

What's New in Orthopedic Oncology

Nader A. Nassif M.D.
OrthoCalifornia
Hoag Orthopedic Institute
Hoag Family Cancer Institute

I have no financial Disclosures

Outline

- New innovations in diagnosis in Orthopedic Oncology
- Surgical Management of Soft Tissue Sarcoma
 - Soft tissue Margin Assessment
- Surgical Management of Bone Sarcoma
 - 3D Navigation
 - Custom Jigs
 - 3D Printed Implants/tumors for planning
- Metastatic disease

Soft Tissue Sarcoma Epidemiology

- 12,000 cases per year diagnosed
- 3.2/100,000
- < 1% of all new cancer diagnoses
- Men > Women (1.42:1)



Soft Tissue Sarcoma Epidemiology

- Age:
 - Mostly Adults with some exceptions
 - 15% younger than 15 yo
 - 40% older than 55 yo
- Location
 - **60% extremity**
 - 20% trunk
 - 20% retroperitoneum, head and neck



Bone Sarcoma Epidemiology

- Malignant: 2,500 cases per year 30-40% mortality

Primary Bone Tumors

0-5	Metastatic Neuroblastoma Rhabdomyosarcoma
5-20	Osteogenic Sarcoma; Ewing's and Chondroblastoma
20-30	Giant Cell Tumor
30+	Chondrosarcoma & Soft Tissue Sarcoma
60+	Metastatic Carcinoma, Multiple Myeloma, Lymphoma

