Review Article

Diagnostic and management considerations in multicentric forms of laryngeal paraganglioma: a systematic review

Saikrishna Ananthapadmanabhan[1]^, Joe Jabbour[1], Anand Suruliraj[1,2], Faruque Riffat[1,2], Mark Smith[1,2], Niranjan Sritharan[1,2]

[1]Department of Otolaryngology, Nepean Hospital, Kingswood, NSW, Australia; [2]Department of Otolaryngology, Westmead Hospital, Westmead, NSW, Australia

Contributions: (I) Conception and design: S Ananthapadmanabhan, N Sritharan; (II) Administrative support: All authors; (III) Provision of study materials or patients: S Ananthapadmanabhan; (IV) Collection and assembly of data: S Ananthapadmanabhan; (V) Data analysis and interpretation: All authors; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Dr. Saikrishna Ananthapadmanabhan, BMed/MD. Department of Otolaryngology, Nepean Hospital, Kingswood, NSW 2747, Australia. Email: saikrishnaanantha96@gmail.com.

Background: Laryngeal paragangliomas (LPs) comprise a small subset of head and neck paragangliomas (HNPGLs), arising from the superior or inferior laryngeal paraganglia. Multicentric forms of LP are rare and should raise suspicion for hereditary disease. A systematic review of the literature was performed to identify all reported cases of multicentric LP and discuss the unique diagnostic and management paradigms in these situations.

Methods: A literature search was performed utilising PRIMA guidelines, and a search algorith the Medline, PubMed, SCOPUS, and EMBASE databases. Further articles were identified using Google Scholar and the references of selected articles. The authors included all article types within the published literature from 1975 to 2022, without exclusion based on language, that reported on LP with multifocal disease.

Results: A total of 11 articles were included, which reported 12 patients who had multicentric cases of LP. Eighteen synchronous lesions were identified and involved the carotid body (n=10), skull base (n=4), jugulotympanic cavity (n=1), parapharyngeal space (n=1), paravertebral space (n=1), and retroperitoneum (n=1). The skull base and parapharyngeal space lesions may represent carotid or vagal paragangliomas. Two patients had cervical lymph node involvement, and 1 patient had multiple cutaneous nodules, each with biopsy confirmed paraganglioma. Three studies reported genetic testing, which revealed succinate dehydrogenase (*SDH*)-*B* mutation, confirming a hereditary component.

Conclusions: Synchronous lesions in patients with LP are uncommon and should prompt suspicion of hereditary disease. Multicentricity is an important consideration in surgical planning and has prognostic implications requiring stricter surveillance and genetic workup. The increasing popularity of whole-body octreotide scanning in the diagnostic workup of paragangliomas is likely to discover more synchronous or metachronous lesions. Multicentricity in LP introduces complexities in surgical management and may alter treatment paradigms and prognosis. Diagnostic modalities should include whole-body scanning to detect synchronous lesions.

Keywords: Larynx; paraganglioma; multicentric disease; systematic review

Received: 17 February 2022; Accepted: 28 October 2022; Published: 11 November 2022.
doi: 10.21037/ajo-22-11
View this article at: https://dx.doi.org/10.21037/ajo-22-11

^ ORCID: 0000-0002-5080-9284.

Introduction

Paragangliomas are rare neoplastic lesions derived from neural crest derivatives and arise from autonomic paraganglion. Head and neck paragangliomas (HNPGLs) typically originate from parasympathetic structures located around the skull base and neck and commonly involve the baroreceptors of the carotid body (60%), glossopharyngeal nerve fibres within the jugulotympanic cavity (40%), or vagal fibres (5%) (1). Rare anatomic locations include the orbit, paranasal sinuses, nasopharynx, parotid, larynx, or thyroid gland. Laryngeal paragangliomas (LPs) comprise a minor subset of HNPGL and arise from either the superior or inferior laryngeal paraganglia, with >90% involving the supraglottis. They are generally non-functional and do not secrete catecholamines, as they are associated with parasympathetic structures. LPs and HNPGLs are usually unifocal and sporadic, with hereditary disease underlying 30–40% of cases (2). Germline mutations of succinate dehydrogenase (*SDH*) are thought to account for 70% of familial paragangliomas (3). Multicentric forms of HNPGL may be present in 10–20% of sporadic cases and up to 80% of familial cases (4). However, multicentricity in LP has been rarely described in the literature, with reports of synchronous lesions reported in the carotid body, jugular bulb, and skull base (5-15). Paragangliomas presenting with multifocal disease, when compared to solitary lesions, are associated with higher rates of recurrence and patients require stricter surveillance and genetic counselling (16). We present a systematic review of all known cases of LP with multifocal disease and provide a comprehensive overview of the patient's clinical presentation, diagnostic workup, and management. The objective of the review is to characterise the demographics of patients with multicentric forms of LP, describe the location of synchronous and metachronous lesions found, the imaging modalities incorporated in the diagnostic workup, and the management employed. It is likely that the literature underreports multicentricity as whole-body scanning with octreotide scintigraphy is a recent imaging modality that has not been employed widely until the last decade. We present the following article in accordance with the PRISMA reporting checklist (available at https://www.theajo.com/article/view/10.21037/ajo-22-11/rc).

