Neurochirurgie 65 (2019) 387–392

Disponible en ligne sur ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com

General review

Paraganglioma of the Lumbar Spine: A case report and literature review

S.I. Honeyman[a,*], W. Warr[a], O.E. Curran[b], A.K. Demetriades[c]

[a] University of Oxford Medical School, Green Templeton College, 43 Woodstock Road, Oxford, OX2 6HG, UK
[b] Department of Neuropathology, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU, UK
[c] Department of Neurosurgery, Western General Hospital, Crewe Road South, Edinburgh, EH4 2XU, UK

ARTICLE INFO

Article history:
Received 13 March 2019
Received in revised form 11 May 2019
Accepted 30 May 2019
Available online 25 June 2019

Keywords:
Paraganglioma
Spinal cord compression
Spinal tumor

ABSTRACT

Introduction. – Lumbar paragangliomas are rare, vascular, neuroendocrine tumors. They are notoriously difficult to diagnose radiologically and can prove challenging to manage intraoperatively, if capable of catecholamine secretion.
Case report. – We report the case of a 45-year-old man, who presented with a lumbar spinal paraganglioma. The patient described a 2-year history of worsening lower back pain and sciatica. Neurological examination was normal. MRI revealed a lesion at L3, with prominent vessels, compressing the cauda equina. Gross total resection (GTR) of the tumor was performed. The patient recovered well, with relief of pain and no neurological deficit.
Discussion. – A literature search of lumbar paraganglioma cases, from January 1970 to April 2018 was carried out. Results of this review highlighted the importance of inclusion of paraganglioma as a differential diagnosis in lumbar spinal tumor and also the requirement for preoperative investigations to determine any potential secretory activity.
Conclusions. – Lumbar paraganglioma behavior is most commonly benign and rates of recurrence are low after GTR. However, long-term postoperative follow-up is crucial, due to findings of late metastatic recurrence.

1. Introduction

Paragangliomas are rare, highly vascular neuroendocrine tumors of the autonomic nervous system [1,2]. They can arise from sympathetic and parasympathetic extra-adrenal paraganglia [1]. Histologically similar tumors, arising from the adrenal medulla, are known as pheochromocytoma [1]. Paraganglionic tumors are predominantly benign [2] and are generally found incidentally, or due to their mass effect [3]. While they can occur throughout the body, as paraganglionic tissue is widely distributed [1], their most common location is the head and neck, which accounts for over 90% of cases [4]. Central nervous system paragangliomas are relatively rare [4] and notoriously difficult to diagnose radiologically [4]. Here, we present a new case of a lumbar spinal paraganglioma, with an extensive literature search to review previously reported cases.

2. Case Report

A 45-year-old man presented to hospital with a 2-year history of chronic lumbosacral pain, radiating to the right leg. The patient reported that, while this sciatic pain was initially intermittent and unilateral, it had progressively worsened, becoming constant, with occasional left-leg involvement. The patient's symptoms were exacerbated upon sitting, standing or mobilizing. There was no significant medical history.

On examination, there was localized tenderness in the lumbosacral region. Motor power was preserved, scoring 5/5 throughout the lower limb. Sensation and reflexes were intact and symmetrical. The patient reported no issues with urinary or fecal continence.

MRI revealed an extramedullary intradural lesion at the level of L3 (Fig. 1). This space-occupying mass was seen to be compressing the cauda equina and had prominent associated vessels. Meningioma and ependymoma were considered as differential diagnoses.

An elective procedure was performed to remove the mass. L2-4 laminectomy was carried out, revealing an encapsulated tumor,

* Corresponding author at: Green Templeton College, 43 Woodstock Road, Oxford, OX2 6HG.
E-mail address: susan.honeyman@gtc.ox.ac.uk (S.I. Honeyman).

