SURGICAL TREATMENT OF GIANT CELL TUMOR: REVIEW ARTICLE

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Abstract:
The 2020 World Health Organization classification defined giant cell tumors of bone (GCTBs) as intermediate malignant tumors. Since the mutated H3F3A was found to be a specific marker for GCTB, it has become very useful in diagnosing GCTB. Curettage is the most common treatment for GCTBs. Preoperative administration of denosumab makes curettage difficult and increases the risk of local recurrence. Curettage is recommended to achieve good functional outcomes, even for local recurrence. For pathological fractures, joints should be preserved as much as possible and curettage should be attempted. Preoperative administration of denosumab for pelvic and spinal GCTBs reduces extraosseous lesions, hardens the tumor, and facilitates en bloc resection. Nerve-sparing surgery after embolization is a possible treatment for sacral GCTBS. Denosumab therapy with or without embolization is indicated for inoperable pelvic, spinal, and sacral GCTBs. It is recommended to first observe lung metastases, then administer denosumab for growing lesions. Radiotherapy is associated with a risk of malignant transformation and should be limited to cases where surgery is impossible and denosumab, zoledronic acid, or embolization is not available. Local recurrence after 2 years or more should be indicative of malignant transformation. This review summarizes the treatment approaches for non-malignant and malignant GCTBs.

Keywords: giant cell tumors, Cryosurgery, Argon Plasma.

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Introduction:

Surgical treatment is the treatment of choice for GCT. Depending on the involvement of the articular surfaces, the tumor can be removed either by resection or with curettage, with or without local adjuvants**.** Surgical outcomes are optimal when the tumor is removed to tumor-free margins, with minimal surgical morbidity and an acceptable functional outcome. Resection with wide (microscopically negative) margins has been associated with few or no recurrences ranging from 0% to 16%, but a poor functional outcome and greater surgical morbidity.[(1)]

Compared to en bloc resection, curettage presents higher recurrence rates (12–65%), but less morbidity and functional impairment for the patients.[(2)]

1. Curettage:

Curettage can be performed alone (simple curettage) or combined with local adjuvants (extended curettage). Curettage alone has the worst recurrence rates (mean: 42%; range: 21–65%).[(3)]

Various physical and chemical agents have been used to control the microscopic disease remaining in the walls after a good curettage. Cryosurgery (Liquid nitrogen), phenol, hydrogen peroxide, alcohol, electrocautery, bone cement, and the argon plasma cautery have been used as adjuvants.[(4)]

Cryosurgery:

Liquid nitrogen is nitrogen in a liquid state at a very low temperature. It is produced industrially by fractional distillation of liquid air. Liquid nitrogen is often referred to by the abbreviation (LN).[(5)]

Cryosurgery is recommended as a physical adjuvant to curettage in the treatment of giant cell tumor of the bone. It extends the margin of a simple curettage or resection curettage and makes it biologically equivalent to that of a wide resection. Compared with other techniques, cryosurgery with composite fixation not only preserves joint function but also significantly decreases the rate of local tumor recurrence.[(6)]

The direct pour technique as described by **Abdelrahman et al**. stated that two freeze and thaw cycles were administered, each cycle lasting 1 to 2 min, and spontaneous thaw was allowed to occur for 3 to 5 min, resulted in tumor cell death less than or equal to 2 cm from the cavity margin (Fig.1).[(6)]

Before introduction of liquid nitrogen, bony perforations were identified and sealed using gel foam. The surrounding skin, soft tissues, and neurovascular bundles were protected and shielded using gelfoam and gauze soaked with saline to prevent extravasations of liquid nitrogen and thus protect the adjacent neurovascular structures and the skin. Large skin flaps were retracted to protect them from any possible spillage of the liquid nitrogen (Fig.2).[(6)]

Figure (1): Photo showing the use of liquid nitrogen by the direct pour technique.[(6)]

