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Original Investigation

Parangliomas of the Spine

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ABSTRACT

AIM: Parangliomas of the spine are rare tumors. Clinical presentations and courses of spinal parangliomas are varied, and there are no standard principles of treatment to date. The purpose of this study was to explore the diagnosis, treatment and prognosis of spinal parangliomas.

MATERIAL and METHODS: The clinical data of 7 consecutive cases, with complete medical records and follow-up results that were treated in our institutions from October 2000 to October 2011, was retrospectively reviewed.

RESULTS: There were 6 males and 1 female with a mean age of 40 years (range, 16–61). The follow-up period ranged from 40 to 98 months (mean, 72 months). Of the 6 primary spinal parangliomas, one lesion was in the cervical intradural extramedullary space, one in the thoracic epidural space and four in the lumbar intradural extramedullary space. All tumors were totally resected and no recurrence was detected during the follow-up period. Of the metastatic case, the lesion of the spine was located in the first lumbar epidural space and vertebra. The patients underwent surgical resection two times with radiotherapy, but the tumor recurred and the patient suffered from the paraplegia of lower limbs and urine and stool incontinence during the follow-up period. No patient died.

CONCLUSION: Spinal parangliomas are rare lesions and seldom considered in the presurgical differential diagnosis due to its rarity and non-specific clinical symptoms and imaging features. Clinical follow-up was necessary to determine the outcome. Complete resection is necessary to prevent recurrence. The role of radiotherapy in the management of these lesions needs further assessment.

KEYWORDS: Paranglioma, Spine, Metastasis

INTRODUCTION

Parangliomas are rare tumors that arise from the paraganglia cells of the neuroendocrine system and account for 0.3% of all neoplasms (2,4). More than 80% of this kind of tumor develops within or near the glomus jugulare and carotid body. Parangliomas of spinal involvement are extremely rare. Primary spinal parangliomas usually take the form of intradural compression of the cauda equina or intra/extradural compression of the thoracic and cervical spinal cord (1). The first case of metastatic spread of a paranglioma to the spine was reported in 1948. So far, less than 30 cases of spinal metastases by parangliomas have been reported in English.

Clinical presentations and courses of spinal parangliomas are varied, and there are no standard principles of treatment to date (1,8). In this article, we report the clinical data of 7 consecutive cases with complete medical records and follow-up results that were treated in our institutions, in an attempt to explore the diagnosis, treatment and prognosis.

MATERIAL and METHODS

A retrospective analysis was performed in 7 patients with spinal paranglioma in our hospital from October 2000 to October 2011. No patient was lost in the follow-up period. There were 6 cases of primary spinal paranglioma and one case



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of metastatic spread of a paraganglioma to the lumbar and thoracic spine from the retroperitoneum (Figure 1A, B). The demographic data, clinical presentation, radiological presentation, distribution, treatment methods and outcome, and histopathology analysis were reviewed.

RESULTS

Clinical Presentation

The age of the patients ranged from 16 to 61 (mean: 40 years), with a male predominance (M/F = 6/1). The presentation of these spinal paragangliomas varied by location of the tumor, but local pain with a gradual and insidious onset was the most common symptom, which occurred in all patients, and was followed by limitation of spinal activity. The duration of pain before a definitive diagnosis is established varied from 2 weeks to 10 years (mean: 35.6 months). In the metastatic case, a 10cm×8cm stiff, non-tender, smooth and fixed mass at the left hypochondriac region and a 2cm×2cm mass at the first lumbar (L1) vertebra level were palpated. Neurological symptoms were seen in all cases (Table I). No adrenergic symptoms were found in any case.

