




Malignant carotid body tumors: What we know, what we do, and what we need to achieve. A systematic review of the literature

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Abstract

Malignant carotid body tumors (MCBT) are rare and diagnosed after detection of nodal or distant metastases. This systematic review (SR) focuses on MCBT initially approached by surgery. Preferred Reporting Items for SR and Meta-Analysis (MA) guided the articles search from 2000 to 2023 on PubMed, Scopus, and Web of Science. Among 3548 papers, 132 (337 patients) were considered for SR; of these, 20 (158 patients) for MA. Malignancy rate was 7.3%, succinate dehydrogenase (SDH) mutation 17%, age at diagnosis between 4th

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and 6th decades, with a higher prevalence of females. MCBTs were mostly Shamblin III, with nodal and distant metastasis in 79.7% and 44.7%, respectively. Malignancy should be suspected if CBT >4 cm, Shamblin III, painful or otherwise symptomatic, at the extremes of age, bilateral, with multifocal disease, and SDHx mutations. Levels II–III clearance should be performed to exclude nodal metastases and adjuvant treatments considered on a case-by-case basis.

KEYWORDS

carotid body tumor, malignant, metastasis, surgery, systematic review

1 | INTRODUCTION

Carotid body tumors (CBTs, also known as carotid body chemoreceptor tumor, chemodectomas, or glomus caroticum) are uncommon neuroendocrine tumors of the head and neck that were first described by Marchand in 1891.¹ These lesions originate from the extra-adrenal chromaffin cells of the chemoreceptor system, located within the adventitia of the posteromedial aspect of the carotid bifurcation. The reported annual incidence is 1:30 000 and they represent 60%–78% of all head and neck paragangliomas.^{2–5} CBTs are most frequently benign, unilateral, asymptomatic, highly vascular, slowly growing (roughly 1 mm/year but may grow faster in persons living at high altitudes),^{6,7} non-functional tumors, usually located in the anterolateral aspect of the neck, at the level of the carotid bifurcation, from where they can sometimes grow upwards into the parapharyngeal space and/or in close relationships with the skull base and cranial nerves IX, X, XI, and XII. CBT may be distinguished as sporadic (the most frequent form, usually diagnosed with a peak around the 5th decade), familial (mostly diagnosed at a younger age, roughly 30% of the overall CBTs, and known for frequently bilateral occurrence, in combination with vagal and jugulo-tympanic paragangliomas as well as pheochromocytomas), and hyperplastic (secondary to chronic hypoxia in subjects with long-lasting lung disease or living at high altitude).

From the surgical point of view, the most accepted three-tiered classification by Shamblin describes the extent to which these tumors encase the common (CCA), internal (ICA), external carotid arteries (ECA), and associated cranial nerves.⁸ According to this classification, Shamblin I CBTs grow in between the ECA and ICA without significantly encircling their circumference, Shamblin II lesions surround about 180° of both vessels, while Shamblin III tumors encase the ECA, ICA, CCA, and adjacent vagal and hypoglossal nerves.⁸ Increasing Shamblin classification levels parallels increasing intraoperative technical

difficulty and complication rates. Recently, Mehanna et al. developed and validated a classification and risk stratification system to better predict combined risk of neurological and neurovascular complications following CBT resection.⁹ This system is based on the assumption that one of the main determinants of complications in surgery for CBT is its cranial extension. Therefore, based on the highest anatomical landmark reached by the most cranial part of the lesion, this classification entails Types I to IV CBTs according to their reaching of the hyoid bone, angle of the mandible, upper aspect of the body of the second cervical vertebra, or above that level. Additional subscript letters can be added to the type of CBT, including E (encircling carotid bifurcation, CCA or ICA, i.e., Shamblin III), F (functional tumor secreting catecholamines), and S (skull base reached or involved).

