Radiosurgery for Benign Vertebral Body Hemangiomas of the Spine: A Systematic Review and Meta-Analysis

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■ OBJECTIVE: **Spinal vertebral hemangiomas (SVHs) are the most common benign tumors of the spine. We performed a systematic review and meta-analysis of radiosurgery (RS) for SVHs.**

■ METHODS: **We reviewed articles published between January 1990 and December 2020 on PubMed. Tumor control, pain relief, and damage to surrounding tissues were evaluated with separate meta-analyses. This study was performed in accordance with the published Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A total of 23 patients with 24 SVHs were reported in 3 studies.**

■ RESULTS: **Follow-up time was 7.3–84 months. The vast majority of lesions were located at dorsal level ($n = 18$; 75%). In 20 (83.3%) patients, pain was the initial clinical presentation. Complete, partial, and stable responses after radiation were reported in 45.7% ($P < 0.001$), 23.6% ($P = 0.02$), and 37.2% ($P = 0.7$) of cases. Overall response was reported in 94.1% ($P = 0.7$). No progressive disease was reported. Pain relief was achieved in 87.5% of patients ($P = 0.2$). Damage to surrounding tissue caused by irradiation was reported in 22.3% ($P = 0.02$) of cases in 1 study, in which higher doses of radiation were delivered.**

■ CONCLUSIONS: **Radiosurgery is safe and effective for SVHs. Pain relief after RS in symptomatic patients was extremely high, while no progressive disease was reported. Damage to surrounding tissues was reported in only 1 series and included osteitis, osteonecrosis, or soft tissue injury after higher radiation doses.**

Key words
- Hemangioma
- Radiosurgery
- Radiotherapy
- Spine

Abbreviations and Acronyms
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RS: Radiosurgery
RT: Radiotherapy
SBRT: Stereotactic body radiotherapy
SVH: Spinal vertebral hemangioma

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INTRODUCTION

Spinal vertebral hemangiomas (SVHs) are the most common benign tumors, accounting for approximately 11% of benign tumors in adults.[1] SVHs are incidentally discovered in a vast majority of cases. However, a small proportion of patients (0.9%–1.2%) present with clinical symptoms, including local pain or signs of nerve root or spinal cord compression.[2] Symptoms are considered to be related to vascular proliferation, irritation of nerves, or bone displacement.[3] Although these tumors are benign, they can also provoke spinal instability, including pathological fractures owing to lytic changes inside the bone.[4] Diagnosis is usually made by neuroimaging assessment using magnetic resonance imaging.[4]

Management of symptomatic patients includes conservative treatment, vertebrectomy, laminectomy, vertebroplasty, endovascular embolization, or radiation.[5] Radiation was classically delivered as multiple fractions (usually 30 Gy in 15 fractions) in the frame of a classical radiotherapy (RT) approach,[6] which causes vascular fibrosis. Recently, radiosurgery (RS) has been considered for SVHs owing to its steep gradient and its capacity to deliver ablative doses, while keeping high conformity and selectivity.[7] Moreover, it is considered that such an approach would potentially improve outcomes and limit potential toxicities.[8] One RS technique is CyberKnife, which allows real-time imaging and adaptive beam pointing during treatment. There are very few data regarding the role of upfront RS/stereotactic body radiation therapy (SBRT) for SVHs. Thus, such a therapeutic option is not a mainstream treatment owing to lack of evidence. Herein, we aimed to perform a systematic review and meta-analysis of current reported series.

MATERIALS AND METHODS

Article Selection and Data Extraction

The PubMed database between January 2000 and December 2020 was searched using the following keywords: hemangioma AND spine AND radiosurgery. We selected 2000 as the starting date because few articles on common indications for spinal RS were published before 2000. Articles that were peer-reviewed clinical studies or case series of SVHs treated with RS (or SBRT using modern techniques), independently of the device, were included; case reports, non−English language studies, and conference papers or abstracts were not included. Further, studies reporting RS for benign spinal conditions, but not specifically detailing cases of SVH, were excluded. This study was performed in accordance with the published Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[9] The article selection process using a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram is presented in Figure 1, which included the studies reported further in Tables 1−3. Three separate reviewers (A.C., D.S., and C.T.) applied the inclusion criteria to the PubMed search result; there were no disagreements. Moreover, 3 separate reviewers applied the exclusion criteria to the remaining articles.

