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Bone graft options for spinal fusion following resection of spinal column tumors: systematic review and meta-analysis

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OBJECTIVE With the advent of new adjunctive therapy, the overall survival of patients harboring spinal column tumors has improved. However, there is limited knowledge regarding the optimal bone graft options following resection of spinal column tumors, due to their relative rarity and because fusion outcomes in this cohort are affected by various factors, such as radiation therapy (RT) and chemotherapy. Furthermore, bone graft options are often limited following tumor resection because the use of local bone grafts and bone morphogenetic proteins (BMPs) are usually avoided in light of microscopic infiltration of tumors into local bone and potential carcinogenicity of BMP. The objective of this study was to review and meta-analyze the relevant clinical literature to provide further clinical insight regarding bone graft options.

METHODS A web-based MEDLINE search was conducted in accordance with preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines, which yielded 27 articles with 383 patients. Information on baseline characteristics, tumor histology, adjunctive treatments, reconstruction methods, bone graft options, fusion rates, and time to fusion were collected. Pooled fusion rates (PFRs) and I^2 values were calculated in meta-analysis. Meta-regression analyses were also performed if each variable appeared to affect fusion outcomes. Furthermore, data on 272 individual patients were available, which were additionally reviewed and statistically analyzed.

RESULTS Overall, fusion rates varied widely from 36.0% to 100.0% due to both inter- and intrastudy heterogeneity, with a PFR of 85.7% (I^2 = 36.4). The studies in which cages were filled with morselized iliac crest autogenic bone graft (ICABG) and/or other bone graft options were used for anterior fusion showed a significantly higher PFR of 92.8, compared with the other studies (83.3%, p = 0.04). In per-patient analysis, anterior plus posterior fusion resulted in a higher fusion rate than anterior fusion only (98.8% vs 86.4%, p < 0.001). Although unmodifiable, RT (90.3% vs 98.6%, p = 0.03) and lumbosacral tumors (74.6% vs 97.9%, p < 0.001) were associated with lower fusion rates in univariate analysis. The mean time to fusion was 5.4 ± 1.4 months (range 3–9 months), whereas 16 of 272 patients died before the confirmation of solid fusion with a mean survival of 3.1 ± 2.1 months (range 0.5–6 months). The average time to fusion of patients who received RT and chemotherapy were significantly longer than those who did not receive these adjunctive treatments (RT: 6.1 months vs 4.3 months, p < 0.001; chemotherapy: 6.0 months vs 4.3 months, p = 0.02).

CONCLUSIONS Due to inter- and intrastudy heterogeneity in patient, disease, fusion criteria, and treatment characteristics, the optimal surgical techniques and factors predictive of fusion remain unclear. Clearly, future prospective, randomized studies will be necessary to better understand the issues surrounding bone graft selection following resection of spinal column tumors.

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KEY WORDS bone graft; spinal fusion; spinal column tumors; cage reconstruction; bone morphogenetic protein; radiation therapy; chemotherapy; spinal oncology

ABBREVIATIONS BMD = bone mineral density; BMP = bone morphogenetic protein; CI = confidence interval; HR = hazard ratio; ICABG = iliac crest autogenic bone graft; OR = odds ratio; PBT = proton beam therapy; PFR = pooled fusion rate; PRISMA = preferred reporting items for systematic review and meta-analysis; RT = radiation therapy.

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With the advent of new adjunctive therapies such as stereotactic body radiation therapy, proton beam therapy, and molecular-targeted therapy, the overall survival rate of patients with spinal column tumors undergoing resection has been improving over the last two decades.[24,28,29,37] Also, due to novel reconstruction techniques, such as titanium mesh cages and expandable cages, and various bone graft and bone graft extender options, more complex reconstructions have become feasible for patients following spinal column tumor resection. Hence, not only overall survival but also other clinical outcomes such as fusion rates, perioperative complications, postoperative neurological deficits, and long-term pain outcomes need to be taken into account to optimize functional outcomes. A significant factor that can significantly alter the quality of life of patients is stability of the spinal column, which is dependent on solid fusion and/or instrumentation.[18] This is particularly true if resection of spinal column tumors involves spondylectomy, sacrectomy, and/or resection of the entire posterior elements.

A major concern related to fusion procedures in spinal oncology is the influence of perioperative radiation therapy (RT) and chemotherapy on bone mineral density (BMD) and fusion outcomes. For instance, Hobusch et al.[33] retrospectively reviewed 127 long-term survivors of chondrosarcoma who underwent RT and/or chemotherapy and concluded that they appear to be at greater risk for having low BMD and suffering from fractures than the healthy population. Proton beam therapy (PBT), which is often used in the treatment of chordomas, is also associated with decreased BMD.[3,43] Furthermore, Emery et al.[25] demonstrated that 4 of 25 patients (16%) who underwent RT for malignant spinal column tumors before spinal fusion developed pseudarthrosis, and the total average radiation dose was higher for the pseudarthrosis group (48.9 Gy) than the fusion group (35.1 Gy). Lastly, Narayan et al.[53] reported a significantly lower fusion rate in patients with spinal column tumors compared with those with degenerative disc disease and trauma (54% vs 91% vs 96%, respectively), which was attributed to "systemic malignancy, local irradiation, and long-term use of systemic steroids." It is interesting that as adjunctive RT and chemotherapy have prolonged life expectancy of patients with spinal column tumors, their detrimental effects on BMD and fusion outcomes have paradoxically become problematic.

Additionally, tumor histology can substantially affect the surgical decision-making process. For instance, patients with primary or benign spinal column tumors often experience prolonged survival,[17] which warrants the need for arthrodesis, although complications such as kyphosis, device subsidence, device loosening, or device fracture may be encountered.[2,4,15,46] In contrast, because patients harboring metastatic spinal column tumors or malignant tumors not amenable to en bloc resection may have relatively limited life expectancy, depending on factors such as tumor histology, extraspinal metastases, and performance status,[64] achievement of fusion may not be required.[21,54]

Lastly, there are some limitations in bone graft options in spinal oncology. In general, the gold standard has been an iliac crest autogenic bone graft (ICABG), although it is associated with donor-site morbidity,[12] as well as a higher pseudarthrosis rate in the setting of spinal oncology.[30] Alternatively, various structural and nonstructural autograft and allograft options as well as various bone graft extenders and enhancers are available. However, the use of local bone grafts such as laminae, facets, pedicles, and/or vertebrae is often avoided for patients with spinal column tumors due to potential microscopic invasion of tumor cells into adjacent areas, which limits the potential bone graft options.[8,9,27,31,40] Additionally, although controversial, the application of bone morphogenetic protein-2 (BMP-2) to patients with tumors is generally contraindicated due to several prior studies that suggested an increased incidence of tumors in patients who received BMP-2.[58,62,63,66]

Because of these issues, it is unclear what bone graft options should be selected in patients with spinal column tumors. The literature is also significantly limited, as a majority of prior reports were either retrospective with small numbers of patients,[1,36] or case reports,[5] focusing on survival outcomes or technical aspects of surgery rather than fusion outcomes.[73] To the best of our knowledge, this is the first systematic review and meta-analysis focusing solely on bone graft options and fusion rates in the setting of spinal column tumor resection, aiming to provide some clinical insight into this controversial issue.