Radiographic Presentation

Plain radiographs showed no abnormality in 5 cases, while there was the sign of bone destruction in L1 in the metastatic case and L4 lumbar spondylolisthesis in the remaining case. Furthermore, lateral radiography of the upper cervical and upper thoracic areas was usually of poor quality. In the

metastatic case, computed tomography (CT) showed a 105 mm × 67 mm × 80 mm well circumscribed mass with soft tissue density, which compressed the tail of the pancreas, the spleen, aorta and left kidney (Figure 2A, K). The mass was heterogeneous, and had a solid parenchyma with some cystic changes. Spotted calcification could be seen. The tumor was irregularly enhanced after contrast injection. The posterior edge of the L1 vertebra, both vertebral arches, the spinous process, left transverse process, and articular process had spotted osteonecrosis (Figure 2A, K). The CT scans found no abnormality in the affected region in the remaining 6 cases. The magnetic resonance imaging (MRI) scans of the lesions were characterized by iso- or hypointense signals on T1-weighted images and high- or isointense signals on T2-weighted images that enhanced with intravenous administration of gadolinium. All the mass except the metastatic one had an irregular oblong oval-shape in the vertebral canal and compressed the spinal cord, cauda equina or nerve root. A paravertebral soft tissue mass were seen in the metastatic case only.

Distribution

There were 7 lesions distributed along the spinal column in 7 patients. Of the 6 primary spinal paragangliomas, one lesion was found in the cervical intradural extramedullary space, one in the thoracic epidural space (Figure 1A, B) and four in the lumbar intradural extramedullary space (Figure 3A, B). Of the metastatic case, the lesion of the spine was located in the first lumbar epidural space and vertebra (including vertebral body and posterior elements) simultaneously at the time of diagnosis.

Table I: Clinical Data on 7 Patients with Spinal Paragangliomas

Case	Sex	Age (years)	History	Location	Treatment	Evolution	Follow-up (years)
1	M	16	Hypaesthesia of the trunk below cartilago ensiformis (xiphoid process) and numbness and weakness of the both legs for 2 weeks	T6-7, extradural	Total resection	DFS	8.2
2	F	38	Lumbago on the left for 5 months, numbness and weakness of the both legs for 19 days	L1, metastatic spread from retroperitoneum	Subtotal resection and radiotherapy	Local recurrence+ progression	8
3	M	61	Lumbago and numbness of the both legs for 5 years	L2-3, intradural	Total resection	DFS	7.2
4	M	52	Lumbago and posterior thigh pain for 10 years	L2-3, intradural	Total resection	DFS	7
5	M	40	Lumbar pain and left leg pain for 2 months.	L2, intradural	Total resection	DFS	4.2
6	M	37	Increasing neck pain over a period of 2 years, numbness and unendurable pain of the right maxillofacial region for 1 month.	C2-3, intradural	Total resection	DFS	4
7	M	36	Lumbago and both legs pain for 3 years.	L2-3, intradural	Surgery	DFS	3.3

F: Female, M: Male, DFS: Disease-free survival.

Treatment

All patients underwent surgical intervention. A posterior approach was employed for tumor resection in the primary cases, and spinal stability was reconstructed by internal fixation. For the metastatic one, the retroperitoneal tumor was resected through the explorative laparotomy first. Two weeks later, L1 laminectomy was performed; the posterior elements of L1, which were visibly infiltrated with tumor and the solid tumor adhesion to the left L1 nerve root, were resected. As fragments of tumor that extended to the anterior portion of the L1 vertebra were not excised, percutaneous vertebroplasty (PVP) with polymethyl methacrylate (PMMA) was done under C-arm X-ray guidance. Then, reconstruction with transpedicular screw instrumentation was performed. ^{131}I MIBG therapy (11.1 GBq) and external beam radiotherapy (40 Gy in 15 fractions) were applied postoperatively.

Biopsy

All patients had a pathologic diagnosis of paraganglioma during surgery.

Clinical Follow-up Period

The 7 patients were followed up for 40 months to 98 months (mean, 72 months). The results showed good outcomes in

the primary cases in which the symptoms disappeared and who had no evidence of active disease at the latest clinical follow-up. Poor outcomes were seen in the metastatic patient. Fifty months after the first surgery, a new lesion was found in the left appendix vertebra of T10-11 with extension into the spinal canal and paravertebral soft tissue, and she underwent surgical resection of the lesion and external beam radiotherapy to at L1 and T10 at our institutions. Six months later, a local recurrence in the left T10 and T11 intervertebral foramen with extension to the vertebral canal was seen. Further surgery was refused. The patient is still alive and no more metastatic site could be found elsewhere at the last follow-up, but she suffered from the paraplegia of lower limbs and urine and stool incontinence.

