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The Clinical, Radiological and Pathological Outcomes Following Treatment of Primary GCTOB with Denosumab

Treatment of Primary GCTOB with Denosumab

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Abstract

Background: Giant cell tumour of bone (GCTOB) is a relatively uncommon, benign, but locally aggressive neoplasm. Denosumab is a fully human monoclonal antibody with inhibitory effects on Receptor Activator of Nuclear Factor Kappa-B Ligand (RANKL) that has shown early promise as a possible treatment adjuvant for GCTB. However, much is still unknown about its current indications, long term effects, the potential risk for rapid relapse and its involvement in sarcomatous transformation.

Methods: We analysed the outcomes of 154 patients with GCTOB. We assessed clinical outcomes via local recurrence free-survival, metastatic free-survival and sarcomatous transformation between those treated without Denosumab and those with neo-adjuvant Denosumab. Our radiological and pathological outcomes where assessed through independent specialist reviews.

Results: Four patients (19.0%) of the neo-adjuvant group had local recurrence of disease versus 16 patients (12.0%) in the surgery alone group, this results in a 3.62 times increased likelihood of developing local recurrence (p=0.030). The median time to local recurrence was shorter for the neoadjuvant group (421.5 days versus 788.5 days) (p=0.01). There was no difference between Denosumab and the surgery groups in terms of metastatic disease (p=0.45). Two patients in our cohort with GCTOB developed sarcomatous transformation, both were treated with Denosumab.

Conclusion: Our use of Denosumab tended to be for those patients who had surgically difficult tumours to halt the progression and allow easier resections. Of concern we noted a trend toward increasing recurrence rates with the potential risk for rapid relapse. Furthermore, 2 cases experienced sarcomatous transformation which is a growing area of concern within the literature.

Keywords:

Orthopaedic Surgery

Surgical Oncology

Introduction

GCTOBs represent 3-5% of all primary bone tumours and 20% of benign bone tumours, typically occurring between 20 and 40 years of age, with a predilection for juxta-articular locations (1-3). Without intervention, GCTOB can expand to obliterate bone, invade into surrounding soft tissue, compromise adjacent structures and rarely metastasise (4, 6). Primary management of GCTOB is surgical. Curettage of the tumour, with chemical cauterisation is the most common form of treatment, with the remaining cavity being filled with either cement or bone graft (7). En-bloc resection, total joint replacement and amputation are less commonly utilised surgical options, reserved for those cases in which joint preservation may not be possible (5).

Systemic therapies are not usually considered in the management of GCTOB given its benign nature. Recently however, Denosumab has emerged as a novel option in the treatment of GCTOB (8-10). Denosumab is a humanised monoclonal antibody that inhibits receptor activator of nuclear factor-kB ligand (RANKL) and thus moderates RANK activation, a key pathway in osteoclast mediated bone resorption (11). Several studies have demonstrated the effectiveness of Denosumab (8, 12-14). However, much is still unknown about its

current indications, long term effects and the potential risk for rapid relapse or the occurrence of sarcomatous transformation (5). Herein we report on 154 cases of GCTOB and the clinical, pathological and radiological outcomes following the use of Denosumab.

Patient and Methods

Data Collection and Ethics

We retrospectively reviewed prospectively collected data on 154 cases of primary GCTOB retrieved from an institutional musculoskeletal tumour data registry spanning the last 20 years. The project complies with the principles of the National Statement on the Ethical Conduct of Human Research (NHMRC; 2007) and received institutional review board approval (Approval number QA 078 / 18).

Patient Demographics

A total of 154 were treated for primary GCTOB over the time period assessed. Of the 154 cases; 133 were treated with surgery alone while 21 received neoadjuvant Denosumab followed by surgery **(Table 1)**.

Surgical Treatment

All cases in this study underwent surgery. Surgeries were categorised into three main groups; 1. Curettage (with cementation +/- internal fixation), 2. Resection (with reconstruction using cement, bone graft, structural allograft or prosthetic replacement), or 3. Amputation. In all curettage operations, high sped burring and phenol/alcohol solution were used as routine.

