Primary Sarcomas of the Spine

A Systematic Review and Pooled Data Analysis

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Study Design: A systematic review of the literature and pooled data analysis of treatment outcomes of primary sarcomas of the spine.

Objective: To examine the current literature and treatment options for primary sarcomas of the spine.

Summary of Background Data: A paucity of literature exists on treatment outcomes of primary sarcomas of the spine.

Materials and Methods: Two authors searched PubMed to identify articles for review, and a pooled data analysis was performed to determine overall survival for each type of surgical resection on spine sarcomas.

Results: In total, 1776 articles were identified, and 11 met our inclusion criteria for review. In chondrosarcoma, overall survival was significantly higher with en bloc excision when compared with piecemeal resection (HR for piecemeal resection: 4.11; 95% CI: 2.08–8.15). Subgroup analysis showed that the addition of radiation therapy after piecemeal excision increased overall survival to 60 months from 48 months with piecemeal excision alone. In osteosarcoma, there was no significant difference in overall survival between en bloc and piecemeal resection (HR for piecemeal resection: 1.76; 95% CI: 0.776–3.99). In Ewing's sarcoma, overall survival was significantly higher when a successful en bloc resection was achieved and coupled with chemotherapy and radiation therapy for local control (HR for piecemeal resection: 7.96; 95% CI: 2.12–20.1). Interestingly, when a successful en bloc resection could not be achieved, chemotherapy and radiation therapy alone had significantly higher survival than piecemeal resection (HR for piecemeal resection: 2.63; 95% CI: 1.01–6.84). A significantly higher number of local recurrences were associated with the piecemeal resection group in all types of spine sarcomas.

Conclusion: This review and pooled data seem to favor en bloc excision for local control as the treatment of choice in primary sarcomas of the spine.

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Primary sarcomas of the spine are rare neoplasms and form less than 5% of primary musculoskeletal sarcomas.[1] The most common types include chondrosarcoma, osteosarcoma, and Ewing's sarcoma (ES).[2] These spinal tumors can cause significant morbidity and mortality due to local invasion and destruction of adjacent structures as well as metastasis to distant organs. Survival outcomes for spinal sarcomas are heterogeneous with regard to tumor size, location, stage, treatment, and the use of adjuvant or neoadjuvant therapies.[3,4] The impact of the type of surgical resection (en bloc versus piecemeal resection) and adjuvant therapies on survival and local recurrence in primary spine sarcomas remains to be determined. Despite sparse data in the literature that favors en bloc resection with wide margins over piecemeal resection, the former is a highly demanding procedure associated with higher surgical morbidity and requires a unique set of technical skills.[5–7]

The purpose of this review is to examine the current literature and treatment options for primary sarcomas of the spine. Particularly, to compare the effect on survival and local recurrence between different surgical strategies in patients with chondrosarcoma, osteosarcoma, and ES.

MATERIALS AND METHODS

Study selection was carried out by 2 authors who searched PubMed to identify articles for review. A broad search strategy using the following search string: [(Sarcoma) OR (osteosarcoma) OR (chondrosarcoma) OR (Ewing's sarcoma) OR (primary bone tumor)) AND (spine)] were used for data extraction. Due to the advancement of adjunct chemotherapy and radiotherapy treatment regimens, only English articles published after January 2000 (within the past 20 y) and until December 2020 were considered for review. The literature search was performed according to the PRISMA guidelines for systematic reviews, and bias was assessed using the risk of bias assessment tool outlined by the Cochrane review.[8]

For inclusion, studies had to meet the following criteria: (1) patients must have a primary diagnosis of a

sarcoma of the spine, (2) present an original article reporting on a case series of greater than 5 patients, and (3) report on the type of treatment performed. Reporting on outcomes may include any of the following: survivorship, recurrence, complications, or the time of death. Specific exclusion criteria were as follows: (1) patients with known hereditary or genetic disorders that would predispose to malignancy, (2) papers published before 2000, (3) case reports or studies not reported in English.

Two authors extracted and summarized data from the included studies as follows: patient demographics, type of tumor, location, stage, treatment type, local recurrence, survivorship, and complications. All publications with insufficient information on the type of surgical resection and associated outcomes were excluded. Since all available studies were observational with a relatively small number of included patients and, therefore, low-quality evidence, we decided to pool the complete data available from each study into 1 database for an exploratory purpose. For each spine sarcoma type, pooled data will serve as a new dataset for the main outcome analysis.