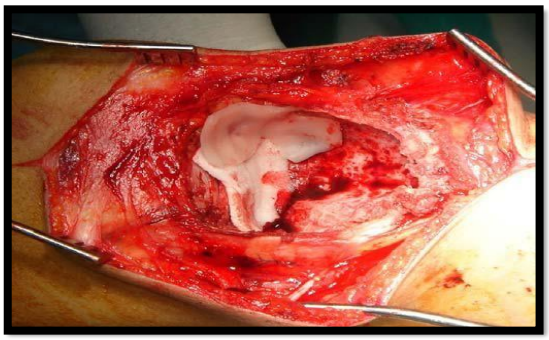

Figure (2): Photo showing that the bony perforations were identified and sealed using gelfoam.[(6)]

Recurrence rates between 11% and 36% were reported after cryotherapy where the lesion subsequently was filled with bone graft.[(7)]

Complications of cryosurgery:

1. Wound infections:

Cryosurgery results in a supplementary amount of tissue necrosis Furthermore, most surgeons are filling the defect with a “dead” homologous bone graft and sometimes an osteosynthesis is added. All these factors are strong mediators for developing a bacterial infection.[(8)]

2. Venous gas embolism:

Since boiling point of LN is -195°C, nitrogen gas-bubbles are rapidly produced at room temperature. So there is the hazard of intravascular introduction of gas-bubbles, especially when pressure is allowed to develop. Gas emboli in the vascular circulation can cause serious hemodynamic complications.[(8)]

3. Fractures:

Postoperative fracture is the most common and serious complication associated with cryosurgery. Fracture is an inherent risk after reconstruction of

any large bone defect and especially after cryosurgery near a weight-bearing joint.

After cryosurgery, bone necrosis and disruption of osteoid extend the period through which reossification occurs and delay bone healing. Vigorous freezing increases the likelihood of cure at the cost of higher rate of pathologic fractures, whereas inadequate freezing of bone surrounding the tumor may predispose to local recurrence.[6]

4. Degenerative osteoarthritis:

Damage of the articular surface, either by the tumor itself (intraarticular fracture) or by the treatment (intralesional excision, cryosurgery) may be anticipated.[8]

5. Damage to nerves:

Nerve palsy is a complication of cryosurgery, which was recognized at the very early beginning of the introduction of cryosurgery for bone tumors.[8]

Phenol:

Phenol causes protein coagulation, damages DNA and causes cell necrosis. Compared to liquid nitrogen, phenol has limited penetration into bone of <1–1.5mm.[4]

Phenol has been shown to kill GCT neoplastic cells when placed in contact of 80% solution in 6 min) [9]. **Agarwal et al.** first showed that application of phenol to tumor cavity lowered the recurrence rate from 29.1% to 9.7% for benign tumors.[4]

There has been no consensus as to the concentration of phenol used; some using 5% poured into cavity while others used 90%solution painted with an applicator. Phenol is a caustic chemical which needs to be handled with care. It can cause severe damage to normal tissues on contact. Even dilute solutions cause severe burns if exposure is prolonged. Inhalation by operating theater personnel can cause irritation to respiratory mucous membranes and can cause systemic toxicity if chronic. Phenol can be absorbed from cancellous bone or exposed soft tissues if used for irrigation in the tumor cavity and can cause systemic toxicity resulting in damage to kidneys, heart, liver, and the nervous system. Phenol is inflammable and electrocautery is to be used with caution in its presence. The potential for skin damage is increased when used with hydrogen peroxide.[4]

Lackman et al. reported a local recurrence rate of 6.3% in their series of 63 patients and recommend the use of 90% phenol applied for 5 min along with burring and cementing in GCTs.[10] **Saizet al.** used 12.5% solution in glycerol painted on the bone cavity surface and reported local recurrence of 12.5%.[11]

Hydrogen peroxide:

Nicholson et al. demonstrated that hydrogen peroxide (H_2O_2) in small concentrations causes' instant, substantial microscopically visible damage to the neoplastic cells of GCT.[12] **Balke et al.** concluded from their series that results with H_2O_2 lavage are comparable to that obtained with phenol. They could not demonstrate the beneficial effect of peroxide when used with high-speed burr and cement packing. Weighing all the evidence, hydrogen peroxide is safer than phenol and can be used in small concentrations to avoid damage to osteoblasts and soft tissues.[13] The usual recommended concentration is 6% or 20 volumes (Fig. 3). It is recommended that one thoroughly wash out the cavity after peroxide treatment, particularly when bone grafting is done as hydrogen peroxide also kills the osteoblast cells.[12]

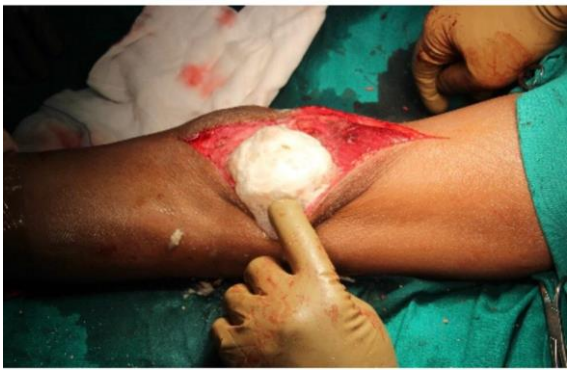

Figure (3): Photo showing hydrogen peroxide used as a chemical adjuvant with the characteristic bubbling.[12]

Argon Plasma Therapy:

The argon plasma cautery is a machine which uses argon gas to generate a coagulative beam like a flame which causes non-contact coagulative necrosis of the tissues. It has been used for endoscopic control of gastrointestinal bleeding and for controlling the bleed from the liver surface in hepatic injuries and surgery. This beam causes instant desiccation, coagulation, and cauterization of tissue. Since the coagulative beam is generated by a hand-heldpiece, it is easy to control and direct the flame (Fig.4) and therefore safer than methods such as cryotherapy and phenol. The cauterized area turns black (Fig.5) aiding the complete cauterization of the cavity surface under visual control. Lewis et al. reported a local recurrence rate of 10% in their series of 37 cases which is similar to that with other adjuvants. More importantly, no complications attributable to this technique were seen.[14]

Benevenia et al. [14] demonstrated equivalence between phenol and argon plasma cauterization in terms of local control. The shortcomings of this method are that amount of treatment depends on the power setting and exposure time. The depth of penetration and long term effects on bone strength and articular cartilage are still not known.[4]

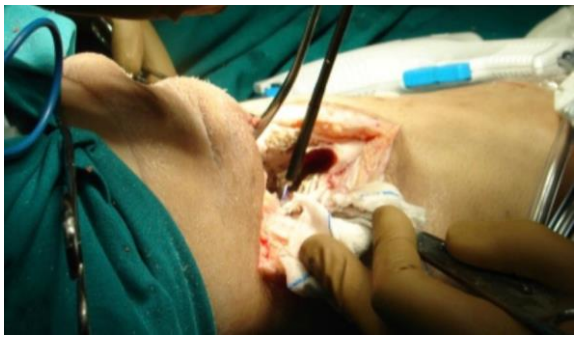

Figure (4): Picture showing the argon plasma cautery being used to cauterize the cavity after curettage of a proximal tibia giant-cell tumor. The argon plasma flame generated by the handpiece is visible.[14]

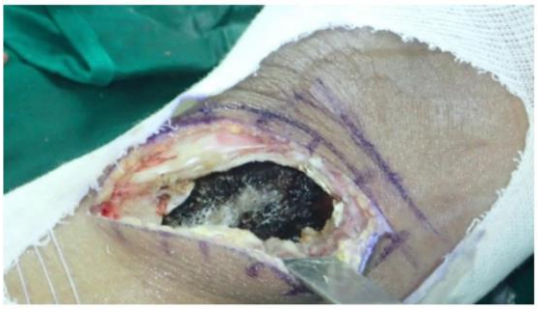

Figure (5): Cauterized walls after use of the argon plasma cautery in the proximal tibia after giant-cell tumor curettage. The blackening seen is useful as a guide to ensure that the entire surface is cauterized.[4]

