ORIGINAL ARTICLE

Malignant head/neck paragangliomas. Comparative Study

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KEYWORDS
Malignant head and neck paraganglioma; Metastases; SDHx mutation; Octreoscan; 18F-FDG-PET

Summary

Background: The objective of this study was to report 11 cases of malignant head and neck paraganglioma and to compare their epidemiological, clinical, and genetic characteristics, their natural history and their treatment with those of a series of 131 benign paragangliomas.

Patients and methods: Retrospective analysis of 142 patients with head and neck paraganglioma managed between 2001 and 2008. Age at the time of diagnosis, gender, primary tumour site, presence of other non-head/neck paragangliomas and/or metastases diagnosed by imaging (CT, MRI, Octreoscan or 18F-FDG PET), histology, urinary catecholamine and metanephrine levels, family history, and genetic test results were recorded.

Results: This series comprised 131 benign head and neck paragangliomas, mostly observed in women with a mean age at diagnosis of 45 years and a predominance of tympanojugular sites (followed by carotid and vagal sites) with 5% of secreting tumours and 20% of multifocal tumours. Eleven patients (7.7%) with a 1:1 sex ratio presented criteria of malignancy. These patients, with a lower mean age (38 years), predominately presented carotid lesions with a higher rate of secreting and multifocal tumours, 27% and 46% respectively. The main sites of metastases were bone and lymph nodes. No tympanic paragangliomas were observed.

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Conclusions: Malignant paragangliomas are mainly observed in young patients with multifocal tumours, particularly carotid tumours, and are predominantly related to subunit SDH-B mutation. The work-up in these high-risk patients must include whole body scintigraphy and spine MRI. Malignancy is not necessarily associated with a poor short-term prognosis due to the slow course of the disease.

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Introduction

The World Health Organisation [1] defines paragangliomas (PG) as neuroendocrine tumours arising from paraganglia, collections of neural crest-derived paraganglionic neuroectodermal cells present throughout the body.

However, malignant paragangliomas are rare and no consensus has been reached concerning the histological criteria of malignancy, although multiple mitotic figures, nuclear polymorphism and capillary effraction may indicate the presence of malignancy. According to Lack [2], two of the following three criteria are required to confirm malignancy: central necrosis, vascular and lymphatic invasion and mitotic abnormalities. There is a general consensus that malignancy is characterised by the presence of metastases, i.e. paraganglionic tissue in organs other than paraganglia. This definition can therefore be used to distinguish malignant tumours from multifocal tumours arising in paraganglia [3].

Limited data are available in the literature concerning malignant head and neck paragangliomas and their natural history is poorly defined. However, it is generally accepted that 6% to 24% of non-adrenal paraganglia are malignant [4]. Recent progress in molecular genetics since 2000 [5] has also revealed that SDHx gene mutation is involved in hereditary paraganglia and that malignant forms are often associated with mutation of the B subunit [6].

This study reports 11 cases of malignant head and neck PG and compares their epidemiological, clinical and genetic characteristics, natural history and treatment with those of a series of 131 benign PG managed over the same period in our institution.

Patients and methods

This retrospective study concerned all patients consulting for a primary diagnosis or referred for head and neck PG in our university hospital between 2001 and 2008.

Age at the time of diagnosis, gender, primary tumour site, presence of other non-head/neck PGs and/or metastases diagnosed by imaging, including CT, MRI or functional whole body imaging (somatostatin scintigraphy, \(^{18}\)FDG or \(^{123}\)I-MIBG PET), sometimes confirmed by histology, urinary metanephrine levels, family history, and genetic test results were recorded. Patients were followed until September 2012 or until death.

Results

This series comprised 142 patients, including 11 (7.7%) patients presenting criteria of malignancy.

Patients with benign PG (group 1)

This group comprised 131 patients (87 females; M:F sex ratio: 1:1.98). The main characteristics of these patients are shown in Table 1.

Mean age at diagnosis of the primary head and neck PG was 45.3 years (range: 15–76). One hundred and thirteen (86.3%) patients presented an isolated head and neck lesion and 18 (13.7%) patients presented multiple lesions (synchronous lesions). Isolated lesions involved tympanic (\(n=32\)), tympanojugular (\(n=37\)), vagal (\(n=18\)), and carotid (\(n=26\)) sites. Six patients (4.6%) had secreting tumours.