We extracted data related to tumor control, pain relief, and adverse radiation events. A complete response was usually defined as a complete and durable resolution of symptoms related to the SVH following radiation.[8] A refractory response was either no clinical response or a relapse of symptoms. One series reported having treated an hemangioma,[14] but further details were not provided. Another case report described the treatment of an epidural thoracic hemangioma.[15] Here, we report only series of cases. For illustration, details of case reports are presented in Tables 1−3, but they are not further discussed.

Four series reported 26 lesions.[4,7,8,11] One series was excluded for consistency reasons, as it was more compatible with RT.[4] Thus, we analyzed 3 series including 24 patients. CyberKnife (Accuray Inc, Sunnyvale, California, USA) was the most common radiation technique. Two case report[12,13] were detailed in the tables 2 to 4 but were not included in the meta-analysis.

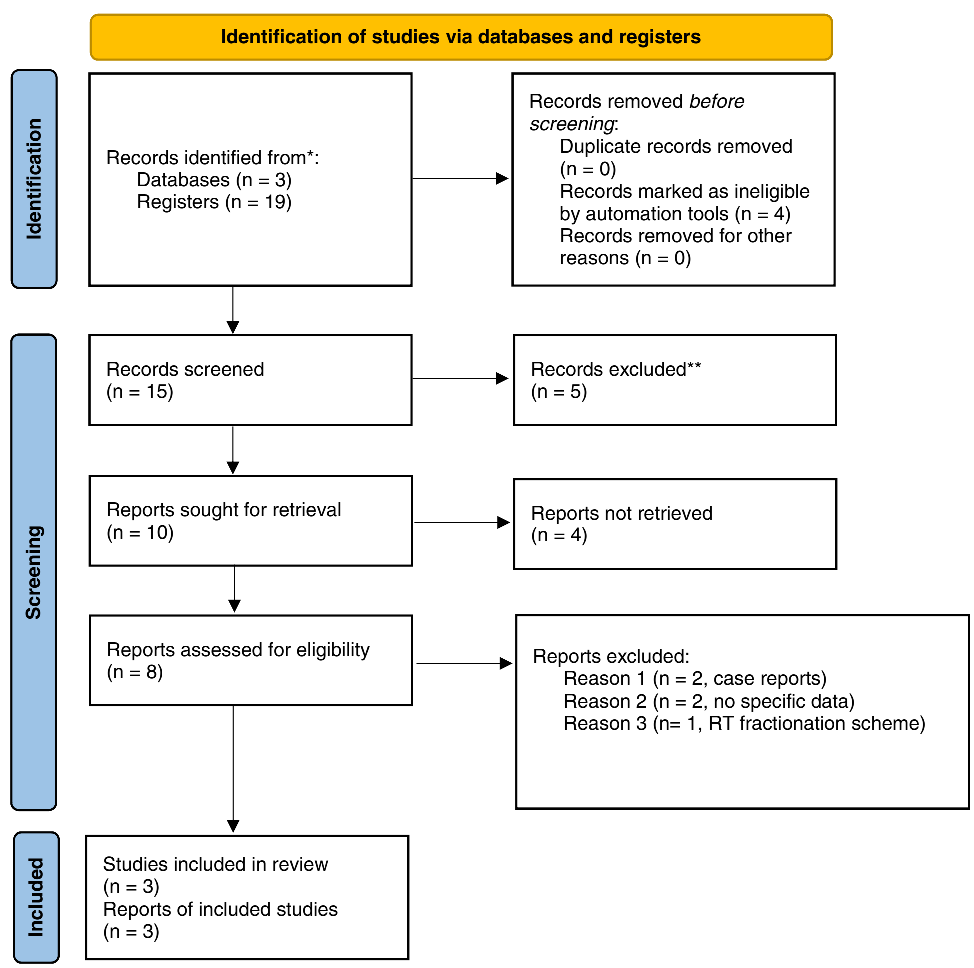

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines with article selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses. (Adapted from Page et al., 2021[10]).

