



The Effect of Denosumab and Risk Factors for Recurrence in Spinal Giant Cell Tumors: A Systematic Review and Meta-Analysis

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Purpose: Giant cell tumors (GCTs) are common benign primary bone tumors and are well known for their locally aggressive performance and tendency to recur. The purpose of this study was to analyze the effects of denosumab and risk factors for recurrent spinal GCTs.

Materials and Methods: We searched PubMed, EMBASE, Web of Science, and Cochrane Library databases to identify differences between individuals treated with and without denosumab and risk factors for spinal GCT recurrence. Patient data, including age, sex, tumor resection range, location, denosumab use, Campanacci grade, and radiotherapy, were documented. Comparable factors were evaluated using odds ratios (ORs) and weighted mean differences (WMDs) with 95% confidence intervals (CIs).

Results: Sixteen studies were included. The overall incidence of spinal GCT recurrence was 29%. Campanacci grade III tumors showed better recurrence outcomes than grades I and II (OR, 16.36; 95% CI, 4.19–63.93; $p < 0.001$). Gross total resection (OR, 0.09; 95% CI, 0.04–0.19; $p < 0.001$), radiotherapy (OR, 0.27; 95% CI, 0.11–0.65; $p = 0.004$), and the use of denosumab during subtotal resection (OR, 2.95; 95% CI, 1.07–8.17; $p = 0.04$) were important factors for reducing recurrence.

Conclusion: Clinicians must consider the effects of gross total resection, radiotherapy use, and denosumab use in cases of subtotal resection during spinal GCT treatment. So far, many researchers have used denosumab in spinal GCT, but none have clearly suggested an endpoint. Most studies, however, recommend using it for more than 6 months.

Key Words: Spinal giant cell tumor, denosumab, gross total resection, recurrence, radiotherapy

INTRODUCTION

Giant cell tumors (GCTs) are benign primary bone tumors and

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are well known for their locally aggressive performance and tendency to recur.¹ According to the World Health Organization, a GCT is a benign but locally invasive primary bone tumor, consisting of proliferated mononuclear (monocyte) cells, multinucleated osteoclast-like giant cells, and stromal spindle cells.² GCTs account for 4%–8% of all primary bone tumors.³ Lung metastases may develop and, in most cases, regress spontaneously.⁴

The incidence of GCTs in the spine is relatively rare, ranging from 1.4% to 9.4%.⁵ If it is technically feasible and a tumor-free margin can be achieved, en bloc resection should always be considered as the first option for mobile spinal GCT treatment to minimize local recurrence and improve survival.^{6,7} Recently, the long-term use of bisphosphonates and zoledronic acid has been thought to significantly reduce the recurrence rate of GCTs in the spine.^{8,9} A new interest in GCTs has begun in re-

sponse to a growing body of literature investigating the potential role of denosumab in addressing unresolved issues, such as the high recurrence rate of inaccessible GCT, as well as the morbidity and technical limitations of resection.¹⁰ More recent results confirm that denosumab is a novel treatment option for patients with GCTs.¹¹ To the best of our knowledge, no study has summarized the effect of denosumab and the recurrence of spinal GCTs. Through this systematic review and meta-analysis, we analyzed the effects of denosumab and risk factors for recurrence in spinal GCTs.

MATERIALS AND METHODS

Data sources and searches

We searched PubMed, EMBASE, Web of Science, and Cochrane Library databases to identify differences between individuals treated with and without denosumab and risk factors for the recurrence of spinal GCTs. We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The search terms included the following: “spinal giant cell tumor” OR “spinal GCT” OR “denosumab” OR “recurrence.” The publication language was limited to English, and only published articles were considered. Three authors independently screened the studies based on inclusion and exclusion criteria and collected data from eligible studies. We also investigated the reference lists of the selected studies, reviews, or comments to identify any other appropriate studies.