Materials and methods

The search strategy aimed to identify all recorded cases of multicentricity in patients with LP in the literature. A literature review was performed on 22nd September 2022 using PubMed, Medline, SCOPUS, and EMBASE databases, with results imported into the reference management software Endnote 20.4 (Clarivate Analytics 2022). Three main search domains were used, which were combined with the Boolean operator "and", whilst search terms contained within each domain were combined with the Boolean operator "or". The keywords within the first search domain were "head and neck" or "larynx", the second search domain was "paraganglioma", and the third search domain was "multicentric", "synchronous", or "metachronous". Our inclusion criteria included any study that reported a patient with confirmed LP and either (I) biopsy confirmed synchronous lesion, (II) somatostatin-avid synchronous lesion on octreotide PET scan, or (III) suspicious lesion on CT or MRI with distinctive features of paraganglioma (this includes contrast enhancement, internal arterial flow voids, and salt and pepper appearance). All article types within the published literature between 1975 and 2022 were eligible for inclusion. Studies were excluded if they described HNPGLs without larynx involvement. Studies were not excluded based on language and 1 study from the non-English literature was included in the analysis. Google, Google Scholar, and article references were examined to further identify any potentially eligible studies. The search results were reviewed for eligibility by a single reviewer based on the title and abstract of the article, and a full text screening of potentially eligible articles was performed to determine inclusion in the study. The expertise of a consultant head and neck surgeon was available if any uncertainty arose. Articles were either case reports or case series, as previous literature or systematic reviews covering this topic have not been performed. The risk of bias was assessed using the Joanna Briggs Institute checklist, standardised tool developed for case reports and series, and is provided in Figure S1 and Appendix 1 (17).

Demographic data of patients and information regarding the diagnostic workup, paraganglioma, and management was compiled into Microsoft Excel version 16.53 (Microsoft Corporation, Redmond, WA, USA) for Mac (Cupertino, CA, USA). Statistical analysis was performed within the Excel spreadsheet.

Results and outcomes

The results of the PRISMA are shown in *Figure 1*.

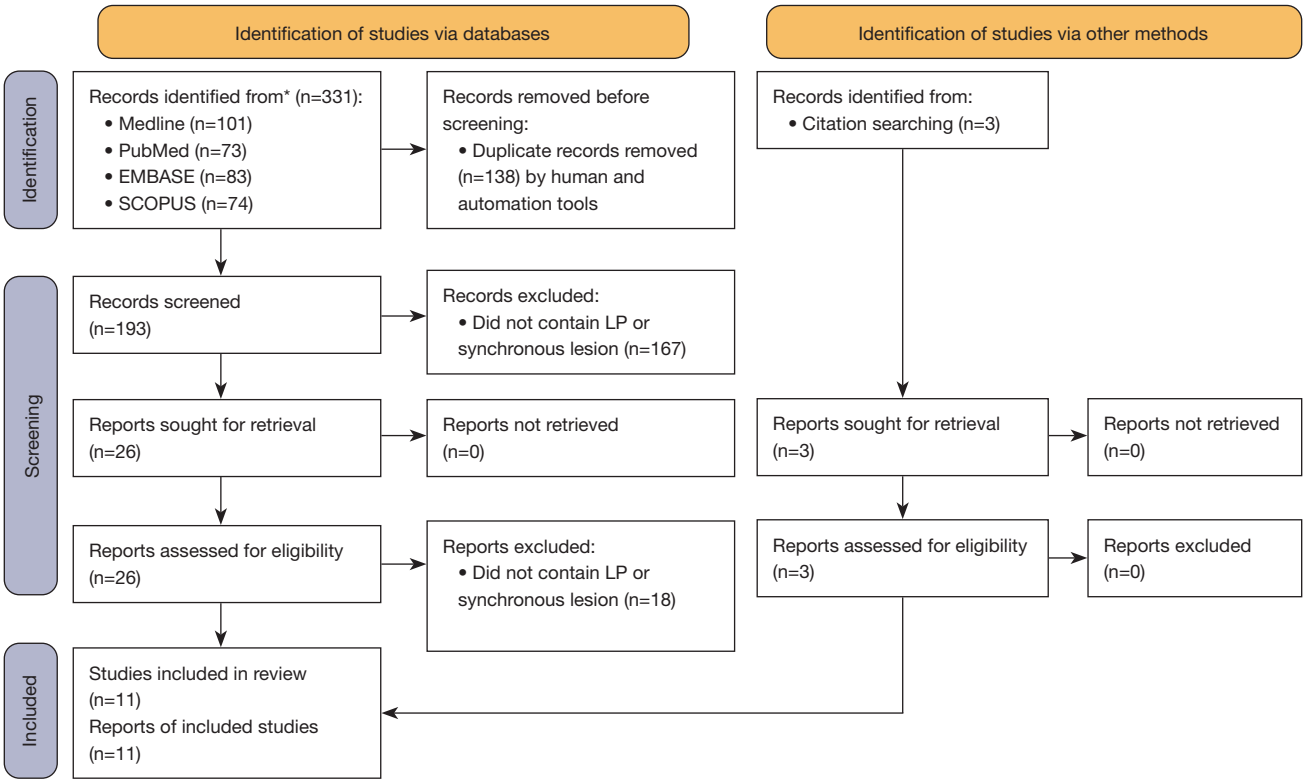

Figure 1 PRISMA flowchart. *, consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). LP, laryngeal paraganglioma; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Eleven articles were included which reported 12 patients who had confirmed LP with a concurrent synchronous biopsy-proven paraganglioma, somatostatin-avid lesion on octreotide scintigraphy, or lesion on CT/MRI with pathognomonic features of paragangliomas. The bias of the included studies was low, with all studies documenting the demographic and clinical characteristics of the patient, the symptomatology of the LP or synchronous lesion, the investigative modalities used, and the type of management for both lesions. One study in a *Radiology* journal did not mention the management of either the LP or synchronous carotid body tumour. Most studies either did not adequately document follow up or had a short follow up duration.

