# THE INCIDENCE OF MALIGNANT INFILTRATION IN HUMAN OSTEOSARCOMA BIOPSY TRACT

BY

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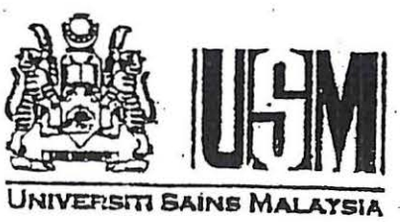


Dissertation Submitted In Partial Fulfilment Of The Requirements For The Degree Of Masters Of Medicine (Orthopaedics)

UNIVERSITI SAINS MALAYSIA

MAY 2006

*In fond memory of*

**Dr. R. Badmanaban**

a true gentleman, on whose shoulders I stand upon.

## ACKNOWLEDGEMENT

My sincere gratitude to Prof. Zulmi Wan, Dr. Wan Faisham Nu'man Wan Ismail from the Orthopaedic Oncology and Reconstructive Unit and Dr. Effat Omar from the Pathology Department, Hospital Universiti Sains Malaysia for their guidance, support and encouragement throughout this study.

I would like to thank the 'Short Term Research Grants' committee of Universiti Sains Malaysia for making this study a possibility.

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## LIST OF ACRONYMS

| | |
|---|---|
| AJCC | American Joint Committee on Cancer |
| CT | Computed Tomography |
| CNB | Core Needle Biopsy |
| FNA | Fine Needle Aspiration |
| HUSM | Hospital Universiti Sains Malaysia |
| LSS | Limb Salvage Surgery |
| MFH | Malignant Fibrous Histiocytoma |
| MRI | Magnetic Resonance Imaging |

**ABSTRAK**

**Latarbelakang**: Osteosarkoma merupakan barah tulang yang paling kerap dikalangan pesakit muda. Biopsi adalah cara yang paling baik untuk memastikan diagnosa osteosarkoma. Tempat di mana trek dan parut biopsi itu terletak adalah amat mustahak kerana parut biopsi itu di bedah dan dikeluarkan bersama barah tersebut semasa pembedahan menyelamatkan anggota. Ini adalah selari dengan tanggapan bahawa trek biopsi tersebut telah dicemari oleh sel-sel barah. Pengekalan tisu bagi memastikan terdapatnya tisu lembut yang cukup, dan pengekalan fungsi anggota masih menjadi cabaran kepada pakar bedah onkologi.

Kajian ini meninjau insiden pencemaran trek biopsi osteosarkoma dengan sel-sel barah iaitu di lapisan 'pseudo' kapsul, otot, fascia, lapisan subkut dan kulit. Ini adalah untuk mengetahui tahap pencemaran bagi membolehkan pembedahan trek dan parut biopsi yang selamat.

**Metadologi**: Kajian ini merupakan kajian "prospective cross-sectional" dan dijalankan di Hospital Universiti Sains Malaysia, Kubang Kerian, di antara bulan Mei 2003 hingga Mac 2005. Dua puluh enam kes yang didiagnosa sebagai osteosarkoma dan menjalani pembedahan menyelamatkan anggota atau amputasi telah dikaji. Trek-trek biopsi dari kes-kes ini di hantar secara keseluruhan untuk diteliti untuk pencemaran sel-sel barah.

**Keputusan**: Daripada dua puluh enam kes yang di analisa, dua puluh satu kes (80.2%) tidak menunjukkan sebarang pencemaran sel-sel barah di trek biopsi. Satu kes (3.8%) menunjukkan pencemaran sel-sel barah di lapisan 'pseudo' kapsul. Dua kes (7.7%) menunjukkan pencemaran sehingga ke lapisan otot dan dua lagi kes (7.7%) menunjukkan pencemaran sehingga ke lapisan tisu subkut. Tiada sebarang pencemaran sel-sel barah di lapisan kulit.

## ABSTRACT

**Background:** Osteosarcoma is the most common non-haemopoetic primary bone malignancy afflicting the young. Biopsy remains the gold standard in the confirmation of the diagnosis. The placement of the biopsy is of utmost importance as the tract is removed en bloc with the tumour during limb sparing surgery, with the assumption that it is contaminated by the tumour. Tissue conservation, to ensure adequate soft tissue cover, and preservation of function still remains a challenge for musculoskeletal oncology surgeons.

This study aims to investigate the incidence of tumour infiltration in osteosarcoma biopsy tract, namely in the pseudocapsule, surrounding muscle, fascia, subcutaneous tissue and skin; in order to explore the margin of tumour infiltration for safe resection of the biopsy scar.

