

Surgical management of primary bone sarcomas

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Abstract

This article aims to address the principles of surgical treatment of primary bone sarcomas including chondrosarcoma, osteosarcoma and Ewing's sarcoma of bone. This piece is aimed at serving as a guide to experienced orthopaedic surgeons who have limited knowledge of dealing with musculoskeletal tumours especially primary bone sarcomas. Important principles surrounding surgery involving bone sarcomas, principles of biopsy of such lesions and reconstruction techniques have been discussed. Limb salvage is the way forward in today's era and though endoprosthesis replacement is an important tool in a surgeon's armoury, biological methods of reconstruction have also shown to be effective in many settings. Chemotherapy and radiotherapy are vital adjuvant therapies associated with these sarcomas, and they have been discussed in this article.

Keywords bone sarcoma; chondrosarcoma; endoprosthesis; Ewing's sarcoma; osteosarcoma

Introduction

Musculoskeletal tumours especially primary bone sarcomas are uncommon. They account for less than 1% of all diagnosed cancers and in 2010, there were 531 new cases of bone sarcoma in the UK, in contrast to nearly 55,000 new cases of carcinoma of breast reported annually. Surgical treatment of bone sarcomas has changed drastically over the last three decades with increased emphasis on limb salvage. Modern chemotherapy regimens coupled with refined surgical techniques and improved implant designs have drastically changed the way we deal with these sarcomas and today we are in an era of 'functional limb salvage' aiming at better quality of life after surgery.

Surgery remains the key to management of bone sarcoma and following proper principles is essential. Numbers of reconstruction options are available after surgery including custom-made and modular endoprosthesis, allograft, vascularized bone graft,

biological methods including cryotherapy and also extra-corporeal radiation and re-implantation of resected bones. Discussion and planning of treatment in a multidisciplinary tumour (MDT) board is essential and has benefits of 'collective wisdom' involving specialists and aims at providing early and most appropriate care to patients.

Adjuvant therapies (chemotherapy and radiotherapy) are essential in osteosarcoma and Ewing's sarcoma but not in chondrosarcoma, where surgery is the mainstay. Timing of surgery is also of utmost importance. In this article we shall discuss the management principles of these malignant bone sarcomas in detail.

Biopsy

'When tumour is the rumour, tissue is the issue.'

Biopsy of any suspected lesion is important and following principles is essential as it determines the extent of limb salvage. Biopsy determines the tumour type and grade. Wherever possible, a biopsy is undertaken under radiological control as exact desired samples are taken for histology analysis. Percutaneous image-guided biopsies ensure that there is no delay in starting any neoadjuvant treatment (which may be delayed with open biopsies as wounds need to heal). Open biopsy is indicated when percutaneous biopsy is inconclusive. It would be prudent to get frozen section sample analysis by pathologists when an open biopsy is done to check adequacy of samples available for pathologists to make a diagnosis.¹

The orientation and location of the biopsy tract are extremely critical, especially as any improper biopsy can hamper limb salvage. Reviewing imaging prior to biopsy is essential and, whenever possible, this should be done by experienced surgeons/radiologists. As with percutaneous biopsy, one should attempt to factor in the future skin incisions needed for surgery. If drains are used, they should exit either from the corner of the wound or close in line with skin incision that will make resection simpler to include in future approaches. Transverse incisions must be avoided.^{2-4,5}

Careful attention to haemostasis to prevent haematoma formation must be adhered to. Biopsy incisions should preferably be made through muscle compartments and neurovascular structures are always avoided (Table 1).

'Biopsy what you culture; culture what you biopsy'

Infection is one of the important mimics of tumour. All biopsy samples should be sent for microbiological culture and sensitivity in addition to histology analysis. Antibiotics should not be delivered until the cultures are obtained.

General treatment principles

The primary goal of the treatment of a malignant bone tumour is to remove the lesion with a clear margin to minimize the chances of local recurrence.²

Whenever and wherever possible, limb salvage is aimed at. This is only possible when the two essential criteria below are met:

- local control of the tumour must be at least equal to that of amputation
- the limb must be functional after salvage.