https://doi.org/10.1016/j.neuchi.2019.05.010
0028-3770/

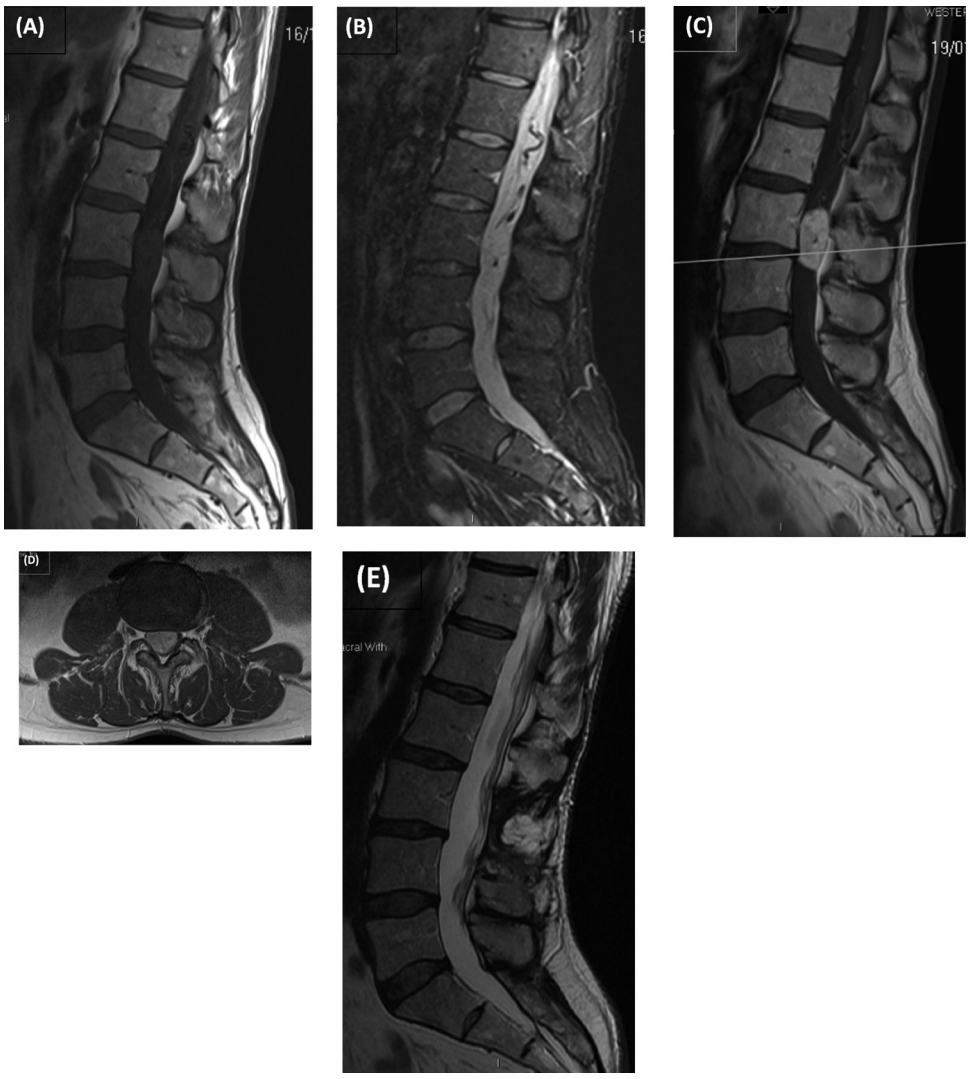

Fig. 1. Preoperative MRI revealing an extramedullary intradural lesion at the level of L3. From left to right (A) Sagittal T1; (B) Sagittal STIR; (C) Sagittal T1 plus contrast; (D) Axial plus contrast at L2; (E) Sagittal T2 postoperative.

which was excised completely, en bloc. Histology reported paraganglioma.

Postoperatively, the patient demonstrated no neurological deficits and experienced relief of lumbar and sciatic pain. At 30 months' follow up, he reported only occasional mild sciatic pain. He could walk without restriction. Surveillance MRI showed no residuum or recurrence.

3. Methods

3.1. Search strategy

A systematic review was carried out in accordance with PRISMA guidelines [5]. Studies which contained original reports of primary lumbar paraganglioma were identified in major electronic databases: PubMed, EMBASE and MEDLINE. References were retrieved from January 1st, 1970 to April 14th, 2018, the final date of our search. Search terms comprised: MeSH headings, free text words and synonyms for: "paraganglioma" and "lumbar spine". Further papers were identified through screening the references of papers already identified. No method, country or language restrictions were applied. Both full-text articles and Abstracts were considered.

