Osteosarcoma

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Primary bone tumors account for 10% of all malignancies of adolescents. In the Third National Cancer Survey, the incidence of bone tumors, primarily osteosarcoma and Ewing's sarcoma, for blacks and whites under 20 years old was 4.8 and 5.6 per million, respectively. Although bone tumors are seen in all age groups, they are most common in those 15 to 19 years of age. The death rate from bone tumors among adolescents is about four times greater than in children, being 11 cases per million population. This peak rate of death from bone tumors parallels the timing of the adolescent growth spurt.

Incidence and Etiology

Osteosarcoma is one of the most common malignancies of adolescence, exceeded only by leukemia, brain tumors, and lymphomas. By definition, this tumor is a malignant sarcoma of bone that originates from osteon. The tumor is more common in males, with a male to female ratio of 1.75:1. Prior to the adolescent years, the frequencies in boys and girls are equal, whereas among teenagers and adults the incidence in males increases. The most common sites of osteosarcoma in order of frequency are femur, tibia, humerus, fibula, scapula, ilium, radius, rib, mandible, and clavicle.Extraskeletal osteosarcomas are rarely seen in children.

Although bone tumors are seen in all age groups, they are most common in those 15 to 19 years of age.

The etiology of osteosarcoma is not clear. Several possible etiologic factors have been suggested, but remain largely unproven. These include accelerated rate of growth, presence of congenital malformations and genetic conditions, trauma, and preexisting diseases, as well as environmental factors such as carcinogens, viral agents, exposure to radiation and radioactive agents. In one study, children with cancer who were treated with radiation had a 2.7-fold higher incidence of these tumors than those who had not been irradiated. A dose-response correlation was identified with patients who received over 6000 cGy to the bones having a 40-fold higher risk of osteosarcoma.

The incidence of osteosarcomas peaks during the adolescent growth spurt. Also, these tumors occur in bones undergoing an earlier growth spurt, such as the humerus, at an earlier age than the later-maturing tibia and femur. This time relationship suggests an etiological correlation between rapid growth and tumor formation. The reported greater mean height for patients with osteosarcoma, as compared with the mean height of patients with nonosseous malignancies, is further circumstantial evidence for such a relationship. However, measurements of levels of growth hormone in osteosarcoma are inconsistent.
Growth hormone was found to be elevated by some, but not by others. Abnormal glucose tolerance tests are common. Further evidence for the role of growth rate in etiology of this tumor is the finding of a much higher incidence of bone tumors among larger breeds of dogs.

Various congenital and genetic conditions are associated with osteosarcoma. Osteosarcomas occur in association with Paget's disease, bilateral retinoblastoma, polyostotic fibrous dysplasia, osteogenesis imperfecta, Waardenburg-like syndrome, Ollier's syndrome, multiple hereditary exostosis, solitary enchondroma, myositis ossificans, and osteopetrosis. Among these conditions, the association of osteosarcoma and retinoblastoma is best known. The occurrence of osteosarcoma in patients with a history of retinoblastoma is probably not solely due to radiation therapy given to the original tumor. In one report, 40% of patients with retinoblastoma treated with bilateral enucleation subsequently developed osteosarcoma. There is also an increased incidence of osteosarcomas in cases of unilateral retinoblastoma. Patients with retinoblastoma treated with radiation therapy are at risk for developing orbital osteosarcoma; this risk is greater in cases of bilateral retinoblastoma.

Children with cancer who are treated with radiation and alkylating agents have an incidence of osteosarcoma 133 times that of the general population. The risk of developing osteosarcoma in Paget's disease is over 10%. However, this disease is rare before the fourth decade of life.

**EXPERIMENTAL ANIMAL MODELS**

Osteosarcoma occurs in many animals, including mice, rats, hamsters, chickens, dogs, rabbits, cats, cattle, horses, pigs, and sheep. The tumor can occur spontaneously or it may be induced by a variety of techniques, such as exposure to radiation or carcinogens, inoculation by viruses, and transplantation of naturally occurring tumors. In addition, this tumor can be cultivated in tissue culture media and well-defined tissue culture cell lines are available.

Osteosarcomas can be produced experimentally by injection of radioactive substances that accumulate in bones. Intravenous injection of radioactive phosphorus, cesium-144, radium-228, plutonium-239, and strontium-90 and others can result in development of osteosarcomas. Likewise, injection of bone-seeking radionuclides such as radioactive phosphorus, cesium-144, radium-228, plutonium-239, and strontium-90 can result in development of osteosarcomas. Radionuclides that accumulate on bone surfaces, such as plutonium-239 and thorium-228, tend to give rise to a higher proportion of osteosarcoma in tubular regions of bones than bone volume seekers, such as radium-226 and radium-223.

Implantation of various radioactive substances such as phosphorus-32, uranium-235, and cesium-144, either directly into bones or subcutaneously, can also result in development of bone tumors, including osteosarcoma. The rate of induction of bone tumors by radionuclides is roughly proportional to the dose administered, and the latent period increases with decreasing doses. Single or multiple bone tumors develop and metastases may occur. External irradiation can also induce osteosarcoma.

Several chemical agents have been used in animals to experimentally induce osteosarcoma. In rabbits, injection of zinc-beryllium silicate or beryllium oxide induces osteosarcomas in one third of the animals.

Osteosarcoma can be produced by RNA viruses isolated from spontaneously occurring tumors in mice. The "CM" type viral agent, however, is species specific. Intravenous injection of SV-40 virus has produced osteosarcoma in weanling hamsters. The same result can be obtained by intraperitoneal injection of Moloney or Harvey murine viruses or sarcoma virus into neonatal rats. Subcutaneous inoculation of the BK type human papovavirus into newborn Wistar rats has induced osteosarcoma in less than a quarter of these animals. Despite the initial reports, cell-free extracts of human osteosarcomas have not been shown to produce the tumor in experimental animals.

**PATHOLOGY**

Osteosarcoma is defined as a malignant bone tumor with proliferating cells that have the potential to produce either osteoid or immature bone. Such a description, although incomplete, is a result of cumulative experience beginning with development of a registry organized by the American College of Surgeons in the 1920s.

Osteosarcoma usually originates in metaphyseal regions of long bones. Central axis lesions are rare, accounting for the primary site in less than 10% of cases in children. Tumor growth usually extends through the cortex, causing varying degrees of bone destruction and expansion of periosteum (Figure 1). Tumor deposits can occur in the medulla of the bone, separate from the initial tumor site. These are referred to as "skip lesions." They occur in about 20% of cases and are located within a distance of 10 cm from the bulk of primary tumor.

