



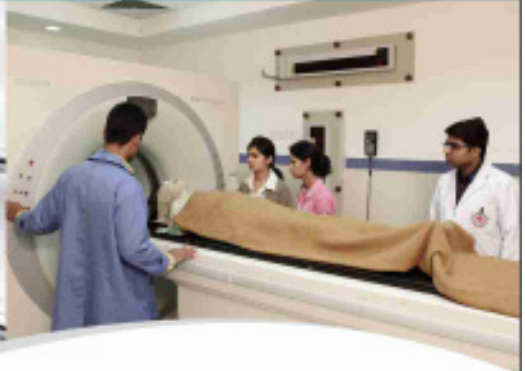
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From the Desk of Director Research

Primary bone cancer is cancer that forms in cells of the bone. Cancers can be discovered in bones in a number of different circumstances. When cancer is located in the bones, it is important to differentiate whether this cancer has spread from another site to the bones or whether it originated in the bone tissue itself. This distinction is important to determine which treatment options are appropriate. Primary bone tumors are fairly rare. Some types of primary bone cancer are osteosarcoma, Ewing sarcoma, malignant fibrous histiocytoma, and chondrosarcoma. Secondary bone cancer is cancer that spreads to the bone from another part of the body (such as the prostate, breast, lungs etc.). Conditions that may simulate primary bone tumors, such as metastases and non-neoplastic conditions like inflammatory processes, by far outnumber the cases of true bone tumors. About 2890 new cases and 1410 deaths from cancer of the bones and joints in the United States have been estimated in the year 2012.

The possibility for the pathologist to correctly diagnose a bone tumor depends to a large extent on the completeness of the clinical and imaging information provided. The histologic classification of bone tumors is based on cytologic findings, architecture, and type of matrix produced by the tumor. Genetic characterization of various bone tumors has helped to better understand their nature and the pathogenetic mechanisms involved and have also given additional support for the morphology-based classifications. The most common symptom of bone tumors is pain which accelerates with time. A person may go weeks, months, and sometimes years before seeking help; the pain increases with the growth of the tumor if left untreated.

Treatment of bone tumors is highly dependent on the nature and the complexity of the tumor. Chemotherapy and radiotherapy are effective in some tumors but the outlook depends on the type of tumor. The mortality rates from bone cancer are also decreasing. This rate reduction could be mostly due to better and advanced treatment of bone cancer as well as disease prevention through public education and awareness in avoiding known risk factors. The outcome is expected to be good for people with noncancerous (benign) tumors, although some types of benign tumors may eventually become cancerous (malignant). With malignant bone tumors that have not spread, most patients achieve a cure, but the cure rate depends on the type of cancer, location, size, and other factors. In the past, treatment of all extremity sarcomas was amputation. But with discovery of effective chemotherapy drugs and schedules, many of the bone cancers can be salvaged with chemotherapy and limb saving surgery. Thus in present era slogan is *"use multimodal treatment and save limbs"*.

This issue of Cancer News includes regular articles under the sections "Special Feature", "Guest Article", "Perspective", "Research & Development", "New Technologies", "Clinical Trials", "Globe Scan", "Cancer Control" and "In Focus".

We appreciate the contribution made by Dr Ashish Gulia, Assistant Professor, Orthopaedic Oncology, Tata Memorial Hospital, Mumbai for providing the "Guest Article".

Suggestions/ comments from the readers are welcome.

Dr D C Doval

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SPECIAL FEATURE

SURGICAL MANAGEMENT OF EXTREMITY OSTEOSARCOMA

Introduction

Osteosarcoma is the most common malignant neoplasm of bone. Over the past 3 decades, the prognosis for patients with osteosarcoma has changed dramatically. Though the development of effective chemotherapy agents has reduced the incidence of metastatic disease and mortality, surgical excision of the tumor remains the most essential component of osteosarcoma management.

The surgical treatment of osteosarcoma has historically been amputation/ disarticulation. It was only in 1970s that the role of chemotherapy in improving survival in osteosarcoma patients was established. While improved survival inclusion of chemotherapy on the one hand, it has been paralleled by a shift of surgical treatment from amputation towards limb salvage surgery. More than 90 % of patients with osteosarcoma undergo limb salvage surgery at most specialized centers. This change has resulted from advancements in prosthetics, surgical techniques, anesthesia, imaging and pathology.

Amputation or Limb Salvage?

It has been established beyond doubt that the survival of patients with osteosarcoma is not adversely affected by the choice of limb salvage as the surgical treatment as against amputation. However, limb salvage should be chosen in a patient only if the surgeon is reasonably confident that surgical excision of the tumor with wide margins is feasible, and that the expected function of the limb after limb salvage surgery will be better than ablative surgery in the form of amputation/ disarticulation. Limb salvage surgery will usually be contra indicated if there is pan compartmental disease with fungation, gross infection, encasement of major neurovascular bundle, and displaced pathological fracture not healing on neoadjuvant chemotherapy. While many workers have suggested marginally higher rates of local recurrence following limb salvage surgery compared to a radical amputation/ disarticulation, it has been observed that this is not translated into statistically significant advantage in survival. On functional and cost of treatment parameters, limb salvage surgery scores above amputation, as recent studies indicate. Surprisingly, however, the long term psychological outcome of patients with LSS is reported to be the same as amputation.

Biopsy

Biopsy is the first and a very important part of the overall management of osteosarcoma. It is vital, like all other malignancies, in the confirmation of diagnosis. Besides, the biopsy also needs to be properly placed and performed by a surgeon experienced in orthopedic oncology. A core needle biopsy carried out as an outpatient/ day care procedure is usually performed in the majority of patients, though an incisional biopsy may be required in a small minority of patients. Usually the soft tissue component is biopsied and the biopsy tract is placed in line with the planned definitive surgical incision, so that it does not violate tissue planes and neurovascular structures, and can be excised during definitive surgery. The biopsy should be performed by an experienced orthopedic oncologist, working as part of a team finally doing the surgery.

Timing of Surgery in Multimodal Management

For low grade osteosarcoma (whether juxtacortical or central), wide surgical excision is the preferred treatment. For high grade osteosarcomas, however, surgery has to be combined with multiagent chemotherapy. Initially, chemotherapy was given as a neoadjuvant (prior to surgery) treatment, with the idea that micrometastases will be addressed earlier, and there will be time to order and manufacture customized prosthesis. The modern prostheses now available are modular and available off the shelf, and do not require the waiting period for manufacture. Moreover, neoadjuvant chemotherapy has shown no improvement in survival in numerous studies. However, neoadjuvant chemotherapy is still usually followed, as it affords the patient and the surgeon time to discuss and plan the resection and reconstruction, facilitates surgery by way of better defined tissue planes and resolved tissue edema, and gives a chance for prognostication of the patient by post operative histopathological inputs. Surgery is then followed by adjuvant therapy, which may or may not be tailor made according to a good or bad histopathological response.

Resection

Surgical margins are defined as intralesional, marginal, wide, and radical. An intralesional margin is created if the tumor is entered at any point during surgery. A marginal margin is created when the dissection extends into or through the reactive zone that surrounds the tumor. A wide margin is created when the reactive zone is not entered and the entire dissection is performed through healthy tissues. A radical margin is created when the entire bony or myofascial compartment or compartments containing the tumor are resected.

The principle of surgical resection of osteosarcoma (as for any sarcoma of bone) is resection with wide margins (removal of tumor with a cuff of normal tissue covering it all around). This usually means removal of 2 cm normal tissue or a good anatomical barrier (e.g. fascial layer/ articular cartilage) and osteotomy of bone 3- 5 cm away from the level of involvement. There have also been recommendations of smaller margins on bone being acceptable for resection after effective neoadjuvant treatment. Joint sparing resections using the open physal cartilage as margin are also oncologically sound, while saving the nearby joint at the same time. Some workers have advocated the use of computer navigation for accurate resection with safe margin based on imaging findings while preserving as much bone as feasible. Similarly, distraction of growth plate is also being done preoperatively to enable preservation of the physis while retaining good margins of excision. An intraoperative frozen section from the bone marrow should be sent for confirmation of negative margin at the osteotomy site. Ablative surgery in the form of amputation or disarticulation is indicated in cases where salvaging the limb is not feasible with resection of tumor with wide margins. One critical aspect in limb-salvage procedures is to achieve a complete resection of the tumor with an adequate margin.

Reconstruction

Reconstruction of large segmental defects following resection is a challenging task. An ideal reconstruction should be durable, compensate for the loss of growth of the involved limb in skeletally immature patients, result in the function and appearance of the limb as

close to normal as possible, be compatible with early rehabilitation, and be cost effective and readily available. Obviously, there is no single ideal method of reconstruction, and the method has to be chosen keeping in mind the requirements of the patient.

Reconstruction Using Megaprosthesis

Reconstruction with megaprosthesis is a common mode of reconstruction as it has a predictable functional outcome, allows early rehabilitation, allows for intra- operative flexibility in the length of the reconstruction required and being non-biological, is unaffected by adjuvant chemotherapy (Figure 1). However, the main disadvantage of megaprosthesis is the vulnerability to wear and tear, leading to loosening/ breakage in the long term. Furthermore, the re-attachment of tendons to the prosthesis is another factor compromising the functional outcome. Availability of expandable prosthesis has minimized the problem of limb length discrepancy in young children with significant remaining growth, as they can be lengthened non-invasively.