Another head and neck paraganglioma (metachronous lesions) was observed during follow-up in 8 of the 113 patients with a single primary tumour and 1 para-aortic PG was detected by \(^{111}\)In-pentetreotide scintigraphy. The global multifocal rate (including head and neck and thoraco-abdominopelvic PG) was therefore 20.6% in group 1.

The mean interval between diagnosis of the primary lesion and recurrence after surgery (\(n=13\)) or diagnosis of a new PG (\(n=9\)) was 9.9 years (range: 4–20) and 13 years (range: 2–39), respectively.

Genetic testing (when available and when accepted by the patient) was performed in 43 patients: 24 patients (55.8%) presented a mutation of the D subunit of the succinate dehydrogenase complex (SDH-D) and 4 (9.3%) presented a mutation of the SDH-B subunit; 15 patients (34.9%) presented no mutation.

Patients with malignant PG (group 2)

Paraganglionic disease

This group consisted of 11 patients (6 females; male to female ratio: 1:1.2). The main patient characteristics are summarized in Table 1. Mean age at the time of diagnosis was 37.8 years (range: 17–65). At the time of diagnosis, paragangliomas were isolated in 9 cases (82%) and multiple in two cases. Isolated tumours involved carotid (\(n=5\)), vagal (\(n=2\)), tympanojugular (\(n=1\)) and nasal cavity (\(n=1\)) sites. The two cases of multiple PG were tympanojugular and carotid. No pure tympanic site was observed in this series. Three patients (27.3%) presented secreting tumours.

Among the 9 patients with an isolated lesion, metachronous PG were diagnosed during follow-up in 3 cases. In these three patients, some of these metachronous tumours were situated in regions other than the head and neck: thoracic (\(n=1\)), retroperitoneal (\(n=1\)), thoracic and retroperitoneal (\(n=1\)). The overall multifocal rate (including multiple head and neck and thoraco-abdominopelvic PGs) was 45.5%.
Table 1  Characteristics of the two groups.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Group 1 (n = 131)</th>
<th>Group 2 (n = 11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>At the time of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of women (%)</td>
<td>87 (66)</td>
<td>6 (55)</td>
</tr>
<tr>
<td>Number of secreting tumours (%)</td>
<td>6 (4.6)</td>
<td>3 (27.3)</td>
</tr>
<tr>
<td>Age at diagnosis of the first head and neck paraganglioma (range: 15–76)</td>
<td>45.3 (65)</td>
<td>37.8 (65)</td>
</tr>
<tr>
<td>Site of paraganglioma</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tympanic (%)</td>
<td>32 (24.4)</td>
<td>0</td>
</tr>
<tr>
<td>Tympanojugular (%)</td>
<td>37 (28.2)</td>
<td>1 (9)</td>
</tr>
<tr>
<td>Vagal nerve (%)</td>
<td>18 (13.7)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Carotid bulb (%)</td>
<td>26 (19.8)</td>
<td>5 (55.6)</td>
</tr>
<tr>
<td>Other (%)</td>
<td>0</td>
<td>1 nasal cavity</td>
</tr>
<tr>
<td>Multiple (%)</td>
<td>18 (13.7)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>Follow-up</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of patients with metachronous lesions (%)</td>
<td>8 (6)</td>
<td>4 (36)</td>
</tr>
<tr>
<td>Number of PG in regions other than the head and neck (%)</td>
<td>1 (8)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Interval between primary PG and recurrence (mean range: 2–15 years)</td>
<td>4.9 (2–20)</td>
<td>4.5 (1.5–7)</td>
</tr>
<tr>
<td>Interval between primary tumour and second tumour (mean range: 2–39 years)</td>
<td>13 (2–39)</td>
<td>5.5 (2–15)</td>
</tr>
<tr>
<td>Number of patients with multifocal tumours (head and neck PG and PG in other regions) (%)</td>
<td>26 (19.8)</td>
<td>5 (45.5)</td>
</tr>
<tr>
<td>Genetic testing</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SDH-D mutation (%)</td>
<td>24 (55.8)</td>
<td>2 (18)</td>
</tr>
<tr>
<td>SDH-B mutation (%)</td>
<td>4 (9.3)</td>
<td>5 (50)</td>
</tr>
<tr>
<td>No mutation (%)</td>
<td>15 (34.9)</td>
<td>3 (27)</td>
</tr>
<tr>
<td>Not performed (%)</td>
<td>88 (67)</td>
<td>1 (9)</td>
</tr>
</tbody>
</table>

The mean interval between diagnosis of the primary lesion and recurrence after surgery (n = 4) or diagnosis of a second PG (n = 4) was 4.5 years (range: 1.5–7) and 5.5 years (range: 2–15), respectively.