Methods

Web-Based Literature Search

A comprehensive web-based literature search was conducted utilizing Medline to collect all articles documenting bone graft options for spinal fusion following resection of spinal column tumors, complying with preferred reporting items for systematic review and meta-analysis (PRISMA) guidelines (Fig. 1).[59] Using the following search terms, 2576 articles were identified from January 1, 1980, to February 1, 2016: "spine tumor" and "fusion" or "spinal tumor" and "fusion" or "spinal metastasis" and "fusion" or "spine metastasis" and "fusion" or "spine tumor" and "bone graft" or "spine tumor" and "autograft" or "spine tumor" and "allograft" or "spine tumor" and "BMP" or "spine tumor" and "bone morphogenetic protein" or "spine tumor" and "demineralized bone matrix" or "spine metastasis" and "autograft" or "spine metastasis" and "allograft" or "spine metastasis" and "BMP" or "spine metastasis" and "bone morphogenetic protein" or "spine metastasis" and "demineralized bone matrix" or "spine tumor" and "arthrodesis" or "spinal tumor" and "arthrodesis" or "spine tumor" and "reconstruction" or "spinal tumor" and "reconstruction" or "spine tumor" and "instrumentation" or "spinal tumor" and "instrumentation." Two independent authors reviewed each paper (B.D.E. and W.I.). If there were differences in opinions as to which articles should be included, a third reviewer was consulted (T.F.W.). Inclusion criteria were as follows: 1) full-texts were available, 2) articles were written in English, 3) studies were on human subjects, 4) more than 5 patients were included, and 5) fusion outcomes and bone graft used were reported. Technical case reports, review articles, ex vivo biomechanical studies, and articles not involving spinal column tumors were excluded. Following application of these inclusion and exclusion criteria, 27 relevant studies[7,8,9,14,16,19,21,22,25,27,31,34,35,38–42,45,48,54,55,67,69–71,74] were

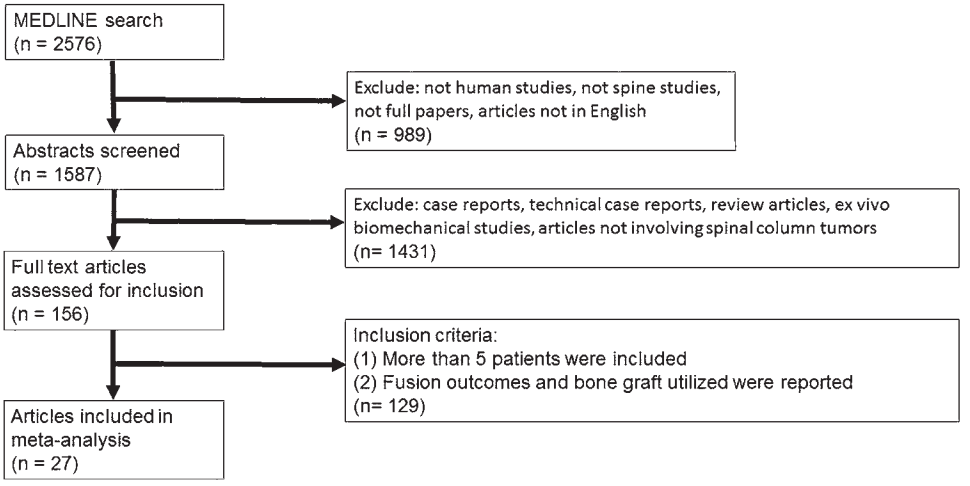

FIG. 1. Literature search results and screening process, based on the PRISMA guidelines.

identified. Clinical information on baseline characteristics, tumor histology, follow-up periods, mortality, adjunctive treatments, reconstruction methods, bone graft options, fusion assessment, fusion outcomes, and time to fusion were collected. Lastly, clinical data on 272 individual patients was available in 25 articles,[7–9,14,16,19,21,22,25,27,31,35,38–42,45,48,54,55,67,69–71] which was further collected and analyzed.

Statistical Analysis

Statistical analyses were performed utilizing GraphPad Prism (version 6; GraphPad Software, Inc.) and Comprehensive Meta-Analysis Software (version 3, Biostat). Initially, a meta-analysis on 27 articles was conducted to calculate the overall pooled fusion rate. Next, the fusion rates, stratified by variables such as tumor histology, bone grafts, and reconstruction methods, were further analyzed. A fixed-effects model was applied in each analysis and the heterogeneity of the meta-analysis was calculated using I^2 statistics. As previously described,[32] I^2 values less than 25% were considered as low heterogeneity, 25%–75% as moderate heterogeneity, and more than 75% as severe heterogeneity. Meta-regression analysis was additionally performed to clarify which variables affected the fusion rates and caused heterogeneity between studies; p values, which tested the null hypothesis that the coefficient of each meta-regression analysis was equal to zero, were also calculated.

For analyses on individual patients' data, a Fisher's exact test was performed to compare intergroup differences stratified by categorical variables. Intergroup comparison of continuous variables was conducted using unpaired t-tests. Data are presented as means ± standard deviations unless noted otherwise. To identify factors related to pseudarthrosis, univariate analysis was initially performed and factors associated with pseudarthrosis in the univariate analysis ($p < 0.10$) were subsequently entered into a multivariate logistic regression analysis. The odds ratios (ORs) for each variable were reported in addition to 95% confidence intervals (CIs). For time-to-fusion analyses, Kaplan-Meier curves, stratified by variables, were drawn and compared between the two groups by the log-rank test. Hazard ratios (HRs) were calculated along with 95% CIs. Finally, publication bias was assessed by drawing a funnel plot for the 27 control groups. The classic fail-safe N test was conducted and p values, which tested the null hypothesis that there was no publication bias and the funnel plot was symmetrical, were obtained.[57] All reported p values were two-sided and $p < 0.05$ was considered to be statistically significant.

Results

Overview of the Included Studies

In 27 articles that met the inclusion criteria, fusion outcomes and bone graft materials were reported for 383 patients following resection of spinal column tumors. In Table 1, basic characteristics of each study are shown. The range of numbers of patients included in each study varied from 5 to 39. The evidence level was III in 2 articles,[19,25] and IV in 25 studies.[7–9,14,16,21,22,27,31,34,35,38–42,45,48,54,55,67,69–71,74] The mean number of levels of tumor involvement ranged from 1 to 4.4, and 5 studies[25,34,35,54,74] did not report this information. The number of articles reporting data on primary tumors, metastatic tumors, and both, were 9, 4, and 14, respectively. The mean follow-up periods of each study varied widely from 9 months to 119 months. At last follow-up, 0%–29% of patients harboring primary tumors had died, whereas mortality of patients with metastatic tumors ranged from 0% to 100%. In Table 2, bone graft options and fusion outcomes are summarized. Thirteen studies[10,14,16,19,22,25,31,34,35,39,40,55,71] used bone grafts solely for anterior fusion, whereas two studies[41,74] solely performed posterior fusion. The other 12 studies[7,8,21,27,38,42,45,48,54,67,69,70] included patients who underwent either anterior fusion, posterior fusion, or both, and were thus substantially heterogeneous. Regarding graft options, 7 studies[16,19,39,42,55,70,71] used cages filled with morselized bone graft or other bone graft extenders, whereas 4 studies,[27,41,48,67] included patients with vascularized autogenic bone grafts either with or without vascular pedicles. Regarding adjunctive therapy, 18 studies,[7,8,14,16,21,22,25,35,38–42,45,48,67,70,74] clearly stated the percentage of patients who underwent RT, which substan-