Denosumab Treatment Protocol

The treatment regimen for our patient cohort was 120mg of subcutaneous Denosumab on days 1, 8 and 15 of the first month, followed by 120mg monthly for 3-6 months thereafter. The most commonly

reported side-effect for all patients was limb pain in the days following injection. No patients ceased therapy earlier than required and no cases of osteonecrosis of the jaw were encountered. The interval of follow-up for all patients was 3 months after commencing Denosumab treatment.

Pathology

All cases underwent histological diagnosis after CT guided core needle biopsy. Histopathological diagnosis was made using standard haematoxylin and eosin (H&E) stain, with three levels examined for each section submitted. Immunohistochemistry, with the use of the macrophage marker CD68, was incorporated into the diagnostic process where there was diagnostic dilemma. The same process was utilised for the surgical specimens which were sent fresh following resection.

Radiology

All of patients underwent baseline orthogonal radiographs, Computerised Tomography (CT) and Positron Emission Tomography (PET) scanning. Following 3 months of Denosumab therapy repeat PET and CT scans were performed. Magnetic Resonance Imaging (MRI) was utilised more variably depending on clinical appropriateness (n=14). All cases were discussed at a weekly sarcoma multi-disciplinary meeting.

Statistical Analysis

We assessed clinical outcomes via local recurrence free-survival, metastatic free-survival and sarcomatous transformation between those treated without Denosumab and those with neo-adjuvant Denosumab. We performed Cox regression analysis to determine which variables were associated with local recurrence. The variables used in analysis included; age, gender, tumour size, tumour compartment, local recurrence or metastatic disease at diagnosis and surgical procedure performed. Whilst chi-square tests were

utilised to determine significant for the metastatic free survival and sarcomatous transformation outcomes. Statistical analysis was performed using Stata 14 software (StataCorp LP, Texas, USA).

Results

Clinical Outcomes

There was no statistical difference between the neo-adjuvant Denosumab group and those treated with surgery alone in terms of age at diagnosis, gender, size of tumour, site of tumour or procedure performed (**Table 1**). However, those in the Denosmab group were more likely to have soft tissue extension (**Table 1**). Four patients (19.0%) of the neo-adjuvant group had local recurrence of disease versus 16 patients (12.0%) in the surgery alone group, this results in a 3.62 times increased likelihood of developing local recurrence (p=0.030). Furthermore, the median time to local recurrence was shorter for the Denosumab group (421.5 days versus 788.5 days) (p=0.01). There was no difference between Denosumab and the surgery groups in terms of metastatic disease (p=0.45). However, there was a significant increase in the occurrence of sarcomatous transformation following treatment with Denosumab (9.5% vs 0%) (p=0.018).

Pathological Findings

Initial diagnosis of GCTOB was made after identification of a lesion composed of fibrous stroma with a proliferation of bland spindled fibroblastic cells arranged in a storiform pattern, as well as scattered larger multi-nucleated osteoclast-type giant cells. Following treatment with Denosumab, we noted a reduction in the presence of giant cells in all 20 samples assessed, with 10 of the 20 (50%) samples having no identifiable giant cells at all. There were several other prominent histological responses to Denosumab therapy, these being fibrosclerotic reaction and reactive new bone formation. The fibrosclerotic reaction we observed were areas of densely hyalinised collagen bundles interspersed with bland fibroblastic cells, and arranged in a

storiform pattern. Reactive new bone formation was noted in all our specimens, with varying zones of irregular osteoid trabeculae and osteoblast rimming, consistent with woven bone.

Radiological Findings

Baseline radiographs obtained in the diagnosis of GCTOB demonstrated the characteristic "soap-bubble" appearance due to osteolysis and thin cortical bone in epiphyseal/metaphyseal regions. The radiological findings for 14 cases in which there was post Denosumab therapy CT, MRI and PET scanning available. In 7 cases (50%) there was a significant reduction in the size of the lesion by on average 20.3%. The other 7 cases didn't demonstrate any measurable or significant reduction in size of the lesion and no case had a significant increase in size. In addition, all of our cases also demonstrated varying degrees of increasing patchy internal ossification and increasing peripheral rim bone thickness following therapy.