Simple curettage

Historically simple curettage of giant cell tumor of long bones was associated with rate of local recurrence between 27 and 55% with or without bone graft. These led many surgeons to adopt wide excision as the treatment of choice and rate of local control increased to more than 90 percent. However, the functional results were not as good as when the joint had been preserved.[15]

So when developing a treatment protocol for giant cell tumor of bone, a surgeon must decide whether to perform an intralesional excision or en bloc resection, whether to use adjuvant therapy to eradicate residual microscopic disease and what material to be used to fill the resultant defect in the bone.[16]

The high risk of recurrence after bone grafting led to the technique of intralesional curettage followed by packing of the defect with methyl methacrylate cement. The higher the temperature and longer the time, the stronger the hyper thermic effect.[17]

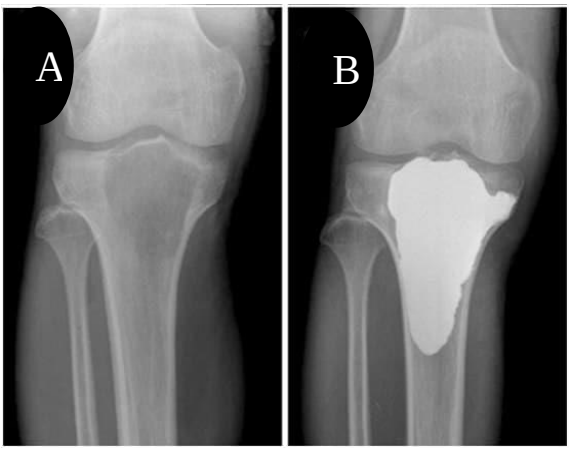

Figure (6): (A) Preoperative x-ray shows a giant cell tumor in proximal end of the tibia. (B) X-ray shows the tumor after treatment with curettage and packing with bone cement. [18]

Extended curettage:

Extended curettage was advocated when at least 2mm of subarticular bone was free of the tumor with no soft tissue spillage as assessed on a recent MRI.[19]

During curettage, an osseous window is osteotomized in the cortex, the size of which depends on the tumor size; in general, it should be of adequate size for optimal curettage. Through this window, the surgeon should have full visibility of the tumor cavity, in order to curette the tumor entirely, without risking an iatrogenic fracture**.** Curettes of different sizes are used to remove as much of the lesion as possible and supplemented by high-speed burring of cavity. Phenol-induced osteonecrosis is limited to a depth of 1.5 mm, thereby reducing the risk of fracture, but has a rate of recurrence of approximately 20–30%. Liquid nitrogen produces osteonecrosis of the tumoral bed, which is 1–2mm deep; three cycles of rapid freezing (−50°C) and slow thawing (20°C) are usually needed to increase margins up to 2cm that is comparable with marginal resection.[20]

Filling the cavity with PMMA, hypothetically lowers recurrence risk, due to cement's hyperthermic properties. Heat created during cement polymerization can sterilize the tumor wall (3–5 mm deep) and augment stability.[21]

However, the role of PMMA for tumor necrosis has not been validated; certainly, PMMA provides immediate mechanical support, early mobilization and facilitates early detection of local recurrences.[1]

2. Resection and Reconstruction

En-bloc resection with a wide margin is required for local control of aggressive or recurrent giant cell tumors that erodes through the cortex into the soft tissue or is associated with a pathological fracture. However if an essential bone and neighboring joint are involved a major reconstruction is required with subsequent functional loss.[22] The reconstructive options include:

A) Custom endo-prosthetic replacement

Endoprosthetic reconstruction is a highly successful and durable method for the restoration of skeletal integrity and joint function. Use of a cemented stem provides immediate fixation, which allows for early mobilization and rehabilitation. Extensive experience in joint replacement has led to the development of materials suited for long-term prosthetic survival; at the same time, advances in the use of local rotational flaps have improved joint stability and simultaneously reduced the risk of infection. Since the mid-1980s custom-manufactured endoprostheses have been replaced by modular systems with standard instrumentation that vastly expands the reconstruction options.