Survivorship is the primary outcome of this pooled analysis. Kaplan-Meier survivorship curves were performed for each type of spine sarcoma, comparing survival according to surgical resection strategy: wide/marginal versus piecemeal (or intralesional) resection. Piecemeal or intralesional resection was defined as a tumor debulking or curettage procedure and included attempted en bloc resections with positive margins that were considered as intralesional resections. Secondary outcomes included local recurrences by surgical strategy, metastasis, and the impact of adjunct treatment therapies. These outcomes were measured according to the type of spine sarcoma: (1) chondrosarcoma, (2) osteosarcoma, and (3) ES.

Statistical analyses were performed using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Statistical analysis was performed using χ^2 tests for comparison between proportions, Student t-test for comparison between means and Mann-Whitney U test to compare ranks of means when 1 of the compared groups has <30 patients. For the survivorship curves, the Kaplan Meier method was used to analyze survival time to primary and secondary outcomes. To compare the survival curves of the different treatments (en bloc, piecemeal, best medical therapy), Cox's Proportional Hazards Model was used to perform a meta-analysis of the Hazards Ratio (HR) and obtain 95% confidence intervals (CI).

RESULTS

In total, 1776 articles were identified through the literature search. Two authors independently screened the titles and abstracts based on the PRISMA guidelines and using the inclusion and exclusion criteria. Any controversy or disagreement was resolved by the senior author after discussion and consensus. This produced 11 articles for evaluation and inclusion for our systematic review.[9–19] A diagram outlining our search results is shown in Figure 1.

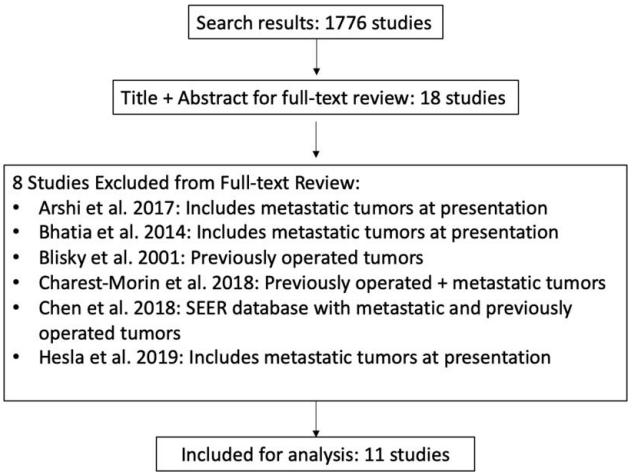

FIGURE 1. Systematic review search results based on PRISMA guidelines.

A summary of the papers included is shown in Table 1. Of the 11 papers included for review, there were 4 chondrosarcoma papers, 4 osteosarcoma papers, and 3 ES papers that met our eligibility criteria. There were no previously published randomized controlled trials concerning surgical treatment of primary bone sarcomas, and all data was based on retrospective case series with level IV quality of evidence and a high risk of bias (Fig. 2). There was no difference in patient demographics, Enneking stage of the tumor, surgical treatment strategy and the use of adjuvant therapies are shown in Table 2. Adjuvant therapy, including chemotherapy and radiation, was often utilized for improved local control when wide or negative margins could not be achieved by surgical excision.

For all 3 types of sarcomas, pooled patients were divided into 2 groups according to the surgical strategy: (1) en bloc resection, and (2) piecemeal resection.

Chondrosarcoma

Overall survival was significantly higher with en bloc excision when compared with piecemeal resection, as shown by the Kaplan-Meier curve with a hazard ratio (HR) of 4.11 and 95% confidence interval (CI) of 2.08–8.15 for piecemeal resection (Fig. 3). The piecemeal resection group received significantly higher adjuvant therapy with chemotherapy and radiation therapy to help achieve disease control. When applying a piecemeal excision, 53% of patients (n = 23/43) received intraoperative or postoperative radiation therapy for local control of the tumor. Subgroup analysis showed that the addition of radiation therapy after piecemeal excision increased overall survival to 60 months from 48 months with piecemeal excision alone; however, this did not reach clinical significance ($P = 0.672$). Local recurrences and metastasis were reported for each tumor subtype and treatment group (Table 3). The number of local recurrences were significantly higher in piecemeal resection (56%) when compared with en bloc excision (10%) ($P = 0.0001$). There were no differences in the development of metastasis between the 2 groups.