Table 1. Demographic Data

Author, Year	Patients	Age (years)	Median Follow-Up (months)	Sex, M:F	Location: Cervical/Dorsal/ Lumbar/Sacral	Symptoms: Pain/ Neurological Signs	Diagnosis: Biopsy/Imaging
Series							
Chen et al., 2021[7]	11	40.8 ±14.6	10.5 (7.3–28)	5:6	2 (18.2%)/7 (63.6%)/2 (18.2%)/0	11 (100%)/1 (9.1%)	9 (81.8%)/2 (18.2%)
Yu et al., 2020[8]	6	50.5 (31–67)	—	4:2	0:6 (100%)/0:0	5 (83%)/0 (0%)	Imaging
Zhang et al., 2017[11]	5 (7 lesions)	50 (30–72)	44 (25–75)	2:3	1 (14.3%)/5 (71.4%)/1 (14.3%)/0	4 (80%)/2 (40%)	Imaging
Case Reports							
Gaviolli et al., 2020[12]	1	56	12	1:0	0/0/1/0	1/0	Imaging
Sung et al., 2019[13]	1	63	84	0:1	0/1/0/0	Both	Imaging

M, male; F, female.

Statistical Analysis Using OpenMeta [Analyst] and Random-Effects Model

Owing to the high variation in study characteristics, a statistical analysis using a binary random-effects model (DerSimonian-Laird method) was performed. We used OpenMeta[Analyst] (http://www.cebm.brown.edu/openmeta/) from the Agency for Healthcare Research and Quality Effective Healthcare Program. Weighted summary rates were determined using meta-analytical models. Testing for heterogeneity was performed for each meta-analysis. Pooled estimates using meta-analytical techniques were obtained for all the outcomes previously described in the same section.

RESULTS

Basic Demographic Data

Demographic data are presented in Table 1. There were 23 patients with 26 SVHs. Follow-up time was 7.3–84 months. A vast majority of lesions were located at the dorsal level ($n = 18$; 75%). Pain was the initial clinical presentation in 20 (83.3%) patients. Three lesions (12.5%) evolved to neurological deficit. Most of the SVHs were diagnosed by imaging, with the exception of 1 series, which described 9 (9/24; 37.5%) lesions diagnosed by biopsy.

Prior Surgery and Dosimetric Details

Prior surgery was performed in 3 lesions (12.5%). Dosimetric data are presented in Table 2. The means of fixation were thermoplastic mask, BodyFIX (Elekta Solutions AB, Stockholm, Sweden), or head first supine position. Lesion tracking was performed using Xsight Spine (Accuray Inc.) or percutaneous fiducial markers in the posterior bony elements. CyberKnife was used in the vast majority of cases, followed by intensity-modulated radiation therapy and Novalis (Brainlab AG, Munich, Germany). The dose regimens are presented in Table 2. The dose constraints were detailed in 1 series and 1 case report: for the series, V14 Gy received by the spinal cord limited to <0.03 cm^3; V10 Gy, <0.35 cm^3; and V7 Gy, <1.2 cm^3.

Local Control: Complete After Radiation

Complete response after radiation was described in 9 of 24 of the reported lesions, which corresponds to a rate of 45.7% ($I^2 = 94.18\%$; P heterogeneity < 0.001; $P < 0.001$) (Figure 2A).

Local Control: Partial Response After Radiation

Partial response after radiation was described in 7 of 24 of the reported lesions, which corresponds to a rate of 23.6% ($I^2 = 72.28\%$; P heterogeneity $= 0.02$; $P = 0.02$) (Figure 2B).

Local Control: Stable Disease After Radiation

Stable disease after radiation was described in 8 of 21 of the reported lesions, which corresponds to a rate of 37.2% ($I^2 = 0$; P heterogeneity $= 0.7$; $P = 0.7$) (Figure 2C).

Local Control: Progressive Disease After Radiation

No progressive disease was reported. Overall control rate was described as stable, partial, and complete responses in 23 of 24 patients, which corresponds to a rate of 94.1% ($I^2 = 0\%$; P heterogeneity $= 0.7$; $P = 0.7$) (Figure 2D).

Pain Relief

Pain relief was described in 18 of 24 of the reported lesions, which corresponds to a rate of 87.5% ($I^2 = 0\%$; P heterogeneity $= 0.7$; $P = 0.2$) (Figure 3).

Reossification

Reossification was described in only 1 series, occurring in 3 of 11 (27.3%) patients.