**Materials and methods**: This is a prospective cross sectional study, carried out from May 2003 to March 2005 at Hospital Universiti Sains Malaysia, Kubang Kerian, Kelantan. A total of twenty six cases which had undergone either limb salvage surgery or amputation by the Orthopaedic Oncology and Reconstructive Unit, School of Medical Sciences, University Science Malaysia, with the histopathological diagnosis of osteosarcoma were collected. The biopsy tracts were submitted as a whole and examined histologically for tumour presence.

**Results:** Of the 26 cases examined, twenty one cases (80.8%) did not show any tumour infiltration in the biopsy tract. One case (3.8%) had tumour infiltration in the pseudocapsule, two cases (7.7%) had infiltration to the muscle and another two cases (7.7%) had infiltration up to the subcutaneous tissue. None had skin infiltration

# 1. INTRODUCTION AND LITERATURE REVIEW

Musculoskeletal malignant neoplasms, whether primary or secondary, bone or soft tissue are now being diagnosed more often as the awareness of its occurrence has increased. A high degree of clinical suspicion, earlier access to specialists and the availability of imaging modalities have dramatically improved the detection, treatment and outcome of these diseases. The progress in radiographic imaging, chemotherapy, radiation therapy, nuclear imaging, bioengineering and technology, and genetics has led to an understanding of the biological behaviour of mesenchymal neoplasms at a molecular level thus, affecting the rationale of diagnosis, staging and treatment.

Osteosarcoma is the tumour of choice for this study, as it is the most common primary malignancy of the bone (20% to 22%), excluding marrow based malignancies such as myeloma, lymphoma and leukaemia (Simon M.A., 1998). In contrast, soft tissue tumours are more heterogenous as they arise from various supporting extraskeletal mesenchymal tissues and they are rare, constituting less 1% of all cancers (Dee R., 1997). Osteosarcoma provides the model on which the treatment of all sarcomas is based upon. Thus, osteosarcoma provides uniformity for the study and minimizes biasness.

Subsequent to clinical and radiological evaluations, biopsy is the most significant step in the diagnosis of osteosarcoma. In this study, the focus is on the osteosarcoma biopsy tract. Among all the musculoskeletal neoplasms, a biopsy performed for osteosarcoma is the most challenging, as it has to penetrate deep down to the bone. The biopsy tracts are

longer and involve multiple anatomical layers, namely, the skin, subcutaneous tissue, muscle and pseudocapsule before reaching the tumour.

In the past, biopsies were performed through large incisions resulting in significant contamination of the surrounding soft tissue with tumour cells. However, the degree of contamination had little significance as the treatment for most malignant tumours was amputation. (Malawer M.M., 2001). In contrast, today 90-95% of patients with malignant tumours are treated with limb sparing surgery (LSS). (Malawer M.M., 2001).The issue of biopsy tract contamination is significant to the present day treatment. The placement of the biopsy, the length of the tract and size of the scar are important variables as they determine whether a limb can be salvaged and the amount of soft tissues to be sacrificed in LSS. These variables also affect the function of the limb. Biopsies that are poorly performed affect the diagnosis, and may lead to amputation of the limb in order to achieve an adequate surgical tumour clearance. In planning the definitive surgery, the biopsy tract has always been assumed to be contaminated with tumour cells, hence it is resected with the same safety margins as the primary tumour. (Malawer M.M., 2001).This leads to increased soft tissue defect and further compromise in limb function restoration.

There are concerns regarding the potential of accelerated growth or metastatic dissemination of a malignant tumour after biopsy, but there are no well established evidence, although the risk of local recurrence has been reported (Davies N.M. *et al.*, 1993).

The treatment of osteosarcoma, before 1975 consisted mainly of amputation with fewer than 20% of patients surviving beyond five years (Sweetnam R. *et al.*, 1971). Majority of these patients developed distant metastases within the first 2 years of treatment (Link M.P. *et al.*, 1986). The dramatic improvement in survival in the last two decades had been mainly contributed by the efficient chemotherapy to combat micro-metastases. The modern treatment programme is multimodal in nature. It incorporates neoadjuvant chemotherapy, surgery to control local disease and adjuvant treatment. The five-year survival rate with multidisciplinary approach varies from 60-70% (Rougraff B.T. *et al.*,1994).