TABLE 1. A summary of Papers Included for Review

Reference	Year	Journal	Study design	Level of evidence	N	EB (n)	PM (n)	Average FU(m)
Chondrosarcoma								
Boriani et al[9]	2000	Spine	Retrospect	IV	22	10	12	81
Schoenfeld et al[10]	2012	Spine	Retrospect	IV	21	8	13	120.5
Strike et al[11]	2011	Iowa Orthop J.	Retrospect	IV	16	14	2	42
Yang et al[12]	2012	J Spinal Disord Tech.	Retrospect	IV	15	3	12	58.7
Osteosarcoma								
Feng et al[13]	2013	World J Surg Oncol.	Retrospect	IV	16	7	9	42.4
Schoenfeld et al[14]	2010	Spine J.	Retrospect	IV	26	7	13	35.9
Bhatia et al[15]	2014	Br J Neurosurg.	Retrospect	IV	26	10	8	22.4
Ozaki et al[16]	2002	Cancer	Retrospect	IV	22	5	7	39
Ewing's sarcoma								
Boriani et al[17]	2011	Eur Rev Med Pharmacol Sci.	Retrospect	IV	27	10	7	65
Mirzaei et al[18]	2015	Neurosurgery.	Retrospect	IV	15	6	0	95
Hesla et al[19]	2019	J Bone Oncol.	Retrospect	IV	24	3	3	132

Osteosarcoma

There was a difference in the location of the tumor as piecemeal resections were higher in the cervical spine and en bloc resections were significantly higher in the thoracic spine (Table 2). In the osteosarcoma group, we found that there was no significant difference in overall survival between en bloc and piecemeal resection (HR of piecemeal resection: 1.76; 95% CI: 0.776–3.99) (Fig. 4). However, survival trends favored outcomes with en bloc excision. Local recurrences were found to be significantly higher in the piecemeal excision group ($P = 0.0293$) (Table 3). There was no difference in the development of metastasis.

Ewing's Sarcoma

Overall survival was significantly higher when a successful en bloc resection was achieved and coupled with chemotherapy and radiation therapy for local control (HR of piecemeal resection: 7.96; 95% CI: 2.12–20.1) (Fig. 5). Interestingly, when a successful en bloc resection could not be achieved, chemotherapy and radiation therapy alone had significantly higher survival than piecemeal resection (HR of piecemeal resection: 2.63; 95% CI: 1.01–6.84). A significantly higher number of local recurrences were associated with the piecemeal resection group ($P = 0.0162$). Intralesional resection or positive margins demonstrated a poor prognosis in ES of the spine.

DISCUSSION

The impact of en bloc versus piecemeal resection on survival and local recurrence for primary sarcomas of the spine has not been proven. From our knowledge, this is the first systematic review of literature analyzing published

