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J Korean Soc Spine Surg 2019 Dec;26(4):117-125.

Originally published online December 31, 2019;

<https://doi.org/10.4184/jkss.2019.26.4.117>

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pISSN 2093-4378 eISSN 2093-4386

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.krspine.org/DOIx.php?id=10.4184/jkss.2019.26.4.117>

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# Clinical Significance of Resection Type and Margin following Surgical Treatment for Primary Sarcoma of the Spine: A Multi-Center Retrospective Study

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**Study Design:** A retrospective multi-center study.

**Objectives:** To analyze oncological outcomes according to the resection type and surgical margin following surgical treatment for primary spinal sarcoma.

**Summary of Literature Review:** Previous studies using registry databases have shown that surgery and negative margins were associated with improved survival for primary spinal sarcoma. However, few studies have comprehensively analyzed the clinical significance of the resection type and surgical margin for the oncological outcomes of this rare malignancy.

**Materials and Methods:** We retrospectively reviewed consecutive patients who underwent surgical resection for primary spinal sarcoma between 1997 and 2016 at two tertiary medical centers. Overall survival and the occurrence of local recurrence and distant metastasis were compared between the groups using Kaplan-Meier curve analysis and the log-rank test.

**Results:** Thirty-three patients (21 males, 12 females) with a mean age of 45.1 years and a median follow-up of 36 months were included. There were 13 (39.4%) chondrosarcomas, 12 (36.4%) osteosarcomas, and eight different histological diagnoses. The cohort was categorized into four groups: 1) total en bloc resection with a negative margin (n=12; 36.4%), 2) total en bloc resection with a positive margin: (n=5; 15.2%), 3) total piecemeal resection (n=12; 36.4%), and 4) subtotal resection (n=4; 12.1%). Total en bloc resection with a negative margin was associated with improved overall survival (p=0.030) and less distant metastasis (p=0.025) and local recurrence (p=0.004).

**Conclusions:** Achieving a negative margin through total en bloc resection, although technically demanding, improves oncological outcomes in primary spinal sarcoma.

**Key words:** Primary spinal sarcoma, En bloc resection, Survival, Recurrence, Metastasis

## Introduction

Primary malignant osseous tumor of the spine accounts for 5% of all primary malignant bone tumors.<sup>1)</sup> In Korea, the estimated annual incidence of malignant neoplasm of the vertebral column is approximately 0.08 per 100,000 persons.<sup>2)</sup> Although it is rare, the primary malignant osseous tumor of the spine can cause significant morbidities, such as pain and paresis, and mortality. According to a recently published study using the National Cancer Database (NCDB) which captures 70% of all newly diagnosed cancers, 5-year survival for spinal osteosarcoma and chondrosarcoma, two common types of

primary malignant bone tumor,<sup>3)</sup> is reported to be 38% and 69%, respectively.<sup>4)</sup>

**Received:** August 14, 2019

**Revised:** August 29, 2019

**Accepted:** September 26, 2019

**Published Online:** December 31, 2019

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Based on studies using the Surveillance, Epidemiology, and End Results (SEER) registry, surgery improves overall survival of spinal osteosarcoma, chondrosarcoma, and Ewing sarcoma.<sup>5-7)</sup> The NCDB study mentioned above also reported that surgical resection and negative margin were significantly associated with improved 5-year survival in primary malignant spinal tumor patients.<sup>4)</sup> However, surgical removal of these malignancies is often challenging and carries high morbidity due to the proximity of tumors to vital anatomical structures such as spinal cord and great vessels, especially when en bloc resection with a negative margin is attempted.

Although clinical results following en bloc resection with negative margins in the primary malignant osseous tumor of the spine have been promising,<sup>8-10)</sup> comprehensive analysis of the clinical significance of resection type (en bloc and piecemeal) and surgical margin (negative and positive) on survival, local recurrence, and distant metastasis is lacking. Therefore, authors from two centers conducted a study to 1) investigate the feasibility of en bloc resection, and 2) analyze the oncological outcome according to the resection type and surgical margin following surgical resections for in primary malignant osseous tumors of the spine.

## Materials and Methods

This study is a retrospective review of prospectively collected data from consecutive patients who received a surgical resection for primary malignant osseous tumor of the spine, between January 1997 and August 2016 in two tertiary medical centers. Chordoma, which is mostly a low-grade and rarely metastasizes, was excluded. The current study obtained ethical approval and waiver of informed consent by the institutional review boards of each center.