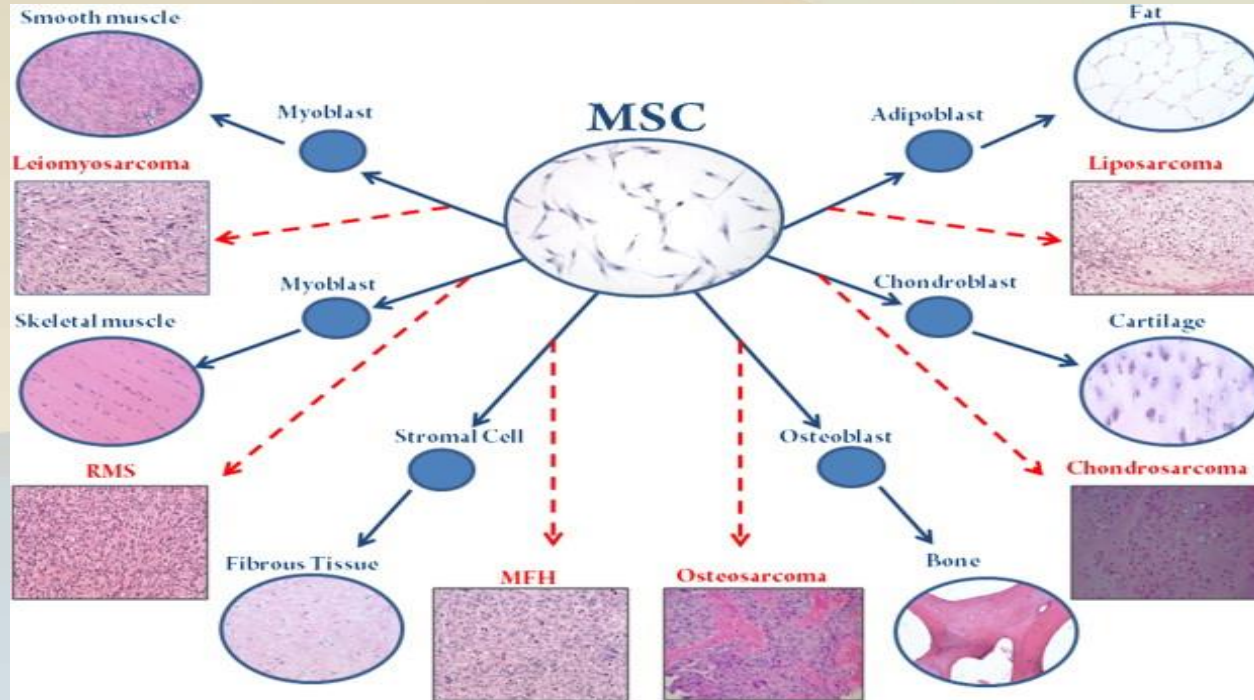


Primary Bone Tumor location

Epiphysis	Chondroblastoma (Immature) Giant Cell Tumor (Mature)
Metaphysis	Osteogenic Sarcoma Chondrosarcoma
Diaphysis	Ewing's Sarcoma, Adamantinoma (Tibia)
Flat Bones	Chondrosarcoma Ewing's Sarcoma
Paraosteal	Osteogenic Sarcoma Chondroma



Sarcoma!



Genetic Translocations

Sarcoma Type	Chromosomal Translocation	Fusion Gene	Year Reported
Ewing sarcoma	t(11;22)(q24;q12)	<i>EWS-FLI1</i>	1992
	t(21;22)(q22;q12)	<i>EWS-ERG</i>	1993
Clear cell sarcoma	t(12;22)(q13;q12)	<i>EWS-ATF1</i>	1993
Desmoplastic small round cell tumor	t(11;22)(p13;112)	<i>EWS-WT1</i>	1994
Extraskeletal myxoid chondrosarcoma	t(9;22)(q22;q12)	<i>EWS-CHN</i>	1995
Myxoid/round cell liposarcoma	t(12;16)(q13;p11)	<i>TLS-CHOP</i>	1993
Angiomatoid fibrous histiocytoma	t(12;16)(q13;p11)	<i>TLS-ATF1</i>	2000
Alveolar rhabdomyosarcoma	t(2;13)(q35;q14)	<i>PAX3-FKHR</i>	1993
	t(1;13)(p36;q14)	<i>PAX7-FKHR</i>	1994
Extraskeletal myxoid chondrosarcoma	t(9;17)(q22;q11)	<i>TAF2N-CHN</i>	1999
Synovial sarcoma	t(X;18)(p11;q11)	<i>SYT-SSX1,2</i>	1994
Dermatofibrosarcoma protuberans	t(17;22)(q22;q13)	<i>COL1A1-PDGFB</i>	1997
Congenital fibrosarcoma	t(12;15)(p13;q25)	<i>ETV6-NTRK3</i>	1998
Inflammatory myofibroblastic tumor	t(2p23)	Various ALK fusions	2000
Alveolar soft part sarcoma	t(X;17)(p11;q25)	<i>ASPL-TFE3</i>	2001
Endometrial stromal sarcoma	t(7;17)(p15;q21)	<i>JAZF1-JJAZ1</i>	2001

Genetic Markers For Diagnosis

- MDM-2 - Liposarcoma
- STAT-6 - Solitary Fibrous Tumor
- TLE-1 - Synovial Sarcoma
- TFE- 3 - Aleolar Sarcoma of Soft parts
- INI -1 - Epitheiloid Sarcoma
- Sox-10



Genetic Markers for Diagnosis

- MDM-2/CDK 4 Osteogenic Sarcoma
- CD 99/O-13 Ewing's Sarcoma
- FGFR-23 Fibrous dysplasia
- H3F3 ABC



Diagnostics

- Increasing reliance on Genomic Analysis



FOUNDATION **ONE**

Hoag
Orthopedic
Institute



Patient Name
Not Given

Report Date
11 November 2015

Tumor Type
Bone marrow
multiple myeloma

Date of Birth	Not Given	Medical Facility	Not Given	Specimen Received	Not Given
Sex	Not Given	Ordering Physician	Not Given	Specimen Site	Bone Marrow
FMI Case #	SRF000H11	Additional Recipient	Not Given	Date of Collection	Not Given
Medical Record #	0	Medical Facility ID #	-1	Specimen Type	Extracted DNA + Extracted RNA
Specimen ID	Not Given	Pathologist	Not Given		

ABOUT THE TEST:

FoundationOne Home is a next-generation sequencing (NGS) based assay that identifies genomic alterations within hundreds of cancer-related genes.