Possible disadvantages are infection, loosening of the prosthesis, breakage of the prosthesis, lack of restoring the active joint motion (due to the inability to effectively re-attach the tendons and ligaments to the corresponding tendon stumps), dislocation of the prosthesis (due to extensive resection and lack of muscle attachment).[22]

The three stages of a limb-sparing procedure are tumor resection; skeletal reconstruction; and soft-tissue coverage and muscle transfers to restore function.[22]

Guidelines for skeletal reconstruction:

1. Endoprosthetic selection and implantation:

Following resection of a segment of bone, the specimen is carefully measured in order to select the best-fitting prosthetic components. Trial components are provided to enable a rapid comparison with the specimen, as well as to perform trial reductions prior to selection and assembly of the final prosthesis. The selection of the stem diameter is dependent upon the anatomy of the canal, which is sequentially reamed in order to accommodate the largest-diameter stem possible.[22]

2. Preparation of the adjacent joint by anatomic site:

The adjacent joint surface must be prepared to accept the endoprosthesis prior to assembly of the final component. The preparation process varies with the anatomic location:

A-Distal femur:

The femoral condyles are resurfaced using a technique similar to that used for a total knee replacement. The femoral canal is opened with a reamer to allow for insertion of an intramedullary guide. A distal femoral cut is performed to remove 8 mm of the condyles. Anterior and posterior chamfers are created with an oscillating saw or a high-speed burr to accommodate the standard-sized femoral component. After trial reduction this component is cemented into place using third-generation cement techniques.[22]

B-Proximal tibia:

The top 1cm of the tibial plateau is removed with an oscillating saw (a neutral cut without posterior slope) and saved for the extracortical onlay bone graft. Trial components are used to select the largest tibial component that fits on the proximal tibia with minimal medial–lateral overlap. Overlap must be avoided to facilitate the soft-tissue closure over the prosthesis. The tibial canal is prepared with a guide placed over the plateau to create a distal bone plug and proximal box to accommodate the stemmed polyethylene tibial bearing component. Following trial reduction of the selected components the tibial insert is cemented into place using third-generation cement techniques. (Fig.7) [22]

Guidelines for soft-tissue reconstruction:

The basic goals of the soft-tissue reconstruction are to provide adequate coverage of the prosthesis and restore muscle power and joint stability. A variety of local and regional muscular rotation flaps must be performed to maximize functional outcome and ensure adequate coverage of the prosthesis. Meticulous attention to handling the soft tissues and preserving the regional blood supply is essential at this step. Complete muscular coverage of the prosthesis minimizes the risk of periprosthetic infection related to superficial wound breakdown (marginal necrosis) that occasionally occurs following the creation of large flaps during an oncologic resection. Muscle transfers also improve stability of the reconstructed joint and restore useful joint function.

Aggressive mobilization of the remaining muscles crossing a given joint, as well as specific muscular rotational flaps, permits the surgeon to achieve all of these goals without creating free flaps. To provide functional power to the limb, soft tissue must be attached to the prosthesis. This entails attaching the major tendons to the prosthesis and creating a musculotendinous cuff around the body of the prosthesis. In addition, restoration of proper limb length helps ensure stability of the reconstruction. As noted previously, the prosthesis has a beaded porous coating at sites of important tissue attachments. The porosity allows both for bone and fibrous ingrowth: a new tendon–bone junction is created by adding bone graft between the porous surface of the prosthesis and the tendon which is held firm to the prosthesis with Dacron sutures. Common muscle transfers include the following:

-Knee: 25% of distal femoral replacements and all proximal tibial replacements require rotation of a gastrocnemius muscle (typically the medial head) to repair the soft-tissue defect following resection of a tumor around the knee. This local flap is incorporated into the reconstruction of the patellar tendon in patients undergoing proximal tibial replacements.[22]