This study intends to verify the truth of the assumption that all biopsy tracts are infiltrated. It determines the evidence of tumour infiltration in the various layers of osteosarcoma biopsy tract. The results of this study could change the subsequent management of osteosarcoma. If infiltration is found to be absent then;

1. The osteosarcoma biopsy tract need not be excised en-bloc during LSS, if the scar is not in line with the surgical incision.
2. Soft tissue resection may be minimized and the indication for free flap can be reduced
3. Osteosarcoma biopsies could be performed in other primary referral centres and the diagnoses obtained earlier.

These will enhance the outcome and decrease the morbidity associated with LSS

## 1.1 OVERVIEW OF MUSCULOSKELETAL TUMOURS

A neoplasm or tumour is defined as an abnormal mass of tissue, the growth of which exceeds and is uncoordinated, with that of the normal tissue, and persists in the same excessive manner after the cessation of the stimuli which evoked it. It can either be benign or malignant. A carcinoma is a malignant tumour of epithelial origin whereas a sarcoma is a malignant tumour of mesenchymal origin.

Neoplasms of the musculoskeletal system are still less common as compared to neoplasms from other systems. Approximately 8000 new cases (6000 soft tissue and 2000 bone) of sarcoma were reported in America in 1995 (Dee R., 1997). Primary musculoskeletal neoplasms whether bone or soft tissue, benign or malignant are generally classified based on their histologic type e.g. chondrogenic, osteogenic, fibrogenic, notochordal, vascular, lipogenic, haematopoeitic or neurogenic. Malignant tumours are differentiated from their benign counterparts by their ability to infiltrate into adjacent tissues as well as distant sites to produce another tumour, deemed metastases. In general, local behaviour of malignant tumours reflects their more aggressive biological activity (Simon M.A., 1998).However some benign mesenchymal tumours such as, giant cell tumour, can be locally aggressive but do not metastasize, they rapidly infiltrate local tissues and have the local characteristics of a malignant lesion and cannot be distinguished from them without a histological examination (Simon M.A., 1998).

## 1.2 OSTEOSARCOMA

Osteosarcoma is a high grade malignant spindle cell tumour arising within a bone. Its distinguishing characteristic is the production of neoplastic osteoid or immature bone, directly from a malignant spindle cell stroma. Secondary osteosarcomas are usually associated with a pre-existent disease such as Paget's disease, (Hadjipavlov *et al.*, 1992) irradiated bones, (Sheppard and Libshitz, 2001) multiple hereditary exostosis, bone infarcts, polyostotic fibrous dysplasia, osteogenesis imperfecta, solitary osteochondroma, chronic osteomyelitis, nonossifying fibroma, aneurysmal bone cyst, previous metallic implant, osteopoikilosis and osteopetrosis. (Simon M.A., 1998). Secondary osteosarcomas are rare in people below 21 years (3 %) and the occurrence is about 26% in adults above 21 years. However it is rather common in patients above 60 years of age, with an incidence of 56%. (Simon M.A., 1998).

Most osteosarcomas (98% to 99%) are solitary neoplasms but occasionally they may be multifocal at similar stages of development. Synchronous osteosarcomas are multifocal tumours in which all the skeletal lesions are identified at nearly identical times (within 6 months of presentation). Metachronous osteosarcomas have longer time interval between patient presentation and discovery of the tumour at other sites (greater than 6 months) (Simon M.A., 1998).

### 1.2.1 INCIDENCE AND EPIDEMIOLOGY

Osteosarcoma is the most common primary malignant bone tumour in children and young adults comprising about 15% of all primary bone tumours confirmed at biopsy (Dahnert W., 2003). In the older age group, osteosarcoma is the second most common primary malignant bone tumour after multiple myeloma.

The worldwide prevalence of osteosarcoma is 4-5:1,000,000. (Dahnert W., 2003). In the Mayo clinic series the prevalence of osteosarcoma was 1-3 per million. (Campbell W.C., 2003). There is no specific data regarding the incidence of osteosarcoma in Malaysia. However according to the National Cancer Registry, in 2003, the incidence of bone cancer was 0.9 per 100,000 population, and in the state of Kelantan it is 1.3 per 100,000.

### 1.2.2 AGE AND GENDER

Osteosarcoma is the most common malignant tumour of adolescence, exceeded only by leukaemia and lymphoma. (Gibbs *et al.*, 2001). It occurs at the adolescent growth spurt, with the peak incidence between 10 to 20 years of age; 75 percent of all cases occur between 10 to 30 years of age. (Vigorita V.J., 1999). Males are affected more frequently with a male to female ratio of 1.5-2:1. (Campannaci M. *et al.*, 1981).

It is a rare tumour in young children and even rarer in infants. However when it occurs, the clinical presentation, radiographic imaging and pathological features are similar to those of the affected age group. (Kazakewich *et al.*, 1991).