Discussion

The aim of this study was to demonstrate the clinical, radiological and pathological outcomes following treatment of GCTOB with Denosumab. We observed no difference in patient demographics such as age, gender or site of tumour which was consistent with published literature (1). Of note, those who were treated with Denosumab did not have a greater size of tumour as would be anticipated. This may be explained by the size being measured at operation and therefore demonstrating the treatment effect in downgrading surgery in patients who had a large tumour (9, 10, 12, 14). The only significant difference noted was the tendency for those treated with Denosumab to have a significant soft tissue extension. This may be explained by a selection bias whereby the use of Denosumab within our cohort to help reduce the morbidity of these resections, which would be in keeping with its proven utility (15, 16).

Clinical Outcomes

Denosumab has been shown to be useful as a neo-adjuvant therapy as it reduces the size of the tumour, may potentially decrease the vascularity of the lesion and increases peripheral rim ossification thus, facilitating local joint preserving surgery (16-18). Previous studies have shown that treatment with Denosumab results in a peripheral zone of ossification, while making a stronger shell to curettage against, may harbour neoplastic cells which increase the rate of recurrence (16, 18, 19). This is consistent with our findings that treatment with neo- adjuvant Denosumab resulted in a 3.62 times higher incidence of local recurrence (p=0.030). In our univariate analysis, only the use of Denosumab was associated with an increased likelihood of developing recurrence. However, we did note that we used Denosumab for those tumours with soft tissue extension and therefore they were likely more difficult to resect, which may impact our results. We also demonstrated a tendency for rapid relapse which has been noted in previous studies that suggested that these recurrences tend to occur on cessation of therapy (5, 20, 21). However, we encountered these episodes of local recurrence even after definitive surgical therapy. Only four of the 154 cases (2.6%) had metastatic disease in keeping with the known low metastatic potential of GCTOB which has been described as between 1% and 3% (4). Denosumab in our study had no significant effect in altering the metastatic potential of GCTOB. However, due to the rarity of GCTOB metastasis this study lacked the statistical power to adequately assess this outcome. No patients in this study died as a result of their disease.

Pathological Outcomes

Our commonly observed histological responses included a significant reduction of the presence of giant cells with a varying degree of fibrosis, reactive bone formation and reactive stromal changes **(Figure 2).** Branstetter et al. and Roitman et al. both observed reduction of giant cells and mononuclear stromal cells with replacement by fibrous tissue and woven bone similar to our findings (10, 22). While Wojcik et al. noted the resemblance of Denosumab treated GCTOB to malignant GCTOB with the exceptions of exhibiting less atypia, less mitotic activity, and less permeative growth patterns (23). We further analysed the four cases of

local recurrence in those patients treated with Denosumab to identify any prominent features that may herald as markers for relapse. All cases demonstrated significant fibrosclerosis and reactive new bone formation consistent with Denosumab use. Two of the cases did show residual giant cells in their biopsy specimens, however this was also true for eight of the cases who did not develop local recurrence. This area remains largely unexplored within the literature and warrants further investigation.

Radiological Outcomes

Our common radiological responses included a reduction in size, varying degrees of increasing patchy internal ossification and increasing peripheral rim bone thickness (**Figure 1**). Reduction in size is an important response to consider as it forms the premise for the use of Denosumab (13). 50% of cases in our series underwent a reduction in size with the average reduction being by 20.3%. Some studies have achieved much higher rates of tumour reduction, with some demonstrating reduction in 100% of cases (13, 24, 25). However, we had similar results to Traub et al. who demonstrated a reduction in size in 36% of their patients treated (26). These discrepancies in findings could be explained by the application of Denosumab. In our series we utilised it in short duration prior to surgery, rather than as a definitive long-term treatment. It should be noted though that while we reported on a significant reduction on size radiologically, this may not truly represent a true reduction in size as the peripheral sclerotic rim, which is often excluded in measurements, may still harbour neoplastic cells. The internal irregular and peripheral rim ossification of GCTOB we observed has been shown repeatedly to be a key hallmark feature of radiological response to Denosumab (2, 13, 18, 26, 27). We also confirmed that functional imaging can measure the tumour response as we noted a marked reduction in FDG uptake in PET scanning. This response has been identified previously as an important measure in assessing tumour response (27, 28). As with the pathological outcomes in our study, we demonstrated that there are consistent radiological findings following the treatment of GCTOB with Denosumab, but there is little suggestion that they may be helpful as predictors for local recurrence.