The gross appearance of the tumor is not specific. Histological examination often reveals uniform sheets of osteoblasts with trabecular bone deposition. The appearance varies with the type of the disease. Positive identification requires adequate tissue samples because 15% to 30% of osteosarcomas, proved after surgical resection, may be missed with fine needle aspiration.

Grading of the tumor based on cellular continued on page 288
Brief Summary
Tavist™ (clemastine) Syrup 0.5 mg/5ml (present as clemastine fumarate 0.67 mg/5ml)

INDICATIONS AND USAGE: Tavist (clemastine fumarate) Syrup is indicated for the relief of symptoms associated with allergic rhinitis such as sneezing, rhinorrhea, pruritus, and lacrimation. Tavist (clemastine fumarate) Syrup is indicated for use in pediatric populations (age 6 years through 12) and adults (see DOSAGE AND ADMINISTRATION). It should be noted that Tavist (clemastine fumarate) is indicated for the relief of mild uncomplicated allergic skin manifestations of urticaria and angioedema at the 2 mg dosage level only.

CONTRAINDICATIONS: Antihistamines are contraindicated in patients hypersensitive to the drug or to other antihistamines of similar chemical structure (see PRECAUTIONS—Drug Interactions). Antihistamines should not be used in newborns or premature infants. Because of the higher risk of antihistamines for infants generally and for newborns and prematures in particular, antihistamine therapy is contraindicated in nursing mothers (see PRECAUTIONS—Nursing Mothers).

WARNINGS: Antihistamines should be used with considerable caution in patients with narrow angle glaucoma, stenosing peptic ulcer, pyloroduodenal obstruction, symptomatic prostatic hypertrophy, and bladder neck obstruction. Use with CNS Depressants. Tavist (clemastine fumarate) has additive effects with alcohol and other CNS depressants (hypnotics, sedatives, tranquilizers, etc.). Use in Activities Requiring Mental Alertness. Patients should be warned about engaging in activities requiring mental alertness such as driving a car or operating appliances, machinery, etc. Use in the Elderly (approximately 60 years or older). Antihistamines are more likely to cause dizziness, sedation, and hypotension in elderly patients.

ADVERSE REACTIONS: The most frequent adverse reactions are underlined:

Nervous System: Sedation, sleepiness, dizziness, disturbed coordination, fatigue, dizziness, restlessness, excitation, nervousness, tremor, irritability, insomnia, euphoria, paraesthesia, blurred vision, diplopia, vertigo, tinnitus, acute labynithitis, hysteric, numbness, convulsions.

Gastrointestinal System: Epigastric distress, anorexia, nausea, vomiting, diarrhea, constipation.

Respiratory System: Thickening of bronchial secretions, tightness of chest and affecting nasal stuffiness.

Cardiovascular System: Hypotension, headache, palpitations, tachycardia, extrasystoles.

Hematologic System: Hemolytic anemia, thrombocytopenia, agranulocytosis.

Genitourinary System: Urinary frequency, difficult urination, urinary retention, early menses.

General: Urticaria, drug rash, anaphylactic shock, photosensitivity, excessive perspiration, thirst, dryness of mouth, nose and throat.

DOSAGE AND ADMINISTRATION: DOSAGE SHOULD BE INDIVIDUALIZED according to the needs and response of the patient.

Pediatric: Children aged 6 to 12 years:

For Symptoms of Allergic Rhinitis—The starting dose is 1 teaspoonful (0.5 mg clemastine) twice daily. Since single doses of up to 2.25 mg clemastine were well tolerated by this age group, dosage may be increased as required, but not to exceed 5 teaspoonsful daily (3 mg clemastin).

For Urticaria and Angioedema—The starting dose is 1 teaspoonful (1 mg clemastine) twice daily, not to exceed 6 teaspoonsful daily (3 mg clemastine).

Adults and Children 12 Years and over:

For Symptoms of Allergic Rhinitis—The starting dose is 1 teaspoonful (1 mg clemastine) twice daily. Dosage may be increased as required, but not to exceed 12 teaspoonsful daily (8 mg clemastine).

For Urticaria and Angioedema—The starting dose is 1 teaspoonful (2 mg clemastine) twice daily, not to exceed 12 teaspoonsful daily (6 mg clemastine).

HOW SUPPLIED: Tavist (clemastine fumarate) Syrup, clemastine 0.5 mg/5 ml (present as clemastine fumarate 0.67 mg/5 ml). A clear, colorless liquid with a citrus flavor in 4 fl oz bottle (NDC 0078-0222-31).

Store and dispense: Below 77°F (25°C), tight, amber glass bottle. Store in an upright position.

Figure 1. Cross-section of a resected bone containing an osteosarcoma.

continued from page 286
dominant tissue content, this type of tumor is subdivided into osteoblastic, fibroblastic, and chondroblastic variants.\textsuperscript{5,107,108} Telangiectatic osteosarcoma is a rare and highly malignant form of the disease, often involving areas adjacent to the diaphysis of the bone.\textsuperscript{109,110} Histologically, this tumor is very cellular and contains sparse matrix, areas of osteoid formation, abundant vascular channels, and frequent areas of hemorrhage. Pathological fractures are common.

Parosteal osteosarcoma is most common in older patients and often occurs in the metaphyseal region of the femur.\textsuperscript{111-113} The tumor can reach a significant size prior to diagnosis. It often surrounds the bone shaft without penetration or involvement of the cortical structure. However, at times there is sclerosis of cortex at the site of involvement. Periosteal changes are usually absent in this form of tumor. Histologically, most of these tumors are well differentiated, with presence of irregular bone trabeculae and elongated, fibroblastic-like cellular stroma usually separated by a thick bundle of collagen. The periphery of the tumor shows a significant degree of atypia and anaplasia. The growth of the tumor is relatively slow, but local recurrences and metastasis to the lung, although delayed, do occur.\textsuperscript{114}

Periosteal osteosarcoma is a rare tumor and is most often seen in adolescents. A common site of involvement is the proximal metaphysis of the tibia. The tumor originates from peristeum with only a minimal attachment or penetration of the cortex. The tumor may have a chondrosarcomatous appearance with lobulation and may contain islands of osteosarcoma. Whether this should be classified as parosteal chondrosarcoma or as osteosarcoma is not clear.\textsuperscript{115}

The small-cell osteosarcoma is characterized by presence of malignant small round cells with areas of osteoid formation.\textsuperscript{116} There may also be areas of differentiation to cartilage and fibrous tissue.