Demographic data and baseline information of the patient cohort is summarised in *Table 1*. Almost equal number of male and female patients were recorded, compared to a 3:1 female predilection reported in most studies of LPs (18). The patient cohort was relatively young with a mean age of 46 years, compatible with the literature suggesting that LP usually manifest between the fourth to sixth decades of life (18). Three patients had a confirmed or suspected positive family history of paraganglioma. Dogan described a patient with a synchronous left carotid body paraganglioma (CBP), whose mother had reported an excision of CBP previously (7). Hall reported a case of right supraglottic paraganglioma with a synchronous right CBP, confirmed on histopathology, in a patient who had a brother and 2 sons with glomus tumours (9). The patient had an *SDH-B* mutation. Schmit reported a patient with left subglottic paraganglioma with a synchronous right skull base lesion demonstrating MRI enhancement, suggestive of a vagal paraganglioma (13). The patient had a grandfather who died from an undiagnosed skull base tumour. The diagnostic workup of LP in our patient cohort included multimodal imaging techniques, with CT and MRI being routine investigations. Whole-body scintigraphy modalities with octreotide-based scans were used in 7 cases. Only 1 LP was functional (i.e., catecholamine

Table 1 Baseline characteristics of the patient population (n=12)

Study parameters	Patient population
Age (years)	46±15
Gender	
Male	5 (41.7)
Female	6 (50.0)
Not specified	1 (8.3)
Country	
USA	4 (33.3)
India	2 (16.7)
Australia	2 (16.7)
Iran	1 (8.3)
Spain	1 (8.3)
Turkey	1 (8.3)
United Kingdom	1 (8.3)
Positive family history	3 (25.0)
Previous LP	4 (33.3)
Functional LP	1 (8.3)
Imaging modality	
Computed tomography	10 (83.3)
Magnetic resonance imaging	9 (75.0)
Octreotide scintigraphy (e.g., 68-gallium DOTATATE)	7 (58.3)
Angiogram (CT or MRI)	5 (41.7)
Ultrasound	3 (25.0)

Values are expressed as n (%), to 1 significant figure, or mean ± standard deviation where appropriate. LP, laryngeal paraganglioma; CT, computed tomography; MRI, magnetic resonance imaging.

secreting), with the overwhelming majority being non-secretory (8).

LP characteristics

Clinical information regarding the characteristics of the identified LP is summarised in *Table 2*. The overwhelming majority of LP was supraglottic, with only 1 case of subglottic paraganglioma arising from the inferior laryngeal paraganglia reported. The main symptoms reported in the literature include neck mass or swelling (n=6), dysphonia (n=5), dyspnea (n=3), dysphagia (n=1), stridor (n=1), and haemoptysis (n=1). The symptoms of neck swelling or palpable neck lump could also be attributable to the synchronous paraganglioma, as 5 of the patients had a carotid body tumour. Four patients had a history of previous LP, with the current presentation being a recurrence. Multicentric disease likely has an underlying genetic component and is associated with higher risk of recurrence and treatment failure. Hall reported a patient with *SDH-B* mutation who had recurrent LP after a previous surgical excision 15 years previously (9). Sankar reported a patient who had endoscopic resection of LP in 2003, 2006, and 2014, and represented in 2017 with supraglottic paraganglioma with multicentric disease present in the cervical lymph nodes and multiple cutaneous nodules of the upper back, abdomen, and pelvis (12). Octreotide scintigraphy showed concern for metastatic disease with avid lesions in the liver. Sharifkashany described a patient who had a recurrence 5 years after suprahyoid incision and resection of LP (14). We have also described a case of LP in a female patient who presented with a left supraglottic LP on a background of previous bilateral carotid body tumours (CBTs) that were managed with angioembolisation and surgical resection.

Synchronous paraganglioma characteristics

Eighteen synchronous lesions were described in the literature in the 12 patients, and summarised in *Table 3*. This includes 10 CBPs in 7 patients, with 3 having bilateral carotid body involvement. Other foci of involvement include the skull base (n=4) and parapharyngeal space, which could represent carotid body or vagal paragangliomas. Rubin described a patient with supraglottic paraganglioma with concurrent disease involvement of the left common carotid bifurcation, the right carotid body, and a small lesion in the petrous temporal bone (10). The skull base lesion likely represented another CBP affecting the proximal portion of the petrous segment of the internal carotid artery (ICA). Schmit reported a synchronous MRI enhancing 1.5 cm lesion located 2 cm below the right skull base posterior to the right ICA, likely representing a vagal paraganglioma near the jugular foramen (13). Sharifkashany reported a patient with recurrent supraglottic paraganglioma with 2 synchronous contrast-enhancing lesions on CT and MRI (14). An expansile-lytic left jugular foramen mass, representing a biopsy-confirmed jugulotympanic

Table 2 Clinical characteristics of LP including presenting symptoms and duration of symptoms, imaging modalities incorporated in diagnostic workup, anatomical features of the paraganglioma, and management