Inclusion and exclusion criteria

Population interventions, comparison results, study design methodology, and PRISMA guidelines were applied to assess study suitability.¹² The inclusion criteria for our meta-analysis were as follows: 1) the patients were diagnosed with spinal GCTs; 2) the follow-up period was longer than 1 year; 3) the spinal GCT patients were treated with or without denosumab; 4) clinical outcomes with patients who were treated with and without denosumab were compared; and 5) sufficient data (means±standard deviations of continuous variables and the numbers of count variables) were available. The exclusion criteria were 1) studies that did not compare cases treated with or without denosumab; 2) available data were not described; and 3) duplicate reports and review articles.

Data extraction

Data were extracted from qualified studies by three authors (SHN, DAS, and SHK) according to the inclusion and exclusion criteria. In cases of disagreement, a consensus was reached through discussion. The extracted data contained reports on study design, patient characteristics, sample size, detailed follow-up information, and outcomes. All significant data reported in each qualified study, including demographic factors, the range of tumor resection, location, the use of de-

nosumab, Campanacci grade, and radiotherapy, were collected and analyzed. En bloc surgical resection was regarded as gross total resection, and others were considered subtotal resection. Risk factors for recurrence and recurrence according to the use of denosumab were also analyzed.

Quality assessment

The Newcastle-Ottawa Quality Assessment Scale (NOQAS) was used to assess the quality of each included study, as most were not randomized comparative studies.⁷ The NOQAS includes three major assessment categories: selection, comparability, and exposure. A maximum of nine stars could be assigned to each study, with six or more stars in the final score indicative of high quality.

Statistical analysis

Review Manager Software (version 5.3; Cochrane Collaboration, Oxford, UK) was adopted for this meta-analysis. Funnel plots were displayed using Meta-Essentials software. The effective size of continuous data was determined using the weighted mean difference (WMD) and corresponding 95% confidence interval (CI). The effective size of categorical data was calculated using 95% CI corresponding to odds ratios (OR). Heterogeneity between studies was assessed using the I^2 index. In instances of significant heterogeneity between studies, the pooled effective size was calculated using a random effects model ($p < 0.05$, $I^2 > 50\%$). Otherwise, a fixed effects model was applied. Statistical significance was set at $p < 0.05$.

RESULTS

Studies included

A total of 780 studies was originally found in the PubMed (648), EMBASE (102), Web of Science (28), and Cochrane Library (2) databases. After excluding duplicate trials, 459 studies remained. After checking the title and abstract, 205 studies were deleted, and 82 studies were excluded based on the exclusion criteria. Eighteen studies were excluded due to insufficient data. Ultimately, 16 studies were included in the meta-analysis. Fig. 1 illustrates the process of document selection. The follow-up period for all studies was at least 12 months. The characteristics of this study are summarized in Table 1.

Quality assessment of the studies

Based on the NOQAS, 12 studies scored 8 points, and four studies scored 7 points (Table 2). Therefore, the quality of each study was relatively high.

Incidence of spinal GCT recurrence

A total of 294 patients was diagnosed with spinal GCTs. Based on the 14 studies, the overall incidence of spinal GCT recurrence was 29%. As presented in seven papers, the recurrence

of spinal GCTs developed after a mean time of 19.2 months after treatment.

Characteristics and risk factors of spinal GCT recurrence

The onset of spinal GCT was more common in the cervical, thoracic, and lumbar spine than in the sacrum (OR, 0.19; 95% CI, 0.05–0.70; $p=0.01$) (Fig. 2). As for grade according to tumor shape, Campanacci grade III showed better recurrence than grades I and II (OR, 16.36; 95% CI, 4.19–63.93; $p<0.001$) (Fig. 3). Gross total resection (OR, 0.09; 95% CI, 0.04–0.19; $p<0.001$), radiotherapy (OR, 0.27; 95% CI, 0.11–0.65; $p=0.004$), and the use of denosumab during subtotal resection (OR, 2.95; 95% CI, 1.07–8.17; $p=0.04$) were identified as important factors for reducing recurrence (Figs. 4–6). Age (WMD, 0.65; 95% CI, -0.2–1.51; $p=0.13$), sex (OR, 0.87; 95% CI, 0.44–1.70; $p=0.69$), and preoperative denosumab treatment (OR, 1.55; 95% CI, 0.59–4.05; $p=0.37$) did not differ significantly between the recurrence and non-recurrence groups. Table 3 depicts the number of studies reporting each risk factor and the results of the forest plot.

