Guidelines for Bone & Soft Tissue Tumors

Vol X

Part B

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Preface

The Centre for Evidence Based Medicine (EBM) defines EBM as "the conscientious, explicit and judicious use of current best evidence in making decisions about the care of individual patients". EBM has percolated into all fields and levels of medical practice and this has been particularly exemplified in current oncology practice. There is an increasing need to update our knowledge and be guided by EBM, especially in an era where there have been rapid developments and innovations in oncology.

Important innovations have been made in diagnostic methods and surgical management of bone and soft tissue tumors. Technological advances with limb prostheses including biological bonding with bone, expandable prostheses for pediatric patients and innovative methods of biological reconstruction have further improved outcomes of limb salvage surgery. Promising advances have been made in clinical research too; identifying various genetic aberrations specific to certain sarcomas, newer targeted therapy in osteosarcoma and bone marrow transplant for Ewing's sarcoma.

In the internet era, information overload can be as much of a problem as paucity of information. The busy clinician is frequently unable to separate real data from sensational hype; the ninth annual EBM meeting and the guidelines

book on bone and soft tissue tumors is planned to do precisely this. As always, in addition to collating the best available evidence, the meeting and book also highlight areas where strong evidence is lacking. Controversies in management can only be resolved with large multi centric studies. I hope that in addition to updating practicing oncologists, this book and meeting serves as a stimulus for investigators to actively participate in clinical research and further improve treatment outcomes.

C S Pramesh
Central Research Secretariat and
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Section I

Imaging in Bone and Soft Tissue Tumors

MRI in Bone and Soft Tissue Tumors

I. Response to therapy: Role of MRI as a marker to assess response to chemotherapy

a. Dynamic contrast enhanced MRI (DCE-MRI)

b. Diffusion MRI (DW-MRI) and spectroscopy

- Fletcher BD, Hanna SL, Fairclough DL, GronemeyerSA.Pediatric musculoskeletal tumors: use of dynamic, contrast-enhanced MR imaging tomonitor response to chemotherapy.Radiology. 1992 Jul; 184(1):243-8.
- VanderWoude HJ, Bloem JL, Verstraete KL, Taminiau AH, Nooy MA, Hogendoorn PC. Osteosarcoma and Ewing's sarcoma after neoadjuvant chemotherapy: value of dynamic MR imaging in detecting viable tumor before surgery. AJR Am J Roentgenol. 1995 Sep;165(3):593-8.
- Ongolo-Zogo P, Thiesse P, Sau J, Desuzinges C, Blay JY, Bonmartin A, Bochu M, Philip T. Assessment of osteosarcoma response to neoadjuvant chemotherapy: comparative usefulness of dynamic gadolinium-enhanced spin-echo magnetic resonance imaging and technetium-99m skeletal angioscintigraphy. EurRadiol. 1999;9(5):907-14.
- Torricelli P, Montanari N, Spina V, Manfrini M, Bertoni F, Saguatti G, Romagnoli R. Dynamic contrast enhanced magnetic resonance imaging subtraction in evaluatingosteosarcoma response to chemotherapy. Radiol Med. 2001 Mar; 101(3):145-51.

- Reddick WE, Wang S, Xiong X, Glass JO, Wu S, Kaste SC, Pratt CB, Meyer WH, Fletcher BD. Dynamic magnetic resonance imaging of regional contrast access as an additional prognostic factor in pediatric osteosarcoma. Cancer. 2001 Jun 15; 91(12):2230-7.
- Uhl M, Saueressig U, Koehler G, Kontny U, Niemeyer C, Reichardt W, Ilyasof K, Bley T, Langer M. Evaluation of tumour necrosis during chemotherapy with diffusion-weighted MR imaging: preliminary results in osteosarcomas. PediatrRadiol. 2006 Dec;36(12):1306-11.
- Uhl M, Saueressig U, van Buiren M, Kontny U, Niemeyer C, Köhler G, Ilyasov K, Langer M. Osteosarcoma: preliminary results of in vivo assessment of tumor necrosis after chemotherapy with diffusion- and perfusion-weighted magnetic resonance imaging. Invest Radiol. 2006 Aug; 41(8):618-23.
- Oka K, Yakushiji T, Sato H, Hirai T, Yamashita Y, Mizuta H. The value of diffusion-weighted imaging for monitoring the chemotherapeutic response of osteosarcoma: a comparison between average apparent diffusion coefficient and minimum apparent diffusion coefficient. Skeletal Radiol. 2010 Feb;39(2):141-6.

Summary: DCE-MRI was first used in 1992, where they showed that tumor slopes after chemotherapy correlated with histopathological findings. This was replicated in a 1995 study where the authors could correlate the presence of viable tissue on DCE-MRI with histopathological findings. A later study in 1999 comparing DCE-MRI and technetium scintigraphy's ability to predict response to chemotherapy by performing the studies at presentation, mid-chemotherapy and at the end of chemotherapy showed that both modalities could predict response only at the end and not at mid-cycle with 91% accuracy. Another similar study in 2001 showed that "pathologic areas subtraction had an accuracy of 95% (specificity: 100%, sensitivity: 93%, PPV: 100%, NPV: 88%), whereas angiographic subtraction had an accuracy of 79%

(specificity: 37%, sensitivity: 100%, PPV: 76%, NPV: 100%)".This study however assessed response only at the end of chemotherapy. Another study at the same time showed that higher the regional contrast access at presentation, greater was the response and that the extent of regional contrast access after chemotherapy and tumor size correlated with response. Since these studies there has been no major paper studying the use of DCE-MRI in the assessment of response to chemotherapy and more importantly in the assessment of prognosis.

The data on diffusion MRI is restricted to three studies, two from 2006 and one from 2010, all of them essentially being proof of concept showing that ADC values correlate with the presence of viable and non-viable tissue as compared to histology.

All studies are restricted by a limitation in numbers of patients and more importantly, no study has independently assessed whether any MRI method can eventually predict extent of survival as an independent test with confidence.

There is no data on proton MRI spectroscopy.

Level of evidence: III

II. Prognosis: Role of MRI as a surrogate marker to assess prognosis and potential response to chemotherapy - DCE-MRI as a surrogate for VEGF

- Hoang BH, Dyke JP, Koutcher JA, Huvos AG, Mizobuchi H, Mazza BA, Gorlick R, Healey JH. VEGF expression in osteosarcoma correlates with vascular permeability by dynamic MRI. ClinOrthopRelat Res. 2004 Sep;(426):32-8.
- Bajpai J, Gamanagatti S, Sharma MC, Kumar R, Vishnubhatla S, Khan SA, Rastogi S, Malhotra A, Bakhshi S. Noninvasive imaging surrogate of angiogenesis in osteosarcoma. Pediatr Blood Cancer. 2010 Apr; 54(4):526-31.

Summary: There are exactly two papers on this subject that have shown that DCE-MRI can correlate with VEGF expression. What this means in terms of estimation of prognosis and eventually survival, is still an extrapolation.

Level of evidence: III

III. Role of whole body MRI (WB-MRI) in bone tumors

- Nakanishi K, Kobayashi M, Nakaguchi K, Kyakuno M, Hashimoto N, Onishi H, Maeda N, Nakata S, Kuwabara M, Murakami T, Nakamura H. Whole-body MRI for detecting metastatic bone tumor: diagnostic value of diffusion-weighted images. MagnReson Med Sci. 2007;6(3):147-55.
- Balliu E, Boada M, Peláez I, Vilanova JC, Barceló-Vidal C, Rubio A, Galofré P, Castro A, Pedraza S. Comparative study of whole-body MRI and bone scintigraphy for the detection of bone metastases. ClinRadiol. 2010 Dec;65(12):989-96.
- Shortt CP, Gleeson TG, Breen KA, McHugh J, O'Connell MJ, O'Gorman PJ, Eustace SJ. Whole-Body MRI versus PET in assessment of multiple myeloma disease activity. AJR Am J Roentgenol. 2009 Apr;192(4):980-6.
- Hillengass J, Fechtner K, Weber MA, Bäuerle T, Ayyaz S, Heiss C, Hielscher T, Moehler TM, Egerer G, Neben K, Ho AD, Kauczor HU, Delorme S, Goldschmidt H. Prognostic significance of focal lesions in whole-body magnetic resonance imaging in patients with asymptomatic multiple myeloma. J ClinOncol. 2010 Mar 20;28(9):1606-10.
- Burdach S, Thiel U, Schöniger M, Haase R, Wawer A, Nathrath M, Kabisch H, Urban C, Laws HJ, Dirksen U, Steinborn M, Dunst J, Jürgens H; Meta-EICESS Study Group. Total body MRI-governed involved compartment irradiation combined with high-dose chemotherapy and stem cell rescue improves long-term survival in Ewing tumor patients with multiple primary bone metastases. Bone Marrow Transplant. 2010 Mar;45(3):483-9.

- Krohmer S, Sorge I, Krausse A, Kluge R, Bierbach U, Marwede D, Kahn T, Hirsch W. Whole-body MRI for primary evaluation of malignant disease in children. EurJ Radiol. 2010 Apr;74(1):256-61.

Summary: While the role of (WB-MRI) in metastases and myeloma has been shown to be significant, as compared to bone scans and PET/CT, its role in the evaluation of Ewing's sarcoma is being investigated as well. In a recent study to assess two different protocols, WB-MRI was the modality used to assess the disease spread and activity to monitor response to treatment.

What is practically more relevant is that as compared to PET/CT, there is no radiation burden with MRI, which makes it an attractive alternative modality to be used wherever PET/CT is indicated for whole body staging in children, as long as it can be proven that WB-MRI is as good as PET/CT, if not better.

Level of evidence: III

PET scan in Bone and Soft Tissue Tumors

I. The role of FDG PET/CT in initial staging in bone and soft tissue sarcomas

- Volker T, Denecke T, Steffen I et al. Positron Emission Tomography for Staging of Pediatric Sarcoma Patients: Results of a Prospective Multicenter Trial. J Clin Oncol. 2007; 25 (34):5435-41.
- Kneisl JS, Patt JC, Johnson JC, Zuger JH. Is PET useful in detecting occult nonpulmonary metastases in pediatric bone sarcomas? Clin Orthop Relat Res 2006;450:101–104.
- Gyorke T, Zajic T, Lange A, et al: Impact of FDG PET for staging of Ewing sarcomas and primitive neuroectodermal tumours. Nucl Med Commun 27:17-24, 2006.

Summary: Volker et al in their study of 46 patients in paediatric sarcomas (Ewing's, OGS & RMS) showed a higher sensitivity of FDG PET (88%) over conventional imaging (37%) for skeletal metastases from Ewing's sarcoma. The sensitivity however was not much different (90% for PET Vs 81% for conventional imaging) for skeletal metastases in OGS. PET was superior to conventional imaging modalities concerning the correct detection of lymph node involvement (sensitivity, 95% *v* 25%

respectively).This was particularly true for Ewing's and RMS.

Kneisl JS etal in a retrospective analysis of 55 patients of Ewing's sarcoma and OGS showed that PET detected metastases in 12/55 (22%) patients. 8 out of 12 patients (67%) had disease outside the lungs. 4/55 patients (7%) were upstaged to stage IV on the basis of PET findings alone. More patients were upstaged in the Ewing's sarcoma group than the OGS group.

Inference:

The use of FDG PET or PET/CT in the initial staging can lead to treatment optimisation particularly in Ewing's sarcoma patients due to the superiority of FDG PET in detecting bone lesions.

Whereas in OGS patients, there is only little impact of FDG-PET on therapy planning because bone scan seems to be equally suited to detect skeletal involvement and chest CT is the method of choice for pulmonary staging.

Level of evidence: II

However with the availability of PET/CT, pulmonary nodules can be diagnosed using the CT component of the PET/CT study with same accuracy as that of a chest CT.

II. The role of FDG PET in assessing response to neoadjuvant therapy in bone and Soft Tissue Sarcomas
(Role of FDG PET as a surrogate marker)

- Franzius C, Sciuk J, Brinkschmidt C, Jürgens H, Schober O. Evaluation of chemotherapy response in primary bone tumors with F-18 FDG positron emission tomography compared with histologically assessed tumor necrosis. Clin Nucl Med 2000;25 (11):874–881.
- Hawkins DS, Rajendran JG, Conrad EU 3rd, Bruckner JD, Eary JF. Evaluation of chemotherapy response in pediatric

bone sarcomas by [F-18]-fluorodeoxy- D-glucose positron emission tomography.Cancer 2002;94(12):3277–3284. [Published correction appears in Cancer 2003;97(12):3130.]

- Hawkins DS, Schuetze SM, Butrynski JE, et al. [18F] Fluorodeoxyglucose positron emission tomography predicts outcome for Ewing sarcoma family of tumors. J Clin Oncol 2005;23(34):8828–8834.
- Dimitrakopoulou-Strauss A etal. Impact of Dynamic 18F-FDG PET on the Early Prediction of Therapy Outcome inPatients with High-Risk Soft-Tissue Sarcomas After Neoadjuvant Chemotherapy: A Feasibility Study. J Nucl Med 2010; 51:551–558.

Summary: Franzius et al evaluated the use of FDG PET in assessing the chemotherapeutic response of primary osseous sarcomas (OGS and Ewing's) in 17 patients on the basis of the degree of necrosis as determined histologically. The authors found good correlation between degree of tumor necrosis following chemotherapy and reduction in FDG uptake within the tumor. In patients classified as having a good response to chemotherapy (Salzer-Kuntschik classification grades I–III), FDG PET showed a greater than 30% decrease in the ratios of tumoral to nontumoral activity. In the same study, FDG PET was found to be superior to bone scintigraphy in assessing histological response to chemotherapy.

Hawkins DS et al examined the prognostic value of FDG PET–measured response to chemotherapy for progression-free survival in 36 patients with Ewing sarcoma. The authors found that a maximum SUV of less than 2.5 following chemotherapy is associated with improved progression-free survival, with a positive predictive value for favorable response (less than 10% viable tumor) of 79%, independent of the initial disease stage.

Hawkins DS, Rajandran JG et al in a study of 33 patients including osteosarcoma and Ewing's sarcoma had

reported a 93% positive predictive value for a favorable response to neoadjuvant chemotherapy (> 90% necrosis or less than 10% viable tumor) with use of an SUV less than 2. However the NPV of an unfavorable response (< 90% necrosis or more than 10% viable cells) was 78%.

Dimitrakopoulou-Strauss A et al used dynamic PET in 31 patients with non metastatic soft-tissue sarcomas, who were treated with neoadjuvant chemotherapy consisting of etoposide, ifosfamide, and doxorubicin. Patients were examined before the onset of therapy and after the completion of the second cycle. Histopathological response served for reference (less than 10% viable cells was considered as response). Of the various parameters available from the dynamic studies the combination of the 2 predictor variables, namely SUV and influx, of each study led to the highest accuracy of 83%. This combination was particularly useful for the prediction of responders (positive predictive value, 92%).

Inference: There is a strong correlation between the degree of tumor necrosis on histology following chemotherapy and FDG concentration in the tumor. PET using FDG can be potentially used as a non-invasive surrogate to predict response as well for prognostication.

A multiparameter analysis based on kinetic 18F-FDG data (dynamic PET) of a baseline study and after 2 cycles is helpful for the early prediction of chemosensitivity in patients with soft-tissue sarcomas receiving neoadjuvant chemotherapy.

Level of evidence: III

III. Role of FDG PET in recurrent bone and soft tissue sarcomas

- Arush MW, Israel O, Postovsky S, et al. Positron emission tomography/computed tomography with 18fluoro-

deoxyglucose in the detection of local recurrence and distant metastases of pediatric sarcoma. Pediatr Blood Cancer 2007;49(7):901–905.

- Franzius C, Daldrup-Link HE, Wagner-Bohn A, et al. FDG-PET for detection of recurrences from malignant primary bone tumors: comparison with conventional imaging. Ann Oncol 2002;13(1):157–160.

Summary: Arush et al in a retrospective study of 19 patients of malignant bone and soft tissue sarcomas found that combined PET/CT helped detect recurrent disease in 80% of cases. In their study, FDG-PET/CT successfully helped detect all cases of proved local recurrence, and, in 15% of patients, was the only modality at which distant metastases were detected.

In a retrospective analysis of 27 patients with osseous sarcomas, Franzius et al demonstrated a high accuracy for FDG PET in the detection of both local and distant tumor recurrence. FDG PET had a sensitivity of 96%, a specificity of 81%, and an accuracy of 90%. The combined use of regional MR imaging, thoracic CT, and bone scintigraphy had a sensitivity of 100%, a specificity of 56%, and an accuracy of 82%.

Inference: FDG PET/CT is useful in detecting recurrence at the primary site and is often complementary to other imaging modalities. It is fairly accurate in detecting sites of distant failure. Its potential benefits and limitations compared to conventional imaging modalities will have to be studied in larger homogenous patient groups.

Level of evidence: III

IV. Role of FDG PET in differentiating high grade and low grade bone and soft tissue tumors

- Charest et al. FDG PET/CT imaging in primary osseous and soft tissue sarcomas: a retrospective review of 212

cases. Eur J Nucl Med Mol Imaging 2009; July (Epub ahead of print).

- Okazumi S et al. Quantitative, dynamic 18F-FDG-PET for the evaluation of soft tissue sarcomas: relation to differential diagnosis, tumor grading and prediction of prognosis. Hell J Nucl Med 2009; 12; 223-28.

Summary: In a retrospective review of 212 cases of bone and soft tissue sarcomas by Charest et al, FDG PET/CT showed an overall sensitivity of 93.9% for all sarcomas, 93.7 % for soft tissue sarcomas and 94.6% for bone sarcomas. The receiver-operating characteristic curve revealed an area under the curve of 94% for the discrimination of low-grade and high-grade sarcomas imaged for initial staging by FDG PET/CT.

Ozazumi et al used dynamic FDG PET in 117 patients of soft tissue sarcomas in order to establish kinetic parameters for evaluation of their histological grade and prognosis. SUV, Ki (global influx), K1- K4 (transport constants) and FD (Fractal dimension) were some of the kinetic parameters used. All the above parameters were higher in sarcomas than benign tumors. SUV and FD were also higher in higher grade tumors.

Inference: The combined metabolic and morphological information of FDG PET/CT imaging allows high sensitivity for the detection of various sarcomas and accurate discrimination between newly diagnosed low-grade and high-grade sarcomas.

Various kinetic parameters obtained from dynamic FDG PET are useful in histological grading and prognosis of bone and soft tissue sarcomas.

Level of evidence: III

Definitions of the appropriateness criteria for the use of PET (IAEA Human Health Series- 2009)

The use of PET for clinical indications can be considered appropriate, potentially appropriate, possibly appropriate or inappropriate. The appropriateness criteria for the usefulness of PET are defined as follows:

Appropriate (all the conditions below must be met) —

There is evidence of improved diagnostic performance (higher sensitivity and specificity) compared with other current techniques.

— The information derived from the PET scan influences clinical practice.

