is *AJCC staging cancer handbook*, 7th ed. New York, NY:

Pathological Evaluation

- Presence of malignant sarcomatous stroma with osteoid (immature bone)
- Osteosarcoma arises from mesenchymal stem cell tissue, so has fibrous tissue, cartilage & bone matrix and bone matrix differentiates osteosarcoma from chondrosarcoma and fibrosarcoma.
- Two main category:
- 1.Conventional (intramedullary) : High grade, 90% adolescents Four subtypes – osteoblastic, chondroblastic, fibroblastic, mixed subtypes
- 2.Surface : three subtypes :

Parosteal(low grade) Periosteal (intermediate grade)-20% transformation High grade surface

3.Rare variety: Extraosseous from soft tissue with h/o radiation exposure

Clinical Presentation & Diagnostic Evaluation

- Localized pain of long duration , waxing & waning
- Soft tissue swelling/mass near knee /shoulder joint
- 10-20% present as macrometastasis
- Common site of metastasis are lung and bone

Diagnostic Evaluation :

X-ray bone : Destruction of normal trabeculae pattern with lytic / sclerotic lesion

Osteoid formation under periosteum(codman triangle)

Ossification of soft tissue

MRI of affected bone : extent of lesion, ST component, neurovascular bundle and joint

CT scan of chest :

Bone scan :

PET scan :

Biopsy from center of tumour :



Conventional Radiography

- medullary and cortical bone destruction
- wide zone of transition, permeative or moth-eaten appearance
- aggressive periosteal reaction
- sunburst type
- Codman triangle
- lamellated (onion skin) reaction: less frequently seen
- soft-tissue mass
- tumour matrix ossification/calcification
- variable: reflects a combination of the amount of tumour bone production, calcified matrix, and osteoid
 - ill-defined "fluffy" or "cloudlike" cf. to the rings and arcs





. A: Plain radiograph of a distal femur osteosarcoma showing a lytic region and Codman triangle in the medial distal femur. B: Magnetic resonance image scan of the same lesion.



Plain radiograph of a sclerotic pelvic osteosarcoma.

MRI of extremity



Treatment

Radiological staging

Biopsy to confirm diagnosis

Preoperative chemotherapy

Repeat radiological staging (access chemo response, finalize surgical treatment plan)

Surgical resection with wide margin

Reconstruction using one of many techniques

Post op chemo based on preop response

Treatment

- Chemotherapy plays critical role
- 10-20% metastatic disease at presentation but majority have subclinical metastasis. Before CT era 80-90% develop distant metastasis despite local control
- For low grade : Surgery alone –wide resection and reconstruction , rarely enblock resection or amputation
- For Intermediate & high grade : NACT is standard of care followed by limb sparing surgery and adjuvant CT. if localized disease 60-70% 5 yr OS, if solitary lung mets 35-40% 5 yr OS if extensive lung mets < 20% 5 yr OS

CHEMOTHERAPHY:

- > Chemo cannot control clinically detectable disease.
- Radiation is ineffective.
- Local control is surgical

The drugs used most often to treat osteosarcoma are: Methotrexate with leucovorin (colonic acid) Doxorubicin (Adriamycin) Cisplatin or carboplatin Etoposide Ifosfamide Cyclophosphamide Actinomycin D (dactinomycin) Bleomycin

Chemotherapy

Study	Treatment	Local Control (%)	Relapse Free Survival (%)	Remarks
MIOS (High grade ex tremity) (NEJM1986, 314,1600-06)	Sx→Obs Sx→CT		17 66 (at 2 yr)	*Add of CT BCD+Mtx+ CDDP+Doxo
POG-8651 (JCO 2003,21,1574-80)	$Sx \rightarrow CT$ NACT $\rightarrow Sx \rightarrow CT$			No diff. OS,RFS, limb salvage
Italian Trial (EJC Clin Oncol 1986, 22, 1337-45) UK Children Cancer Study Group (Med Ped Oncol 1987,15,69-70)	 Dose of Mtx 200mg/m2 vs 2000mg/m2. no advantage of HD-Mtx Dose of Mtx 690mg/m2 vs 7500mg/m2. no advantage of HD-Mtx & Mtx does not contribute in disease control 			
European OsteoSA Intergroup (n=198) (JCO 1994,12,1137-49)	HD-Mtx+Doxo+CDDP Doxo+CDDP \rightarrow Sx		41 57 at 5 yr	