Surgical margins are graded according to the system of the Musculoskeletal Tumour Society.

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Principles of biopsy in musculoskeletal tumours

Principle	Rationale
Longitudinal incision in line with future resection and biopsy through a single compartment	Longitudinal incision is extensile Biopsy tract can be excised with final resection remaining extensile
Avoid critical structures, i.e. neurovascular bundles	Contamination of critical structures precludes limb salvage
Biopsy the soft tissue component when present	Bone is weakened when its cortex is disrupted Bone requires decalcification for evaluation and this process may affect pathology
Maintain strict haemostasis Use a drain in line with the incision when needed Advisable to be performed by the surgeon/in the centre where the definitive surgery is planned to be done	Avoid increased contamination outside of the biopsy tract by iatrogenic tumour spread Helps in planning for definitive limb salvage surgery
Always culture the biopsy samples	Infection is a common tumour-mimic

Table 1

- **Intralesional margin:** The plane of dissection is directly through the tumour. When the surgery involves malignant bone tumours, an intralesional margin results in 100% local recurrence. Intralesional surgeries are performed only in benign tumours, giant cell tumours (GCT) and low-grade cartilage tumours.
- **Marginal margin:** A marginal line of resection goes through the reactive zone of the tumour; the reactive zone of any tumour contains inflammatory cells, fibrous tissue, and sparse areas of tumour cells. When malignant tumours are resected through the reactive zone, there is an increased chance of local recurrence (25–50%). A marginal margin may be safe and effective if the response to neoadjuvant chemotherapy has been excellent (95–100% tumour necrosis).
- **Wide margin:** This is the preferred margin of resection in primary bone sarcomas. A wide line of surgical resection is accomplished when the entire tumour is removed with a cuff of normal tissue. The local recurrence rate is around 10% when such a surgical margin is achieved. A 2-cm normal margin of tissue is aimed at while planning for resections.^{2,6–8}
- **Radical margin:** A radical margin is achieved when the entire tumour and the compartment it involves (surrounding muscles, ligaments, and connective tissues) are removed.

Staging of bone sarcomas is essential prior to surgery and the American Joint Committee on Cancer (AJCC) staging system⁹ is followed routinely (Table 2). Positron emission tomography (PET) scans are used to identify any distant disease but if not

routinely available, other modalities of imaging are employed. Current evidence-based staging investigations include:

- Osteosarcoma – CT chest, bone scan
- Ewing's sarcoma – PET-CT scan
- Chondrosarcoma – CT chest and isotope bone scan if possible.

Osteosarcoma

- Spindle cell neoplasms that produce osteoid cells are arbitrarily termed as osteosarcoma.
- The most common sub-types are 'classic' osteosarcoma, periosteal osteosarcoma, parosteal osteosarcoma, telangiectatic osteosarcoma, osteosarcoma occurring with Paget's disease, and radiation-induced osteosarcoma (Table 3).
- Historically, osteosarcoma was treated by amputation; long-term studies showed a survival rate of less than 15% with metastatic lung disease being the common cause of death.
- With the advent of multi-agent modern chemotherapy regimens, there has been a dramatic improvement in long-term survival and enhanced potential for limb salvage. The standard regime is:
 - doxorubicin (common side effect: cardiac toxicity)
 - cisplatin (common side effect: neuro toxicity)
 - methotrexate.
- The aim of giving chemotherapy is to kill the micro-metastases that are present in nearly 75% of patients at time of diagnosis and presentation. It also effectively sterilizes the inflammatory reactive zone around the tumour.
- Osteosarcoma metastasizes most commonly to the lung.
- With current treatment regimens the 5-year survival rate is approximately 60–70%.
- The prognostic factors that adversely affect survival include:
 - expression of P-glycoprotein, high serum alkaline phosphatase (ALP), high lactic dehydrogenase level (LDH), vascular invasion, and no alteration of DNA ploidy after chemotherapy

American Joint Committee on Cancer staging system for primary malignant tumours of bone for those tumours diagnosed on or after 1 January 2010

Stage	Tumour grade	Tumour size
IA	Low	<8 cm
IB	Low	>8 cm
IIA	High	<8 cm
IIB	High	>8 cm
III	Any tumour grade, skip metastasis ^a	
IV	Any tumour grade, any tumour size, distant metastasis	

^a Skip metastasis: discontinuous tumours in the primary bone site.