— The information derived from the PET scan has a plausible impact on the patient's outcome, either through adoption of more effective therapeutic strategies or through non-adoption of ineffective or harmful practices.

Potentially appropriate (potentially useful) -
There is evidence of improved diagnostic performance (greater sensitivity and specificity) compared with other current techniques, but evidence of it impact on treatment and outcome is lacking.

Possibly appropriate (appropriateness not yet documented) -
There is insufficient evidence for assessment, although there is a strong rationale for clinical benefit from PET.

Indication for PET/CT in bone and soft tissue sarcomas	Relevance of Test
Staging	Potentially appropriate
Response evaluation	Potentially appropriate
Suspected recurrence	Potentially appropriate
Histological grading	Possibly appropriate

Section II

Pathology – Bone and Soft Tissue Tumors

The Role of FNAC and Ancillary Techniques in Diagrams of Bone and Soft Tissue Tumors

The role of fine needle aspiration cytology (FNAC) in bone and soft tissue tumours

- Khalbuss WE, Teot LA, Monaco SE. Diagnostic accuracy and limitations of fine-needle aspiration cytology of bone and soft tissue lesions: a review of 1114 cases with cytological-histological correlation. Cancer Cytopathol. 2010; 118(1): 24-32.
- Rekhi B, Gorad BD, Kakade AC, et al. Scope of FNAC in the diagnosis of soft tissue tumors—a study from a tertiary cancer referral center in India. Cytojournal. 2007; 4:20.
- Bennert KW, Abdul-Karim FW. Fine needle aspiration cytology vs. needle core biopsy of soft tissue tumors. A comparison. Acta Cytol. 1994; 38(3): 381-384.
- Silverman JF, Joshi VV. FNA biopsy of small round cell tumors of childhood: cytomorphologic features and the role of ancillary studies. Diagn Cytopathol. 1994; 10(3): 245-255.
- Renshaw AA, Perez-Atayde AR, Fletcher JA, Granter SR. Cytology of typical and atypical Ewing's sarcoma/PNET. Am J Clin Pathol. 1996 Nov;106(5):620-4.
- Pohar-Marinsek Z. Difficulties in diagnosing small round cell tumours of childhood from fine needle aspiration cytology samples. Cytopathology. 2008 Apr;19(2):67-79.

- Bommer KK, Ramzy I, Mody D. Fine-needle aspiration biopsy in the diagnosis and management of bone lesions: a study of 450 cases. Cancer. 1997; 81(3): 148-156.
- Layfield LJ, Glasgow BJ, Anders KH, Mirra JM. Fine needle aspiration cytology of primary bone lesions. Acta Cytol. 1987 Mar-Apr;31(2):177-84.
- Abdul-Karim FW, Bauer TW, Kilpatrick SE, Raymond KA, Siegal GP; Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of bone tumors. Association of Directors of Anatomic and Surgical Pathology. Hum Pathol. 2004 Oct;35(10):1173-8.
- Klijanienko J, Caillaud JM, Orbach D, Brisse H, Lagacé R, Sastre-Gareau X. Cyto-histological correlations in primary, recurrent, and metastatic bone and soft tissue osteosarcoma. Institut Curie's experience. Diagn Cytopathol. 2007 May;35(5):270-5.
- Akerman M. Benign fibrous lesions masquerading as sarcomas. Clinical and morphological pitfalls. Acta Orthop Scand Suppl. 1997 Feb;273:37-40.
- Walaas L, Kindblom LG. Lipomatous tumors: a correlative cytologic and histologic study of 27 tumors examined by fine needle aspiration cytology. Hum Pathol. 1985 Jan;16(1):6-18.
- Jones C, Liu K, Hirschowitz S, et al. Concordance of histopathologic and cytologic grading in musculoskeletal sarcomas: can grades obtained from analysis of the fine-needle aspirates serve as the basis for therapeutic decisions? Cancer Cytopathol 2002; 96: 83-91.
- Dey P, Mallik MK, Gupta SK, Vasishta RK. Role of fine needle aspiration cytology in the diagnosis of soft tissue tumours and tumour-like lesions. Cytopathology. 2004 Feb;15(1):32-7.

Summary: Fine needle aspiration cytology (FNAC) for bone and soft tissue lesions, in expert hands, has been purported to show high diagnostic accuracy and predictive value with results comparable to those obtained by needle core biopsy.

The diagnosis of malignant small round cell tumour (Ewing sarcoma/PNET, rhabdomyosarcoma, etc.), though easily suggested on cytology, needs immunohistochemistry and molecular analysis for correct tumour identification. The material obtained from biopsy is superior (in amount and viability) compared to that obtained by FNAC. Moreover, the more material obtained from the biopsy can be used for tissue banking and research at a later date (with all the requisite approvals). The role of FNAC in small round cell tumours would be suitable for detecting recurrence and metastasis.

Bone tumours have been diagnosed with variable accuracy on cytology. However, cytology is not even mentioned in the recommendations for reporting of bone tumors. The interpretation of bony lesions is a complex process requiring histological, clinical and radiological correlation, with a whole lot of differential diagnoses to be considered. The value of FNAC in bony lesions is in diagnosing bony metastasis with minimal intervention.

Fine needle aspiration cytology is a tempting option in soft tissue tumours, especially if they are superficial. However, they too require ancillary studies for diagnosis. Distinguishing benign from malignant conditions may not be altogether straightforward and the diagnostic attempts are strewn with potential pitfalls. Another area of difficulty is the grading and the exact typing of soft tissue tumours which are the cornerstone of treatment. As reactive conditions can simulate malignancy, FNAC is not the best mode of investigation for recurrence and metastasis of soft tissue sarcomas.

Inference and Recommendations: Fine needle aspiration cytology has a role in the diagnosis of certain lesions and its benefits include early, minimally invasive diagnosis. FNAC would help in channelizing further

investigations. The drawbacks include inadequate material for ancillary studies and future research, correct typing and grading of certain tumours.

The following table lays down certain non-binding recommendations on the role of FNAC in the diagnosis and management of Bone and Soft Tissue Tumors.

Tumor	Situation	Role of FNAC
Malignant Round Tumor Small Cell	Primary diagnosis	No; Can be used only if adequate material is obtained for immunohistochemistry and molecular analysis.
	Recurrence (early)	Yes.
	Recurrence (late)	No, biopsy is recommended as a second primary is a possibility.
	Metastasis	Yes.
Bone lesions	Primary bone lesion	No, (except in cases with typical clinical and classical radiological findings eg. Giant cell tumour of bone.)
	Suspected myeloma metastasis to bone	Yes.
Soft tissue tumours	Primary diagnosis	No; Sometimes cytological features may be confusing and exact grading and tumour typing may be an issue.
	Recurrence	Yes (but it might not distinguish florid reactive changes from low grade tumours).
Suspected inflammation / infection in Bone and Soft Tissue lesions		Yes, to rule out tumour.

The role of Ancillary techniques in the diagnosis of Musculoskeletal Tumors

I. Importance of Morphology and need of ancillary techniques in diagnosis of Bone and Soft Tissue Tumors.

- Marchevsky AM.The application of special technologies in diagnostic anatomic pathology: is it consistent with the principles of evidence-based medicine? Semin Diagn Pathol. 2005;22:156-166.
- Rosai J. Why microscopy will remain a cornerstone of surgical pathology. Laboratory investigation 2007 87, 403 -408

Summary: The two main ancillary techniques which have ushered in an element of objectivity of evaluation in musculoskeletal tumours, and also in case of other tumours, are Immunohistochemistry and Molecular techniques. These techniques provide vital supplementary information but cannot replace morphology. The information provided will have an increasing role both for diagnosis and for prediction of response to treatment.

For example, Ewing's sarcoma with the standard translocation respond better to treatment than Ewing's sarcoma with the variant translocations ; also Rhabdomysarcomas of the Alveolar RMS subtype do worse than those of the embryonal subtype. The former often show PAX-FKHR fusion positivity unlike the ERMS which are fusion Negative.

II. The role of IHC in diagnosis of Bone & Soft Tissue Tumors.

- Binh MB et al. MDM2 and CDK4 immunostainings are useful adjuncts in diagnosing well-differentiated and dedifferentiated liposarcoma subtypes: a comparative analysis of 559 soft tissue neoplasms with genetic data. Am J Surg Pathol 2005; 29; 1340-1347
- Wachtel M, Runge, T, Leuschner I, SteigmaierS, et al. Subtype and prognostic classification of

Rhabdomyosarcoma by Immunohostochemistry J Clin Oncol 24:816-822 , 2006

- Parham DM and Ellison DA. Rhabdomyosarcoma in adults and children : an update (Review) Arch Pathol Lab Med 130: 1454-1465, 2006
- Fletcher CD et al Diagnosis of gastrointestinal stromal tumours : a consensus approach Hum Pathol 2002;33:459-65
- West RB. The novel marker DOG1 is expressed ubiquitously in gastrointestinal stromal tumours irrespective of KIT or PDGFR mutation status Am J Pathol 2004 165 (1) : 107-13
- Dei Tos AP et al. Immunohistochemical demonstration of p30/32MIC2 (CD99) in Synovial sarcoma. A potential cause of Diagnostic confusion. Appl Immunohistochem 4:167-175, 1996
- Guillou L et al S-100 protein reactivity: in synovial sarcoma: A potentially frequent diagnostic pitfall > Immunohistochemical analysis of 100 cases. Appl Immunohistochem 4 ; 167-175 , 1996
- Murphy AJ et al. A new molecular variant of Desmoplastic small round cell tumour : significance of WT1 immunostaining in this entity Hum Pathol 2008; 39: 1763-70

Summary: For several years the surgical pathologist had to be content with the H&E stain , and the routine "special stains '' such as PAS, mucicarmine , reticulin etc. However with the discovery of monoclonal antibodies and more importantly the application of this knowledge to pathology histology sections by way of Immunohistochemistry since the late 1970s, gave a tremendous boost to the diagnostic skills of the pathologist. Immunohistochemistry (IHC) today is a powerful tool in the surgical pathologist's armamentarium. It's immense success can be attributed to the ease of application because it is done on routinely processed material ; further IHC interpretation is done with usual microscopes and no separate additional gadgetry is needed . Archiving and storing IHC slides is on lines

identical to H&E slides. Retrieval and subsequent review is easy. However the role of IHC in musculoskeletal tumours has not been and cannot be expected to be as phenomenal as with lymphomas or breast diseases. The role of IHC with respect to bone and soft tissue tumours in a practical setting will depend on the experience of the pathologist, the availability of the antibodies in a particular laboratory and the size of the specimen (which will be a definite limiting factor), in addition to the all important consideration of cost.

In this context the following comments on IHC for musculoskeletal tumours would be relevant.

A. Bone tumours:

i. The maximum role of IHC is in the workup of Malignant Round cell tumours MRCT. Ewing's sarcomas/PNETs stain with MIC2 (CD99) and FLi1. They can also occasionally react for Cytokeratin and Desmin. Lymphomas of bone are mostly B-cell Lymphomas and stain with LCA and CD20. The Anapalstic Large cell Lymphoma of bone usually shows immunoexpression of CD3, CD30 and ALK1. Lymphoblastic Lymphoma / Leukaemia and Burkitts Lymphomas can also involve bone primarily. The former would stain with tdt, CD3 and MIC2; the latter would stain with CD10 and show a proliferative index of almost 100% with Mib1 IHC stain. Rarely metastatic rhabdomyosarcoma can manifest as a bone tumour in a patient who has been apparently "cured "of the tumour in childhood; in such a situation the myogenic markers as listed in the next section on soft tissue tumors would help.

ii. IHC has unfortunately almost no role in the Bone forming tumors. Although osteonectin and osteopontin have been investigated as markers for osteoid they have no utility in a practical setting and hence they have no role.

iii. There is a minimum role of IHC in cartilage tumours because chondrocytes stain with S-100 protein. However the

staining is good in cases where the cartilage is hyaline and in that case it is easily recognizable even on the H& E stain. S-100 has not been found to be of any value in chondromyxoid fibroma, chondroblastomas, mesenchymal chondrosarcomas which are the lesions wherein the chondroid lineage is sometimes difficult to gauge and an IHC stain would have helped in the diagnosis. A new antibody SOX2, under investigation is presently used in research setting.

iv. Finally there are no IHC stains for recognizing small cell osteosarcoma, or mesenchymal chondrosarcoma.

v. Plasma cell tumours and Metastatic tumours are the most common bone tumours and are the first in differentials in elderly patients. Most Plasma cell tumours will react with EMA, CD138, and also show Kappa, or Lambda light chain restriction. Metastatic tumours stain with Cytokeratin (CK), EMA, and depending on the primary site may also stain with CEA and BerEP4 in case the origin is from the GIT. An algorithmic approach and then judicious use of a combination of Cytokeratin stains comprising CK7 /CK20 followed by lineage specific markers such as TTF1 /SPB for suspected Lung cancer , or HepPar for suspected Hepatocellular cancer , or HMB45, Melan A and S-100 protein for suspected metastatic melanomas help to figure out the primary tumour.

B. Soft tissue tumours:

Immunohistochemistry has much more relevance and utility in the Differential Diagnosis of soft tissue tumours.

i. The routinely used markers for the common tumours soft tissue which may also rarely occur within the bone are as follows: for Synovial sarcoma: CK, Bcl2, Mic2; for Rhabdomysarcoma: Myogenin is powerful immunostain for diagnosis of RMS. The other stains include MyoD1, Desmin, Myoglobin; for Leiomyosarcoman : Smooth muscle actin SMA, Calponin and to some extent also Desmin,

Myoglobin ; for PNET/EWS Mic2, Fli1 ;

ii. Certain markers are quite "diagnostic " for certain tumours such as CD34 for Solitary fibrous Tumous, C-kit for GIST or Gastrointestinal stromal tumours which is a tumour that occurs not only in GI sites but also in several sites outside the GI .

iii. The newer markers include, TFE3 for synovial sarcomas, TLE 3 for Alveolar soft part sarcomas, Brachyury for Chordomas.

The panel of IHC antibodies projected as being more sensitive or more specific is ever expanding. But it is worth noting that several markers considered as very "Good markers" at the time of first introduction - sometimes gradually fade into oblivion over a period of time; this is because with increasing usage issues regarding cross reactivity , lack of specificity etc unfold themselves in a practical set up . Also quality control in IHC is an area of major concern worldwide and will remain particularly relevant in good measure in our part of the world mainly due to the extreme preanalytic variables which cannot be controlled and which will continue to remain uniform across the country for a long time to come. Delay in fixation, improper and inadequate fixation, suboptimal processing of tissues are matters which are difficult to monitor and control.

Inference: Hence all Immunohistochemistry stains need to be interpreted in the correct H& E morphology setting. "Surprise" positivity should be viewed with skepticism and interpreting in a void needs to be avoided.

III. The role of molecular techniques in musculoskeletal tumours

- Mangham DC, Williams A et al Ewing's sarcoma of Bone: the detection of specific transcripts in a large, consecutive

series of formalin-fixed, decalcified , paraffin-embedded tissue samples usingh the reverse transcriptase – polymerase chain reaction Histopathology 2006; 48 : 363-376

- Flanagan AM, Delaney, O' Donell P. Benefits of molecular pathology in the diagnosis of Musculoskeletal disease. Part I of a two-part review : soft tissue tumors Skeletal Radiol 2010: 39;105-115
- Flanagan AM , Delaney, O' Donell P. Benefits of molecular pathology in the diagnosis of Musculoskeletal disease Part II of a two-part review : bone tumors.Skeletal Radiol 2010; 39, 213-224
- Oliveira AM, His BL,et al. USP6 (Tre2) fusion oncogenes in aneurysmal bone cyst. Cancer Res 2004; 64:1920-1923
- Barr FG , Qualman SJ, Macris MH, Melynk N, Lawlor ER Strzelecki DM et al . Genetic Heterogeneity in the alveolar Rhabdomyosarcoma subset without typical gene fusions. Cancer Res 62:4704-4710, 8-15 , 2002
- Lae M, Ahn EH, Mercado GE et al. Global gene expression profiling of PAX-FKHR fusion –positive alveolar and PAX-FKHR fusion-negative embryonal rhabdpmyosarcomas J Pathol 2007 ; 212 : 143-151
- Kawai et al. SYT-SSX gene fusion as a determinant of morphology and prognosis in Synovial sarcoma. N Eng J Med 338:153-160, 1998
- Panagopoulas I, Storlazz CT, Fletcher CD et al .The chimeric FUS/CREB312 gene is specific for low grade fibromyxoid sarcoma. Genes Chromosomes Cancer 2004; 40:218-218
- McArthur et al. Molecular and clinical analysis of locally advanced dermatofibrosarcoma protuberans treated with imitanib : Imitanib Target Exploration Consortium study B2225 J Clin Oncol 2005;23;866-873

Summary: Next to IHC the next ancillary techniques which are increasingly assuming an important role in the work up several diseases are the molecular techniques.

These are based on the DNA/ RNA components in the cells and tissues. Molecular pathology is particularly useful

in distinguishing tumours with similar or overlapping morphology and IHC profile and also when tumours occur at a totally unexpected site esp Synovial sarcoma in the bone. Further new light has been thrown on well-known entities esp: aneurysmal bone cyst which, until recently was classified as a "tumour-like lesion" actually represents a benign neoplastic process and shows USP6 fusion oncogenes. The secondary aneurysmal bone cysts do not reveal the USP6 and CDH11 oncogenes seen in primary aneurysmal bone cysts.Information on the molecular abnormalities is also useful for treatment esp: DFSPs show the rearrangement of Chromosome 17 & 22 leading to activation of PDFGR beta enhances tumour growth. Hence targeting the protein tyrosine kinase has shown effectiveness in treatment of DFSP

These are mainly of two types: PCR based or Fluorerscent in situ Hybridisation (FISH) based.

PCR has a very wide application and is routinely used to detect various chromosomal translocation like t11; 22 in EWS/PNET: SSX; SYT in Synovial sarcoma, or mutational analysis of Ckit as in GIST. In PNET/EWS the EWS rearrangement can be detected in 96% of cases on formalin fixed paraffin embedded tissues. However molecular techniques do not provide an answer in each and every case. About 30-50% of ARMS contain PAX3/FKHR and about 20% show PAX7/FKHR. A good number of Alveolar rhabdomyosarcomas do not contain a demonstrable gene fusion. In such cases the analysis of Global expression profiles of ARMS and ERMS using oligonuleotide arrays which has led to the development of a ten-gene microarray based predictor that distinguishes ARMS from ERMS would be useful. The gene expression signatures can be utilized for both diagnostic purpose and therapeutic targets.

