INTRODUCTION

Giant cell tumors (GCT) are benign to aggressive lesions which are frequently encountered in orthopaedic practice. Last two decades have envisaged technical advances in surgical management of GCTs with introduction of new techniques and improvising of the existing techniques. There is a universal consensus in favour of extended curettage with or without adjuvants even in recurrent cases. Current evidence suggests that cavities <60 cm$^3$ do not require filling and those with <5 mm of subchondral bone are well managed with sandwich technique. Elucidation of pathway of pathogenesis of GCT and involvement of OPG-RANK-RANKL pathway has led to the introduction of newer molecular therapies of GCT in the form of denusomab and interferons. Bisphosphonates inhibit the osteoclastic activity and they have been found to have a beneficial effect on tumour size and recurrence rate. Tumour cells express calcitonin receptors, with this idea calcitonin is being tried though it is yet to taste any success. Radiotherapy should be used if it is anticipated that surgery would result in significant functional morbidity and at sites where recurrence rate is high and there is potential for significant morbidity. This editorial deals with the current padigrams in management of GCT.

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et al. gave the Radiographic staging of the tumour[4]. The lesion may expand or even break through the cortex though intra articular extension is rare as subchondral bone usually remains intact. MRI is used to reveal the extent of the tumour within the bone and beyond. The lesion is usually dark on T1 and bright on T2 weighted images. In 20% of the cases the fluid-fluid levels, typical of Aneurysmal Bone Cyst can be appreciated[1-3].

Technical advances in surgical management with introduction of new techniques and improvising of the existing techniques along with advances in radiotherapy and introduction of molecular therapies mandated a review. The current article, deals with the current padigrams in management of GCT.

**SURGERY**

Excision or en bloc resection of the tumor was proposed as the first line treatment for these tumors due to failure of histological findings to prognosticate its recurrence, which was as high as 60% after intra lesional curettage and autologous bone grafting[8]. However, wide resection has been found to be associated with higher morbidity and complications as compared to intralesional curettage[6,7]. The only drawback of intralesional curettage over en block resection was a higher recurrence rate resulting from inadequate clearance of tumour cells[2,3]. With the advent of extended curettage, using high speed burrs, the recurrence rate has fallen dramatically. High speed bur aids in getting ample clearance of the tumour by entering the small areas more efficiently. It also induces thermal necrosis of the cells at the margin of the cavity, by the heat energy so produced as a result of friction to the high speed. The use of high speed bur is accepted worldwide by all surgeons and it has shown to decrease recurrence after curettage to 25%[1,2,8]. To further decrease the incidence of recurrence a number of adjuvant therapies have been proposed which include hydrogen peroxide, alcohol, phenol, liquid nitrogen and zinc chloride and argon laser beam coagulation[6,9]. Gortzak et al compared the cytotoxic effect of sterile water, 95% ethanol, 5% phenol, 3% hydrogen peroxide and 50% zinc chloride on GCT monolayer tumour cultures established from six patients. The treated samples showed significant reductions in DNA content and metabolic activity 24 hours after treatment which was sustained for up to 120 hours for all except water which showed an initial decline in DNA content but the cells survived and proliferated, thus suggesting that adjuvants aid in attaining local tumour control[9,10]. However, the controversy remains as others have revealed no significant difference in the recurrence rate with or without adjuvants[10].

In the current scenario, the target is to achieve meticulous local clearance of the tumour with or without adjuvants and preserve the joint whenever possible[1-3]. Successful management of recurrence with further curettage, questions the appropriateness of an extensive surgery to obtain wide margins[1,2,8,10]. However, the treatment of GCT cannot be generalized, and needs to be tailored according to the site, size, and nature of the lesion[1,2,8,10]. It has been reported in the literature that majority of the benign defects of bone coalesce with curettage without supplementation (Figure 1). In their series of 146 patients (47% of which were GCTs) followed for 18 months, Hirn et al identified that curettage alone in cysts of <60 cm³ (about 5 cm in diameter) yielded satisfactory results, and lesions greater than this size were treated with curettage and bone grafting[11]. However, lesions in which more than 2/3 of the cortex of the bone is destroyed in a single view, prophylactic fixation is advised[9].