Adapted from reference 9.

Table 2

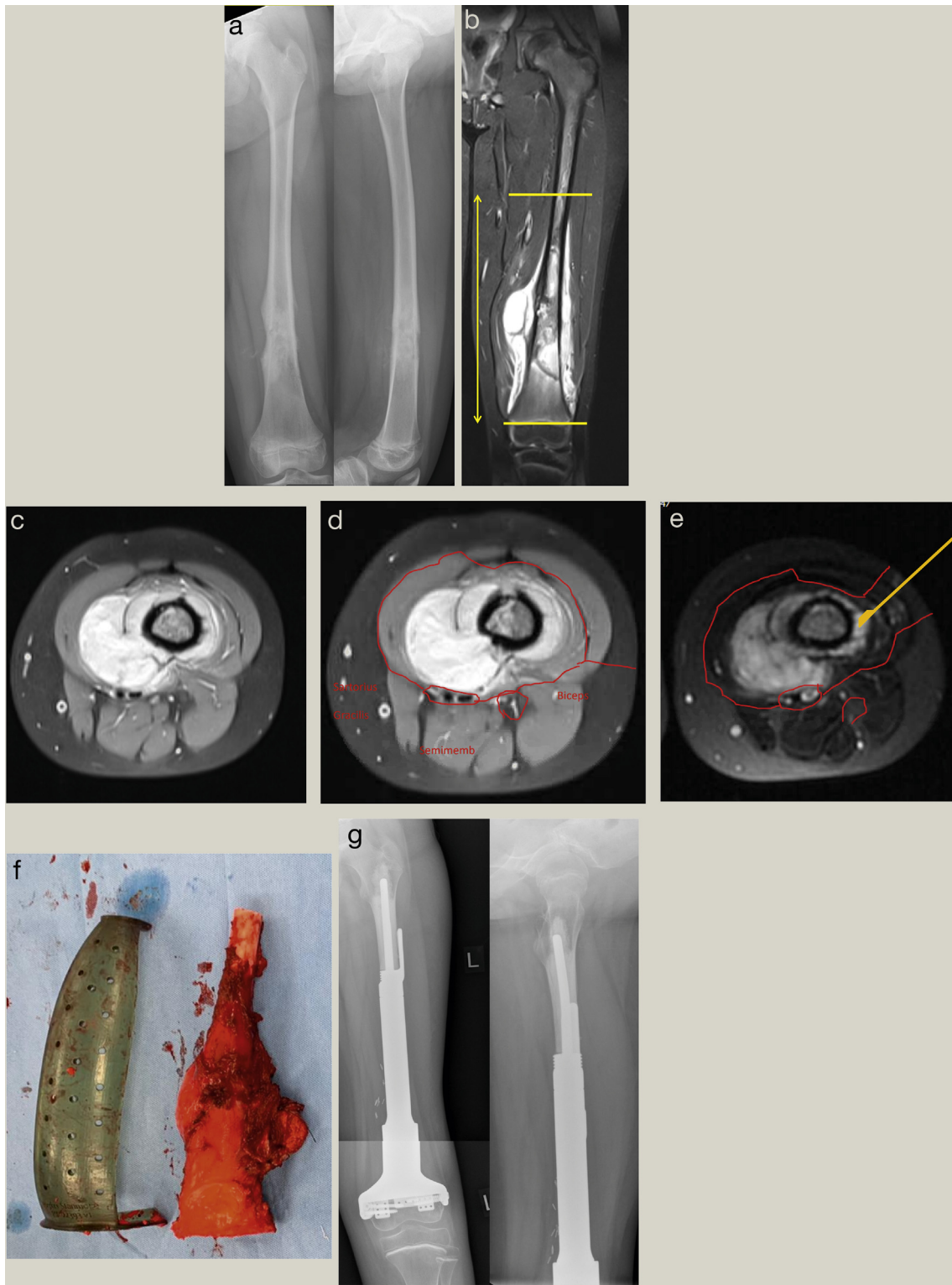


Figure 1 Radiographs of a 12-year-old girl who was referred by the GP to a tertiary sarcoma centre following symptoms of pain and swelling around the thigh. Radiographs show a poorly differentiated bone-forming lesion involving the intramedullary aspect of femur with a Codman's triangle periosteal reaction (a, b) suggestive of an aggressive bone sarcoma. MRI scans (c–e) showing the soft tissue extent of the tumour and the extent of reactive oedema. Biopsy was planned through a lateral approach under fluoroscopic guidance (e). Histology was consistent with a high-grade osteosarcoma. Following chemotherapy, preoperative planning is always done based on the imaging prior to treatment. Pre-surgical planning involves resection of tumour with margins of normal muscle around it (d) and the yellow marking (b) shows the extent of planned resection which involves 2 cm of normal bone and also complete excision of the biopsy tract. As the patient was a growing child and had significant years of growth left, a custom-made expandable prosthesis was planned using patient-specific jigs. Following wide-excision (f) using jigs, the custom-made expandable prosthesis (g) was implanted to reconstruct the defect. The excised specimen was sent for histological analysis to see for the extent of resection and assess the tumour response to neoadjuvant chemotherapy.

- Absence of anti-shock protein-90 antibodies after chemotherapy
- Poor response to neoadjuvant chemotherapy as seen on histologic tumour necrosis (<90%)
- Metastasis at the time of presentation is associated with poor prognosis.
- Osteosarcoma is associated with an abnormality in the tumour suppressor genes – p53 (Li–Fraumeni syndrome) and Rb (retinoblastoma).

We shall discuss the various sub-types of osteosarcoma below:

High-grade intramedullary osteosarcoma

- Also known as ‘classic’ osteosarcoma, this neoplasm is the most common type. The most frequent site affected is around the distal femur followed by the proximal tibia. It is