TABLE 1. Summary of basic characteristics of each study

Authors & Year	No. of Patients (% female)	Mean Age in Yrs (range)	Mean Levels of Tumor Involvement (range)	Location	Tumor Histology	Benign or Malignant	Primary or Metastatic	Mean FU in Mos (range)	Mortality Rate at Last FU (%)	1-Yr OS Rate (%)
Bohlman et al., 1986	16 (31)	38 (16–69)	1	C: 16	CH 4, HA 2, OB 1, OC 1, SP 1, ISH 1, MFH 1, OO 1, SA 1	Mixed	Mixed	63 (1– 216)	44	88
Emery et al., 1994	25 (44)	NR	NR	C: 4 T: 12 L: 9	BC 6, PC 4, CH 2, LC 2, MM 2, CC 1, HA 1, OSS 1, RCC 1, others 5	Mixed	Mixed	21 (6–65)	52	NR
Jackson & Gokaslan, 2000	13 (39)	45 (26–74)	NR	LS: 13	CH 3, GCT 2, RCC 2, BC 1, CC 1, CS 1, ME 1, SCS 1, SEM 1	Mixed	Mixed	20 (3–50)	31	77
Fidler, 2001	10 (50)	32 (21–68)	2.4 (1–6)	T: 9 L: 1	GCT	Benign	Primary	89 (30–144)	10	100
Coumans et al., 2002	15 (NR)	59 (31–81)	1.7 (1–3)	C: 12 T: 3	LC 4, RCC 2, ISH 2, BC 1, CC 1, MM 1, PA 1, PC 1, SP 1, unknown 1	Mixed	Mixed	9 (0.5–15)	27	70
Boriani et al., 2002	39 (43)	45 (7–69)	1.2 (1–3)	T: 14 L: 28	Primary malignant tumor 26, benign tumor 7, solitary metastatic tumor 6, plasmacytoma 3	Mixed	Mixed	26 (6–60)	14	NR
Heidecke et al., 2003	14 (57)	51 (19–66)	1.4 (1–2)	C	BC 6, MM 2, HS 1, LC 1, ML 1, PC 1, RCC 1, SEM 1	Malignant	Metastatic	24 (3–60)	86	57
Lewandrowski et al., 2004	30 (60)	47 (17–76)	1.3 (1–5)	T: 14 L: 16	CS 7, OS 6, CH 4, 3 RCC 3, BC 2, CC 1, TC 1, others 6	Mixed	Mixed	14 (7–60)	100	NR
Wilden et al., 2006	13 (62)	44 (18–73)	4.4 (1–10)	NR	CS 3, PG 2, PT 2, ABC 1, ES 1, mGCT 1, GN 1, LES 1, RCC 1	Mixed	Mixed	25 (14–50)	15	100
Oda et al., 2006	5 (unclear)	Unclear	NR	NR	Unclear	Malignant	Metastatic	22	100	NR
Denaro et al., 2007	8 (25)	21 (13–24)	1	C-1: 1 C-2: 1 C: 6	OB	Benign	Primary	39 (32–44)	0	100
Barrenechea et al., 2007	7 (43)	34 (6–61)	2.9 (2–4)	C-2: 1 C: 6	CH	Malignant	Primary	59 (7–163)	29	86
Liljenqvist et al., 2008	21 (NR)	30 (9–68)	1.4 (1–4)	T: 10 TL: 1 L: 10	ES 8, OSS 6, RCC 3, CS 1, DF 1, MHF 1, PG 1	Malignant	Mixed	41 (8–114)	24	90
Junming et al., 2008	19 (32)	35 (17–52)	1.6 (1–3)	C-2: 4 C: 15	GCT 19	Benign	Primary	67 (36–124)	16	100
Chuang et al., 2008	17 (41)	55 (34–77)	1	C	LC 7, CC 4, NAC 2, BC 2, HC 1, CHC 1	Malignant	Metastatic	NR	NR	NR
Moran et al., 2009	7 (29)	30 (14–55)	3.3 (2–5)	LS: 4 SAC: 3	CS 2, ES 1, ME 1, mGCT 1, OSS 1, SCS 1	Malignant	Mixed	45 (19–98)	14	NR
Omeis et al., 2010	5 (60)	67 (58–77)	2.6 (2–4)	C: 3 CVT: 2	BC 2, CC 2, LC 1	Malignant	Metastatic	13 (1–27)	0	100

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TABLE 1. Summary of basic characteristics of each study

Authors & Year	No. of Patients (% female)	Mean Age in Yrs (range)	Mean Levels of Tumor Involvement (range)	Location	Tumor Histology	Benign or Malignant	Primary or Metastatic	Mean FU in Mos (range)	Mortality Rate at Last FU (%)	1-Yr OS Rate (%)
Hu et al., 2010	18 (33)	48 (34–65)	NR	TL or L	GCT 2, SP 2, CS 1, ES 1, BC 2, LC 2, PC 2, RCC 2, LES 1, TC 1, unknown 2	Mixed	Mixed	24 (18–36)	17	83
Yang et al., 2011[70]	11 (36)	50 (23–77)	1.4 (1–3)	C-2	CH 2, GCT 2, SP 2, EG 1, HP 1, LC 1, NAC 1, PC 1	Mixed	Mixed	21 (12–37)	27	90
Yang et al., 2011[69]	9 (56)	39 (19–61)	1.2 (1–2)	C-1	OC 3, OB 2, CS 1, EG 1, GCT 1, SP 1	Mixed	Primary	53 (16–100)	11	100
Kawahara et al., 2011	10 (50)	42 (16–59)	1.6 (1–3)	L	GCT 4, BC 2, ABC 1, HA 1, LPS, RCC 1	Mixed	Mixed	52 (14–124)	20	100
Lewis et al., 2012	17 (29)	51 (16–74)	2.1 (1–3)	T: 17	LC 10, CS 3, OO 3, OSS 1	Mixed	Mixed	28 (2–72)	35	65
Yoshioka et al., 2013	22 (59)	33 (52–68)	3.3 (3–5)	CVT: 2 T: 15 TL: 5	RCC 7, BC 3, GCT 3, TC 3, AS 1, CH 1, CS 1, LC 1, LES 1, SM 1	Mixed	Mixed	26 (12–67)	14	100
Zheng et al., 2014	6 (17)	31.8 (18–52)	NR	CVJ	EG	Benign	Primary	77 (37–140)	0	100
Menezes et al., 2014	13 (31)	11 (4–17)	1.3 (1–2)	CVJ	CH 4, FD 3, ABC 2, OB 2, EG 1, OC 1	Mixed	Primary	119 (24–204)	0	100
Domovitov et al., 2016	8 (63)	33 (25–55)	2.4 (1–4)	SAC	GCT	Benign	Primary	99 (2–288)	25	88
Chen et al., 2015	5 (60)	31 (23–45)	1	C	GCT	Benign	Primary	32 (10–48)	0	100

ABC = aneurysmal bone cyst; AS = angiosarcoma; BC = breast cancer; C = cervical; CC = colon cancer; CH = chordoma; CHC = cholangiocarcinoma; CS = chondrosarcoma; CVJ = craniovertebral junction; CVT = cervicothoracic; DF = desmoplastic fibroma; EG = eosinophilic granuloma; ES = epithelioid sarcoma; FD = fibrous dysplasia; FU = follow-up; GCT = giant cell tumor; GN = ganglionic neuroblastoma; HA = hemangioma; HC = hepatic cancer; HP = hemangioperithelioma; HS = histiocytoma; ISH = intraosseous schwannoma; L = lumbar; LC = lung cancer; LES = leiomyosarcoma; LPS = liposarcoma; LS = lumbosacral; ME = myxopapillary ependymoma; MFH = malignant fibrous histiocytoma; ML = melanoma; MM = multiple myeloma; mGCT = malignant GCT; NAC = nasopharyngeal cancer; NR = not reported, OB = osteoblastoma; OC = osteochondroma; OO = osteoid osteoma; OS = overall survival; OSS = osteosarcoma; PA = parotid adenocarcinoma; PC = prostate cancer; PG = paraganglioma; PT = pancoast tumor; RCC = renal cell carcinoma; SA = other sarcomas; SAC = sacral; SCS = spindle cell sarcoma; SEM = seminoma; SM = "Salida of macilla"; SP = solitary plasmacytoma; T = thoracic; TC = thyroid cancer; TL = thoracolumbar.
All studies were single-center, retrospective study designs, except for Emery et al., 1994 (multicenter, retrospective), and Coumans et al., 2002 (single-center, prospective). The quality of each study was Level IV, except for Coumans et al., 2002, and Emery et al., 1994 (both Level III).

tially varied from 0% to 100%, whereas 14 studies[7,8,21,22,25,34,35,39,41,42,45,67,70,74] provided the percentage of those who underwent chemotherapy, which ranged from 0% to 59%. Information on preoperative embolization was available in 8 studies.[7,21,22,39–41,45,74]

Meta-Analysis and Meta-Regression Analysis

Overall, fusion rates varied widely from 36.0% to 100.0%, with a pooled fusion rate (PFR) of 85.7% (95% CI 80.6%–89.6%). The I^2 value was 36.4, which suggested moderate heterogeneity (Fig. 2). Following stratification into primary tumors and metastatic tumors, the PFRs and I^2 values were 91.9% and 0 for primary tumors, and 79.5% and 58.3 for metastatic tumors, respectively ($p = 0.21$; Fig. 3). The studies in which cages were used for anterior fusion showed a PFR of 92.8 and I^2 value of 0, whereas those without use of cages demonstrated a PFR of 83.3% and an I^2 value of 47.1 ($p = 0.04$; Fig. 4). The comparison between vascularized bone grafts and others revealed that the PFR was higher in the vascularized bone graft group (93.0% vs 84.8%), although this difference was not statistically significant in the meta-regression analysis ($p = 0.21$; Fig. 5). Lastly, the PFRs and the I^2 values for the articles whose primary outcomes were fusion outcomes versus others were 81.7% and 55.1 versus 91.6% and 0, respectively ($p = 0.04$; Fig. 6).