### 1.2.3 ANATOMIC DISTRIBUTION OF OSTEOSARCOMA

Osteosarcoma may arise in any skeletal site with the majority of them arising from the metaphyses of long bones. Fifty six percent of all osteosarcomas occur at the knee resulting in it being the most common primary osseous knee tumour reported in literature. (Vigorita V.J., 1999). Of this figure, 64% occur in the distal femur, 32% in the proximal tibia, about 4% in the proximal fibula and less than 1% in the patella. (Figure 1.1) Osteosarcoma is rare in the spine, pelvis, skull and fibula and the other flat bones in the body (Simon M.A., 1998).

Osteosarcoma predominantly arises from the metaphysis (80 to 90%) and followed by the diaphysis (10 to 20%) and the epiphysis (<1%). (Simon M.A., 1998).

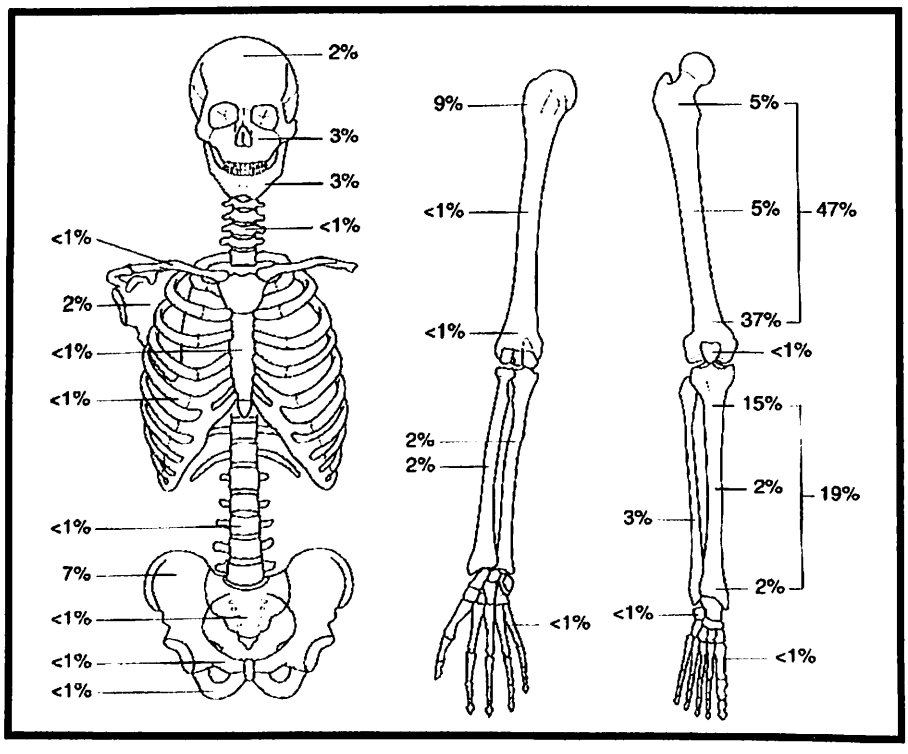


Figure 1.1: Skeletal Distribution Of Osteosarcoma

Extraskeletal osteosarcoma is located within the soft tissue, without attachment to the bone or periosteum. Extraskeletal osteosarcomas contribute 4% to the incidence of all osteosarcomas and constitute 1% of all soft tissue sarcomas. (Dahnert W., 2003). Anatomically, they may arise anywhere, with the thigh, upper extremity including the shoulder girdle and retroperitoneum being the most common locations. (Vigorita V.J., 1999). The mean age of presentation is 50 years with 94% of patients presenting after the age of 30. (Dahnert W., 2003). They present as painful or painless masses in various sizes and consistencies.

X-rays may reveal different levels of mineralization without bony involvement. Magnetic Resonance Imaging (MRI ) demonstrates a well demarcated non homogenous soft tissue mass with a mixed T1 weighted signal and is hyperintense on T2 weighted images. Bone scans show hot spots, reflecting the vascularity and mineralization activity of the tumour. Microscopically they are similar to osteosarcoma predominantly osteoblastic to fibroblastic, malignant fibrous histiocytoma (MFH) like and giant-cell rich. (Vigorita V.J., 1999).

Extraskeletal osteosarcoma have a high chance of local recurrence, approximately 50% and metastasise 62% of the time. (Vigorita V.J., 1999). Lee *et al.* reported a 5 year survival rate of 37 %. The lungs, bone and soft tissue are the most frequent sites for metastases. (Vigorita V.J., 1999).

