e-ISSN 2083–4640
ISSN 1507–1367

Reports of Practical Oncology and Radiotherapy
2023, Volume 28, Number 1, pages: 93–101
DOI: 10.5603/RPOR.a2023.0009
Submitted: 21.07.2021
Accepted: 06.02.2023

REVIEW ARTICLE

Vertebral hemangioma — the current radiation therapy perspective

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ABSTRACT

Vertebral hemangiomas are benign tumors of the spine, most often detected incidentally and on other instances, when signs and symptoms of the disease arise. About 10% of the population are affected worldwide with a female to male ratio of 2:1. The majority of these cases are asymptomatic and no intervention is generally required. Less often, back pain and neurological deficit may occur. Such hemangiomas are termed aggressive by the Enneking staging and warrant treatment. In this review, staging and diagnostics are discussed in detail followed by treatment options. Treatment options entail Surgical intervention, Percutaneous ethanol injection, radiofrequency ablation and Radiation Therapy. There are no set guidelines on preference or order of the treatment options. Further, in this review, studies favouring Radiation therapy regimes and their outcomes are elaborated.

Key words: VH; RT; EQD2

Rep Pract Oncol Radiother 2023;28(1):93–101

Introduction

A hemangioma is a benign tumor of the vasculature that develops from the different blood vessel types. Vertebral hemangiomas are benign tumors with amalgamation of blood vessels of normal anatomy and no arteriovenous malformation. They are the most prevalent tumors of the spinal axis that are detected incidentally with an estimated incidence of 10–12% [1]. Demographically, these tumors can occur in any age group but are most commonly diagnosed in or after the 5th decade.

Histologically, vertebral hemangiomas (VH) are grouped into 2 types. Cavernous Hemangiomas comprise dilated blood vessels grouped together along with bone tissue. They are typically not characterized as tumors but as malformation of vessels [2]. Capillary hemangiomas consist of thin walled blood vessels of varying sizes separated by usual bone tissue [3, 4]. Vertebral hemangiomas, listed as 18.09 in International Classification of Diseases 10th revision (ICD-10), are sporadic and identified fortuitously on imaging. About 20–30% VH are usually discovered in the thoracolumbar spine but multilevel involvement have been reported. A female predisposition is noted with female to male ratio of 2:1 [5]. Vertebral hemangiomas vary in size ranging from subcentimetric lesions to large lesions replacing entire vertebrae.

Vertebral hemangiomas are asymptomatic and are graded by the Enneking staging. Enneking Staging is a widely used, universally accepted staging for all musculoskeletal tumors. VH are also staged accordingly [6–8].

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Stage I/latent: well demarcated borders, lesions grow slowly and stop. May heal spontaneously. There is negligible recurrence after intracapsular resection.

Stage II/active: there are well defined borders but may show cortical thinning. Tumor growth is limited by natural barriers, chances of recurrence after resection are still low.

Stage III/aggressive: tumors with indistinct borders, where there are 5% chances of harbouring metastases.

Tumors in Enneking stage 1 are latent and do not warrant medical intervention upfront; 1% of these lesions may become symptomatic. Aggressive haemangioma is termed as such when there is extraosseous extension of tumor into the spinal canal [9]. The manifestation of Symptoms depend on the location of the tumor and the degree of nerve root compression. Females are more likely to experience symptoms in the last trimester of pregnancy owing to the effects of the gravid uterus [10]. Symptoms of aggressive VH are back pain and progressive neurologic deficit [11]. Enneking stage 3 refers to the lesion eroding the bony structures to enter the spinal canal that leads to neurological deficits and warrants treatment [12]. Symptoms develop in less than 2% cases and such cases then warrant intervention in the form of surgery, Radiation therapy, Radiofrequency ablation, injection of intra-lesional ethanol or a combination of above therapies [13].

Diagnosis

Radiological assessment is the foremost step towards establishing a diagnosis. Most VHs are accidently detected on routine radiographs. Perlman, in 1926 described the features of a classic VH on a plain radiograph. On a lateral radiograph, VH may or may not show reduction in bone density, thickened trabeculae shows striated vertical appearance due to the aggregate of blood vessels in it (Fig. 1A and 1B). They are termed as the "Jail bar" sign or the "Corduroy cloth" appearance.