Malignant CBT (MCBT) is an even rarer diagnosis (representing 4.1% of CBTs in the largest meta-analysis so far available in the literature),¹⁰ with an incidence reported to be around 0.02 cases per 100 000 persons per year in a recent study performed on patients from the SEER database.¹¹ Most MCBTs result from a germline mutation in one of the succinate dehydrogenase (SDH) genes (SDHA, SDHB, SDHC, and SDHD) which encode the four subunits of the above mentioned enzyme.^{12–14} SDHB mutations are known to be associated with malignant behavior (with a rate from 30% to 70%).¹⁵ A diagnosis of MCBT, however, is not based on histological features (like degree of vascularization, invasion of surrounding vascular and/or soft tissues, mitotic rate, staining for specific proteins or identification of other known markers) but, rather, on the detection of histologically proven metastases to the adjacent neck lymph nodes (mostly within levels IIA–B and III) or distant sites (bone, lung, liver, kidney, retroperitoneum, or brain among the commonest), even though there is no general consensus on the relative frequency of the two clinical scenarios.

Apart from different presentation and clinical history, many aspects related to overall behavior and clinical

management of MCBTs are scarcely known and only sparsely reported in the literature due to the rarity of the disease and its frequently late diagnosis (i.e. when regional and/or distant metastases occur). The primary objective of this paper was therefore to perform a systematic review (SR) of current knowledge regarding presentation, treatment, and survival of patients affected by MCBTs initially approached by surgery, providing pooled proportions of the most relevant characteristics.

2 | METHODS

2.1 | Article collection

A SR of the literature was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement.¹⁶ The search was conducted on the PubMed, Scopus, and Web of Science online databases, and updated on August 31, 2023. To retrieve all publications describing cases of MCBT, the following query was used: “(malignant OR malignancy OR cancer OR metastatic OR metastasis) AND carotid AND (((body OR bulb OR glomus) AND ((tumor OR tumour OR caroticum)) OR paraganglioma OR chemodectoma) OR glomus caroticum).”

The references of the papers included and relevant reviews found through the literature search were screened to find additional original series. The search was conducted by two authors (C.P. and D.L.) who independently assessed the eligibility of the studies by screening article titles and abstracts, and then discussed their inclusion by reading the full-text of the selected publications. Discrepancies were clarified by discussion between authors.

2.2 | Eligibility criteria

The Population/problem, Intervention/exposure, Comparison, Outcome, and Study design (PICOS) model was adopted for the review.¹⁷ Selection criteria were: (a) original articles, including case reports; (b) reporting data on MCBT initially treated with surgery; and (c) published from January 1, 2000 to August 31, 2023. Exclusion criteria were: (a) non-English literature; (b) non-surgical treatments of MCBTs (i.e., purely palliative management from the beginning due to very advanced systemic disease at diagnosis); (c) original articles focusing only on radiological, genetic, clinical or histopathological diagnosis or embolization procedures; and (d) national/international databases or registries. Only patients with proven nodal and/or distant metastasis were considered as MCBTs. In case of duplicated original data from the same center, the most recent and/or

largest publication was considered. For proportion meta-analysis (MA), only case series with at least five consecutive cases were considered (Table 1).^{18–39} All the other case series describing less than five patients (including case reports) were considered only for the SR and detailed in Table S1.^{3,40–152}

2.3 | Quality assessment

The quality of each study included was independently estimated by two authors (M.T. and D.L.) through the Joanna Briggs Institute (JBI) checklist for case series.¹⁵³ A senior author (C.P.) was consulted in case of discrepancies (Table S2).

2.4 | Data collection and statistical analysis

Data on study design, number of patients, age, gender, genetic testing, tumor's maximum diameter, Shamblin classification, site(s) of metastases, time of malignancy diagnosis, therapeutic approaches adopted after surgical resection of the primary tumor, and oncological outcomes were collected, and a specific database was built.

