Risk of Malignant or Sarcomatous Transformation of Giant Cell Tumors of Bone is Eight Times Lower with Megavoltage Radiation Therapy Compared with Orthovoltage Therapy
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INTRODUCTION:
Giant cell tumor of bone is a benign yet aggressive lesion that is primarily treated surgically when accessible. Radiation therapy has been typically reserved for surgically unresectable giant cell tumors and is often cited as associated with a high rate of malignant or sarcomatous transformation, limiting its routine use. External beam radiation therapy has undergone a dramatic change in technology over the past few decades. The era of treating giant cell tumors with orthovoltage radiation, which utilizes x-ray beams with an energy of 150-500 kV, has been replaced by megavoltage radiation, which utilizes linear accelerators, Van de Graaf generators, or cobalt teletherapy units to produce x rays and gamma rays with an average energy above 1 million electron volts. Previous research has suggested that the incidence of secondary malignant neoplasms may be higher following orthovoltage radiation compared with megavoltage radiation, however there have been no studies specifically addressing this question in giant cell tumors of bone. The purpose of this study was therefore to evaluate whether there is a difference in the rate of malignant or secondary transformation of giant cell tumors of bone following radiation therapy with orthovoltage compared with megavoltage radiation. Our hypothesis was that modern radiation techniques are associated with a low rate of malignant transformation when treating giant cell tumor of bone.

METHODS:
We performed a systematic review utilizing the PRISMA method on PubMed, Embase, Cochrane, Web of Science, and Scopus. Inclusion criteria were manuscripts in the English language reporting patients whose treatment included radiation therapy for benign giant cell tumors from 1900 to December 2019. Studies which do not report the details of radiation therapy modality, or where the results are not reported separately for orthovoltage and megavoltage patients, were excluded. We also included patients from our own institution in the analysis. Data was collected on the rate of malignant or sarcomatous transformation, time to transformation, and rate of recurrence. Statistical analysis was performed using SPSS. Odds ratio (OR) was used to compare the odds of transformation and recurrence between orthovoltage and megavoltage groups, and independent sample T-test was used to compare the mean time to transformation between the groups. Significance was set at 0.05.

RESULTS:
A total of 22 studies were included in the analysis in addition to 6 patients from our institution. Five studies reported orthovoltage treatment only, 14 reported megavoltage only, and 3 reported both. A total of 168 giant cell tumors underwent treatment which included orthovoltage radiation therapy, and a total of 393 underwent treatment which included megavoltage radiation therapy. The rate of malignant or sarcomatous transformation was 14.3% (n = 24) for tumors treated with orthovoltage radiation compared to 1.78% (n = 7) for tumors treated with megavoltage radiation (OR 8.0, 95% confidence interval 3.4 to 19.0, p<0.001). Mean time to transformation was 8.7 years for the orthovoltage group and 11.2 years for the megavoltage group (p = 0.28). The rate of recurrence was 37.7% (63/167) for the orthovoltage group compared with 16.8% (66/393) of the megavoltage group (OR 2.2, 95% confidence interval 1.5 to 3.3, p < 0.001).

DISCUSSION AND CONCLUSION:
Although the primary treatment modality for giant cell tumors of bone remains surgical, some tumors may benefit from radiation therapy in cases where surgery may involve significant morbidity or in the setting of local recurrence. The use of radiation therapy has likely been limited due to the historically unacceptable high rate of malignant transformation associated with its use. This study reports that the incidence of developing a malignancy following radiation therapy of benign giant cell tumor of bone is significantly decreased (8-fold) using current megavoltage radiation compared to older orthovoltage radiation techniques.

Clinical Significance: Radiation therapy for benign giant cell tumor of bone may have a role for inoperable or refractory disease. The concern of malignant transformation using modern day techniques, while not zero, is lower than historical series.