Computed tomography (CT) of spine shows classical features of thickening of trabeculae of vertebrae, represented as areas of hyperdensities. These areas of hyperdensities look like densely packed dots on the background of hypodense stroma and are thus termed as the "Polka-Dot sign" or the "Salt and Pepper sign". This pathognomonic

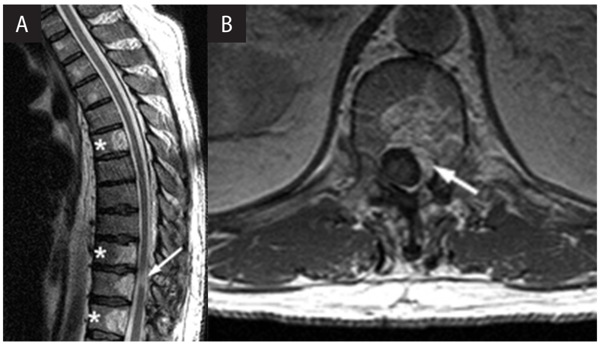

Figure 1. A. Sagittal view of thoracic spine revealing multiple VH on a T2 weighted MR image. White arrow shows epidural extension in the lower thoracic area; **B.** Epidural encroachment of VH with enhancement of the stroma (arrow) on an axial T1 contrast sequence [16]

picture is mostly seen on an axial sequence. VHs can be categorized as typical, atypical, and aggressive on the basis of imaging and are described in Table 1 along with management options [14].

Magnetic resonance imaging (MRI) shows hyperintensity on both T1 and T2 non-contrast scans [15]. Typical VH exhibits hyperintensity on a T1 sequence and is attributed to increase in lipid constituent of these tumors, relative to the adjacent marrow. The hyperintensity on T2 sequence is due to higher water content in hemangiomas. Sometimes, isointense to hypointense T1 images are also seen when the lipid content decreases in these tumors and are termed atypical hemangiomas. Figure 1 and Figure 2 corresponds to typical MR and CT findings.

Management

Till date, no well-defined guidelines exist for the treatment of VH. The cases of aggressive (i.e. Enneking stage III, S3) vertebral hemangiomas are symptomatic, therefore some form of treatment becomes imminent

Surgery

Surgery is one of the treatment options, however , no optimal time of surgery has been established. Indications for surgery include a deteriorating neurological condition, spinal canal stenosis and instability. In a rapidly progressing case, urgent surgical decompression with or without posterior instrumentation and reconstruction may be needed. In cases where symptoms have set in but there

Table 1. Imaging findings corresponding with management and treatment options of vertebral hemangiomas (VH)

<table>
<tr><th></th><th>CT and MR imaging findings</th><th colspan="2">Management</th><th>Treatment options</th></tr>
<tr><td>Typical VH</td><td>CT
Hypodense well-defined lesion with "polka-dot" or "corduroy "sign
MR
Hyperintense lesion on T1-WI, T2-WI, and fluid-sensitive sequences variable post-contrast enhancement</td><td colspan="2">No further imaging modality needed</td><td>No treatment if in symptomatic (back pain):medical therapy</td></tr>
<tr><td>Atypical VH</td><td>MR
Iso- to hypointense lesion on T1-WI
Hyperintense lesion on T2-WI and fluid-sensitive sequences
Variable post-contrast enhancement</td><td colspan="2">CT
To look for "polka dot" or "corduroy" signs</td><td>Same as "typical VH"</td></tr>
<tr><td>Aggressive VH</td><td>CT
Hypodense mass with:
Variable involvement of vertebral body and posterior elements
Cortical expansion/infiltration Soft-tissue extension
Spinal cord/nerve roots compression
MR
Hypointense lesion on T1-WI
Variable signal intensity on T2-WI, and fluid-sensitive sequences
Variable post-contrast enhancement</td><td>MR
To reduce ddx
CT
To look for "polka-dot" or" corduroy" signs</td><td>Angiography and/or biopsy</td><td>Symptomatic (compressive myelopathy or radiculopathy):
Vertebroplasty
Surgery
Surgery with or without POE</td></tr>
</table>

CT — computed tomography; MR — magnetic resonance

is a neurologic stability, a preoperative embolization may first be done followed by tumor resection ± fixation and reconstruction [18].