Study, year	Symptoms	Duration (months)	Imaging modalities	LP characteristics	Management
Abt, 2020	Neck mass	N/A	CT, MRI, octreotide	17 mm left supraglottic mass involving AE fold	External cervical approach[#]
Ananthapadmanabhan, 2022	Dysphonia, dyspnea, dysphagia	24	CT, MRI, octreotide	21 mm left supraglottic mass involving AE fold and false vocal cord	External cervical approach
	Dyspnea	N/A	CT, octreotide	Left supraglottic mass involving false vocal cord	External cervical approach
Dogan, 2015	Neck mass	18	CT, MRI, octreotide, USS, angiogram	10 mm × 12 mm right supraglottic mass involving pre-epiglottic space; DSA: STA feeding vessel	Angioembolisation STA; external cervical approach
García-Martín, 2010	Dysphonia, dyspnea	36	CT, MRI, octreotide, angiogram	32 mm × 20 mm × 22 mm right supraglottic mass involving AE fold	Angioembolisation; external cervical approach
Hall, 2010	Neck mass	12	CT, MRI, USS, angiogram	16 mm × 12 mm right glottic mass involving true vocal cord, extending into subglottis	Angioembolisation STA; external cervical approach
Rubin, 2005	Dysphonia, neck mass, stridor	24	CT, MRI, angiogram	Left supraglottic mass involving AE fold with 50% airway obstruction; angiogram: STA feeding vessel	Angioembolisation STA; external cervical approach
Sanders, 2001	Haemoptysis	N/A	CT, MRI, angiogram	Left supraglottic mass; angiogram: SLA feeding vessel	Angioembolisation STA; external cervical approach; supraglottic laryngectomy
Sankar, 2018	Dysphonia	N/A	CT, octreotide (technetium-99m scan)	Supraglottic mass involving bilateral AE folds	Previous endoscopic resection ×3; chemotherapy for current recurrent presentation
Schmit, 2006	Neck mass	N/A	MRI, USS	30 mm × 30 mm × 25 mm left subglottic mass	External cervical approach
Sharifkashany, 2014	Dysphonia	60	CT, MRI	20 mm × 15 mm left supraglottic mass involving AE fold and pre-epiglottic space	Previous external cervical approach; radiotherapy for current recurrent presentation
Tripathy, 2017	Neck mass	6	CT, octreotide	8 mm × 10 mm left supraglottic mass involving false vocal cord	N/A

[#], Majority of patients underwent external cervical approach for surgical resection of the lesion. Five patients underwent pre-operative angioembolisation of the superior thyroid artery, which was identified on angiogram as the feeding artery to the lesion. LP, laryngeal paraganglioma; N/A, not applicable; CT, computed tomography; MRI, magnetic resonance imaging; AE, aryepiglottic; USS, ultrasound scan; DSA, digital subtraction angiography; STA, superior thyroid artery; SLA, superior laryngeal artery.

paraganglioma (or glomus jugulare or tympanicum), demonstrated erosion of the skull base including the petrous apex and the bony septum between the jugular foramen and carotid canal. The mass extended into the middle ear cleft causing obstruction of the mastoid antrum with air cell opacification. A second synchronous lesion was observed in the right parapharyngeal space, involving the right pharyngeal mucosal space of the nasopharynx—the absence of splaying of the carotid bifurcation and posterior displacement of the ICA is suggestive of a vagal,

Table 3 Clinical and anatomic characteristics of the synchronous paraganglioma and management of the lesion

Study, year	Symptoms	Synchronous paraganglioma characteristics	Management	Genetic mutation
Abt, 2020	Neck mass	28 mm left CBP, 17 mm right CBP	Staged resection via external cervical approach	*SDH-B*
Ananthapadmanabhan, 2022	Nil	21 mm left para-aortic mass	Laparoscopic resection	Dual *SDH-A*, *SDH-B*
	Nil	Octreotide avid lesions at right and left skull base, left paravertebral region at C2	Monitoring with serial octreotide scans; previous bilateral CBTs 15 years ago managed with angioembolisation of STA and surgical resection with external cervical approach	N/A
Dogan, 2015	Neck mass	25 mm × 32 mm left carotid bifurcation mass; angiogram: left ascending pharyngeal artery, feeding vessel	Angioembolisation of left ascending pharyngeal artery; external cervical approach for resection	N/A
García-Martín, 2010	Nil	22 mm × 14 mm × 12 mm right CBP	Angioembolisation; external cervical approach for resection	N/A
Hall, 2010	Neck mass	Right CBP; right level V cervical lymph node	Angioembolisation; external cervical approach for resection	*SDH-B*
Rubin, 2005	Neck mass, right otalgia	30 mm × 20 mm left CBP, small right CBP, petrous temporal bone lesion	Angioembolisation and resection of left CBP; monitoring of right CBP and skull base lesion	N/A
Sanders, 2001	Nil	40 mm left CBP	External cervical approach for resection	N/A
Sankar, 2018	Multiple painful cutaneous nodules	Multiple cutaneous nodules on back, abdomen, pelvis; segment V, VIII liver; cervical lymph nodes	Chemotherapy	N/A
Schmit, 2006	Nil	15 mm right skull base, likely vagal paraganglioma	Monitoring via imaging	N/A
Sharifkashany, 2014	Left otalgia, CN VII palsy, mixed hearing loss	35 mm × 25 mm right parapharyngeal space lesion; 30 mm × 25 mm left jugulo-tympanic mass	Radiotherapy	N/A
Tripathy, 2017	Neck mass	24 mm × 16 mm × 30 mm right CBP; 40 mm × 35 mm × 52 mm left CBP	N/A	N/A

CBP, carotid body paraganglioma; *SDH*, succinate dehydrogenase; CBTs, carotid body tumours; N/A, not applicable; CN, cranial nerve.

rather than a carotid body, paraganglioma (19). Finally, the authors have previously described a case of supraglottic paraganglioma with a left para-aortic paraganglioma, as an incidental finding on octreotide scan, representing the first confirmed synchronous lesion in patients with LP outside the head and neck (*Figure 2*) (6). In this paper, we also reported a case with synchronous octreotide-avid lesions in the bilateral skull base and left paravertebral space.

Management

Surgical management of LP via an external cervical approach is associated with less chance of recurrence compared to an endoscopic or microlaryngeal approach.