Information retrieved from the electronic medical record system includes patient demographics, histological diagnosis and location of the tumor, and clinical status of patients (initial presenting symptom and preoperative neurological status by Frankel grade).<sup>11)</sup> Regarding the treatment, information on the type of surgical resection, and status of surgical margin, adjuvant treatment were also collected. Surgery was stratified into total and subtotal removal of the tumor, and total removal was further divided into en bloc resection and piecemeal resection. In general, total en bloc resection was planned and

attempted whenever technically feasible considering the vital anatomical structures surrounding the tumor. However, when the patient refused to accept the unavoidable neurological deficits resulting from the en bloc resection, piecemeal total resection or subtotal resection preserving the neurovascular structures was performed. Patients who were initially planned for en bloc resection but converted to piecemeal resection intraoperatively due to technical difficulties were also classified as the piecemeal resection group. The status of the resection margin was recorded as either positive or negative based on a permanent pathology report. Therefore, the total cohort was divided into four groups based on the resection type and surgical margin as follows; 1) total en bloc resection with a negative margin, 2) total en bloc resection with a positive margin, 3) total piecemeal resection, and 4) subtotal resection.

The primary outcome was the postoperative survival defined as the time interval between the dates of operation and death or the last follow up. Secondary outcomes were time interval from the operation to local recurrence and distant metastasis. For each outcome, median survival derived from Kaplan – Meier survivorship curve analysis was used for the assessment. Additionally, the final oncological status of the patients was also determined, which was categorized as 1) death of disease (DOD), 2) alive with disease (AWD), and 3) no evidence of disease (NED).

For statistical analysis, information on surgical resection, margin status, and oncological status were presented using descriptive statistics. Survival analysis was performed using Kaplan – Meier curves and a log-rank test to evaluate the significance of resection type and surgical margin on postoperative survival, local recurrence, and distant metastasis. A  $p$ -value of  $<0.05$  was considered statistically significant. SPSS Statistics version 25.0 (IBM Corp., Armonk, NY, USA) was used for the statistical analysis.

## Results

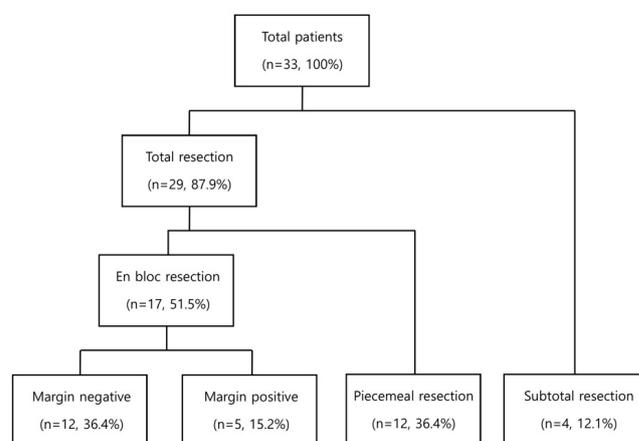
A total of 33 patients (21 males and 12 females) with a mean age at operation of 45.1 years (range, 9–76) was included in this study. As for the histological diagnosis of tumors, chondrosarcoma ( $n=13$ , 39.4%) was the most common type of tumor, followed by osteosarcoma ( $n=12$ , 36.4%). Eight patients had eight different histological diagnoses as

follows: Ewing's sarcoma, leiomyosarcoma, synovial sarcoma, undifferentiated pleomorphic sarcoma, rhabdomyosarcoma, Langerhans cell sarcoma, spindle cell sarcoma, and epithelioid sarcoma. Thoracic spine (n=19, 57.6%) was the most common site for malignancy, followed by lumbar (n=6, 18.2%), cervical (n=4, 12.1%), and sacral (n=4, 12.1%) region.