Surgery in the form of vertebroplasty is useful for spinal stabilization and prevention of epidural bleeding in patients with a compression fracture of the vertebral body. It is recommended in neurologically stable cases or in patients with large vertebral body distortions caused by the tumor [13]. Percutaneous cement vertebroplasty is a relatively less-invasive procedure to provide quick relief of pain in cases without neurological deficit. The procedure may help in long term relief from pain in most cases [19]. Cement vertebroplasty along with ethanol injection has been reported to be safe and effective [20]. However, hemangioma may not be completely wiped out with vertebroplasty and it may further expand and cause cord compression. Also, cases of leakage of acrylic cement into the spinal canal causing damage to the spinal cord have been reported [21].

However, in cases of severe neurological deficit, especially those involving paraparesis, surgical decompression may be necessary if other forms of treatments have not helped. It may involve hemilaminectomy or laminectomy and resection of the hemangioma tissue compressing the spinal cord [22]. In cases of fast progressing neurological deficit, decompressive laminectomy may be necessary. The procedures are quite safe and complications related to healing of surgical wounds are very rare. Recurrent myelopathy is possible in few cases, who may have to undergo decompression again. In some cases, where the tumor growth compresses the cord, staged vertebrectomy or corpectomy may become necessary [21]. Decompression may be supported with balloon kyphoplasty or intraoperative vertebroplasty [22].

The type of surgical procedure and the approach to it, whether anterior or posterior is decided based on the location of VH and its associated symptoms. Hemorrhage is a dreaded complication of surgery and to avoid this situation, pre-operative embolization is a good option, in stable patients. Profuse bleeding might lead to hypovolumic shock. Mortality following hypovolemic shock may be as high as 6% [23]. Convalescence may also be very long following surgery.