Biological Methods of Reconstruction

Biological reconstruction may be used for intercalary reconstruction, arthrodesis or osteoarticular graft. It depends on bone healing for rehabilitation, which is subject to effects of adjuvant therapy and is associated with a long rehabilitation time. Osteoarticular allografts offer the advantage of good re-attachment of tendons for optimal function, particularly at sites, such as proximal tibia, proximal femur and proximal humerus. However, the availability of cadaveric grafts is limited, and the issues of infection,

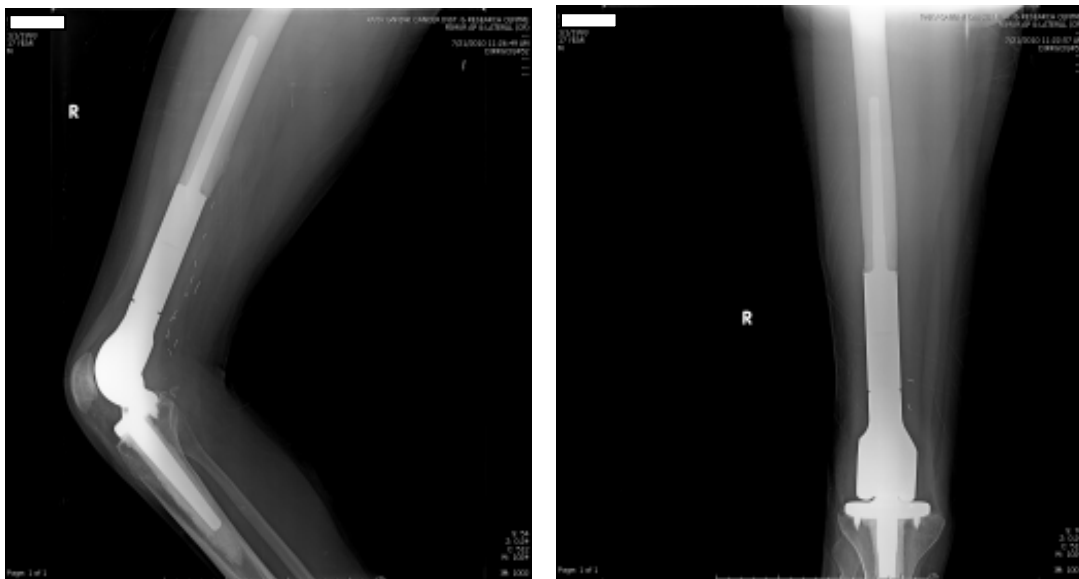


Figure 1: Reconstruction with a modular megaprosthesis for osteosarcoma

graft fracture, non union and osteoarthritis are reasons for concern. They can also be used as allograft-prosthesis composite to avoid development of early osteoarthritis.

In centers not having cadaveric bone bank access, resected tumor may be extracorporeally treated (radiotherapy/ liquid nitrogen/ pasteurization) and reimplanted to reconstruct the defect. This method offers a massive bone graft exactly matching the requirement of the defect created, and is highly cost effective (being the patient's own bone). However, the indications are limited and the post operative histopathological input is suboptimal.

Vascularised autografts are also used for intercalary defects, arthrodesis, or as growing osteoarticular grafts. They unite more predictably and show earlier hypertrophy compared to non-vascular autografts. Vascular autografts are also very useful when combined with allograft/ irradiated bone, providing vascularity to these massive grafts and making the outcome more predictable.

Management of Complications

Infection: Periprosthetic infections are a frequent (reported rates approximately 10%) complication of limb-salvage surgery which is largely due to prolonged and repeated surgeries, as well as to the immunocompromised condition of the patients. Furthermore, the large exposure of tissues and extensive dissection across vascular distributions also contribute to the high risk of infection. The highest risk of infection has been observed after proximal tibia resection due to the poor soft tissue coverage and pelvic resection due to dead space and vicinity to pelvic viscera. Radiation therapy and expandable prosthesis are also reported to be risk factors for infection.

Usually one or more attempts at debridement with antibiotic therapy (systemic and local antibiotic cement beads) are indicated as first line treatment of infection of tumor megaprotheses, particularly in the early postoperative setting. If these measures don't work, implant removal and thorough debridement and lavage is indicated. Usually an antibiotic impregnated cement spacer is placed before a new implant is inserted as a two staged procedure. Amputation may be ultimately required in a fair proportion of these patients.

Local Recurrence: Local recurrence occurs in about 5% of patients undergoing limb salvage surgery for extremity and girdle osteosarcomas at specialized

centers. The treatment of a local recurrence depends on the timing of recurrence, association with distant metastases, and resectability. Resectability is decided on the same criteria as a primary tumor, and local recurrence does not always warrant an amputation. A short disease-free survival or an association with pulmonary metastases may warrant first or second line chemotherapy. While local recurrence of osteosarcoma usually carries a poor prognosis, there have also been reports of local recurrence not having a significant impact on overall survival.

Implant Failure: Mechanical failure is the commonest reason for failure of reconstruction with megaprosthesis. Long term series report a survival rate of tumor megaprosthesis at 10 years ranging from 50-90% approximately of megaprosthesis for limb salvage surgery, the highest revision rates being with proximal tibia implants. There has been a lot of research into efforts to enhance the longevity of tumor megaprosthesis, and improve prosthetic technology (rotating platform design, HA coated collar and stem, porous tantalum and compression osteointegration technology). These hold promise in overcoming these limitations of this useful method of reconstruction.

Management of Metastatic Disease

Metastatic osteosarcoma generally carries a poor prognosis. The treatment has to be individualized to the patient, depending on the site (pulmonary or extrapulmonary), number and time of presentation. Pulmonary metastases, few in number, resectable and presenting late with a long doubling time, carry a better prognosis and are good candidates for pulmonary metastectomy.

Conclusion

Surgical management of patients with osteosarcoma is challenging. No difference in survival has been shown between amputations and adequately performed limb-salvaging procedures. Optimal tumor resection and a functional residual limb with increased survival of both the patient and the reconstruction are the goals of today's orthopedic oncology. Removal of tumor with adequate margins should be the primary consideration, whether the surgery is limb sparing or limb sacrificing. Reconstruction should be individualized to the needs of the patient, keeping in mind the oncological, functional and social requirements.

(Dr Akshay Tiwari, Consultant Musculoskeletal Oncologist)

GUEST ARTICLE

LIMB SALVAGE SURGERY FOR PRIMARY BONE TUMORS - CURRENT CONCEPTS

Introduction

Amputations of the extremities were routine for the local treatment of malignant bone tumors till late 1970s. There has been a sea change in the management of bone tumors in the last 3 to 4 decades. Better understanding of anatomy, advent of chemotherapy, advances in imaging, refinements in surgical techniques, and easy availability of affordable durable mega prosthesis have made limb salvage a norm in today's era. Eventhough limb salvage is superior to amputation in providing better function and much required psychological benefits, it has its own limitations in the form of high treatment cost, prolonged rehabilitation and risks of related short and long term complications. If properly executed in indicated cases, the benefits of limb salvage weigh much more than its limitations and should always be considered as first choice in the local treatment of malignant bone tumors.

Limb salvage has two basic components, resection and reconstruction. The main principle of limb salvage lies in the fine balance of the two, which implies that resection procedure should be able to provide adequate disease clearance and the salvaged limb should be reconstructed in a manner that it has better function than amputation and external prosthesis.

There are various contraindications for limb salvage. These mainly include major vascular involvement, encasement of a major motor nerve, poorly placed biopsy incisions, preoperative infection, intra-articular disease extension, non-union of pathological fracture and inadequate motors. Last two are the only two absolute contraindications, others are relative ones and can be managed with additional help from various microsurgical techniques like vessel and nerve grafting and soft tissue reconstructions.

The two main prerequisites for limb salvage are: (1) ability to achieve wide margin, and (2) ability to reconstruct the limb in a way to provide better function than amputation. Eventhough two prerequisites are related to each other but one should never govern to guide the other. The first and foremost goal of onco-surgery is to achieve complete disease clearance and reconstruction should always take a second place in the priority.

Resection

Concept of Margins: Based on the concept of pseudo-capsule and reactive zone and its relationship of the dissection plane to the tumour, Enneking described four types of surgical excisions:

Margin	Surgical Procedure	Result
Intralesional	Piecemeal debulkin or curettage	Leaves macroscopic disease
Marginal	Shell outen enbloc through pseudbcapsule or reactive zone	May leave either 'satellite' or "skip" lesions
Wide	Intracompaitmental en bloc with cuff of normal tissue	May occasionally leave "skip" lesion if not recognized by prior imaging
Radical	Extracompartmental en block entire compartment	Noresidual local disease

Depending on the pathological aggressiveness of the tumor, the appropriate surgical procedure is chosen to achieve adequate disease clearance. For example, a benign or locally aggressive bone tumor like a giant cell tumor or an aneurismal bone cyst may be treated with intralesional curettage while on the other hand, malignant bone tumors like osteosarcoma, Ewing's sarcoma or chondrosarcoma will require wide excision or radical excision to achieve adequate disease clearance.