DISCUSSION

Paragangliomas are rare tumors that arise from the paraganglia cells of the neuroendocrine system. Although paragangliomas may occur in any age group, they are mainly seen in adults, and are uncommon in children and adolescents. In our study, only one patient was under 18 years of age and the male/female ratio was 6:1. More than 80% of paragangliomas, generally corresponding to the designation chemodectomas, occur in or near the glomus jugulare and carotid body. Spinal paragangliomas are extremely rare. To date, approximately 250 cases have been reported and the vast majority were intradural in the cauda equina. In our study, only one lesion was found in the cervical intradural extramedullary space and one in the thoracic epidural space. Some prior case reports indicated that thoracic paragangliomas are as a group distinct from the paragangliomas of the cauda equina in that they are generally extradural and have a greater predilection for distant metastasis (3).

The best-known type of paraganglioma is the pheochromocytoma, which secretes catecholamines and leads to labile hypertension. Although all paraganglia sequester catecholamines in cytoplasmic granules, paragangliomas arising from non-adrenal tissue are rarely active in neuroendocrine production (10). Only a few cases of spinal paraganglioma have been

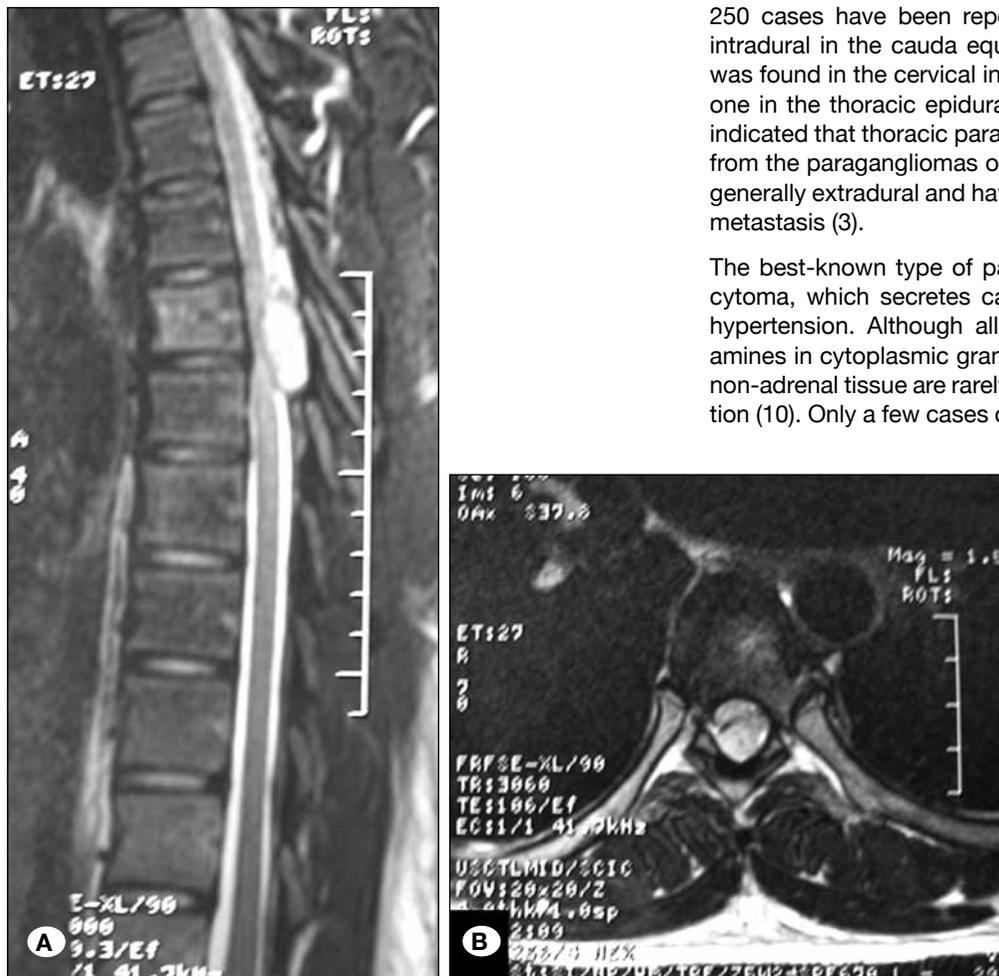


Figure 1: (Case 1) Magnetic Resonance Imaging **A)** T2-weighted sagittal image, showing a well circumscribed, homogeneously enhancing extradural tumor filling the spinal canal at the T6-7 level. **B)** Axial T2-weighted image, showing the mass lesion displaced the cord to the front of the spinal canal.