FISH techniques permit detection of nucleic acids RNA, DNA in tissue sections, or in cells grown on cell cultures, and on conventional chromosome preparations. Unlike PCR wherein the tissue is homogenized with resultant loss of morphology, with the FIH based techniques there is preservation of morphology; thus the nucleic acid of interest can be detected in the light of the right morphological context. Also unlike the PCR technique which entails several steps, the FISH techniques is essentially one single test entailing a few steps on a single glass slide; hence it is a rapid diagnostic test. It can be done on metaphase spreads obtained from cultures, or on the interphase nuclei of histology sections of paraffin embedded tissue sections. The special probes are labeled nucleic acid molecules which have a sequence which is complementary to the nucleic acid which is to be detected. However the number of FISH probes which are commercially available are very limited in general, but particularly so in case of Bone and soft tissue sarcomas. Further FISH is useful to detect translocations and amplifications but not for point mutations. Therefore the application of FISH in a service laboratory for Bone and soft tissue sarcomas is rather restricted and limited to a handful of tumors. FISH is presently applicable to detect the translocations in Ewings sarcoma, rhabdomyosarcoma, synovial sarcomas, and Desmoplastic small round cell tumours.

The list of tests to investigate tumours will expand but as of today several musculoskeletal tumours and particularly the two most common tumours of bone namely, Giant cell tumour and osteosarcoma have neither an IHC marker nor any molecular signature on the horizon.

Inference: At one end results of clinical trials would be meaningless and misleading if the entities included actually

represent a variety of diseases, but at the other end the field of molecular pathology is as yet in its "infancy" (Flanagan, 2010).

Specialised centres which have molecular diagnostic laboratory with the capacity for research and investigational activity replete with the expertise and skill to develop and validate "home brewn probes", are the ones who will lead the molecular diagnostic field and will decide the extent of the test menu most other diagnostic laboratories will be able to offer in future.

Finally to quote Dr Juan Rosai "The amount of information that can be obtained from a simple H&E slide represents a windfall in terms of data quality, quantity and cost compared to any other available technique"(Rosai, 2007).

Section III

Osteosarcoma

Chemotherapy in Osteosarcoma

I. Role of high dose Methotrexate in Osteosarcoma?

- Van Dalen EC, de Camargo B. Methotrexate for high-grade osteosarcoma in children and young adults. Cochrane Database Syst Rev,Pediatric Oncology 2009; 1:CD006325.
- Norman Jaffe, Richard Gorlick,Bronx, NY. High-Dose Methotrexate in Osteosarcoma: Let the Questions Surcease—Time for Final Acceptance JCO 2008; 26: 27
- Bacci G, Briccoli A, Rocca M, et al. Neoadjuvant chemotherapy for osteosarcoma of the extremities with metastases at presentation: recent experience at the Rizzoli Institute in 57 patients treated with cisplatin, doxorubicin, and a high dose of methotrexate and ifosfamide.Ann Oncol. 2003;14(7):1126-34
- Bacci G, Gherlinzoni F, Picci P, et al: Doxorubicin-methotrexate high dose versus doxorubicin-methotrexate moderate dose as adjuvant chemotherapy for osteosarcoma of the extremities: A randomized study. Eur J Cancer Clin Oncol 22:1337-1345, 1986
- Meyers PA, Gorlick R, Heller G, et al: Intensification of preoperative chemotherapy for osteogenic sarcoma: Results of the Memorial Sloan Kettering (T-12) protocol. J Clin Oncol 16:2452-2458, 1998
- Bramwell VH, Burgers M, Sneath R, et al: A comparison of two short intensive adjuvant chemotherapy regimens in

operable osteosarcoma of limbs in children and young adults: The first study of the European Osteosarcoma Intergroup. J Clin Oncol 10:1579-1591, 1992

- Souhami RL, Craft AW, Van der Eijken JW et al. Randomised trial of two regimens of chemotherapy in operable osteosarcoma: a study of the European Osteosarcoma Intergroup. Lancet.1997 27;350 (9082):900-1

Summary: This question is yet to reach a final conclusion since the evidence in literature is controversial. The recent Cochrane review did not identify any RCTs or CCTs in which only the use of MTX differed between the treatment groups. Hence, no definitive conclusions can be made about the effects of high dose MTX on antitumour efficacy, the toxicities and quality of life, in the treatment of children and young adults with primary high-grade osteosarcoma.

Bacci et al confirmed that, the prognosis of patients with osteosarcoma of the extremity, metastatic at presentation, remains poor, despite the use of aggressive treatments including HDMTX. Another study from the same group showed that use of either HDMTX or Intermediate dose MTX could not change outcome. Souhami et al found that there was no difference in survival between the two-drug and multi-drug regimens (including high dose MTX) in operable, non-metastatic Osteosarcoma; however the two-drug regimen was shorter in duration and was better tolerated. Literature search also shows studies where HDMTX did improve survivals but these were either nonrandomized phase II trials or were non-optimally designed to answer the question.

Inference: Based on currently available evidence no recommendation for or against the use of HDMTX can be made. Future, well designed, adequately powered,

randomized clinical trials to answer this specific question are needed.

Level of Evidence: III

II. Role of MTP (Muramyl transpeptidase) in Osteosarcoma

- Bielack S S.Editorial Comment Osteosarcoma: Time to move on? Europian journal of cancer 2010, 4 6: 1 9 4 2 –1 9 4 5
- Paul A. Meyers, Cindy L. Schwartz, Mark D. Krailo, e al . Osteosarcoma: The Addition of Muramyl Tripeptide to Chemotherapy Improves Overall Survival - A Report From the Children's Oncology Group J Clin Oncol 2008 26:633-638.
- Meyers PA,. Schwartz CL, Krailo M Et al.Osteosarcoma: A Randomized, Prospective Trial of the Addition of Ifosfamide and/or Muramyl Tripeptide to Cisplatin, Doxorubicin, and High-Dose Methotrexate. J Clin Oncol 2005,23:2004-2011.
- Pete Anderson , Lisa Kopp , Nicholas Anderson et al. Novel bone cancer drugs: investigational agents and control paradigms for primary bone sarcomas (Ewing's sarcoma and osteosarcoma). 008.17: 11 :1703-1715
- Jeremy Whelan, Beatrice Seddon, Martha Perisoglou, et al. Management of Osteosarcoma.Current Treatment Options in Oncology 2006, 7:444–455

Summary: The survival rates in osteosarcoma haven't improved further beyond those achieved after the introduction of combination chemotherapy. Mifamurtide, a modulator of innate immunity, which activates macrophages and monocytes, which in turn release chemicals with potential tumoricidal effects, may help to control microscopic metastatic disease and has been safely given together with standard adjuvant chemotherapy to patients with high-grade osteosarcoma. Results of the recently published intergroup study 0133 trial from the

Children's Cancer and Pediatric Oncology Groups demonstrated a relative reduction in the risk of recurrence of 25% and a relative reduction in the risk of death of 30% in patients who received L-MTP-PE. In another COG study it was found the addition of ifosfamide to cisplatin, doxorubicin, and methotrexate did not enhance EFS or overall survival for patients with osteosarcoma. The addition of MTP to chemotherapy resulted in a statistically significant improvement in overall survival and a trend toward better EFS.

Inference: L-MTP-PE seems to be the first agent in two decades to promise a meaningful improval of survival in osteosarcoma. Future studes are necessary to confirm the clinical value of L-MTP-PE, either as a single agent or in combination with conventional chemotherapy.

Level of Evidence - II

III. Future trends in Osteosarcoma

- Jaffe N. Osteosarcoma: review of the past, impact on the future. The american experience.Cancer Treat Res. 2010.152:239-62.
- Dae-Geun Jeon, Won Seok Song. How can survival be improved in localized osteosarcoma? Expert Review of Anticancer Therapy. 2010 Vol. 10, No. 8, Pages 1313-1325
- Alexander J Chou, Richard Gorlick. Chemotherapy resistance in osteosarcoma: current challenges and future directions. Expert Review of Anticancer Therapy 2006, Vol. 6, No. 7, 1075-1085.
- Richard Greg Gorlick, Paul A. Meyers, Neyssa Marina, et al.Osteosarcoma: A Review of Current Management and Future Clinical Trial Directions. 2006 American Society of Clinical Oncology(ASCO) Educational Book
- Jeremy Whelan, Beatrice Seddon Martha Perisoglou, et al. Management of Osteosarcoma Current Treatment Options in Oncology 2006, 7:444–455

Summary: With the usage of multi-agent chemotherapy, major advances have been achieved in the treatment of osteosarcoma. Disease free survivals has improved from <20% prior to the introduction of effective chemotherapy to 55-75%; and overall survival to 85%. Limb salvage is now available to almost 80% of patients. Further, a number of new drugs are currently undergoing investigations in patients who have relapsed and/or failed conventional therapy. These agents include gemcitabine, docetaxel, novel antifolate compounds, and a liposomal formulation of doxorubicin. High dose methotrexate, doxorubicin, cisplatin and gemcitabine interact with radiation therapy to potentiate its therapeutic effect. Occasionally, the combination of radiation and chemotherapy may render a tumor suitable for surgical ablation. This combination is also particularly useful in palliation. Samarium (153), a radioactive agent, is under evaluation as palliative therapy for bone metastases.

Despite the advances in the last three and half decades the improved cure rate reported initially has not been bettered in the recent past. A particularly vexing problem is that of rescuing patients who develop pulmonary metastases after receiving multidisciplinary treatment. Approximately 15-25% of such patients are rendered free of disease with reintroduction of chemotherapy and resection of metastases. Extrapulmonary metastases and multifocal osteosarcoma also constitute a major problem, and new chemotherapeutic agents are urgently required to improve treatment and outcome in these patients. Additional strategies under evaluation are targeted tumor therapy, anti tumor angiogenesis, biotherapy and therapy based upon molecular profiles and implementation of strategies to overcome chemoresistance. Immunotherapy

has been utilized in the therapy for osteosarcoma for several decades; the effect of maintenance pegylated interferon alpha is currently being studied in the EURAMOS1 trial in patients with good response to neoadjuvant chemotherapy.

IV. Role of Repsonse Adapted Adjuvant chemotherapy strategy in osteosarcoma

- Bacci G, Ferrari S, Bertoni F, et al.: Long-term outcome for patients with nonmetastatic osteosarcoma of the extremity treated at the Istituto Ortopedico Rizzoli according to the Istituto Ortopedico Rizzoli/Osteosarcoma- 2 protocol: an updated report. J Clin Oncol 2000, 18:4016–4027.
- Provisor AJ, Ettinger LJ, Nachman JB, et al.: Treatment of nonmetastatic osteosarcoma of the extremity with preoperative and postoperative chemotherapy: a reportfrom the Children's Cancer Group. J Clin Oncol 1997, 15:76–84.
- Meyers PA, Heller G, Healey J, et al. Chemotherapy for nonmetastatic osteogenic sarcoma: the Memorial Sloan-Kettering experience. Journal of Clinical Oncology 10(1): 5-15, 1992
- Winkler K, Beron G, Delling G, et al.: Neoadjuvant chemotherapy of osteosarcoma: results of a randomized cooperative trial (COSS-82) with salvage chemotherapy based on histological tumor response. J Clin Oncol 1988, 6:329–337.
- Rosen G, Capaeros B,Huvos AG, et al: Preoperative chemotherapy for osteogenic sarcoma: selection of postop adjuvant chemotherapy based on the response of the primary tumour to preoperative chemotherapy.Cancer 1982;49:1221-1230.
- Bacci G, Picci P, Ferrari S, et al.: Neoadjuvant chemotherapy for nonmetastatic osteosarcoma of the extremities: the

recent experience at the Rizzoli Institute. Cancer Treat Res 1993, 62:299–308.

- Bacci G, Picci P, Ruggieri P, et al.: Primary chemotherapy and delayed surgery (neoadjuvant chemotherapy) for osteosarcoma of the extremities. The Istituto Rizzoli Experience in 127 patients treated preoperatively with intravenous methotrexate (high versus moderate doses) and intraarterial cisplatin. Cancer 1990, 65:2539–2553.

Summary: As prognostic significance of a poor response to neoadjuvant chemotherapy has been consistently observed in various studies, it is hypothesized that changing poor responders to a different chemotherapy regimen postoperatively might improve their long-term survival. Early reports of the T10 regimen claimed that such salvage of poor responders was actually achievable, but later publication of 10-year follow-ups did not substantiate the early findings. Following the early positive claims, a number of groups adopted this approach, but few have been able to demonstrate salvage of poor responders. Bucci et al in their study reported 5-year event-free survival rates of 67% for good responders and 51% for poor responders, claiming success on the basis of the difference not being statistically significant. However, this study might have been underpowered to detect a significant difference. Thus, it appears that there is little evidence to support the concept that modification of postoperative chemotherapy can salvage patients whose tumors demonstrate a poor histologic response to preoperative chemotherapy. An explanation for this may be that response to neoadjuvant chemotherapy is a surrogate measure of biologic aggressiveness and chemoresistance which may not be modifiable by currently available therapies.

Inference: Based on current evidence we cannot recommend modification of postoperative chemotherapy based on response to neo-adjuvant chemotherapy.

Level of Evidence: III

V. Role of salvage chemotherapy in relapse setting in osteosarcoma?

- Bielack BK, Bielack SS, Ju¨rgens H et al., Osteosarcoma Relapse After Combined Modality Therapy: An Analysis of Unselected Patients in the Cooperative Osteosarcoma Study Group (COSS).J Clin Oncol 2005. 23:559-568.
- Bacci G, Briccoli A, Longhi A et al. Treatment and outcome of recurrent osteosarcoma: Experience at Rizzoli in 235 patients initially treated with neoadjuvant chemotherapy Acta Oncologica, 2005; 44: 748-755
- Chou AJ, Merola PR, Wexler LH, et al. Treatment of Osteosarcoma at First Recurrence after Contemporary Therapy. The Memorial Sloan-Kettering Cancer Center Experience Cancer. 2005;104:2214–21
- Navid F, Willert JR, McCarville MB et al.Combination of Gemcitabine and Docetaxel in the Treatment of Children and Young Adults With Refractory Bone Sarcoma. Cancer 2008;113:419–25.
- Massimo B, Giovanni G, Stefano F et al. Cyclophosphamide and Etoposide for Relapsed High-risk Osteosarcoma Patients. Cancer 2009;115:2980–7
- Miser JS, Kinsella TJ, Triche TJ et al. Ifosfamide With Mesna Uroprotection and Etoposide: An Effective Regimen in the Treatment of Recurrent Sarcomas and Other Tumors of Children and Young Adults. J Clin Oncol 1987.5:1191-1198.
- Bacci G, Longhi A, Bertoni Fet al. Bone metastases in osteosarcoma patients treated with neoadjuvant or adjuvant chemotherapy The Rizzoli experience in 52 patients Acta Orthopaedica 2006; 77 (6): 938–943

Sauerbrey A, Bielack S, Bielack BK et al. High-dose chemotherapy (HDC) and autologous hematopoietic stem cell transplantation (ASCT) as salvage therapy for relapsed osteosarcoma. Bone Marrow Transplantation 2001. 27, 933–937.

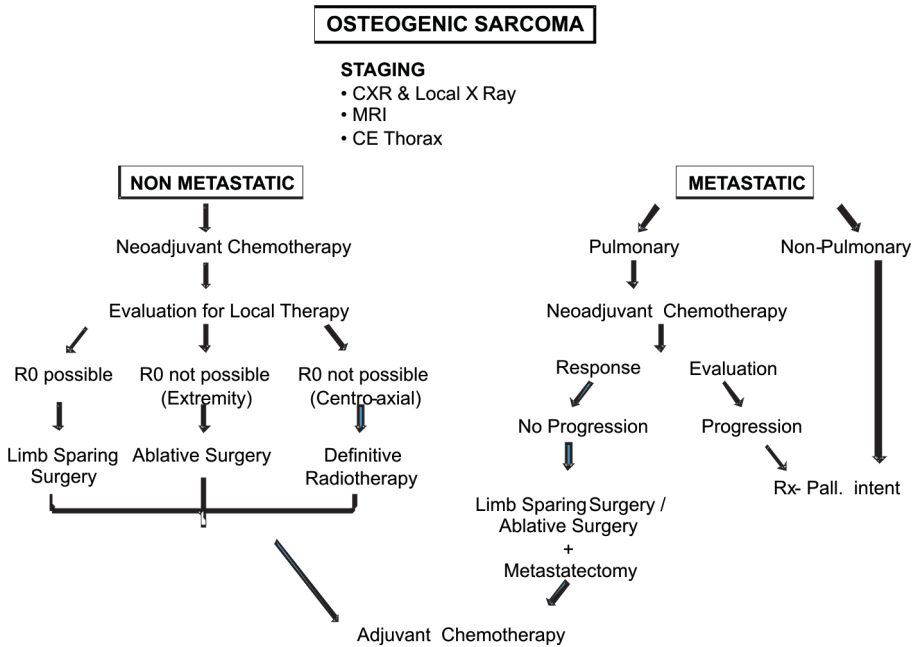
Fagioli F, Aglietta M, Tienghi A et al. High-Dose Chemotherapy in the Treatment of Relapsed Osteosarcoma: An Italian Sarcoma Group Study. J Clin Oncol 2002.20:2150-2156.

Summary: Post- relapse outcome in osteosarcoma depends on the time to relapse (<18 months worse than >18 months), the site of relapse (non-pulmonary worse than pulmonary) and in case of pulmonary metastases presence of unilateral, solitary lesion and the absence of pleural disruption are the favorable features. The prognosis of patients who relapse with bone metastases unless they have a single late appearing metastasis is worse than that of patients who first relapse with lung metastases.

Studies have shown that it is possible to obtain prolonged survival and cure in about 1/4 of relapsing osteosarcoma patients with aggressive treatments. Complete surgery is an essential component of curative second-line therapy. Poly-chemotherapy may contribute to limited improvements in outcome. Ifosfamide and Etoposide were found highly active in the treatment of recurrent sarcomas; Gemcitabine and docetaxel combination was also shown activity in recurrent or refractory osteosarcoma. In a phase II trial it was found that cyclophosphamide and etoposide arrested disease progression in a significant number of patients (54%) which translates in a better OS with a favorable toxicity profile. In a study, high dose chemotherapy consisted of carboplatin and etoposide (two courses) followed by stem-cell rescue combined with

surgery can induce CR in a large portion of patient who are chemosensitive to induction treatment, however most patients again relapse. Thus novel strategies are needed to maintain the remission status or to treat patients who do not respond to induction treatment.

Inference: Further evaluation of chemotherapeutic agents is warranted in relapse setting and till then at present definitive role of chemotherapy and transplant need to be defined in these patients.