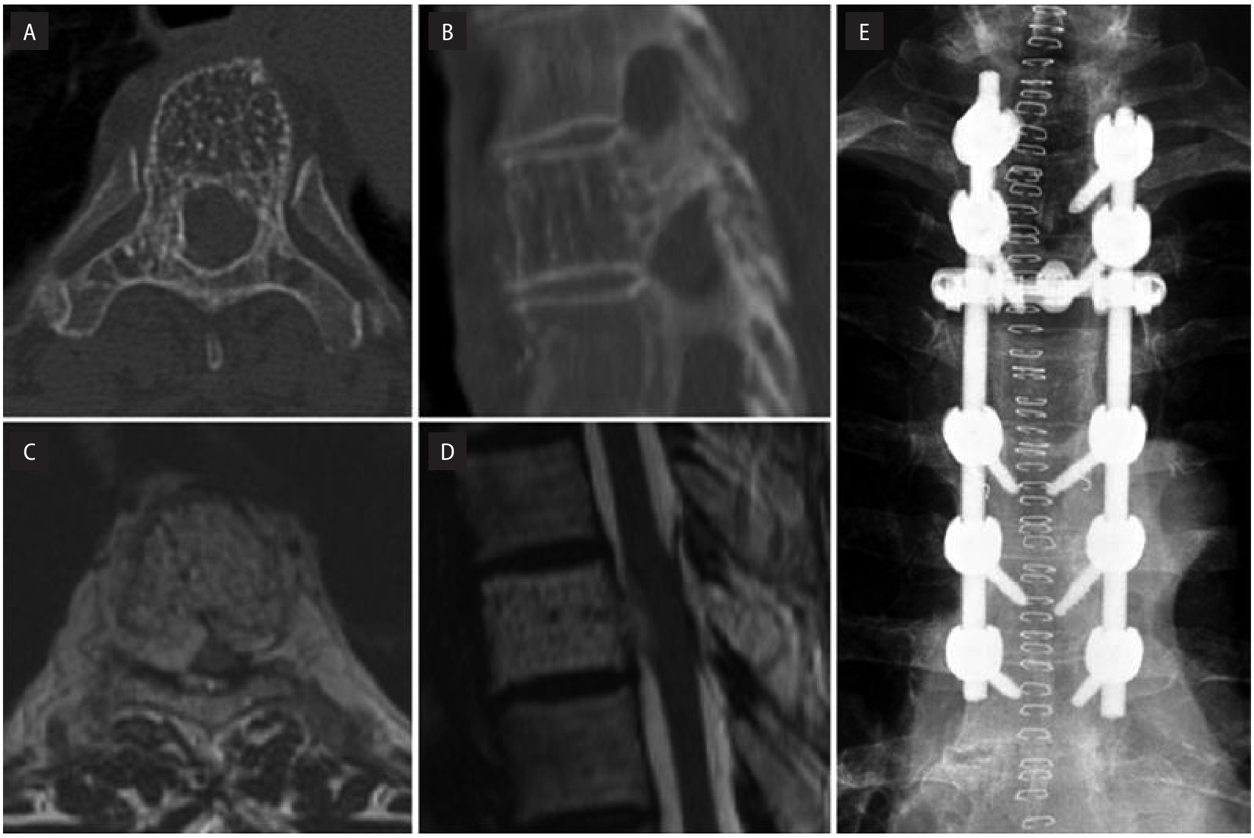

Figure 2. Images obtained in Case 2 which involved a 63-year-old woman who presented with myelopathy. **A.** Axial computed tomography (CT) image demonstrating an aggressive vertebral hemangioma at T-4 with a characteristic honeycomb pattern that expands the cortex and involves the entire vertebral body and both pedicles and extends into the posterior elements. **B.** Sagittal CT image showing a corduroy pattern characteristic of vertebral hemangiomas. **CD.** Axial (C) and sagittal (D) T2-weighted MR images showing epidural spread of disease. This patient underwent a decompressive laminectomy and instrumented fusion for subtotal resection of the tumor followed by a course of radiation therapy. **E.** Postoperative anteroposterior radiograph [17]

Radio frequency ablation

There are no head-on comparisons between Minimally invasive techniques and surgery in published literature. These techniques are proven to be cost effective and achieve good disease control. One of the widely used minimally invasive techniques is radio frequency ablation (RFA).

Principally, RFA applies thermal energy at the nerve endings that carry the sensation of pain at the desired spinal cord level. This is achieved via a RF probe that is connected to a RF generator which in turn generates alternating current. The current passing through the probe produces heat (in the range of 60–100°C) which then leads to charring of tissues and denaturation of proteins. The procedure is carried out under anesthesia cover by strict fluoroscopic guidance. RFA is a relatively safe procedure when patients are chosen judiciously. Post procedure pain is almost always reported although it is transient [24]. Other complications include ablation injuries and ablation induced fractures [25].

Preoperative embolization

in 1951, Manning described the mortality associated with VA because of bleeding. Subsequently, the first ever endovascular embolization was done by Gross et al. in 1976 who reported an improvement of neurological condition of the patient following the procedure [26]. Preoperative embolization is done to halt the blood flow in the tumor by congesting the feeding vessels. The advantage of this technique is that not only does it bring down the size of the lesion, it also substantially reduces the blood loss during surgery. When used as a single treatment modality, recurrences may be a problem. To address this problem, a biportal approach has been suggested where percutaneous surgical techniques like kyphoplasty, vertebroplasty may be used following embolization [27, 28]. Complications are extremely rare and include stroke, peripheral arterial occlusion, cord ischemia and allergic reactions to the agents [29].