Chemotherapy

Study	Treatment	Local Control (%)	RFS (%)	Remarks
COSS-80(Ger-Aus- Swiss Co-op OsteoSA Study Group (JCO 1984,2,617-24)	$Mtx+Dox+CDDP(MAP) \rightarrow Sx$ Dox+Mtx+BCD \rightarrow Sx			No difference
COSS-82 (JCO 1988,6,329-37)	$Mtx+Dox+CDDP(MAP) \rightarrow Sx$ $Mtx+BCD \rightarrow Sx$			Early start of Doxo+CDDP improves DFS
European OsteoSA Intergroup (n=391) (Lancet 1997, 350, 911-17)	Doxo+CDDP \rightarrow Sx BCD \rightarrow Sx			No difference in OS, DFS. BCD abandoned
European OsteoSA Intergroup(n=497) (JNCI 2007,99,112-28)	Doxo+CDDP→Sx (@2weekly) Doxo+CDDP→Sx (@3weekly)			No advantage of dose dense regimen

Chemotherapy

Study	Treatment	Local Control (%)	RFS (%)	Remarks
Italian Sarcoma Group(n=246) (JCO 2012,30,2112-18)	MAP→Sx MAP+Ifos→Sx			No difference in RR, RFS, OS. Ifos to be added in poor response gp
North America Intergroup (n=677) (JCO 2005, 23,2004-11)	MAP→Sx MAP+Ifos→Sx			No difference in RR, RFS,OS .No advantage of addition of Ifos
French society Ped Oncol Study(n=234) OsteoSA 94 (EJC 2007,43,752-66)	HD-Mtx+Doxo HD- Mtx+Ifos+Epi			Single agent Doxo is not useful & CDDP to be added. High degree of tumour necrosis with Ifos
EURAMOS-I (Loncet Oncol 2016, 17, 1396-1408)	MAP→Sx if >10% viable tumour →MAP+IE			Addition of Ifos+Epirubicin does not improve outcome



- MAP(Mtx+Adria+Cisplatin) is standard of care chemotherapy
- Ifosfamide is an active agent to added after MAP chemotherapy in poor responders

(JCO 1998,16,3641-48) (JCO 2012,30,2112-18)

• Ifosfamide with Epirubicin is most active 2nd line regimen for recurrent and metastatic osteosarcoma

(JCO 2002,20,426-33)

 Docetaxel+Gem is another active regimen used as 2nd or 3rd line for recurrent and metastatic osteosarcoma

Surgery

- Complete enblock resection of tumour with limb sparing to maintain limb function
- No advantage of amputation over limb sparing surgery with adequate negative margin

Contraindication of limb sparing surgery:

- 1. Neurovascular bundle encasement
- 2. Biopsy related large hematoma
- 3. Pathological fracture

Reconstructive options : Allografts, Endoprosthesis, Rotation plasty Pelvic tumours have poor prognosis than extremity.

Type of Surgery in pelvic osteosarcoma : Internal hemipelvictomy –Resection of hemipelvis with extremity preservation External hemipelvictomy–Enblock resection of hemipelvis or hind quarter amputation if Ro resection not possible

Radiation Therapy

- Chemotherapy & optimal surgery obviates the need of RT
- Relatively radio resistant tumour
- High local failure with Radiation alone
- With effective NACT and specialized surgical technique with negative margin leads to 90-95% local control
- Preop RT +CT+Sx vs. CT+Sx (no benefit of RT in retrospective series)
- In Cross study (n=100) 5 yr LC =22% in CT+RT vs 44% with addition of Sx to CT+RT
- Indication of Radiation therapy :
 - Tumour resection with inadequate or positive margin
 - Unresectable tumour
 - Incomplete tumour resection in difficult location as pelvis, spine and skull
 - If patient requires amputation but refuses ,so. RT is used for local control

Radiation Therapy

- Proper immobilization with VAC lock and cast
- 4-5cm margin for extremity and 2 cm for axial lesions dose for microscopic - 60Gy/30# for macroscopic - 66Gy/33# for gross disease - 70Gy/35#
- EBRT by photon : 3D-CRT/IMRT
- Intra operative Radiation Therapy(IORT)
- Proton Beam Therapy
- Palliation by radionuclide therapy using samarium, Strontium
- For dose response relation experiment shown that >90Gy required for tumour control(MGH series), so Extracorporeal Radiation Therapy

Radiation Therapy

Whole Lung Irradiation (WLI):

In pre chemotherapy era WLI (20Gy/20#) was found useful in improving DFS and OS, but now in effective CT era two RCT (EORTC-20781 and SIOP-03, n=240) no advantage in DFS and OS with WLI, so WLI has been abandoned now.

Care Management of Osteosarcoma

- Preoperative preparation (crucial)
- Support during adjustment to concept of amputation, surgical resection
- Body image concerns: issues of adolescents
- Pain management
 - Phantom limb pain

Follow up

- Regular CT/MRI of primary site
- X-ray and CT chest
- Physiotherapy to avoid fibrosis