3.2. Selection process

Papers obtained through the literature search were then imported into Endnote Reference Manager. Here, duplicates were removed and screening for relevance was performed through examination of titles and Abstracts by two independent reviewers. Articles were finally retained if they met inclusion criteria based on full-text article review. A record of all papers obtained and excluded and the exclusion justification was kept. Papers suitable for inclusion contained original case reports of primary lumbar spinal paraganglioma, with details of clinical presentation. No restrictions were imposed on patient age, gender, ethnicity, or geographical location. Papers were excluded if they were review articles, contained insufficient clinical details of the case or if there was uncertainty of diagnosis.

3.3. Screening and data extraction

Full manuscripts of suitable papers that had been identified were then obtained and inclusion finalized. Subsequently, two independent reviewers extracted data on patient demographics, clinical presentation, examination findings, radiological features of the tumors, histology results, operative outcomes and long-term

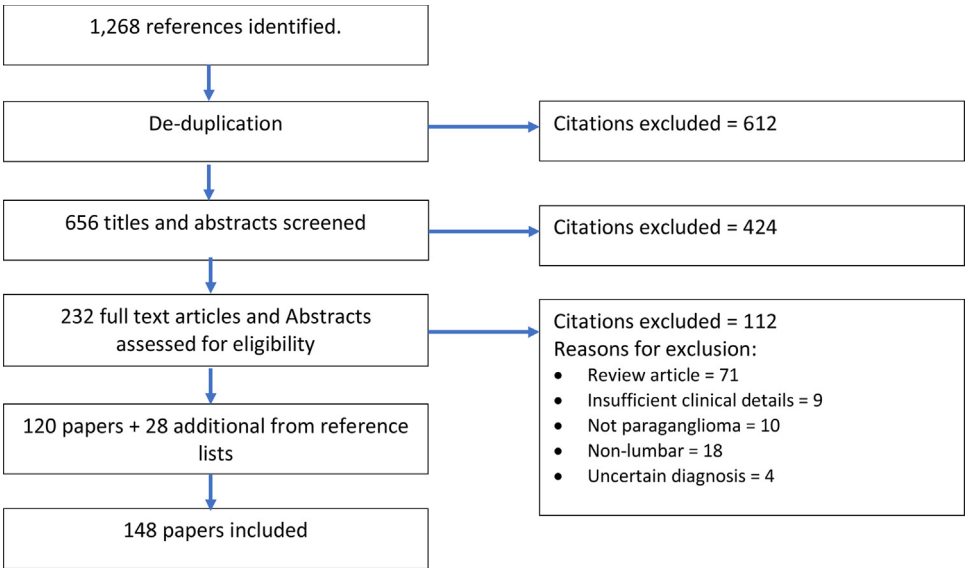

Fig. 2. Flowchart illustrating paper selection.

follow-up. These data were entered in a pre-formulated electronic database. If any discrepancies were found between reviewers' inputs during extraction, they were resolved by a third senior reviewer.

3.4. Results

The literature search yielded 656 citations, following removal of duplicates. Of these articles, 424 were rejected during title and Abstract screening and 232 were selected for full-text reading. In total, 120 papers met the inclusion criteria, along with an addition 28 papers identified from the reference lists of included papers. The 148 papers finally included reported a total of 296 cases. The selection process is presented schematically in Fig. 2.

4. Results & discussion

4.1. 4.1 Background

The paraganglionic system is a network of widely distributed neuroendocrine tissue [6]. It originates from the neural crest and co-migrates with the autonomic nervous system and large blood vessels during development [7]. The tissue is composed primarily of chief cells and sustentacular cells [8]. Functionally, paraganglia are thought to be responsible for the maintenance of fetal blood pressure [9], through the secretion of catecholamines [6]. However, as the adrenal medulla and autonomic nervous system assume this role post-partum [6], there is notable regression of the paraganglionic system during early childhood, leaving widespread residual tissue. The most prominent example of this is the organ of Zuckerkandl [9], located at the origin of the inferior mesenteric artery.

The paraganglia can be divided into sympathetic and parasympathetic classes, depending on their associations within the nervous system. Sympathetic paraganglia are located paravertebrally in the trunk and demonstrate catecholamine secretory activity [6]. In contrast, parasympathetic paraganglia are localized in the head and neck region. They are generally associated with vascular structures and demonstrate functionality as chemoreceptors. Both classes of paraganglia can give rise to paraganglioma.