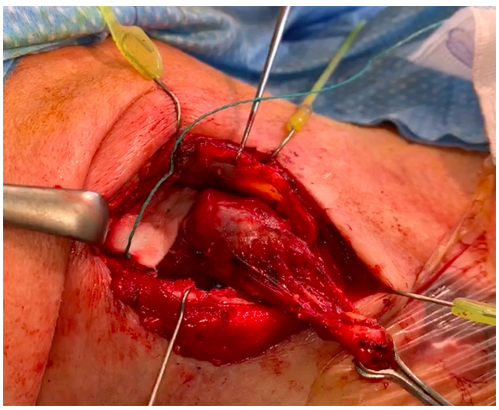

Figure 2 Intra-operative view of left supraglottic paraganglioma with excision via the external cervical approach. The laryngofissure is clearly noted.

This was the preferred treatment modality in 9 patients, with 5 who also had pre-operative angioembolisation of the feeding vessel, the superior thyroid artery. The patient in Sharifkashany was referred for radiotherapy for recurrent disease with multicentric lesions occurring in areas with difficult surgical access (14). Sankar *et al.* referred their patient for chemotherapy for metastatic and malignant disease involving cervical lymph nodes, cutaneous nodules, and suspicious hepatic nodules (12). There were additional management considerations for synchronous HNPGLs, especially in vagal, tympanic, and skull base lesions where surgical access is complicated compared to CBP and LPs. The size, symptom profile, and bilaterality of lesions affected decision to resect versus monitor the disease. Post-management follow-up was reported in only 7 studies with a mean duration of 5.1±2.7 months, with no study reporting residual or recurrent disease. Genetic testing was only performed in 3 studies, all confirming *SDH-B* mutation, with 1 patient having combined *SDH-A* and *SDH-B* germline mutation (5,6,9).

Discussion

Genetic considerations

Multicentric forms of disease in paragangliomas has prognostic implications. They are more likely to have an underlying hereditary component occurring in up to 80% of familial paragangliomas compared to 10–20% of sporadic paragangliomas (4). Germline loss-of-function mutations in *SDH* are recognised as susceptibility genes for familial paragangliomas. These genes encode mitochondrial complex proteins and are transmitted in an autosomal dominant pattern with incomplete penetrance. Other genes of interest include hypoxia-inducible factor (*HIF*)-*2* and von Hippel-Lindau (*VHL*). These genes coordinate angiogenesis and cellular proliferation in hypoxia, and mutations can lead to inappropriate activation of hypoxia pathways. It is postulated that the oxygen-sensing capabilities of paraganglionic tissues including the carotid body and glossopharyngeal and vagal fibres are defective, leading to chronic hypoxic stimulation, cell proliferation, and tumorigenesis (20). A retrospective review of 214 patients with HNPGL, of which 47 had confirmed genetic mutation of *SDH*, showed that mutation-positive patients had higher incidence of bilateral, functional, malignant, and metachronous tumours, as well as higher rates of recurrence and treatment failure (16). Papaspyrou *et al.* studied 175 patients with 225 HNPGLs, in which 19% of patients had multicentric disease—the incidence in mutation-positive patients was 65% (21). In our systematic review, 4 patients presented with recurrent LP. However, the short mean follow-up period in the included studies was a limitation as we cannot satisfactorily determine whether there was oncologic clearance or disease recurrence post intervention—in most studies, recurrence manifests several months or years after resection. The importance of detecting multicentric disease is manyfold. It stratifies patients into high-risk groups that require more stricter and regular surveillance, and allows us to refer patients for targeted genetic workup and appropriate counselling, as family members may need screening for hereditary paragangliomas. Hereditary disease is also likely underreported—only 3 patients with multicentric LP in our systematic review underwent genetic testing and all had *SDH-B* mutations. It is probable that genetic mutations were implicated in some of the other patients as well.

Clinical manifestations of LPs and synchronous lesions

In our systematic review it is important to note that LPs are more likely, compared to synchronous lesions, to become symptomatic as they readily affect voicing, swallowing, or breathing. Supraglottic lesions can create mass effect that can affect the oscillatory function of the vocal cords, manifesting as dysphonia, and create a mechanical obstruction to food bolus transit, causing dysphagia or aspiration. Airway obstruction from lesions overlying the glottis can manifest with exertional, or in severe cases, resting, dyspnea and inspiratory stridor.

Synchronous HNPGL presented with neck masses if significant in size. Otherwise, symptoms only arose if the paraganglioma caused compression of anatomical structures or destruction of normal anatomy—1 notable case was the patient with facial palsy and mixed hearing loss secondary to an expansile jugulotympanic paraganglioma that caused erosion of the petrous temporal bone and invasion into the middle ear space (14). This is important to consider in the diagnostic workup of the suspected LP—synchronous lesions outside the head and neck region are likely to be asymptomatic, unless secretory, and will be missed if imaging is restricted to the head and neck. Nevertheless, most synchronous lesions in HNPGL also occur in the head and neck. This may be because the underlying mutation affects oxygen-sensing structures that are restricted to the head and neck.