Analysis on Individual Patient Data

For variables difficult to assess in the meta-analyses above due to intrastudy heterogeneity, analyses on avail-

TABLE 2. Summary of fusion methods and fusion outcomes of each study

Authors & Year	Device	Ant Bone Graft	Struct	Pst Bone Graft	Struct	Embo (%)	RT		Chemo (%)	Fusion		Mean Mos to Fusion (range)
							%	Dose (Gy)		Assessment	%	
Bohlman et al., 1986	NR	ICABG, fibula autograft	Yes	ICABG, fibula autograft	Yes	NR	38	NR	13	Radiography	100 (9/9)	NR
Emery et al., 1994	NR	ICABG 21, fibula autograft 2, rib autograft 1, humerus allograft 1	Yes			NR	100	37	24	Radiography	84 (21/25)	NR
Jackson & Gokaslan, 2000	Modified Galveston technique	ICABG + allograft + DBM	Yes			NR	54	NR	46	Radiography	31 (4/13)	NR
Fidler, 2001	AP ± PI	ICABG 7, ICABG + vascularized rib autograft 2, fibula autograft 1	Yes	ICABG 9	Yes	NR	10 (unclear)	45	10 (unclear)	Radiography, CT	100 (10/10)	NR
Coumans et al., 2002	Cage	Cage + DBM and CHA 13, local autograft 2	No			NR	"most"	NR	NR	CT	100 (9/9)	NR
Boriani et al., 2002	AP + cage 8, PI + cage 34	ICABG or rib autograft	No			NR	66 (unclear)	NR	59 (unclear)	Radiography, CT	80 (34/42)	16 (3–24)
Heidecke et al., 2003	AP	ICABG	Yes			NR	85 (unclear)	NR	43 (unclear)	Radiography	100 (14/14)	NR
Lewandrowski et al., 2004	AP + PI	Femur allograft 12, humerus allograft 11, tibia allograft 3, fibula allograft 2, clavicle allograft 1, rib allograft 1, + morselized ICABG or rib autograft	Yes			10	100	60–77	Unclear	Radiography, CT	93 (28/30)	w/in 6
Wilden et al., 2006	AP + cage	Vascularized rib graft	Yes	Vascularized rib graft	Yes	NR	77	NR	31	Radiography, DXP, CT	100 (13/13)	6.8 (3–14)
Oda et al., 2006	Unclear	Autologous bone graft	Yes	Autologous bone graft	Unclear	NR	NR	NR	NR	Unclear	40 (2/5)	NR
Denaro et al., 2007	AP or absorbable wire + PI	ICABG	Yes	ICABG	Yes	100	0		0	Radiography, DXP, CT	100 (8/8)	3 (3–3)
Barrenechea, et al. 2007	AP + PI 5, PI 2	Fibular allograft + DBM 3, ICABG 2	Yes	ICABG	Unclear	0	71	79	29	Radiography, CT	100 (7/7)	NR
Liljenqvist et al., 2008	TRC + PI	TRC + autograft chips 19, fibula autograft 2	No	ICABG 16, fibula allograft 5	Yes	NR	19	NR	19	Radiography, CT	95 (20/21)	NR
Junming et al., 2008	AP ± TMC ± PI	ICABG 7, ICABG + AP 6, TMC + autograft chips 5	No	NR	Unclear	NR	84	NR	NR	Radiography, CT	100 (19/19)	NR
Chuang et al., 2008	TMC + AP	TMC + TCP/HA	No			NR	100	NR	NR	Radiography, CT	100 (9/9)	NR
Moran et al., 2009	PI	Vascularized fibula graft 3	Yes	Vascularized fibula graft 4	Yes	NR	57	NR	NR	Radiography, CT	83 (5/6)	3.8 (3–5)
Omeis et al., 2010	EC + PI	Allograft + DBM + EC	No			NR	NR	NR	NR	Radiography, CT	100 (4/4)	NR
Hu et al., 2010	TMC + PI	Allograft 15, rib autograft 3	Yes			NR	NR	NR	17	Radiography, CT	100 (18/18)	NR

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TABLE 2. Summary of fusion methods and fusion outcomes of each study

Authors & Year	Device	Ant Bone Graft	Struct	Pst Bone Graft	Struct	Embo (%)	RT		Chemo (%)	Fusion		Mean Mos to Fusion (range)
							%	Dose (Gy)		Assessment	%	
Yang et al., 201170	TMC + PI	ICABG + TMC	No	ICABG	Yes	NR	90	40–55	18	Radiography, CT	100 (11/11)	NR
Yang et al., 201169	C0–C3 PI	ICABG	Yes	ICABG	Yes	NR	NR	NR	NR	Radiography, CT	100 (9/9)	NR
Kawahara et al., 2011	TMC + PI	ICABG 2, ICABG + TMC 8	No			100	0		0	Radiography, CT	90 (9/10)	NR
Lewis et al., 2012	AP ± TMC ± PI			Rib autograft 9, vascularized rib autograft 8	Yes	0	59	NR	59	Radiography, CT	100 (11/11)	6 (6–6)
Yoshioka et al., 2013	TMC + PI	TMC filled w/ autograft	No			NR	NR	NR	NR	Radiography, CT	91 (19/21)	NR
Zheng et al., 2014	PI			Autograft	Yes	0	0		0	Radiography, CT	100 (6/6)	NR
Menezes et al., 2014	AP ± PI	Rib autograft 10	Yes	Rib autograft 3	Yes	23	38	NR	0	Radiography, CT	80 (4/5)	4.5 (4–5)
Domovitov et al., 2016	AP 5, no hardware 3	ICABG 4, allograft 2, fibula autograft + allograft 1, NR 1	Yes			63	50	44–66	0	Radiography, CT	83 (5/6)	NR
Chen et al., 2015	AP 2, no hardware 3	β-TCP 3, ICABG 2	No			NR	100	30–456	NR	Radiography	100 (5/5)	9 (9–9)

Ant = anterior; AP = anterior plate; CHA = coralline hydroxyapatite; Chemo = chemotherapy; DBM = demineralized bone matrix; DXP = dynamic radiography; EC = expandable cage; Embo = embolization; PI = posterior instrumentation; Pst = posterior; Struct = structural graft; TCP/HA = tricalcium phosphate/hydroxyapatite; TMC = titanium mesh cage; TRC = titanium ring cage; β-TCP = beta-tricalcium phosphate.