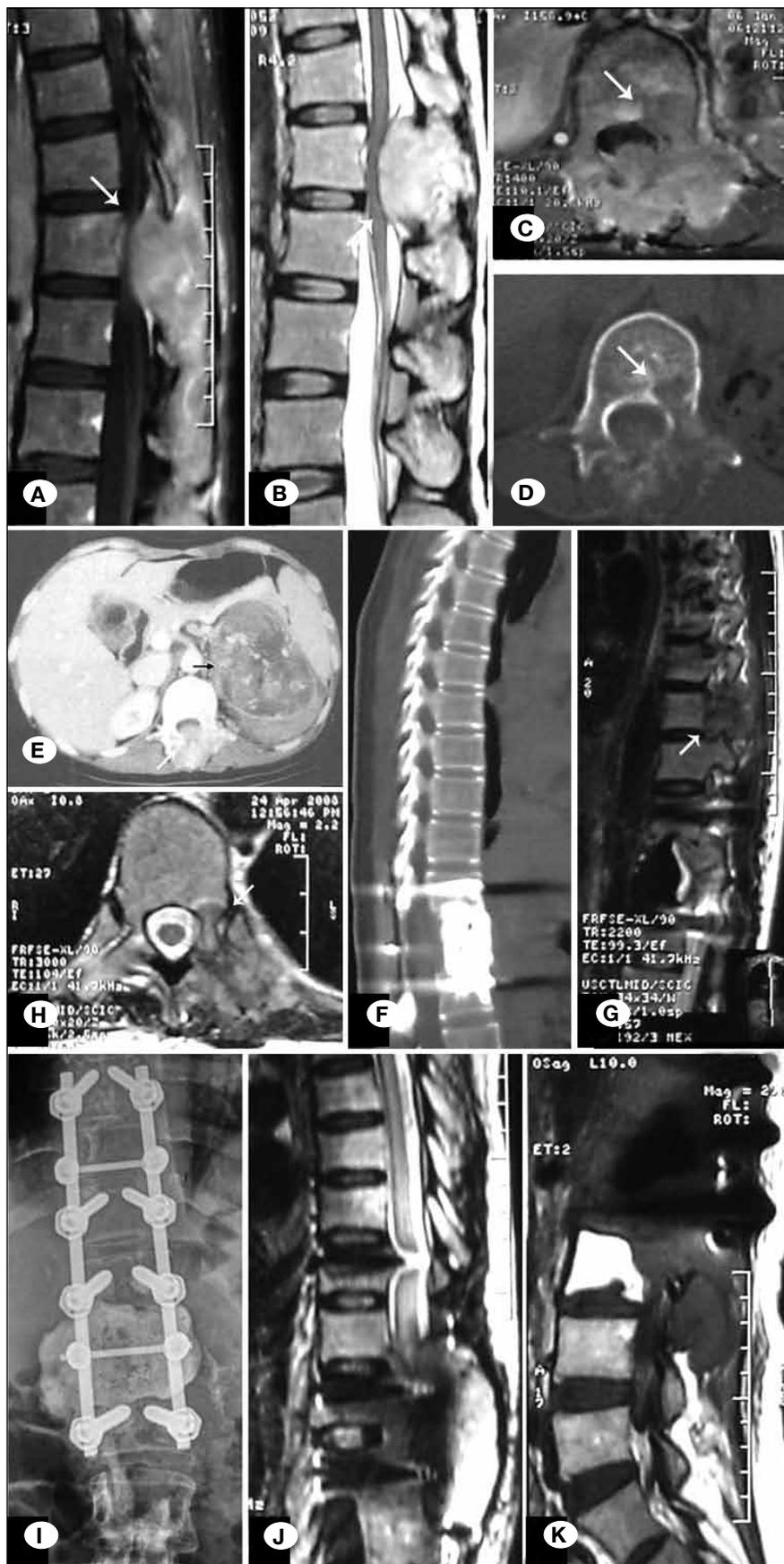


Figure 2: (Case 2) **A)** T1-weighted sagittal image and **B)** T2-weighted sagittal image showing spinal cord extradural compression at the vertebral body of L1 (white arrow). **C)** Axial magnetic resonance image and **D)** CT showing the posterior edge of L1 vertebrae, both vertebral arches, spinous process, left transverse process, and articular process had spotted osteonecrosis (white arrow). **E)** CT scan of abdomen showing a well-circumscribed, heterogeneous mass that was irregularly enhanced at 80.05 Hounsfield units after contrast injection, and compressed the tail of pancreas, spleen, aorta and left kidney (black arrow). The posterior edge of L1 vertebrae, both vertebral arches, spinous process, left transverse process, and articular process had spotted osteonecrosis (white arrow). **F)** CT scanning after the first surgery, showing no loosening and rupture of the screws, and no local recurrence. **G)** Sagittal MRI 50 months after the first surgery, showing a new mass of appendix of T10-11, and **H)** axial MRI revealing an infiltrative tumor in the left appendix vertebra of T10-11 with extension into the spinal canal and to the paravertebral soft tissue. **I)** Anterior-posterior radiograph demonstrating no loosening and rupture of the screws after the second surgery. **J, K)** MRI 6 months after the second surgery revealing that the spinal canal between T10 and L2 was filled with tumor, extending through the foramina to the paravertebral soft tissue.