Genetic testing was performed in 10 patients: 2 patients presented a mutation of the D subunit (SDH-D), 5 patients presented a mutation of the B subunit (SDH-B) and 3 patients had no mutation.

Metastases
Metastases were present at the time of diagnosis of the primary lesion in 3 patients and were diagnosed during follow-up in another 8 patients, with a mean metastasis-free interval of 8 years (1–25). These metastases involved bone (n = 7), cervical lymph nodes (n = 7), liver (n = 2), lung (n = 1), and thyroid (n = 1) (Table 2).

Bone metastases were symptomatic in four cases and detected by systematic imaging in three cases. They predominantly involved the spine, but also the iliac bone, ribs, sternum or calvarium.

MRI demonstrated two types of lesions: nodular and expanding. Nodular lesions presented a specific radiological appearance, as we have previously described [7], consisting of a central low-intensity signal surrounded by a single fat-like halo or a double halo with a fat-density inner circle and an outer circle suggestive of oedema (Fig. 1a, b). In some patients, these lesions coexisted with expanding lesions characterized by cortical destruction and soft tissue involvement, especially bone marrow.

$1^{11}$In-pentetreotide (Octreoscan) scintigraphy revealed only one of these bone lesions (Table 2). $1^{123}$Iodine-labelled metaiodobenzylguanidine ($1^{23}$I-MIBG) scintigraphy was performed in 4 patients and revealed only slight contrast enhancement of the spine in one patient. $1^{18}$FDG-PET was performed in two patients and was negative in one case and strongly positive in the other case.

Cervical lymph node metastases were detected in 7 cases, either on neck palpation or by imaging showing a mass situated in a zone clearly distinct from the carotid bulb or subdigastric region.

Two patients had nodular liver metastases and another patient had lung metastases. One patient had a thyroid metastasis, incorrectly diagnosed as papillary thyroid tumour and treated by surgery and $1^{131}$iodine therapy. Three years later, this patient developed vertebral metastases and retrospective analysis of the thyroid operative specimen established the correct diagnosis.

Follow-up
Mean follow-up was 4.25 years (range: 1–10.5 years). One foreign patient died in his country of origin 56 months after management in our institution, apparently from metastatic cachexia. Two patients were lost to follow-up, one after 1 month and the other after 5 years.