### 1.2.4 CLINICAL PRESENTATION

Pain is the most common complaint on presentation, occurring in 85% of patients. However it occurs late relative to the disease process itself, as the pain is due to tumour expansion into surrounding tissues associated with local bone destruction and cortical erosion. (Malawer M.M., 1992). Presence of a firm soft tissue mass fixed to the underlying bone is found on physical examination. Local inflammatory signs, venous stasis and engorgement with decreased range of motion of the adjacent joints are found in advanced tumours.

Presentation with a pathological fracture occurs in less than 1% of patients with osteosarcoma. (Malawer M.M., 1992).Systemic symptoms are rare unless associated with late complications of pulmonary metastases (Dee R., 1997). As most osteosarcomas are high grade, development of metastases occurs early in the disease. Link *et al.* described that 80% of patients will have microscopic spread of tumour at the time of diagnosis. Like other sarcomas, osteosarcoma spreads is via hematogenous route and 90% is to the lungs. (Simon M.A., 1998).

### 1.2.5 IMAGING

The distinctive features of osteosarcoma on plain radiography are medullary and cortical bone destruction, an aggressive periosteal reaction, a soft tissue mass, and tumour bone either within the destructive lesion or at its periphery. The most common types of periosteal reaction encountered in osteosarcoma are the "sunburst" type and Codman's triangle. The lamellated or onion skin type of reaction is less frequently seen. (Greenspan A., 2000). Osteosarcoma lesions may present as purely sclerotic in about 45% of cases, purely osteolytic in 30% or a combination of both, in 25% of cases. (Forest M., 1988). The tumour borders are indistinct with a wide zone of transition. The type of bone destruction is either moth-eaten or permeative, rarely geographical. In some cases, the type of bone destruction may not be obvious on plain radiographs but patchy densities representing tumour bone and an aggressive periosteal reaction should help lead to the diagnosis.

Magnetic resonance imaging (MRI) is the preferred modality and has become the current standard technique for evaluating these tumours, in particular for intraosseous tumour extension and soft tissue involvement (Gillepsy *et al.*, 1998). MRI is superior in detecting skip lesions and transphyseal spread which occurs in 70-80% of cases (Norton *et al.*, 1991). On MRI, the tumour is of intermediate signal intensity on T1 weighted images (T1WI) and high signal intensity on T2 weighted images (T2WI). Marrow extension is clearly defined and best appreciated on T1WI images. Both neurovascular and soft tissue

involvement are delineated with the latter best demonstrated on T2WI images. (Dahnert W., 2003).

Before the advent of MRI, Computer Tomography (CT) was the modality of choice for staging osteosarcoma. It is highly accurate for determining the extent of bone involvement because there is high contrast between tumour and fatty marrow. However CT is inferior to MRI in defining muscular involvement and delineating the neurovascular structures. (Simon M.A., 1998). Currently, CT is useful in detecting pulmonary metastases which is the most common site for metastases.

Bone scintigraphy has an important role in tumour staging. It establishes areas of primary involvement, local extent, skip metastases and sites of synchronous metastases. The tumour shows intense increased activity on blood flow, blood pool and delayed images, indicating hypervascularity and the presence of new bone formation. (Dahnert W., 2003). The extent of involvement may easily be overestimated on bone scans due to the intensity of uptake by the tumour, and must be correlated with the findings on other imaging modalities.

### 1.2.6 BIOLOGICAL BEHAVIOUR OF THE TUMOUR

Sarcomas in general, form a solid mass that grow centrifugally with the periphery of the lesion being the least mature and is enclosed by a reactive zone or pseudocapsule. Pseudocapsule is an area composed of compressed tumour cells and a fibrovascular network of variable inflammatory components that interacts with surrounding normal tissue. Lesions within the pseudocapsule are known as "satellite nodules". High grade sarcomas have a poorly defined pseudocapsule which may be locally invaded by the tumour.

Osteosarcomasas respect anatomical barriers and take the path of least resistance during growth in the earlier stages. In the later stages, the walls of the compartment i.e. bone cortex or aponeurosis of a muscle, is violated and the tumour breaks into the surrounding compartments. At the time of presentation, most osteosarcomas are extracompartmental (Malawer M.M., 2001), they destroy the overlying cortex and extend directly into the surrounding soft tissue. The anatomical barrier is important in delineating the surgical margin. In the immature skeleton with an intact growth plate, the epiphysis may act as a relative barrier to its growth. However in more than half the cases, epiphyseal extension is massive, with the plate being partially or completely crossed and the tumour abutting against the articular cartilage. The articular cartilage is an anatomical barrier and is rarely invaded by the tumour. This phenomenon allows intrarticular resection of osteosarcomas (Simon and Bos, 1980). Invasion of the joints may occur in 19-24% of cases and there is no corelation with tumour size, except for very large tumours. (Vigorita V.J., 1999).