reported to secrete catecholamines (1,2,16). In our study, all the cases were non-functional paragangliomas, and vanillylmandelic acid and catecholamine were in normal range in the urine and blood of these patients. For those patients with a non-functional paraganglioma, it was difficult to make a correct preoperative diagnosis due to the absence of typical clinical symptoms. Local dull pain was the most common symptom, and other clinical manifestations included limited motion, radiating pain, and limb paresis, which was due to spinal cord or nerve root compression. The neurological dysfunctions were the main reasons why patients went to hospital for medical help.

The origin of primary paraganglioma in the spine is uncertain, since the existence of paraganglia cells in the CNS remains unclear. Sundgren et al. (17) suggest that a spinal paraganglioma may originate from sympathetic neurons in the thoracic and lumbar lateral horns of the spinal cord or heterotopic neurons, which lie along these branches proximal to the sympathetic trunk. Guevara et al. (7) believed that paraganglioma developed from the incomplete regression of fetal paraganglia, with persistence of vestigial tissue till adult life.

MRI examination is sensitive in detecting the mass and could delineate its location, outline, internal structure as well as

Table II: Immunohistochemical Features of 7 Cases

Case	S100	Vimentin	NSE	Cytokeratin	EMA	Chromogranin	Synaptophysin	Nf	CD34	CD68	Ki67
1	±	+	++	-	-			-	-		
2	+	+++	-	-	-	+	+	-		-	
3	-	+	+	-	-	+	+	-	-		
4	+		+	±		+	+	+			
5	+		+	Focal+	-	+	+				<2%
6	++			-		+	±		+		
7	++	++	++	-	Focal+	++	++			-	<5%

NSE: Neuron-specific enolase, Nf: Neurofilament proteins, EMA: Epithelial membrane antigen.