Seven patients were followed for vertebral bone lesions.
<table>
<thead>
<tr>
<th>Patient</th>
<th>SDH mutation</th>
<th>Site</th>
<th>Mode of discovery</th>
<th>¹¹¹In-pentetreotide scintigraphy (Octreoscan)</th>
<th>¹⁸FDG-PET</th>
<th>¹²³I-MIBG</th>
<th>Spine MRI</th>
<th>Follow-up (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>B</td>
<td>Bone, lymph nodes</td>
<td>Imaging</td>
<td>Ribs, sternum</td>
<td>Not done</td>
<td>Metastases not visualized</td>
<td>Multiple lesions of cervical, thoracic and lumbar spine</td>
<td>96</td>
</tr>
<tr>
<td>2</td>
<td>B</td>
<td>Bone</td>
<td>Dorsal pain</td>
<td>Multiple lesions of cervical, thoracic and lumbar spine, sacrum, occipital bone</td>
<td>Not done</td>
<td>Metastases not visualized</td>
<td>Multiple lesions of cervical, thoracic and lumbar spine</td>
<td>Dead (56)</td>
</tr>
<tr>
<td>3</td>
<td>No mutation</td>
<td>Bone</td>
<td>Weakness of lower limbs + pyramidal syndrome</td>
<td>L3 + right clavicle</td>
<td>Not done</td>
<td>Metastases not visualized</td>
<td>Multiple lesions of cervical, thoracic and lumbar spine</td>
<td>303</td>
</tr>
<tr>
<td>4</td>
<td>D</td>
<td>Bone</td>
<td>Imaging</td>
<td>Metastases not visualized</td>
<td>Metastases not visualized</td>
<td>Not done</td>
<td>Multiple lesions of cervical, thoracic and lumbar spine</td>
<td>348</td>
</tr>
<tr>
<td>5</td>
<td>B</td>
<td>Lymph node bone</td>
<td>Low back pain Palpation</td>
<td>Metastases not visualized</td>
<td>Metastases not visualized</td>
<td>Not done</td>
<td>Lesions of lumbar spine</td>
<td>Lost to follow-up at 1 month</td>
</tr>
<tr>
<td>6</td>
<td>No mutation</td>
<td>Bone</td>
<td>Bone pain Imaging Palpation</td>
<td>Vertebral column, ribs, pelvis, liver</td>
<td>Vertebrae, sternum, sacrum, pelvis, ribs</td>
<td>Lesion of thoracic spine</td>
<td>Multiple lesions of cervical, thoracic and lumbar spine</td>
<td>247</td>
</tr>
<tr>
<td>7</td>
<td>B</td>
<td>Lymph nodes</td>
<td>Palpation</td>
<td>Metastases not visualized</td>
<td>Not done</td>
<td>Not done</td>
<td>Metastases not visualized</td>
<td>250</td>
</tr>
<tr>
<td>8</td>
<td>Not tested</td>
<td>Lymph nodes</td>
<td>Palpation</td>
<td>Metastases not visualized</td>
<td>Not done</td>
<td>Not done</td>
<td>Metastases not visualized</td>
<td>Lost to follow-up at 144 months</td>
</tr>
<tr>
<td>9</td>
<td>B</td>
<td>Lymph nodes Bone</td>
<td>Palpation Imaging</td>
<td>Thoracic spine+ liver</td>
<td>Not done</td>
<td>Not done</td>
<td>Not done</td>
<td>21</td>
</tr>
<tr>
<td>10</td>
<td>No mutation</td>
<td>Lymph nodes</td>
<td>Palpation</td>
<td>Metastases not visualized</td>
<td>Not done</td>
<td>Not done</td>
<td>Metastases not visualized</td>
<td>14</td>
</tr>
<tr>
<td>11</td>
<td>D</td>
<td>Lymph nodes Lung</td>
<td>Palpation Imaging</td>
<td>Metastases not visualized</td>
<td>Not done</td>
<td>Not done</td>
<td>Metastases not visualized</td>
<td>111</td>
</tr>
</tbody>
</table>
Malignant nature and decreased signal by two, (8).

However, detailed analysis of signal intensity on T1- and T2-weighted sequences showed decreased oedema of the outer halo of two vertebral lesions in two patients.

The last patient (patient 1) was operated for left vagal PG in 2001 and, two years later presented a very large left temporal lesion with intracranial extension and multiple metastases of the cervicothoracic vertebrae, calvarium and one rib. Radiotherapy at a dose of 45 Gy was delivered to the temporal lesion but bone metastases did not require any treatment, as they remained asymptomatic. After a long period of apparent stabilization, the patient consulted in November 2012 following the appearance of two left cervical masses. CT and scintigraphy confirmed the metastatic nature of these masses, but also revealed marked progression of the C6 and C7 lesions (that initially had an osteolytic appearance) associated with epiduritis (Fig. 2). The risk of short-term spinal cord lesions justified radiotherapy of the vertebral lesion. Cervical lymph node dissection confirmed the presence of metastases. This case illustrates the relatively slow rate of progression of metastatic disease.

The 7 patients with lymph node metastases were treated by neck dissection concomitant with surgical treatment of the tympanojugular or carotid tumour in 6 cases (patients 5, 7, 8, 9, 10 and 11), while the seventh patient corresponded to patient 1 described above. Two of these 6 patients were lost to follow-up, one at 1 month, and the other at 5 years. Three patients have not developed any local recurrence and are currently alive with no signs of progression of their paraganglioma. The last patient (patient 10), who initially presented a vagal PG with cervical lymph node metastases treated by surgery and external beam radiotherapy, developed multiple bone and liver metastases during the following year and is currently in palliative care.