Thick fascial planes and aponeuroses are barriers to tumour extension. In the thigh, the lateral intermuscular septum acts as an anatomical barrier to tumours arising from the anterior compartment to the hamstrings.

"Skip metastases" within the same anatomic compartment is formed by the breakage through the pseudocapsule. They are solitary, separate tumour foci, not in continuity with the main tumour mass, occurring synchronously without pulmonary metastases, with an incidence up to 19% in one series (Enneking and Kagan, 1975).The occurrence of local recurrence, inspite of an adequate surgical resection is attributed to skip lesions. (Malawer M.M., 2001).

### 1.2.7 PATHOLOGY OF OSTEOSARCOMA

The pathology of osteosarcoma incorporates both the gross pathology as well as the detailed histopathology. The hallmark in diagnosing osteosarcoma is by histologic examination of biopsied tissue.(Vigorita V.J., 1999).

#### 1.2.7.1 GROSS PATHOLOGY

On gross appearance osteosarcoma is a hard, compact tumour which appears as a yellow-white dense, sclerotic and calcified mass. Usually the tumour originates from the medullary canal, penetrates the cortex, raises the periosteoum and invades the soft tissue. Although predominantly it is osteoblastic there may be a fibrous or cartilaginous foci. The fibrous component appears gray-white and the tumoural cartilage is generally blue-gray. Bone necrosis, hemorrhage and cystic degeneration are common. Undifferentiated tumours are soft and fleshy. (Forest M., 1988). The pseudocapsule is frequently seen enveloping the soft tissue component at the periphery of the osteosarcoma. (Vigorita V.J., 1999).

### 1.2.7.2 HISTOPATHOLOGY

Histopathologically, osteogenic sarcoma is characterized by the presence of sarcomatous osteoblast cells producing a disorganized maze of calcified tissue including osteoid and bone (Vigorita V.J., 1999). Masses of osteoid without accompanying groups of cells is highly suspicious foe osteosarcoma. As with other bone and soft tissue neoplasms, osteosarcoma has a characteristic pattern of biological behaviour which is the basis of grading. Histologically it is graded as low (eg.parosteal), intermediate (eg.periosteal) or high grade (conventional intramedullary). This grading system is based on tumour morphology, extent of pleomorphism, cellular atypia, mitosis and necrosis. The grades represent the biological aggressiveness of the tumour and correlates with the likelihood of metastases.

Dahlin in 1977 established the histologic classification separating osteoblastic, chondroblastic and fibroblastic types. In osteoblastic type, tumoural osteoid appear as a fine lacelike network with interlacing network. The chondroid component of the chondroblastic osteosarcoma may appear as scattered foci or as a predominantly cartilaginous matrix with a malignant appearance. The fibroblastic osteosarcoma may mimic fibrosarcoma .(Forest M., 1988). Although all the above variants have histologically different predominating cells, there is no mention on the difference in the management or the prognosis.

The Broder's system is a histologic classification established by Dahlin and Unni (1977, revised 1984). According to this system the numerical grade indicates the degree of malignancy with grade 1 indicating the least undifferentiated tumour and grade 4 the most undifferentiated tumour (Table 1.1). For example, parosteal osteosarcomas are regarded as grade 1, periosteal osteosarcomas as grade 2, conventional osteosarcomas as grade 3 or 4 and telangiectatic osteosarcomas, pagetic osteosarcomas, multifocal osteosarcoma and post irradiation osteosarcomas as grade 4 (Greenspan A., 2000).

This grading has clinical, therapeutic and prognostic importance. Pulmonary metastases is commonly seen in the high grade osteosarcoma (Greenspan A., 2000).This system is also incorporated in the Enneking staging system described later.

Mirra in 1989 stated that 75% of osteosarcomas demonstrate sufficient anaplastic changes to establish a diagnosis, but the remaining 25% have a confusing histological picture that needed to be correlated clinically and radiologically for diagnosis. For the diagnosis of osteosarcoma, identification of tumour bone production and distinguishing it from reactive bone formation associated with callus or periosteal response, as well as the deposition of chondroid matrix, collagen and fibrin is important as they may mimic tumour osteoid. (Simon M.A., 1998).