Regarding the preoperative clinical status of the patients, the most common symptom at initial presentation was axial pain (n=16, 48.5%) followed by radiating pain or weakness in extremities (n=14, 36.4%). In 3 (9.1%) patients, the tumor was diagnosed as an incidental finding by an imaging study. The mean interval between symptom and diagnosis of the malignancy was 5.8 months (range, 0–12). As for the neurologic status, 24 (72.7%) patients had Frankel grade E, while 7 (21.2%) was classified as grade D and 2 (6.1%) as grade C. Twenty-seven (81.8%) patients had normal gait without assistance. 5 (15.2%) patients used cane or walker, and 1 (3.0%) was bedridden before the operation. One chondrosarcoma patient had a lung metastasis at the initial presentation and was classified as AJCC stage IV at the time of operation. All other patients had no distant metastasis at the time of operation.

Among 33 patients, 29 (87.9%) underwent total resection, and 4 (12.1%) had subtotal resection of the tumor. In the total resection group, 17 (51.5%) patients were planned for total

en bloc resection including total en bloc spondylectomy and sagittal resection, while 12 (36.4%) patients underwent total piecemeal excision such as total piecemeal spondylectomy. For 17 patients who received total en bloc resection, the final pathology report showed a negative margin in 12 (70.6%) patients, and a positive margin in 5 (29.4%) patients. All 12 patients who underwent piecemeal total resection had a negative surgical margin and no gross tumor was left after an operation. Fig. 1 summarizes the types of resection and resection margins of the total cohort. Eleven (33.3%) patients received neoadjuvant chemotherapy, and 15 (45.5%) and



**Fig. 1.** Distribution of patients according to the type of surgical resection and surgical margin.

**Table 1.** Summary of Osteosarcoma Patients

Case	Gender/Age	Site	Resection type	Surgical Margin	Local recurrence	Distant metastasis	Follow up (month)	Final status
1	M/23	L2	Total, En bloc	Negative	No	No	96	NED
2	M/49	Sacrum	Total, En bloc	Negative	No	No	56	NED
3	F/63	T6-7-8	Total, En bloc	Negative	No	No	48	NED
4	F/71	C4-5-6	Total, En bloc	Negative	No	No	21	NED
5	M/16	T9	Total, En bloc	Positive	No	No	43	NED
6	M/74	T3	Total, En bloc	Positive	No	No	12	NED
7	F/34	Sacrum	Total, En bloc	Positive	Yes	Yes	33	DOD
8	M/65	T11-12	Total, Piecemeal		Yes	No	20	AWD
9	M/9	T10-11	Total, Piecemeal		No	No	27	NED
10	F/60	T12	Subtotal		NA	Yes	36	AWD
11	M/55	T9-10	Subtotal		NA	Yes	41	DOD
12	M/74	L3	Subtotal		NA	Yes	12	DOD

\*Abbreviations: NED, \*no evidence of disease: AWD, alive with disease, \*DOD, death of disease: NA, not applicable.

22 (66.7%) had adjuvant chemotherapy and radiotherapy following the surgery, respectively.

Final oncological status for the total cohort was NED in 19 (57.6%) patients, AWD in 7 (21.2%) and DOD in 7 (21.2%) patients at a median follow-up period of 36 months (range, 12–255). Local recurrence occurred in 12 (36.4%) at the mean interval of 14.0 months from operation to recurrence. Distant metastasis was diagnosed in 13 (39.4%) patients, and the mean interval from surgery to metastasis was 20.5 months.

Osteosarcoma patients (n=12, 8 males and 4 females) had a mean age at operation of 49.4 years and a mean postoperative follow-up period of 37.1 months. Five (41.6%) patients had a local recurrence, and 4 (33.3%) had a distant metastasis. Nine (75.0%) patients were alive, and all four (33.3%) patients who underwent en bloc total resection with a negative margin were in NED state at the last follow-up. Information on osteosarcoma patients is described in Table 1.

Chondrosarcoma patients (n=13, 8 males and 5 females) had a mean age at operation of 49.8 years, and a mean postoperative follow-up period of 54.5 months. Five (38.4%) patients had a local recurrence, and 5 (38.4%) had a distant metastasis. Eleven (75.0%) patients were alive, and all four

(30.8%) patients who underwent en bloc total resection with a negative margin were in NED state at the last follow-up (Table 2). For other types of sarcomas, all four (50.0%) patients who had en bloc total resection and a negative margin were in NED state as well (Table 3).