Achieving a wide margin is the main aim during the resection of a malignant extremity tumor. A margin is considered wide when it ensures adequate removal of the primary disease and the focal disease skips in the reactive zone. A 3-cm marrow margin on the T1 weighted MRI image for the bone and a 2-cm margin in soft tissue is considered adequate. Principles of limb salvage allow focal close margins in order to preserve vital neurovascular structures. This is where the concept of 'barrier effect' by Kawaguchi is helpful in understanding the qualitative assessment of margins. The barrier is described as a tissue that has resistance against tumor invasion, and can include muscle fascia, joint capsule, tendon, tendon sheath, epineurium, vascular sheath and cartilage. With the exception of joint cartilage, each of these tissues can be classified as either a thick barrier or a thin barrier. A thick barrier is considered equivalent of 3-cm thickness of normal tissue and a thin barrier is considered to be 2 cm while joint cartilage is 5 cm.

Reconstruction

A number of reconstruction methods are available for the reconstruction of the skeletal defects. These include both biological and non-biological methods (Table 1). The list is quite extensive and usually

confusing. The right choice of reconstruction for a patient has to be tailored and depends on number of factors. These include age of patient, the diagnosis, the site of the tumor, the extent of disease, response of the tumor to neoadjuvant chemotherapy, patient's lifestyle and socio-economic status, functional demand, the

Table 1: Options for Reconstruction

<p>Non-Biological</p> <p>A) Megaprosthesis</p> <ul style="list-style-type: none"> • Standard megaprosthesis <ul style="list-style-type: none"> i) Osteoarticular ii) Diaphyseal • Expandable megaprosthesis <ul style="list-style-type: none"> i) Depending on mechanism of expansion <ul style="list-style-type: none"> a) Minimally invasive expandable prosthesis b) Non invasive expandable prosthesis ii) Depending on extent of reconstruction <ul style="list-style-type: none"> a) Osteoarticular b) Diaphyseal <p>B) Nail cement spacers</p> <ul style="list-style-type: none"> • Osteoarticular/Across the joint • Diaphyseal <p>Biological</p> <p>A) Allografts</p> <p>B) Non-vascularised auto-grafts</p> <p>C) Vascularised auto-grafts</p> <p>D) Patients own sterilized tumor bone</p> <p>E) Combination of allografts/ sterilized tumor bone and vascularised auto-grafts</p> <p>F) Ilizarov</p> <p>G) Rotationplasty</p>

surgeon's own expertise and the infrastructure available to execute these complex surgeries.

Depending on the extent of the resection, these surgeries can be divided in to two major types: (1) Osteo-articular resections, where joint surface is sacrificed; (2) Intercalary resections, mainly diaphyseal or diaphysio-metaphyseal resections where joint surface is preserved.

For osteoarticular resctions, megaprosthesis is the preferred method of reconstruction as it provides immediate structural stability and excellent function. The functional rehabilitation is also not affected by the

adjuvant therapy which may be the case if biological modes of reconstruction are used. With the introduction of rotating hinge which has reduced the stress on the fixation site and hydroxyl appetite coating of stem collar which helps to form an extra cortical bridging at bone implant junction and acts as sealant to prevent aseptic loosening due to ploy debris, these implants have become more durable and the rates of complications like implant failure and aseptic loosening have been reduced drastically. Eventhough refined to the present elite forms, these are mechanical devices and will always be prone to fatigue failure due to repeated stress loading.

In the lower extremity, megaprotheses are regularly used for the tumors located in the distal femur, proximal tibia and proximal femur. In addition to regular reconstruction, a gastrocnemius flap is essential for proximal tibia replacements as it provides muscle cover for the implant which is otherwise subcutaneous and reduces infection. It also provides a dynamic attachment for the quariceps tendon attachment which is essential for knee extension. In proximal femur replacement, the abductor muscles should be anchored back to the implant. If greater trochanter is not involved, abductors are elevated with a bony flake which is much easier to anchor to the implant. Due to loss of proximal musculature and part of hip joint capsule, hip dislocation is always a worry and can be addressed with judicious use of prolene mesh or trivera tube. Total bone involvement of the femur can also be reconstructed with total femoral prosthesis. Such reconstructions may not be possible with any other methods of reconstruction and megaprotheses provide good function in these situations. Eventhough megaprotheses are available for distal tibial reconstructions, but are not popular due to high failure rate and higher rates of infections which are due to inherent anatomical problems of lack of adequate soft tissue coverage and bony anchorage distally.

In upper limb, megaprosthees are used for proximal humeral, distal humeral and total humeral involvements. Distal humeral replacements provide excellent functional outcomes, whereas in proximal humeral replacements, these prostheses merely act as spacers to provide a stable shoulder fulcrum to have good elbow and hand function. Shoulder function is lost due to sacrifices of rotator cuff muscles and axillary nerve which are involved by the tumors in most of the cases. In rare instances where axillary nerve can be preserved, a reverse shoulder prosthesis provides much better function. Total humeral replacements

provide function comparable to the proximal humeral replacements, with good elbow and hand function in spite of loss of shoulder movements.

Biological methods are not very popular for reconstruction of osteoarticular defects. Though osteoarticular allografts can be used but the use is limited due to its limited availability and requirement of a bone bank for procurement and processing. Other non-articular grafts like allografts and auto fibula may be used but will result in arthrodesis as they will not enable articular reconstruction. A combination of allograft and prosthesis, i.e. allo-prosthetic composite may be used in special circumstances.

Intercalary resections can also be reconstructed with a number of biological and non-biological options. Non-biological methods of reconstruction include diaphyseal prosthesis or nail cement spacers. Non-biological methods have advantage of immediate weight bearing and early function but are costly and are associated with risk of mechanical failure in long term. Recent developments in the field of implant technology have made it possible to use these prostheses in situations where resection level is very close to the joint surface and a miniscule amount of bone is present for anchorage. These size-matched implants which are customized to fit at pre-decided resection level have HA coating at both the ends for rapid integration between bone and implant. If physis is sacrificed in skeletally immature patients, the expandable version of these prostheses would be to address limb length discrepancy.

Nail-cement spacers, though a temporary solution may be reserved for cases that are metastatic at presentation or for the patients with financial constraints and wish to have limb salvage. If patient is survivor, this may be converted to a more biological permanent reconstruction later on.

Allografts alone have been used in the past for reconstruction of intercalary defects. Though popular earlier, are not used as frequently now, due to high rates of early and late complications, like infection, delayed union, non-union and graft resorption and fractures. Vascularised fibula provides good osteogenic potential but is not suitable for large defects, especially in lower limbs as it is structurally weak. Use of a combination of vascularised fibula with allograft is an excellent method of biological reconstruction which has

structural stability provided by the allograft and great osteogenic potential delivered by vascularised fibula.

Patient's own sterilized tumor bone may be used as a biological reconstruction modality. This can be done by a number of ways, like autoclaving, microwave, pasteurization, cryotherapy and radiotherapy (extracorporeal radiotherapy). The principle is the same; the tumor bearing bone is excised as usual, all soft tissues and macroscopic tumor removed and the remaining bone sterilized by any of the above methods before being reimplanted. This procedure may not be suitable for structurally weak bone and bone with pathological fracture. This method is quite useful as it is cheap and provides a size-matched autograft and also avoids the logistic issues involved in allograft procurement and risk of disease transmission. In large defect reconstructions, it may be combined with a vascularized bone graft.

Reconstruction Challenges in Children

Reconstruction of tumor defects in children is further more challenging due to number of factors, like dynamic nature of growing bones, narrow medullary cavity (which limits the size of intramedullary prosthetic stems), continually remodelling bone, greater functional demand and limb length discrepancy. Limb length discrepancy is a major problem in lower limb. This can be addressed by either vascularized epiphyseal transfers (proximal fibular epiphysis, iliac crest, lateral scapular crest), use of minimally invasive or non-invasive expandable prosthesis or by ilizarov lengthening at a later stage. A properly planned rotationplasty can help ensure that the opposite knee and the repositioned rotated ankle of the operated limb lie at the same level at skeletal maturity.

Conclusion

The treatment of bone tumors is a multi-modality management. If done carefully in indicated cases, limb salvage is effective in local disease control and results in much better functional and psychological outcome. There are numbers of reconstruction options and needs to be individualized for each patient. These procedures are complex and should be carried out by well trained onco-surgeons in sarcoma treatment centres where all infrastructure required is available.

(Dr Ashish Gulia, Assistant Professor & Orthopedic Oncologist, Bone and Soft Tissue Services, Tata Memorial Hospital, Mumbai)

PERSPECTIVE

APPROACH TO DIAGNOSIS OF BONE TUMORS — A BROAD OVERVIEW

Introduction

Bone tumors are uncommon and consequently the exposure of a general pathologist to bone tumors is limited. A structured algorithmic approach, assisted by clinical and radiological inputs, helps overcome the difficult task of diagnosis in bone tumor pathology.

Bone tumors are divided as primary and secondary. Secondary tumors are more frequent and include (a) metastatic tumors (b) soft tissue tumors (STT) extending to bone, and (c) benign lesions undergoing malignant transformation.