Publication bias

All funnel plots were symmetric, indicating the absence of significant publication bias among the studies. The Egger test results for each risk factor were gross total resection ($p=0.12$), radiotherapy ($p=0.249$), use of denosumab during subtotal resection ($p=0.836$), and location ($p=0.623$). These results show that there was no real evidence of publication bias in the dataset.

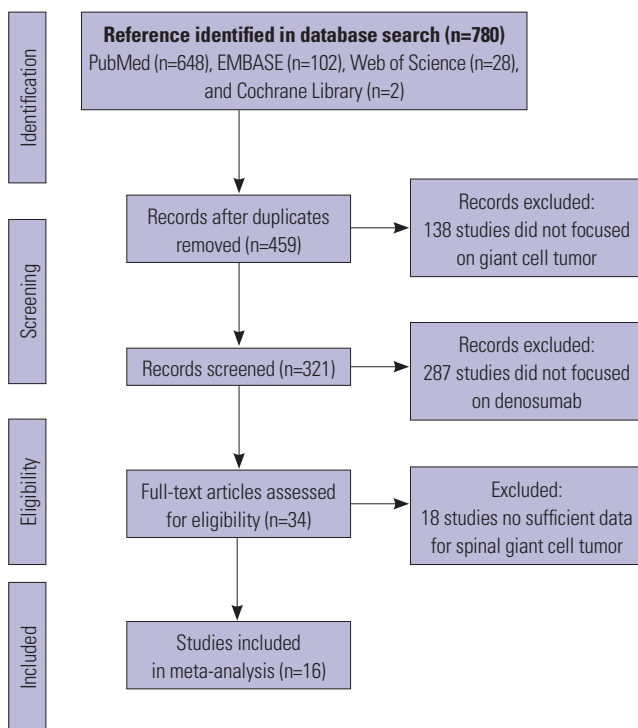


Fig. 1. Flow chart of the study selection process.

Table 1. Characteristics of Studies Included in the Meta-Analysis

Study	Year	Country	N	Study period	Gross total resection	Subtotal resection	Use of denosumab	Radiotherapy	Mean age (yrs)	Recurrence	F/U period (month)
Junming, et al. ²⁶	2008	China	21	1990–2003	14	7	No	Yes (n=18)	35.5	6	≥36
Martin, et al. ²⁵	2010	USA	23	ND	13	10	No	Yes (n=6)	35.2	6	≥24
Boriani, et al. ⁶	2012	Italy	49	1970–2005	13	36	No	No	30	11	≥19
Goldschlager, et al. ¹⁸	2015	USA	5	ND	2	3	Yes (n=5)	No	38.2	0	≥24
Chen, et al. ²²	2018	China	30	2014–2016	ND	ND	Yes (n=20)	No	34.7	6	≥24
Kim, et al. ³¹	2015	Korea	19	2000–2012	6	13	No	Yes (n=9)	31	7	≥18
Domovitev, et al. ³⁰	2016	USA	24	1973–2012	ND	ND	No	Yes (n=14)	31.8	8	≥24
Ouyang, et al. ²⁷	2017	China	94	1995–2014	43	30	No	No	33.4	27	≥24
Jamshidi, et al. ¹⁶	2017	Iran	19	1990–2014	3	16	No	No	29.47	8	≥25
Yang, et al. ²⁰	2018	China	16	2007–2014	ND	ND	Yes (n=6)	No	ND	4	≥12
Yokogawa, et al. ²⁸	2018	Japan	25	1994–2015	13	12	Yes (n=1)	No	34.2	2	≥24
Jia, et al. ¹⁴	2019	China	31	1998–2017	4	27	No	Yes (n=11)	15.9	12	≥24
Sambri, et al. ¹⁹	2020	Italy	26	2006–2016	3	8	Yes (n=26)	No	46	5	≥12
Lim, et al. ²³	2020	China	62	2011–2017	36	26	Yes (n=26)	No	ND	17	≥24
Wang, et al. ¹⁷	2020	China	15	2007–2018	1	14	Yes (n=4)	No	15.7	6	≥24
Tsukamoto, et al. ³²	2021	Japan	15	2005–2020	0	9	Yes (n=12)	No	35	4	≥25