The median postoperative survival derived from Kaplan–Meier curve analysis for the total cohort was 144.0 months. When the total cohort was stratified into four types of resection, patients who underwent a total en bloc resection with a negative margin had a significantly longer overall postoperative survival (p=0.030) (Fig. 2). Furthermore, patients who had a total en bloc resection with a negative margin showed less distant metastasis (p=0.025) and local recurrence (p=0.004) when examined by survival analysis using a log-rank test (Fig. 3).

## Discussion

Due to their rarity, most researches on the primary malignant osseous tumor of the spine are either those from a registry database or small case series. Studies with the largest scale are from the 30-year data of SEER registry, which includes 30%

**Table 2.** Summary of Chondrosarcoma Patients

Case	Gender/Age	Site	Resection type	Surgical Margin	Local recurrence	Distant metastasis	Follow up (month)	Final status
1	F/41	T7	Total, En bloc	Negative	No	No	255	NED
2	F/63	T10-11-12	Total, En bloc	Negative	No	No	20	NED
3	M/32	L2-3	Total, En bloc	Negative	No	No	25	NED
4	F/60	T4-8	Total, En bloc	Negative	No	No	24	NED
5	F/55	T9-10-11	Total, En bloc	Positive	Yes	Yes	36	AWD
6	F/25	L1	Total, Piecemeal		No	No	78	NED
7	M/76	T11	Total, Piecemeal		No	No	51	NED
8	M/71	T9-11	Total, Piecemeal		No	No	6	NED
9	M/48	C4-5	Total, Piecemeal		Yes	Yes	47	AWD
10	M/36	T4-6	Total, Piecemeal		Yes	Yes	41	AWD
11	M/43	L4-5	Total, Piecemeal		Yes	Yes*	56	DOD
12	M/48	T9-12	Total, Piecemeal		Yes	Yes	22	DOD
13	M/33	C5	Subtotal		NA	No	47	AWD

\*Abbreviations: NED, \*no evidence of disease: AWD, alive with disease, \*DOD, death of disease: NA, not applicable.

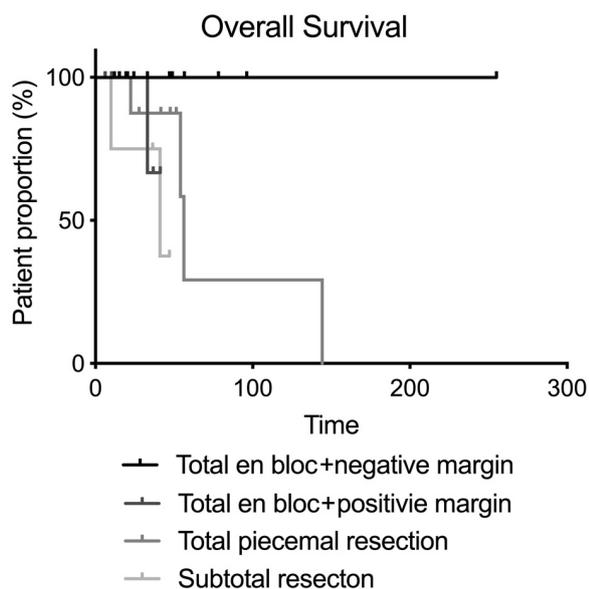
\*The patient had a lung metastasis at the initial presentation of malignancy and was excluded from the survival analysis for the occurrence of distant metastasis.