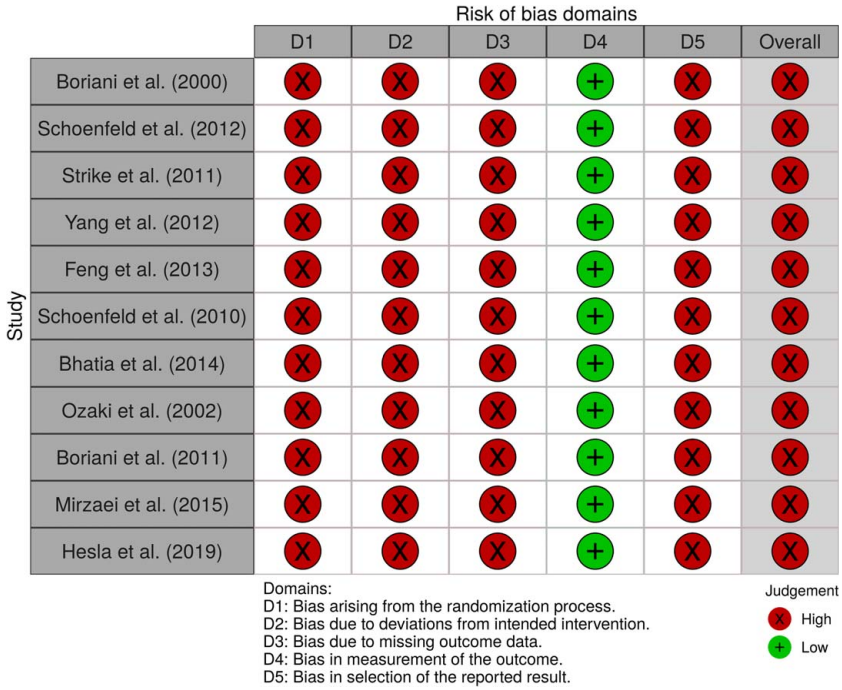

FIGURE 2. Risk of bias assessment of included studies. full color online

TABLE 2. Demographics

Chondrosarcoma	PM (n = 43)	EB (n = 31)	*P*
Age (mean)	44	46	0.274
Sex (M/F)	29/14	21/10	1
Location			
C	9	8	0.781
T	24	13	0.241
L	9	10	0.419
Enneking Stage			
I	23	20	0.642
II	19	12	0.638
III	1	1	—
Adjuvant therapy			
CHT	6	0	0.0369
RT	23	4	0.0005
Osteosarcoma	PM (n = 25)	EB (n = 22)	
Age (mean)	30	34	0.461
Sex (M/F)	11/13	10/12	1
Location			
C	9	2	0.041
T	6	12	0.040
L	10	8	1
Enneking Stage			
I	0	1	—
II	15	19	0.398
III	4	1	0.172
Adjuvant therapy			
CHT	24	21	1
RT	16	15	1
Ewing's sarcoma	PM (n = 14)	EB (n = 15)	
Age (mean)	20	19	0.815
Sex (M/F)	7/7	5/10	0.462
Location			
C	2	0	0.482
T	7	8	1
L	5	6	1
Enneking Stage			
I	0	0	—
II	10	5	0.895
III	1	1	—
Adjuvant therapy			
CHT	14	14	—
RT	13	13	—

observational studies in primary spine sarcomas. We aimed to consolidate data from a small number of retrospective case series and low-powered studies to show promising treatment trends for these tumors. We pooled the results from these studies and explored how the outcomes differed based on the treatment strategy with respect to survival, local recurrence, and metastasis. This will help guide surgical management when dealing with such rare and challenging cases. Our systematic review yielded 11 heterogeneous case series (4 for chondrosarcoma, 4 for osteosarcoma, and 3 for ES), all of which showed similar results favoring en bloc resection in increased overall survival and decreased local recurrence.

Chondrosarcoma

The 4 articles that reported on chondrosarcoma support the use of aggressive surgical resection to obtain wide or marginal excision whenever possible. Our results show that overall survival was significantly higher with a successful en bloc resection when compared with the piecemeal group (Fig. 3). Furthermore, we found that en bloc resection was associated with significantly less local recurrence (en bloc = 3/31 vs. piecemeal = 24/43) when compared with a piecemeal excision ($P = 0.0001$). This is similar to reports in the literature where some studies have shown intralesional excisions to be associated with nearly 100% local recurrence in chondrosarcomas of the spine.[5,20]

Compared with peripheral skeletal tumors, chondrosarcomas of the spine tend to be smaller and more difficult to excise and have a decreased survival and increased local recurrence rate.[9,21,22] Although en bloc excision is strongly advocated, it has also been considered the more technically demanding procedure with a greater risk for postsurgical morbidity. Depending on the location of the tumor and the involvement of nearby structures, surgeons have often presumed that a piecemeal resection is better warranted to prevent morbidity related to the more aggressive surgery.[5] As well, it would be inferred that a tumor with a more advanced stage would undergo piecemeal excision, and thus biasing outcomes to be worse. However, when comparing these confounding factors, we found there were no differences in the stage of tumor and the corresponding surgical resection performed (Table 2). With this, we recommend that an en bloc excision with negative margins should be the primary goal of surgical resection.

The use of adjunct therapy in chondrosarcoma is limited as this type of tumor is found to be typically resistant to chemotherapy or radiation.[9–12] However, when a wide margin or excision is not possible, adjuvant therapy is often utilized at the time of primary surgery in an effort to optimize local control.[5,6] Thus, we found that adjunct radiation therapy was used in 53% of piecemeal resections and only 13% of en bloc excisions (Table 3). Subgroup analysis showed that adjuvant radiotherapy treatment slightly increased overall survival compared with piecemeal excision alone; however, this did not reach clinical significance. Due to the heterogeneity of reporting in radiation protocols and lack of consistent findings, it is difficult to conclusively state a clear benefit of adjunct radiation. The results of this review have shown that radiation is often used as an adjunct to surgery when the primary benefit is improvement in local control with a piecemeal resection.