A **B**

Figure (7): (A) The first proximal tibial component with porous coating along the entire body to permit soft-tissue attachments of the adjacent muscles as well as attachments of the patellar extensor mechanism. (B) Plain lateral radiograph of a similar prosthesis. [22]

b) Arthrodesis:

In early days of limb salvage, resection arthrodesis was the main method of reconstruction. Its primary advantages were to restore skeletal stability and produce a long-term, durable reconstruction. No attempt was made to restore motion at the resected joint, however, and many patients expressed dissatisfaction with their loss of function. Today, the use of rotational flaps can restore function when muscle is lost. As a result, resection arthrodesis is rarely recommended as the primary method of reconstruction today.[22]

Complications of giant cell tumor

1- Local Recurrence in GCT:

Local recurrences appear to be related to the surgical margin and are clinically characterized by pain and radiologically by progressive lysis of the bone graft or the adjacent cancellous bone.

Following curettage and cementation an osteolytic zone caused by thermal injury measuring 2 mm surrounds the cement. This radiolucent zone is bordered by a thin outer sclerotic rim for about six months. Lysis or failed development of the sclerotic rim between the cement and cancellous bone may suggest recurrence.[23]

Soft tissue recurrence is visible on plain radiographs because of its tendency towards peripheral calcification. A study by **Akhane et al** suggests that total serum acid phosphatase (TACP) could be used as a tumor marker for monitoring response to the treatment of GCT. Total serum acid phosphatase level in GCT patients correlated with tumor size. The high preoperative TACP values in GCT patients became normalized after surgery but reappeared in three of five patients with local recurrence.[24]

Though the majority of recurrences usually occur within the first two years, late recurrences are known and long-term surveillance is recommended in these patients**.** Even though the increasing grade from I to III is not a reflection of the biologic aggressiveness of the tumor, various authors have documented an increased rate of recurrence in Grade III lesions. This could be due to the difficulty in achieving complete clearance once the tumor has breached its normal anatomic boundaries and extended into soft tissue.[25]

Steyern et al. retrospectively studied (n = 137) local recurrence of GCT in long bones following treatment with curettage and cementing. They concluded that local recurrence after curettage and cementing in long bones can generally be successfully treated with further curettage and cementing, with only a minor risk `of increased morbidity.[26]