Damage to Surrounding Tissue by Irradiation

Damage to surrounding tissue caused by irradiation was described in 6 of 21 of the reported lesions, which corresponds to a rate of 22.3% ($I^2 = 73.4\%$; P heterogeneity $= 0.02$; $P = 0.1$) (Figure 4).

DISCUSSION

Symptomatic vertebral hemangiomas have been classically approached by traditional RT as first intention treatment and/or in combination with surgery. Such an approach achieved pain relief in 78.4%–100% cases.[16] Here, we performed a systematic review and meta-analysis of RS or SBRT with modern techniques in this indication. RS or SBRT is seldom considered as a primary treatment strategy for SVHs, although this might be related in part to the limited evidence currently available. In the present systematic review, complete, partial, and stable response after radiation were described in 45.7%, 23.6%, and 37.2% of the cases, respectively. Overall positive response (complete, partial, and stable responses included) was 94.1%. Pain relief was achieved in 87.5% of patients. No progressive disease was reported. Damage to surrounding tissue caused by irradiation was described in 22.3% by only 1 series, using high doses of radiation, although fractionated, and limited to osteitis, osteonecrosis, or soft tissue injury.

Surgical Resection

Some authors advocated for en bloc resection of aggressive vertebral hemangiomas. Although this provides high rates of local control, it is technically challenging and associated with high mortality rates, as previously suggested.[17,18] Another therapeutic option that has been used in past years was surgical decompression[11] or subtotal resection followed by radiation techniques.[17] Other authors[19] performed first-intention radiation (hypofractionated stereotactic RS) followed by surgery 7 days later in the context of a paraparesis already present at the time of radiation treatments.

Traditional RT versus RS/SBRT

An open question is whether CyberKnife RS would be more effective compared with classical RT. Zhang et al.[11] suggested that 40% of the treated patients experienced a reduction in lesion size. The largest series by Miszczyk and Tukiendorf[16] reported 101 patients with 137 SVHs treated with different RT regimen doses and suggested 60.5%, 65.4%, 68.3%, and 78.4% pain relief at 1, 6, 12, and 18 months after RT, respectively.

Heyd et al.[20] reported on 84 patients with 96 symptomatic lesions treated with conventional RT. The authors concluded that doses ≥34 Gy resulted in significantly improved responses compared with doses <34 Gy. The complete symptom response occurred in 62% of cases.[20] In the present meta-analysis, such a response was achieved in >90% of cases (all techniques pooled).

Local Control After RS

The mainstream focus of RS for SVH is local control. Such lesions do not exhibit metastasis, and thus there is no concern

Table 2. Prior Surgery and Dosimetric Data

Author, Year	Patients	Prior Surgery	Fixation	Lesion Tracking	Device	Dose	Dose Constraints	Volume
Series								
Chen et al., 2021[7]	11	No	Cervical: thermoplastic mask Thoracic: BodyFIX	Xsight Spine	CyberKnife	30–35 Gy in 5 fractions	—	—
Yu et al., 2020[8]	6	1/6 (16.7%) surgery	BodyFIX	—	6 MV IMRT with VMAT	18 (13–20) Gy in 1 fraction at 83.1–92.6%	V14 Gy received by spinal cord limited to <0.03 cm³; V10 Gy, <0.35 cm³; V7 Gy < 1.2 cm³	0.83–24.03 mL
Zhang et al., 2017[11]	5 (7 lesions)	2/5 (40%)	Aquaplast face mask (Aquaplast RT, Orfit, Wijnegem, Belgium)	Percutaneous fiducial markers in posterior bony elements	CyberKnife	15–27.5 Gy: 72%–83% isodose line in 1–5 fractions Single fraction: 15–18 (median 18) Gy	—	0.6–70.9 mL
Case Reports								
Gaviolli et al., 2020[12]	1	Vertebroplasty	—	—	CyberKnife	2.400 cGy (BED = 96 Gy) in 2 fractions	—	—
Sung et al., 2019[13]	1	No	—	—	Novalis	30 Gy: 90% in 5 fractions	Spinal cord: 0.99–5.72 Gy	14.954 mL

IMRT, intensity-modulated radiation therapy; VMAT, volumetric modulated arc therapy; BED, biologically equivalent dose.