most common in children and teenage and young adults (TYA), but it does have a second peak in late adulthood.

- Other common sites include proximal femur, proximal humerus and pelvis.
- Patients present primarily with non-mechanical pain and swelling.
- More than 90% of intramedullary osteosarcomas are high-grade and penetrate the cortex early to form a soft tissue mass (stage IIB).
- Nearly 20% of affected patients have pulmonary metastases at time of diagnosis.
- Radiographs demonstrate a lesion in which there is bone destruction and bone formation with the typical Codman’s triangle type of periosteal reaction seen on radiographs. MRI defines the anatomy of the lesion with regards to the neurovascular bundle.

Comparison of sub-types of osteosarcoma

	Classic (intramedullary)	Periosteal	Parosteal
Age (years)	<30 and >60	<30	<45
Presentation	Pain and swelling	Pain and swelling	Painless swelling
Histology	Poorly arranged osseous trabeculae with malignant osteoblasts Atypical spindle cells	Osseous trabeculae and chondroblastic elements	Regularly arranged osseous trabeculae, minimally atypical spindle cells
Five-year survival	65%	80%	95%
Management	Chemotherapy and limb salvage surgery	Chemotherapy and limb salvage surgery	Limb salvage surgery

Table 3

Comparison of cartilage tumours

	Enchondroma	Osteochondroma	Chondrosarcoma
Age (years)	Any age	Any age	>50
Presentation	Incidental	Mechanical	Pain
Histology	Bland cartilage with minimal cellular elements	Mature bone stalk with a benign, well mature cartilage cap	Various degrees of cellular atypia and high rate of mitotic activity
Management	Observation (Presence of endosteal scalloping may indicate aggressiveness)	Observation unless mechanical symptoms	Wide surgical excision
Caveats	Nuclear scans can show aggressiveness of tumour High degree of cellularity can be confused with chondrosarcoma	Cartilage cap >2 cm needs observation	Chemotherapy is indicated in de-differentiated and mesenchymal chondrosarcoma
Associated syndromes	Ollier’s disease Maffucci syndrome	Multiple hereditary exostoses (MHE)	Ollier’s disease MHE Maffucci syndrome