Intralesional ethanol

Intralesional injection of ethanol is a less practiced procedure, albeit effective and affordable. Injection of ethanol destroys the endothelium which is the primary fabric of a hemangioma and causes intravascular thrombosis. The lesion shrinks after being devoid of its blood supply — relieving neurological signs and symptoms. The procedure entails injecting dry ethanol (100% ethanol) in the most vascularized part of VH producing symptoms. CT angiography is a prerequisite to precisely locate the lesion prior to inserting the needle. The needle point is often positioned in the posterior half of the vertebral body, near the junction of body and pedicle to facilitate filling of the hyper vascularized area. This follows the injection of contrast material and the subsequent injection of ethanol, which should be injected forcefully so that the network of hemangiomatous vessels can be fully obliterated [30].

This technique has also been used in other vascular tumors and has proven itself to be safe, thus offering an exciting alternative to other treatment options on VH. There may be incomplete obliteration of hemangiomatous vessels following one injection. In such scenarios, the procedure can be repeated again which is a big advantage associated with this technique. Extremely rare incidences of neurological complication, seizure-like episodes have been reported. To minimize the risk of such a complication, vertebral flow and infusion rates must be kept in check [31].

Radiation therapy

Radiation therapy (RT) is an acceptable treatment option in aggressive cases, where neurological deficits may be gradually developing or when surgery cannot be performed due to serious comorbidities. RT has been used as a first line treatment or as definite treatment in such patients and has proved to be effective and safe. The downside of using radiotherapy as the primary treatment option is slow neurological recovery and also slow overall response to treatment. Wang et al. reported a significant improvement in symptoms in 65% patients in a retrospective review of 20 patients. The condition of remaining patients with severe neurologic deficit worsened and led to surgical intervention [32].

Adjuvant RT is routinely recommended in cases of partial resection where tumors are extensive or where pathological fractures have already taken place [33]. Complete surgical exploration is often not possible due to a weakened spinal cord. Therefore, a common approach to follow is subtotal resection of hemangioma followed by adjuvant Radiation therapy to a dose of 20–36 Gy in conventional fractionation. The recurrence rate can be as high as 30–50% without the addition of radiotherapy after subtotal resection [34].

The German cooperative group on Radiotherapy proved the safety and effectiveness of RT after administering the median radiation dose of 34 Gy over 4–5 fractions per week to a cohort of patients of VH referred for RT over the span of 39 years. 90% of patients showed complete to partial response to pain following RT. Neither acute nor chronic side effects, beyond grade 2, were observed in any patient. The limitation of the series includes a retrospective study design, extremely long follow up and 2D mode of treatment delivery. Unfortunately, no predictive factors on pain control could be established [35]. Radiobiologically, the target of RT are the abnormal vasculature within the hemangioma. Once the vascular endothelium is disrupted, the circulation suffers, causing the size of the lesion to reduce with eventual fibrosis of capillaries.

RT has shown excellent pain control in various studies, with minimal toxicities. The dose schedule preferred is 45 Gy/25 fractions at 1.8 Gy per fraction. Rades et al. performed a retrospective analysis of patients treated with RT since 1929 and suggested that a “dose-effect” relationship exists in these patients. A similar retrospective analysis comparing treatments by Radiosurgery and conventional fractionations between the doses of 8–30 Gy revealed predictive factors, such as older age, higher hemoglobin content, female sex, that correlated with positive outcome and concluded that pain relief effectively depended on fractionation and total dose. The higher the dose and fractionation the better pain control was obtained [36].

EQD_2 of various schedules, of single fraction and fractionated regimes, were calculated on the basis of Linear Quadratic (LQ) model. As hemangioma is a slow growing benign tumor, the alpha/beta ratio for VH was suggested as 3 for use in the LQ model. The study revealed that excellent outcome was achieved when EQD_2 of 40 Gy was used [37].

The planning CT scan of the patient is acquired in a supine position using an immobilization device like the vacloc or thermoplastic cast such that the patient is in a comfortable position and the position can be reproduced at the time of treatment. Conventionally, 2D or 3D-CRT techniques were used to deliver radiation using either posterior or combination of parallel opposed (AP/PA) beams with relatively higher weightage of posterior beam. At present, Image guided Radiation Therapy which includes Intensity Modulated Radiation Therapy (IMRT), volumetric arc modulated radiation therapy (VMAT) with daily imaging, is used to treat VH to deliver conventional dose fractionation. Various dose fractionation schedules are reported in literature.