OSTEOGENIC SARCOMA
STAGING
• CXR & Local X Ray
• MRI
• CE Thorax
NON METASTATIC
Neoadjuvant Chemotherapy
Evaluation for Local Therapy
R0 possible
R0 not possible (Extremity)
R0 not possible (Centro-axial)
Limb Sparing Surgery
Ablative Surgery
Definitive Radiotherapy
METASTATIC
Pulmonary
Non-Pulmonary
Neoadjuvant Chemotherapy
Response
Evaluation
No Progression
Progression
Rx- Pall. intent
Limb Sparing Surgery / Ablative Surgery
+
Metastatectomy
Adjuvant Chemotherapy

Section IV

Ewing's Sarcoma

Chemotherapy

I. Role of Dose Intensification of chemotherapy

- Bruget E, Nesbit M, Garnsey L, et al. Multimodal therapy for management of nonpelvic, localized Ewing's sarcoma of bone: a long term follow up of the first intergroup study. J Clin Oncol 1990;8,1664-74
- Granowetter L, Womer R, Devidas M, et al. Dose intensified compared with standard chemotherapy for nonmetastatic Ewing sarcoma family of tumors: a Children's Oncology Group Study. J Clin Oncol 2009; 27:2536-41
- Womer R, West D, Krailo M, et al. Chemotherapy intensification by interval compression in localized Ewing sarcoma family tumors (ESFT). Proc Am Soc Clin Oncol 2008: abstr 10504

Summary: The superiority of earlier dose intensity of doxorubicin was established in IESS-I regimen by Bruget et al (overall survival 77% vs 56%). Decreasing the length of treatment and increasing the doses of cyclophosphamide and ifosfamide intensity did not add to survival but increased toxicity as shown by Granowetter et al in the INT-0154 COG study. AEWS0031 study from COG compared VDC-IE treatment 2 weeks with VDC-IE treatment every 3 weeks with 14 cycles and equal

cumulative doses in both groups. Dose intensity of all agents was increased by 25% without increase in toxicity. Overall and event free survival, both improved in the interval-compressed group (EFS 79% vs 70% at 4 yrs: p = 0.023)

Inference: The above studies have demonstrated the superior efficacy of dose intensification in the treatment of localized ESFT.

Level of Evidence: II

II. Role of Risk adopted chemotherapy

- Paulussen M, Ahrens S, Dunst J, et al. Localized Ewing tumor of bone: final results of the coopertive Ewing's Sarcoma Study CESS 86. *J Clin Oncol* 2001; **19:** 1818–29.
- Paulussen M, Craft A, Lewis I, et al. Results of the EICESS-92 Study: two randomized trials of Ewing's sarcoma treatment- cyclophosphamide compared with ifosfamide in standard-risk patients and assessment of benefit of etoposide added to standard treatment in high-risk patients. *J Clin Oncol* 2008; **26:** 4385–93.
- Grier H, Krailo M, Tarbell N, et al. Addition of ifosfamide and etoposide to standard chemotherapy for Ewing's sarcoma and Primitive neuroctodermal tumor of bone. *N Engl J Med* 2003; **348:** 694–701.
- Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. *Pediatr Blood Cancer* 2006; **47:** 22–29.

Summary: The CESS study identified localized EFTS with volumes less than 200 ml as standard risk and those with metastases or higher volumes as high risk. In addition response to chemotherapy was identified as a prognostic factor for overall survival. The only randomized trial to adopt a risk group adopted chemotherapy regimens was

EICESS-92 which found no difference between VACA and VAIA for the standard risk patients and a slight advantage (though statistically insignificant) for EVAIA over VAIA in patients with high risk or metastatic EFTS. The addition of ifosfamide–etoposide to vincristine–doxorubicin–cyclophosphamide in the INT-0091 study did not improve the outcome for patients with metastases.

Inference: Risk stratification has a role as prognostic factor in ESFT. (Level 2). The addition of ifosfamide- etoposide may confer survival advantage in low risk ESFT but the advantage in metastatic and high risk ESFT is unclear.

Level of Evidence: III

III. Role of Bone Marrow Transplant in ESFT

- Meyers P, Krailo M, Ladany M, et al. High-dose melphalan, etoposide, total-body irradiation, and autologous stem-cell reconstitution as consoldation therapy for high-risk Ewing's sarcoma does not improve prognosis. *J Clin Oncol* 2001; 19: 2812–20.
- Oberlin O, Rey A, Desfachelles A, et al. Impact of high-dose busulfan plus melphalan as consolidation in metastatic Ewing tumors: a study by the Societe Francaise des Cancers de l'Enfant. *J Clin Oncol* 2006; 24: 3997–4002.
- Burdach S, van Kaick B, Laws H, et al. Allogeneic and autologous stem-cell transplantation in advanced Ewing tumors: an update after long-term follow-up from two centers of the Europen Intergroup Study EICESS. *Ann Oncol* 2000; 11: 1451–62.
- Burdach S, Meyer-Bahlburg A, Laws H, et al. High-dose therapy for patients with primary multifocal and early relapsed Ewing's tumors: results of two consecutive regimens assessing the role of total-body irradiation. *J Clin Oncol* 2003; 21: 3072–78.
- Juergens C, Weston C, Lewis I, et al. Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin and etoposide (VIDE) in the treatment of

Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. *Pediatr Blood Cancer* 2006; **47**: 22–29.

- Ladenstein R, Potschger U, Le Deley M et al. Primary Disseminated Multifocal Ewing Sarcoma: Results of the Euro-EWING 99 Trial *J Clin Oncol* July 10 2010 28:3284-3291

Summary: Most of the published literature assessing the impact of BMT in patients with metastatic ESFT are single arm studies restricted by numbers and non-uniformity of designs and conditioning chemotherapy schedules, which have shown conflicting results. Patients with only lung metastases at presentation in complete remission post induction chemotherapy have shown benefit with BMT, but no randomized trials are available for comparison. Very few patients with relapsed ESFT achieve a second remission and are eligible for BMT; and the benefit of BMT for them is uncertain.

In the Euro-EWING 99 trial, after a median follow-up of 3.8 years, event-free survival (EFS) and overall survival (OS) for all 281 patients were 27% and 34% respectively. 169 patients (60%) received HDT/SCT. The estimated 3-year EFS from the start of HDT/SCT was 45% for 46 children younger than 14 years. Cox regression analyses demonstrated increased risk at diagnosis for patients older than 14 years, a primary tumor volume more than 200 mL, more than one bone metastatic site, bone marrow metastases, and additional lung metastases. Preliminary comparative results for BMT versus no-BMT were presented in SIOP 2008 (Societe Internationale Oncologie Pediatrique) meeting and suggested significant improvement in survival with BMT.

Inference: Several non-randomized trials have assessed the value of more intensive, time-compressed or high-dose chemotherapy approaches, followed by autologous stem cell rescue, but evidence of benefit, e.g. resulting from

published randomized trials, is lacking. In patients with lung metastases, the resection of residual metastases after chemotherapy, and possibly whole lung irradiation, may offer a survival advantage.

Level of Evidence: III

IV. Role of Salvage chemotherapy for ESFT

- Saylors R, Stine KC, Sullivan J, et al. Cyclophosphamide plus topotecan in children with recurrent or refractory solid tumors: a Pediatric Oncology Group Phase II study. J Clin Oncol 2001 ; 19 (15): 3463 -9
- Hunold A, Weddeling N, Paulussen M. Topotecan and cyclophosphamide in patients with refractory or relapsed Ewing tumors. Pediatr Blood Cancer 2006 ; 47 (6): 795 - 800
- De Angulo G, Hernandez M, Morales-Arias J, et al. Early lymphocyte recovery as a prognostic indicator for high-risk Ewing sarcoma. J Pediatr Hematol Oncol 2007 ; 29 (1): 48 -52
- Wagner LM, Crews KR, Iacono LC, et al. Phase I trial of temozolomide and protracted irinotecan in pediatric patients with refractory solid tumors. Clin Cancer Res 2004 ; 10 (3): 840 -8
- Wagner LM, McAllister N, Goldsby RE, et al. Temozolomide and intravenous irinotecan for treatment of advanced Ewing sarcoma. Pediatr Blood Cancer 2007; 48 (2): 132 -9
- Anderson P, Kopp L, Anderson N, et al. Novel bone cancer drugs: investigational agents and control paradigms for primary bone sarcomas (Ewing's sarcoma and osteosarcomas) Expert Opin. Investig. Drugs 2008 17 (11):1703-1715

Summary: Two phase II studies have demonstrated upto 33% partial responses in relapsed refractory Ewing's sarcoma with the combination of Topotecan and Cyclophosphamide. German results confirmed the above with further surgery and radiotherapy improving the

complete response rates. Bernstein et al showed better outcomes with combination than with topotecan alone.

Houghton et al demonstrated preclinical activity of temozolomide + irinotecan which was proven to be clinically active by Wagner et al. The combination is lymphocyte sparing and lymphocyte recovery rates have been proven to be an independent prognostic factor in Ewing's sarcoma. Three phase II trials, though limited by the number of patients, have shown impressive outcomes with this combination, with high tolerance and patient acceptance.

Inference: The only prognostic factor identified in relapsed ESFT seems to be time to relapse: patients relapsing later than 2 years from initial diagnosis have a better outcome. Chemotherapy regimens in relapse situations are not standardized and are commonly based on alkylating agents (cyclophosphamide, ifosfamide) in combination with topoisomerase inhibitors (etoposide, topotecan) or irinotecan with temozolomide

Level of Evidence: II

V. Role of Response Adapted Therapy

- http://www.cancer.gov/clinicaltrials/EURO-EWING-INTERGROUP-EE99
- Ladenstein R, Pötschger U, Le Deley MC, et al.: Primary disseminated multifocal Ewing sarcoma: results of the Euro-EWING 99 trial. J Clin Oncol 28 (20): 3284-91, 2010.
- Juergens C, Weston C, Lewis I, et al.: Safety assessment of intensive induction with vincristine, ifosfamide, doxorubicin, and etoposide (VIDE) in the treatment of Ewing tumors in the EURO-E.W.I.N.G. 99 clinical trial. Pediatr Blood Cancer 47 (1): 22-9, 2006
- Cotterill SJ, Ahrens S, Paulussen M et al. Prognostic factors in Ewing's tumor of bone: analysis of 975 patients from

the European Intergroup Cooperative Ewing's Sarcoma Study Group. J Clin Oncol 2000; 18: 3108–3114.

Summary: The ongoing Euro-Ewings 99 trial studies histological response-adopted strategy comparing VAC with VAI as continuing chemotherapy for patients with good histological responses to induction VIDE, or small tumors treated with radiation. For large tumors or patients with poor histological responses, the study compared VAI with megatherapy and bone marrow rescue. The results to infer response adopted treatment strategy are still awaited. Response-adopted chemotherapy strategies still need further results from ongoing trials.

Inference: Under treatment, poor histological response to preoperative chemotherapy is an adverse prognostic factor II.The results of trials investigating response adapted therapy are awaited. Until then, this cannot be recommended outside of clinical trials.

Level of Evidence: III

Radiotherapy

Post-Operative Radiation Therapy in Ewing's Sarcoma

I. How much benefit in local control does RT provide after marginal resection

- Ozaki T, Hillmann A, Hoffmann C, et al. Significance of surgical margin on the prognosis of patients with Ewing's sarcoma.Areport from the Cooperative Ewing's Sarcoma Study. Cancer 1996; 78:892–900.
- Bacci G, Longhi A, Briccoli A, et al. The role of surgical margins in treatment of Ewing's sarcoma family tumors: Experience of a single institution with 512 patients treated with adjuvant andneoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 2006; 65:766–772.
- Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: Results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys 2003;55:168–177.

Summary: Bacci et al. noted a 16% absolute benefit in EFS with RT after inadequate surgery but it was not statistically significant. In the combined analysis of RT in the CESS and EICESS trials, the rates of local failure for marginal resection with or without RT were 5.8% and 5.6% respectively. This apparent lack of significant benefit must

be put in context. Since RT is usually indicated after marginal resections in most institutional or cooperative protocols, those not receiving PORT usually have favorable disease characteristics. In the analysis by Schuck et al., a much higher proportion of patients receiving RT had a poor histological response. Despite this, the two groups show equivalent local control. Can RT be omitted in marginal resections, if there has been a good histopathological response to chemotherapy? There is no direct evidence to suggest that surgical margins have a lesser impact in good responders. In the analysis by Bacci et al. the poor local control after inadequate surgical margins were irrespective of the histological response.

Inference: Patients with marginal or R1 resection irrespective of histopathological response to chemotherapy should receive RT

Level of Evidence: II

II. What is the Role of RT after intralesional resection?

- Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: Results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys 2003;55:168–177.
- Donaldson SS. Ewing sarcoma: Radiation dose and target volume. Pediatr Blood Cancer 2004;42:471–476.

Summary: RT administered after intralesional resection reduces the chances of local failure. In an analysis of CESS and EICESS data, the local failure rate was reduced from 28.6% to 20.5% with RT after intralesional resections. However, the outcomes after surgery and PORT were similar to control rates with RT alone. There is, therefore, little role for debulking surgery in EFT. Current consensus favors the use of PORT in all patients with marginal or

intralesional resection. Current Children's Oncology Group (COG) protocols have more specifically defined adequate margin status. Complete resection is defined as a minimum of 1 cm margin and ideally 2–5 cm around the involved bone. The minimum soft tissue margin for fat or muscle planes is at least 5 mm and for fascial planes at least 2 mm.

Inference: Post-operative RT is indicated in all patients with intralesional resection (R2). In cases where pre-operative evaluation suggests that R0 resection is not feasible, definitive RT is recommended.

Level of Evidence: II

III. Does PORT actually benefit patients with poor response to chemotherapy?

- Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: Results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys 2003;55:168–177.
- Lin PP, Jaffe N, Herzog CE, et al. Chemotherapy response is an important predictor of local recurrence in Ewing sarcoma. Cancer 2007;109:603–611.
- Wunder JS, Paulian G, Huvos AG, et al. The histological response to chemotherapy as a predictor of the oncological outcome of operative treatment of Ewing sarcoma. J Bone Joint Surg Am 1998;80:1020–1033.
- Elomaa I, Blomqvist CP, Saeter G, et al. Five-year results in Ewing's sarcoma. The Scandinavian Sarcoma Group experience with the SSG IX protocol. Eur J Cancer 2000;36:875–880.
- Oberlin O, Deley MC, Bui BN, et al. Prognostic factors in localized Ewing's tumours and peripheral neuroectodermal tumours: The third study of the French Society of Pediatric Oncology (EW88 study). Br J Cancer 2001;85:1646–1654.

Summary: The EICESS 92 was perhaps the first cooperative group trial to include poor histologic response

(<90% necrosis) as an indication for PORT even with clear surgical margins. In their analysis there was reduction in local failures (5% vs.12%) in the poor responders if they received PORT. The impact of this benefit on overall survival is not yet clear, but it seems rational to incorporate histopathological response to chemotherapy in the decision making process on PORT.

The best threshold for the extent of necrosis for the addition of PORT is yet unknown. According to the CESS and EICESS results, the local control rates with more than 90% necrosis seem low enough for omitting RT. Wunder et al. found no difference in outcomes between those who had 90–99% necrosis and those with 100% necrosis. In contrast, analyses by Elomaa et al., Oberlin et al. and Lin et al. seem to show that there is scope for improvement in those with necrosis up to 95% or 99%.

Inference: The inclusion of PORT, solely based on suboptimal response to chemotherapy, still requires further evaluation under clinical trials. The decision should be made after evaluating the risks vs. benefit of adjuvant PORT based on multiple factors after discussion with the treating multi-disciplinary team.

Level of Evidence: III

IV. Does tumor location influence the indication for PORT?

- Lin PP, Jaffe N, Herzog CE, et al. Chemotherapy response is an important predictor of local recurrence in Ewing sarcoma. Cancer 2007;109:603–611.
- Schuck A, Ahrens S, Paulussen M, et al. Local therapy in localized Ewing tumors: Results of 1058 patients treated in the CESS 81, CESS 86, and EICESS 92 trials. Int J Radiat Oncol Biol Phys 2003;55:168–177.

Summary: In the CESS and EICESS trials, the local failure rate for central primaries was reduced by 50% with PORT. Lin et al. also found an independent prognostic relevance for tumor site with PORT. However, the potential advantage of using PORT in all central primary disease sites must be weighed against the long term effects of RT to the pelvis or chest wall.

Inference: In patients with lesions involving the centro-axial skeleton where surgical margins are likely to be close the need for PORT even in patients with negative surgical margins should be discussed in the multi-disciplinary therapy (MDT) clinic.

Level of Evidence III

V. Does a poor histological response with microscopic margins merit a higher dose?

- Donaldson SS. Ewing sarcoma: Radiation dose and target volume. Pediatr Blood Cancer 2004;42:471–476.

Summary: However, no clear dose response relationship has been demonstrated in EFT for doses above 40 Gy. Also, in the CESS and EICESS studies, a dose of 45 Gy for post-operative cases with marginal resection and/or poor histological response demonstrated excellent local control, with local failure rates of only 5%.

Inference: In patients without gross residual disease receiving PORT, there is no benefit of PORT doses more than 45Gy in conventional fractionation.

Level of Evidence II

VI. Are lower radiation doses for selected patients an acceptable alternative?

- Merchant TE, Kushner BH, Sheldon JM, et al. Effect of low-dose radiation therapy when combined with surgical

resection for Ewing sarcoma. Med Pediatr Oncol 1999;33:65–70.
- Rosen G, Caparros B, Nirenberg A, et al. Ewing's sarcoma: Ten year experience with adjuvant chemotherapy. Cancer 1981; 47:2204–2213.
- Sauer R, Jurgens H, Burgers JM, et al. Prognostic factors in the treatment of Ewing's sarcoma. The Ewing's Sarcoma Study Group of the German Society of Pediatric Oncology CESS 81. Radiother Oncol 1987;10:101–110.

Summary: Results with low-dose radiation have been reported in radical and adjuvant settings with the intention of reducing long term sequelae while testing its efficacy in local disease control. Merchant et al. have reported a series of patients from Memorial Sloan-Kettering Cancer Center (MSKCC) treated with low dose RT (30–36 Gy) following limited surgery and demonstrated no local failures. Rosen et al. reported outcomes on patients treated with surgery and PORT with 30 Gy and reported satisfactory local control and a trend towards an overall survival benefit over surgery alone. A subset of patients in the CESS 81 trial also received low dose RT 36 Gy after inadequate resection with acceptable results. In contrast, Krasin et al. reported a trend towards inferior outcomes with PORT doses of $<$40 Gy in patients treated at St. Jude Children's Research Hospital (SJCRH). The rates of local failure with doses$<$40Gy was 15.5-7%versus 0-0%with higher doses.

Inference: Currently used adjuvant RT doses of 45 Gy result in excellent rates of local control ($>$90%) with only a small risk of severe late toxicity. Unless lower RT doses show local control rates that are unequivocally at par with these results, this dose may be considered the standard safe and effective dose in the post-operative setting.

Level of Evidence II

VII. What should be the Optimal timing for postoperative radiotherapy?

- Dunst J, Sauer R, Burgers JM, et al. Radiation therapy as local treatment in Ewing's sarcoma. Results of the Cooperative Ewing's Sarcoma Studies CESS 81 and CESS 86. Cancer 1991;67:2818–2825.
- Schuck A, Rube C, Konemann S, et al. Postoperative radiotherapy in the treatment of Ewing tumors: Influence of the interval between surgery and radiotherapy. Strahlenther Onkol 2002;178:25–31.