Metastatic tumors are the most frequent and are characterized by bimodal age distribution; in middle aged adults and children in the first decade of life. These are multifocal and involve hematopoietic marrow. Commonly affected sites are axial skeleton, e.g. vertebrae, pelvis, ribs and cranium. Proximal long bones, especially humerus and femur, are other common sites. Involvement distal to the elbows and knees is unusual and secondaries to the small bones of the hands and feet are inordinately rare. Occasionally, metastases may appear as solitary lesions (particularly true for the lung, kidney and thyroid cancer). Most common malignancies producing skeletal metastases in an adult originate from carcinomas of the prostate, breast, kidney, lung, thyroid and colon. Melanoma is another dreaded tumor involving bone secondarily. In children, clear cell sarcoma of kidney, neuroblastoma, rhabdomyosarcoma are common. X-ray shows pure

lytic lesions in kidney, lung, colon, and melanoma; blastic in prostate and breast carcinoma and mixed lytic and blastic in others.

Primary bone tumors occur mostly in the first 3 decades of life, during the ages of the greatest skeletal growth except chondrosarcoma which are usual in 5th decade. Some tumors prefer immature skeleton while other arise in a mature skeleton. Some are associated with pain, e.g. osteoid osteoma and other mimic osteomyelitis in their presentation as Ewing’s sarcoma. Many primary tumors have predilection for particular bone types and involve only a specific anatomical site in the bones. Some amongst these, have classical radiographic appearances while some others provide reasonable clues and cues to their identity. It is the combination of these clinical and radiological features combined with histological findings that allows correct rendering of diagnosis in otherwise difficult domain of bone tumors.

Approach to Bone Tumor Diagnosis

The clinical details to be considered are:

Age: The most significant clinical correlate is the age of the patient. The diagram below (Fig 1) shows age-wise distribution of the bone tumors.

Pain: Although a non-specific symptom may help in differential diagnosis. generally, benign non-growing lesions tend to be asymptomatic and represent incidental findings. Pain is a symptom of rapidly growing lesions, e.g. aggressive osteoblastoma, GCT and malignant tumors. Osteoid osteoma, however, causes night pain relieved by NSAIDS. Pain is a useful distinguishing feature between difficult differential diagnosis of enchondroma vs. chondrosarcoma, grade 1, where the presence of pain signifies low-grade

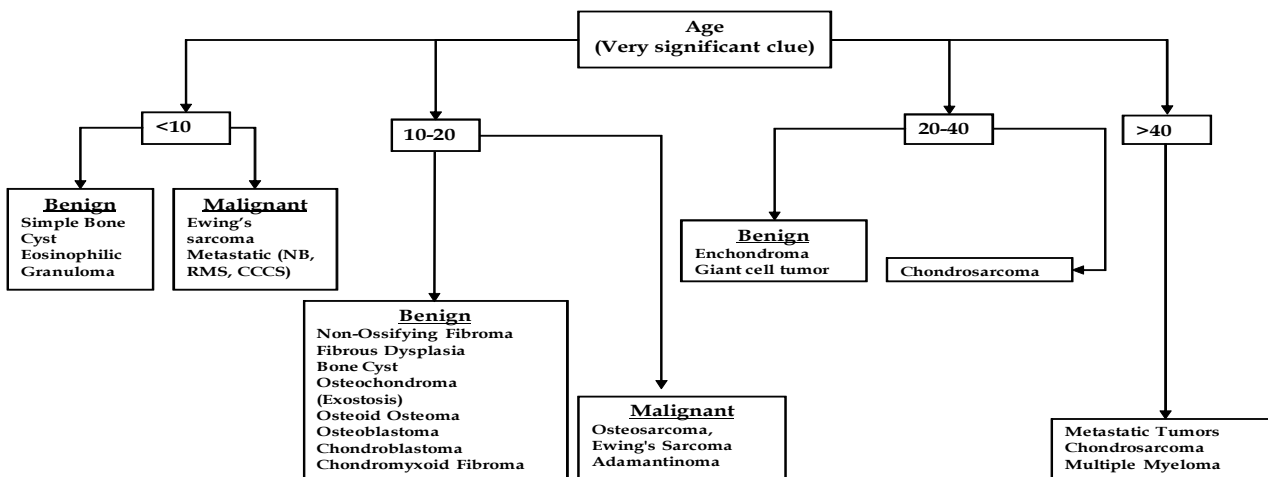


Fig 1: Age-wise distribution of primary bone tumors

chondrosarcoma and enchondromas tend to be asymptomatic, unless associated with a pathologic fracture.

Symmetry: Multifocality can be seen in both benign and malignant tumors, however, the former are symmetrically distributed.

Radiological Correlation

Plain radiograph, CT scan, MRI scans and bone scintigraphy are used for assessment of bone tumors. **Radiographic examination should answer the following questions.** A pathologist shall try and find the answer himself but shall never shy away from approaching the radiologist when confronted by a difficult case. The multidisciplinary approach serves the patient interest best.

1. What is the precise location of the lesion (type of bone and, if the long bone is affected, where exactly the lesion is centered—cortex or medulla; epiphysis, metaphysis or diaphysis)? Some tumors almost exclusively occur at specific sites; many others favor certain locations. The preferential involvement of certain bone by specific tumor type is shown in Table 1. Fig 2 and Table 2 identify the relationship of certain primary bone tumors with anatomical sites within a bone.
2. Is there any evidence of underlying bone abnormality (eg. bone infarct, Paget’s disease)? High-grade sarcomas tend to arise in damaged bone.
3. Is the lesion multifocal? Symmetrical multifocality is a feature of benign tumors.

Table 1: Preference of Tumor Types for Specific Bones

Lesions	Most Common Skeletal Sites
Ewing's sarcoma Multiple myeloma Leukemia/lymphoma Metastatic cancers	Hematopoietic marrow sites in the axial skeleton (vertebrae, ribs, sternum, pelvis, cranium) and proximal long bones (femur, humerus)
Non-ossifying fibroma	Metadiaphyseal regions of the tibia and distal femur (80%). Does not occur in the flat bones, craniofacial bones, the spine, or the small bones of the hands/feet.
Simple bone cyst	The vast majority of SBCs is found in the proximal humerus (55%) and proximal femur (20%)
Chordoma	Base of the skull or sacrum (90%)
Adamantinoma	Mid-shaft of tibia (90%), jaw bones
Chondroblastoma	Long bones (knee area, proximal humerus)-(70%)
Giant cell tumor	Knee area, distal radius (65%)
Enchondroma	Small bones of the hands and feet (60%). This is in fact the commonest tumor at these sites.
Chondrosarcoma (primary, and to the less extent secondary)	Tends to develop in the axial skeleton with 25% to 30% occurring in the pelvic bones
Fibrous dysplasia	Femur, tibia, skull and ribs
Osteochondroma	Knee area, proximal humerus, pelvis
Osteoblastoma	Spine (30%), mandible, long bones
Aneurysmal bone cyst	Any bone; common in the spine
Chondromyxoid fibroma	Knee area (30%), pelvis, small bones of the feet
Hemangioma	Spine, craniofacial bones

Table 2: Relation of Anatomical Location in Bone with Tumor Type

Anatomical Location in Bone	Tumor Types
Epiphyseal lesions	Chondroblastoma (Ch) and Giant Cell Tumor (GCT). GCT often shows metaphyseal extension
Metaphyseal intramedullary lesions	Osteosarcoma is usually centered in the metaphysis. Chondrosarcoma and fibrosarcoma often present as metaphyseal lesions. Osteoblastoma, enchondroma, fibrous dysplasia, simple bone cyst, and aneurysmal bone cyst are common in this location.
Metaphyseal lesions centered in the cortex	Classic location for a non-ossifying fibroma (NOF). Also a common site for osteoid osteoma.
Metaphyseal exostosis	Osteochondroma
Diaphyseal intramedullary lesions	Favored location for Ewing's sarcoma, lymphoma, myeloma. Common for fibrous dysplasia and enchondroma
Diaphyseal lesions centered in the cortex	Adamantinoma, osteoid osteoma

4. Does the tumor have a well-defined margin? Is there a rim of sclerotic bone? The presence of a well-defined margin and a sclerotic rim strongly suggests a benign non-growing lesion.
5. Is there evidence of significant cortical expansion or destruction? These findings are seen with locally aggressive or malignant tumors.
6. Is there an associated periosteal reaction and, if so, of what type?
7. Does the lesion produce mineralized matrix (osteoid or cartilage)?
8. Is there a soft tissue mass?