Table 1.1: Histologic Grading Of Osteosarcoma (according to Unni KK, Dahlin DC 1984)

| GRADE | HISTOLOGIC FEATURES |
|---|---|
| 1 | Cellularity: slightly increased<br>Cytologic atypia: minimal to slight<br>Mitotic activity: low<br>Osteoid matrix: regular |
| 2 | Cellularity: moderate<br>Cytologic atypia: mild to moderate<br>Mitotic activity: low to moderate<br>Osteoid matrix: regular |
| 3 | Cellularity: increased<br>Cytologic atypia: moderate to marked<br>Mitotic activity: moderate to high<br>Osteoid matrix: irregular |
| 4 | Cellularity: markedly increased<br>Cytologic atypia: markedly pleomorphic cells<br>Mitotic activity: high<br>Osteoid matrix: irregular, abundant |

### 1.2.8 STAGING

Staging is a process of classifying a malignant tumour by taking into account its degree of differentiation and its local and distant extent in order to determine the type of treatment necessary as well as to estimate the prognosis. It is based on the clinical findings, radiological features and the histopathological diagnosis. For sarcomas of the bone, there are two systems, one developed by Enneking (Table 1.2) and the other by American Joint Committee on Cancer (AJCC). (Table 1.3). Both use the same prognostic variables except that the Enneking system groups involvement of regional lymph nodes and distant metastases into a single group.

Enneking's classical staging for musculoskeletal sarcomas is based on 3 factors: histological grade (G), anatomical site (T) and the presence or absence of metastases (M). (Enneking *et al.*1980). (Table 1.2).

With regards to the histological grading, G, low grade lesions, G1, correspond to Broder's 1 and/or 2, and have a low risk for metastases, less than 25% risk (Simon M.A., 1998). High grade lesions, G2, which correspond to Broder's 3 and 4 have a significant higher incidence of metastases.

The anatomical site of the lesion is subdivided into intracompartmental (T1) or extracompartmental (T2). Extracompartmental tumours are those that have extended beyond the natural barriers either by growth or contamination (via biopsy) and may indicate the invasiveness of the tumour. Smaller intracompartmental tumours are further

in proximity to the vital neurovascular structures and allow a wider surgical margin of normal soft tissue and a greater probability of local control.

The third factor, presence or absence of metastases relates to the prognosis. Hematogenous spread to the lungs and regional metastases to the lymph nodes, the former being more common, have the same ominous prognostic significance. Both indicate little chance for prolonged survival. (Enneking *et al.*, 1980)

Table 1.2: Enneking system for staging of musculoskeletal sarcomas

| STAGE | GRADE | SITE | METASTASES |
|---|---|---|---|
| IA | Low | Intracompartmental | None |
| IB | Low | Extracompartmental | None |
| IIA | High | Intracompartmental | None |
| IIB | High | Extracompartmental | None |
| III | Any | Any | Regional or distant metastases |

Table 1.3: AJCC system for staging of bone sarcomas

| | GRADE | PRIMARY TUMOUR | REGIONAL NODES | DISTANT METASTASES |
|---|---|---|---|---|
| IA | Low | Within cortex | None | None |
| IB | Low | Beyond cortex | None | None |
| IIA | High | Within cortex | None | None |
| IIB | High | Beyond cortex | None | None |
| III (not defined) | | | | |
| IVA | Any | Any | Present | None |
| IVB | Any | Any | Any | Present |

### 1.2.9 TREATMENT

The goal of treatment in patients with osteosarcoma is to make them disease free and to preserve as much function of the limb as possible. In advanced cases, treatment is aimed at minimising pain and improving the quality of life. The dramatic improvement in survival in the last two decades is mainly attributed to the combination of efficient chemotherapy for control of micrometastases at diagnosis, followed by surgery for local control of disease and adjuvant chemotherapy.

In the era where chemotherapy was not routinely used for osteosarcoma, immediate wide or radical amputation was performed. It was observed that although local control of disease was adequate, 80% of patients eventually died of metastases even though metastases was absent at presentation, leading to the inference that these patients had micrometases at presentation. (Sweetnam R. *et al.*, 1971). With the advent of modern chemotherapy protocols combined with surgery, the current 5-year survival rate is approximately 70%. Two year survival rate of 54% with a median follow-up of 24 months was obtained in a study conducted in this centre. (Faisham W.I. *et al.*, 2004)