Summary: The timing of radiation after surgery is still an issue to be resolved. In an analysis of patients receiving PORT in the CESS 86 and EICESS trials, Schuck et al. reported no significant difference in the local control and survival of patients who received RT within 60 days of surgery or later. This is in contrast to the improved local control in CESS 86 over CESS 81 when the timing of RT was brought forward from the 18th week to the 10th week. Though there were other factors (including centralized radiation review and more intensive chemotherapy) that contributed to improved local control, it would be unadvisable to delay local treatment if it is to provide the maximum possible benefit.

Inference: There is at present no consensus regarding the optimal timing for post operative RT. It should be started within 6–8 weeks of surgery (though there is no evidence to suggest that a further delay leads to inferior outcomes)

Level of Evidence: III

VIII. Does PORT increase the chances of failure of flaps and prostheses?

- Spierer MM, Alektiar KM, Zelefsky MJ, et al. Tolerance of tissue transfers to adjuvant radiation therapy in primary

soft tissue sarcoma of the extremity. Int J Radiat Oncol Biol Phys 2003;56: 1112–1116.
- Jeys LM, Luscombe JS, Grimer RJ, et al. The risks and benefits of radiotherapy with massive endoprosthetic replacement. J Bone Joint Surg Br 2007;89:1352–1355.
- Safran MR, Kody MH, Namba RS, et al. 151 endoprosthetic reconstructions for patients with primary tumors involving bone. Contemp Orthop 1994;29:15–25.

Summary: PORT is frequently used in the presence of flap reconstruction in bone and soft-tissue sarcomas. In an institutional experience from MSKCC, 95% of flap reconstructions remain viable after RT for extremity sarcomas. The effect of RT on the viability of endoprostheses is a subject of debate. A higher incidence of infection following radiotherapy in the setting of massive endoprostheses has been reported. However, complications following endoprosthetic replacements may be common at certain sites even without adjuvant radiation, especially the distal femur, proximal tibia and the pelvis.

Inference: The decision should be made after evaluating the risks vs. benefit of adjuvant PORT based on multiple factors after discussion with the treating multi-disciplinary team.

Level of Evidence: III

IX. What is the incidence of second malignancies after radiotherapy?

- Craft AW, Cotterill SJ, Bullimore JA, et al. Long-term results from the first UKCCSGEwing's Tumor Study (ET-1). United Kingdom Children's Cancer Study Group (UKCCSG) and the Medical Research Council Bone Sarcoma Working Party. Eur J Cancer 1997;33:1061–1069.
- Dunst J, Ahrens S, Paulussen M, et al. Second malignancies after treatment for Ewing's sarcoma: A report of the CESS-studies. Int J Radiat Oncol Biol Phys 1998;42:379–384.

- Gasparini M, Lombardi F, Ballerini E, et al. Long-term outcome of patients with monostotic Ewing's sarcoma treated with combined modality. Med Pediatr Oncol 1994;23:406–412.
- Kuttesch JF Jr,Wexler LH, Marcus RB, et al. Second malignancies after Ewing's sarcoma: Radiation dose-dependency of secondary sarcomas. J Clin Oncol 1996;14:2818–2825.
- McLean TW, Hertel C, Young ML, et al. Late events in pediatric patients with Ewing sarcoma/primitive neuroectodermal tumor of bone: The Dana-Farber Cancer Institute/Children's Hospital experience. J Pediatr Hematol Oncol 1999;21:486–493.
- Paulussen M, Ahrens S, Lehnert M, et al. Second malignancies after ewing tumor treatment in 690 patients from a cooperative German/Austrian/Dutch study. Ann Oncol 2001;12:1619–1630.

Summary: Several authors have evaluated the incidence of second malignancies after treatment of EFT. The incidence has been in the range of 2–10% in these reports. While 50–60% of these have been sarcomas induced by RT, the remaining were hematological malignancies, mainly acute myeloid leukemia and myelodysplastic syndromes, induced by chemotherapy. In a radiation dose-dependency analysis from a multi-institutional database of patients with EFT, Kuttesch et al. found no second cancers among patients receiving less than 48 Gy. Most of the patients receiving PORT receive doses of about 45 Gy that may be safe from this viewpoint. Moreover, in the CESS experience, most secondary bone sarcomas could be easily resected and did not contribute to mortality.

Inference: Second malignancy is a known late adverse event after treatment of ESFT. Based on currently available evidence a dose less than 48Gy has been found to be safe in terms of development of radiation induced second malignancies.

Level of Evidence: III

Role of local Treatment in metastatic Ewing's sarcoma

Patients of Ewing's sarcoma with metastasis only to the lungs

- Odile Oberlin, Annie Rey, Anne Sophie et al, Impact of High-Dose Busulfan plus Melphalan As Consolidation in Metastatic Ewing Tumors: A Study by the Société Francaise des Cancers de l'Enfant. J Clin Oncol 2006;24:3997-4002
- Bölling T, Schuck A, Paulussen M et al. Whole lung irradiation in patients with exclusively pulmonary metastases of Ewing tumors.Toxicity analysis and treatment results of the EICESS-92 trial. StrahlentherOnkol. 2008 Apr;184(4):193-7. (Article seems to be in German)
- Paulussen M, Ahrens S, Craft AW et al. Ewing's tumors with primary lung metastases: survival analysis of 114 (European Intergroup) Cooperative Ewing's Sarcoma Studies patients. J ClinOncol. 1998 Sep;16(9):3044-52.
- M. Paulussen, S. Bielack, H. Jürgens, P. G. Casali On behalf of the ESMO Guidelines Working Group Ewing's sarcoma of the bone: ESMO Clinical Recommendations for diagnosis, treatment and follow-up. Annals of Oncology. 20;14:140 -142
- Pinkerton CR, Bataillard A, Guillo S et al. Treatment strategies for metastatic Ewing's sarcoma. Eur J Cancer. 2001 Jul;37(11):1338-44.

Summary: Odile Oberlin et al. in their study of 99 patients with metastatic Ewing's sarcoma recommended surgery for local treatment of the primary tumor. Lung irradiation was not delivered as Busulfan itself causes pulmonary toxicity. The EFS for the 44 patients with lung-only metastases was 52%, whereas it was 36% for patients with bone metastases without bone marrow involvement. Among the 23 patients with bone marrow metastases, only one survived. Univariate analysis found that patients with lung-only metastases had a better outcome than patients with combined metastases or other metastatic sites. Patients with lung-only metastases had a better prognosis than patients who had bone metastases at diagnosis (with or without lung metastases) without bone marrow involvement. The third group (patients with bone marrow involvement) had the worst prognosis. Treatment failures in patients with lung-only metastases mainly were due to pulmonary/pleural relapses, either isolated or combined with local failure (12 of 13). Based on this observation, Odile et al. raised the question of the role of local therapy for the lungs and pleural space. They therefore suggest that bilateral lung irradiation with 15 to 20 Gy therefore could be an attractive alternative to busulfan-based HDCT.

Bolling T et al. studied 99 patients who were registered into the EICESS-92-study trial with exclusively pulmonary metastases of Ewing tumors. The multimodal treatment regimen included polychemotherapy and local therapy to the primary tumor. Whole Lung Irradiation (WLI) was performed with a dose between 12-21 Gy. Overall survival (OAS) showed a trend towards better results for patients with WLI (5-year-OAS: 0.61 for WLI vs. 0.49 for no WLI, $p = 0.36$). They concluded that these data indicate a benefit and acceptable toxicity for WLI in the presented collective

of patients. As long as there is no randomized prospective analysis, the present data confirm the indication for WLI in Ewing tumor patients with primary exclusively lung metastases.

Paulussen M et al. studied 114 patients of Ewing sarcoma with synchronous pulmonary/pleural metastasis. Patients underwent neoadjuvant therapy and local treatment of the primary tumor. Whole-lung irradiation 15 to 18 Gy was applied to 75 pts. Risk factors identified in univariate and multivariate tests were poor response to chemotherapy, metastatic lesions in both lungs, and treatment without additional lung irradiation.

Paulussen M et al.Ewing's sarcoma of the bone: ESMO Clinical Recommendations for diagnosis, treatment and follow-up clearly state that outside specific clinical trials, patients with metastatic disease ought to receive similar therapy to that given for localized disease, with appropriate local treatment of metastases, commonly applied as radiotherapy. In patients with lung metastases, the resection of residual metastases after chemotherapy, and possibly whole lung irradiation, may confer a survival advantage

Pinkerton CR et al. after reviewing several articles concluded that it appears that patients with isolated lung metastases do significantly better (approximately 40% EFS) than those presenting with combined sites such as bone, bone marrow and lung. The use of lung irradiation in children with lung metastases is associated with a reduced incidence of subsequent lung recurrence and a consistently better overall relapse-free survival (RFS).

Patients of ES with only extrapulmonary metastasis

- Haeusler J, Ranft A, Boelling T, Gosheger G et al. The value of local treatment in patients with primary,

disseminated, multifocal Ewing sarcoma (PDMES). Cancer. 2010 Jan 15;116(2):443-50.

This article discusses the results of 120 patients registered into the European Ewing Tumor Working Initiative of National Groups (EURO-E.W.I.N.G. 99) trial at the trial center of Muenster from 1998 to 2006. A cohort of 120 patients with newly diagnosed, extrapulmonary, primary, disseminated multifocal Ewing sarcoma (PDMES) and were analyzed. The univariate analysis on the value of local treatment modalities showed a significantly lower 3-year EFS rate in patients who had no local therapy of the primary tumor (0.13) when compared with those who received either surgery (0.25) or radiotherapy of the primary tumor (0.23). Remarkably, an even higher 3-year EFS of 0.47 was achieved when surgery and radiotherapy of the primary tumor were combined ($P < .001$). Similar results were found by univariate analysis of the local treatment given to extrapulmonary metastases. Without local treatment of metastases, 3-year EFS was 0.16, when compared with 0.33 for surgery, and 0.35 for radiotherapy of extrapulmonary metastases. In a small group of patients ($n = 9$) who had surgery and radiotherapy of extrapulmonary metastases, the combined 3-year EFS even reached 0.56 ($p = .003$). Patients who received any local treatment of both primary tumor and metastases had a 3-year EFS of 0.39 ,compared with 0.17 in those who received any local treatment of either the primary tumor or extrapulmonary metastases and 0.14 in patients without any local therapy ($P < .001$). When 17 patients with progression of disease within 0.6 years from diagnosis, i.e., before local therapy or highdose chemotherapy according to the EURO-E.W.I.N.G. 99 treatment protocol were excluded, multivariate analysis proved the absence of local therapy to be the only significant risk factor in the

remaining population (HR =2.21; P = .027). Combined modality treatment is widely accepted to be an essential requirement in localized or pulmonary metastatic Ewing sarcoma. This is the first report on the value of local therapy in patients with multifocally disseminated disease, excluding patients with lung metastases only. Local treatment significantly improved the prognosis in patients with primarily, disseminated Ewing sarcoma. Outcome with local treatment of both primary tumor and extrapulmonary metastases was superior (3-year EFS = 0.39; n = 47) to results with local treatment of either the primary tumor or extrapulmonary metastases (3-year EFS = 0.17; n = 41) or with no local treatment (3-year EFS = 0.14; n = 32) (P < .001). Furthermore, local treatment modalities (surgery, radiotherapy, surgery and radiotherapy combined) had an impact on EFS. Regarding local treatment of both the primary tumor and extrapulmonary metastases, combined-modality treatment was associated with a significantly better EFS than single-modality local treatment and no local treatment. This data clearly shows that combined-modality treatment has a major impact on survival. In summary, local therapy of the primary tumor and of viable metastases could improve the prognosis in patients with highly advanced, extrapulmonary, metastatic Ewing tumor and warrants further investigation.

In summary local treatment of both, primary site and the extra-pulmonary metastatic focus is important. Local treatment can be either in the form of Surgery or Radiotherapy or a combination of both . Combining both Surgery and Radiotherapy for local treatment gives the best EFS, while using either Surgery or Radiotherapy gives lower EFS, but is still better than no local treatment.

Recommendations: Role of local Treatment in metastatic Ewing's sarcoma

- **In patients with primary bone tumor with only pulmonary/pleural metastasis:**

➢ Surgery + Radiotherapy (as indicated) of the primary site

➢ Whole Lung irradiation

➢ To consider – resection of the pulmonary nodules if possible before lung irradiation.

- **In patients with primary bone tumor with extra-pulmonary (bone- metastasis) without marrow disease:**

➢ Local treatment of both primary site and the extra-pulmonary metastatic focus is important.

➢ Local treatment can be either in the form of Surgery or Radiotherapy or a combination of both

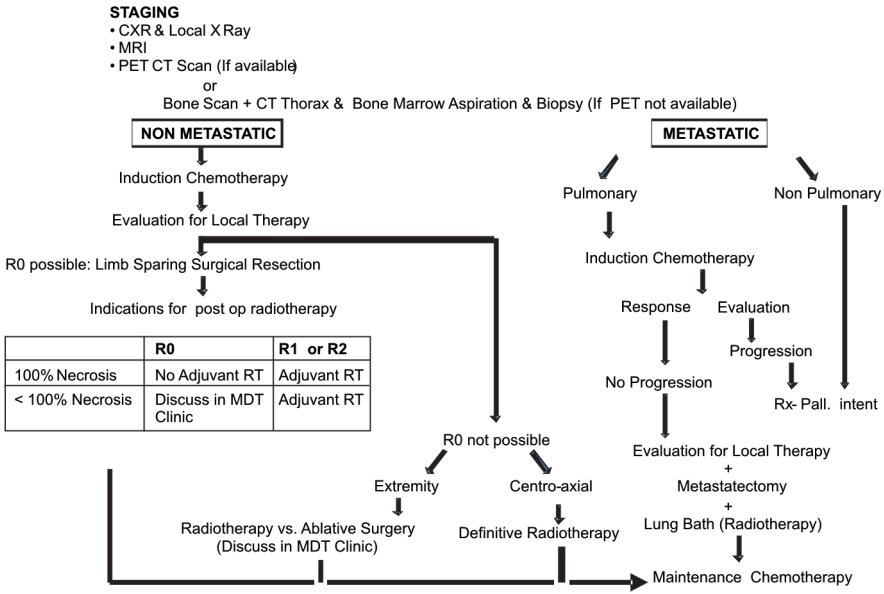
➢ Using both Surgery and Radiotherapy for local treatment gives the best EFS, while using either Surgery or Radiotherapy gives lower EFS, but this is still better than no local treatment.

- **In patients with primary bone tumor with marrow disease with/without other metastasis:**

➢ All the studies project a very poor prognosis for patients with bone marrow involvement. Many studies have shown that with current high dose chemotherapeutic regimes (Busulphan – Melphelan) and autologous transplantation, these patients could still be treated with curative intent.

➢ Local treatment should be on similar lines as In patients with primary bone tumor with extra-pulmonary (bone- metastasis) without marrow disease.

EWING'S SARCOMA



Section V

Soft Tissue Sarcomas

Current classification system for soft tissue tumors

- Fletcher CDM. The evolving classification of soft tissue tumors: an update based on the new WHO Classification. Histopathology 2006; 48: 3-12.
- Green FL, Page DL, Fleming ID, Fritz AG, Balch CM, Haller DG, Morrow M (2002). AJCC Cancer Staging Manual. 6th ed. Springer: New York.
- Coindre JM, Terrier P, Guillou L, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: a study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001; 91:1914–1926.
- Fletcher CDM, Unni KK, Mertens F. WHO classification of soft tissue tumors. *Pathology and Genetics: Tumors of Soft Tissue and Bone.* Lyon, France: IARC Press, 2002.
- Guillou, L, J. M. Coindre, and F. Bonichon, et al. Comparative study of the National Cancer Institute and French Federation of Cancer Centers Sarcoma Group grading systems in a population of 410 patients with soft tissue sarcoma. J Clin Oncol 1997; 15: 350–362.
- Brown FM, Fletcher CDM. Problems in Grading Soft Tissue Sarcomas. Am J Clin Pathol 2000; 114(Suppl 1):S82-S89.
- Hoeber I, Spillane AJ, Fisher C, Thomas JM. Accuracy of biopsy techniques for limb and girdle soft tissue tumors. Ann Surg Oncol 2001; 8: 80-87.

- Antonescu AR. The role of genetic testing in soft tissue sarcoma. Histopathology 2006; 48: 13-21.
- Demetri G, Antonia S, Benjamin RS. The NCCN. Soft tissue sarcoma. Clinical practice guidelines in oncology J Natl Comprehensive Cancer Network; 2010 (8): 630-74.
- Association of Directors of Anatomic and Surgical Pathology. Recommendations for the reporting of soft tissue sarcomas. Hum Pathol 1999; 30: 3–7.
- Hasegawa T, Yamamoto S, Yokoyama R, Umeda T, Matsuno Y, Hirohashi S. Prognostic significance of grading and staging systems using MIB-1 score in adult patients with soft tissue sarcoma of the extremities and trunk. Cancer 2002; 95: 843–851.

Summary: Soft tissue tumors (STTs), including sarcomas are a complex, heterogenous group of tumors. A considerable histopathological overlap within the different tumor types creates a substantial challenge for a pathologist, especially the one who is not familiar with evaluating these uncommon tumors. At the same time, identification of more than 100 histologic subtypes can be baffling to the treating oncosurgeon. During the past two decades there have been tremendous advances in the diagnosis of these tumors. Diagnosis of soft tissue tumors has moved ahead of the 'time honored' histopathological approach, based on "pattern recognition" and "pattern analysis", into the 'brown revolution' of immunohistochemistry and has embraced the next, molecular "genetic revolution"; all that have refined its classification systems, finally leading to facilitate reproducible diagnosis and more sophisticated prognostication.

Evaluation of a soft tissue sarcoma (STS) essentially includes staging, histological grading, and assigning a 'histogenetic label', the latter is vital for all soft tissue tumors.

The major staging system used for STS formed by International Union against Cancer (UICC) and American Joint Committee on Cancer (AJCC) appears to be clinically useful and of prognostic value. The TNM system incorporates histologic grade, tumor size, depth, regional lymph node involvement and distant metastasis. Among various parameters, histological grading of sarcomas has been found to have the most prognostic significance. Presently, the most acceptable histological grading system for STS is the National Cancer Institute (NCI) grading system and the French/Trojani (FNCLCC) system. Both are three-tier systems. The FNCLCC system is based upon parameters like tumor differentiation (the controversial parameter, but clarified), mitosis and percentage of tumor necrosis. This limits grading sarcomas like myxoid liposarcoma, alveolar soft part sarcoma, synovial sarcoma, extraskeletal myxoid chondrosarcoma and desmoplastic round cell tumor. While the former most is included as an intermediate grade sarcoma, all the latter entities are counted as high grade sarcomas, based on their histological types. In this way morphology and grading are complementary. It is noteworthy that staging and grading cannot substitute for a histogenetic 'label'. Specific examples include pediatric soft tissue sarcomas; de-differentiated liposarcomas etc.