Role of whole-body scanning in detection of multicentric disease

Octreotide scintigraphy with 68-gallium labelled somatostatin scanning is emerging as a useful imaging modality in the standard diagnostic workup of a patient with suspected paraganglioma. Whereas conventional cross-sectional imaging techniques including CT and MRI are limited to a region of interest, octreotide-based scans screen the whole body for somatostatin-receptor expression to diagnose synchronous, metachronous, and metastatic disease. The increasing incidence of multicentric LP in recent literature likely coincides with the utilisation of whole-body screening techniques. In our systematic review, all 3 studies prior to 2010 did not utilise scintigraphy, whilst 6 of the 8 studies during or after 2010 incorporated octreotide based scanning techniques (5-15). Previous studies in patients with HNPGL showed that 68-gallium octreotide scans demonstrate superiority over conventional CT/MRI neck in detecting smaller lesions (22-24). The higher disease sensitivity and diagnostic accuracy is attributable to the improved spatial resolution. Naswa *et al.* showed that incorporating 68-gallium octreotide scanning altered management in 3 out of 5 patients with HNPGL by detecting synchronous or metastatic disease (25). The intent or modality of treatment in these patients were affected, with some requiring palliative rather than curative management and some requiring radiotherapy. Furthermore, patients with concurrent disease outside the head and neck region are less likely to be symptomatic unless the lesion is secretory or large enough to cause a mass effect. Hence, synchronous disease would be missed if whole-body scintigraphy is omitted in the baseline evaluation. It is likely that older literature underestimated the prevalence of multicentric disease in both HNPGL and LP. Some authors have hypothesised that undiagnosed synchronous lesions may act as a nidus for recurrence (15), though this may also be driven by an underlying genetic mutation.

Management considerations in multicentric paragangliomas

Surgical resection of paragangliomas remains the only curative treatment modality for LPs. The management of unifocal LP is straightforward and not controversial—the lesions are amenable to excision via an external cervical approach, with complete resection of the lesion and preservation of laryngeal structures. An open approach is favourable to an endoscopic approach, by providing good surgical access to and visualisation of the lesion, easy vascular control, and lower rates of treatment failure. This achieves good tumour clearance without the need for adjuvant treatment modalities. However, in the patient with multicentric disease, surgical planning must take into account multiple factors including the size and anatomic location of the synchronous lesions, unilaterality versus bilaterality, association with cranial nerve deficits, and if they are symptomatic or asymptomatic (3,5,26). Whereas laryngeal and carotid body tumours can be easily accessed by an external cervical approach, the surgical access to skull base paragangliomas, including jugulotympanic and vagal lesions, is complex and high-risk for injury to vascular and cranial nerve structures. A retrospective review of 24 cases of multicentric HNPGL at a single institution showed high incidence of post-operative cranial nerve deficits, affecting the facial (19.2%), glossopharyngeal (7.7%), vagus (30.7%), spinal accessory (11.5%), and hypoglossal (7.7%) nerves (3). Hence, the surgeon must decide whether surgical excision is feasible and safe, consider both patient and tumour factors, and if alternate modalities should be considered including stereotactic radiotherapy or careful monitoring with serial imaging.

Bilaterality is commonly seen in patients with CBP, including 4 patients in our systematic review, and is associated with multicentric and hereditary disease. The literature suggests that bilateral HNPGL is present in 4.4% of sporadic disease and 31.8% of familial disease (27). A staged approach to surgical excision is required in bilateral

disease to minimise the risk of iatrogenic injury to bilateral lower cranial nerves, which causes significant disability in terms of voice and swallow outcomes (3,26). Current literature recommends excision of the synchronous lesion on the same side of the LP first to avoid bilateral neuropraxia. In cases with bilateral carotid or vagal paraganglioma, if there is a large tumour it is recommended to excise the smaller lesion first. An interval of 6 months between procedures is advised to allow the initial carotid body to heal in order to avoid baroreceptor reflex syndrome, a condition of secondary hypertension due to bilateral denervation of the carotid body baroreceptors (3,28). In patients with CBP and other HNPGL on the contralateral side, the carotid body tumour should be excised first as the easy surgical access via a transcervical approach is associated with the least risk of lower cranial nerve damage (3). In patients with synchronous HNPGL who present with cranial nerve deficits, it is advised to excise the lesion on the side of the palsy first. In our systematic review, the patients with LP and a synchronous skull base paraganglioma, all had non-surgical management of the synchronous lesion. Skull base tumours can be accessed by an infratemporal, transmastoid, or transcondylar approach, with risk of injuring lower cranial nerves, especially the vagus. Observation with serial imaging should be considered in elderly patients, poor surgical candidates, small asymptomatic lesions, patients with bilateral or recurrent disease, and patients with a post-operative cranial nerve palsy after excision of a previous paraganglioma. This is reasonable as the overwhelming majority of paragangliomas are slow growing. Large lesions with concern for osseous destruction of the skull base and intradural invasion should be considered for surgical intervention in ideal candidates. It is important to recognise that the size of the tumour is directly proportional to the risk of post-operative cranial nerve deficits (3). Pre-operative selective angioembolisation of the feeding vessel can assist in shrinking the second lesion prior to resection to minimise accidental nerve trauma. In skull base paragangliomas, stereotactic radiotherapy has demonstrated adequate tumour control with lower morbidity compared to surgery (29,30). It should be considered in cases with difficult access, in patients presenting with cranial nerve deficits, and in bilateral multicentric disease. Radiotherapy is not curative and only halts tumour growth. Patient preference is another important factor in deciding management.

Detecting recurrent and metastatic lesions has important implications in surgical planning, as patients may require adjuvant treatment modalities such as stereotactic radiotherapy or chemotherapy. Malignant or metastatic disease has no specific histopathological features and lacks strict definition within the literature—it could be considered as lymph node involvement, destructive or erosive lesions, or distant metastases. The existence of metastatic or malignant LPs are controversial in the literature, with some experts in the field believing may represent misdiagnosed atypical carcinoid tumours (31,32). The presence of widespread or destructive paragangliomas is more common in multicentric or hereditary disease and may require palliative treatment modalities if surgical resection and tumour clearance is unfeasible.