Morselized bone allograft, allows presence in abundance when filling large cavities and there is no donor site morbidity, but it carries with itself the risk of transmission of infection and has issues with availability. Bone substitutes have been shown to restore the bone stock adequately, but are quite expensive particularly so when used to fill large defects[1,2,3,12,14,19]. Bone graft harvested at the time of surgery is extensively used for filling bone cavities resulting after curettage. It has best osteoconductive, osteoinductive and osteogenic properties. It contains viable osteogenic cells, bone matrix proteins and supports bone growth but is associated with donor site morbidity[1-3,12,14,19].

Use of cement is in vogue these days as it acts both as a adjuvant and as a filler of void after curettage. Poly methylmeth acrylate induces thermal necrosis at the bone cement interface and its monomer induces hypoxia in the adjacent cells causing direct cell death[13]. A recurrence rate <25% with cement as against >50% with other fillers highlights its effectiveness as an adjuvant[11,16,17]. Its advantages over bone grafting include immediate structural support, early ambulation and easier detection of recurrence[1,2,3,14,18,19]. Cement also is used as a carrier for other adjuvant materials. A recent in vitro study examining elution of chemotherapy from cement in the treatment of GCT showed a future for using cement as a structural delivery device for biologics[20,21]. Progressive lysis of more than 5 mm at cement bone interface, or peripheral calcification around a soft tissue mass of uniform density are suggestive of recurrence[18,19,19].

There are varied views about tolerance of cement close to the joint
surface, while some reports suggest that its subchondral presence does not incite any troubles\cite{8,16,17,22}, there are others suggesting that it can induce heat necrosis a few millimeters to the adjacent articular cartilage and the long term presence of cement in a weight bearing subchondral location can induce degenerative changes in the articular surface\cite{23,24}. Also there is threat to articular cartilage during removal of bone cement, if any recurrence is spotted. Gaston et al have reported that use of cement is associated with a higher risk of subsequent joint replacement\cite{25}.

In Giant cell tumours abutting the joint margin (<5 mm subchondral bone) sandwich technique has been found to give good results (Figure 2). In it bone graft is packed adjacent to the subarticular surface, for a thickness of 5 to 8 mm and a layer of gel foam is placed over it, to avoid cement spillage into the subchondral space and allow hemostasis. The remaining cavity is than filled with bone cement. Bone graft protects articular cartilage from the cytotoxic effect of bone cement and restores bone stock thereby improving future options. The short-term follow-up patients in our study suggested that sandwich technique after an extended curettage leads to good knee function with minimum complications and can survive without fractures or articular collapse. In case of recurrence, during removal of the cement, the incorporated subchondral bone prevents damage to the articular cartilage and also makes up for subsequent joint reconstruction, if required\cite{24,26}.

Joint salvage however is not always feasible and it becomes necessary to resect the tumour en bloc sometimes\cite{5}. Resection of GCT in so called expandable bones like distal end of ulna, proximal end of fibula and iliac wing is usually not followed by reconstruction. However even such sites need precise management to minimize co-morbidities. For example resection of proximal fibula, can hamper the knee stability which can be restituted by reconstruction of the