Sarcomatous Transformation

Although rare, malignant transformation of GCTOB has been reported within the literature. In our study two patients experienced osteosarcomatous transformation and both had been treated with Denosumab. Aponte-Tiano et al. were the first to report on a case on sarcomatous transformation of young 20-year-old female with a recurrent GCTOB treated with Denosumab (29). Broehm et al. followed by highlighting two episodes of malignant sarcomatous transformation of GCTOB out of only six patients treated at their centre following treatment (30). In all of these reports, the patients had been receiving long courses of Denosumab (29, 30). Our two cases both received courses of pre-operative Denosumab for 3 months and developed rapid local recurrence within 6 months of their surgical resection, with the local recurrence proven to be osteosarcoma. Both cases initial biopsies were re-evaluated for potential misdiagnosis, however there was no evidence of sarcoma found. Despite this, there still may be sampling error involved in the initial sample. In their formative study, Chawla et al. noted 2 cases of sarcomatous transformation of which one was retrospectively suspected to be present at baseline and the other was thought to be a malignant transformation (9). Whilst they judged that none of these events were related, our study adds to the burgeoning call for further research into Denosumab induced osteosarcoma transformation.

Limitations of Study

The strength of this study lies within its high sample size relative to the previous literature and its ability to report on clinical, radiological and pathological outcomes. However, we do acknowledge this paper has some limitations. Firstly, our registry did not capture any patient-relevant outcomes such as pain, physical functioning or side effects of therapy. Secondly, despite our larger sample size than previously, we were still underpowered to appropriately investigate metastasis and the pathological/radiological predictors of local

recurrence. Finally, despite this being one of the larger reports within the literature of GCTOB treatment with Denosumab, we were underpowered to investigate our outcomes with multivariate analysis.

Conclusion

Similar to previous studies, our use of Denosumab tended to be for those patients who had recurrence and for those who had surgically difficult tumours to reduce the tumour burden and allow less morbid resections. While we demonstrated similar histopathological and radiological responses to Denosumab as previously reported, we were unable to identify any significant marker of successful response or predictor of recurrence. Of concern, we noted a trend toward increasing recurrence rates with the potential risk for rapid relapse following treatment with Denosumab. Whether this was due to retention of neoplastic cells within the new peripheral rim bone and consequently preventing a complete curettage warrants further investigation. Furthermore, the two cases of osteosarcomatous transformation in our study adds to the increasing concern regarding potential Denosumab propagated malignancy.

References

1. Thomas DM, Skubitz KM. Giant cell tumour of bone. Current opinion in oncology. 2009;21(4):338-44.
2. Hakozaki M, Tajino T, Yamada H, Hasegawa O, Tasaki K, Watanabe K, et al. Radiological and pathological characteristics of giant cell tumor of bone treated with denosumab. Diagnostic pathology. 2014;9:111.
3. Campanacci M, Baldini N, Boriani S, Sudanese A. Giant-cell tumor of bone. The Journal of bone and joint surgery American volume. 1987;69(1):106-14.
4. Szendroi M. Giant-cell tumour of bone. The Journal of bone and joint surgery British volume. 2004;86(1):5-12.
5. Thornley P, Habib A, Bozzo A, Evaniew N, Ghert M. The Role of Denosumab in the Modern Treatment of Giant Cell Tumor of Bone. JBJS reviews. 2017.
6. Luengo-Alonso G, Mellado-Romero M, Shemesh S, Ramos-Pascua L, Pretell-Mazzini J. Denosumab treatment for giant-cell tumor of bone: a systematic review of the literature. 2019.
7. Sobti A, Agrawal P, Agarwala S, Agarwal M. Giant Cell Tumor of Bone - An Overview. Archives of Bone and Joint Surgery. 2016;4(1):2-9.