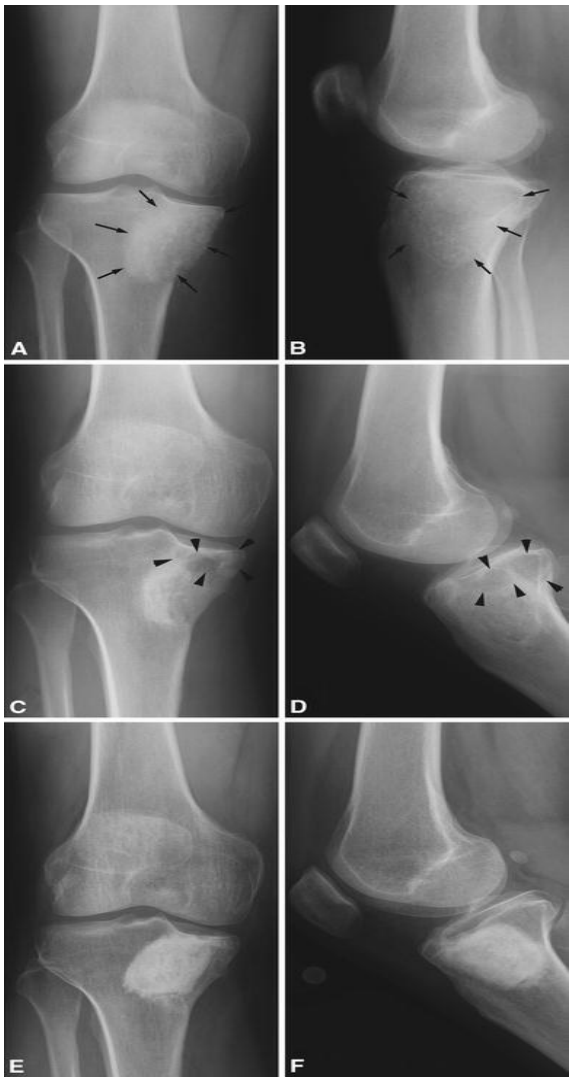

Figure (8): (A) AP and (B) lateral radiographs show the radiographic situation after curettage and bone grafting of the primary tumor (former tumor cavity filled with bone graft is marked by arrows). (C) AP and (D) lateral radiographs show regions of osteolysis of the proximal tibia that indicate local recurrence (osteolytic lesions marked by arrowheads). (E) AP and (F) lateral radiographs show the tibia after treatment of the recurrence with intralesional curettage, PMMA void filling.[27]

2-Pathologic fractures:

Pathologic fracture is a relatively infrequent complication of giant cell tumor of bone, being a purely osteolytic primary skeletal lesion.[28]

It is occurs at first presentation in 9% to 30% of all patients with giant cell tumor of bone.

It can occur through lytic lesions of long bones and may be the reason for initial evaluation and pain, especially in weight-bearing bones. Because the tumor occurs in the epiphyseal region of long bones, the fracture line may extend through the articular surface of the joint. In such cases, management and reconstruction may be particularly difficult because of the shell-like appearance of bone surrounding the tumor. If the joint is congruent, it is sometimes appropriate to wait for the fracture to heal before performing surgery.

Curettage with adjuvants and en bloc resection are both considered treatment options for giant cell tumor of bone with a pathologic fracture. The use of curettage with adjuvants reportedly is associated with relatively high local recurrence rates (12%–34%).[29]

3-Metastasis in Giant Cell Tumors:

Although GCT is classified as a benign lesion, few patients develop progressive lung metastases with poor outcomes. Metastases after GCT of bone are rare, occurring in only 3% of patients the behavior of pulmonary metastases is unpredictable. There is an increased risk of pulmonary metastasis of GCT of bone in patients who are younger, present with Enneking stage-III disease, develop local recurrence, and/or present with axial disease.[16]

The metastatic lesions are histologically identical to the primary lesions. The mean interval between the onset of the tumor and the detection of lung metastases is about 18 to 24 months. The natural history of metastatic lesions is unpredictable. Complete excision of metastases has been very successful with good long-term survival, but those with inoperable disease may die from metastases. Hence, metastatic lesions should be resected if possible. Radiation and chemotherapy have enjoyed limited success. Steroids have been successfully used in the control of unrespectable metastases. Metastatic disease in giant cell tumor does not carry the same poor prognosis as malignant tumors. Therapy should be direct at achieving adequate local control and if possible complete excision of the metastatic lesions.[30]

4-Postoperative infection:

Occurs in 2%–25% of patients treated with curettage and cement placement. The prevalence of infection is probably increased with more extensive surgery involving en bloc resection and placement of an endoprosthesis; however, the data on this point are currently limited.[31]

5-Malignant transformation:

The malignant transformation of giant cell tumor (GCT) of bone is a relatively rare phenomenon. The diagnosis in most cases is unexpected and is usually discovered incidentally upon pathological analysis of the resected specimen.[32]

Malignant GCTs are divided into primary and secondary forms. Primary malignant GCTs are those with malignant sarcomatous components that are present de novo in conjunction with a giant cell tumor of bone and are exceedingly rare.

The term 'dedifferentiated GCT' is also used to describe these tumors.

Secondary malignant GCTs are high-grade sarcomas occurring at the sites of previously treated GCT of bone. Most malignancies in GCTs fall into this latter category and occur several years after radiation therapy or, much less frequently, after surgery. [33]

There are no recognized radiological appearances that can be used to reliably differentiate benign from malignant GCT.[32]

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