N, number; F/U, follow up; ND, not described.

DISCUSSION

A spinal GCT is a locally invasive benign bone tumor that can appear anywhere along the spine. Although there have been several studies on spinal GCT treatment, treatment remains difficult. This meta-analysis was performed to evaluate the effect of denosumab and the risk factors for recurrence of spinal GCT.

Luksanapruksa, et al.¹³ reported that the incidence rate of GCTs was high in the sacrum and in patients aged 20–40 years

Table 2. Quality Assessment of Included Studies in the Meta-Analysis According to NOQAS

Study	Selection	Comparability	Exposure	Total score
Junming, et al. ²⁶	3	2	3	8
Martin, et al. ²⁵	3	2	3	8
Boriani, et al. ⁶	2	2	3	7
Goldschlager, et al. ¹⁸	3	2	3	8
Chen, et al. ²²	3	2	3	8
Kim, et al. ³¹	2	2	3	7
Domovitev, et al. ³⁰	3	2	3	8
Ouyang, et al. ²⁷	3	2	3	8
Jamshidi, et al. ¹⁶	3	2	3	8
Yang, et al. ²⁰	3	2	3	8
Yokogawa, et al. ²⁸	3	2	3	8
Jia, et al. ¹⁴	3	2	3	8
Sambri, et al. ¹⁹	2	2	3	7
Lim, et al. ²³	3	2	3	8
Wang, et al. ¹⁷	2	2	3	7
Tsukamoto, et al. ³²	3	2	3	8

NOQAS, Newcastle-Ottawa Quality Assessment Scale.

of age. Jia, et al.¹⁴ reported that the distribution of women in the study was 71.0%, which is within the reported range of 60%–82%. In our study, spinal GCTs were found more in the cervical, thoracic, and lumbar spine than in the sacrum, except for studies that analyzed GCTs only in the sacrum (OR, 0.19; 95% CI, 0.05–0.70; $p=0.01$). However, it was not statistically significant in the sensitivity test. Further studies with more data are needed in the future. According to 11 papers that reported low data, the age of onset was 29.7 ± 7.9 years old. The proportion of women diagnosed with spinal GCTs was 61%.

Through imaging of spinal GCTs, Campanacci grades can be classified according to their shape.¹⁵ Grade I tumors in the Campanacci system are the least common and describe latent or slow-growing tumors. Grade II tumors are not demarcated and are characterized by active lesions without sclerosis. Grade III tumors are bulky, bone-destroying, and display highly aggressive features, with tumors infiltrating the surrounding soft tissue. Recurrence by Campanacci grade was analyzed in three papers included in this study.^{14,16,17} As a result of the meta-analysis, Campanacci grade III was found to have a higher recurrence rate than grades I and II (OR, 16.36; 95% CI, 4.19–63.93; $p<0.001$). Campanacci grade III had a 16-fold higher OR of recurrence than grades I and II.