Of the two cases of liver metastases diagnosed at the time of diagnosis of the primary tumour (patient 6 and 9), one also presented lung metastasis and died after 56 months. The other patient is alive with no apparent signs of progression.

Discussion

This retrospective, comparative study of one of the largest series published to date defines certain aspects of the natural history of malignant head and neck paraganglioma.

In line with the literature, patients with benign head and neck PG were predominantly females (66%) and tumours were predominantly located in tympanojugular sites (followed by vagal and carotid sites), with a mean age of 45 years at the time of diagnosis, with low rates of secreting and multifocal tumours: 5% and 20%, respectively.

In contrast, patients with malignant head and neck PG (7.7% of the population of this series, i.e. a comparable rate to that reported in the literature [8]) did not present any gender predominance, mainly presented carotid sites, had a younger mean age at the time of diagnosis (38 years), and presented high rates of secreting (27%) and multifocal tumours (46%). These characteristics appear to constitute risk factors for malignancy.

No purely tympanic lesion was observed in this series. These forms are classically not multifocal, occur in the absence of a family history and treatment is based on surgical resection, which is usually straightforward. This series confirms that pure tympanic lesions are never accompanied by metastases [9] and therefore do not require genetic testing or staging assessment.

Metastatic spread may be haematogenous or lymphatic and mainly involve bone and lymph nodes [4,7,10]. Liver and lung metastases are observed more rarely. Metastases may be either synchronous, at the time of diagnosis of PG, or metachronous, in which case they appear to be associated with a better prognosis [11].

Bone metastases may remain asymptomatic or may present clinically in the form of neurological deficits or pain, or radiologically according to two modalities: osteolytic and expanding or nodular surrounded by a single or double fat-density and water-density halo. Reduction of the water-density zone and increase of the fat-density zone were observed during follow-up, suggesting possible spontaneous involution. The results of our series indicate the generally slow rate of progression of PG. However, two patients developed signs of extension to the spinal cord, requiring surgery in one case and radiotherapy in the other case.

Lymph node metastases are usually detected by neck palpation or by X-rays or scintigraphy. Tumours situated too inferiorly or too anteriorly to correspond to carotid

Figure 1  MRI of the lumbar spine, sagittal section, T1- (a) and gadolinium-enhanced T1-weighted (b) sequences: presence of nodular bone metastases with a double halo.
or vagal tumours must be considered to be possible lymph node metastases. They are sometimes discovered on surgical exploration and are confirmed by histological examination. They appear to be associated with a relatively favourable prognosis, as lymph node recurrences appear to be rare.

Functional imaging does not appear to be a reliable modality for the detection of bone metastases. Although functional imaging can detect primary PG of the head and neck or other sites with sensitivity close to 100% [12], $^{111}$In-pentetreotide scintigraphy failed to visualize all metastases in the present series. This poor performance has also been reported by Timmers et al. [13], who described poor uptake of $^{123/131}$I-MIBG [14] by non-adrenal PG. $^{123}$I-MIBG revealed bone metastasis in only one of the four cases of our series.

PET-CT has been proposed in the literature for the assessment of phaeochromocytomas and PG. $^{18}$F-FDG is more reliable for the detection of PG than their metastases [13,15]. $^{18}$F-DOPA has a high sensitivity for the detection of benign head and neck PG [16], but a low sensitivity for the detection of metastases, particularly in subjects with SDH-B mutation. The low performance of these specific agents can be explained by loss of differentiation of metastases related to SDH-B mutation.

A recent study demonstrated that plasma levels of a metabolite of dopamine, methoxytyramine, higher than 0.2 nmol/L constituted a useful biomarker to detect the presence of metastases [17].