4.2. Etiology

Paraganglionic tumors arise sporadically in the majority of cases [1]. However, an estimated 30% are thought to be associated with hereditary mutations [1]. Mutations associated with familial paraganglioma risk are heterogeneous, but around 50% involve genes coding for subunits A, B, C and D of succinate dehydrogenase [1]. It is postulated that the resulting deficiency in this enzyme leads to accumulation of succinate intracellularly and increased activation of the hypoxia-inducible factor (HIF) pathway, giving rise to pseudohypoxia [10]. This can explain the highly vascular nature of the tumor and the association between living at high altitude and much higher incidence of paraganglioma [10]. Additional notable conditions associated with increased genetic risk of paraganglioma include: multiple endocrine neoplasia 2, in which there is a mutation in the RET gene; von Hippel Lindau syndrome, in which there is a mutant VHL gene; and neurofibromatosis type 1, with a mutant NF1 gene [1].

4.3. Epidemiology

The peak incidence of lumbar spinal paraganglioma is in the 5th decade (age 40–49 years), with a mean age at presentation of 47.0 years (range 9–77 years). There is male predominance, with a male/female ratio of 1.54:1 (180 male cases to 117 female cases). Fig. 3 illustrates the age distribution of the 297 reported cases.

4.4. Clinical features

Symptom duration prior to presentation is highly variable, ranging from 1 day to 480 months (mean, 36.6 months). The most commonly described clinical symptom was chronic lumbar pain, which occurred in 79.8% of cases. In 53.2% of patients, lumbar pain occurred in conjunction with sciatica. The sciatic pain was predominantly bilateral (73.8%). Over 22% of patients reported sensory deficit, while 24.9% reported motor disturbance. Urinary or fecal continence was impaired in 11.4% of patients.

Additional less common modes of presentation included impotence (1.0%) and pseudo-claudication (0.7%). Three percent of patients presented with papilledema and symptoms of raised intracranial pressure (ICP). The pathogenesis of ICP elevation in lumbar paraganglioma is uncertain. However, it has been suggested

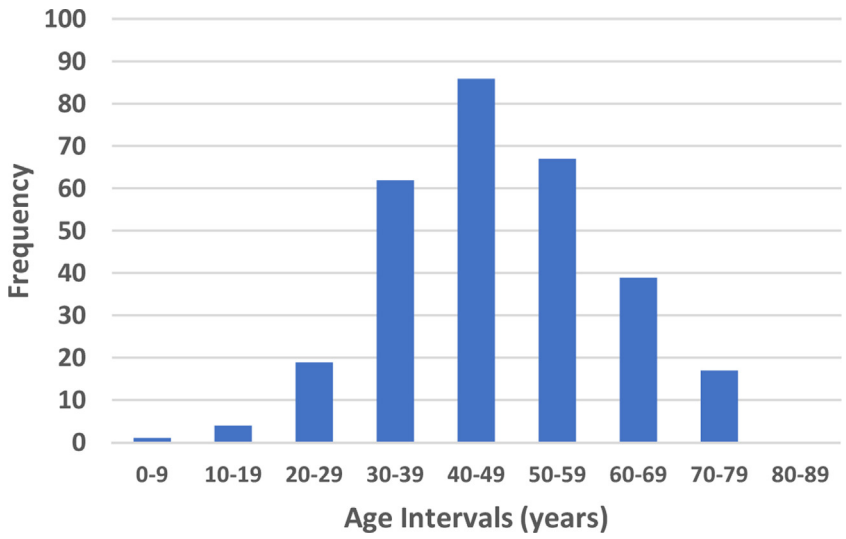

Fig. 3. Age distribution in a population of 297 patients with lumbar spinal paraganglioma. Maximum frequency is in the 5th decade (age 40–49 years).

that it may be attributable to an elevated cerebrospinal fluid (CSF) protein component impairing reabsorption, increased fluid secretion from tumor cells or impairment of CSF flow [6]. Few patients presented sudden onset symptoms; however, 3 of these had experienced lesional hemorrhage, which must be considered in such vascular tumors. Although paragangliomas have functional potential, only 2.4% of reported tumors demonstrated catecholamine secreting activity. Clinical features of reported cases are summarized in Table 1.