VMAT and IMRT both achieve the intensity modulation using multileaf collimator (MLC); IMRT technique is only capable of changing the speed of MLC at a fixed gantry angle whereas gantry angle/speed, dose rate and MLC speed all change simultaneously in VMAT. The major difference is reduction in total treatment time using VMAT as compared to IMRT. The treatment time can be further reduced using FFF beams in newer technologies of LINAC. The high resolution multi leaf collimators (~2.5 mm or 5 mm width) are used to shape the radiation field as per tumor anatomy so as to minimally expose the normal tissues to radiation in conventional linear accelerators (Varian and Elekta).

Stereotactic radiosurgery/stereotactic body radiation therapy is a technique of treatment planning where high doses are delivered with rapid fall off of dose outside the target (generally in ~1–5 fractions) and is actively being used to treat VH. Identifying the correct clinical target volume (CTV) is of particular importance because the steep dose gradients associated with stereotactic radiosurgery (SRS) result in subtherapeutic doses within millimeters of the planning target volume (PTV), and the adjacent normal tissues are at risk of injury from high dose-per fraction regimens.

A meta-analysis on radiosurgery of spinal hemangiomas reflected on radiosurgery and stereotactic body radiotherapy (SBRT) have been carried out over the years at various institutions. Doses in varied fractionation from 30–35 Gy/5#, 13–20 Gy/1#, 39 Gy/5#, 24 Gy/2#, 15–18 Gy/1# were used by various authors. All authors had used immobilization for their patients. Complete local control was achieved in 45.7% of patients. Partial response in 23.6% patients and stable disease in 37.2% patients were seen. The meta-analysis concluded that both local control and pain showed high responses and that Radiosurgery offered an excellent upfront treatment option [38].

With the advent of technology, tomotherapy has also emerged as an efficient option to deliver dose using binary collimators. Further SRS/SBRT can also be delivered with more sophisticated Cyberknife radiation delivery equipment. Linear accelerator and tomotherapy are integrated with in-room CT/cone beam computed tomography (CBCT) and scans of patients are acquired before treatment to confirm the reproducibility of the patient anatomy. However, these are not viable options for intra-fraction imaging of the tumor since any submillimetric movement of the patient might result in unintended dose delivery to the spinal canal which might lead to serious treatment toxicities. The surface guidance or non-coplanar X-ray imaging can be used as intra fraction imaging in such scenarios.

The acceptable plan criterion is to cover the target with at least 95% of the prescription dose with heterogeneity in the range of –5% – +7% with the minimal dose to surrounding normal structures. Various RT dose fractionation schedules have been suggested to treat VH (Tab. 2). The most commonly used fractional dose is 1.8–3 Gy and a threshold dose to achieve the control is 34 Gy. Nowadays, SRS and SBRT of the spine is gaining interest and acceptable local control is reported in a study treating spinal tumors with SRS/SBRT [46, 47]. A clinical trial is underway to test the efficacy of SBRT for VH for 25 Gy/5# dose regimen and results are awaited [48]. SBRT is beneficial in terms of reducing normal tissue complication probability (NTCP) and maximizing tumor control probability (TCP) since sharp fall off of dose is possible (Fig. 3).

While Radiation therapy has contributed markedly to the treatment of VH, its major concern is