**CLINICAL PRESENTATION**

Pain is the most common complaint of patients with osteosarcoma. This can be severe and require large doses of analgesic drugs for relief. Frequently, a history of trauma is present. The median duration of symptoms prior to establishment of the diagnosis is three months, but this interval varies from a few weeks to several months.\textsuperscript{114} Pain often increases with activity, especially weight bearing, and can result in a limp. Depending on the site of the tumor, the mass may or may not be clinically palpable. When therapy is neglected, the tumor can assume a tremendous size (Figure 2). Local edema, tenderness, or decreased range of motion may be present, and occasionally a pulsation or bruit can be found. Pathological fractures are uncommon at presentation, but are seen in up to 30% of cases with the telangiectatic type of osteosarcoma.

![Figure 2. Osteosarcoma in a patient whose parents, due to religious beliefs, had not sought treatment until the tumor had achieved a tremendous size and had seeded numerous metastases.](image)

Osteosarcoma has a propensity to occur in the metaphyses of long bones. Often areas of bone destruction and new bone formation are seen; however, the lesion may be entirely lytic or blastic. In two thirds of cases, a soft tissue mass is present. The initial work-up should include plain roentgenograms of the involved bone, which often are diagnostic. The extension of the tumor through the periosteum may result in a so-called "sun burst" sign (Figure 3), which is demonstrated in 60% of cases.\textsuperscript{117} Periosteal reaction and the laying down of the newly formed bone can also produce an "onion peel" appearance. Computed tomography (CT) and magnetic resonance imaging (MRI)\textsuperscript{118,119} can delineate the extent of the cortical bone involvement and the presence of intramedullary spread, as well as presence of skip lesions and soft tissue extensions (Figure 4). These can assist in planning for the surgical procedure.

The initial evaluation should determine whether there are metastases to chest and skeletal system. At the time of diagnosis, only 10% to 20% of patients
have metastases. These figures may be an underestimation; with use of more sensitive techniques, more metastases will be found.\textsuperscript{115-120} By far, the lung is the most common site of spread of the tumor (Figure 5). Lung involvement may result in pneumothorax. Pneumothorax may occur in the absence of any demonstrable lesion and may be the first sign of metastasis.\textsuperscript{121,122} Less common sites of metastases include bones, pleura, lymph nodes, pericardium, kidney, and brain.

Recognition of pulmonary metastases on plain chest x-rays is not always possible.\textsuperscript{123} Use of conventional tomography and computed tomography (CT) may disclose the presence of tumor, which may not have been apparent with use of standard techniques. About 10\% to 30\% of patients with normal standard chest x-rays have metastases identified with linear x-ray tomograms. Furthermore, as many as 15\% of those with negative tomograms may have positive CT scans.\textsuperscript{124} Even with current technology of CT scanning, tumors less than 3 mm in diameter are not detected. During surgical exploration of the lungs, the number of metastases identified is usually several times larger than the number seen on CT scan. On the other hand, the number of false-positive findings in CT scans of the lung can be substantial, because it is not always possible to differentiate tumors from granulomas, pleural-based lymph nodes, and nodules of scar tissue. Patients who have undergone surgery for removal of metastases may pose additional diagnostic difficulties. The role of MRI in detection of metastases is now under study.

Radionuclide scintigraphy with technetium-99m methylene disphosphonate can detect the extent of the primary tumor and presence of metastases.\textsuperscript{124} Generally, the primary bone tumor shows increased concentration of the radionuclide ("hot spots"); however, "cold spots" at the primary site of osteosarcoma have also been observed. The technique may allow early detection of asymptomatic metastases in bones as well as in soft tissues.\textsuperscript{125-128} Radionuclide scans also are accurate for detecting intramedullary tumor involvement, but often the scans show a falsely extended uptake pattern in tissues adjacent to the tumor.\textsuperscript{125} Metastatic lesions can be identified with accuracy by presence of areas of increased radionuclide uptake (Figure 6).

At the time of diagnosis, nearly half of patients have increased levels of serum alkaline phosphatase.\textsuperscript{129,130} This finding is associated with an increased likelihood continued on page 292
LOTRIMIN®
(clotrimazole, USP)
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IDEAL FOR BABY’S TENDER SKIN

FOR DERMATOLOGIC USE ONLY — NOT FOR OPHTHALMIC USE

INDICATIONS AND USAGE: LOTRIMIN products are indicated for the
topic treatment of the following dermat infections: tinea pedis, tinea cruris, and tinea corporis due to Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, and Microsporum canis; candidiasis due to Candida albicans; and tinea versicolor due to Malassezia furfur.

CONTRAINDICATIONS: LOTRIMIN products are contraindicated in individuals who have shown hypersensitivity to any of their components.

WARNINGS: LOTRIMIN products are not for ophthalmic use.

PRECAUTIONS: General: If irritation or sensitivity develops with the use of clotrimazole, treatment should be discontinued and appropriate therapy instituted.

Information For Patients: The patient should be advised to:
1. Use the medication for the full treatment time even though the symptoms may have improved. Notify the physician if there is no improvement after four weeks of treatment.
2. Inform the physician if the area of application shows signs of increased irritation (redness, itching, burning, blistering, swelling, oozing) indicative of possible sensitization.
3. Avoid the use of occlusive wrappings or dressings.
4. Avoid sources of infection or infection.

Laboratory Tests: If there is no response to clotrimazole, appropriate microbiological studies should be repeated to confirm the diagnosis and rule out other pathogens before instituting another course of antifungal therapy.

Drug Interactions: Synergism or antagonism between clotrimazole and miconazole, or amphotericin B, or fusidic acid against strains of C. albicans has not been reported.

CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY: No adequate and well-controlled studies in pregnant women in their second and third trimesters have not been associated with fetal effects. There are, however, no adequate and well-controlled studies in pregnant women during the first trimester of pregnancy.

Studies in pregnant rats with intravenous doses of 100 mg/kg have revealed no evidence of harm to the fetus due to clotrimazole. High oral doses of clotrimazole in rats and mice ranging from 50 to 120 mg/kg resulted in embryo toxicity (possibly secondary to maternal toxicity), impaired implantation, decreased litter size and number of viable young and decreased pup survival to weaning. However, clotrimazole was not teratogenic in mice, rabbits or rats at oral doses up to 200, 180 and 100 mg/kg, respectively.