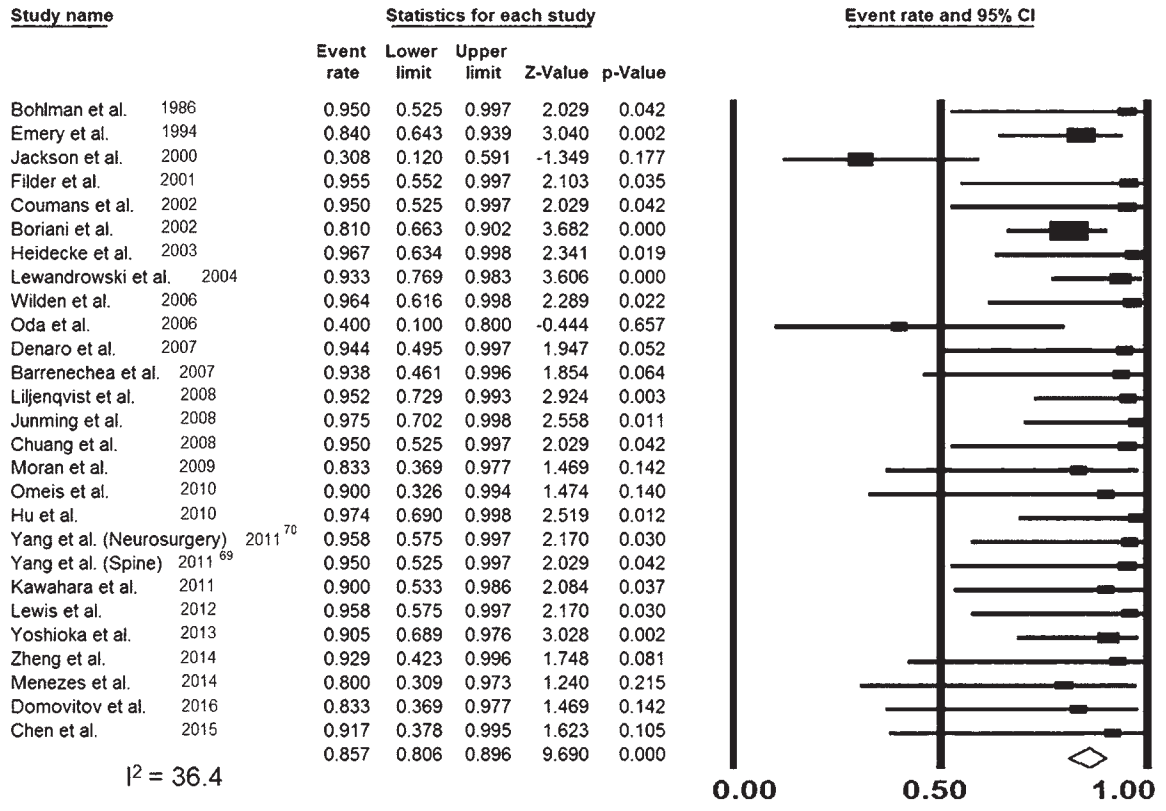

FIG. 2. Fusion rates of each study and the result of the meta-analysis.

able individual patient data were further performed. The fusion rates stratified by each variable are shown in Table 3. In univariate analyses, tumors at junctional locations had a significantly lower fusion rate of 84.5% as opposed to 94.1% for nonjunctional tumors ($p = 0.02$). Furthermore, tumors in lumbar and/or sacral regions demonstrated a significantly lower fusion rate of 74.6% compared with other regions of the spine (97.9%, $p < 0.001$). In terms of adjunctive treatments, perioperative radiation was associated with lower fusion rates (90.3% vs 98.6%, $p = 0.03$). Perioperative chemotherapy and preoperative embolization were not related to fusion status with statistical significance. For analyses on reconstruction techniques, the combined anterior and posterior fusion group resulted in a higher fusion

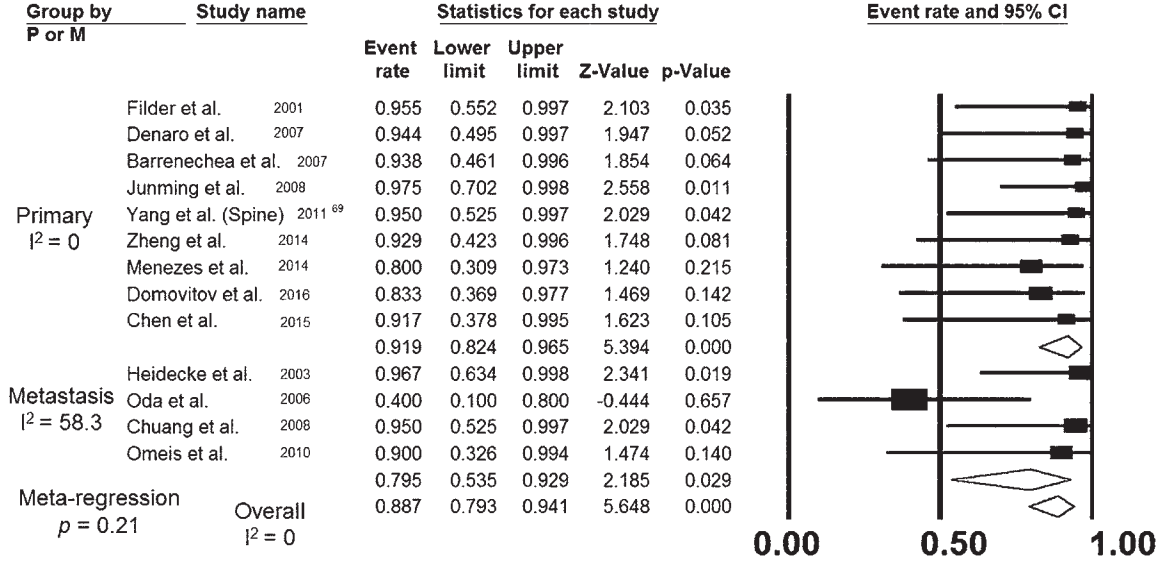

FIG. 3. The result of the meta-analysis and the meta-regression analysis, stratified by primary (P) tumors versus metastatic (M) tumors.

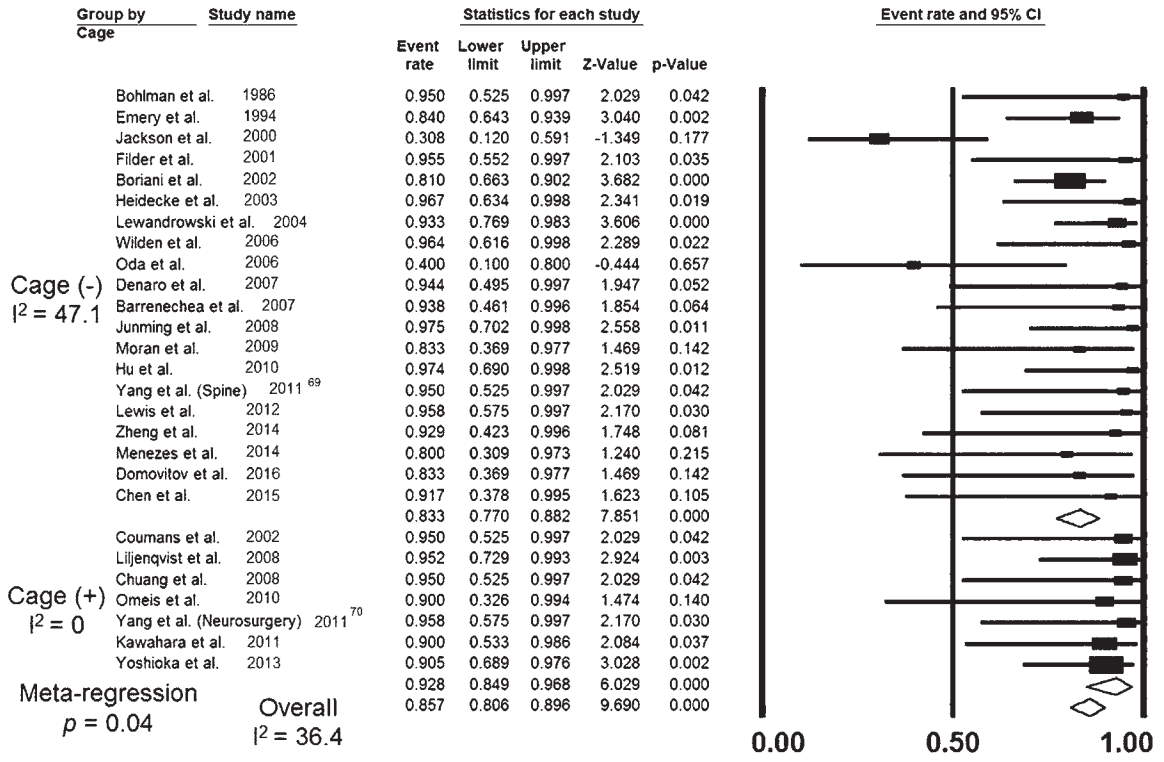

FIG. 4. The result of the meta-analysis and the meta-regression analysis, stratified by the use of cages for anterior fusion.