Figure 2: A: Sandwich technique being performed for a Giant cell tumour of the tibia. To begin with de roofing of the lesion is done. The window should be as large as the cavity to prevent any remnant tumour cells under the overhanging shelves. B: It should than be cleaned using various straight and angled curretts. C: Extended curettage using high speed burr has been universally accepted and its use has shown to decrease recurrence rate. D: This is how the cavity looks after extended curettage. E: Bone graft is packed adjacent to the subarticular surface, for a thickness of 5 to 8 mm and a layer of gel foam is placed over it, to avoid cement spillage into the subchondral space and allow hemostasis. F: The remaining cavity is than filled with bone cement.
Bisphosphonates inhibit the osteoclastic activity, with Nisisho et al. of neurological complications, including loss of bowel and bladder to inadequate clearance increased risk of recurrence. Also there is high risk of recurrence due to blood loss, potential damage to nerve roots, and higher recurrence rate and is often fatal. Curettage for sacral GCT is challenging due to blood loss, potential damage to nerve roots, and increased risk of recurrence. Also there is high risk of recurrence due to inadequate clearance. En bloc excision has a high incidence of neurological complications, including loss of bowel and bladder control and impotence in men. Selective arterial embolization (RSAE) of the tumor has been shown to devascularize tumors, reduce their size, cause calcification of their margins and alleviate pain. Use of adjuvants like bisphosphonates, denosumab and Interferon alpha have been found to be effective tools in its management. Conservative surgery (intralesional curettage or partial excision) aided by effective intraoperative hemorrhage control in patients with giant cell tumors of the sacrum is advocated. Although there have been reports on multimodality treatment of Sacral GCTs (resection, controlled cryosurgery, lumbopelvic reconstruction using allografts), we need further studies to gather enough evidence to support this treatment.

Molecular Therapy

Bisphosphonates

Bisphosphonates can be administered both systemically (oral or parenteral) and locally.

Systemic: Bisphosphonates inhibit the osteoclastic activity, with this idea they were tested in patients with Giant cell tumours and were found to have a beneficial effect on tumour size and recurrence rate, besides it’s bisphosphonates are recognised to have an analgesic effect on bone tumours. In 25 cases of GCTs treated with bisphosphonates, most of which were inoperable primary sacral and pelvic GCTs, Balke et al found that after commencing oral or intravenous bisphosphonates the progression of the lesions halted and some even showed radiological evidence of bone formation. Treatment also resulted in control of cases of persistently recurrent GCT, also it was noted that lung nodules of GCT did not increase in size and no further nodules developed in the course of bisphosphonate treatment.

Locally: Nisisho et al infiltrated the tumour lesion with 4 mg of zoledronic acid. Histopathological examination of the curettage after two months, revealed massive tumor cell death in the lesion in which both stromal cells and osteoclast-like giant cells were necrotic. Following local infiltration, the giant cell lesions shrank in size. It is suggested that their use in Grade III lesions can avoid a potential en bloc resection, although there is not enough evidence at present to support this statement.

Interferon alpha

Interferon alpha is a angiogenesis inhibitor and has been successfully used to treat primary giant cell tumor of long bones and facial bones. In chemotherapy refractory giant-cell tumours, treatment with interferon alpha 2a in increasing dosage from 4×10^6 IU (three times a week) to 9×10^6 IU (three times a week) has been reported to stabilise the disease and significant decrease of pulmonary metastases after 12 months of treatment. Interferon alfa-2b at a dose of 3×10^6 IU administered subcutaneously daily has been used with successfully as ar stand-alone treatment for unresectable, recurrent, and metastatic giant cell tumor originating from the spine. A pegylated formulation of interferon which is comparable biologically to the nonpegylated form and has a longer plasma half-life is administered once a week. Although rare, it is urged to have caution while initiating treatment with interferons it as it has been reported to cause drug-induced lupus erythematosus and pancreatitis.

Denosumab

As a novel way to reduce osteoclastic activity and bone resorption. It was thought to interrupt the RANK-RANKL interaction essential for osteoclastogenesis. Denosumab is a monoclonal antibody, an inhibitor of RANKL, which was initially launched for post
menopausal osteoporosis, and is now being evaluated for giant cell tumours. In a phase II trial by Branstetter et al, twenty adult patients with recurrent or unrespectable giant-cell tumor of the bone were administered subcutaneous denosumab 120 mg every four weeks (with additional doses on days 8 and 15). After treatment, all 20 of the patients had a decrease in giant cells of 90 percent or greater, an indicator of a reduction of tumor burden. In addition, results indicated that 65 percent of the patients had new bone growth in areas where the RANK ligand had previously caused bone destruction[46].