Oral ingestion in the rat amounts to approximately 90% of the administered dose.

Because reproduction studies are not always predictive of human response, this drug should be used only if clearly indicated during the first trimester of pregnancy.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when clotrimazole is used by a nursing woman.

Pediatric Use: Safety and effectiveness in children have been established for clotrimazole when used as indicated and in the recommended dosage.

ADVERSE REACTIONS: The following adverse reactions have been reported in connection with the use of clotrimazole: erythema, stinging, blisters, itching, peeling, edema, pruritus, urticaria, burning, and general irritation of the skin.

OVERDOSAGE: Acute overdosage with topical application of clotrimazole is unlikely and would not be expected to lead to a life-threatening situation.

DOSEAGE AND ADMINISTRATION: Gently massage sufficient
LOTIRMIN into the affected and surrounding skin areas twice a day,
in the morning and evening.

Clinical improvement, with relief of pruritus, usually occurs within the first week of treatment with LOTRIMIN. If the patient shows no clinical improvement after four weeks of treatment with LOTRIMIN, the diagnosis should be reviewed.

HOW SUPPLIED: LOTRIMIN Cream 1% is supplied in 15, 30, 45 and 90-g tubes (NDC 0085-0051-02, 03, 04, 03, respectively); boxes of one.
LOTIRMIN Lotion 1% is supplied in 30 ml bottles (NDC 0085-0107-001); boxes of one.
Shake well before using.

LOTRIMIN Solution 1% is supplied in 10 ml and 30 ml plastic bottles (NDC 0085-0182-02, 04, respectively); boxes of one.
Store LOTRIMIN products between 2° and 30° (30° and 86°F).


Figure 6. Radionuclide scintigraphy with technetium-99 methylene disphosphonate showing lung metastases in a patient who had previously undergone amputation.

continued from page 290

of subsequent pulmonary metastases. Nevertheless, presence of a normal serum alkaline phosphatase level in patients with detectable metastases is not unusual. Non-specific tests, such as erythrocyte sedimentation rate (ESR) and serum ceruloplasmin level, are of little value in the diagnosis and assessment of patients with osteosarcomas. Despite early enthusiasm, determination of somatostatin level and assay of growth hormone are not useful in assessing these patients. Accurate diagnosis of osteosarcoma ultimately depends on histopathological examination of the tumor. Biopsy of the tumor should be obtained prior to definitive surgery. Opinions differ as to whether biopsy should be obtained at the same time as definitive surgery is done. The difficulty in obtaining immediate and reliable pathological diagnosis at the time of biopsy is a limiting factor. No difference in the rate of relapse-free survival could be shown in a prospective comparison of patients who had immediate amputations as compared to those who had amputations several days after biopsy.

THERAPY OF OSTEOSARCOMA

There is no uniformly accepted treatment of osteosarcomas. In general, the current treatment of this tumor includes surgery and chemotherapy. In many centers, surgery is tailored to the extent of the patient's disease. The choice of surgical technique, that is, continued on page 293
amputation or limb salvage, depends on several factors. These factors include age, size and degree of skeletal maturity, anatomical location, extent of the tumor, presence of soft tissue and neurovascular involvement, expected postoperative function, and availability of surgical expertise, together with an evaluation of the patient's attitude and desires. In view of the results of recent studies clearly indicating the usefulness of chemotherapy, most centers combine surgery with this modality for treatment of all patients. In those patients who will undergo limb salvage operations, chemotherapy is administered intravenously or intraarterially in advance of the surgical operation.

Amputation

Historically, amputation has been the primary treatment for osteosarcoma. This is often possible because the tumor occurs predominantly in the extremities. A major controversy concerns the level of amputation. Clinically undetected “skip lesions,” in the form of intramedullary tumor deposits separated from the major area of tumor, are known to occur. These skip lesions are seen in approximately 20% of cases and are not always detectable with use of x-ray examination, scintigraphic scans, or magnetic resonance imaging. The lesions may be found beyond the epiphyseal plate. Extension of tumor into the bony medulla may occur, with tumor extending into a proximal joint. The usual practice is to remove the entire extremity, allowing a safety margin of 7 cm to 10 cm, or to excise the whole bone at or above the contiguous joint. For a proximal lesion of the tibia, an above-the-knee amputation or disarticulation of the knee is performed. For a proximal femoral tumor, depending on its location, a hip disarticulation or hemipelvectomy is done. A Van Nes rotationplasty, using the inverted heel as a knee joint, is possible. Segmental arthrodesis and metallic implants are also used. After bone replacement, most patients are given adjuvant chemotherapy.

Limb-Sparing Techniques

En bloc resection of tumor as an alternative to amputation is increasingly favored. For this technique to be used, the patient’s bone growth must be near the stage of epiphyseal closure, and the tumor should preferably be predominantly intrasosseous with only a small degree of soft tissue extension. Limb-sparing procedures are most applicable to patients with a small tumor located above the knee. The soft tissues, as well as vascular and nerve structures, must be free of tumor. A careful preoperative evaluation, including a biomechanical profile, is essential.

Patients are often given preoperative chemotherapy as an initial effort to destroy micrometastases. This therapy may also reduce tumor mass or better delineate the margins of the tumor and can transform a case not suitable for limb-sparing surgery into an operable one. Prophylactic radiation therapy to the lungs in the preoperative or postoperative period has not improved prognosis. Intra-articular preoperative chemotherapy in the area of the lesion can also be used. Sclerotic replacement, such as a cross-leg graft, is possible. Segmental arthrodesis and metallic implants are also used. After bone replacement, most patients are given adjuvant chemotherapy.

Presence of metastases was previously considered a contraindication to limb salvage surgery. However, with improved results of adjuvant chemotherapy this is no longer necessarily true.