In familial forms of benign head and neck PG, a mutation of the D subunit of the SDH gene is identified in 50% to 94% of cases, while a mutation of the B subunit is identified in 10% to 20% of cases [18,19]. In sporadic forms, a SDH gene mutation, mainly involving the D subunit, is reported in 11% to 29% of cases [18]. However, SDH-B mutations are mainly reported in malignant head and neck PG [6,8,18,20]. The results of the present series confirm these published results, with a predominance of SDH-D mutation (56%) in the benign PG group and SDH-B mutation (5 of the 10 patients tested, i.e. 50%) in the malignant PG group. However, two patients of the malignant PG group presented a SDH-D mutation, as previously reported by other authors [21,22]. No mutation

Figure 2  a: neck MRI, gadolinium-enhanced T1-weighted sequence, axial section: two left cervical lymph node metastases; b: spine MRI, T2-weighted sequence, sagittal section: spinal cord compression over C7; c: octreoscan, coronal section: increased uptake in a lymph node; d, e: octreoscan, axial and coronal sections: increased uptake of C7 vertebra.
was identified in the remaining 3 patients. Note that four patients of the benign PG group presented SDH-B mutation with no signs malignancy during follow-up.

Demonstration of an SDH-B gene mutation in a patient with head and neck PG therefore appears to constitute the most relevant risk factor for malignancy, justifying radiological work-up, especially when the other risk factors described above are also present: young subject, multiple sites, particularly carotid, possibly secreting, with a family history of PG.

The free interval between diagnosis of the primary tumour and metastases can be long and therefore justifies long-term follow-up, especially for high-risk patients. Although the 5-year overall survival reported in the literature for phaeochromocytomas and malignant PG ranges from 40% to 74% [5,7,9], the individual prognosis is unpredictable. In our study, all patients of the malignant PG group (group 2) were alive at last follow-up (with a follow-up of up to 29 years), except for one patient (with SDH-B mutation). In a series of 5 patients, Havekes et al. [14] described the case of a patient who died after a follow-up of 32 years: this woman with SDH-D mutation developed multiple cervical lymph node and bone metastases.

Surgery is theoretically the only curative treatment for metastases of malignant PG. However, the treatment options for metastases depend on their site and their operability. Surgery is clearly indicated in the case of isolated or multiple lymph node metastases, in the neck, chest or abdomen, especially as surgery also allows histological confirmation of malignancy. Similarly, isolated liver metastases can be treated by resection, sometimes allowing long-term survival.

However, two-thirds of metastases involve bone and are usually vertebral and therefore unresectable. A combined medical and surgical approach is indicated in these cases: analgesics and anti-inflammatory drugs to control pain and nerve compression, but also bisphosphonates and localized radiotherapy or sometimes embolization and radiofrequency ablation [23,24]. Surgical decompression followed by vertebroplasty can be proposed in the presence of signs of spinal cord compression.

Another attractive treatment option is metabolic radiotherapy based on the property of paraganglionic cells to express somatostatin receptors on their cell surface. This modality uses a marker labelled with a highly radioactive agent such as 131I-MIBG or 90Ytrium- or 111Indium-labelled octreotide. However, in practice, this type of treatment is limited by the fact that almost one-half of PG metastases do not take up the tracer and one-third of potential candidates for this therapy fail to respond [25]. This treatment is also very expensive and the results of metabolic radiotherapy for metastases of tympanojugular PG have not been reported to date. The only published studies concern metastases of phaeochromocytomas [7,25–27].

Randomized trials of chemotherapy are methodologically difficult to perform, but the addition of chemotherapy appeared to provide improvement of symptoms and short-term remissions in some studies based on small sample sizes [26,27].

Targeted molecular therapy remains a promising approach, based on the principle of the molecular effects of SDH-B gene mutations, resulting in activation (or deregulation) of genes targeted by hypoxia-induced factors. Targeted molecular therapies are therefore designed to inhibit these genes. Sunitinib, an oral multi-target tyrosine kinase receptor inhibitor with anti-angiogenic and antitumour activity, has been recently used in some cases with promising results [28].

Conclusion

This retrospective study indicates the following conclusions:

- malignant paragangliomas are observed more frequently among young patients with multifocal and secreting tumours, particularly, in carotid sites;
- malignant head and neck paragangliomas are mainly associated with mutation of the B subunit of the SDH gene, but a mutation of the D subunit is sometimes observed;
- staging of high-risk patients must include spine MRI, as Octreoscan fails to detect all metastases;
- pure tympanic forms are never malignant and do not justify genetic testing or staging;
- metastases generally present a low rate of progression and are compatible with often prolonged survival;
- treatment of metastases must be adapted to symptoms.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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