rate than the anterior fusion only group (98.8% vs 86.4%, p < 0.001). Lastly, none of the specific graft options analyzed here, including structural ICABG, structural allograft, rib structural autograft, vascularized autograft, or cage filled with bone graft or bone graft substitute/extender, demonstrated better or worse fusion outcomes with statistical significance. In multivariate analyses, tumors in the lumbar spine and/or sacrum were significantly associated with a

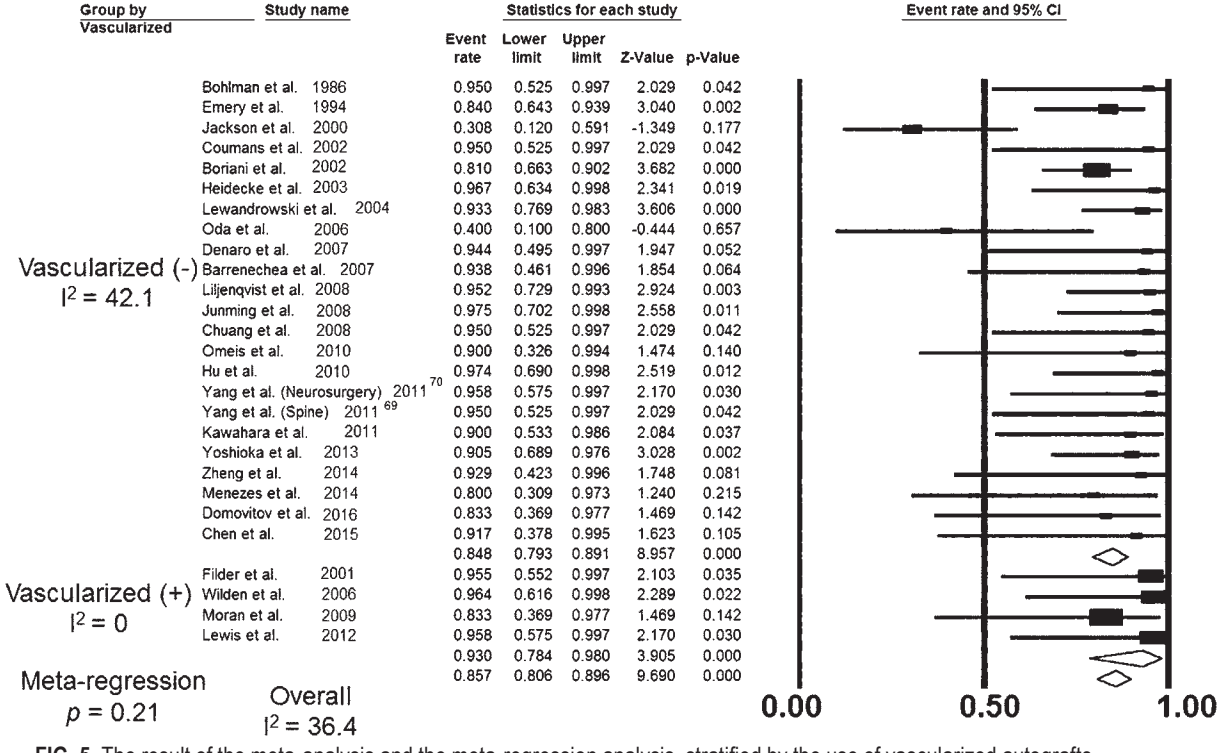

FIG. 5. The result of the meta-analysis and the meta-regression analysis, stratified by the use of vascularized autografts.

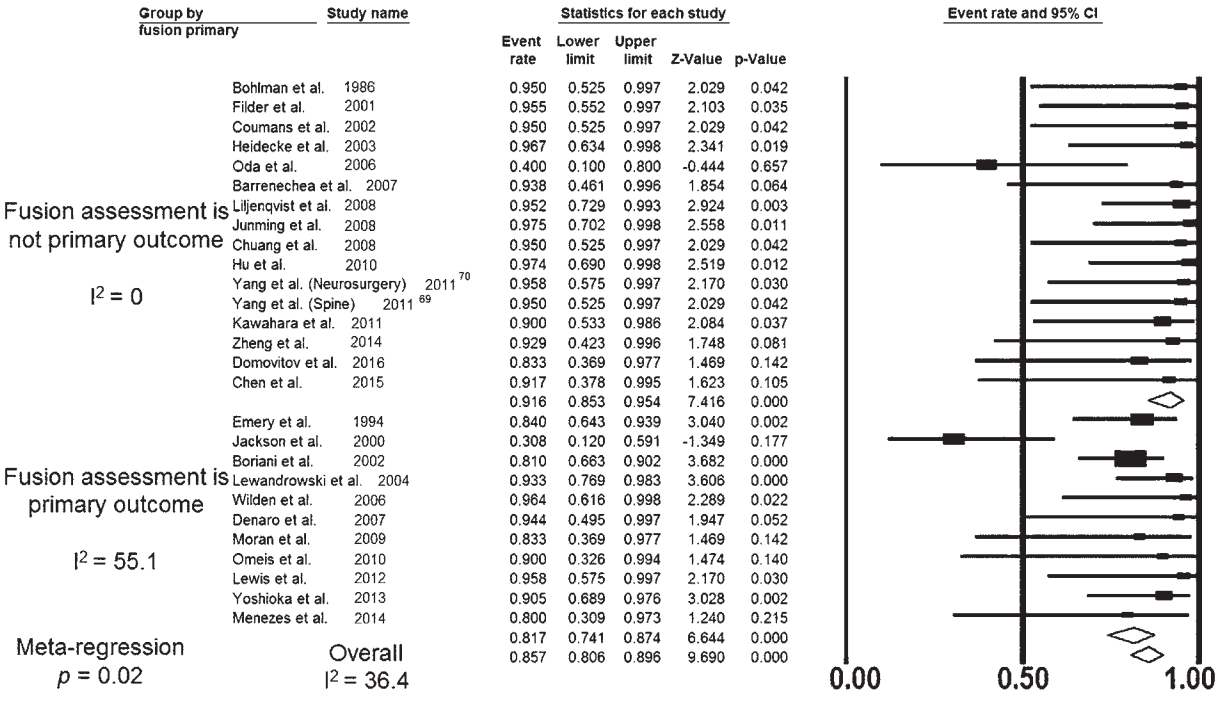

FIG. 6. The result of the meta-analysis and the meta-regression analysis, stratified by primary outcomes.

lower fusion rate (OR 0.12, 95% CI 0.02–0.74, p = 0.02), whereas perioperative radiation trended toward a worse fusion outcome (OR 0.19, 95% CI 0.02–1.68, p = 0.10).

Time to Fusion Analysis

Time to fusion was reported for 58 patients with an overall mean time to fusion of 5.4 ± 1.4 months (range 3–9 months), whereas 16 of 272 patients died before the confirmation of solid fusion with a mean survival of 3.1 ± 2.1 months (range 0.5–6 months). The mean time to fusion was significantly longer in patients harboring metastatic tumors (6.0 vs 5.1 months, p = 0.01), patients who underwent perioperative radiation therapy (6.1 vs 4.3 months, p < 0.001), patients who received perioperative chemotherapy (6.0 vs 4.3 months, p = 0.02), and patients who did not undergo preoperative embolization of tumors (5.9 vs 3.9 months, p < 0.001; Table 4). Additionally, Kaplan-Meier analysis revealed that vascularized grafts were associated with earlier fusion, compared with other graft options (p = 0.03), with an HR of 5.2 (95% CI 1.2–22.6; Fig. 7).

Publication Bias

The funnel plot is shown in Fig. 8, where the logit event rate = log (fusion rate/[1 – fusion rate]). A potential publication bias was suggested, with the p value of the classic fail-safe N test calculated to be 0.002.