Thirty-three percent of patients undergoing en bloc resection of distal femoral lesions at a later date may require conventional amputation. Complications that may render amputation necessary include infection, tumor recurrence, or prosthesis breakage. When limb-salvaging surgery is done in a lower extremity, a prosthesis is fitted postoperatively.
TABLE 1

<table>
<thead>
<tr>
<th>Agent</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methotrexate (various dose-schedules)</td>
<td>24%-85%</td>
</tr>
<tr>
<td>Melphalan (various doses)</td>
<td>15%-67%</td>
</tr>
<tr>
<td>Ifosfamide</td>
<td>33%</td>
</tr>
<tr>
<td>Cis-diaminedichloroplatinum</td>
<td>20%-30%</td>
</tr>
<tr>
<td>Adriamycin (various schedules &amp; doses)</td>
<td>18%-39%</td>
</tr>
<tr>
<td>5-Fluouracil</td>
<td>17%</td>
</tr>
<tr>
<td>Cyclophosphamide (various doses)</td>
<td>12%-50%</td>
</tr>
<tr>
<td>Mitomycin C</td>
<td>3%</td>
</tr>
<tr>
<td>Interferon</td>
<td>0%</td>
</tr>
</tbody>
</table>

scapulothoracic resection. This operation appears to preserve more function than is possible after a forequarter amputation or a shoulder disarticulation. In the Tikoff-Lindberg procedure the distal humerus is fixed to the chest wall with a metallic rod.136 Upper extremity preservation is much better than use of any external prosthetic device attempting to replace forequarter amputation or a shoulder disarticulation.154 Radial nerve palsy may be treated with a cock-up splint or tendon transfer.155 Shoulder padding or plastic fillers can conceal the cosmetic defect. Cryotherapy with liquid nitrogen has been used to control pain.151 There is no evidence that this therapy can affect the growth of the tumor.

With the definite improvement in long-term survival with contemporary adjuvant chemotherapy,155,161-166 it is likely that performance of limb-sparing procedures will become more common. Improved survival implies that chemotherapy provides better control of micrometastases. So far, available studies have shown no difference in disease-free survival in use of radical surgery as compared to non-radical surgery.167,168

RADIATION THERAPY
Osteosarcoma is a radioresistant tumor and use of radiation does not now play a major role in the therapy of this disease. After a full course of radiation therapy, viable tumor cells were noted to be still present in as many as two thirds of primary tumors.156 The tumoricidal dose is greater than 6,000 cGy.169,170 Pre-operative radiation and surgery has not produced better results than surgery alone.171,172 Complications frequently occur after radiation. In one study, 23% of patients treated with 8,000 to 9,000 cGy were relapse-free at two years, but 43% of these surviving patients eventually required an amputation because of complications.173

Prior to the use of adjuvant chemotherapy, a radiotherapy regimen developed by Cade was commonly used in Europe.149 The aim of radiation therapy was to spare those 80% of the patients, who would have died, from the added burden of an amputation. Over a period of six to nine weeks, the tumor was irradiated with 6,000 to 8,000 cGy.174 Amputation was performed six to nine months later only in those patients who had no evidence of metastases. The survival rate of patients treated in this way was equal to that of patients whose affected limbs were amputated immediately after diagnosis.

Radiation, even in doses of 4,000 to 6,000 cGy, may not relieve local symptoms.175 Large doses of radiation ranging from 12,000 to 16,000 cGy after tumor-implanted hypoxia of local tissue, produced less than 50% local tumor control.176 Likewise, prophylactic whole lung radiation, in general, did not decrease the rate of relapse-free survival of patients with osteosarcoma.177 The use of radiation has only a very small role in current therapy of osteosarcoma.

CHEMOTHERAPY
Until recently, the beneficial effects of chemotherapy in osteosarcoma were controversial. In the Mayo Clinic studies performed in the 1970s, after 18 months of follow-up, the survival rate of patients treated with surgery alone was 52%. These results were no different than the survival rate of patients who received adjuvant chemotherapy with a combination of high dose methotrexate and vincristine. These findings cast doubt on the value of giving chemotherapy in osteosarcoma,178,179 and even resulted in proposal of a theory that the biological nature of this disease may have changed with time. Because of lack of a large randomized study comparing surgery alone with use of surgery and chemotherapy, the notion that adjuvant chemotherapy was useless could not be refuted.

From recent controlled studies, however, it is now clear that chemotherapy does significantly increase the survival of these patients.161,180 Conclusive results were reported from two large multicenter studies. In these studies, the actuarial relapse-free survival rates of patients with osteosarcoma of the extremity treated with adjuvant chemotherapy were compared with survival of control patients not given chemotherapy.161 The control group was randomly assigned to observation alone following definitive surgery. In one study, at two years, the actuarial relapse-free survival of controls was only 17%, as opposed to 66% for the patients given chemotherapy.161 In a similar randomized study, disease-free survival at two years of 27 patients who were treated with surgery alone was 20% compared to a two-year survival rate of 55% for 32 patients who were given adjuvant chemotherapy. The demographic make up of the patients and the type and extent of the tumors in both groups were similar, thus eliminating any obvious bias to account for the
observed differences in survival rates. It should be
noted that the survival rate of patients treated with
surgery alone in the 1980s\(^{145,161}\) is similar to the
survival rates of patients similarly treated in earlier
studies, ranging from 17\% to 20\%. It was concluded
from these studies that the natural course of osteosar-
coma of the extremity has remained unchanged, and
adjunct chemotherapy increases the rate of prolonged
relapse-free survival of patients with this tumor.

Use of Single Agents in Chemotherapy

Used alone, only a few chemotherapeutic agents
have shown effectiveness against osteosarcoma. These
drugs include methotrexate, melphalan, cisplatin,
adriamycin, 5-fluorouracil, cyclophosphamide and
mitomycin C (Table). Drugs that when given alone
have no demonstrable efficacy include actinomycin
diaziquone-D (AZQ), the epiphalotoxins (etoposide
and teniposide), dacarbazine (DTIC), mitoxantrone
HCl (DHAD), acriderin amide (m-AMSA), and
vincristine. The presumed lack of efficacy, however,
is based on a very small number of trials carried out in
patients with advanced disease.