In 2015, Goldschlager, et al.¹⁸ published a study administering denosumab to treat spinal GCTs for the first time. It was reported that denosumab was used in five cases and that good results were obtained.¹⁸ Sambri, et al.¹⁹ reported that 92% (24/26) of the patients who received denosumab had an adequate clinical response with a significant reduction in pain level after an average of 6 weeks of treatment. In addition, they reported that 70% of patients (18/26) had a partial or good X-ray re-

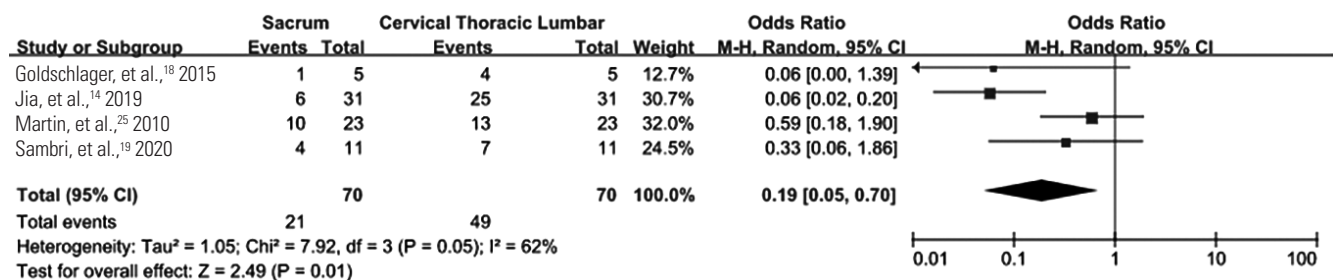


Fig. 2. Forest plot showing the relationship between spinal giant cell tumor and location. CI, confidence interval.

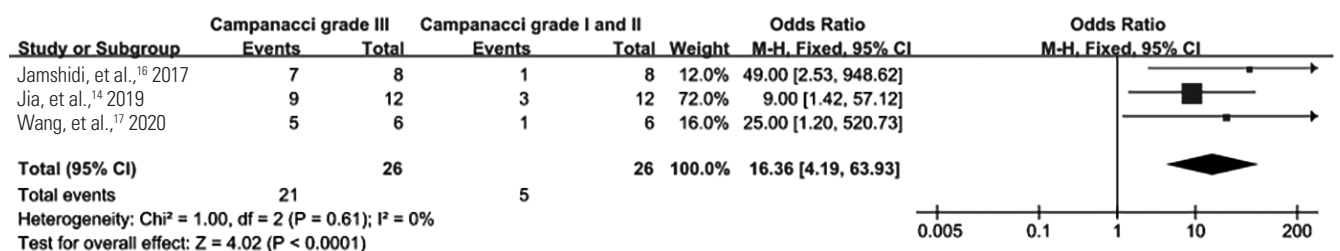


Fig. 3. Forest plot showing the relationship between Campanacci grade and spinal giant cell tumor recurrence. CI, confidence interval.

sponse after an average of 49 weeks of treatment. Boriani, et al.⁶ reported that denosumab ought to be considered an excellent treatment for spinal GCTs associated with poorly per-

formed or unacceptable pathological conditions or surgical loss of function. However, Yang, et al.²⁰ reported that administering denosumab before surgery increases sclerosis and bony