Osteosarcoma

Wide resection and adjuvant chemotherapy have revolutionized the treatment of osteosarcoma in the extremities; however, the prognosis of the tumors in the spine remains poor.[23–25] Anatomic constraints of the spine may limit the ability to achieve an en bloc resection, as wide margins are not always possible. Our results indicate that there was no difference in survival when en bloc excision was compared with piecemeal resection of osteosarcoma of the spine (Fig. 4). The findings from the 4 papers included in this review showed mixed results as 2 reports found that en bloc excision, negative margins

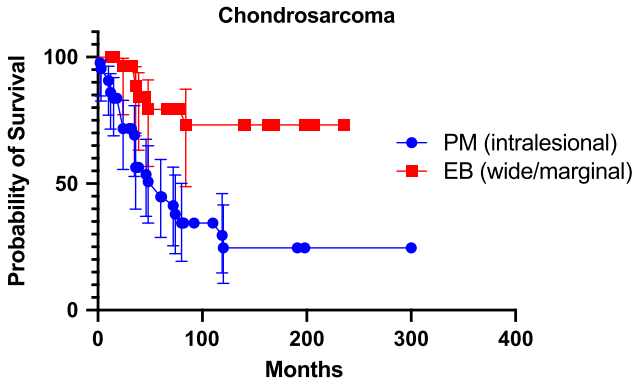

FIGURE 3. Chondrosarcoma Kaplan-Meier survivorship curves. full color online

or the use of adjuvant chemotherapy or radiation therapy were not found to positively influence outcomes.[13,14] This differs from the other 2 reports in which en bloc excision with wide margins improved overall survival.[15,16] This inconsistency in reporting of literature makes it difficult to guide the clinical decision-making process and highlights the limitations of the small case series' presented. Although wide margins are the preferred choice of treatment outcomes, the morbidity of the procedure and significantly high rate of complications may not increase overall survival when compared with piecemeal resection.

When survival results are compared with earlier reports in the literature, there is an overall trend of increased survival outcomes for patients with osteosarcoma of the spine. Our systematic review found that the overall survival of patients undergoing either an en bloc or piecemeal resection was an average of 48 months. Early reports showed consistently poor outcomes, with mortality occurring shortly after the presentation. Shives et al[26] published a series of 27 patients with osteosarcoma of the spine in 1986 and found a 96% patient mortality with a median survival of 10 months. Barwick et al[27] reported a 90% mortality and median survival of 6 months on a cohort of 10 patients in 1980. This illustrates the advances in the understanding of osteosarcoma and the impact of evolving treatment modalities on disease course and outcomes. Technical improvements in surgery and more aggressive approaches to surgical excision combined with improved adjuvant therapies have ultimately led to increased survival. The results of this review show that for patients with surgically accessible tumors, wide or marginal excision is the favored treatment of choice. A combination of chemotherapy and postoperative radiation may be of benefit in selected patients.[22] Further research should strive for the establishment of prospective databases with standardized management protocols so we may answer these clinical questions with more certainty.

Ewing's Sarcoma

The introduction of multidrug chemotherapy and radiotherapy combined with surgery has significantly improved the prognosis of ES.[28,29] Primary ES of the spine remains a rare entity comprising 3%–5% of primary bone tumors in the spine and is considered a worse prognosis when compared with occurrences at other sites.[30] However, recent reports have supported the concept of en bloc resection combined with multimodal chemotherapy and radiotherapy in providing as effective control of ES of the spine like those of the limbs.[17–19] Our results indicate that en bloc resection combined with chemotherapy and radiotherapy significantly increased survival and decreased local recurrence when compared with piecemeal resection (Fig. 5). Interestingly, when chemotherapy and radiotherapy alone were compared with piecemeal resection, Kaplan-Meier curves showed significantly higher survival for the chemotherapy and radiotherapy group. These results corroborated those by Boriani et al[17] who also demonstrated that tumor-free margin en bloc resection provided longer survival and better disease control than intralesional excision. They also found that piecemeal excision combined with chemotherapy and radiotherapy was less effective than chemotherapy and radiotherapy alone in achieving local disease control. These findings seem to demonstrate that piecemeal surgery with violation of margins are associated with high rates of recurrence and worse overall prognosis. We recommend attempting en bloc excision whenever feasible while still considering the morbidity and risks of the procedure. If this is not possible due to the lack of the criteria to perform en bloc resection, then chemotherapy and

TABLE 3. Reported Local Recurrence (LR) or Metastasis (M): Piecemeal (PM) and En Bloc (EB)