Table 3. Outcomes

Author, Year	Complete Response	Partial Response	Stable Response	Disease	Reossification	Damage to Surrounding Tissues	Pain Relief	Neurological Signs Alleviation
Series								
Chen et al., 2021[7]	0/11 (0%)	6/11 (54.5%)	5/11 (45.4%)	0/11 (0%)	3/11 (27.3%)	6/11 (54.5%) Radiation-induced osteitis Osteoradionecrosis Soft tissue radiation injury	11/11 (100%)	1/1 (100%)
Yu et al., 2020[8]	3/6 (50%)	1/6 (16.7%)	2/6 (33.4%) 1/2 radiofrequency ablation and vertebroplasty 1/2 vertebroplasty	0/6 (0%)	—	0/6 (0%)	4/6 (67%)	—
Zhang et al., 2017[11]	6/7 (85.7%)	—	1/5 (20%)	—	—	0/5 (0%)	3/4 after mean period of 1 year	1/2 (50%)
Case Reports								
Gaviolli et al., 2020[12]	1/1 (100%)	—	—	—	—	0/1 (0%)	1/1 (100%) at 3 months	—
Sung et al., 2019[13]	1/1 (100%)	—	—	—	—	0/1 (0%)	1/1 (100%) at 7 months	1/1 (100%)

with regard to potential systemic therapies.[17] In the present meta-analysis, local control was 100%.

Positive Predictors of Pain Control

Zhang et al.[11] suggested that favorable factors for pain control were initial decompression, RS therapy, and further decrease in lesion size during follow-up.

Neuroimaging Changes During Follow-Up

Several studies suggested that despite clinical improvement, there might not be any visible associated neuroimaging changes as late as 5 years after treatment.[21] However, recent studies[7] have suggested a potential role of quantitative parameters from dynamic contrast-enhanced magnetic resonance imaging, which change significantly after CyberKnife RS for SVH. Thus, such studies[7] would depict early CyberKnife efficacy in this pathology.

Other studies suggested that reduction in enhancement after radiation would potentially represent occlusion or fibrosis of capillaries in tumor tissue.[22] Another potentially useful neuroimaging modality was three-dimensional volumetric sagittal time-resolved imaging of contrast kinetics,[19] which showed disappearance of hypervascularity in an aggressive SVH.[1] In 2 of 5 cases, Zhang et al.[11] reported a 20%–40% reduction in lesion size during follow-up. In a case report of 2 lesions[4] treated with CyberKnife, 1 lesion decreased in size after RS.

Single-Fraction RS—Minimal Required Radiation Dose of 18 Gy?

One series[8] suggested that lower radiation doses might be associated with pain relapse. In that series,[8] one patient presented with symptom relapse following SBRT and was treated with 13 Gy in 1 fraction, whereas all other patients received significantly higher doses of 18 or 20 Gy in 1 fraction. Common hypofractionated RS dose regimens include 32 Gy in 4 fractions[15] or 30 Gy in 5 fractions.[17]

Retreatment with RS

In 1 series,[11] a patient with persistent dorsal pain following RS was retreated with the same technique 6 months later, with 30% further reduction in