Discussion

To the best of our knowledge, this is the first systematic review and meta-analysis of bone graft options for spinal fusion following resection of spinal column tumors. The objective of this study was to review and meta-analyze the current literature and provide some insight into arthrodesis outcomes in spinal oncology surgery. With a growing understanding of the biology of spinal tumors and the advent of novel adjunctive treatment options and reconstruction techniques, the overall survival of patients with spinal column tumors has been increasing.[28,29,37] Thus, in addition to survival outcomes, other clinical considerations such as fusion outcomes, neurological outcomes, and pain outcomes should be taken into consideration to improve quality of life of the patients. Achieving solid arthrodesis is an important factor in the setting of resection of spinal column tumors, given the potentially long overall survival with likely instrumentation failure in the absence of arthrodesis. To achieve fusion, a wide variety of bone grafts, bone graft substitutes, and bone graft extenders have been explored in combination with instrumentation such as cages and pedicle screw/rod constructs.[7,8,10,14,19,21,22,25,27,31,34,35,38–42,45,48,54,55,67,69–71,74] However, because the majority of previous studies have been case reports, technical notes, or retrospective studies with small numbers of patients, it remains challenging to determine which patient populations benefit most from achieving fusion and what types of bone grafts should be used to maximize fusion rates.

The most significant limitation of this study was that the fusion rates reported in the reviewed literature varied widely from 36% to 100%, which may be explained by the fact that articles included in the review were moderately heterogeneous. For instance, 14 articles included patients with both primary tumors and malignant tumors (intrastudy heterogeneity); the number of articles that included patients who underwent anterior fusion only, posterior fusion only, and miscellaneous, were 13, 2, and 12, respectively (intra- and interstudy heterogeneity). Graft options used in each study varied widely within and between studies (intra- and interstudy heterogeneity), and the details on

TABLE 3. Fusion rates stratified by each variable

Variable	Univariate Analysis				Multivariate Analysis		
	Fusion (n = 250)	Nonfusion (n = 22)	Fusion rate (%)	p Value	OR	95% CI	p Value
Baseline characteristics							
Mean age ± SD (yrs)	40.9 ± 18.0	32.7 ± 18.7		0.18			
Mean tumor levels ± SD	1.8 ± 1.1	1.8 ± 1.0		0.96			
Mean FU period ± SD (mos)	44.6 ± 36.4	56.6 ± 82.6		0.28			
Tumor characteristics							
Primary	138	9	93.9	0.46			
Metastatic	91	9	91.0				
Benign	90	4	95.7	0.21			
Malignant	139	14	90.8				
Osteolytic (+)	43	7	86.0	0.32			
Osteolytic (−)	46	3	93.9				
Junction (+)	60	11	84.5	**0.02**	0.62	(0.05–7.40)	0.71
Junction (−)	177	11	94.1				
Lumbar and/or sacrum	53	18	74.6	**<0.001**	0.12	(0.02–0.74)	**0.02**
Others	184	4	97.9				
Adjunctive treatment							
RT (+)	93	10	90.3	**0.03**	0.19	(0.02–1.68)	**0.10**
RT (−)	70	1	98.6				
Chemo (+)	14	0	100.0	1			
Chemo (−)	85	4	95.5				
Embo (+)	23	3	88.5	0.18			
Embo (−)	55	2	96.5				
Graft							
Anterior & pst fusion	85	1	98.8	**<0.001**	0.42	(0.04–4.21)	0.46
Anterior fusion only	127	20	86.4				
Structural ICABG (+)	75	5	93.8	0.63			
Structural ICABG (−)	175	17	91.1				
Structural allograft (+)	39	3	92.9	1			
Structural allograft (−)	211	19	91.7				
Rib structural autograft (+)	30	1	96.8	0.49			
Rib structural autograft (−)	220	21	91.3				
Vascularized autograft (+)	23	1	95.8	0.70			
Vascularized autograft (−)	227	21	91.5				
Cage (+)	74	3	96.1	0.14			
Cage (−)	176	19	90.3				

(+) = positive; (−) = negative.
Boldface type indicates statistical significance.

adjunctive treatments were suboptimally reported across 27 studies (intra- and interstudy heterogeneity). Variables with interstudy heterogeneity, such as cage and vascularized graft status, were further analyzed with a meta-regression model, which revealed that the use of cages filled with morselized ICABG and/or other bone graft options was significantly associated with a higher fusion rate. This result suggests a potential advantage to reconstruction of the anterior column with a cage to provide early structural support, although the result may be biased as tumors are more likely to involve the vertebral body. On the other hand, vascularized bone graft did not demonstrate better fusion outcomes, presumably due to the limited number of studies.

Variables with intrastudy heterogeneity prevented further meta-analyses or meta-regression analyses, which warranted subsequent per-patient analyses. In per-patient analyses, the location of spinal column tumors in the lumbosacral spine was the only independent factor related to pseudarthrosis, which is compatible with nontumor studies and potentially due to the higher biomechanical loads in those areas. While perioperative RT demonstrated a trend toward a lower fusion rate, none of the modifiable factors, namely, graft and reconstruction options, were associated

TABLE 4. Time to fusion stratified by each variable

Variable	No. of Patients	Mean Time to Fusion ± SD (mos)	p Value
Patient characteristics			
Male	19	4.7 ± 1.8	0.47
Female	9	5.2 ± 1.9	
Tumor characteristics			
Primary	33	5.1 ± 1.7	**0.01**
Metastatic	25	6.0 ± 0.2	
Junction (+)	7	5.4 ± 2.6	0.97
Junction (−)	51	5.5 ± 1.2	
Lumbosacral	21	5.5 ± 1.1	0.91
Others	37	5.4 ± 1.5	
Adjunctive treatment			
RT (+)	39	6.1 ± 0.9	**<0.001**
RT (−)	16	4.3 ± 1.4	
Chemo (+)	5	6.0 ± 0.0	**0.02**
Chemo (−)	16	4.3 ± 1.4	
Embo (+)	12	3.9 ± 3.8	**<0.001**
Embo (−)	39	5.9 ± 0.3	
Graft			
ICABG (+)	4	6.0 ± 3.5	0.41
ICABG (−)	54	5.4 ± 1.1	
Rib autograft (+)	13	5.8 ± 0.6	0.34
Rib autograft (−)	45	5.4 ± 1.5	
Vacularized autograft (+)	9	4.8 ± 1.3	**0.09**
Vacularized autograft (−)	49	5.6 ± 1.0	

Boldface type indicates statistical significance or trend toward significance.

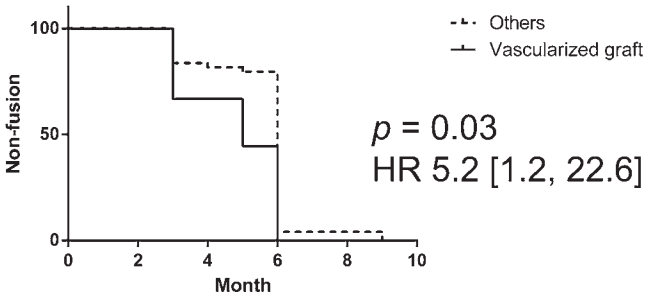

FIG. 7. Kaplan-Meier curves on time to fusion, stratified by the use of vascularized autografts.

with fusion outcomes in multivariate analysis. However, if meta-regression and univariate analysis of this study were taken into consideration, the use of cages filled with morselized ICABG and/or other bone graft options, and combined anterior and posterior fusion, were associated with better fusion outcomes. In terms of bone graft options for posterior fusion, only 2 studies reported posterior-only fusion in 23 patients, which made it impossible to separately analyze the data.

BMP-2 was not used in any of the patients included in this study, which indicated that there remains significant concern regarding potential carcinogenicity and contraindications in oncology patients. While a recent meta-analysis by Cahill et al.[11] revealed that there was no conclusive evidence that BMP-2 was associated with the formation of cancer locally or at a distant site, there remains concern regarding its potential carcinogenicity.[58,62,63,66]

Although the use of local bone grafts are relatively contraindicated following spinal column tumor resection, patients in 3 studies[19,41,54] received morselized local bone grafts. Of note, Coumans et al.[19] reported the use of a vertebral autograft that contained tumor, after the diagnosis of benign intraosseous schwannoma was confirmed by intraoperative pathological diagnosis. Also, it has been demonstrated that following spondylectomy, vertebral bodies with tumors could be used as morselized bone grafts in conjunction with cages if they were placed into liquid nitrogen (–196°C) for 20 minutes.[49–52,61] Surprisingly, this technique was applied to malignant tumors as well, and with an average follow-up of 14 months, none of the 56 patients (49 with metastatic tumors) developed recurrence in the grafted bone inside cages.[51] It was also demonstrated that the implantation of a tumor-bearing graft could systemically induce antitumor immune response in human studies.[49,50] Future multicenter, prospective studies regarding these intriguing treatments with longer follow-up periods would be necessary to better elucidate their safety features and true advantages. This surgical strategy remains controversial, considering the possibility of tumor recurrence or malignant transformation of some tumor histologies.