8. Thomas D, Henshaw R, Skubitz K, Chawla S, Staddon A, Blay JY, et al. Denosumab in patients with giant-cell tumour of bone: an open-label, phase 2 study. The Lancet Oncology. 2010;11(3):275-80.
9. Chawla S, Henshaw R, Seeger L, Choy E, Blay JY, Ferrari S, et al. Safety and efficacy of denosumab for adults and skeletally mature adolescents with giant cell tumour of bone: interim analysis of an open-label, parallel-group, phase 2 study. The Lancet Oncology. 2013;14(9):901-8.
10. Branstetter DG, Nelson SD, Manivel JC, Blay JY, Chawla S, Thomas DM, et al. Denosumab induces tumor reduction and bone formation in patients with giant-cell tumor of bone. Clinical cancer research : an official journal of the American Association for Cancer Research. 2012;18(16):4415-24.
11. Thomas DM. RANKL, denosumab, and giant cell tumor of bone. Current opinion in oncology. 2012;24(4):397-403.
12. Jamshidi K, Gharehdaghi M, Hajialiloo SS, Mirkazemi M, Ghaffarzadehgan K, Izanloo A. Denosumab in Patients with Giant Cell Tumor and Its Recurrence: A Systematic Review. Archives of Bone and Joint Surgery. 2018;6(4):260-8.
13. Rutkowski P, Ferrari S, Grimer RJ, Stalley PD, Dijkstra SP, Pienkowski A, et al. Surgical downstaging in an open-label phase II trial of denosumab in patients with giant cell tumor of bone. Annals of surgical oncology. 2015;22(9):2860-8.
14. Ueda T, Morioka H, Nishida Y, Kakunaga S, Tsuchiya H, Matsumoto Y, et al. Objective tumor response to denosumab in patients with giant cell tumor of bone: a multicenter phase II trial. Annals of oncology : official journal of the European Society for Medical Oncology. 2015;26(10):2149-54.
15. Agarwal A, Larsen BT, Buadu LD, Dunn J, Crawford R, Daniel J, et al. Denosumab chemotherapy for recurrent giant-cell tumor of bone: a case report of neoadjuvant use enabling complete surgical resection. Case reports in oncological medicine. 2013;2013:496351.
16. Gaston CL, Grimer RJ. Current status and unanswered questions on the use of Denosumab in giant cell tumor of bone. 2016;6(1):15.
17. Watanabe N, Matsumoto S, Shimoji T, Ae K, Tanizawa T, Gokita T, et al. Early evaluation of the therapeutic effect of denosumab on tartrate-resistant acid phosphatase 5b expression in a giant cell tumor of bone: a case report. BMC research notes. 2014;7:608.
18. Müller DA, Beltrami G, Scoccianti G, Campanacci DA, Franchi A, Capanna R. Risks and benefits of combining denosumab and surgery in giant cell tumor of bone-a case series. World journal of surgical oncology. 2016;14(1):281.
19. Errani C, Tsukamoto S, Leone G, Righi A, Akahane M, Tanaka Y, et al. Denosumab May Increase the Risk of Local Recurrence in Patients with Giant-Cell Tumor of Bone Treated with Curettage. The Journal of bone and joint surgery American volume. 2018;100(6):496-504.
20. Matcuk GR, Jr., Patel DB, Schein AJ, White EA, Menendez LR. Giant cell tumor: rapid recurrence after cessation of long-term denosumab therapy. Skeletal radiology. 2015;44(7):1027-31.
21. Brodowicz T, Hemetsberger M, Windhager R. Denosumab for the treatment of giant cell tumor of the bone. Future oncology (London, England). 2015;11(13):1881-94.
22. Roitman PD, Jauk F, Farfalli GL, Albergo JI, Aponte-Tinao LA. Denosumab-treated giant cell tumor of bone. Its histologic spectrum and potential diagnostic pitfalls. Human pathology. 2017;63:89-97.
23. Wojcik J, Rosenberg AE, Bredella MA, Choy E, Hornicek FJ, Nielsen GP, et al. Denosumab-treated Giant Cell Tumor of Bone Exhibits Morphologic Overlap With Malignant Giant Cell Tumor of Bone. The American journal of surgical pathology. 2016;40(1):72-80.
24. Goldschlager T, Dea N, Boyd M, Reynolds J, Patel S, Rhines LD, et al. Giant cell tumors of the spine: has denosumab changed the treatment paradigm? Journal of neurosurgery Spine. 2015;22(5):526-33.
25. Dubory A, Missenard G, Domont J, Court C. Interest of Denosumab for the Treatment of Giant-cells Tumors and Aneurysmal Bone Cysts of the Spine. About Nine Cases. Spine. 2016;41(11):E654-60.