4.5. Radiology

Magnetic resonance imaging is the optimum mode of imaging for visualization of spinal paraganglioma [4]. However, diagnosis of these rare tumors proves challenging due to the non-specific nature of radiological findings. From cases reviewed in the literature, on T1 weighted imaging the tumors were isointense to the spinal cord in 76.6% of patients. On T2 weighted imaging the tumors varied in presentation, appearing as isointense (22.0%), hyperintense (39.0%), hypointense (34.1%) or mixed intensity (4.9%) in relation to cerebrospinal fluid. Following contrast administration, marked homogenous (61.0%) or heterogeneous (39.0%) enhancement of the tumors was observed. Many of these radiological features are common to other lumbar tumors, and thus a broad range of differential diagnoses can be considered radiologically, including ependymoma, meningioma, schwannoma, lipoma, teratoma and hemangioblastoma [4,11].

Radiological features that can be more characteristic of paraganglionic tumors have been proposed. On T2 weighting, a “salt and pepper” appearance has often been described, which results from hemorrhagic foci within this highly vascular tumor [12]. Additionally, hypointense tumor margins on T2 weighted images have been observed, which can be suggestive of hemosiderin and ferritin deposition, from previous hemorrhage [13]. Finally, flow voids may be noted surrounding the lesion or within the tumor itself, which can be indicative of high velocity flow and dilated vessels [11]. Presence of these radiological features may aid in the consideration of paraganglioma as a differential diagnosis.

Table 1
Summary of patient characteristics and clinical features of reported cases of lumbar paraganglioma.

Patient Characteristics	
Reported cases	297
Mean age at presentation	47.0 years
Gender (F/M)	117/180
Clinical Characteristics	
Mean duration of symptom history	36.6 months
Secretory	7/297 (2.4%)
Lower back pain	237/297 (79.8%)
Lower back pain + sciatica	158/297 (53.2%)
Sciatica	183/297 (61.6%)
→Unilateral sciatica	48/183 (26.2%)
Sensory deficit	67/297 (22.6%)
Motor deficit	74/297 (24.9%)
Sphincter dysfunction	34/297 (11.4%)
Raised ICP	9/297 (3.0%)
Erectile dysfunction	3/297 (1.0%)
Hemorrhage	3/297 (1.0%)

4.6. Operative considerations

Consideration of a paraganglioma as a differential diagnosis in lumbar tumor is important. Preoperatively, this can allow for appropriate clinical, laboratory and imaging investigations. While rare, sympathetic paragangliomas have the potential to secrete high levels of catecholamines [2] and produce a hypertensive effect [1], which can be challenging to manage intraoperatively [14]. Patients should be screened for tumor activity through assessment for sustained or paroxysmal hypertension and tachycardia, as well as other symptoms, such as headache, sweating and palpitations [14]. Urinalysis can be carried out to determine levels of the catecholamine metabolites produced over 24 hours, including vanillylmandelic acid, metanephrine and normetanephrine [14]. These are sensitive markers for secretory tumor activity [14].

Operatively, if there is potential for catecholamine secretion, patients can benefit from advanced preparation for hemodynamic instability, in particular administration of alpha adrenergic blockade and constant intraoperative monitoring of blood pressure [14]. Additional surgical care can be taken to avoid unnecessary tumor manipulation [4]. The importance of thorough investigation for potential presence of paraganglioma, to permit preoperative planning for hypertensive crises is emphasized in a case presented by Hong et al., in which catecholamine secretory activity of a lumbar paraganglioma only became apparent intraoperatively [15].