Table 2. Studies on dose regimens and their results

Series	Patients	Follow-up	RT dose	Tumor control/Toxicity/Remarks
Guedea [39]	5	36–80 months	2–3 Gy/#, 30–40 Gy dose	Pain relieved/no complications
Rades [37]	117	6–312/median 36 months	EQD_2: 20–34 Gy and 36–44 Gy	36–44 Gy group has complete pain relief in 82% cases (39% in other group)
Sahgal [40]	16	2–37/median 25 months	21 Gy (10–30 Gy), 3 Fx (1–5 Fx), 80% isodose	Acceptable local control
Heyd [35]	84	68 months (median)	34 Gy/2 Gy/# (median)	Pain relief (CR: 61.9, PR: 28.6, NR: 9.5%)
Miszczyk [41]	19	3 months (median)	20–40 Gy, 2 Gy/Fx	Symptomatic relief (17 patients) CR (7 patients)
Dipak Parekh [42]	10	21.2 years (5.1–49.1 years)	Mean 47 Gy (30–60 Gy in 1.7–2 Gy/#) (1.8 Gy/#mostly used)	90% tumor control
Miszczyk [36]	137	18 months	2 to 15 Gy/ #, 8–30 Gy (111 cases 24 Gy/12#), fractionated SRS	78% pain relief, fractional dose impact the result, 24 Gy is insufficient
Aksu [43]	28	18 (1.5–63) months	40 Gy/20#	24/28 symptomatic relief; CR: 54%, PR: 32%
Aich [44]	7	2 years	40 Gy/20#	100% pain relief; tumor control not evaluated
Zhang [45]	5	1 year	15–27.5 Gy/1–5#	20–40% reduction in lesion size, symptomatic relief in 4/5 patients

EQD2 — equivalent dose in 2 Gy fractions; CR — complete response; PR — partial response; NR — no response; SRS — stereotactic radiosurgery

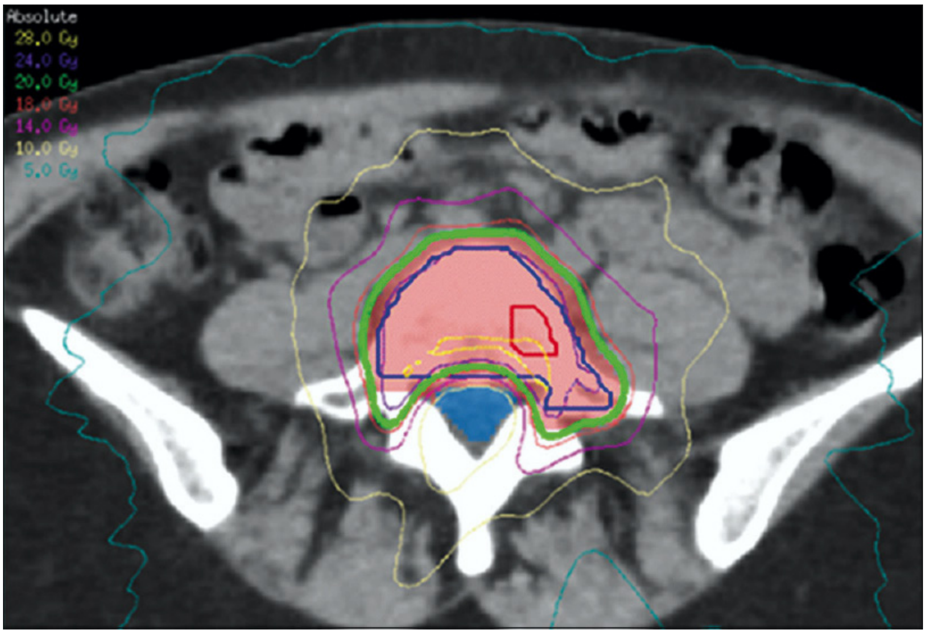

Figure 3. Dosimetric image treated by stereotactic body radiotherapy (SBRT), of a lumbar spine demonstrating steep dose distribution between the target and the thecal sac (blue) [49]

the possibility of developing radiation induced secondary malignancies. Although no secondary cancer has been found, the calculated mean carcinogenesis risk factor is 0.6 percent for single irradiation portals and 0.9 percent for double irradiation portals overall [50].

Conclusion

Vertebral hemangioma is a rare disorder which seldom warrants treatment. Radiation therapy has proven benefits compared to other treatment strategies, such as RFA, Vertebroplasty, surgical decompression, Intralesional injection etc. EQD_2 dose in the order of 40 Gy resulted in symptomatic relief in pain and control of the disease.

Acknowledgement

None declared.

Conflict of interest

There are no conflicts of interest.

Funding

None declared.

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