Table 4

- Diagnosis depends on two main histologic criteria:¹⁰ the tumour cells producing osteoid and¹¹ the stromal cells that are frankly malignant.
- Treatment: neoadjuvant chemotherapy (prior to surgery), followed by wide-margin surgical resection (a 2 cm normal tissue) followed adjuvant chemotherapy (after surgery).⁶
- It is important to plan surgical resection margins using the MRI taken prior to neoadjuvant chemotherapy.¹²
- **Surgical reconstruction** usually involves endoprosthesis replacement to reconstruct the bone after resection although in a younger patient, biological reconstruction using autografts and allografts are employed (Figure 1).
- **Expandable prostheses** can be employed in growing children where the prosthesis will elongate as the individual grows with age. Historically this required multiple visits to theatre but with modern devices using external electromagnets and internal servo-motors, lengthening can now be achieved in outpatient settings. The rate of elongation is carefully monitored and a rate of 5 mm every 4 weeks is aimed at with careful monitoring of neurological function at the same time. The cost and time involved in manufacturing this prosthesis are also important factors that need to be taken into consideration while planning treatment (Figure 1).
- **Rotationplasty** (commonly known as Van Nes rotationplasty) involves attaching the distal tibia and foot to the distal femur after resection of tumour and is rotated through 180°, such that the foot points backwards. In doing so, the ankle functions as the 'new-knee' with an otherwise above knee amputation converted into a below knee amputation. Patient with rotationplasties have better outcome scores than patients with amputations and is a commonly practised surgery in countries where endoprosthesis replacements are a constraint.
- **Pedicle cryotherapy** – initiated in Japan – involving clearing the tumour in resected bone and dipping in liquid nitrogen to effectively kill all tumour cells is also being followed in recent times.⁶
- **Extracorporeal irradiation which involves** en-bloc removal of the tumour-bearing bone segment, complete macroscopic removal of the tumour from the involved bone, irradiation (usually 50 Gy/single fraction), and re-implantation back is a technically feasible procedure which is associated with good local control of disease.
- **Amputation** is sometimes recommended in order to try to achieve a radical resection in cases of advanced disease. If chosen well, patients with amputation have good outcomes with relation to function. A residual limb with good soft tissue cover and appropriate length may be fitted with a prosthetic leg.

Periosteal osteosarcoma (intermediate-grade surface tumour)

This is a rare surface form of osteosarcoma which occurs most often in the diaphysis of long bones (typically the tibia and femur). The prognosis for periosteal osteosarcoma is intermediate between those of low-grade parosteal osteosarcoma and high-grade osteosarcoma. Preoperative chemotherapy, resection, and

maintenance chemotherapy constitute the preferred mode of treatment. The risk of pulmonary metastasis is around 15%.

Parosteal osteosarcoma (low-grade surface tumour)

This is typically a low-grade osteosarcoma that occurs on the surface of the metaphysis of long bones and the most commonly affected sites are the posterior aspect of the distal femur, proximal tibia, and proximal humerus. The delay to diagnosis is frequently even longer in these cases compared to conventional osteosarcoma. Resection with a wide margin is usually the preferred mode of treatment and, as this is a low-grade lesion, chemotherapy is not recommended.

High-grade surface osteosarcoma

This extremely rare form of surface osteosarcoma has the same treatment as a conventional osteosarcoma and similar prognosis to it too.

Telangiectatic osteosarcoma

This form of osteosarcoma presents as a destructive, lytic and expansile lesion. Radiographically this should not be confused with a simple aneurysmal bone cyst as it mimics the same in location and presentation. Initially, associated with poor prognosis, the advent of neoadjuvant chemotherapy and resection is associated with better outcomes in this type of osteosarcoma.