A variety of biological response modifiers, including
transfer factor, nonspecific immunotherapy, and inter-
feron, have been tried in the therapy of osteosar-
coma.\(^{181-186}\) During the past decade, interferons,
because of their antiproliferative activity, have been
used in the treatment of osteosarcoma.\(^{183,185}\) Human
osteosarcoma xenografts in nude mice were found to
respond to human interferon, but not to murine inter-
feron. This finding indicated that the antitumor
effects may be related to a direct anticellular action
and not due to immune modulation.\(^{181}\) Isolated
reports show efficacy of interferon in treatment of a
small number of patients with osteosarcoma. In one
report, 10\(^6\) units of interferon given three times a week
produced observed reduction in metastatic tumors in
two out of three patients.\(^{182}\) A nonrandomized
clinical trial done in Sweden, using naturally occur-
ing partially purified interferon, was originally
thought to be successful. But after longer follow-up,
the results did not indicate enough improvement in
survival to warrant wider use of this agent.\(^{183}\) More
recently, the German-Austrian Cooperative Group
found that addition of interferon to chemotherapy
produced no prolongation of disease-free survival of
patients with osteosarcoma.\(^{152}\)

In a very limited study, the results of treatment with
transfer factor were comparable to combination che-
motherapy consisting of methotrexate, doxorubicin,
adriamycin, and vincristine.\(^{184}\) Survival at 18 months
in patients given transfer factor was 55%.\(^{184}\) The result
of this study has not been confirmed.

Use of Combination Chemotherapy

Chemotherapy regimens containing two or more
drugs produce results superior to use of a single
agent.\(^{161}\) Chemotherapy of osteosarcoma has usually
consisted of giving these agents prior to surgery or
postoperatively.

Postoperative Chemotherapy

Postoperative chemotherapy is administered with
the goal of destroying residual tumor cells not removed
by surgery. Many drug combinations, and varying
doses and schedules, have been tried. The rational
basis for multidrug regimens is the finding that che-
motherapeutic agents are often more effective when given
in combination.

Earlier studies demonstrated that methotrexate in
doses ranging from 3 to 7.5 g/m\(^2\) followed by citro-
vorum factor rescue is clearly an effective agent in
osteosarcoma. Methotrexate given in this way pro-
duced a response rate of approximately 40%.\(^{187,188}\)
Because it was observed that vincristine can facilitate
the intracellular influx of methotrexate, this agent was
added to the methotrexate-citrovorum regimen. This
new study showed a disease-free survival rate of 43% at
two years. The addition of adriamycin to this regimen
did not improve the results.\(^{189}\) Adjuvant chemother-
apy with the classic combination of cyclophos-
phamide, vincristine, and actinomycin D (VAC) was
not effective in patients with osteosarcoma, producing
a disease-free survival rate of only 20%.\(^{15}\)

The combination of cyclophosphamide, Oncovin®,
phenylalanine mustard and adriamycin (COM-
PADRI-I) produced significantly better results. In 44
newly diagnosed patients with nonmetastatic osteosar-
coma of an extremity, this regimen produced a relapse-
free survival rate of 55\% after 37 months of follow-
up.\(^{190}\) This combination of drugs was later modified by
addition of high dose methotrexate (COMPADRI-II).
Treatment with this combination in 60 evaluable
patients yielded a disease-free survival rate of only
37\%. In a subsequent study, the same drugs were used;
however, doses of methotrexate were given on a weekly
basis and the total dose of adriamycin was increased to
360 mg/m\(^2\) (COMPADRI-III). The relapse-free sur-
vival rate in 44 patients followed for a median of 14.5
months was 42%.\(^ {191}\) Another study used vincristine,
high dose methotrexate with citrovorum factor rescue,
and adriamycin in conjunction with radiotherapy and
amputation. The rate of prolonged survival was 30%.
In one study, patients given L-phenylalanine mustard
and cyclophosphamide together with high dose meth-
отrexate showed a prolonged disease-free survival rate
of 50%.\(^{192}\) The combination of cyclophosphamide,
vincristine, adriamycin, and DTIC produced a disease-
free survival rate of 61\% with a median follow-up of
60 months.

After adriamycin was shown to be effective in osteo-
sarcoma,\(^{193,194}\) it was added to combination che-
motherapy regimens. A combination of intermediet-
dose methotrexate and adriamycin given at regular
intervals for one year postoperatively in 11 patients
Used alone, only a few chemotherapeutic agents have shown effectiveness against osteosarcoma.

produce a 64% disease-free survival rate at 42 to 62 months.\textsuperscript{195} In 22 patients treated with high dose methotrexate and Adriamycin for 16 months, the disease-free survival rate after a median of three years follow-up was 54%.\textsuperscript{115} Addition of Adriamycin to vincristine and high dose methotrexate with citrovorum factor rescue in 16 patients who had undergone amputation resulted in a survival rate of 37% after 24 to 36 months follow-up.\textsuperscript{196} A combination of Adriamycin, vincristine, high dose methotrexate used in 23 patients produced a survival rate of 52%. The use of Adriamycin plus vincristine and high dose methotrexate resulted in a disease-free survival rate of 30% in a group of 16 patients who had received radiation therapy and amputation.\textsuperscript{192} Administration of six courses of Adriamycin followed by high dose methotrexate, cyclophosphamide, and L-phenylalanine mustard in 12 patients produced a disease-free survival rate of 50% after 24 months of follow-up. The use of Adriamycin and vincristine given in combination with high or medium dose methotrexate has not improved the results.\textsuperscript{197} Only 38% of patients remained disease-free at four years after diagnosis. A regimen consisting of Adriamycin, vincristine, mitomycin-C, DTIC, cyclophosphamide, and BCG used in 21 patients with osteosarcoma of the limbs produced a disease-free survival rate of 85%. However, these patients were followed for only six to 29 months.\textsuperscript{198}

Cisplatin has been shown to be a valuable agent for the treatment of osteosarcoma. Given as a single agent, cisplatin produces a partial or complete response in about one third of patients.\textsuperscript{199-204} This response is observed in newly diagnosed patients as well as in those with recurrent tumor.\textsuperscript{205} In one study, this agent was given together with methotrexate. This combination produced complete control of tumor in nine patients for a mean follow-up of 19 months.\textsuperscript{206} Cisplatin is effective when combined with Adriamycin for therapy of osteosarcoma.\textsuperscript{207,208} This combination produced complete response of tumor in 14 of 22 patients (64%), with a median follow-up of 70 months.

Chemotherapy combinations containing cisplatin, while effective, can cause severe renal toxicity.\textsuperscript{209} Patients who receive multiple courses of cisplatin show progressive reduction in kidney function as evidenced by decreased creatinine clearance and delayed excretion of serum methotrexate. In one study, the first indication of toxicity was seen after a cumulative dose of 450 mg/m². Even after termination of therapy, renal impairment persists.\textsuperscript{209,210} Attempts are being made to reduce the cumulative toxicity of this group of drugs using analogues with less renal and autotoxicity.