There are advantages to using vascularized autografts, either from ribs or fibulas, which merit further discussion, although these should be weighed against the more invasive surgical procedure. In this analysis, time to fusion was discovered to be shorter in patients receiving vascularized autografts, but the fusion rate itself did not differ significantly from the other bone graft options. This is partly because the number of patients was small in this group but also potentially because 57% to 77% of patients with vascularized autografts received perioperative RT. However, it should be considered that complication rates for this procedure are relatively high, and should be weighed against the potential benefit.[1,27,36,41,48,67] For instance, Minami et al.[47] reported that the procedure had to be abandoned in 3 of 16 patients because of difficulties with microsurgical anastomosis. Also, the mean ± standard deviation time needed for the harvest, rib preparation, and anastomosis was 58 ± 13 minutes.[51] To the best of knowledge, there are no studies comparing morbidities associated with surgical technique between ICABG,[12] fibula autograft,[65] and vascularized autografts. Considering the significant morbidity, vascularized grafting procedures should not be recommended for patients with limited life expectancy. In summary, there is not overwhelming data to support the use of vascularized autografts, although they are likely beneficial in particularly challenging fusion environments in which survival greater than 12 months is expected, and future prospective studies should be performed.

Regarding other factors related to fusion outcomes, it was found that adjunctive treatment was significantly associated with fusion rates as well as time to fusion, which is similar to the results of previous studies. For instance, Orgel et al.[56] reported that patients receiving chemotherapy

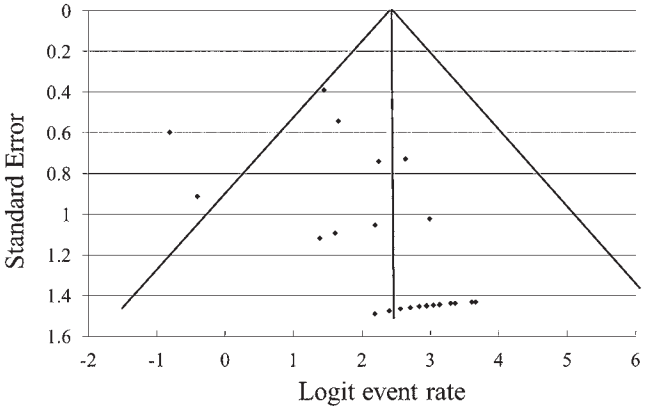

FIG. 8. Funnel plot of standard error by logit event rate, where the logit event rate = log (fusion rate/[1 − fusion rate]).

for acute lymphoblastic leukemia had substantial injury to corticocancellous bones. Additionally, the impact of RT and PBT[3,23,25,43,44] on BMD and fusion outcomes has been previously described. Interestingly, denosumab is currently used as treatment for giant cell tumors as well as osteoporosis.[20,72] Long-term follow-up of patients who underwent postoperative PBT with or without denosumab might be warranted to clarify a supplemental benefit of this newly developed molecular-targeted therapy. Additionally, the potential influence of preoperative embolization on time to fusion was observed in this study. It can be hypothesized that reduced bleeding from the surgical cavity contributed to less dissection and less coagulation of surrounding tissues, which in turn, resulted in a more vascularized fusion bed to promote formation of fusion mass. Alternatively, the hypoxic preconditioning of mesenchymal stem cells in the fusion bed can induce neo-vascularization in an early stage, as several in vitro studies have previously demonstrated.[6,26]

Lastly, intention to achieve arthrodesis based on expected survival merits further discussion. For instance, Coumans et al.[19] advocated 6 months as a cutoff value for the indication of fusion, while Oda et al.[54] proposed 12 months. However, others stated that factors related to spinal instability such as lumbosacral involvement,[48] or more than 3-level spondylectomies,[71] should be considered. Clearly, this decision is patient-specific, but should be considered further given increasing survival times with potential for hardware failure in the absence of arthrodesis. In our systematic review, an ad-hoc analysis revealed that 16 of 272 patients died before the confirmation of solid fusion with a mean survival of 3.1 ± 2.1 months (range 0.5–6 months). In contrast, the mean time to fusion was 5.4 ± 1.4 months (range 3–9 months). Considering these results, we recommend that in patients with estimated life expectancy less than 6–12 months, such as those with a Tokuhashi score < 8 (i.e., harboring an unresectable lung cancer with multiple extraspinal and spinal bone metastases), instrumented stabilization with no attempted arthrodesis would be most reasonable. However, in patients with breast metastases with minimal systemic tumor burden, life expectancy often exceeds 1 year,[13,60] and an attempted arthrodesis should be strongly considered. Additionally, in patients with primary tumors in whom an en bloc resection can be performed successfully, there is often greater longevity; therefore, an attempted arthrodesis should be performed, as the hardware will eventually fail in the absence of fusion. To further clarify this issue, it would be interesting to investigate other studies in which cages without any bone graft were used for reconstruction to determine how long instrumentation itself can last without causing significant complications such as device subsidence,[44,68] device fractures, and kyphosis in adjacent levels, in the oncological patient population.

The general limitations of meta-analyses can be applied to this meta-analysis as well, such as the influences of bias that existed in each study on the results of the meta-analysis. Furthermore, as shown in Fig. 8, a publication bias existed in this meta-analysis, which was mainly due to negative publication bias, i.e., articles in which fusion rates were suboptimal (less than PFR of 85.7%) might have been missing from the included studies. In addition, heterogeneity among patient, disease, surgical, and study characteristics significantly limits drawing strong conclusions from our study. Moreover, as discussed above, some of the missing data on materials and methods in certain articles, particularly relevant variables such as perioperative chemotherapy, RT, and preoperative embolization, biased the results. It is notable that the studies in which arthrodesis was assessed as a primary outcome showed a significantly lower fusion rate than the others, because their fusion criteria were usually more stringent. For instance, Denaro et al.[21] used strict motion criteria along with an assessment of bridging bone, while Zheng et al.[74] ambiguously defined the follow-up strategy based on plain radiographs without any specific fusion criteria. Therefore, to further optimize the quality of each clinical study involving spinal column tumors in the future, authors should more specifically report fusion assessments and fusion outcomes.

Conclusions

To the best of our knowledge, this is the first systematic review and meta-analysis of bone graft options for spinal fusion following resection of spinal column tumors. Overall, fusion rates varied from 36.0% to 100.0% due to both inter- and intrastudy heterogeneity, with a PFR of 85.7%. Due to overall differences in patient, disease, fusion criteria, and treatment characteristics, the optimal surgical techniques and factors predictive of fusion remain unclear. In terms of the intention to achieve arthrodesis, patients with an estimated life expectancy less than 6–12 months do not necessarily require fusion procedures, whereas in patients expected to live longer than 1 year, attempted arthrodesis should be strongly considered in addition to factors related to procedural morbidity. Because the impact of RT, chemotherapy, embolization, and fusion assessment on fusion outcomes was significant, it is highly recommended that in future studies, each relevant variable—such as tumor histology, tumor location, adjunctive treatment, bone graft, fusion criteria, and fusion outcomes—should be appropriately investigated.

Acknowledgments

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Conception and design: Elder, Ishida, Goodwin, Sciubba, Wolinsky. Acquisition of data: Elder, Ishida. Analysis and interpretation of data: Elder, Ishida, Goodwin, Bydon, Gokaslan, Sciubba, Witham. Drafting the article: Elder, Ishida. Critically revising the article: Elder, Goodwin, Bydon, Gokaslan, Sciubba, Wolinsky, Witham. Reviewed submitted version of manuscript: all authors. Approved the final version of the manuscript on behalf of all authors: Elder. Statistical analysis: Ishida. Study supervision: Gokaslan, Sciubba, Wolinsky, Witham.

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