26. Traub F, Singh J, Dickson BC, Leung S, Mohankumar R, Blackstein ME, et al. Efficacy of denosumab in joint preservation for patients with giant cell tumour of the bone. European journal of cancer (Oxford, England : 1990). 2016;59:1-12.
27. Palmerini E, Chawla NS, Ferrari S, Sudan M, Picci P, Marchesi E, et al. Denosumab in advanced/unresectable giant-cell tumour of bone (GCTB): For how long? European journal of cancer (Oxford, England : 1990). 2017;76:118-24.
28. Boye K, Jebsen NL, Zaikova O, Knobel H, Londalen AM, Trovik CS, et al. Denosumab in patients with giant-cell tumor of bone in Norway: results from a nationwide cohort. Acta oncologica (Stockholm, Sweden). 2017;56(3):479-83.
29. Aponte-Tinao LA, Piuzzi NS, Roitman P, Farfalli GL. A High-grade Sarcoma Arising in a Patient With Recurrent Benign Giant Cell Tumor of the Proximal Tibia While Receiving Treatment With Denosumab. Clinical orthopaedics and related research. 2015;473(9):3050-5.
30. Broehm CJ, Garbrecht EL, Wood J, Bocklage T. Two Cases of Sarcoma Arising in Giant Cell Tumor of Bone Treated with Denosumab. Case reports in medicine. 2015;2015:767198.