The World Health Organization (WHO) 2002 classification of tumors is the most acceptable system of classifying soft tissue tumors. Apart from the conventional, benign and malignant counterparts, this new classification includes a revised categorization of biological behavior that now allows for two designations of intermediate malignancy: locally aggressive and rarely metastasizing. Examples for the former category include desmoid fibromatosis and for the latter include an angiomatoid fibrous histiocytoma

(AFH), inflammatory myofibroblastic tumor etc. This classification system essentially stratifies the various tumors based upon the line of differentiation, namely adipocytic, fibroblastic/myofibroblstic, so-called fibrohistiocytic, smooth muscle, pericytic (perivascular), skeletal muscle, vascular, chondo-osseous and tumors of uncertain differentiation. This classification also redefines certain existing lesions; for example, the term malignant fibrous histiocytoma (MFH) has been replaced with the term undifferentiated pleomorphic sarcoma that forms not more than 5% of sarcomas, The earlier "waste basket" of MFH should be cleared by sorting out these pleomorphic sarcomas into specific lineages, wherein pleomorphic sarcoma with myogenic differentiation has been found to have a relatively aggressive outcome. The other significant conceptual advances, include the formal recognition that morphologically benign lesions (such as cutaneous fibrous histiocytomas) may very rarely metastasize; most lesions formerly known as hemangioperictyomas, show no evidence of pericytic differentiation and instead form a morphologic continuum with solitary fibrous tumor; identification of tumors that do not display a specific lineage/line of differentiation into the category of 'uncertain differentiation'. These include tumors like synovial sarcoma, alveolar soft part sarcoma (ASPS), clear cell sarcoma of soft parts that are included as high grade sarcomas, along with benign tumors like intramuscular myxomas intermediate malignant tumors like AFH and entities like PECOMAS.

The limitations of the current classification systems include challenge in interpretation on Tru-cut / core needle biopsies in some cases. The tumor heterogeneity within soft tissue tumors can lead to under diagnosis of entities like low-grade fibromyxoid sarcoma, certain liposarcomas, to name

a few, as a result of tissue sampling. While on one hand it has been stated that grading based on limited biopsy material may be an underestimate or non representative, experience form Royal Marsden hospital in over 500 patients has indicated that core needle biopsy accurately discriminated benign and malignant soft tissue tumors with a sensitivity of > 98%. In the same study exact histologic subtype was identified in 80% cases and sarcoma grading in 85% cases. Increasing diagnosis on limited biopsies necessitates a more representative sample, including with image guided techniques (PET imaging), as well as the diagnosing pathologist to develop expertise. Identification of cases within the category of tumors with uncertain differentiation, as per WHO classification, leaves a subset of cases with unclear treatment guidelines. Further, round cell sarcomas with unclear line of differentiation after application of a battery of Immunohistochemical markers may be subjected to molecular analysis for a specific 'genetic signature' that could be helpful in triaging such cases for specific line of treatment, especially chemotherapy. In that league, several lines of evidence suggest that sarcomas can also be divided into two major genetic groups: 1) sarcomas with specific genetic alterations and simple karyotypes, such as reciprocal translocation (e.g. SYT-SSX in synovial sarcomas) and specific oncogenic mutations (e.g. KIT mutation in gastrointestinal stromal tumors); and 2) sarcomas with non-specific genetic alterations and complex unbalanced karyotypes. This stratification has been found to have diagnostic and prognostic relevance. However, this needs to be validated with prospective study designs, uniformity in application of molecular techniques and appropriate statistical methods for generating a robust evidence for its usage in clinical practice.

Classification of STSs has clinical relevance. After diagnosis and the metastatic work-up (that includes option for certain imaging modalities for example CNS imaging in ASPS and angiosarcomas), a multidisciplinary team decides upon a treatment plan. Surgery forms the treatment mainstay wherein the tumor extent excision is balanced with preservation of limb functions, especially in extremity sarcomas. For larger, high grade sarcomas, adjuvant or neoadjuvant chemotherapy (CT) is offered, based upon histologic subtypes, especially pediatric soft tissue sarcomas like rhabdomyosarcoma, PNET and DSRCT that are candidates for specific CT. CT is also offered in adult STSs like synovial sarcomas and myxoid/round cell liposarcomas. Identification of several gene transcripts within STSs is unraveling a new 'era' of targeted therapy that can be explored.

The WHO classification system is the most acceptable system that to a large extent, defines various STTs into diagnostic and prognostic subtypes. By univariate analysis, histologic type and grading have been found to be predictive for metastatic outcomes of STS. Apart from its impact on metastatic risk, histological grading is predictive of local recurrence for adult STS and therefore, it is recommended in pathology reporting of STS. The challenge of grading sarcomas on small biopsies can be overcome by application of MIB 1 staining (proliferation marker) that has been found to have better predictive value over mitosis; usage of 2-tier classification (low and high grade) and achieving more representative biopsies with image guidance. The limitation of grading pediatric sarcomas by the usual system and staging retroperitoneal sarcomas is being overcome by alternate classification systems.

Above all is the clinic-radio-pathological approach that is most helpful is translating the various classifications into clinical relevance. Increasing evidence is generating for molecular stratification of soft tissue sarcomas along with newer ways of prognostication like nomograms. These need to be validated with prospective cohort studies.

Radiation therapy for Soft Tissue Sarcomas

I. What is the Role of Radiation Therapy in Limb Salvage?

- The treatment of soft-tissue sarcomas of the extremities: prospective randomized evaluations of (1) limb-sparing surgery plus radiation therapy compared with amputation and (2) the role of adjuvant chemotherapy. Rosenberg SA, Tepper J, Glatstein E, Costa J, Baker A, Brennan M, DeMoss EV, Seipp C, Sindelar WF, Sugarbaker P, Wesley R; Ann Surg. 1982 Sep;196(3):305-15.
- Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, DeLaney T, Glatstein E, Steinberg SM, Merino MJ, Rosenberg SA ; J Clin Oncol; 16(1):197-203 1998.
- Long-term results of a prospective randomized trial of adjuvant brachytherapy in soft tissue sarcoma. Pisters PW, Harrison LB, Leung DH, Woodruff JM, Casper ES, Brennan MF.; J Clin Oncol 1996 Mar;14(3):859-68.

Summary: The only randomized trial published till date comparing limb sparing surgery followed by adjuvant radiation therapy versus amputation showed that there was no difference in local disease control & overall survival between the two treatment groups. This study formed the basis for limb conservation in soft tissue sarcomas.

Another randomized study that compared the results of limb sparing surgery alone compared to limb sparing surgery & adjuvant external beam radiotherapy (EBRT) showed that there was a significant decrease in the local recurrence rates in the patients receiving EBRT. This improvement in local control was not only seen amongst patients with high/ intermediate grade tumors but also in patients with low grade tumors. Similar results were reported from a randomized trial comparing limb sparing surgery versus limb sparing surgery followed by adjuvant interstitial brachytherapy (BRT) although the improvement was significant only in patients with high grade tumors & not with low grade sarcomas.

Inference: A published randomized trial addressing the efficacy of adjuvant radiation therapy suggests that radiation therapy either in the form of EBRT & BRT improves local disease control in patients undergoing limb preserving surgery.

Level of evidence – II

II. Can Radical Interstitial Brachytherapy obviate the need for External Beam Radiation Therapy?

- Perioperative Interstitial Brachytherapy for Soft Tissue Sarcomas: Prognostic Factors and Long-Term Results of 155 Patients. Siddhartha Laskar, Gaurav Bahl, Ajay Puri, Manish G. Agarwal, MaryAnn Muckaden, Nikhilesh Patil, Nirmala Jambhekar, Sudeep Gupta, Deepak D. Deshpande, Shyam K. Shrivastava, and Ketayun A. Dinshaw. Annals of Surgical Oncology. 2007: 14: 560-567.
- Interstitial Brachytherapy for Childhood Soft Tissue Sarcoma. Siddhartha Laskar, Gaurav Bahl, Mary Ann Muckaden, Ajay Puri, Manish G. Agarwal, Nikhilesh Patil, Shyam K. Shrivastava, and Ketayun A. Dinshaw. Pediatric Blood & Cancer. 2007: 49: 649-655.

Summary: There are no published randomized trials comparing radical BRT with EBRT. Relatively large prospective and retrospective studies have reported similar local control rates with radical BRT compared to post-operative adjuvant EBRT in appropriately selected patients where the entire tumour bed could be adequately included in the brachytherapy volume. Radical interstitial brachytherapy also resulted in lesser soft tissue complication rates & a shorter duration of hospital visit for the patient.

Inference: Radical interstitial brachytherapy is an effective modality of adjuvant treatment for optimally selected patients with soft tissue sarcomas undergoing WLE.

Level of evidence - III

III. Pre-operative versus Post-operative Radiotherapy?

- Preoperative versus postoperative radiotherapy in soft-tissue sarcoma of the limbs: a randomised trial. - O'Sullivan B, Davis AM, Turcotte R, Bell R, Catton C, Chabot P, Wunder J, Kandel R, Goddard K, Sadura A, Pater J, Zee B. ; Lancet. 2002 Jun 29;359 (9325):2235-41.
- Preoperative vs. postoperative radiotherapy in the treatment of soft tissue sarcomas: a matter of presentation - Pollack A, Zagars GK, Goswitz MS, Pollock RA, Feig BW, Pisters PW.

Summary: The only randomized trial published till date comparing pre-operative versus post-operative radiotherapy showed that post-operative wound complications (120 days post-op) were significantly higher in the pre-operative RT group. The overall survival was marginally superior in the patients receiving pre-operative radiotherapy arm. Similar improvement in local disease control was noticed in another non-randomized trial

comparing the two difference approaches of radiotherapy. An important finding of this study was that the improvement in local control with pre-op EBRT was only in patients with gross disease while the benefit of post-op EBRT was significant in the patients presenting with unknown margins after gross total resection.

Inference: Pre-operative radiotherapy is beneficial for patients with gross disease/ primary disease while post-operative radiotherapy is of benefit for patients with unknown surgical margins after gross total resection. Pre-op EBRT results in a significant increase in the incidence of post-op wound complications.

Level of evidence - II

IV. Can we avoid Radiation Therapy for High Grade STS with Wide Surgical Margins?

- Long-term results of prospective trial of surgery alone with selective use of radiation for patients with T1 extremity and trunk soft tissue sarcomas. Pisters PW, Pollock RE, Lewis VO, Yasko AW, Cormier JN, Respondek PM, Feig BW, Hunt KK, Lin PP, Zagars G, Wei C, Ballo MT. Ann Surg. 2007 Oct;246(4):675-81; discussion 681-2.
- Surgery alone is adequate treatment for early stage soft tissue sarcoma of the extremity. Al-Refaie WB, Habermann EB, Jensen EH, Tuttle TM, Pisters PW, Virnig BA. Br J Surg. 2010 May;97(5):707-13.
- Improved survival with radiation therapy in high-grade soft tissue Sarcomas of the extremities: a SEER analysis. Matthew Koshy, Shayna E. Rich, Majid M. Mohiuddin. Int. J. Radiation Oncology Biol. Phys., Vol. 77, No. 1, pp. 203–209, 2010.
- Association of local recurrence with subsequent survival in extremity soft tissue sarcoma.- Lewis JJ, Leung D, Heslin M, Woodruff JM, Brennan MF. J Clin Oncol. 1997 Feb;15(2):646-52.

Summary: There are no randomized trials comparing the local control rates of wide local excision versus wide local

excision (WLE) followed by radiation therapy for high grade sarcomas. The study from MD Anderson Cancer Centre reported local recurrence rates of 8% & 11% at 5 & 10 years for patients with T1a lesions having undergone R0 resection and no further adjuvant therapy. A recent publication based on the SEER data suggested that adjuvant radiation therapy could possibly be avoided in patients with T1 (<5cm) who have undergone WLE with negative surgical margins. The results need to be interpreted in the correct perspective as this being a non-randomized study and patients with poor prognostic features went on to receive adjuvant radiotherapy, thus nullifying the possible beneficial effect of adjuvant radiotherapy. In another recent SEER data publication, the authors recommended radiation therapy for all patients with high grade sarcomas. The other important fact is that adjuvant radiotherapy could only be expected to improve local disease control and not overall survival as suggested in the publication. The importance of local disease control in preventing distant metastasis has also been reported.

Inference: In the absence of randomized trial addressing the issue of adjuvant radiotherapy for T1 high grade STS; it would be advisable to treat such patients with radical interstitial brachytherapy that would be ideal for patients with such small lesions.

Level of evidence - II

V. What is the benefit of Radiation Therapy for Low Grade STS?

- Randomized prospective study of the benefit of adjuvant radiation therapy in the treatment of soft tissue sarcomas of the extremity. Yang JC, Chang AE, Baker AR, Sindelar WF, Danforth DN, Topalian SL, DeLaney T, Glatstein E, Steinberg SM, Merino MJ, Rosenberg SA ; J Clin Oncol; 16(1):197-203 1998.

Summary: In this only randomized trial addressing the role of adjuvant EBRT in patients with low grade STS undergoing WLE, the authors reported 50 patients with low-grade lesions (24 randomized to resection alone and 26 to resection and postoperative XRT), there was a lower probability of local recurrence ($p = 0.016$) in patients receiving adjuvant radiotherapy, although without a difference in overall survival.

Inference: Adjuvant radiotherapy can be avoided only in very select group of patients in the absence of any of the adverse prognostic factors like deep seated tumor, >5cm, & close or positive surgical margins.

Level of evidence - II

VI. Is there any benefit of Advanced Radiotherapy Techniques like IMRT for STS?

- Impact of intensity-modulated radiation therapy on local control in primary soft-tissue sarcoma of the extremity. Alektiar KM, Brennan MF, Healey JH, Singer S. J Clin Oncol. 2008 Jul 10;26(20):3440-4.
- Intensity modulated radiation therapy for retroperitoneal sarcoma: a case for dose escalation and organ at risk toxicity reduction. Koshy M, Landry JC, Lawson JD, Staley CA, Esiashvili N, Howell R, Ghavidel S, Davis LW. Sarcoma. 2003;7(3-4):137-48.

Summary: IMRT in STS of the extremity provides excellent local control in a group of patients with high risk features. This suggests that the precision with which IMRT dose is distributed has a beneficiary effect in sparing normal tissue and improving local control. This is of greater significance for retroperitoneal sarcomas where radiation dose delivery is often difficult due to the proximity to critical structures like the spinal cord, kidneys, liver, intestines, urinary bladder & rectum.

Level of evidence - III

VII. Impact of Interval between Surgery & Radiation Therapy?

- Interval between surgery and radiotherapy: effect on local control of soft tissue sarcoma. Ballo MT, Zagars GK, Cormier JN, Hunt KK, Feig BW, Patel SR, Pisters PW. Int J Radiat Oncol Biol Phys. 2004 Apr 1;58 (5):1461-7.

Summary: The records of 799 patients who underwent postoperative RT for soft tissue sarcoma between 1960 and 2000 were retrospectively reviewed. Univariate and multivariate analyses were used to evaluate the potential impact of the timing of postoperative RT on the rate of local control (LC). A delay between surgery and the start of RT of >30 days was associated with a decreased 10-year LC rate, but this association was not statistically significant (76% vs. 83%, p = 0.07). The potential association between RT delay and inferior LC attributed to an imbalance in the distribution of other prognostic factors. The authors concluded that the interval between surgery and RT did not significantly impact the 10-year LC rate and that their findings indicated that an RT delay should not be viewed as an independent adverse factor for LC and that treatment intensification may not be necessary for patients in whom a treatment delay has already occurred.

Level of evidence - III

Chemotherapy in Soft Tissue Sarcomas

I. Role of adjuvant chemotherapy in soft tissue sarcoma

- Sarcoma Meta-Analysis Collaboration. Adjuvant chemotherapy for localised resectable soft-tissue sarcoma of adults: Meta-analysis of individual data. Lancet 1997;350: 1647–1654. N. Pervaiz, N. Colterjohn, F. Farrokhyar, R. Tozer, A.
- Figueredo, and M. Ghert, "A systematic meta-analysis of randomized controlled trials of adjuvant chemotherapy for localized resectable soft-tissue sarcoma," Cancer, vol. 113, no.3, pp. 573–581, 2008.
- Frustaci S, Gherlinzoni F, De Paoli A et al. Adjuvant chemotherapy for adult soft tissue sarcomas of the extremities and girdles: Results of the Italian randomized cooperative trial. J Clin Oncol 2001;19:1238 –1247.
- P. J. Woll, M. van Glabbeke, P. Hohenberger, et al., "Adjuvant chemotherapy with doxorubicin and ifosfamide in resected soft tissue sarcoma: interim analysis of a randomised phase III trial," Journal of Clinical Oncology, vol. 25, p. 18S, 2007, ASCO Annual Meeting Proceedings.
- Le Cesne A, Van Glabbeke M, Woll PJ et al. The end of adjuvant chemotherapy (adCT) era with doxorubicin-based regimen in resected high-grade soft tissue sarcoma (STS):

Pooled analysis of the two STBSG-EORTC phase III clinical trials [abstract 10525]. J Clin Oncol 2008;26(15 suppl):559s.

Summary: Adjuvant chemotherapy in soft tissue sarcoma still remains an area of controversy. The first meta analysis of adjuvant chemotherapy using doxorubicin based chemotherapy showed a significant benefit in local recurrence free interval(RFI) (Hazard ratio (HR) 0.73, p=0.016, absolute benefit 6%) and distant recurrence (HR-0.70, p=0.003, absolute benefit 10%) but no significant benefit in overall survival (OS) (HR 0.89, p=0.12, absolute benefit 4%, at 10 years) (1). The subsequent meta analysis of pooled odds ratio in 2008 which included trials using Ifosfamide and doxorubicin showed a significant benefit in relapse free survival (RFS) and OS. The second meta analysis included a more recent trial from the Italian Sarcoma Group showed a significantly longer OS duration for patients with high-risk sarcoma of the extremities receiving adjuvant chemotherapy with ifosfamide. In 2007, the largest adjuvant trial of chemotherapy with doxorubicin and ifosfamide in soft tissue sarcoma performed by the European Organization for Research and Treatment of Cancer (EORTC) Soft Tissue and Bone Sarcoma Group (STBSG) was reported at the ASCO Annual Meeting and failed to demonstrate any significant difference in the RFS or OS rate. The probable reason for the discrepancy in results is due to clubbing of different histologic subgroups and different sub sites. Also the same chemotherapy has been used for all sarcomas. Hence the full report of the EORTC 62391 is eagerly awaited.

Adjuvant chemotherapy cannot be recommended as standard for all patients of soft tissue sarcoma. It may be considered in a select population of high grade extremity sarcoma, more than 5 cm or recurrent high grade tumors.