Limitations

Limitations in this systematic review warrant discussion. The rarity of LPs, and to a greater extent the co-existence with synchronous disease, is reflected in the paucity of the literature. The evidence largely stems from case reports and case series, and hence the quality of the evidence must be taken into account. Even the literature on HNPGLs in general is limited, and mostly focussed on carotid body tumours with some representation from glomus vagale, tympanicum, or jugulare. The evidence from the HNPGL literature was used to guide the discussion on diagnosis and management in our review of multicentric LPs, as the majority of synchronous disease has been historically described in the head and neck region.

The bias of the included studies was low (see Figure S1 and Appendix 1) as the main data that was extracted included whether there was a diagnosis of LP and synchronous disease and how each were managed. As there is no quantitative data or effect estimate being measured, publication bias cannot be measured. Possible limitations in the included studies arose in heterogeneity in post-operative follow-up, with most studies reporting either no follow up or a short duration—this would likely underestimate the incidence of disease recurrence and treatment failure. Different studies also do not report the exact same type of data, which can limit comparisons being made. Finally, the single-author screening in the systematic review is a potential limitation—however given the data extraction was whether the included studies reported a LP with multifocal disease or not, it is unlikely to have been affected by significant bias. If uncertainty arose, it was escalated to a consultant head and neck surgeon for expert opinion.

This study represents the first review article on

LP with synchronous or multicentric disease and can provide otolaryngologists and clinicians with important information on how to approach and manage this rare condition.

Conclusions

Multicentricity accounts for a minor subset of LPs but has clinically significant impact on surgical management and prognosis. They are associated with increased risk of recurrence and familial disease, and mandate stricter surveillance and consideration for genetic workup. The incidence of multicentric disease in LPs is likely underestimated and incorporating whole-body octreotide scanning can improve detection of synchronous and metachronous lesions.

Acknowledgments

None.

Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://www.theajo.com/article/view/10.21037/ajo-22-11/rc

Peer Review File: Available at https://www.theajo.com/article/view/10.21037/ajo-22-11/prf

Funding: None.

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://www.theajo.com/article/view/10.21037/ajo-22-11/coif). FR serves as an unpaid editorial board member of *Australian Journal of Otolaryngology* from January 2019 to December 2022. The other authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Pellitteri PK, Rinaldo A, Myssiorek D, et al. Paragangliomas of the head and neck. Oral Oncol 2004;40:563-75.
2. Williams MD. Paragangliomas of the Head and Neck: An Overview from Diagnosis to Genetics. Head Neck Pathol 2017;11:278-87.
3. Álvarez-Morujo RJ, Ruiz MÁ, Serafini DP, et al. Management of multicentric paragangliomas: Review of 24 patients with 60 tumors. Head Neck 2016;38:267-76.
4. Lee JH, Barich F, Karnell LH, et al. National Cancer Data Base report on malignant paragangliomas of the head and neck. Cancer 2002;94:730-7.
5. Abt NB, Holcomb AJ, Shroff S, et al. Intralaryngeal paraganglioma workup and discussion of surgical approach. BMJ Case Rep 2020;13:234745.
6. Ananthapadmanabhan S, Jabbour J, Tseros E, et al. Operative technique in laryngeal paraganglioma: A case series and literature review. Laryngoscope Investig Otolaryngol 2022;7:467-75.
7. Dogan S, Senol S, Imamoglu H, et al. An Unusual Case of Laryngeal Paraganglioma in a Patient with Carotid Body Paraganglioma: Multimodality Imaging Findings. Case Rep Radiol 2015;2015:342312.
8. García-Martín A, Cortés-Berdonces M, Muros MA, et al. Dysphonia as first and single symptom of multicenter paraganglioma. Rev Clin Esp 2010;210:e29-30.
9. Hall TC, Renwick P, Stafford ND. Recurrent familial malignant carotid body tumour presenting with lymph node metastasis: case report, and review of diagnosis and management of familial carotid body tumours. J Laryngol Otol 2010;124:1344-6.
10. Rubin AD, Cheng SS, Bradford CR. Laryngeal paraganglioma in a patient with multiple head and neck paragangliomas. Otolaryngol Head Neck Surg 2005;132:520-2.
11. Sanders KW, Abreo F, Rivera E, et al. A diagnostic and therapeutic approach to paragangliomas of the larynx. Arch Otolaryngol Head Neck Surg 2001;127:565-9.
12. Sankar G, Rajaraman V, Ganesh RN, et al. Multiple Cutaneous Metastases on 99mTC-HYNIC-TOC Scan