Figure 1: Imaging Demonstrating Denosumab Effect

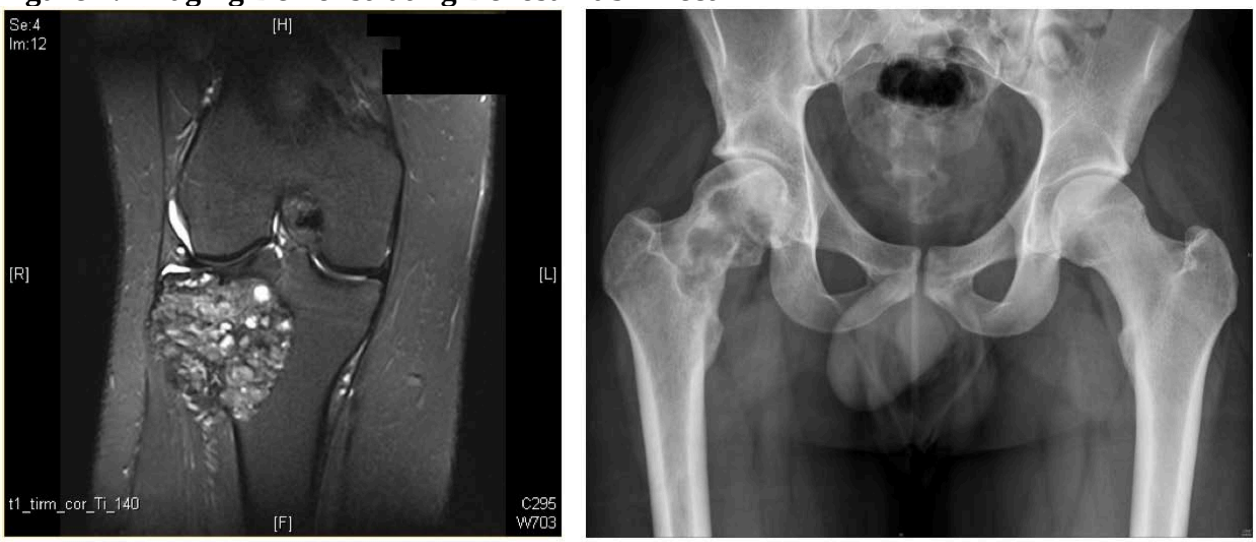

Figure 2: Surgical Specimen Demonstrating the Denosumab Effect

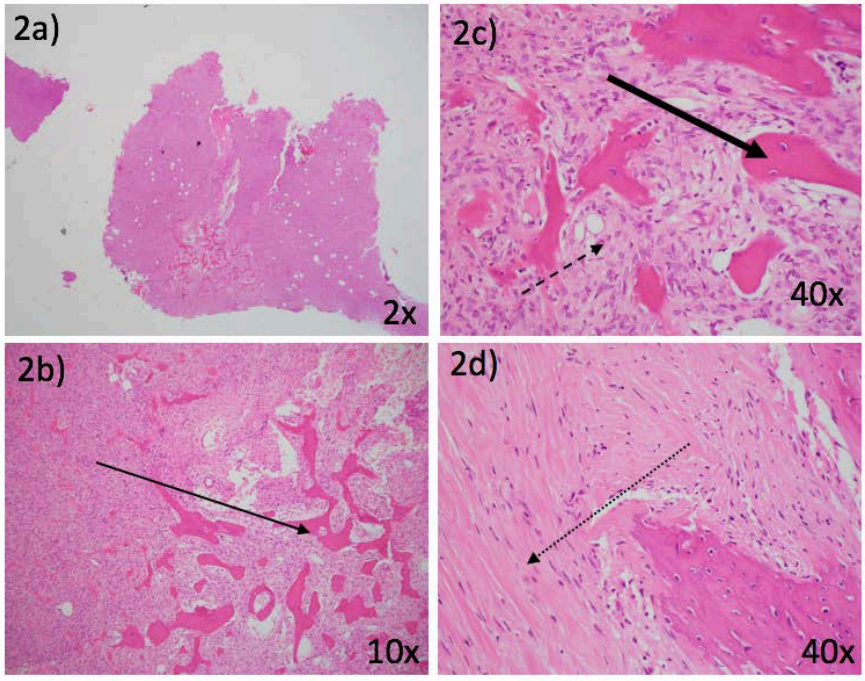

Table 1 Patient Demographics

Variable	No Denosumab N (%) or mean (+/- SD)	Denosumab N (%) or mean (+/- SD)	P Value
Number	133	21	
Age at Diagnosis	36.84 (22.72 – 50.96)	32.81 (21.59– 44.03)	.254
Male	74 (55.6%)	11 (52.4%)	.921
Tumour Size	5.23 (2.43 – 8.03)	6.76 (2.81 – 10.71)	.178
Tumour Compartment			
• **Intraosseous**	112 (84.2%)	12 (57.1%)	**.001**
• **Extraosseous**	21 (15.8%)	9 (43.9%)	
Tumour Location			
• **Lower limb**	100 (75.2%)	18 (85.7%)	.120
• **Upper limb**	32 (24.1%)	2 (9.5%)	
• **Axial**	1 (0.8%)	1 (4.8%)	
Procedure			
1. **Curettage**	91 (68.4%)	11 (52.4%)	.053
2. **Resection**	40 (30.1%)	9 (42.9%)	
3. **Amputation**	2 (1.5%)	1 (4.8%)	

Table 2: Patients with local recurrence

Variable	Surgery Alone N (%) or Mean (+/- SD)	Denosumab + Surgery N (%) Or Mean (+/- SD)
Number	16 (12.0%)	4 (19.0%)
Age at Diagnosis	37.1 (30.6 - 43.7)	27.75 (20.1 – 35.4)
Tumour Size	4.3cm (3.1 - 5.4)	8.0cm (3.7 – 12.3)
Tumour Location		
• Lower limb	9	2
• Upper limb	7	1
• Axial	0	1
Procedure		
1. Curettage	13	3
2. Resection	3	1
3. Amputation	0	0
Time of Recurrence*	788.5 days (272.5 – 1,304.5)	421.5 days (276.9 – 566.1)

*Median time to recurrence reported