Questions 4 and 5 are extremely important for correct diagnosis and are not difficult to evaluate. Table 3 highlights the pattern of bone involvement

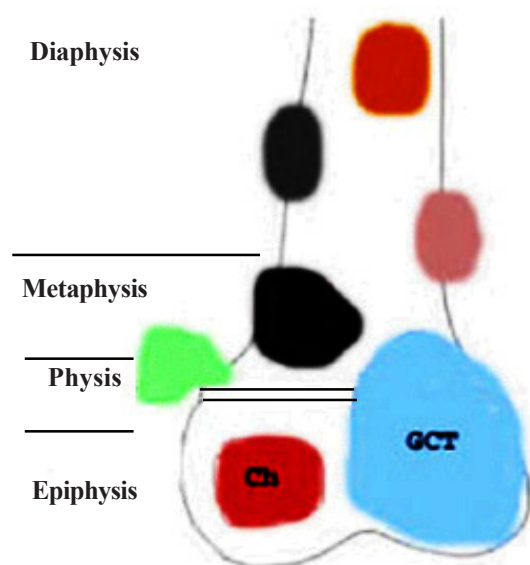






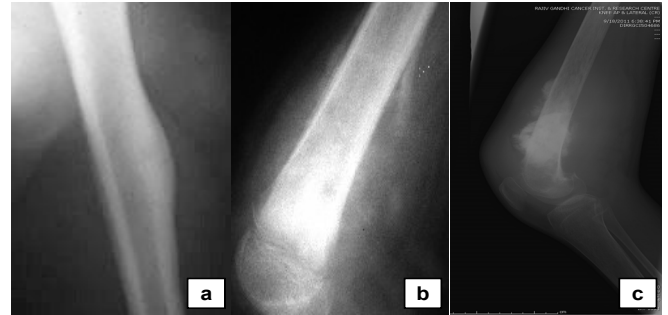
Fig 2: Anatomical location of common bone tumors

Table 3: Pattern of Bone Involvement

	<p>Geographic pattern of bone destruction with a sclerotic rim. Geographic pattern refers to a well-defined area of lysis. The sclerotic rim is more commonly seen in the weight-bearing bones and represents bone reaction to the lesion. Its presence means that the bone has been given sufficient time to react. Some authors say that the sclerotic rim signifies benignancy to about 95%.</p>
	<p>If the lesion is growing more rapidly, it may still show a well-demarcated zone of bone destruction (geographic pattern), but it will lack a sclerotic rim. With continued growth, such lesions may show cortical expansion. Expansile growth pattern is defined as visible widening of the affected portion of bone. In many cases, an interrupted periosteal rim will surround the expanded portion of bone. This pattern may be seen in locally aggressive tumors and in low-grade malignancies.</p>
	<p>Rapidly growing lesions are poorly defined and may show aggressive, infiltrative patterns of bone destruction (permeative or “moth-eaten”). “Moth-eaten” pattern is defined as an ill-defined zone of multiple small radiolucencies that may coalesce.</p>
	<p>Permeative pattern is characterized by numerous tiny radiolucencies in between the residual bone trabeculae. Due to the minute size of radiolucencies, the lesion may be difficult to see and to delineate on the plain film. Generally, the more rapidly growing a lesion, the more difficult it is to see on plain film. “Moth-eaten” and permeative patterns are indicative of destruction involving both medullary and cortical bone. They are seen in high-grade malignant neoplasms and in osteomyelitis.</p>

Types of Periosteal Resection

The periosteum responds to traumatic stimuli or pressure from an underlying growing tumor by depositing new bone. The radiographic appearances of this response reflect the degree of aggressiveness of the tumor.



*Fig 3: (a) **Focal cortical thickening** (buttress type reaction). Seen in slow growing tumor. (b) Rapidly growing tumor lifts the periosteum at acute angle at edges and evokes formation of lamellated new bone (Codman's Triangle). Seen in malignant bone tumors and aneurysmal bone cyst. (c) Hair on end (sunray appearance) of periosteal reaction seen in osteosarcoma*

Histological Evaluation

The following are the most important histologic features to consider:

- Pattern of growth (e.g. sheets of cells vs. lobular architecture).
- Cytological characteristics of the constituent cells
- Presence of necrosis and/or hemorrhage and/or cystic change
- Matrix production
- Relationship between the lesional tissue and the surrounding bone (e.g. sharp border vs. infiltrative growth)

Conclusion

Pathological examination alone rarely culminates in a correct diagnosis. A variety of lesions/tumors produce giant cell rich histological picture. It will be suicidal to label it as giant cell tumor based on morphology alone. Radiology and clinical inputs will be essential for correct diagnosis. It is, therefore, reiterated that one should never try to make a diagnosis of bone tumor without integrating clinical, radiological, and histologic appearances. Biologically different types of tumors may have overlapping histologic features. Always obtain a list of differential diagnoses after viewing the clinical and radiological details and discussing the case with a radiologist and an orthopedic surgeon. Remember “You are all, a team”.

(Dr Anurag Mehta, Director Laboratory Services)

RESEARCH & DEVELOPMENT

Biomarker in Sarcomas

A new study has identified a predictive biomarker for insulin-like growth factor Type 1 receptor (IGF-1R) therapy in sarcomas. The study covered patients with unresectable or metastatic soft tissue sarcomas (STS), Ewing's sarcoma (ES) and osteosarcoma treated with IGF-1R antibody. Tumor samples were analysed by immunohistochemistry for expression of IGF-1R, insulin-like growth factor binding protein Type 3 (IGFBP-3), Ki67, epidermal growth factor receptor (HER1) and human epidermal growth factor receptor 2 (HER2). Predictive factors for progression-free survival (PFS) and overall survival (OS) were investigated. All tumor samples had a positive IGF-1R immunostaining on 60% to 100% of tumor cells. IGFBP-3 immunostaining was observed in 12 (75%) samples with 5% to 100% of positive cells. IGF-1R immunostaining was nuclear (n=9, 56%), cytoplasmic (n=4, 25%), or nuclear + cytoplasmic (n=3, 19%). Exclusive intra-nuclear immunoreactivity for IGF-1R was significantly associated with a better PFS (p=0.01) and OS (p=0.007). Nuclear localisation of IGF-1R in tumor cells might be a hallmark of pathway activation.

(Eur J Cancer, Jun 6, 2012)

miR-34a and Survival in Ewing's Sarcoma

Researchers at Rizzoli Institute, Italy, have analysed the miRNAs discriminating Ewing's sarcoma (EWS) patients with different clinical outcomes in order to identify new indicators of prognosis. Micro-array analysis in 49 primary EWSs defined a signature of five miRNAs (miR-34a, miR-23a, miR-92a, miR-490-3p, and miR-130b) as an independent predictor of risk for disease progression and survival. miR-34a particularly appeared associated with either event-free or overall survival and emerged as a significant predictor also. Patients with the highest expression of miR-34a did not experience adverse events in 5 years. In contrast, patients with the lowest expression recurred within 2 years. Functional analysis of miR-34a in EWS cell lines indicated that when miR-34a expression was enforced, cells were less proliferative, less malignant, and sensitized to doxorubicin and vincristine. The data indicates that miR-34a expression is a strong predictor of outcome in EWS. Restoration of miR-34a activity may be useful to decrease malignancy and increase tumor sensitivity to current

drugs, so sparing excessive long-term toxicity to EWS patients.

(J Pathol, Apr 2012)

Oncologic Outcomes in MRCLS

A multicenter, retrospective study of myxoid/round cell liposarcoma (MRCLS) cases primarily managed by Canadian multi-disciplinary sarcoma teams was conducted to evaluate oncologic outcomes and to provide guidelines for the management of primary myxoid (MLS) and round cell liposarcoma (RCLS). The study included 311 MLS and 107 RCLS patients with a median age of 45 years and a median follow-up of 5.2 years. The majority of patients underwent surgical resection and radiotherapy, with a small percentage (6%) receiving chemotherapy. The overall 10-year local control rate was 93% with no difference between MLS and RCLS. Radiotherapy was significant in preventing local relapse and reducing tumor diameter (median=18%) and improving microscopic margin status, but did not impact survival. The 5- and 10-year metastatic-free survivals were 84 and 77% respectively for MLS and 69 and 46% for RCLS. Round cell percent (>5%) and tumor diameter (>10 cm) correlated with increased risk for metastasis and death. MLS and RCLS showed different metastatic risk but equally good local control. Radiotherapy was effective in preventing local recurrence and should be delivered as neoadjuvant. New staging strategies are to be defined to account for the unusual metastatic pattern.

(Ann Surg Oncol, Apr 2012)

Radiotherapy for Giant Cell Tumors of Bone

Giant cell tumor of the bone (GCTB) is a benign or sometimes semi-malignant neoplasm, accounting for 5% of all primary bone tumors. This type of tumor has been historically considered as radioresistant. Six German institutions collected data from 35 patients treated during the last 35 years and analyzed them. From 1975-2010, 16 male and 19 female patients with 39 lesions were irradiated for GCTB. The median age was 30 years with median follow-up of 65 months. Nineteen patients had undergone RT for recurrent or unresectable disease and 16 patients for non-in-sano resection. The actuarial 5-year overall and disease-free survival rates were 90% and 59%, respectively. RT is an easy, safe and effective method for the treatment of GCTB and may provide an attractive alternative to mutilating surgery.

(Anticancer Res, May 2012)

NEW TECHNOLOGIES

Carbon Ion Radiotherapy for Osteosarcoma

A multi-institutional study in Japan has concluded that carbon ion radiotherapy (CIRT) is safe and effective modality for the management of unresectable osteosarcoma. Retrospective analysis of 78 patients of inoperable osteosarcoma of the trunk who received treatment with CIRT from 1996-2009 was performed. The median applied CIRT dose was 70.4 Gray equivalent in a total of 16 fractions over 4 weeks. The 5-year overall survival rate was 33%, and the local control rate was 62%. Thirty-eight patients who had a clinical target volume <math><500\text{ cm}^3</math> had a 5-year overall survival rate of 46% and a 5-year local control rate of 88%. Three patients experienced severe skin/soft tissue complications requiring skin grafts. Of 9 patients who were continuously disease-free for >5 years, 8 were able to walk with or without the help of a cane, and 6 were free from pain killers. CIRT appeared to be a safe and effective modality providing good local control and offering a survival advantage and good long-term functional results without unacceptable morbidity.