Chondrosarcoma

- Intramedullary chondrosarcoma:
 - Malignant neoplasm of cartilage occurring in older adults
 - The most commonly affected sites are the shoulder and pelvic girdles, knee and spine
 - Differentiating malignant cartilage may be extremely difficult on the basis of histologic features alone and biopsy is frequently relatively unhelpful (Table 4)
 - Nuclear medicine scans (quantitative single photon emission computed tomography (SPECT)/CT) are often employed to assess the aggressiveness of these chondroid tumours
 - Histologically these lesions contain abundant cells with plump nuclei, more than an occasional cell with multiple nuclei, especially large cartilage cells with large single or multiple nuclei containing clumps of chromatin and infiltration of trabeculae
 - Presence of endosteal scalloping (erosion of inner cortex) indicates aggressiveness of disease and may require surgical treatment involving disease clearance (extended curettage) and stabilization if necessary
 - Grade I chondrosarcomas are managed effectively by extended intralesional curettage followed by cementing.
 - Surgical treatment must be meticulous to ensure clearance of disease to prevent recurrence and usually involves several steps:
 - Mechanical macroscopic clearance of tumour tissue by surgical excision and macroscopic curettage
 - Coating the cavity in methylene blue followed by use of a high-speed burr to clear the cavity. Only when all the blue has been

- cleared can the surgeon be assured the cavity has been sufficiently curetted
- Phenol can be used as an adjuvant to chemically lyse tumour cells
- Hydrogen peroxide wash (with due care to nearby neuro-vascular structures) to lyse tumour cells
- Bone cement can be inserted into the cavity to provide structural support and to therapeutically kill the remaining tumour cells.

Grade II and grade III chondrosarcomas are managed with wide surgical resection and disease clearance. Chemotherapy has not been shown to offer an advantage in survival in chondrosarcoma.

Dedifferentiated chondrosarcoma

This is the most malignant cartilaginous tumour and has characteristic bimorphic histologic and radiographic appearances. The prognosis is very poor with less than 10% long term survival. Wide-margin resection and multi-agent chemotherapy is followed as treatment modality.

Ewing's sarcoma of bone

- Distinctive small, round cell sarcoma that occurs most often in children and young adults.
- It should also be remembered that when a small blue cell tumour is found in a child younger than 5 years, metastatic neuroblastoma and leukaemia are the main differential diagnoses. In patients older than 30 years, metastatic carcinoma should be considered.
- Affected patients may demonstrate a raised erythrocyte sedimentation rate, leucocytosis, anaemia, and an elevated white blood cell count and hence it should be differentiated from infection. Immunohistochemistry studies demonstrate CD99 positivity; the classic 11:22 chromosomal translocation produces the EWS/FLI1 fusion gene.
- Radiation therapy has a role in Ewing's sarcoma unlike osteosarcoma. Standard treatment includes high-dose neo-adjuvant chemotherapy.
- Local tumour control may be achieved by irradiation or surgery.
- Major benefits of wide-margin surgical resection are a decrease in the risk of local recurrence and the avoidance of the potential for post-irradiation sarcoma. Wide margin of excision is always preferred. Unlike Ewing's tumour is somewhat radiosensitive and radiotherapy may be used primarily in diseases in region which are difficult to surgically access like spine and pelvis or as an adjunct to surgery to maintain good function while sparing critical structures.
- Multimodal treatment (multi-agent chemotherapy/radiotherapy) has improved long-term survival up to 60–70% at 5 years.
- Poor prognostic factors include:
 - Spine and pelvic tumours

- Tumours larger than 100 cm³ in volume
- Poor response to chemotherapy (<90% tumour necrosis)
- Elevated lactate dehydrogenase levels
- p53 mutation and gene fusion products other than EWS-FLI-1.

Adamantinoma

- Adamantinoma is a rare low-grade, malignant tumour of long bones that contains epithelium-like islands of cells and the tibia is by far the most commonly affected site.
- Histologically the cells are arranged in a palisading or glandular pattern; the epithelial cells occur in fibrous stroma.
- Treatment is usually via wide-margin surgical resection and reconstruction. Reconstruction may be challenging because of the frequent diaphyseal location of the tumour and therefore intercalary implants and biological methods of reconstruction can be used. Bone transport has been employed in few centres if possible. ◆

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