in a Rare Case of Malignant Laryngeal Paraganglioma. Indian J Nucl Med 2018;33:348-50.
13. Schmit GD, Gorman B, van Heerden JA, et al. Inferior laryngeal paraganglioma mimicking a primary thyroid tumor. Endocr Pract 2006;12:432-5.
14. Sharifkashany S, Yazdani N, Ghazavi H, et al. Laryngeal paraganglioma: a case report. Iran J Radiol 2014;11:e21011.
15. Tripathy S, Mukherjee A, Singh CA, et al. Glomus Tumor of the Larynx: A Rare Synchronous Paraganglioma in a Patient with Bilateral Carotid Body Tumor Detected on 68Ga-DOTANOC PET/CT. Indian J Nucl Med 2017;32:241-2.
16. Sen I, Young WF Jr, Kasperbauer JL, et al. Tumor-specific prognosis of mutation-positive patients with head and neck paragangliomas. J Vasc Surg 2020;71:1602-12.e2.
17. Joanna Briggs Institute. Critical Appraisal Tools. Available online: https://jbi.global/critical-appraisal-tools
18. Ferlito A, Devaney KO, Rinaldo A. Neuroendocrine neoplasms of the larynx: advances in identification, understanding, and management. Oral Oncol 2006;42:770-88.
19. Wang X, Chen Y, Chen X, et al. Parapharyngeal space paraganglioma: distinguishing vagal paragangliomas from carotid body tumours using standard MRI. Clin Radiol 2019;74:734.e1-6.
20. Baysal BE. Genetics of familial paragangliomas: past, present, and future. Otolaryngol Clin North Am 2001;34:863-79, vi.
21. Papaspyrou K, Mewes T, Rossmann H, et al. Head and neck paragangliomas: Report of 175 patients (1989-2010). Head Neck 2012;34:632-7.
22. Tan TH, Hussein Z, Saad FF, et al. Diagnostic Performance of (68)Ga-DOTATATE PET/CT, (18)F-FDG PET/CT and (131)I-MIBG Scintigraphy in Mapping Metastatic Pheochromocytoma and Paraganglioma. Nucl Med Mol Imaging 2015;49:143-51.
23. Jaiswal SK, Sarathi V, Malhotra G, et al. The utility of 68Ga-DOTATATE PET/CT in localizing primary/metastatic pheochromocytoma and paraganglioma in children and adolescents - a single-center experience. J Pediatr Endocrinol Metab 2020;34:109-19.
24. Sharma P, Thakar A, Suman K C S, et al. 68Ga-DOTANOC PET/CT for baseline evaluation of patients with head and neck paraganglioma. J Nucl Med 2013;54:841-7.
25. Naswa N, Kumar A, Sharma P, et al. Imaging carotid body chemodectomas with ^{68}Ga-DOTA-NOC PET-CT. Br J Radiol 2012;85:1140-5.
26. Szymańska A, Szymański M, Czekajska-Chehab E, et al. Diagnosis and management of multiple paragangliomas of the head and neck. Eur Arch Otorhinolaryngol 2015;272:1991-9.
27. Myssiorek D, Ferlito A, Silver CE, et al. Screening for familial paragangliomas. Oral Oncol 2008;44:532-7.
28. De Toma G, Nicolanti V, Plocco M, et al. Baroreflex failure syndrome after bilateral excision of carotid body tumors: an underestimated problem. J Vasc Surg 2000;31:806-10.
29. Hinerman RW, Mendenhall WM, Amdur RJ, et al. Definitive radiotherapy in the management of chemodectomas arising in the temporal bone, carotid body, and glomus vagale. Head Neck 2001;23:363-71.
30. Foote RL, Pollock BE, Gorman DA, et al. Glomus jugulare tumor: tumor control and complications after stereotactic radiosurgery. Head Neck 2002;24:332-8; discussion 338-9.
31. Myssiorek D, Rinaldo A, Barnes L, et al. Laryngeal paraganglioma: an updated critical review. Acta Otolaryngol 2004;124:995-9.
32. Suárez C, Rodrigo JP, Ferlito A, et al. Tumours of familial origin in the head and neck. Oral Oncol 2006;42:965-78.

doi: 10.21037/ajo-22-11
Cite this article as: Ananthapadmanabhan S, Jabbour J, Suruliraj A, Riffat F, Smith M, Sritharan N. Diagnostic and management considerations in multicentric forms of laryngeal paraganglioma: a systematic review. Aust J Otolaryngol 2022;5:30.

Supplementary

Study	1	2	3	4	5	6	7	8	9	10	JBI score	Comments
Abt, 2020											7/10	Case series of laryngeal paraganglioma, with only one having multicentric disease
Ananthapadmanabhan, 2022											8/10	None
Dogan, 2015											6/8	Inadequate documentation of follow-up
García-Martín, 2010											7/8	None
Hall, 2010											7/8	None
Rubin, 2005											7/8	None
Sanders, 2001											7/8	None
Sankar, 2018											6/8	Inadequate documentation of follow-up
Schmit, 2006											6/8	Inadequate documentation of follow-up
Sharifkashany, 2014											6/8	Patient lost to follow-up
Tripathy, 2017											5/8	Radiologic study that did not describe management of either laryngeal or synchronous paraganglioma Inadequate documentation of follow-up

Figure S1 Risk of bias assessment of included 11 studies. Green: point awarded; red: no point awarded; yellow: not applicable to the study. The JBI checklist for case reports and series consists of 8 and 10 questions respectively and is available online from https://jbi.global/critical-appraisal-tools.

Appendix 1

JBI checklist for case reports

1. Were patient's demographic characteristics clearly described?
2. Was the patient's history clearly described and presented as a timeline?
3. Was the current clinical condition of the patient on presentation clearly described?
4. Were diagnostic tests or assessment methods and the results clearly described?
5. Was the intervention(s) or treatment procedure(s) clearly described?
6. Was the post-intervention clinical condition clearly described?
7. Were adverse events (harms) or unanticipated events identified and described?
8. Does the case report provide takeaway lessons?

JBI checklist for case series

1. Were there clear criteria for inclusion in the case series?
2. Was the condition measured in a standard, reliable way for all participants included in the case series?
3. Were valid methods used for identification of the condition for all participants included in the case series?
4. Did the case series have consecutive inclusion of participants?
5. Did the case series have complete inclusion of participants?
6. Was there clear reporting of the demographics of the participants in the study?
7. Was there clear reporting of clinical information of the participants?
8. Were the outcomes or follow up results of cases clearly reported?
9. Was there clear reporting of the presenting site(s)/clinic(s) demographic information?
10. Was statistical analysis appropriate?

https://dx.doi.org/10.21037/ajo-22-11