**Table 3.** Summary of Patients with Other Types of Sarcoma

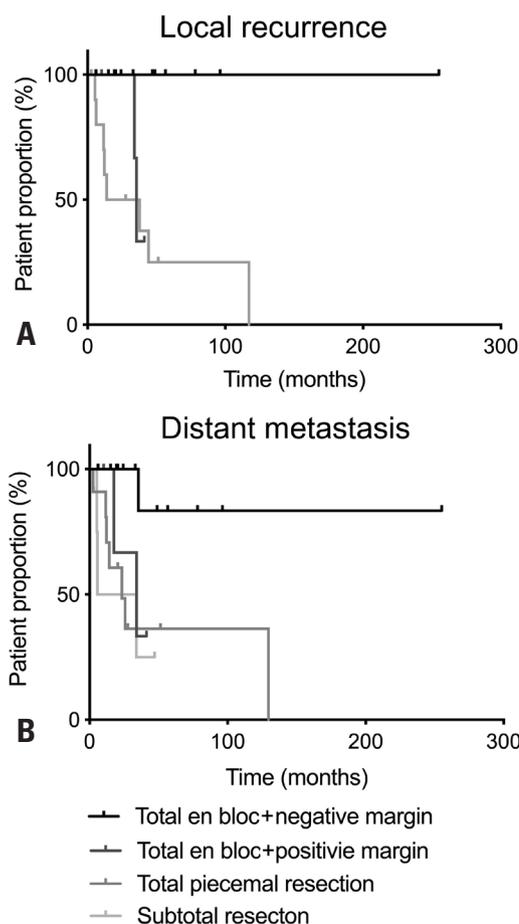
Case	Gender/ Age	Diagnosis	Site	Resection type	Surgical margin	Local recurrence	Distant metastasis	Follow up (month)	Final status
1	F/30	Langerhans cell sarcoma	T12	Total, En bloc	Negative	No	No	33	NED
2	M/60	Spindle cell sarcoma	T12	Total, En bloc	Negative	No	No	24	NED
3	F/40	Rhabdomyosarcoma	Sacrum	Total, En bloc	Negative	No	No	15	NED
4	M/38	Synovial sarcoma	C6-7-T1	Total, En bloc	Negative	No	Yes	47	NED
5	M/10	Epithelioid sarcoma	Sacrum	Total, En bloc	Positive	No	No	27	NED
6	M/37	Leiomyosarcoma	T3	Total, Piecemeal		Yes	Yes	15	AWD
7	F/36	Undifferentiated pleomorphic sarcoma	L5	Total, Piecemeal		Yes	Yes	144	DOD
8	M/16	Ewing's sarcoma	T6	Total, Piecemeal		Yes	Yes	54	DOD

\*Abbreviations: NED, \*no evidence of disease; AWD, \*alive with disease; DOD, death of disease.

\*The patient is in NED state after lung metastectomy.

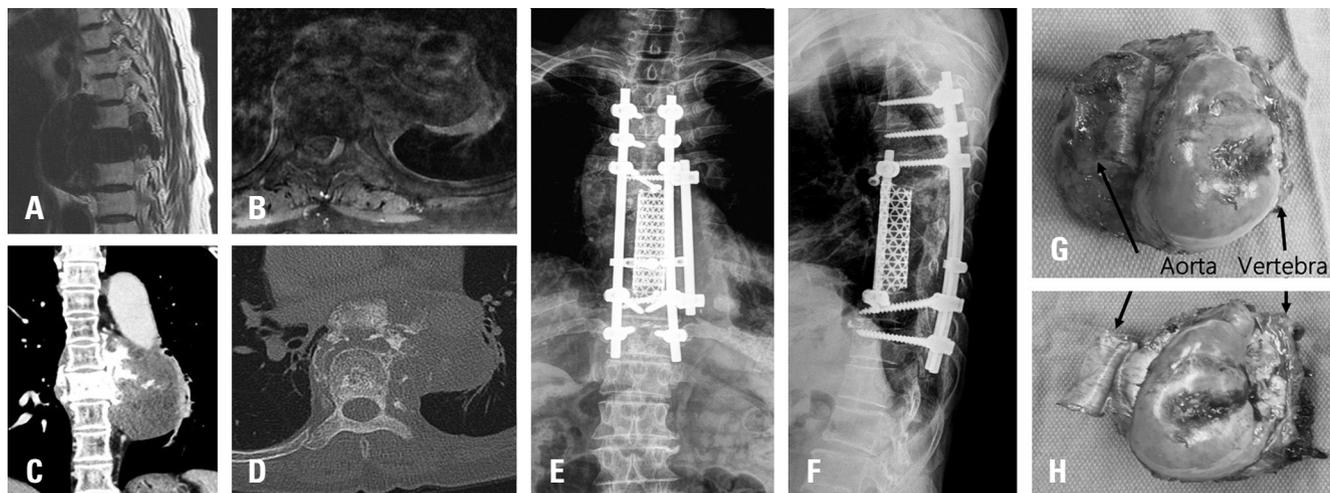


**Fig. 2.** Kaplan-Meier survival curve of the total cohort showing an improvement in overall postoperative survival in patients who underwent total en bloc resection and had a negative margin