Lumbar paragangliomas are generally reported to be well-encapsulated masses, facilitating gross total resection (GTR) [4]. They are slow growing, with an estimated mean growth rate of

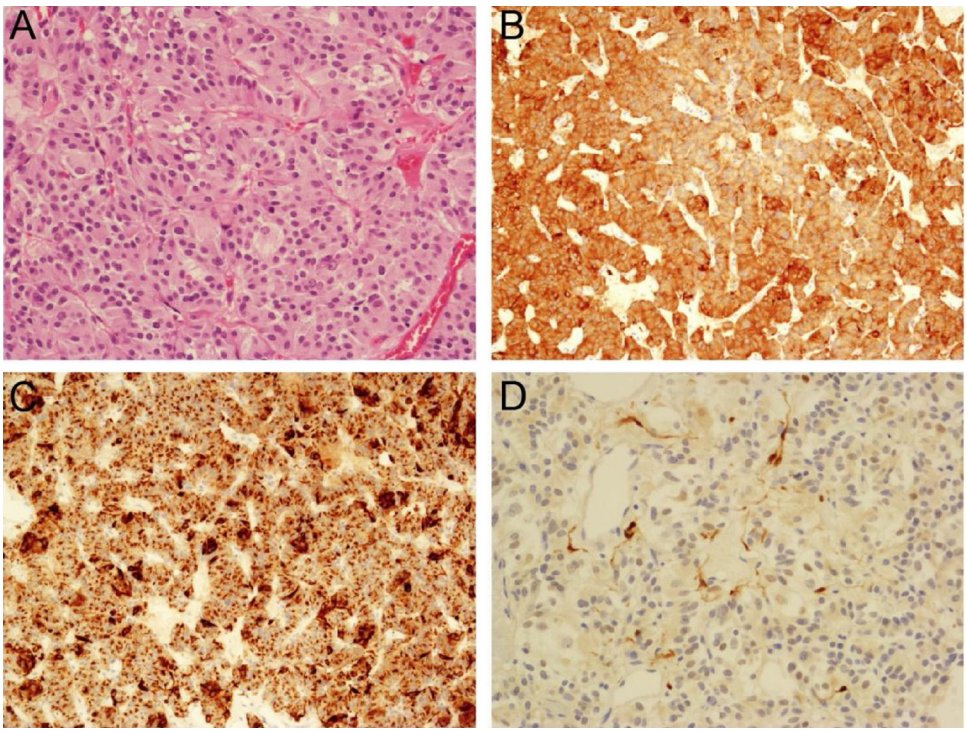

Fig. 4. Paraganglioma histology. (A) Hematoxylin and eosin section showing a tumor composed of uniform cells arranged in a typical acinar pattern ("Zellballen"). Immunohistochemistry with the antibodies to (B) synaptophysin, and (C) chromogranin A highlights the chief cells. (D) Small bipolar sustentacular cells incompletely surround some acini, as highlighted with the S-100 antibody.

1 mm/year [8]. Across 194 reported cases, they have presented an average diameter of 3.5 cm (range: 0.7–15.0 cm). Paragangliomas are commonly attached to surrounding structures, in particular nerve roots (44.2%), the filum terminale (42.5%), cauda equina (10.5%) and conus medullaris (2.8%). Dissection away from adherent structures is generally possible. Due to the highly vascular nature of these tumors, there is an inherent risk of significant operative blood loss [4]. Preoperative embolization has been used in some cases to reduce bleeding risk on resection and to reduce potential catecholamine load entering circulation upon manipulation [4,13].

4.7. Histology

On histology, paragangliomas have characteristically been described as producing a Zellballen pattern (Fig. 4) [4]. This appearance results from the arrangement of polygonal chief cells in small clusters, which are nested within surrounding sustentacular cells and fibrovascular stoma [13]. The neuroendocrine chief cells are identifiable by their eosinophilic cytoplasm, which is dense with neurosecretory granules [4], and their typically round, hyperchromatic nuclei [16]. Surrounding sustentacular cells can be distinguished by their spindle-like morphology and their immunoreactivity for S-100 protein [17]. The chief cells are immunoreactive for synaptophysin and chromogranin A, and other immunohistochemical markers, such as neuron-specific enolase or tyrosine hydroxylase [17–19]. These markers are non-specific and are also expressed by other neuroendocrine tumors [18]. Paragangliomas can also express cytokeratins, but this should not be interpreted as evidence of an epithelial lesion, such as carcinoma.

4.8. Patient outcomes and postoperative management

Spinal paragangliomas are benign WHO grade I tumors, with fewer than 1% of lumbar paragangliomas reported to demonstrate aggressive behavior [4,17]. Overall, their prognosis is good, particularly following GTR [4]. Of the cases reviewed here, 272 reported outcomes of attempted surgical removal: GTR was achievable in 88.6% of patients.