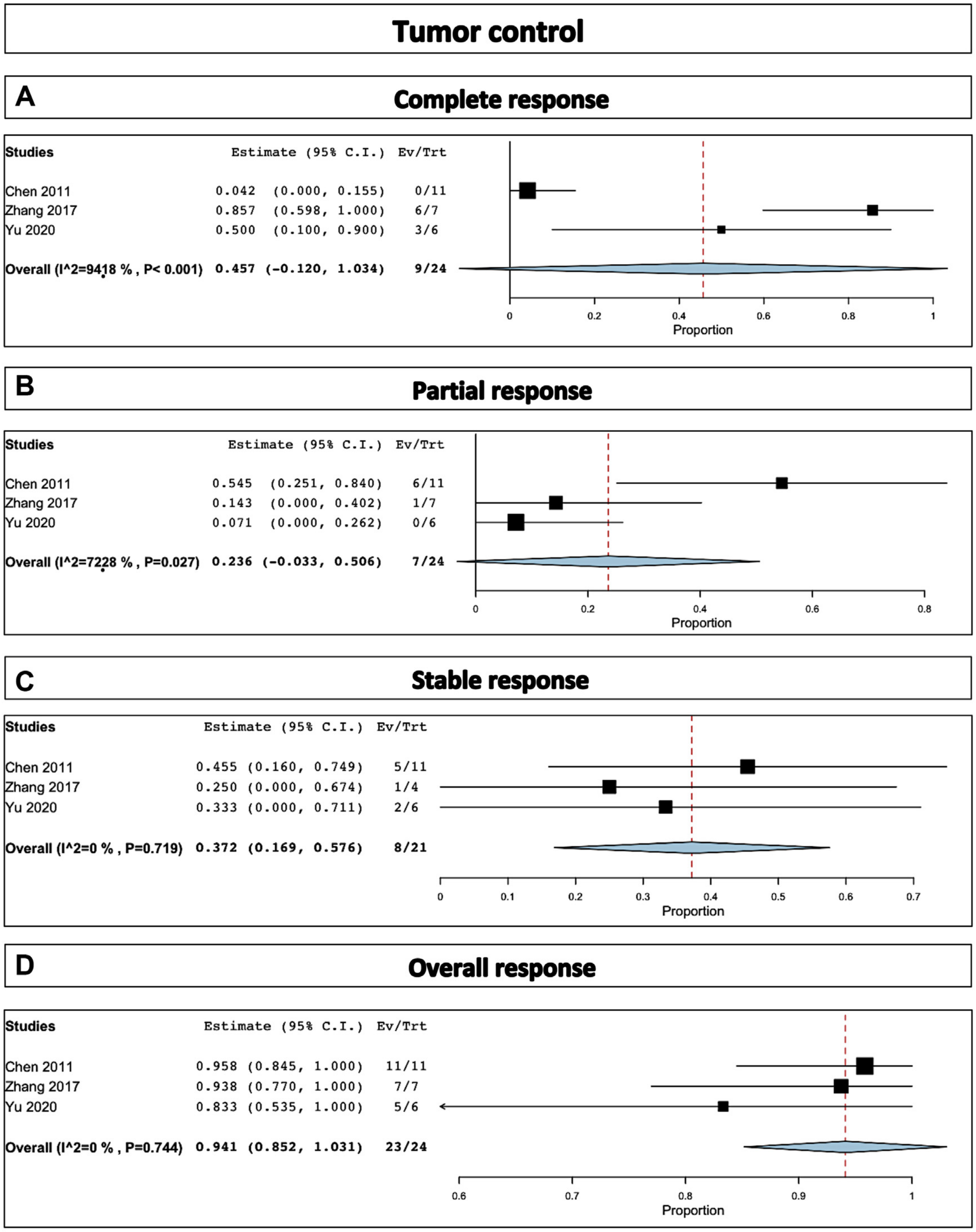

Figure 2. Local tumor control with complete (**A**), partial (**B**), stable (**C**), or overall (**D**) response. C.I., confidence interval.

pain and no adverse radiation event. In this respect, retreatment seems feasible, although there are limited available data.

Spinal Cord Delineation and Further Radiation Tolerance

Practice varies in terms of delineation of the spinal cord. Some authors suggest delineating the exact spinal cord as defined by T2-weighted magnetic resonance imaging or computed tomography myelography as the planning organ-at-risk

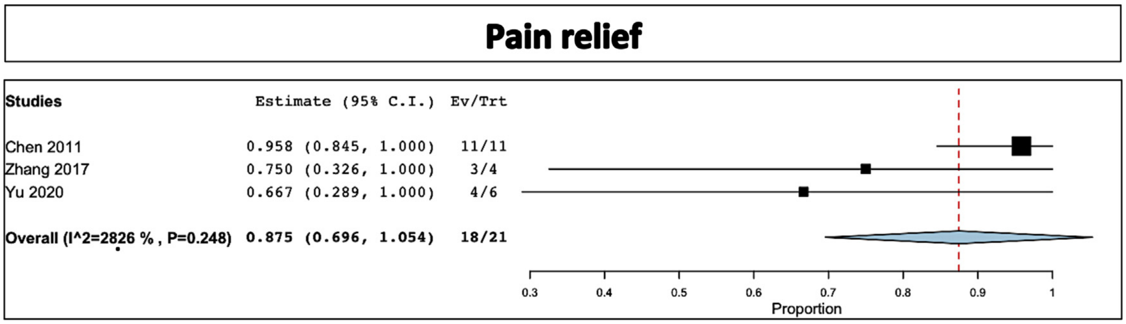

Figure 3. Pain relief. C.I., confidence interval.