**Fig. 3. (A)** Kaplan-Meier survival curve for local recurrence showing significantly less recurrence in patients who underwent total en bloc resection with a negative margin ( $p=0.004$ , log-rank test). **(B)** Kaplan-Meier survival curve for distant metastasis showing significantly less metastasis in patients who underwent total en bloc resection with a negative margin ( $p=0.025$ , log-rank test).

of the United States' population.<sup>5-7)</sup> In these studies, surgical resection was associated with overall and disease-free survival improvement. However, types of surgical resection and status of surgical margin were not considered in these studies because of a lack of detailed data. Although a recently published study using NCDB showed that surgical resection and negative margin are associated with improved survival, the study did not specify the surgical techniques.<sup>4)</sup> Several case series reported favorable outcomes following total en bloc resection of these



**Fig 4.** (A–D) A 63-year-old woman was diagnosed with osteosarcoma at the T7 level, which encased the descending thoracic aorta over the T5–8 levels. (E, F) The patient underwent total en bloc resection of the tumor, combined with replacement of the descending thoracic aorta by a thoracic surgeon. The postoperative X-ray is shown. (G, H) The specimen from the operation is shown. The patient experienced transient paraplegia due to spinal cord infarction, and currently ambulates using a walker. The patient had no evidence of disease after 4 years of follow-up.

malignancies but didn't compare them to those of other surgical resections, such as piecemeal resection.<sup>12,13</sup>

In the current study, 17 of 33 (51.5%) patients underwent total en bloc resection (spondylectomy or sagittal resection) and a negative margin was achieved in 12 of 33 (36.4%) patients. Among these 12 patients who had a total en bloc resection with a negative margin, only one patient with a cervical synovial sarcoma had a lung metastasis which was surgically removed. Otherwise, this group had no local recurrence, distant metastasis or death of disease, and therefore was in NED state at the follow-up period. In contrast, for 5 of 33 (15.2%) patients who underwent a total en bloc resection but showed a positive margin in the final pathology report, 2 patients were diagnosed with a local recurrence and distant metastasis despite adjuvant chemotherapy and radiotherapy. One of these two patients was alive with disease, and the other had expired at the last follow-up. Therefore, achieving a negative margin during total en bloc resection, in other words, a marginal resection margin, seems to be a crucial 'game-changer' in the surgical management of primary malignant spinal neoplasms.

However, total en bloc resection of primary malignant spinal neoplasm often carries a high risk of surgical morbidity and sometimes impossible to perform due to the proximity to or involvement of vital anatomical structures such as spinal cord and great vessels. Shah and colleagues reported an overall postoperative complication rate of 52% following en

bloc spondylectomy.<sup>12</sup> Among 12 patients who underwent a total en bloc resection and achieved a negative margin in this study, 3 (25.0%) patients had a neurological complication after surgery; one paraplegia due to spinal cord infarction (Fig. 4), one transient hemiplegia and one Horner syndrome. For the other 21 cases, there were no significant neurological complications. Although there is a clear benefit of the total en bloc resection on the oncological outcome, a higher risk for neurological complications should be taken into account when planning and performing a total en bloc resection for these malignancies.

In the perspective of oncological surgical margin, only patient who underwent a total en bloc resection with a negative margin achieved a marginal surgical margin, while all other patients had an intralesional surgical margin in the current study. As anticipated, patients who were able to obtain marginal surgical margin showed superior results when compared to those of intralesional margin patients in survival analysis of this study, which is a similar result to previously published studies.<sup>14–16</sup> It should also be noted that the group of patients who had a total en bloc resection, but a positive surgical margin is different from the subtotal resection group. The former group only had a microscopic tumor left, predominantly in the interface between the tumor and the dural sac, but the latter group had a gross tumor unresected which was confirmed on the postoperative imaging studies. When two groups were

compared, the prognosis was poor in the subtotal resection group where half of the patients had expired at the last follow-up, no statistical difference was found due to the small sample size.

Talac and colleagues conducted a study in which they stratified primary spinal sarcoma into 3 groups: 1) en bloc resection with negative margins, 2) piecemeal resection with negative margins, and 3) all resections with positive margins, and reported local recurrence rates of 11, 33, and 50–70%, respectively.<sup>17)</sup> The difference in our study is that we divided the third group (all resections with positive margin) into total en bloc resection with positive margin and subtotal resection. Two groups are different in that the former has no macroscopic tumor found in the postoperative imaging study, but the latter has an evident remnant disease. The oncological outcomes of the latter group (subtotal resection) were generally poor, but statistical significance could not be found when compared to the former group (en bloc resection with positive margin). Further study with larger sample size and longer follow-up is required for clarification.