The importance of complete tumor resection must be highlighted. In the present cases, the probability of tumor recurrence following subtotal resection (STR) was more than 17-fold greater than following GTR (RR: 17.1, 95% CI: 6.36–46.0). On a mean 47.2 months' follow-up, there were just 5 cases of tumor recurrence in 241 cases of GTR (2.5%), compared to 11 in 31 cases of STR (35.5%).

Surgical resection is the primary treatment for lumbar paragangliomas, with little evidence supporting any other treatment modalities. There has been controversy over the potential value of adjuvant radiotherapy following surgery, particularly if the resection has been subtotal [4]. From the literature, tumor regrowth following STR alone was reported in 9 out of 25 patients (36.0%), compared to 3 out of 6 cases (50.0%) following STR with adjuvant radiotherapy. The mean interval to recurrence following resection alone was 110 months, compared to just 38 months with STR and adjuvant radiotherapy. This suggests little benefit for associating radiotherapy to surgery. However, it must be acknowledged that sample size was very small and the tumors treated with radiotherapy in conjunction with surgery had demonstrated aggressive behavior [20,21].

To the authors' knowledge, there have been no studies evaluating the relative benefit of STR alone versus in combination with radiotherapy for survival or recurrence in spinal paraganglioma. In other anatomical locations, namely head and neck, paragangliomas

have been demonstrated to be well-controlled by radiotherapy [22]. However, there is limited evidence that radiotherapy in conjunction with surgical resection provides any benefit [23].

Tumor recurrence can occur both locally and distantly as metastases. The importance of long-term follow-up is emphasized by reported cases of late recurrence, such as at up to 22 years after GTR [24]. Additionally, tumor recurrence can be asymptomatic [25], meaning routine imaging is essential.

Malignant behavior in lumbar paraganglioma is rare, with only 8 cases reported in the literature [17,20,21,24,26–29]. Malignancy, in the context of paragangliomas, is defined by the presence of metastasis from the primary tumor, as opposed to local invasion [6]. Two of the reported cases presented metastatic lesions, following only a short symptomatic course [26,27]. Six patients developed metastases, following surgical intervention [17,20,21,24,28,29]. Locations of reported metastases included intracranial and widespread leptomeningeal dissemination. This should highlight the value of screening for metastases both at time of presentation and throughout long-term follow-up. There have been no reports of distinguishing radiological or histopathological features that would predict aggressive behavior of metastatic paraganglioma [4].

5. Conclusions

Paragangliomas of the lumbar spine are rare benign tumors, with generally good prognosis. They most commonly present with symptoms of spinal cord compression. Radiologically they can be difficult to diagnose due to imaging features common to other spinal neoplasms. Diagnosis can be confirmed histologically. The importance of preoperative screening for catecholamine secretory activity is emphasized, along with the benefit of GTR to prevent tumor recurrence. Moreover, the value of long-term follow-up for both local and metastatic recurrence is highlighted.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure of interest

The authors declare that they have no competing interests.