PATIENT RESULTS

6 genomic alterations

4 therapies associated with potential clinical benefit

0 therapies associated with lack of response

15 clinical trials

TUMOR TYPE: BONE MARROW MULTIPLE MYELOMA

Genomic Alterations Identified*

KRAS Q61H
MTOR D2512Y
IGH IGH-MAF rearrangement
NTRK3 UBE2R2-NTRK3 fusion
TRAF3 S84*
CXCR4 S323fs*25

*For a complete list of the genes assayed and performance specifications, please refer to the Appendix

²⁵See Appendix for details

THERAPEUTIC IMPLICATIONS

Genomic Alterations Detected	FDA Approved Therapies (in patient's tumor type)	FDA Approved Therapies (in another tumor type)	Potential Clinical Trials
<i>KRAS</i> Q61H	None	Idelalisib Trametinib	Yes, see clinical trials section
<i>MTOR</i> D2512Y	None	Everolimus Temsirrolimus	Yes, see clinical trials section
<i>IGH</i> IGH-MAF rearrangement	None	None	Yes, see clinical trials section
<i>NTRK3</i> UBE2R2-NTRK3 fusion	None	None	Yes, see clinical trials section
<i>TRAF3</i> S84*	None	None	Yes, see clinical trials section
<i>CXCR4</i> S323fs*25	None	None	None

Soft Tissue Sarcoma: Treatment

- Surgery
- Radiation
- Chemotherapy

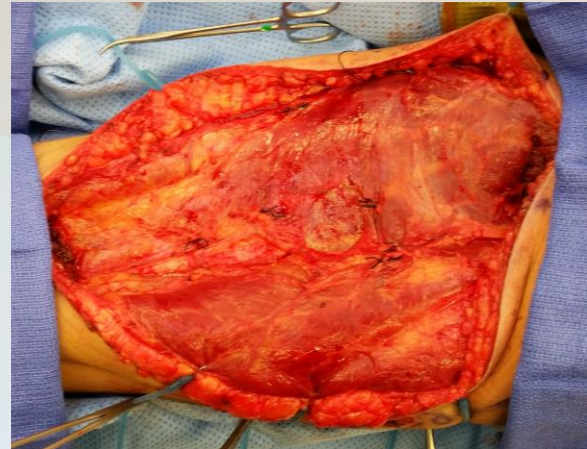
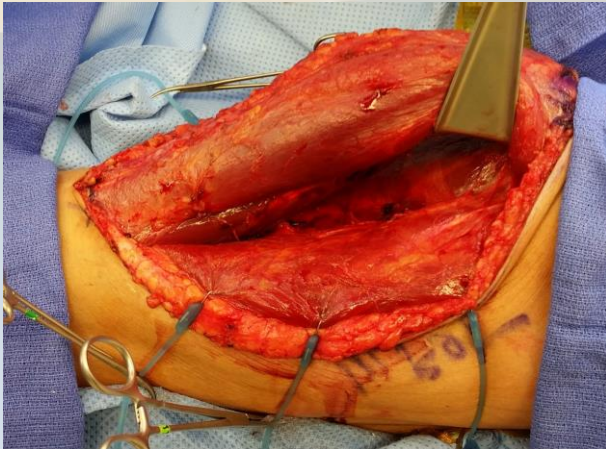
Surgical Treatment of STS

- Biopsy
 - paramount importance
 - Important to discuss technique and location with orthopedic oncologist to ensure appropriate location and orientation