	Piecemeal (n = 43)	En bloc (n = 31)		*P*
Chondrosarcoma				
Local recurrence n (%)	24 (56)	3 (10)	—	0.0001
Metastasis n (%)	12 (28)	5 (16)	—	0.2745
	Piecemeal (n = 25)	En bloc (n = 22)	—	
Osteosarcoma				
Local recurrence n (%)	11 (44)	3 (14)	—	0.0293
Metastasis n (%)	11 (44)	4 (18)	—	0.0698
	Piecemeal (n = 14)	En bloc (n = 15)	CHT + RT (n = 18)	
Ewing's sarcoma				
Local recurrence n (%)	9 (64)	2 (13)	6 (33)	0.0162
Metastasis n (%)	1 (7)	3 (20)	4 (22)	0.495

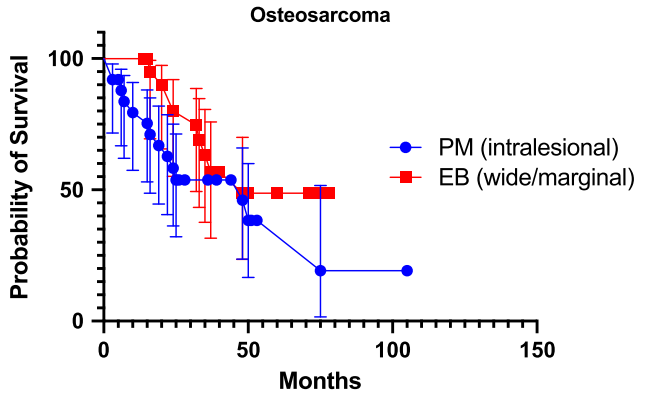

FIGURE 4. Osteosarcoma Kaplan-Meier survivorship curves. full color online

radiation alone seem to be the best option rather than intralesional surgery. Further research is warranted to support these results.

Limitations

While conducting this review, we highlight the many limitations of the study of primary sarcomas of the spine. The inconsistency in reporting of literature and the heterogeneity of the data presented highlights the inherent limitations of small case series in providing significant clinical evidence. Studies are often underpowered, with extremely small sample sizes with varying adjuvant and treatment regimens. To consolidate evidence for these rare tumors, this systematic review will help guide the decision-making process. We compared groups of patients for confounders whenever possible; however, heterogeneity in the reporting of data has made it difficult. The intrinsic characteristics of these tumors and confounding patient variables made it difficult to standardize therapy as they are often treated on a case-by-case basis. Limited data on the timing of local recurrences and metastasis prevented us from performing disease-free survival analyses. Therefore, we used the rate of recurrences and metastasis and compared the means between groups. Furthermore, many studies did not report on the specific outcomes or complications of the type of surgical resection performed, leading to exclusion from this review. Lastly, these tumors are extremely rare, and study results span many decades, making it difficult to draw conclusions due to constantly evolving management protocols, advances in surgical technique, and advances in adjuvant therapies. The purpose of this review is to consolidate these results to better understand this highly morbid condition and explore the treatment strategies available and their outcomes.

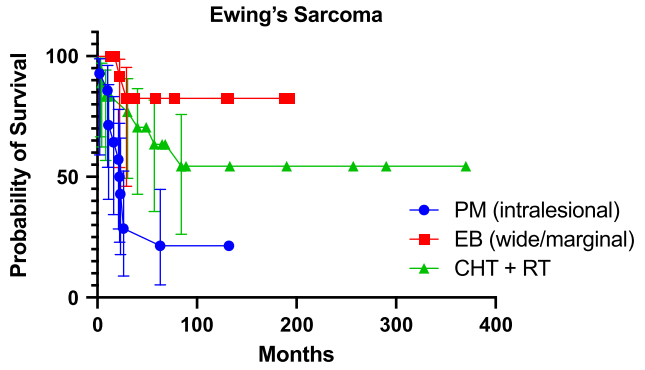

FIGURE 5. Ewing's Sarcoma Kaplan-Meier survivorship curves. full color online

CONCLUSION

This review and pooled data seem to favor en bloc excision for local control as the treatment of choice in primary sarcomas of the spine. In summary, removing the whole tumor mass together with a continuous wide or marginal shell of healthy tissue was found to give the patient the best chance of survival and the lowest rate of local recurrence. However, anatomic constraints, high morbidity, and technical demands of the procedure limit its ability for widespread utilization. For this reason, we must strive for multicenter prospective treatment protocols where specialized surgeons who are equipped to meet the technical demands of the procedure are able to give patients the most favorable results. Furthermore, with standardized therapy and prospective databases, we will be able to answer further research questions with more certainty.

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