(Cancer, Feb 22, 2012)

miRNA Signatures for Osteosarcoma

Scientists from the Center for Children's Cancer Research, USA, identified for the first time an miRNA signature reflecting the pathogenesis of osteosarcoma in human patients. The signature includes high expression of miR-181a, miR-181b, and miR-181c as well as reduced expression of miR-16, miR-29b, and miR-142-5p. It was also shown that miR-181b and miR-29b exhibit restricted expression to distinct cell populations in the tumor tissue and higher expression of miR-27a and miR-181c in pre-treatment biopsy samples characterized patients who developed clinical metastatic disease. In addition, higher expression of miR-451 and miR-15b in pre-treatment samples correlated with subsequent positive response to chemotherapy. Analysis revealed positive and negative correlations highlighting pathways of known importance to osteosarcoma, as well as novel genes. The findings establishes a miRNA signature associated with pathogenesis of osteosarcoma as well as critical pre-treatment biomarkers of metastasis and response to therapy.

(Cancer Res, Apr 1, 2012)

State-of-the-Art Scanning Detects Cancer in Bone

Researchers from Stanford University Medical Center revealed at the Society of Nuclear Medicine 2012 Annual Meeting that a combination of molecular imaging, radiography and dual imaging probes detects more cancerous bone lesions than other methods. This study is the first of its kind that compares the use of positron emission tomography (PET) involving both F-18 NaF, a sodium fluoride probe with affinity for bone, and F-18 FDG with CT alone in the detection of bone metastases. Malignant bone tumors also remodel the adjacent bone at an increased speed, which NaF is able to detect. The combined use of these biomarkers provides a multilayered view of the biological processes involved in tumor growth in bone. This study demonstrates that the addition of molecular imaging with combined radiopharmaceuticals to conventional CT improves the power of imaging for cancer diagnosis. The simultaneous administration of F-18 NaF and F-18 FDG imaging agents in a single PET/CT scan has the potential to improve diagnostic accuracy and patient convenience.

(SNM's Annual Meeting, Jun 2012)

Unicondylar Osteoallograft Prosthesis Composite in Tumor Limb Salvage Surgery

Researchers from The Fourth Military Medical University, China, have shown a unicondylar osteoallograft prosthesis composite reconstruction replacing only one side of the joint to reduce compartment degeneration and avoid contamination of the tibia. Twelve patients who underwent unicondylar osteoallograft prosthesis composite reconstructions after unicondylar resection for tumors were analyzed. One patient died from tumor-related causes without unicondylar osteoallograft prosthesis composite failure after 18 months. Survival rate of unicondylar osteoallograft prosthesis composite reconstruction and related complications were observed. The minimum followup was 8 months. At last followup, 10 of 12 unicondylar osteoallograft prosthesis composite reconstructions were still in place. Three reconstructions failed owing to two local recurrences and one infection. The average Musculoskeletal Tumor Society functional score at last followup was 27 points and the radiographic score 91%. Observations suggest unicondylar osteoallograft prosthesis composite reconstruction might be a reliable technique with relatively few major complications and short-term maintenance of the tibial cartilage.

(Clin Orthop Relat Res, July 3, 2012)

CLINICAL TRIALS

Chemotherapy-Induced Toxicity & Overall Survival

Researchers from University College, London investigated relationship between chemotherapy-induced toxicity and improved survival in patients with high grade localized extremity osteosarcoma. Lack of chemotherapy-induced toxicity may provide early evidence of reduced chemo-sensitivity, and predict poorer outcome. They analysed 533 patients treated within three consecutive randomised controlled trials of the European Osteosarcoma Intergroup. These patients were given six cycles of doxorubicin 75 mg/m² and cisplatin 100 mg/m² and toxicity data were collected and graded according to the World Health Organisation (WHO) criteria. Five- and 10-year overall survival was 57% and 53% respectively. Grades 3-4 oral mucositis, grades 1-2 nausea/vomiting, grades 1-2 thrombocytopenia and distal tumour site were associated with improved survival; only older age and chondroblastic tumor did not show good response. The overall results confirmed that chemotherapy-induced toxicity predicts survival in patients with localised extremity osteosarcoma.

(Eur J Cancer, Mar 2012)

Docetaxel and Gemcitabine for Bone Sarcoma

A prospective multicenter phase II study covering 30 patients previously treated with ifosfamide and anthracycline-based chemotherapies with advanced soft tissue and bone sarcoma, evaluated the efficacy and toxicity of weekly docetaxel and fixed dose rate gemcitabine. The patients were treated with docetaxel (35 mg/m² over 60 min) and gemcitabine (1,000 mg/m² over 100 min) on days 1 and 8 of every 3-week cycle. The patients received a total of 136 cycles of therapy (median 4 cycles per patient). Of these 30 patients, none achieved complete response, five patients achieved a partial response and 12 patients had stable disease. Median progression-free survival was 2.5 months (range 0.8-15.3 months), and median overall survival was 8.4 months (range 1.4-22.3 months). Febrile neutropenia or bleeding events were not present in any patient and all non-hematologic toxicities were manageable. They concluded that combination of weekly docetaxel and fixed dose rate gemcitabine may be an active regimen in patients with previously treated advanced sarcoma.

(Cancer Chemother Pharmacol, Mar 2012)

Intrasomatic Injection of Corticosteroid in Vertebral Bone Neoplasms

A prospective multicenter study assessed the effectiveness of corticosteroid and vertebroplasty in the analgesic treatment of single-level vertebral neoplasms or pathological fractures. Twenty consecutive patients (11 women, nine men; mean age 65.1 years) with single-level vertebral neoplasm or pathological fractures refractory to vertebroplasty were randomly divided into two groups. Group A patients (six male and six female) underwent intrasomatic injections of 4 mg/ml of dexamethasone phosphate followed by a cement injection; patients in group B (three male and five female) underwent standard vertebroplasty. Pre-intervention VAS (Visual Analogue Score) in group A and B was 8 points. VAS score was evaluated and compared between both groups of patients and it was found that patients in group A had a higher reduction in VAS compared to patients in group B, with a difference of 25.4% at 6 h post-intervention, 24.5% at 24 h, 25% at 48 h, 23% at 7 days, 16.4% at 30 days, 8.9% at 3 months. These results suggest that adding injection of intrasomatic corticosteroid to vertebroplasty is able to increase pain relief.

(Skeletal Radiol, Apr 2012)

Trabectedin for Ewing Sarcoma

Scientists from Toronto conducted phase II trial to evaluate the the toxicity, efficacy and pharmacokinetics of trabectedin given over 24h every 3 weeks to children with recurrent Ewing sarcoma and rhabdomyosarcoma. Fifty patients were enrolled in the study. Trabectedin was administered as a 24-h intravenous infusion every 21 days. Two dose levels were evaluated (1.3 and 1.5mg/m²) for safety; efficacy was then evaluated using a traditional 2-stage design (10+10) at the 1.5mg/m² dose level. Of the fifty patients, eight received the drug dose 1.3mg/m² and 42 received 1.5mg/m². Efficacy was evaluated in 42 patients enrolled at the 1.5mg/m² dose of whom 22% had reversible grade 3 or 4 toxicities that included thrombosis aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase elevation, myelosuppression and deep venous thrombosis. Partial response was seen in one patient of rhabdomyosarcoma and stable disease was seen in one patient each of Ewing sarcoma, rhabdomyosarcoma and spindle cell sarcoma. Results showed that trabectedin is not sufficient as single agent but it is safe if administered over 24h at 1.5mg/m².

(Eur J Cancer, March 2012)

GLOBE SCAN

Thallium-201 Scintigraphy

A study was conducted in order to confirm the prognostic value of (201)Tl scintigraphy in the midcourse of preoperative chemotherapy in patients with osteosarcoma. The 28 patients with biopsy-proven osteosarcoma were enrolled retrospectively in this study. Planar scintigraphy was performed 15 min after injection of 111 MBq (201)Tl before preoperative chemotherapy and after third course (midcourse) of chemotherapy in all patients. The (201)Tl uptake ratio was calculated by dividing the count density of the lesion by that of the contralateral normal area. Good histopathological response was observed in 16 patients. Mean follow-up period was 58.0 ± 41 months. There was a significant correlation between pre-chemotherapeutic effect evaluated with (201)Tl scintigraphy and overall and event-free survival rate in all patients ($P = 0.045$ and $P = 0.017$, respectively), and in patients without metastasis at initial diagnosis ($P = 0.043$ and $P = 0.031$, respectively). Thus (201)Tl scintigraphy performed in the middle of neoadjuvant chemotherapy can predict overall survival and event-free survival in patients with osteosarcoma.

(Japan: *Ann Nucl Med*, May 19, 2012)

Limb Salvage in Osteosarcoma

Tumor prostheses currently give the best short- and medium-term results for limb-salvage reconstruction procedures in the treatment of bone tumors. However, in developing countries, the cost of a tumor prosthesis is beyond the reach of much of the population. The use of autoclaved tumor-bearing bone in 10 patients, as an affordable alternative to the use of prostheses is reported. Bone union occurred in seven patients over mean duration of 12 months (range 8-17). Three patients had non-union. Two of these had associated implant failure, with one of them also developing chronic infection, and the third is still being followed up. Two other patients had local recurrence. Hence, the use of autoclaved tumor grafts provides an inexpensive limb-salvage option without sacrificing appropriate oncologic principles. A painless and stable limb is achievable, and the use of these technique can be further refined.