Level of evidence: II

II. Role of chemotherapy in metastatic soft tissue sarcoma

- M. van Glabbeke, A. T. van Oosterom, J. W. Oosterhuis, et al., "Prognostic factors for the outcome of chemotherapy in advanced soft tissue sarcoma: an analysis of 2,185 patients treated with anthracycline- containing first-line regimens—an European organization for research and treatment of cancer soft tissue and bone sarcoma group study," Journal of Clinical Oncology, vol. 17, no. 1, pp. 150–157, 1999.
- Santoro A, Tursz T, MouridsenHet al. Doxorubicin versus CYVADIC versus doxorubicin plus ifosfamide in first-line treatment of advanced soft tissue sarcoma: A randomized study of the European Organization for Research and Treatment of Cancer Soft Tissue and Bone Sarcoma Group. J Clin Oncol 1995; 13:1537–1545.
- Sleijfer S, Ouali M, Van Glabbeke M et al. Prognostic and predictive factors for outcome to first-line ifosfamide-containing chemotherapy for adult patients with advanced soft tissue sarcomas. An exploratory, retrospective analysis on large series from the European Organization for Research and Treatment of Cancer-Soft Tissue and Bone Sarcoma Group (EORTC-STBSG). Eur J Cancer 2010; 46: 72–83.
- R. G. Maki, J. K. Wathen, S. R. Patel, et al., "Randomized phase II study of gemcitabine and docetaxel compared with gemcitabine alone in patients with metastatic soft tissue sarcomas: results of sarcoma alliance for research through collaboration study," Journal of Clinical Oncology 2007; 25 (19): 2755–2763.
- Pene N, Nguyen Bui B, Jacques-Olivier Bay, et al. Phase II Trial of Weekly Paclitaxel for Unresectable Angiosarcoma: The ANGIOTAX Study: J Clin Oncol. 2008; 26(32):5269-74.
- G. D. Demetri, S. P. Chawla, M. von Mehren, et al., "Efficacy and safety of trabectedin in patients with advanced or metastatic liposarcoma or leiomyosarcoma after failure of

prior anthracyclines and ifosfamide: results of a randomized phase II study of two different schedules," Journal of Clinical Oncology 2009; 27 (25): 4188–4196.

- Eriksson M., Histology-driven chemotherapy of soft-tissue sarcoma:Annals of Oncology 2010; 21 (Supplement 7): 270–276.

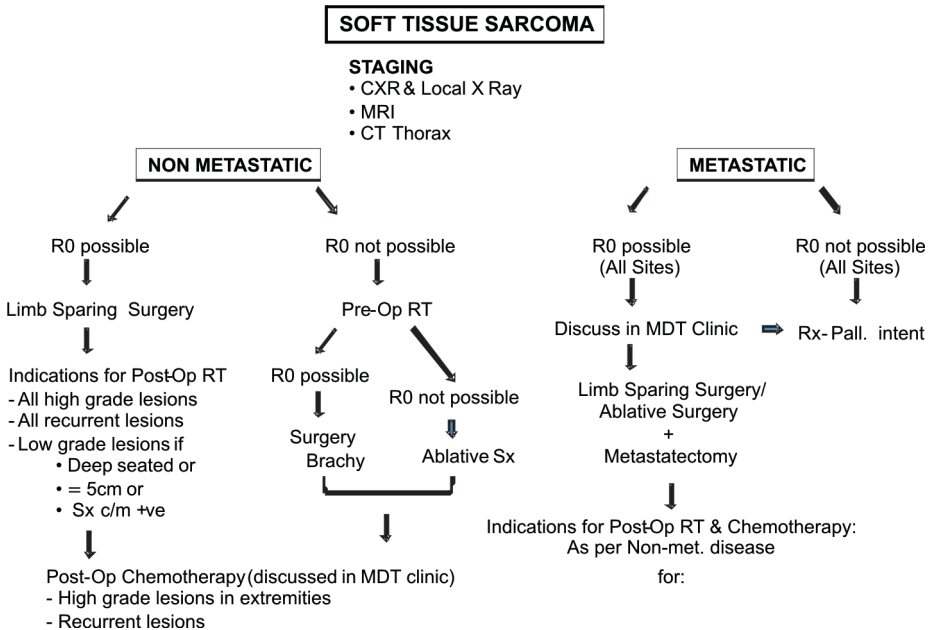
Summary: Patients with resectable soft tissue sarcoma, though achieve local control with surgery and radiotherapy, about 40% eventually recur at distant sites, of whom >90% will ultimately die of this malignancy. The median survival of patients with metastatic disease is about 12 months .The most important predictor for distant metastases is the histological grade. Palliative chemotherapy may be beneficial in approximately half of patients with advanced STS. It has been established that good performance status, young age, and absence of liver metastasis predicts a good response to chemotherapy and improved survival time. Different histologic subtypes have different sensitivity to chemotherapy. Synovial sarcoma ,myxoid and round cell liposarcoma are chemo sensitive, pleomorphic liposarcoma, myxofibrosarcoma, epithelioid sarcoma, leiomyosarcoma, malignant peripheral nerve sheath tumour, angiosarcoma, desmoplastic small round cell tumour, scalp and face angiosarcoma have only moderate sensitivity to chemotherapy, while dedifferentiated liposarcoma and clear cell sarcoma are relatively chemo insensitive. Alveolar soft part sarcoma and extra skeletal myxoid chondrosarcoma are chemo resistant. Doxorubicin is the backbone of treating patients with advanced disease with response rates of around 24% and median survival of 12 months. Dose response relationship for doxorubicin is important. Combination therapy with ifosfamide although has shown high response rate in non randomised study of 50-60%, no difference in response

rate or overall survival was seen in the randomised trial. There is no standard second line treatment of soft tissue sarcoma. Ifosfamide may be considered in patients whom it has not been used previously. In a retrospective exploratory analysis of 1337 patients of advanced soft tissue sarcoma, Ifosfamide based treatments compared to doxorubicin had higher response rates, though not statistically significant in patients with synovial sarcoma, while leiomyosarcoma and liposarcoma had lower response rates with ifosfamide based therapy. The combination of gemcitabine and docetaxel has shown to be active in leiomyosarcoma with response rates of 16%. Weekly paclitaxel has shown activity in angiosarcoma with a progression free survival (PFS) of 45% at 4 months with a median overall survival (OS) of 8 months. Trabectedin has been shown to be active in myxoid liposarcoma and leiomyosarcoma with median PFS of 3.3 months and OS of 13.9 months. Hence palliative chemotherapy in patients with advanced and metastatic disease should take into account the performance status and histologic subtype.

Recommendations:

1. Palliative chemotherapy in metastatic soft tissue sarcoma should be considered in patients with good performance status using single agent chemotherapy preferably Doxorubicin.
2. Other chemotherapy regimens like Ifosfamide, paclitaxel, gemcitabine-docetaxel or trabectidin can be considered depending on histology in second line.

Level of evidence: II


SOFT TISSUE SARCOMA
STAGING
• CXR & Local X Ray
• MRI
• CT Thorax
NON METASTATIC
METASTATIC
R0 possible
R0 not possible
R0 possible (All Sites)
R0 not possible (All Sites)
Limb Sparing Surgery
Pre-Op RT
Discuss in MDT Clinic
Rx- Pall. intent
Indications for Post-Op RT
- All high grade lesions
- All recurrent lesions
- Low grade lesions if
• Deep seated or
• = 5cm or
• Sx c/m +ve
R0 possible
R0 not possible
Surgery Brachy
Ablative Sx
Limb Sparing Surgery/ Ablative Surgery + Metastatectomy
Indications for Post-Op RT & Chemotherapy: As per Non-met. disease for:
Post-Op Chemotherapy (discussed in MDT clinic)
- High grade lesions in extremities
- Recurrent lesions

Section VI

Pulmonary Metastases in Bone & Soft Tissue Sarcomas

Role of Pulmonary Metastasectomy in Treatment of Sarcomas

I. Which is the radiological investigation of choice for detection of pulmonary metastases?

- Pfannschmidt J, Bischoff M, Muley T, Kunz J, Zamecnik P, Schnabel PA, Hoffmann H, Dienemann H, Heussel CP. Diagnosis of pulmonary metastases with helical CT: the effect of imaging techniques. Thorac Cardiovasc Surg 2008;56:471—5.
- Fortes DL, Allen MS, Lowe VJ, Shen KH, Wigle DA, Cassivi SD, Nichols FC, Deschamps C. The sensitivity of 18F-fluorodeoxyglucose positron emission tomography in the evaluation of metastatic pulmonary nodules. Eur J Cardiothorac Surg 2008;34:1223—7

Summary: Conventional CT scan with a slice thickness of 5 mm is sufficient to detect most palpable pulmonary metastases. It has a sensitivity of 83.7% in the detection of pulmonary nodules. Decreasing the slice thickness to 3 mm increases the sensitivity marginally to 88%.

Contrast enhancement may not add to the accuracy of CT scan in identifying pulmonary metastases. Lung metastases are viewed in the lung window where the effects of contrast enhancement are negated by the lung window settings. Several series have shown similar sensitivity and

specificity rates with CT scans with and without contrast enhancement. However there are no head to head comparisons.

PET-CT has not demonstrated an increased sensitivity in the detection of pulmonary nodules, probably due to the lack of resolution of the PET component. The sensitivity of PET may be as low as 29% for nodules less than 10 mm in size. The histology of the tumour may also affect the sensitivity of PET, ranging from 93% for squamous carcinomas to 44% for sarcomas. However, it may be useful in the exclusion of extrapulmonary disease.

Non contrast helical CT scan of the thorax with a slice thickness of 5mm or less is recommended for screening for pulmonary metastases.

II. What are the minimum criteria to be satisfied for considering a patient for pulmonary metastasectomy?

- Alexander J, Haight C. Pulmonary resection for solitary metastatic sarcomas and carcinomas. Surg Gynecol Obstet 1947;85:129—46.
- Thomford NR, Woolner LB, Clagett OT. The surgical treament of metastatic tumors in the lungs. J Thorac Cardiovasc Surg 1965;49:357—63.

Summary: The primary selection criteria for considering a patient for pulmonary metastasectomy were proposed by Alexander and Haight in 1947. These criteria have withstood the test of time and remain relevant even today, with minor modifications

1. R0 resection should be technically possible
2. Primary disease should be controlled or controllable
3. Absence of extrapulmonary metastatic disease except for hepatic metastases which can be resected either simultaneously or as a staged procedure

4. Patient should have the physiological reserve to withstand the procedure.

III. What are the prognostic factors which may affect survival after metastasectomy?

- Long-term results of lung metastasectomy: prognostic analyses based on 5206 cases. The International Registry of Lung Metastases. J Thorac Cardiovasc Surg 1997;113:37—49.
- Billingsley KG, Burt ME, Jara E, Ginsberg RJ, Woodruff JM, Leung DH, Brennan MF. Pulmonary metastases from soft tissue sarcoma: analysis of patterns of diseases and postmetastasis survival. Ann Surg 1999;229:602—10
- Casson AG, Putnam JB, Natarajan G, Johnston DA, Mountain C, McMurtrey M, Roth JA. Five-year survival after pulmonary metastasectomy for adult soft tissue sarcoma. Cancer 1992;69:662—8.
- Chen F, Miyahara R, Bando T, Okubo K, Watanabe K, Nakayama T, Toguchida J, Date H. Prognostic factors of pulmonary metastasectomy for osteosarcomas of the extremities. Eur J Cardiothorac Surg 2008;34:1235-1239.

Summary: Many prognostic factors have been identified which may affect survival after pulmonary metastasectomy. However since the evidence supporting these criteria is weak, they should not be considered as absolute criteria. A judicious decision should be taken after considering all the factors

Disease free interval (DFI) - Disease free interval has long been considered an important prognostic factor for pulmonary metastasectomy. Various studies have proposed different durations of DFI as significant. Pastorino et al on analysis of data from the International Registry of Lung Metastases proposed a DFI of more than 36 months as a good prognostic factor. Similarly Billingsley et al suggested a DFI of more than 12 months as a good prognostic factor. A common thread that is seen in most studies is that, the longer the DFI, more favourable the prognosis. This

however does not necessarily exclude patients with a short DFI from metastasectomy, although their prognosis will be guarded.

Number of metastases - Number of metastases has been shown to be a key prognostic factor in several studies. However, no concordance has been reached regarding the the critical number of resectable metastases. Numbers range from solitary metastases as suggested by Pastorino et al to five as suggested by Chen et al. To summarise the data, the fewer the number of metastases, better is the prognosis.

Pathology - Some histologies have been shown to have a better prognosis. Osteogenic sarcoma, malignant fibrous histiocytoma, rhabdomyosarcoma and synovial sarcoma have a favourable prognosis. Liposarcoma and peripheral nerve sarcoma have a relatively poorer prognosis.

IV. What is the ideal surgical approach for metastatectomy?

- Younes RN, Gross JL, Deheinzelin D. Surgical resection of unilateral lung metastases: is bilateral thoracotomy necessary? World J Surg 2002;26:1112—6.
- Karplus G, McCarville MB, Smeltzer MP, Spyridis G, Rao BN, Davidoff A, Li CS, Shochat S. Should contralateral exploratory thoracotomy be advocated for children with osteosarcoma and early unilateral pulmonary metastases? J Pediatr Surg 2009;44:665-671.
- Roth JA, Pass HI, Wesley MN, White D, Putnam JB, Seipp C. Comparison of median sternotomy and thoracotomy for resection of pulmonary metastases in patients with adult soft-tissue sarcomas. Ann Thorac Surg 1986;42:134—8.
- Mutsaerts EL, Zoetmulder FA, Meijer S, Baas P, Hart AA, Rutgers EJ. Outcome of thoracoscopic pulmonary metastasectomy evaluated by confirmatory thoracotomy. Ann Thorac Surg 2001;72:230—3.

- Carballo M, Maish MS, Jaroszewski DE, Holmes CE. Video-assisted thoracic surgery (VATS) as a safe alternative for the resection of pulmonary metastases: a retrospective cohort study. J Cardiothorac Surg 2009;4:13.

Summary:

Unilateral metastases **-** Posterolateral thoracotomy, preferably muscle sparing is probably the preferred approach. This provides the best access for bimanual palpation of the entire lung. Tiny metastases which are not detected by imaging may be picked up by bimanual palpation.

Historically, bilateral exploration was performed for unilateral metastases. This was because of the possibility of picking up radiologically undetectable metastases by careful bimanual palpation. However with advances in radiology, the possibility of picking up additional clinically relevant metastases by bimanual palpation has decreased. Karplus et al in a retrospective analysis of 109 patients demonstrated that patients undergoing unilateral thoracotomy for unilateral metastases did not have a higher rate of recurrence in the opposite lung. The hypothesis is that although the contralateral lung may harbour early metastases not detected radiologically, the possibility of preventing a clinically significant metastases by early thoracotomy is minimal. Hence bilateral exploration for unilateral metastases is no longer recommended.

Bilateral metastases - Various approaches are available, including bilateral anterolateral thoracotomy, clamshell thoracotomy, median sternotomy and bilateral posterolateral thoracotomy. An approach which provides adequate access for an R0 clearance with minimum morbidity should be chosen.

Video Assisted Thoracoscopic Surgery (VATS) - Thoracoscopic surgery was initially considered unsuitable for metastasectomy because of the loss of tactile sensation. However recent studies have demonstrated the efficacy of VATS metastasectomy in a select group of patients. Mutsaerts et al in a study evaluating VATS resection followed by confirmatory thoracotomy found VATS resection as effective as thoracotomy in solitary metastases larger than 3 cm. Carballo et al in their retrospective analysis of 280 procedures in 186 patients found VATS metastasectomy non inferior to open thoracotomy in patients with limited number of nodules, of smaller size amenable to wedge excision. In conclusion, VATS excision may be used in conjunction with a high quality CT for solitary peripherally located metastases.

V. What is the role of mediastinal lymph node dissection in pulmonary metastasectomy?

- Pfannschmidt J, Klode J, Muley T, Dienemann H, Hoffmann H. Nodal involvement at the time of pulmonary metastasectomy: experiences in 245 patients. Ann Thorac Surg 2006;81:448—54.

Summary: Mediastinal lymph node involvement of up to 20% has been reported in sarcomas and the prognosis is unfavorable. Unlike the case of carcinomas, the impact of mediastinal lymph node dissection on survival in sarcomas is unknown; however, it may help in prognostication.

VI. What is the role of metastasectomy in recurrent pulmonary metastases?

- Briccoli A, Rocca M, Salone M, Bacci G, Ferrari S, Balladelli A, Mercuri M. Resection of recurrent pulmonary metastases in patients with osteosar- coma. Cancer 2005;104:1721—5.
- Rehders A, Hosch SB, Scheunemann P, Stoecklein NH, Knoefel WT, Peiper M. Benefit of surgical treatment of

lung metastasis in soft tissue sarcoma. Arch Surg 2007;142:70—5

Summary: The most common site of recurrence after pulmonary metastasectomy is the lung. Five year survival rates between 32 to 36% have been seen in several studies with repeated pulmonary metastasectomy. Repeat metastasectomy should be attempted as long as complete resection is possible, patients who are not operated have a dismal prognosis. All criteria considered for the initial surgery should be satisfied while evaluating a patient for a redo metastasectomy. The decision for repeated metastasectomy should be tempered by judgment of the patient's ability to withstand repeated surgical procedures.

VII. Is metastasis at presentation a contraindication for metastasectomy?

- Tsuchiya H, Kanazawa Y, Abdel-Wanis ME, Asada N, Abe S, Isu K, Sugita T, Tomita K. Effect of timing of pulmonary metastases identification on prognosis of patients with osteosarcoma: the Japanese Musculoskeletal Oncology Group study. J Clin Oncol 2002;20:3470—7.
- Kager L, Zoubek A, Potschger U, Kastner U, Flege S, Kempf-Bielack B, Branscheid D, Kotz R, Salzer-Kuntschik M, Winkelmann W, Jundt G, Kabisch H, Reichardt P, Jurgens H, Gadner H, Bielack SS. Primary metastatic osteosarcoma: presentation and outcome of patients treated on neoadjuvant Cooperative Osteosarcoma Study Group protocols. J Clin Oncol 2003;21:2011-2018.

Summary: Metastases at presentation, although a poor prognostic factor, is not a contraindication to metastasectomy. Tsuchiya et al in their series demonstrated a 5 year survival of 18% in osteogenic sarcoma patients with pulmonary metastases at presentation, who underwent metastasectomy. This was however; lower than the 31% survival seen in patients who underwent metastasectomy in a metachronous setting. Other series have shown survival rates as high as 75% in patients with

solitary lung metastases at presentation treated aggressively. Most patients received chemotherapy initially before being evaluated for surgery. In conclusion, a select subset of patients with metastases at presentation may achieve long term survival with aggressive treatment strategies in which surgery forms an integral part.