Proportion MA was conducted through an inverse variance random-effect model based on arcsin transformation and presented as forest plots. The pooled proportion estimates and corresponding 95% confidence intervals (CIs) were calculated according to the random-effects models of DerSimonian and Laird.¹⁵⁴ For each study, proportions are depicted as gray squares, and relative 95% CI as horizontal lines. The weight of each study on the overall effect estimate is reported and represented by the square size. The pooled proportions estimates with relative 95% CI are depicted as black diamonds at the bottom of the Forest plot. Heterogeneity between studies was assessed with Higgins I^2 and τ^2 tests,¹⁵⁵ defined as low if <25%, moderate if between 25% and 50%, and substantial if >50%.¹⁵⁶

Publication bias was assessed through funnel plot assessment and Egger's test.¹⁵⁷ Statistical analysis was performed with R (version 4.3.1, R foundation for Statistical Computing, Vienna, Austria); packages “meta” and “metafor.” Statistical significance was defined as $p < 0.05$.

3 | RESULTS

3.1 | Article collection

The initial literature search yielded 3541 titles (1843 records came from PubMed, 1215 from Scopus, and 483 from Web

TABLE 1 Meta-analysis of 20 English-language non-overlapping surgical series^{18–39} including 5 or more patients affected by MCBTs treated surgically and published between January 1, 2000 and August 31, 2023 (No. of pts = 158).

First author (year of publication)	Country	Study design	Period	No. of CBTs treated with surgery	No. of Males (%)	Age at diagnosis (mean ± SD; years old)	No. of cases with family history	Shamblin III	Mean largest diameter ± SD (range), mm	Presentation of MCBTs				Postop diagnosis	Postop treatments	Oncologic outcome
										N+	M+	N+	M+			
Boedeker (2007) ¹⁸	Germany, Poland, France, Italy, Switzerland, Finland, Spain	Re, Mc	2000–2005	—	6	83%	40 ± 14 (2 pts >40 years old)	—	—	2 (33%)	5 (83%)	0	0	—	—	2 DOD, 4 AWD or NED
Zhang (2009) ¹⁹	China	Re, Uc	1956–2006	105	9	44%	Median 46	8 (88%)	—	3 (37%)	5 (62%)	0	4 (44%)	2 RT	1 DOD, 7 NED, 1 Lost	
Moskovic (2010) ²⁰	Texas	Re, Uc	1970–2005	—	10	10%	3 pts >40 years old	—	—	0	3 (30%)	7 (70%)	—	3 CRT, 3 chemo (2 missing data)	5 AWD, 5 Lost	
Kruger (2010) ²¹	Australia	Re, Uc	1982–2007	49	7	—	—	—	—	3 (50%)	3 (50%)	0	4 (57%)	4 RT	3 DOD, 4 NED	
Chapman (2010) ²²	North Carolina	Re, Uc	1976–2010	—	6	50%	—	—	—	6 (100%)	0	0	0	6 RT	—	
Lian (2011) ²³	China	Re, Uc	1949–2011	117	8	—	—	—	—	—	—	—	—	—	6 DOD, 2 NED	
Power (2012) ²⁴	Minnesota	Re, Uc	1985–2010	144	10	—	—	—	—	8 (80%)	2 (20%)	0	2 (20%)	—	—	
Papaspayrou (2012) ^{25a}	Germany	Re, Uc	1989–2010	68	5	—	3 (1 SDHC, 2 SDHD)	—	—	1 (20%)	4 (80%)	0	1 (20%)	—	—	
Ellis (2014) ²⁷	Maryland	Re, Uc	—	41	6	—	—	—	—	0	6 (100%)	0	0	—	—	
Mediouni (2014) ²⁸	France	Re, Uc	2001–2008	31	5	—	4 (3 SDHB, 1 SDHD) [1 not tested]	—	—	2 (40%)	0	3 (60%)	5 (100%)	0	1 AWD, 2 NED, 2 Lost	
Pacheco-Ojeda (2017) ^{29b}	Ecuador	Re, Uc	1980–2015	215	7	—	—	—	—	2 (40%)	3 (60%)	0	—	—	4 DOD, 3 NED	
Ikeda (2018) ³¹	Japan	Re, Mc	1995–2015	150	7	—	—	—	—	4 (57%)	2 (28%)	1 (14%)	—	—	—	
Jiang (2020) ³²	China	Re, Uc	2008–2018	203	13	—	—	—	—	13 (100%)	0	0	0	0	—	
Gu (2020) ³³	China	Re, Uc	2005–2018	—	9	—	42 ± 11 (5 >40 years)	8 (88%)	67 ± 26 (27–115)	4 (44%)	0	5 (55%)	0	3 RT, 1 CHT	5-year dMFS 72%, 10-year dMFS 36%	
Valero (2020) ³⁴	New York	Re, Uc	1986–2017	59	5	—	—	—	—	2 (50%)	2 (50%)	0	0	3 RT	—	