(Malaysia: *World J Surg Oncol*, June 8, 2012)

Clues to Aetiology

The aetiology of bone cancers is poorly understood. A study was done to examine geographical patterning in incidence of primary bone cancers diagnosed in 49-year olds in Great Britain during 1980-2005 to provide information on factors linked with disease development. The authors investigated putative associations with deprivation and population density. The study analyzed 2566 osteosarcoma and 1650 Ewing sarcoma cases. Higher incidence of osteosarcoma was observed for females in areas with lower deprivation levels indicating that increased risk is linked to some aspect of affluent living. Higher incidence of Ewing sarcoma occurred in areas of low population density and where more people owned cars, both characteristic of rural environments. The study adds substantially to evidence associating Ewing sarcoma risk with rural environmental exposures. Putative risk factors include agricultural exposures, such as pesticides and zoonotic agents.

(UK: *BMC Cancer*, Jun 27, 2012)

Building Bone from Cartilage

A person has a tumor removed from her femur. A child undergoes chemotherapy for osteosarcoma but part of the bone dies as a result. Every year, millions of Americans lose bone that isn't successfully grafted. But a study offers new hope for those who sustain these traumas. Orthopaedic researchers with the University of California, San Francisco (UCSF), have found a very promising, novel way to regenerate bone. Cartilage graft induces bone that actually integrates with the host bone and vascularizes it. Cartilage graft is very different from the current methods used for bone grafting—autograft bone (a person's own bone) or allograft materials (donor bone). For various reasons, these two grafting techniques can result in poor graft integration and osteonecrosis. The researchers concede their approach is less orthodox. The cartilage is naturally bioactive. It makes factors that help induce vascularization and bone formation. When people use a bone graft, it is often dead bone which requires something exogenous to be added to it or some property of the matrix in the graft. "Healing of the transplanted cartilage grafts supported the hypothesis by producing a well-vascularized bone that integrated well with the host. A cartilage graft could offer a promising alternative approach for stimulating bone regeneration". Future work will focus on developing a translatable technology suitable for repairing bone through a cartilage intermediate at a clinical level.

(USA: *Science Daily*, Feb 14, 2012)

CANCER CONTROL

Alizarin - Drug for the Treatment of Bone Tumors

In spite of clinical improvements, conventional therapies for bone cancer treatment remain limited by significant systemic toxicity and lack of specific targeting. A study was conducted at the Laboratory for Pathophysiology, Istituto Ortopedico Rizzoli, Italy on Alizarin, a natural hydroxyanthraquinone derived from madder root with high affinity to calcium and remarkable osteotropic features. It is being considered as a novel approach for bone cancer treatment. Having demonstrated antitumor properties in colon cancer cells, and its tropism to bone, Alizarin may be an ideal drug to reduce bone tumor growth. It has been shown that low dosages of Alizarin strongly inhibited the osteosarcoma [IC(50) for Saos-2, MG-63, and U-2 OS cells, 27.5, 29.0, and 69.9 $\mu\text{g/ml}$, respectively] and breast carcinoma [IC(50) for MDA-MB-231 cells, 62.1 $\mu\text{g/ml}$] cell proliferation in vitro. Importantly, Alizarin had a significantly lower inhibitory activity on normal cells [IC(50) for MSC, 828.6 $\mu\text{g/ml}$], thereby revealing a selective activity towards malignant cells. Furthermore, it was found that Alizarin acted through the inhibition of ERK phosphorylation and cell cycle arrest in the S-phase. Finally, Alizarin significantly and strongly impaired both osteosarcoma and breast cancer tumorigenesis. The results highlight a selective and effective inhibitory activity of Alizarin towards cancerous cells, laying the basis for further studies to investigate its application in bone cancer therapy.

(J Orthop Res, Mar 12, 2012)

New Target in Ewing's Sarcoma

Researchers at the University of Colorado Cancer Center, USA have identified that the existence of higher levels of protein EYA3 may help to give an accurate prognosis and guide the treatment of Ewing's sarcoma. EYA3 acts as DNA-repair molecule and has a similar role in Ewing's sarcoma. The elevated levels of EYA3 facilitate the tissue survival and recovery after treatment with chemotherapy. The mutation, known as EWS/FLI1 which leads to the development of Ewing's sarcoma also expresses the high levels of protein, EYA3. The mutation turns off the ability of a cell to make miR-708, a microRNA which helps to decide that which part of genome does and does not get read and translated into proteins. In healthy tissue, miR-708 stops the production of

EYA3. Conversely, in Ewing's sarcoma, the levels of miR-708 are low and that of EYA3 are high. It was observed that loss of EYA3 decreases survival of Ewing's sarcoma cells. Most importantly, knockdown of EYA3 in Ewing's sarcoma cells makes the cells sensitive to DNA-damaging chemotherapeutics and repairs the DNA damage less effectively. These studies find EYA3 as a novel mediator of chemoresistance in Ewing's sarcoma and identify the molecular mechanisms of both EYA3 overexpression and EYA3 - mediated chemoresistance. The investigators of the study hope that recognizing EYA3 levels, and intervening in the steps which lead to its over-production will help predict outcomes, make decisions about existing treatments, and finally lead to new treatments for Ewing's sarcoma.

(Mol Cancer Res, Jun 20, 2012)

QoL After Malignant Bone Tumor Surgery

A study was conducted at the Department of Physical Therapy, Leiden University Medical Center, The Netherlands, to assess the quality of life (QoL) and functioning of young patients undergoing surgical procedures for malignant bone tumors around the knee joint. The aim of study was to evaluate patients' quality of life, functional ability and physical activity during a 2-year post-operative period. It was a prospective study and included 44 patients who underwent surgery for a malignant bone tumor around the knee joint between 2004 and 2008. The assessments were done at 3, 6, 9, 12, 18, and 24 months after surgery. QoL was measured with the Adult's Quality of Life Questionnaires, the Short Form-36 (SF-36) and bone tumor-DUX; functional ability with the Toronto Extremity Salvage Scale, the 6-minute walk test and four functional performance tests; and physical activity with the Baecke questionnaire and the ActiLog® activity monitor. Statistical analysis included linear mixed model analysis. Twenty patients were lost during the 2 years follow-up as a consequence of oncological complications. Over the first year, survivors showed significant improvement of QoL, functional ability and physical activity, except for the mental dimension of the SF-36 and the activity monitor results. Over the second year, these improvements were less pronounced. It was concluded that in the first 2 years after bone tumor surgery, survivors improved significantly with respect to QoL, functional ability, and physical activity levels.

(Pediatr Blood Cancer, Jun 2012)

IN FOCUS

CHEMOTHERAPY IN OSTEOSARCOMA

The survival of patients with malignant bone sarcomas has improved dramatically over the past 30 years, largely as a result of the use of effective chemotherapy. Previously 80 to 90% of patients with bone sarcomas developed metastases despite achieving local tumor control, and died of their disease. It was surmised and subsequently demonstrated that subclinical metastatic disease was present at the time of diagnosis in the majority of patients and that chemotherapy can successfully eradicate these deposits if initiated at a time when disease burden is low. The benefits of chemotherapy are best illustrated by a systematic review of the literature, which shows that long-term survival after local tumor control without chemotherapy was only 16% (95% CI 9 to 23%). In contrast, the addition of systemic chemotherapy with three or more drugs provided a five-year overall survival rate of 70%.

Chemotherapy is now considered a standard component of osteosarcoma treatment, both in children and in adults. The choice of regimen and optimal timing (ie, pre-operative versus post-operative) are controversial; however, many centers preferentially utilize pre-operative chemotherapy, particularly if a limb-sparing procedure is being contemplated for an extremity osteosarcoma.

Adjuvant Chemotherapy

More than 80% of patients with osteosarcoma treated with surgery alone develop metastatic disease, despite achieving local control. It is presumed that subclinical metastases are present at diagnosis in the majority of patients. Chemotherapy can eradicate these deposits if initiated at a time when disease burden is low.

Initially, post-operative chemotherapy was used, and five-year survival rates rose from less than 20% to between 40 and 60% in the 1970s. Two subsequent randomized studies conducted in the 1980s demonstrated a significant relapse-free and overall survival benefit for adjuvant chemotherapy, although the trials were limited in size and the survival benefits modest. The chemotherapy regimens used in these studies included high-dose methotrexate (HDMTX), doxorubicin, bleomycin, cyclophosphamide and dactinomycin.

Neoadjuvant Chemotherapy

The concept of induction of neoadjuvant

chemotherapy arose in concert with the evolving use of limb-sparing surgery. Because of the time needed for fabrication of custom metallic endoprostheses, chemotherapy was often given while awaiting definitive surgery.

Neoadjuvant versus Adjuvant Chemotherapy

To resolve the issue of adjuvant or neoadjuvant chemotherapy, Pediatric Oncology Group (POG trial 8651) compared immediate surgery and post-operative chemotherapy with 10 weeks of the same chemotherapy regimen followed by surgery in 100 patients under the age of 30 with nonmetastatic high-grade osteosarcoma. The five-year relapse-free survival rates were similar between the two groups (65 versus 61% for adjuvant and neoadjuvant therapy, respectively) as was the limb salvage rate (55 and 50% for immediate and delayed surgery, respectively). This trial established that survival was similarly improved by either presurgical or postsurgical chemotherapy and established a benchmark outcome for future studies (five-year event-free survival 65%). The study was criticized for the relatively low rate of limb-sparing surgery in both groups (by modern standards) and the inclusion of BCD as a component of the regimen. The contribution of BCD to the therapeutic efficacy of this regimen is unclear, while it can clearly contribute to long-term bleomycin-related pulmonary toxicity.