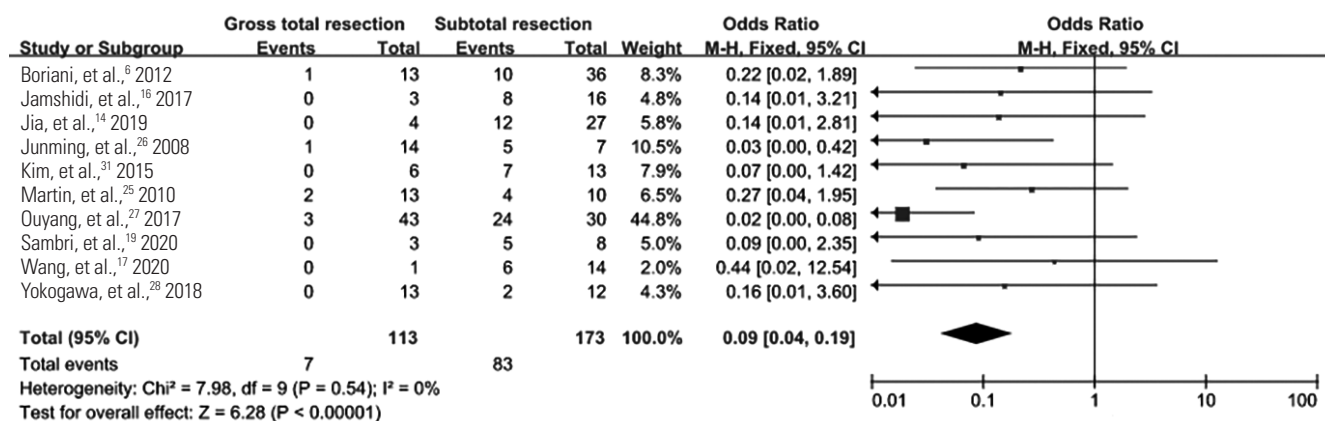


Fig. 4. Forest plot showing the relationship between range of resection and spinal giant cell tumor recurrence. CI, confidence interval.

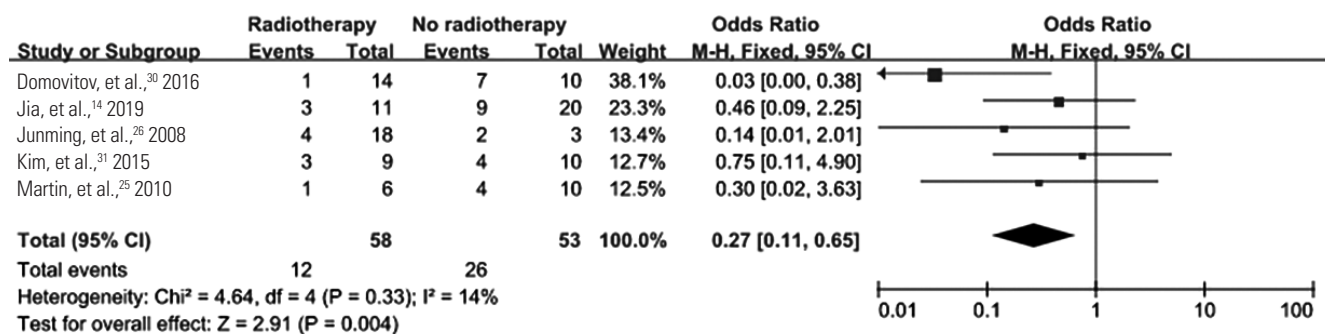


Fig. 5. Forest plot showing the relationship between radiotherapy and spinal giant cell tumor recurrence. CI, confidence interval.

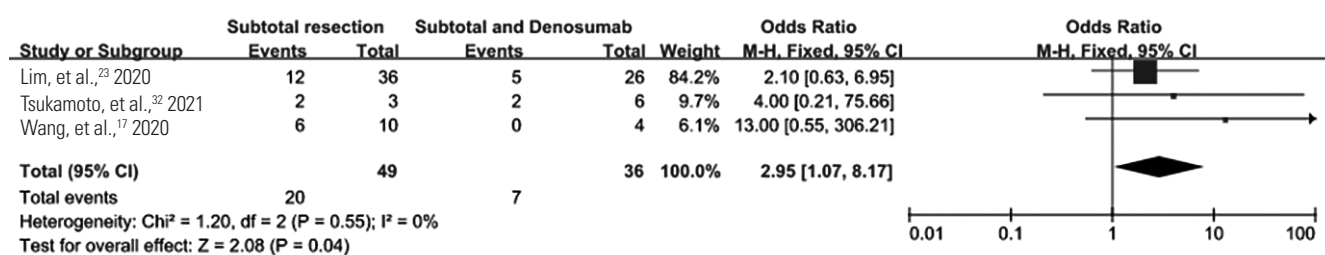


Fig. 6. Forest plot showing the relationship between denosumab during subtotal resection and spinal giant cell tumor recurrence. CI, confidence interval.