To assess the role of chemotherapy in a randomized prospective study, a postoperative chemotherapy regimen consisting of Adriamycin, high dose methotrexate, bleomycin, cyclophosphamide, and actinomycin D was given to 32 patients. The control group consisted of 27 patients who received no adjuvant chemotherapy. At a median follow-up of two years, the disease-free survival rate of the group given chemotherapy was 55% compared with 20% for controls. The disease-free survival rate of the controls was comparable to the survival rates reported in earlier studies.\textsuperscript{145} Likewise, another large multicenter study reported a two-year relapse-free survival rate of 66% in patients with osteosarcoma of the extremity given adjuvant chemotherapy.\textsuperscript{211} The control group, treated only with surgery, showed a relapse-free survival rate of only 17%. This study confirmed that the natural history of osteosarcoma has not changed and adjuvant chemotherapy increases the rate of prolonged relapse-free survival of patients with high-grade disease.

**Preoperative Chemotherapy**

The administration of chemotherapy prior to amputation or segmental resection of the involved bone can provide important information regarding the biological responsiveness of the tumor. In effect, giving chemotherapy prior to surgery is an in vivo test for assessment of the tumor's sensitivity to chemotherapeutic agents and helps in the selection of appropriate regimens for postoperative therapy.\textsuperscript{212} Histological examination of the resected tumor permits immediate assessment of the degree of tumor necrosis and allows for change of therapy or increased doses. Based on these findings, a grading system has been developed.\textsuperscript{149} Accordingly, four levels of chemotherapy effect, ranging from minor changes (grade I) to presence of areas of a cellular tumor; fibrosis and necrosis admixed with areas of histologically viable tumor (grade II); predominance of tumor destruction with scattered foci of viable tumor (grade III); and complete effacement of viable tumor (grade IV), are identified. Grades I and II response are associated with more frequent recurrence of the disease as compared with those with grade III and IV responses.\textsuperscript{149,213} One report indicated a positive correlation between a "good" radiologic response and histological grading of the resected bones.\textsuperscript{214}

Other advantages of preoperative chemotherapy include reducing tumor size in order to make possible or to facilitate an en bloc resection and limb preservation, and allowing time for preparation of a custom fit prosthetic bone replacement. A variety of
preoperative chemotherapy schedules have been developed. Earliest attempts included therapy of patients in whom it was thought that en bloc resection of their tumor could be achieved with the insertion of a custom-fitted prosthetic bone to replace the resected bone. In this study, newly diagnosed patients with biopsy-proven osteosarcoma received repeated sequential preoperative chemotherapy, including vincristine, high dose methotrexate with citrovorum factor rescue, followed in ten to 14 days by Adriamycin for a period of two to three months. After en bloc tumor resection, postoperative chemotherapy included courses of agents used prior to surgery along with high doses of cyclophosphamide two weeks prior to and after each methotrexate course (T5 protocol). The dose of methotrexate was increased when no early response in the primary tumor was noted. In 31 patients treated in this fashion, the disease-free survival was 58%. The overall survival at four years was 77%, with a disease-free survival rate of 50%. The survival rate of these patients is clearly superior to the 52% four-year overall survival rate observed in 23 patients who were given similar therapy after amputation. These findings indicate that preoperative chemotherapy produces an improved survival rate.

In a subsequent study, a combination of bleomycin, cyclophosphamide, and actinomycin D (BCD) was substituted for cyclophosphamide. Also, more frequent courses of methotrexate with higher doses (12 g) were given to young children (T7 protocol). This therapy resulted in an overall survival rate of 81%, and a disease-free survival rate of 76% in 37 patients. Since the degree of necrosis due to chemotherapy showed correlation with the outcome of the disease, the postoperative chemotherapy regimen was modified by substituting cisplatin for methotrexate (T10 protocol) in patients who showed a grade 1 or II response. In the initial report of this study, out of 57 evaluable patients, 22 had a grade I or II response. A recent update on 87 patients treated, out of 57 protocol showed that 77% have survived free of the disease after a median of 58 months follow-up. The overall survival was 82%. More recently, in complete responders, preoperative chemotherapy with high dose methotrexate plus bleomycin, cyclophosphamide, and actinomycin D is followed postoperatively by one course of BCD and two courses of high dose methotrexate for a total of 15 weeks (T12 protocol). Of the 51 patients entered in this study, 75% are disease-free and 76% are alive after 25 months of follow-up.

But not all patients undergoing preoperative chemotherapy are candidates for limb salvage procedures. In two reported studies, only 48% and 58% of patients had limb-sparing operations. The degree of necrosis in the resected bone can serve as a prognostic sign and offer guidance in prescribing further chemotherapy. However, even with the finding of over 90% necrosis of tumor, further extensive chemotherapy is indicated. In one study among patients receiving preoperative chemotherapy with methotrexate and cisplatin and having a grade IV necrosis of tumor, the group given 24 weeks of postoperative chemotherapy had a superior rate of prolonged survival as compared with those receiving only four weeks of treatment.

**The spread of the tumor is most often to the lungs and bones; however, metastases also occur in other organs.**

**Intra-Arterial Chemotherapy**

Intra-arterial chemotherapy provides localized perfusion and produces maximum concentration of drug in the tumor. This technique exposes the tumor to a local concentration of drug, which cannot be achieved without life-threatening side effects by intravenous chemotherapy. Furthermore, the systemic effects of intra-arterial treatment are similar to those of standard therapy. Intra-arterial therapy is most effective using drugs with a short half-life. The serum concentration of cisplatin achieved by this technique is four times higher in the afferent artery of the tumor as compared with the efferent veins. Intra-arterial adriamycin as well as cisplatin and methotrexate are used alone or in combination, with or without intravenous adjuvant chemotherapy, for the treatment of osteosarcoma.

After intra-arterial infusion, CT scans may show decrease in tumor size. The effects of high dose methotrexate with citrovorum factor (MTX-CF) given intravenously were compared with intra-arterial cisplatin. The responses of intra-arterial therapy were found superior to the conventional method of parenteral chemotherapy. Furthermore, two patients who failed on intravenous chemotherapy responded to intra-arterial therapy.