Surgical Management

- Wide Resection
- Dead space management
- Soft tissue coverage if necessary



New Drugs for Benign Disease

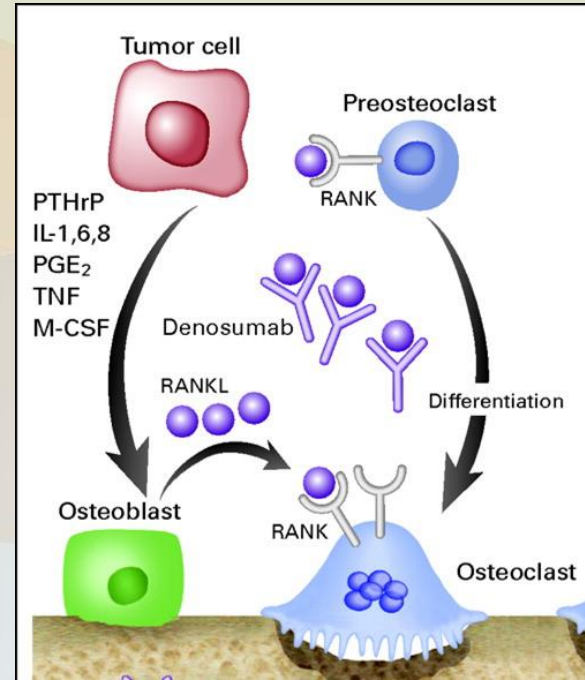
- Giant Cell Tumor of Bone - Denosumab
- Giant Cell Tumor of Tendon sheath - CSF-1R Kinase Inhibitor



Giant Cell Tumor of Bone

Denosumab - rank-L inhibitor

- Phase II Clinical Trials
 - 86% response rate
 - 48% - avoided surgery
 - 38% - downstaged surgery
 - 120 mg SC qmonth



Rutkowski et al Ann Surg Onc Sept 2015

Concerns regarding Denosumab

- Possible malignant transformation?
- Treated bone demonstrated morphologic overlap with malignant GCT

Wojcik et al. Am J of Surg Pathology Jan 2016

PVNS/GCT of Tendon sheath

- CSF-1R Kinase Inhibitor Trials
 - Phase 2: 38 pts, median 12 mo, min 6 months
 - Results (out of 25):
 - 1 metastatic disease (4%)
 - 3 progressive disease (12%)
 - 5 stable disease (20%)
 - 12 partial response (48%)
 - 0 complete response

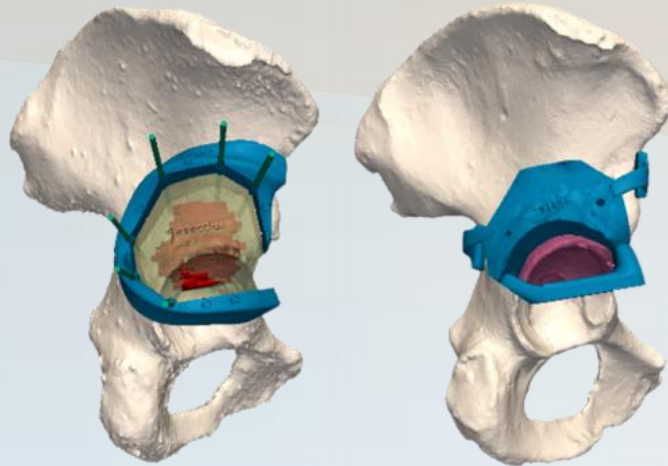
Surgical Reconstructions

- Custom cutting blocks
- 3D printing
- Infection Resistant implants



Custom Cutting Blocks

- CT/MRI Registration
- Alternative to Intraoperative navigation
- 3D Printed custom guides for tumor and allograft



On the Horizon: 3D Printed Implants

- 3D Printing Technology is improving at a rapid rate
- Printing Metal implants with a high degree of complexity is feasible.



Infection Resistant Implants

- Silver Coated Implants
 - Not FDA approved in the US yet
 - Promising Preliminary results
 - 2% vs 10.5% in retrospective study fo 158 pts
 - 11 vs 22% in retrospective study of 170 pts



Hoag
Orthopedic
Institute