Table 3. Related Factors of Spinal Giant Cell Tumor Recurrence

Related factors	Number of study	Test of differences		Test of heterogeneity		Model
		WMD/OR (95% CI)	p value	I ² (%)	p value	
Age	9	0.65 [‡] (-0.20 to 1.51)	0.130	6	0.390	F
Sex	9	0.87 [‡] (0.44 to 1.70)	0.690	0	0.570	F
Location	4	0.19 [‡] (0.69 to 5.34)	0.010*	62	0.050	R
Campanacci grade	3	16.36 [‡] (4.19 to 63.93)	0.001*	0	0.610	F
Use of pre-operative denosumab	5	1.55 [‡] (0.59 to 4.05)	0.370	48	0.100	F
Radiotherapy	5	0.27 [‡] (0.11 to 0.65)	0.004*	14	0.330	F
Range of resection	10	0.09 [‡] (0.04 to 0.19)	0.001*	0	0.540	F
Use of denosumab when subtotal resection	3	2.95 [‡] (1.07 to 8.17)	0.040*	0	0.550	F

WMD, weighted mean difference; OR, odds ratio; CI, confidence interval.

*Statistically significant; [‡]Values are WMD; [‡]Values are OR.

separation, making it difficult to remove the tumor during surgery. Chen, et al.²¹ published a meta-analysis of 10 papers investigating the administration of denosumab before surgery. They reported that the administration of denosumab is associated with an increased risk of recurrence, but has proven effective in relieving pain and improving functional outcomes. Our study included five papers that described the use of denosumab before surgery and compared the recurrence rate. Although the results were not statistically significant, the use of denosumab before surgery did not decrease the recurrence rate.²² However, in the case of subtotal resection of the tumor, the recurrence rate was lower in the denosumab-treated group than in the non-denosumab-treated group²² (OR, 2.95; 95% CI, 1.07–8.17; $p=0.04$). During subtotal resection, the OR for recurrence in the group without denosumab was 2.95 times higher than that of the group that did receive denosumab. Goldschlager, et al.¹⁸ reported that there was no recurrence after using denosumab for an average of 6 months. Sambri, et al.¹⁹ used denosumab for an average of 12 months in 11 cases. Recurrence occurred in 5 cases, and an average of 12 months was used. There was no recurrence in 6 cases, but an average of 13 months was used. Chen, et al.²² reported that denosumab was used in a total of 20 cases. In 11 cases after 4 months of use, 3 cases recurred, and in the group after 12 months of use, there was no recurrence. In a review article published by Lukanapraksa, et al.,¹³ the use of denosumab for 6 months after surgery was recommended. So far, many papers have used denosumab in spinal GCT, but none has clearly suggested an optimal endpoint. Therefore, denosumab is recommended for 6 to 12 months after subtotal resection.^{13,23,24} In the case of gross total resection, the effect of denosumab could not be analyzed because there was no paper comparing treatment with and without denosumab during gross total resection.

Surgery is the treatment of choice for spinal GCTs. The goal of spinal GCT removal is to remove as many tumors as possible, decompress the affected nerves, and stabilize the spine.¹³ Complete resection of spinal GCTs with a disease-free margin has a lower recurrence rate and higher disease-free survival rate than intralesional resection.⁶ However, mass resection of the spine carries a serious risk of postoperative neurological defects, especially if performed in the cervical spine.²⁵ Therefore, the surgical treatment plan for a spinal GCT should weigh the neurological risk against the disadvantages of complete tumor resection. Junming, et al.²⁶ reported that the most aggressive approach provides the best chance of fully curing the disease. If gross total resection is not possible, subtotal resection is required.²⁶ Ouyang, et al.²⁷ reported that tumors located in the thoracolumbar (T2–L3) vertebrae and with few perivertebral types could be removed only through a posterior approach. In the cervical spine, the posterior structures, especially the transverse processes and the pedicle, were removed using the piecemeal technique to release the vertebral arteries and nerve roots. In our study, recurrence rates were com-