Section VII

Chondrosarcoma

- Grimer RJ, Gosheger G, Taminiau A et al. Dedifferentiated chondrosarcoma: Prognostic factors and outcome from a European group. Eur J Cancer 2007;43:2060 –2065.
- Mitchell AD, Ayoub K, Mangham DC et al. Experience in the treatment of dedifferentiated chondrosarcoma. J Bone Joint Surg Br 2000;82:55– 61.
- Staals EL, Bacchini P, Bertoni F. Dedifferentiated central chondrosarcoma. Cancer 2006;106:2682–2691.
- Dickey ID, Rose PS, Fuchs B et al. Dedifferentiated chondrosarcoma: The role of chemotherapy with updated outcomes. J Bone Joint Surg Am 2004; 86-A:2412–2418.
- Staals EL, Bacchini P, MercuriMet al. Dedifferentiated chondrosarcomas arising in preexisting osteochondromas. J Bone Joint Surg Am 2007;89:987–993.
- Nooij MA, Whelan J, Bramwell VH et al. Doxorubicin and cisplatin chemotherapy in high-grade spindle cell sarcomas of the bone, other than osteosarcoma or malignant fibrous histiocytoma: A European Osteosarcoma Intergroup Study. Eur J Cancer 2005;41:225–230.
- Huvos AG, Rosen G, Dabska M et al. Mesenchymal chondrosarcoma. A clinicopathologic analysis of 35 patients with emphasis on treatment. Cancer 1983;51:1230 –1237.

Summary: Due to the lack of clear evidence chemotherapy is still controversial in chondrosarcoma. In dedifferentiated chondrosarcoma, Mitchell et al showed an effect on

survival; however it could not be reproduced in 3 other studies by Grimer, Staals and Dickey et al. Staals in a small retrospective report showed that in peripheral dedifferentiated chondrosarcoma, arising in osteochondroma, chemotherapy led to longer survival. In a small prospective study by Nooij et al it was shown that with doxorubicin and cisplatin chemotherapy, patients with dedifferentiated chondrosarcoma had a poor response in their primary tumor, although two of four patients had a complete response of metastases.

For mesenchymal chondrosarcoma, there seems to be a role for chemotherapy, although the number of reported cases is even smaller and prospective studies are lacking. Huvos et al. in a small retrospective series showed that three complete and three partial responses (all T-10 or T-11 protocols) could be obtained while three were nonresponders (all high-dose methotrexate monotherapy). Nooij et al. prospectively observed one of two good pathological responses in the primary tumor after preoperative doxorubicin– cisplatin combination therapy, but only a limited effect in four patients treated with the same regimen in the metastatic setting (two with stable diseases). Huvos showed that tumors with a high percentage of small cells and limited cartilage content are thought to be most sensitive to chemotherapy and RT, as with other small cell sarcomas.

Inference: Chemotherapy is possibly only effective in mesenchymal chondrosarcoma, and is of uncertain value in dedifferentiated chondrosarcoma; both subtypes are rare and bear a poor prognosis. Chemotherapy should preferably be used in clinical trials to define its definite role in chondrosarcoma.

Level of evidence: III

Role of Intralesional Surgery for Grade I Chondrosarcoma

- Mohler DG, Chiu R, McCall DA, Avedian RS. Curettage and cryosurgery for low grade cartilage tumors is associated with low recurrence and high function. Clin Orthop Relat Res. 2010 Oct;468(10):2765-73. Epub 2010 Jun 24.
- Souna BS, Belot N, Duval H, Langlais F, Thomazeau H. No recurrences in selected patients after curettage with cryotherapy for Grade I chondrosarcomas. Clin Orthop Relat Res. 2010 Jul;468(7):1956-62. Epub 2010 Jan 7.
- Hanna SA, Whittingham-Jones P, Sewell MD, Pollock RC, Skinner JA, Saifuddin A, Flanagan A, Cannon SR, Briggs TW. Outcome of intralesional curettage for low grade chondrosarcoma of bone. Eur J Surg Oncol. 2009 Dec;35(12):1343-7. Epub 2009 Jun 30.
- Streitbu¨rger A, Ahrens H, Balke M, Buerger H, Winkelmann W, Gosheger G, Hardes J. Grade I chondrosarcoma of bone: the Munster experience. J Cancer Res Clin Oncol.2009; 135:543–550.
- Leerapun T, Hugate RR, Inwards CY, Scully SP, Sim FH. Surgical management of conventional grade I chondrosarcoma of long bones. Clin Orthop Relat Res. 2007;463:166–172.
- Donati D, Colangeli S, Colangeli M, Di Bella C, Bertoni F. Surgical treatment for grade I central chondrosarcomas. Clin Orthop Relat Res. 2010 Feb;468(2):581-9. Epub 2009 Aug 29.

- Aarons C, Potter BK, Adams SC, Pitcher JD Jr, Temple HT. Extended intralesional treatment versus resection of low-grade chondrosarcomas. Clin Orthop Relat Res. 2009;467:2105–2111.
- van der Geest IC, de Valk MH, de Rooy JW, Pruszczynski M, Veth RP, Schreuder HW. Oncological and functional results of cryosurgical therapy of enchondromas and chondrosarcomas grade 1. J Surg Oncol. 2008;98:421–426.
- Ahlmann ER, Menendez LR, Fedenko AN, Learch T. Influence of cryosurgery on treatment outcome of low-grade chondrosarcoma. Clin Orthop Relat Res. 2006;451:201–207.
- Etchebehere M, de Camargo OP, Croci AT, Oliveira CR, Baptista AM. Relationship between surgical procedure and outcome for patients with grade I chondrosarcomas. Clinics (Sao Paulo). 2005 Apr;60(2):121-6. Epub 2005 Apr 26.
- Schreuder HW, Pruszczynski M, Veth RP, Lemmens JA. Treatment of benign and low-grade malignant intramedullary chondroid tumors with curettage and cryosurgery. Eur J Surg Oncol. 1998;24:120–126.
- Bauer HC, Brosjö O, Kreicbergs A, Lindholm J. Low risk of recurrence of enchondroma and low-grade chondrosarcoma in extremities. 80 patients followed for 2-25 years. Acta Orthop Scand. 1995 Jun;66(3):283-8.
- Hickey M, Farrokhyar F, Deheshi B, Turcotte R, Ghert M.: A Systematic Review and Meta-analysis of Intralesional Versus Wide Resection for Intramedullary Grade I Chondrosarcoma of the Extremities. Ann Surg Oncol. 2011 Jan 22. [Epub ahead of print]

Summary: Mohler et al analysed retrospectively 46 cases of grade 1 chondrosarcoma or enchondroma (difficult to differentiate the two on radiology or pathology) treated by curettage and cryosurgery. With a recurrence rate of 4.3% and 3 fractures as complications they conclude that curettage with adjuvant cryosurgery is an effective

treatment for cartilaginous bone tumors of uncertain malignant potential. They believe the key to success of this treatment approach is meticulous surgical technique to address the entire tumor cavity, avoid contamination of uninvolved anatomy, and minimize tumor seeding of the soft tissues in the surgical approach site. Souna et al carefully selected 15 cases of low grade chondrosarcoma in the proximal humerus (10) and distal femur (5). Stringent radiographic and histological criteria were used, like less than 50% thickness of cortex eroded, no soft tissue mass and bone scan uptake more than ipsilateral iliac crest. At a minimum follow up of 5 years and median follow up of 8 years, there were no local recurrences. Cryotherapy was used but no cementing was used. Instead the bone window was put back. They conclude that conventional wide excision treatment can be "de-escalated" in selected cases of grade 1 chondrosarcoma. Hanna et al had 2 local recurrences from 39 patients of grade 1 chondrosarcoma treated with intralesional surgery with minimum follow up 3 years and mean 5.5 years. There were no complications or metastases. Both LR happened in first two years and were treated with recurettage. Both the recurrences did not have metastatic disease. In the series by Streitberger et al 9 of 80 low grade chondrosarcomas were intentionally treated by curettage in the extremities. Three developed a local recurrence at periods from 18-53 months (33%). Leerapun et al also reported low recurrence in the 13 cases treated with extended curettage. They conclude that a combination of radiographic and histologic findings should be used to select cases suitable for intralesional surgery. Grade IA and IB may be histologically similar but the Grade IB cases are likely to have a higher risk of Local recurrence due to the difficulty in eradicating microscopic disease using adjuvants. Their

series excluded enchondromas, tumors in axial skeleton and flat bones and tumors in bones of the hands and feet. Only Grade IA lesion were selected for intralesional surgery. Donati et al compared intralesional treatment to wide resection in grade 1 chondrosarcomas. There were 2 recurrences from the 15 treated by intralesional surgery, both in proximal femur and were treated by resection with no metastases at last follow up. The minimum follow up was 66 months. Phenol and/or cement was used as adjuvant in 9 cases and liquid nitrogen in 3 cases. They suggest selecting patients on the basis of radiographic appearance and avoiding curettage in patients presenting with bone enlargement associated with thinning of the cortex and deep scalloping. Presence of myxoid areas and necrosis also indicate aggressiveness in their opinion. Permeative infiltration with the inclusion of host bone trabeculae was present in 80% cases and was used to differentiate Grade I Chondrosarcoma from enchondroma. Aarons et al in a retrospective analysis compared grade 1 chondrosarcomas treated with extended intralesional curettage with those resected. The group was carefully chosen based on accepted imaging and histological criteria. Patients with high grade, recurrent tumors or those with soft tissue masses were excluded as also those in sites such as hand, feet, spine or pelvis. Their minimum follow up was 24 months with a median of 55 months. They found one recurrence in each group without any grade transformation. The complication rate was much higher in the resection group. The average MSTS score was higher in the intralesionally treated group. Various adjuvants like electrocautery, phenol, cement or hydrogen peroxide were used in the intralesionally treated group. They conclude that in selected cases of grade I chondrosarcoma, extended intralesional treatment

provided low rates of complications and better function than resection with similar risk of local recurrence. Van der Geest et al treated 78 aggressive enchondromas and 55 grade 1 chondrosarcomas with curettage and cryotherapy making this the largest reported series. They had 2 local recurrences in the enchondroma group and none in the chondrosarcomas. Ahlman et al found no local recurrence in 10cases (3 Femur, 3 Humerus, 1 tibia, 2 scapula and 1 acetabulum) at a follow up of 24-60 months with cryosurgery used as an adjuvant. Etchebehere et al also found no local recurrence in the 17 cases of Grade IA chondrosarcoma. Cauterization or cement was used as an adjuvant. Schreuder et al found no local recurrences in the group of 9 patients treated with intralesional surgery at a follow up of 15-40 months. Bauer et al in 1995 reported 3 recurrences of 23 cases of low grade chondrosarcoma. 2 of the 3 recurrences were in stage IB lesions of the foot with an extraosseous mass. One tibial Grade IA lesion recurred and was treated with intralesional surgery only to recur again when an amputation was done. Recurrences were seen as late as 6 years after surgery and no metastases developed.

A word of caution:

- Normand AN, Cannon CP, Lewis VO, Lin PP, Yasko AW. Curettage of biopsy-diagnosed grade 1 periacetabular chondrosarcoma. Clin Orthop Relat Res. 2007;459:146–149.
- Schwab JH, Wenger D, Unni K, Sim FH. Does local recurrence impact survival in low-grade chondrosarcoma of the long bones? Clin Orthop Relat Res. 2007;462:175–180
- Skeletal Lesions Interobserver Correlation among Expert Diagnosticians (SLICED) Study Group. Reliability of histopathologic and radiologic grading of cartilaginous

neoplasms in long bones. J Bone Joint Surg Am. 2007 Oct;89(10):2113-23.

Normand et al specifically selected 8 pelvic chondrosarcomas diagnosed as grade I on preoperative workup for intralesional "joint-sparing" treatment. All patients had a percutaneous biopsy that was interpreted as grade 1 chondrosarcoma. The final histology after curettage indicated grade 1 chondrosarcoma in five patients, grade 2 in two, and dedifferentiated chondrosarcoma in one. The interpretation of biopsy obtained tissue for cartilaginous neoplasms is fraught with errors and has a likelihood of underestimating the true grade of the lesion. Irrespective of the biopsy technique, even when performed by experienced, knowledgeable experts, the biopsy diagnosis of cartilage tumors can be misleading and unreliable. Selecting the area of the lesion to biopsy can be difficult, and the heterogeneous nature of cartilage tumors can compromise representative sampling. Radiological features of aggressiveness may not be seen in the pelvic location making a judgment of grade even more difficult. Even under favorable circumstances—for example, when biopsy results are correct and treatment is appropriately aggressive—pelvic chondrosarcoma has been reported to recur locally with higher frequency than in other sites and with a propensity to upgrade histologically with local recurrence. Two of the five such cases in this series recurred as higher-grade tumors. Three patients with a higher grade died of high-grade chondrosarcoma at a median of 23 months (range 17–72 months). Based on these observations, in the absence of a predictable method to identify the true intraosseous grade 1 chondrosarcomas of the pelvis, curettage may not be a safe method for controlling these tumors in the pelvis.

Schwab et al studied the impact of local recurrence in grade I chondrosarcoma. Some studies of recurrent Grade 1 chondrosarcoma in the pelvis and scapula show recurrence can be associated with progression of tumor grade and metastasis. However, others have not confirmed this association. One explanation for these different findings is that the diagnosis of low-grade chondrosarcoma is subjective and the diagnostic criteria are not universally standardized. Therefore, our ability to reliably predict which tumors will recur and become more aggressive remains poor. There are some interesting observations from this study. 4 of the 6 local recurrences treated with intralesional surgery recurred again probably indicating more biological aggressiveness. Furthermore, this study shows the importance of long follow up. The difference in survival was seen only after 10 years and was not apparent at 5 years.

Since the determination of grade is crucial to the selection of cases of grade I chondrosarcoma for curettage, it is important to know how reliable is the diagnosis in the hands of experienced musculoskeletal radiologists and pathologists. The SLICED group study evaluated the interobserver reliability of the determination of grade for cartilaginous neoplasms among a group of experienced musculoskeletal pathologists and radiologists. Nine recognized musculoskeletal pathologists and eight recognized musculoskeletal radiologists reviewed forty-six consecutive cases of cartilaginous lesions in long bones that underwent open biopsy or intralesional curettage. All diagnosticians had a bulleted history and preoperative conventional radiographs for review. Pathologists reviewed the original hematoxylin and eosin-stained glass slides from each case. Radiologists reviewed any additional imaging that was available, variably including serial

radiographs, magnetic resonance imaging, and computed tomography scans. Each diagnostician classified a lesion as benign, low-grade malignant or high-grade malignant.

This study demonstrates low reliability for the grading of cartilaginous lesions in long bones, even among specialized and experienced pathologists and radiologists. This included low reliability both in differentiating benign from malignant lesions and in differentiating high-grade from low-grade malignant lesions, both of which are critical to the safe treatment of these neoplasms. This may explain in part the wide variation in outcomes reported for chondrosarcomas treated in different medical centers.

Summary: The reports of high risk of recurrence for intralesional treatment were mainly with higher grade chondrosarcomas. Intralesional treatment provides very good functional as well as oncological results in highly selected cases. Case selection is currently based on imaging characteristics like endosteal scalloping and cortical erosion on X ray, contrast uptake and soft tissue mass on MRI, and an uptake more than that of the ipsilateral iliac crest on bone scan. Histological characteristics like cellularity, necrosis and permeation are used to separate the grade 1 chondrosarcomas from higher grade or from enchondromas. Apart from a meticulous curetting and burring, most series have described the use of adjuvants to extend the curettage. Recurrences can be treated either by recurettage or by a wide excision depending on aggressiveness. Most authors have not found any grade change or higher risk of metastases with recurrence but a few studies have cautioned against this risk. Most series have excluded the axial skeleton or flat bones and bones of hands and feet from this method of treatment. The recurrence rates in the pelvis have been higher with more difficulty in managing the recurrence. The functional results

have been shown to be far superior to similar cases treated with resection thereby "de-escalating" the treatment. The current accuracy of preoperative diagnosis through imaging and needle biopsy is poor and in future it is possible that functional imaging like a PET scan will be used for grading.

Inference: Hickey M, Farrokhyar F, Deheshi B, Turcotte R, Ghert M.: A Systematic Review and Meta-analysis of Intralesional Versus Wide Resection for Intramedullary Grade I Chondrosarcoma of the Extremities. Ann Surg Oncol. 2011 Jan 22. [Epub ahead of print]

This meta analysis supports the concept that extremity grade I chondrosarcoma can be safely treated with extended intralesional curettage without increasing the risk for local recurrence or metastatic disease. Randomized studies are not feasible based on volume and prevalence of disease. Therefore, in the absence of randomized data, this metaanalysis provides the best available evidence to support the paradigm shift to intralesional curettage for extrapelvic grade I chondrosarcoma.

Level of evidence – I

Notes

Levels of Evidence for Primary Research Question

Level	Types of Studies			
	Therapeutic Studies - Investigating the results of treatment	Prognostic Studies - Investigating the effect of patient characteristic on the outcome of disease	Diagnostic Studies - Investigating a diagnostic test	Economic and Decision Analyses - Developing an economic or decision model
Level-I	• High quality randomized trial with statistically significant difference or no statistically significant difference but narrow confidence intervals • Systematic Review[2] of Level I RCTs (and study results were homogenous[3])	• High quality prospective study4 (all patients were enrolled at the same point in their disease with 80% follow-up of enrolled patients) • Systematic review[2] of Level I studies	• Testing of previously developed diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) • Systematic review[2] of Level I studies	• Sensible costs and alternatives; values obtained from many studies; with multiway sensitivity analyses • Systematic review of Level I studies

Level	Types of Studies			
Level-II	• Lesser quality RCT (eg, 80% follow-up, no blinding, or improper randomization) • Prospective[4] comparative study[5] • Systematic review[2] of Level II studies or Level 1 studies with inconsistent results	• Retrospective[6] study • Untreated controls from an RCT • Lesser quality prospective study (eg, patients enrolled at different points in their disease or 80% followup.) • Systematic review[2] of Level II studies	• Development of diagnostic criteria on consecutive patients (with universally applied reference "gold" standard) • Systematic review[2] of Level II studies	• Sensible costs and alternatives; values obtained from limited studies; with multiway sensitivity analyses • Systematic review[2] of Level II studies
Level-III	• Case control study[7] • Retrospective[6] comparative study[5] • Systematic review[2] of Level III studies	• Case control study[7]	• Study of nonconsecutive patients; without consistently applied reference "gold" standard • Systematic review[2] of Level III studies	• Analyses based on limited alternatives and costs; and poor estimates • Systematic review[2] of Level III studies

Level	Types of Studies			
Level-IV	Case Series[8]	Case Series	• Case-control study • Poor reference standard	• Analyses with no sensitivity analyses
Level-V	Expert Opinion	Expert Opinion	Expert Opinion	Expert Opinion

1. A complete assessment of quality of individual studies requires critical appraisal of all aspects of the study design.
2. A combination of results from two or more prior studies.
3. Studies provided consistent results.
4. Study was started before the first patient enrolled.
5. Patients treated one way (eg, cemented hip arthroplasty) compared with a group of patients treated in another way (eg, uncemented hip arthroplasty) at the same institution.
6. The study was started after the first patient enrolled.
7. Patients identified for the study based on their outcome, called "cases"; eg, failed total arthroplasty, are compared with patients who did not have outcome, called "controls"; e.g., successful total hip arthroplasty.
8. Patients treated one way with no comparison group of patients treated in another way