There are several limitations present in this study. First, the current study is limited by small sample size and short follow-up period. Second, besides osteosarcoma and chondrosarcoma, eight different types of sarcoma are included in this study, making the cohort heterogenous. Third, we could not stratify patients according to the tumor staging system due to inconsistent reports on histologic grades in the retrospective review. Since the staging of a tumor is an important prognostic factor in sarcoma patients, lack of this data can have a significant confounding effect on the result of this study. Fourth, surgery was performed by six different surgeons in two different hospitals, and therefore, the surgeon factor on surgical outcomes cannot be ruled out. Finally, our retrospective review may have caused selection bias and underestimation of complications. Nevertheless, the current study provides useful information regarding the significance of resection type and surgical margin on this rare disease, the primary malignant osseous tumor of the spine.

## Conclusions

In conclusion, often challenging due to a high risk of neurological complications, total en bloc resection of primary

malignant osseous tumor of the spine with a negative margin was associated with the improvement of postoperative survival and reduction of local recurrence and distant metastasis in the current case series.

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## 원발성 악성 척추 종양에서 수술적 절제 방법과 절제연의 임상적 의의: 다기관 후향적 연구

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**연구 계획:** 후향적 다기관 연구

**목적:** 본 연구진은 원발성 악성 척추 종양 환자에서 절제 방법 및 수술 절제연이 생존 기간, 국소 재발 및 원격 전이 등 임상적 결과에 미치는 영향을 분석하고자 하였다.

**선행 연구문헌의 요약:** 원발성 악성 척추 종양에서 수술적 치료와 음성 절제연은 생존 기간의 연장 등 보다 좋은 임상 결과와 연관이 되어 있다고 알려져 있다. 하지만 절제 방법 및 수술 절제연을 종합적으로 분석한 연구는 이제까지 많지 않았다.

**대상 및 방법:** 1997년부터 2016년까지 두 개의 기관에서 원발성 척추 종양으로 수술을 시행 받은 환자를 후향적으로 분석하였으며, 절제 방법(일괄 및 분할)과 수술 절제연(양성 및 음성)이 생존 기간, 국소 재발 및 원격 전이 등에 미치는 영향을 생존 분석(Kaplan-Meier curve analysis and log rank test)으로 평가하였다.

**결과:** 총 33명(남자 21명, 여자 12명)의 환자가 연구에 포함되었으며, 평균 나이는 45.1세, 추시 기간의 중간값은 36개월이었다. 13(39.4%)의 연골육종, 12(36.4%)의 골육종이 가장 많은 조직학적 진단을 차지하였다. 전체 환자를 절제 방법 및 절제연을 기준으로 네 그룹으로 나누었을 때, 그 분포는 다음과 같았다. 1) 완전 일괄 절제 (total en bloc resection) 및 음성 절제연: n=12(36.4%), 2) 완전 일괄 절제 및 양성 절제연: n=5(15.2%), 3) 완전 분할 절제 (total piecemeal resection): n=12(36.4%), and 4) 불완전 절제(subtotal resection): n=4(12.1%). 생존 분석을 시행하였을 때, 완전 일괄 절제 및 음성 절제연을 시행 받은 환자들에서 유의하게 긴 생존 기간( $p=0.030$ ), 적은 원격 전이 ( $p=0.025$ ) 및 국소 재발 ( $p=0.004$ )의 발생이 관찰되었다.

**결론:** 원발성 악성 척추 종양에서 보다 좋은 종양학적 결과(oncological outcome)를 얻기 위해서는 완전 일괄 절제술을 통해 음성 절제연을 얻고자 하는 노력이 필요하겠다.

**색인 단어:** 원발성 척추 종양, 일괄절제술, 생존 분석, 국소 재발, 원격 전이

**약칭 제목:** 원발성 척추암의 수술적 치료

**접수일:** 2019년 8월 14일

**수정일:** 2019년 8월 29일

**게재확정일:** 2019년 9월 26일

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