Figure 3: (Case 4) Magnetic Resonance Imaging
A) Sagittal T1-Weighted image, showing a well-circumscribed, intradural tumor isointense to the spinal cord in the spinal canal at the L2/L3 level.
B) Sagittal T1-Weighted image with gadolinium showing that the mass is strongly homogeneously enhanced.

its relationship with the surrounding tissue and organs. T1-weighted images give better spatial resolution and better show the highly vascular internal matrix of the tumor. T2-weighted images give better tissue contrast, making smaller lesions more conspicuous. In general, the tumors exhibited relatively prolonged T1 and T2 relaxation times. On T1-weighted images, 3 tumors were of approximately equal signal intensity to adjacent muscle, while 4 tumors were slightly higher in intensity than surrounding muscle. On T2-weighted images, 5 tumors showed variable but greater signal intensity than muscle, while 2 tumors were of equal signal intensity. All the masses enhanced with intravenous administration of gadolinium. The T1-weighted and T2-weighted imaging characteristics differentiated dermoid tumor and lipoma from paragangliomas. In 4 of the 7 tumors, there were multiple punctate and serpiginous areas of signal void, named "salt-and-pepper" appearance, due to high-velocity flow in tumor vessels seen on T2-weighted imaging. Because of the hypervascular nature, the "salt-and-pepper" appearance on T2-weighted imaging was characteristic of paragangliomas. However, this appearance can also be seen in other hypervascular tumors such as hemangioblastoma, angioma, and metastatic thyroid carcinoma, which are more common in the spine region.

The diagnosis of paraganglioma still relies on the postoperative histological examination. Parangliomas have a variety of histological growth patterns, but the characteristic "Zellballen" pattern, a nesting or clustering of cell groups, and the trabecular cords of cells within thin compartments of connective tissue stroma, is the primary histological feature of paragangliomas (14). In our study, 4 of the 7 tumors presented with the above characteristic morphologic appearance. The ependymoma, the main lesion in the differential diagnosis, is characterized by perivascular pseudorosettes, radially oriented cell groups surrounding small vessels. When none of the above classical patterns is found, it is very difficult to differentiate paragangliomas from ependymomas on routine staining. Immunohistochemical staining was most commonly used for differential diagnosis. Chromogranin, which is demonstrated in granules, and synaptophysin, a membrane glycoprotein specific for presynaptic vesicles (5), and neuron specific enolase, are positive in paragangliomas, whereas negativity for glial fibrillary acidic protein exclude ependymomas with ease. Table II summarizes the result of the immunohistochemical staining. It is difficult to differentiate between benign and malignant tumors, though several reviews have examined series of paraganglioma to determine gross features, microscopic characteristics and biologic actions that might help predicting which ones have a propensity for metastatic spread. Both tumors show cellular pleomorphism and local or vascular invasion (4). Clinical follow-up was necessary to determine the outcome.

Total removal of the tumor was adequate treatment and the goal of surgery. The recurrence for the metastatic patient was due to incomplete removal. When removal of the entire tumor is not possible, radiation treatment is recommended (9,18). The general recommended dose is 4,000 to 4,500 cGy. However this is largely based on studies done on giant cell tumors and

chordomas (6,9). The use of chemotherapy is controversial. U-King-Im et al. (18) reported successful therapeutic use of octreotide in a patient with carotid body paraganglioma that metastasized to multiple vertebrae. Mertens demonstrated the successful regression and palliation of metastases of paraganglioma with chemotherapy, particularly with combined cyclophosphamide, vincristine and dacarbazine (13). However, there were also a number of disappointing reports on chemotherapy for this type of tumor (8,11,12,15). In our study, 6 patients with primary paraganglioma only underwent surgery and the follow-up showed good outcomes and no recurrence. For our metastatic case, postoperative radiotherapy seemed to be of no value in preventing local recurrence. Subtotal resection was the main reason for the tumor recurrence. Consecutive radiotherapy should be restricted to malignant or recurring paragangliomas.

■ CONCLUSION

Spinal paragangliomas are very rare lesions. They will seldom be considered in the pre-surgical differential diagnosis due to their rarity and non-specific clinical symptoms and imaging features. The diagnosis is made by histopathological examination. Clinical follow-up is necessary to determine the outcome. Complete resection is necessary to prevent recurrence. The role of radiotherapy in the management of these lesions needs further assessment and should be restricted to malignant or recurring paragangliomas.

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