References

[1] Welander J, Soderkvist P, Gimm O. Genetics and clinical characteristics of hereditary pheochromocytomas and paragangliomas. Endocr Relat Cancer 2011;18:R253–76.
[2] Dahia PL. Pheochromocytoma and paraganglioma pathogenesis: learning from genetic heterogeneity. Nat Rev Cancer 2014;14(2):108–19.
[3] Ellison DA, Parham DM. Tumours of the Autonomic Nervous System. Am J Clin Pathol 2001;115(suppl 1):S46–55.
[4] Corinaldesi R, Novegno F, Giovenali P, et al. Paraganglioma of the cauda equina region. The Spine Journal 2015;15(3):e1–8.
[5] PRISMA Guidelines Checklist 2009. http://prisma-statement.org/documents/PRISMA%202009%20checklist.pdf–last accessed April 26, 2019.
[6] McNicol AM. Chapter 12: adrenal medulla and paraganglia. In: Endocrine pathology: differential diagnosis and molecular advance. Springer edition; 2010. p. 281–91.
[7] Barnes L, Tse LLY, Hunt JL, Michaels L. Chapter 8 Tumours of the Paraganglionic system. https://www.iarc.fr/en/publications/pdfs-online/pat-gen/bb9/bb9-chap8.pdf - last accessed Nov 6, 2018.
[8] Persky MS, Kenneth SHU. Chapter 25: paragangliomas of the head and neck. In: Head and neck cancer: a multidisciplinary approach. 3rd edition. Wolters Kluwer; 2009. p. 655.
[9] Schober A, Parlato R, Huber K, et al. Cell loss and autophagy in the extra-adrenal chromaffin organ of Zuckerkandl are regulated by glucocorticoid signaling. J Neuroendocrinol 2013;25(1):34–47.
[10] Her YF, Maher JL. Succinate dehydrogenase loss in familial paraganglioma: biochemistry genetics, and epigenetics. Int J Endocrinol 2015;2015 [14 pages].
[11] Yang C, Li G, Fang J, et al. Clinical characteristics and surgical outcomes of primary spinal paragangliomas. Journal of Neuro-Oncology 2015;122:539–47.
[12] Kalani MA, Change SD, Vu B. Paraganglioma of the filum terminale: case report. Pathology and review of the literature. Cureus 2015;7(10):e354.
[13] Gelabert-González M. Paraganglioma of the lumbar region. Report of two cases and review of the literature. J Neurosurg Spine 2005;2:354–65.
[14] Colen TY, Mihm FG, Mason TP, et al. Catecholamine-secreting paragangliomas: recent progress in diagnosis and perioperative management. Skull Base 2009;19:377–85.
[15] Hong JY, Hur CY, Modi H, et al. Paraganglioma in the cauda equina. A case report. Acta Orthopaedica Belgica 2012;78(3):418–23.
[16] Wieneke JA, Smith A. Paraganglioma: carotid body tumor. Head Neck Pathol 2009;3(4):303–6.
[17] Moran CA, Rush W, Mena H. Primary spinal paragangliomas: a clinicopathological and immunohistochemical study of 30 cases. Histopathology 1997;31:167–73.
[18] Fraga M, García-Caballero T, et al. A comparative immunohistochemical study of phaeochromocytomas and paragangliomas. Histol Histopath 1993;8:429–36.
[19] Tischler AS, deKrijger RR. 15 years of paraganglioma: pathology of pheochromocytoma and paraganglioma. Endocrine Related Cancer 2015;22(4):t123–33.
[20] Roche PH, Figarella-Branger D, Regis J, Peragut JC. Cauda equina paraganglioma with subsequent intracranial and intraspinal metastases. Acta Neurochir 1996;138:475–9.
[21] Sundgren P, Annertz M, Englund E, et al. Paragangliomas of the spinal canal. Neuroradiology 1999;41:788–94.
[22] Van Hulsteijn LT, Corssmit EPM, et al. Regression and local control rates after radiotherapy for jugulotympanic paragangliomas: Systematic review and meta-analysis. Radiotherapy Oncol 2013;106:161–8.
[23] Trombetta M. The role of radiotherapy in the management of paraganglioma. Otorhinolaryngol Clin: Int J 2011;3:25–9.
[24] Strommer KN, Brandner S, Sarioglu AC, Sure U, Yonekawa Y. Symptomatic cerebellar metastasis and late local recurrence of a cauda equina paraganglioma. Case report. J Neurosurg 1995;83:166–9.
[25] Aggarwal S, Deck JH, Kucharczyk W. Neuroendocrine tumor (paraganglioma) of the cauda equina: MR and pathologic findings. AJNR Am J Neuroradiol 1993;14:1003–7.
[26] Warrier S, Owler BK, Besser M. Paraganglioma and paragangliomatosis of the cauda equina. ANZ J Surg 2006;76:1033–7.
[27] Asad S, Peters-Willke J, Nott L. Malignant paraganglioma, a rare presentation with foot drop: a case report. J Spine Surg 2015;1(1):99–102.
[28] Thines L, Lejeune JP, Ruchoux MM, Assaker R. Management of delayed intracranial and intraspinal metastases of intradural spinal paragangliomas. Acta Neurochir 2006;148:63–6.
[29] Thomson N, Pacak K, et al. Leptomeningeal dissemination of a low-grade lumbar paraganglioma: case report. J Neurosurg Spine 2017;26(4):501–6.