Adjuvant chemotherapy refers to chemotherapy administered postoperatively to treat the presumed micrometastases. Neoadjuvant chemotherapy refers to chemotherapy administered before surgical resection of the primary tumour. It presumably decreases the spread of tumour cells at the time of surgery, and can be started immediately, thus

effectively treating micrometstases at the earliest time possible. It also avoids tumour progression in cases of delay in surgery. Neoadjuvant chemotherapy administered, followed by surgical resection allows for histological evaluation of the resected specimen for the effectiveness of the treatment. The percentage of tumour necrosis is determined according to the Huvos grading system ( Huvos and Rosen .,1987). Patients who are poor chemotherapy responders, who have less than 90% tumour necrosis, could be subjected to an altered adjuvant chemotherapy regime. The definitive surgical procedure is performed 3 to 4 weeks after the last dose of neoadjuvant chemotherapy has been administered. Adjuvant chemotherapy is then restarted two weeks post operatively after the wound has healed. (Campbell W.C., 2003).

There are two kinds of protocols for adjuvant chemotherapy followed in different parts of the world. The American and the Italian groups prefer to use the more complicated, high dose intensive methotrexate based regime (Bacci G., *et al.*, 1993). On the contrary, European centres follow simple two drug regime with a combination of cisplatinum and adriamycin (Bramwell V.H., *et al.*, 1992). The outcome of dose intense regimen versus European Osteosarcoma Intergroup protocol was similar (Souhami R.L. *et al.*, 1997). In this centre, due to poor patient compliance and intolerance to the high doses in the intensive methotrexate regime, the European protocol is used, which is easy to administer and is reproducible.

Amputation was the mode of treatment for osteosarcoma previously. Today, more than 90% of patients with osteosarcoma undergo limb sparing procedures at major centers

specializing in musculoskeletal oncology. (Malawer M.M., 2001). Advances in diagnostic imaging, adjuvant and neoadjuvant chemotherapy, surgical reconstructive techniques and the development of a reliable, stable modular prosthesis for reconstruction of the hip, shoulder and knee have contributed greatly to the success of LSS. A study done at this centre proved that LSS did not compromise survival when compared to amputation (Faisham W.I. *et al.*, 2004).This results of this study was comparable to other studies around this region (Chang H.C. *et al.*, 2002). For osteosarcoma of the distal femur, the rate of local recurrence after wide resection and limb salvage is approximately 5% to 10% which is comparable to transfemoral amputation, provided a wide surgical margin is obtained. (Campbell W.C., 2003). LSS however is associated with greater perioperative and long term morbidity as compared to amputation. The surgical procedure is more extensive with greater risks for infection, wound dehiscence, flap necrosis, blood loss and deep venous thrombosis. Depending on the type of reconstruction, the long term complications include periprosthetic fractures, prosthetic loosening or dislocation, nonunion of the graft-host junction, allograft fracture, leg length discrepancy and late infection.

The choice between LSS and amputation must be made on the basis of the expectation and desires of the individual patient and family. When LSS is chosen, the outcome has to be equal or superior to amputation with regards to function and psychosocial benefit to the patient. The survival after LSS, and the immediate and delayed morbidity for each type of reconstruction has to be considered. (Simon M.A., 1998).

Successful limb salvage procedures consist of three surgical phases: (Dee R., 1997).

1. *Resection of the tumour;* This strictly follows the principles of oncologic surgery. Avoiding local recurrence is the main criterion of success and determines the amount of bone and soft tissue that has to be removed.
2. *Skeletal reconstruction;* The average skeletal defect following adequate tumour resection is 15-20 cm. Techniques of reconstruction are many. They include prosthetic replacement, arthrodesis, allograft or various combinations. These vary and are independent of the resection.

3. *Soft tissue and muscle transfer;* Muscle transfers are to cover the resection site and to restore motor power. Adequate skin and muscle coverage is necessary to decrease postoperative morbidity. Distal tissue transfers are not used due to the possibility of contamination.

The surgical guidelines and techniques of limb salvage surgeries are rather strict but vary from patient to patient. In general, the major neurovascular bundle must be free of tumour. Wide resection of the affected bone must be performed, with a normal tissue cuff in all directions. The standard practice is to excise en bloc all previous biopsy sites and potentially contaminated tissues. Bone resection is done 3 to 4 cm beyond the abnormal bone (based on MRI delineation) as to avoid intraosseous tumour extension. (Dee R., 1997). The relative contraindications to limb salvage surgery are involvement of major neurovascular bundle, the presence of pathological fractures, inappropriate biopsy sites, infection, immature skeletal age and extensive muscle involvement. The presence of pathological fractures increases the risk of local recurrence, but neoadjuvant