TABLE 1 (Continued)

First author (year of publication)	Country	Study design	Period	No. of CBTs treated with surgery	No. of Males (%)	Age at diagnosis (mean \pm SD; years)	No. of cases with family history	Shamblin III	Mean largest diameter \pm SD (range), mm	Presentation of MCBTs				Oncologic outcome		
										N+	M+	N+	M+			
Fathalla (2020) ³⁵	Egypt	Re, Uc	2009–2019	19	5	—	0	—	—	1 (20%)	0	4 (80%)	0	2 RT	5-year OS 60%, 2-year DFS 30%	
Zhang (2021) ³⁶	China	Re, Uc	2005–2018	237	16	18%	36 \pm 13 (6 pts >40 years)	1	12 (75%)	38 \pm 11 (20–60)	15 (93%)	0	1 (6%)	0	—	3 AWD, 13 NED
Ma (2022) ³⁷	China	Re, Uc	1976–2020	134	9	—	—	—	—	—	9 (100%)	0	0	0	6 RT	—
Yang (2022) ³⁸	China	Re, Uc	2002–2018	133	10	30%	50 \pm 14	0	7 (70%)	54 (25–113)	9 (90%)	0	1 (10%)	0	—	1 DOD, 1 AWD, 8 NED
Reitz (2022) ³⁹	Pennsylvania	Re, Mc	2000–2019	63	5	—	—	3 (2 SDHD, 1 other)	—	—	—	—	—	0	—	—

Abbreviations: AWD, alive with disease; CHT, chemotherapy; DFS, disease free survival; dmFS, distant metastasis free survival; DOD, dead of the disease; M+, distant metastasis; Mc, multicentric; N+, nodal metastasis; NED, no evidence of disease; OS, overall survival; SDH (B,C,D), succinate dehydrogenase (subunits) genes; Re, retrospective; RT, radiotherapy; SD, standard deviation; Uc, unicentric.

^aThe paper from Papasparyou et al. (2012)²⁵ is an adjournment of a previous series from the same authors, that is, Papasparyou et al. (2009).²⁶

^bThe paper from Pacheco-Ojeda (2017)²⁹ includes also patients already detailed in a previous publication from the same author, that is, Pacheco-Ojeda (2001).³⁰