volume, while others use a 1- to 2-mm expansion from the true spinal cord and thecal sac.[8] The spinal cord maximal tolerance dose is classically considered 10–14 Gy.[23] Further studies are needed to determine whether such dose constraints should be applied to the true spinal cord or the extended spinal cord planning organ-at-risk volume, as available data on this topic are limited.[23]

Dose to the Esophagus in Thoracic Spine SBRT

The recommended dose constraint to the esophagus is no more than 14 Gy to 2.5 cm^3, to avoid toxicity, which was 6.8% in 1 series.[24] Moreover, the same authors recommended V12 Gy to <3.78 cm^3, V15 Gy to <1.87 cm^3, V20 to Gy <0.11 cm^3, and a maximum point dose <22 Gy.[24]

Timing to Clinical Response

Data are limited with regard to the timing to clinical response. Moreover, the existing data are heterogeneous. A response might appear as quickly as a couple of days after radiation.[15] Other authors reported a mean period of delay to symptom improvement of 1 year.[11] In the same series,[11] 1 patient was able to completely stop opioid medication by 2 years after treatment.

Biologically Effective Dose

A better conformity index of the RS is thought to allow for the delivery of a higher biologically equivalent dose, improving the probability of better clinical outcomes.[12] A higher biologically equivalent dose was recently suggested to play a role in single-fraction RS.[25-27] The α/β ratio for VBH is considered to be 4.

Toxicity After RS

The toxicity of radiation techniques is an important consideration. RT can cause tissue damage, which needs to be further differentiated from tumor recurrence.[28] In a study included in this systematic review, 6 patients (54.5%) presented with radiation injury, including radiation-induced osteitis, osteoradionecrosis, and soft tissue radiation injury.[7] Radiation injury might be related to a higher prescribed dose, even if the dose is fractionated. Other complications that might appear are compression fractures, esophagitis, or myelopathy.

Limitations

The current systematic review and meta-analysis has limitations. The first is related to the small number of series. Second, we conventionally included

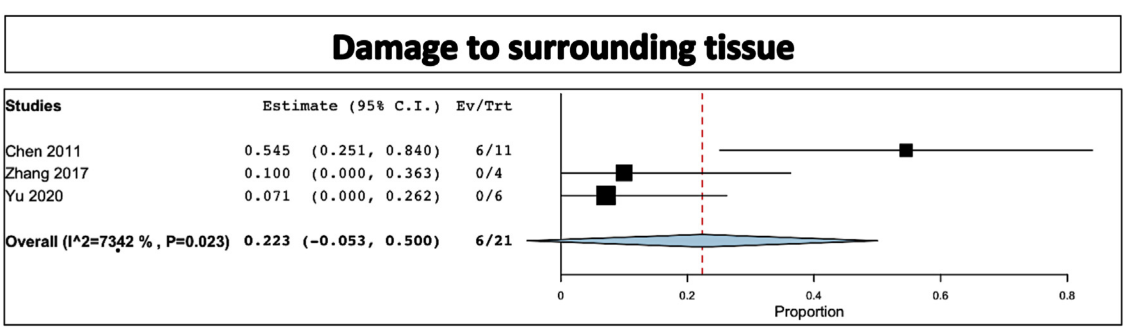

Figure 4. Damage to surrounding tissues. C.I., confidence interval.

outcomes mixed between single-fraction and hypofractionated regimens; however, this was done because of the limited sample size.

CONCLUSIONS

RS is safe and effective for SVHs. Pain relief in symptomatic patients was extremely high, approximately 90%, while local control was close to 100%. Damage to surrounding tissues was reported in only 1 series and included osteitis, osteonecrosis, or soft tissue injury after higher radiation doses.

CRediT AUTHORSHIP CONTRIBUTION STATEMENT

Alfredo Conti: Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Revised submited version. **Daniele Starnoni:** Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Revised submited version. **Juan Barges-Coll:** Writing – review & editing, Revised submited version. **Kyriakos Papadimitriou:** Writing – review & editing, Revised submited version. **Marc Levivier:** Writing – review & editing, Revised submited version. **Constantin Tuleasca:** Conceptualization, Methodology, Formal analysis, Data curation, Writing – original draft, Writing – review & editing, Supervision, Revised submited version.

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