pared according to the extent of surgical resection in 10 studies. As a result of the meta-analysis, gross total resection had a lower recurrence rate than subtotal resection²⁸ (OR, 0.09; 95% CI, 0.04–0.19; $p<0.001$). The OR for recurrence of gross total resection was 0.09 times that of subtotal resection. Removal of the tumor with en bloc resection, if possible, appears to be a good way to lower recurrence rates.

Since a spinal GCT is moderately radiosensitive, post-incomplete resection radiation should be considered to increase local control and reduce recurrence rates.²⁹ In one study by Domovitev, et al.,³⁰ 14 patients received radiotherapy and 10 did not; of these patients, one patient who underwent radiotherapy with a median dose of 50 Gy (range: 30–66 Gy) and seven who did not experienced recurrence. Adaptations to radiotherapy include: 1) cases where it is difficult to achieve negative surgical resection ends with acceptable morbidity, 2) tumors with the longest dimension greater than 8.5 cm, and 3) cases of local recurrence. Moreover, Domovitev, et al.³⁰ reported that one patient experienced spontaneous malignant formation after radiotherapy. This is a complication that occurs after radiotherapy and should be considered in the future. The largest study of cervical spine GCTs recommends radiotherapy in cases of infeasible vertebral resection to reduce recurrence rates.²⁶ Junming, et al.²⁶ reported that local conventional radiotherapy was performed for 20 fractions in the range of 30–50 Gy for 4–6 weeks after surgery. In our study, six papers compared groups who received radiotherapy with those who did not.^{14,25,26,31,32} Meta-analysis showed a lower recurrence rate in the group that received radiotherapy (OR, 0.27; 95% CI, 0.11–0.65; $p=0.004$). However, it was not statistically significant in the sensitivity test. Further studies with more data are needed in the future.

There are some limitations to this meta-analysis. First, only 16 concordant studies were selected, most of which were retrospective in study design, which may have affected the reliability of the results. Second, patient demographics, surgical indications, and techniques may vary at each center. Finally, in addition to the aforementioned treatments, selective arterial embolization, argon beam coagulation, cryotherapy, bisphosphonates, and interferon alpha-2b were not analyzed as potential adjuvant therapy for spinal GCTs because there were insufficient data for meta-analysis. Despite these limitations, the results from this study will broaden the understanding of spinal GCTs and provide potential guidance for the prevention of recurrence after spinal GCT surgery. However, further studies are required to form a comprehensive understanding of spinal GCT treatment and the risk factors for recurrence.

According to this meta-analysis, the recurrence rate after spinal GCT treatment was 29%. Gross total resection, radiotherapy, and the use of denosumab during subtotal resection were identified as important factors in lowering the recurrence rate of spinal GCTs. To date, many papers have used denosumab in spinal GCT, but none has clearly suggested an endpoint.

Notwithstanding, most studies recommend using it for more than 6 months. Regarding grade according to tumor shape, Campanacci grade III showed better recurrence outcomes than grades I and II. Clinicians must understand these factors when considering spinal GCT treatment.

AUTHOR CONTRIBUTIONS

Conceptualization: Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Data curation:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Formal analysis:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Funding acquisition:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Investigation:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Methodology:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Project administration:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Resources:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Software:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Supervision:** Sung Hyun Noh, Yoon Ha, Pyung Goo Cho, Keung Nyun Kim, Sang Hyun Kim, and Dong Ah Shin. **Validation:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Visualization:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Writing—original draft:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Writing—review & editing:** Sung Hyun Noh, Sang Hyun Kim, and Dong Ah Shin. **Approval of final manuscript:** all authors.

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