While it is clear that the number of patients with osteosarcoma who are deemed suitable candidates for limb-sparing surgery, has increased in parallel with the increasing use of presurgical chemotherapy, this finding may reflect improvements in reconstructive techniques and the increased experience and confidence of tumor surgeons rather than a benefit attributable to the use of induction chemotherapy. A major concern in this regard is the possibility that inexperienced surgeons may expand selection criteria to accommodate inappropriate candidates who might be better served by amputation. Neoadjuvant chemotherapy is never a substitute for sound surgical principles.

Histology and Response to Chemotherapy

Response to neoadjuvant chemotherapy is histology dependent. In the larger series, in which 1058 patients received presurgical chemotherapy for osteosarcoma over a 20-year period, the likelihood of a "good" response (>90% necrosis) was significantly higher for fibroblastic and telangiectatic osteosarcomas (83 and 80%, respectively) compared to chondroblastic (43%) or osteoblastic osteosarcomas (58%). Five-year survival rates were in tune with the quality of the response to induction chemotherapy (83, 75, 62, and

60% for fibroblastic, telangiectatic, osteoblastic, and chondroblastic osteosarcomas, respectively).

Tailored Post-operative Chemotherapy Based upon Initial Response

One of the most compelling rationales for neoadjuvant chemotherapy is its ability to function as an in vivo drug trial to determine the drug sensitivity of an individual tumor and to customize post-operative therapy. A grading system for assessing the effect of pre-operative chemotherapy on the tumor was developed at Memorial Sloan Kettering and is in widespread use.

Responsiveness of an osteosarcoma to neoadjuvant chemotherapy is a major determinant of clinical outcome. Five-year survival rates for patients with an extremity sarcoma and a “good” response to chemotherapy (as defined by 90% or more necrosis in the surgical specimen) are significantly higher than for those with a lesser response (71 to 80 versus 45 to 60%, respectively).

Patients with a near-complete absence of viable tumor cells in the resection specimen after neoadjuvant therapy tend to do well when the same therapy is continued after surgery. However, when the tumor contains 10% or more residual viable cells after neoadjuvant chemotherapy, a change in the chemotherapeutic regimen might be beneficial. This strategy of altering the post-operative chemotherapy regimen based upon the response to the neoadjuvant regimen was pioneered in the T10 protocol at the Memorial Sloan-Kettering Cancer Center (MSKCC) and confirmed by at least one other group.

However, this strategy came under scrutiny for the following reasons:

- With more mature follow-up, the initial beneficial results from the T10 protocol have not been sustained at MSKCC.
- Major cooperative groups (eg, Children’s Cancer Group, German Society for Pediatric Oncology, Scandinavian Sarcoma Group) have been unable to confirm that altering the post-operative chemotherapy regimen in patients with a less than complete response to presurgical chemotherapy improves their overall outcome.
- An international multigroup trial (COG AOST 0331) has been designed to test prospectively the benefit of altering post-operative chemotherapy based upon the response to initial chemotherapy; this study has completed accruing patients with resectable osteosarcoma, but results are not yet available. Unless the results of this trial are available, change of chemotherapy after surgery in patients who have poor histological response is not warranted.

Choice of Chemotherapy

There is no worldwide consensus on a standard chemotherapy approach for osteosarcoma. The development of adjuvant chemotherapy has been largely empiric, with the majority of regimens incorporating doxorubicin and cisplatin, with or without high-dose methotrexate (HDMTX, 6 to 12 g/m² withleucovorin rescue). In children, usually HDMtx is preferred whereas in adults usually a combination of doxorubicin and cisplatin is preferred.

Treatment of Patients with Metastatic Disease at Diagnosis

Patients who present with overtly metastatic osteosarcoma have a poor prognosis; long-term survival rates with standard chemotherapy and surgery range from 10 to 50%. This is in contrast to patients with apparently localized disease at presentation, two-thirds of whom will achieve long-term survival with appropriate therapy.

Analogous to the situation with primary osteosarcomas, the ability to control all foci of macroscopic disease is an essential element for successful treatment. The minority of patients with overt metastatic disease who achieve long-term survival and are presumably cured, have usually been treated with a combination of surgery, chemotherapy, and sometimes RT.

The location of the metastases is of prognostic importance. Patients with only pulmonary disease appear to have a chance of long-term event-free survival of the order of 20 to 30%. In contrast, most series report a dismal prognosis for patients with bone metastases.

Summary

Surgery and systemic chemotherapy are the mainstays of treatment for patients with nonmetastatic osteosarcomas. Pre-operative as compared to post-operative administration may permit a greater number of patients with extremity tumors to undergo limb-sparing procedures. However, chemotherapy is not a substitute for sound surgical judgment when assessing the need for amputation. It is reasonable to proceed to immediate surgery followed by adjuvant chemotherapy if the nature of the resection would not necessarily be influenced by a good response to chemotherapy.

Response to neoadjuvant chemotherapy is a major prognostic factor. It is unclear whether outcomes can be improved in poor responders by changes in the post-operative chemotherapy regimen.

(Dr Ullas Batra, Consultant, Department of Medical Oncology)

EXPERTS CONVERGE

World Cancer Congress

Date: 27-30 August 2012
 Venue: Palais des Congrès Montréal Canada
 Host: Organised by UICC and hosted by
 Fondation Québécoise du Cancer, McGill
 University and Université de Montréal
 Email: congress@uicc.org
<http://www.worldcancercongress.org>

The 2nd World Congress on Controversies in Hematology (COHEM)

Date: 06-08 September 2012
 Venue: Barcelona, Spain
 Host: Prof Eliezer Rachmilewitz
 Contact name: Julia Klein
 E-mail: juliak@comtecmed.com
<http://www.comtecmed.com/cohem/2012/Default.aspx>

Reconstruction and Rehabilitation in Head and Neck Cancer

Date: 08-09 September 2012
 Venue: Pune, India
 Host: Smile-Inn Dental Clinic
 E-mail: docsrinivasan@gmail.com
smileinn@gmail.com

37th ESMO Congress

Date: 28 Septemer -02 October 2012
 Venue: Viganello-Lugano, Switzerland
 Host: ACV - Austria Center Vienna
 E-mail: congress@esmo.org
<http://www.esmo.org>

The Global Summit on International Breast Health: Guidelines for International Breast Health and Cancer Control-Supportive Care and Quality of Life

Date: 03-05 October 2012
 Venue: Vienna, Austria
 Host: Breast Health Global Initiative (BHGI),
 in co-operation with the International Atomic
 Energy Agency (IAEA) Programme of
 Action for Cancer Therapy (PACT)
 E-mail: jchase@fhcrc.org
<http://portal.bhgi.org/Pages/Default.aspx>

Ethics and Compliance in Oncology Research

Date: 06-08 October 2012
 Venue: Houston, United States

Host: University of Texas MD Anderson
 Cancer Center
 Email: lmgriffin@mdanderson.org
ECOR@mdanderson.org

19th International Congress on Palliative Care

Date: 09-12 October 2012
 Venue: Montreal, Canada
 Host: Palliative Care McGill
 Email: april@odon.ca
frank@odon.ca
<http://www.palliativecare.ca>

17th World Congress on Advances in Oncology and 15th International Symposium on Molecular Medicine

Date: 11-13 October 2012
 Venue: Hersonissos, Crete, Greece
 Host: Hotel Creta Maris Resort
 Email: conference@spandidos-publications.com

Innovations in Oncological Treatments and Tumor Markers

Date: 13-18 October 2012
 Venue: Jerusalem, Israel
 Host: ISOBM
 Email: Info@isobm-congress.org
www.isobm-congress.org

The AICR Annual Research Conference 2012 on Food, Nutrition, Physical Activity & Cancer

Date: 01-02 November 2012
 Venue: Washington, USA
 Host: American Institute for Cancer Research
 Email: research@aicr.org
library@aicr.org
<http://www.aicr.org/conference>

4th ESO-SIOP Europe Masterclass in Paediatric Oncology

Date: 24-30 November 2012
 Venue: Bellinzona - Switzerland
 Host: European School of Oncology (ESO)
 International Society of Paediatric Oncology
 (SIOP)
 Email: dknupfer@eso.net
<http://www.eso.net/events-2.html>

35th Annual San Antoni Breast Cancer Symposium

Date: 04-08 December 2012
 Venue: San Antonio, United States
 Host: Cancer Therapy
 Email: rmarkow@ctrc.net
<http://www.uicc.org/events/upcoming>



Rajiv Gandhi Cancer Institute and Research Centre

A Unit of Indraprastha Cancer Society
Registered under "Societies Registration Act 1860"

RAJIV GANDHI CANCER INSTITUTE & RESEARCH CENTRE



Gastrocon 2012

Hepatobiliary & Pancreatic Malignancies

(CME & Live Endoscopy Workshop)

Schedule:

25th & 26th August 2012

Venue:

Hotel Crowne Plaza (Crystal Ballroom), Rohini, Delhi-85 (INDIA)

Hosted by:

**Department of Gastroenterology & GI Oncosurgery
Rajiv Gandhi Cancer Institute & Research Centre**