Calcitonin
As giant cell tumors express calcitonin receptors, there have been recent studies to evaluate the effect of calcitonin after curettage in GCTs. Nouri et al retrospectively reviewed 25 patients with giant cell tumor of the appendicular skeleton followed for 68 months after curettage and calcitonin administration and concluded that the use of calcitonin as adjuvant is not effective in preventing recurrence in GCTs[47].

RADIATION
Since its first application for GCT in 1923, there have been several reports of development of post-radiation sarcoma. These days radiotherapy is reserved for inaccessible sites and for aggressive, multiply recurrent tumors and even here newer molecular adjunct therapies have superseeded its place. For GCT of the spine except sacrum excision as per Weinstein-Boriani-Biagini grading system along with stabilization of the spine and adjuvant irradiation (45 Gy in 4.5 weeks), is advocated on the assumption that tumour debris may still be present. The high rate of malignant transformation during the era of orthovoltage radiation can be brought down with the advent of newer techniques and megavoltage radiation[48-50]. In a retrospective review of 21 localized giant cell tumors of the bone treated with radiotherapy, and followed for a mean of 15.4 years (2 to 35 years), Malone et al concluded that radiotherapy in modest doses (35 Gy in 15 fractions or equivalent) is a safe and effective option for primary and recurrent giant cell tumors of the bone. They suggested that radiotherapy should be used if it is anticipated that surgery would result in significant functional morbidity and at sites where recurrence rate is high and there is potential for significant morbidity from tumor relapse or subsequent surgery[51].

EMBOLIZATION
Interest in arterial embolization of sacral and pelvic tumors followed its success in resolution of pain and tumor shrinkage. Repeated serial arterial embolization (SAE) of the tumor may have to be performed if excessive blood loss is anticipated during resection of a GCT, a technique has been shown to prevent the progression of the mets and even promote healing in some cases. Target is to achieve adequate local control and if possible complete excision of the metastatic lesions, or else administration of suitable adjuvant molecular therapy[52-54].

GCT arising in setting of Pagets disease
A GCT rarely occurs with Page’s disease of Bone (PDB). The characteristics of GCT arising in PDB are typically different in 3 ways from the conventional GCTs, viz tendency to involve cranio facial bones, unlike long bones, it presents itself in a polyostotic or metachronous form unlike a solitary lesion, and as PDB is seen in elderly, they too affect elderly cohort. Bisphosphonates, which are currently the first line of drug for treatment of PDB, are useful in managing GCTs as well. Radiotherapy and steroids have been used with varied success in the treatment of these lesions and surgical resection is reserved for lesions not responding to these measures[55,56].

CONCLUSION
The last two decades have envisaged a large number of molecular therapies being introduced for GCTs, however, the target remains the same viz adequate clearance with minimal morbidity. The current concensus is that extended curettage be the initial treatment in all cases, except those where extent of the disease mandates resection to ensure adequate disease clearance. Cavities >60 cm³ do not require filling and those with < 5 mm of subchondral bone are well managed with sandwich technique. Pathogenesis of GCT has been studied in detail and elucidation of RANK-RANKL pathway has led to the introduction of newer molecular therapies of GCT in the form of denosumab and interferons. Bisphosphonates inhibit the osteoclastic activity and they have been found to have a beneficial effect on tumour size and recurrence rate. SAE of sacral and pelvic tumours be performed if excessive blood loss is anticipated during resection of a GCT Use of radiotherapy is restricted to sites where recurrence rate is high and surgery is expected to cause significant functional morbidity.

CONFLICT OF INTERESTS
There are no conflicts of interest with regard to the present study.

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