Continuous infusion of cisplatin and adriamycin, accompanied by obstruction of blood flow after infusion in the hope of increasing perfusion of the tumor, has been tried. Severe skin and soft tissue necrosis, however, limits this technique. Intra-arterial infusion of 5-bromodeoxyuridine (BUdR) as a radiosensitizer, combined with hyperfractionated irradiation and adjuvant systemic chemotherapy, has resulted in local control in seven of nine patients in whom primary tumors were not resectable. Significant soft tissue injury occurred in five patients, and distant metastases developed in six. Histopathological study of the tumor after intra-arterial therapy may still demonstrate viable tumor cells in half of the patients, and gross residual tumor may persist even in areas of tumor supplied by an artery.
At the time of diagnosis, an estimate level of the patient's emotional maturity and physical development should be made to plan a program for rehabilitation and counseling.

TREATMENT OF METASTASES

Following treatment of osteosarcoma, local tumor recurrence at the margins of the primary lesion and distant metastasis can occur. The spread of the tumor is most often to the lungs and bones; however, metastases also occur in other organs, including the heart, kidneys, and epidural spaces.\textsuperscript{124-227} Pulmonary metastases in 20\% to 45\% of patients are bilateral.\textsuperscript{128,229} If overt metastases are not treated, the majority of patients die within one year.\textsuperscript{128,229} Complete evaluation, including radiological examinations and bone scans, is essential in designing a plan for treatment. Spread of tumor ranges from development of only one or two metastatic lesions, which may be resectable without recurrence, to development of multiple and recurring lesions. This behavior may reflect the degree of differentiation of the tumor.\textsuperscript{212} It is also possible that treatment may alter the pattern of metastases, with nonpulmonary metastases becoming more prevalent.\textsuperscript{230} The histological picture of a metastasis may be different from that of the primary tumor. Furthermore, the histological pattern may also vary among metastatic lesions, as shown in lesions excised during consecutive thoracotomies from the same patient.\textsuperscript{231} Usually, the number of metastases found during surgery is several times higher than the number seen in radiographic studies.

The therapy of metastases includes surgical removal and chemotherapy. Surgical resection helps to control the local growth of the tumor, and prevent pulmonary hemorrhage and airway obstruction. Some patients require repeated resection of metastases. Aggressive surgical treatment is warranted, however, and can prolong survival, including disease-free survival, and may even produce "cures." Based on various studies, nearly half of patients undergoing one or more thoracotomies for resection of metastatic disease, with or without accompanying adjuvant chemotherapy, survive two to three years after the operation. Furthermore, 23\% to 56\% have a chance of long-term, disease-free survival.\textsuperscript{132-240} Factors influencing survival in patients with lung metastasis include sex, number of nodules detected radiographically and resected, completeness of resection, tumor doubling time, disease-free interval, and unilateral or bilateral location of lesions.\textsuperscript{238-245}

The surgical technique used for resection of pulmonary metastasis varies among surgeons. When the location of detectable tumor allows, a midline sternal-splitting incision is advocated.\textsuperscript{243} This approach allows access to both pleural cavities and the mediastinum; thus, the extent of chest involvement can be fully assessed and complete resection can be done in one operation. Furthermore, this technique is associated with a faster recovery as well as with less postoperative pain and fewer disturbances of pulmonary function.\textsuperscript{246} Wedge or segmental resections are usually adequate. In one review, only five out of 60 patients needed lobectomies.\textsuperscript{247} Since lymph nodes, bronchial tree and mediastinum are rarely involved, node dissection is not usually recommended.\textsuperscript{160} The surgical mortality rate of this procedure is extremely low,\textsuperscript{248} and morbidity is not excessive. In addition to pulmonary metastases, resection of other metastases should also be attempted. Involvement of vertebral bodies by metastatic osteosarcoma may require urgent surgical decompression.\textsuperscript{249} Chemotherapy of metastatic lesions should be tailored to suit the needs of the individual patient, with consideration given to prior treatments.

MANAGING PSYCHOSOCIAL EFFECTS

Cancer diagnosis, plus the medical and surgical treatments, have profound psychological effects. With increased duration of survival of patients, the long-term effects of cancer, including psychosocial disturbances, have become increasingly important. Knowledge of factors that play a role in helping patients cope with their disease and its associated disabilities can serve, to a large extent, to ameliorate the psychosocial difficulties. The peak incidence of osteosarcoma is during the second decade of life, a time when physical attributes and body image are of utmost importance. The psychological trauma caused by cancer itself, as well as by surgery and chemotherapy, during this sensitive stage of life can be devastating. Incomplete development of adaptive mechanisms in adolescents, coupled with the stress of disease, fear of the unknown, alterations in body image, and isolation from peers, as well as interrupted educational, vocational and life plans, can produce a crisis of major proportions.

At the time of diagnosis, an estimate of the level of the patient's emotional maturity and physical development should be made in order to plan a program for rehabilitation and counseling. Prior experience shows that despite all obstacles, when properly managed, these patients can adapt well to the situation. In fact, the majority can live useful and productive independent lives.\textsuperscript{250-251} In one long-term study of 27 cancer patients who had amputations, mainly for treatment of osteosarcomas, 41\% of those older than 18 years of age had attended college and only 14\% had not completed high school. In this group, 46\% were married and nearly all patients were gainfully employed. Based on
educational, vocational, and social achievement of these patients, over 85% were judged to be well-adapted. A positive attitude and open discussions with health care providers can help provide a justifiably optimistic view of life, especially during the early and highly distressful times of diagnosis and treatment.

SUMMARY

Osteosarcoma is the most common bone tumor of children and adolescents. The peak incidence of the disease is in the 15 to 19 year age group. The disease is more commonly seen in males than females. While several factors, including exposure to radiation, genetic disorders such as retinoblastoma, and high rate of bone growth, have been associated with osteosarcoma, in most cases no definite etiology can be established. Osteosarcoma usually originates in the metaphyseal region of long bones and extends through the cortex, causing varying degrees of bone destruction and expansion of periosteum. The radiographic appearance caused by this process is often referred to as "sun burst" sign.

Positive diagnosis of osteosarcoma is made by histopathology. The histopathological classification of osteosarcoma can also predict the degree of aggressive behavior of this tumor and thus has prognostic significance. Surgery, including amputation or limb-salvage procedure, is the mainstay of treatment of osteosarcoma. It is now unequivocally established that adjunct chemotherapy will prolong the survival of patients with this disease. Chemotherapy agents often used include platinum derivatives, methotrexate, vincristine, cyclophosphamide, adriamycin, actinomycin D, bleomycin and DTIC. Depending on surgical decision, these agents can be used prior to or after the operation. Immediate fitting with prosthesis and provision of appropriate medical and psychological support in the care of these patients is essential.

REFERENCES
