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Title: Denosumab As Adjuvant Treatment For Giant Cell Tumor Of Bone - Risks And Benefits For The Oncologic Surgeon

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BACKGROUND
Giant-cell tumor of bone (GCTB) is a locally aggressive, benign osteolytic tumor in which bone destruction is mediated by RANK ligand (RANKL). The RANKL inhibitor denosumab is being investigated for treatment of GTCB but the available data in the literature remains sparse and controversial. Especially, the proposed indication for denosumab ranges from neo-adjuvant treatment facilitating surgery to maintenance treatment after surgery or stand-alone treatment..

QUESTIONS/PURPOSES
This study analyzes the results of combining denosumab with surgical treatment. The study questions are as folloes: Does neo-adjuvant denosumab influence the surgical indication and technique? What is the local recurrence rate after surgical and adjuvant denosumab treatment? What are the relevant histologic changes under denosumab?

PATIENTS AND METHODS
A total of 91 patients were treated surgically for GCTB between 2010 and 2014 in one institution. But only the 25 patients (13 male; 12 female) who additionally received denosumab were included in this study. The mean age was 35 years (Range:15-72). The lesion was most frequently localized in the lower extremity (n=19;76%) followed by the upper extremity (n=4;16%) and the pelvis (n=2;8%). 12 patients (48%) received denosumab as a neo-adjuvant and adjuvant treatment, whereas in 6 patients (24%) the denosumab treatment was applied only before the surgery and in 7 patients (28%) only after the surgery. The preoperative dosage was 120mg weekly for 3 weeks and then monthly for 3 to 6 months. Postoperatively the treatment regimen was 120mg monthly for 6 months. The surgical treatment of the GCTB was achieved in 19 cases (76%) with curettage, in 5 cases (20%) with a bone resection (2 proximal fibula, 1 proximal tibia, 1 distal femur, 1 proximal radius) and in 1 case (45) with a soft tissue excision. Every patient underwent a preoperative biopsy. Later, tissue was harvested from the lesion intraoperative and compared histologically with the biopsy material.

RESULTS
After a mean follow up of 21 months (Range:9-40) no adverse effects of the denosumab treatment was observed. 4 patients (16%) showed no response to the drug treatment. In the remaining 21 patients (84%) a surgical “downstaging” was achieved: either the resection (14%) or curettage (30%) was significantly facilitated, or a previously planned resection was abandoned and changed in curettage (40%). One proven recurrence occurred in the patella, which was treated with a second curettage. Another suspicious lesion was found in the distal humerus but which remains stable without further surgery. The histologic examination of the surgical specimen revealed a lower proliferative index as well as a lower microvascular density after the denosumab treatment (see figure 1). The giant cells disappeared almost completely but the stromal cells persisted, which represent the true neoplastic cells. Although they are fewer and less proliferating, they are still alive and likely able to reactivate after the end of therapy. After complete curettage a peripheral rim of new- formed bone is present with multiple lacunae inside where tumor cells remain (“honey comb”).

CONCLUSION

Denosumab seems to be an important help to the oncologic surgeon by reconstituting a peripheral rim, reducing intraoperative bleeding and switching the stage from aggressive to active or latent disease. All these factors lead to a surgical "downstaging" facilitating the procedure. But as tumor cells remain in the new-formed bone the surgical technique of curettage has to be changed from gentle to more aggressive using high-speed burr and local adjuvant treatments such as cryotherapy.

FIGURES

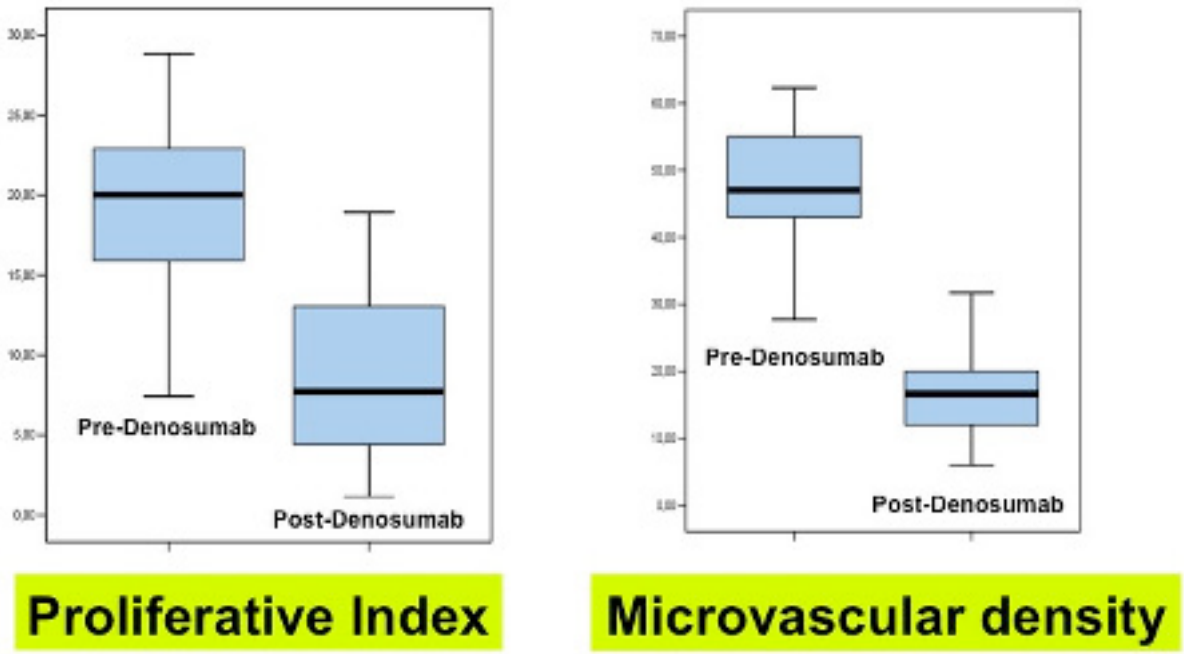

Figure 1: Histologic changes comparing preoperative biopsy and intraoperative specimen.