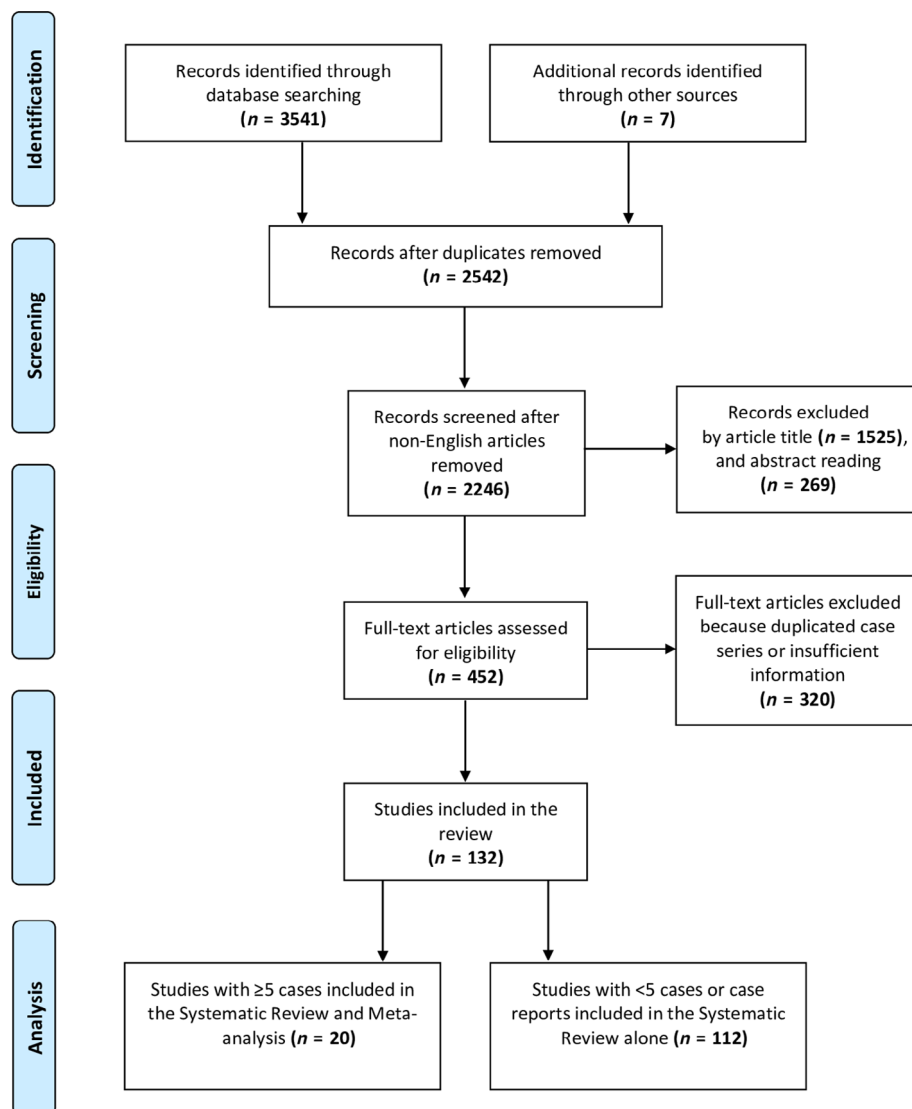


FIGURE 1 Flowchart showing the study selection process according to the PRISMA statement. [Color figure can be viewed at wileyonlinelibrary.com]

of Science). Seven papers were added through other sources. Among these, 1006 articles were excluded because they were duplicates, and 296 due to publication in a language other than English; 1525 articles were excluded after review of the title, and 269 by the abstract. From the remaining 452 full-text articles, 320 were excluded because they did not meet the eligibility criteria. Finally, 132 papers were considered appropriate for the present SR, for a total of 337 patients (Figure 1). Among these articles, 20 (158 patients) included 5 or more patients (Table 1)^{18–39} and were considered for the proportion MA. The remaining 112 studies (179 patients), represented by case reports or case series with <5 patients, are reported in Table S1.^{3,40–152}

3.2 | Quality assessment

Detailed scores according to the JBI checklist¹⁵³ for each article considered in the pooled MA are reported in

Table S2. All included manuscripts were retrospective case series^{18–39}; of these 3 (15%) were multicentric.^{18,31,39}

3.3 | Demographics and clinical presentation

Overall, 158 patients with MCBTs were included in the MA from the 20 case series with five or more patients.^{18–39} The diagnosis of MCBT in these surgical series was a rare occurrence, with a pooled proportion of 7.3% (95% CI: 5.8%–8.9%; $I^2 = 33\%$). Funnel plot inspection and Egger's test ($p < 0.001$) revealed a publication bias.

Regarding demographics, the mean age at the time of surgery for MCBT was in the 5th decade for three papers,^{18,19,33} while in the 4th and 6th for one paper each.^{36,38} A slightly lower proportion of male patients was observed (40.4%; 95% CI: 21.4%–61%), but in the presence of high heterogeneity ($I^2 = 65\%$) and publication bias

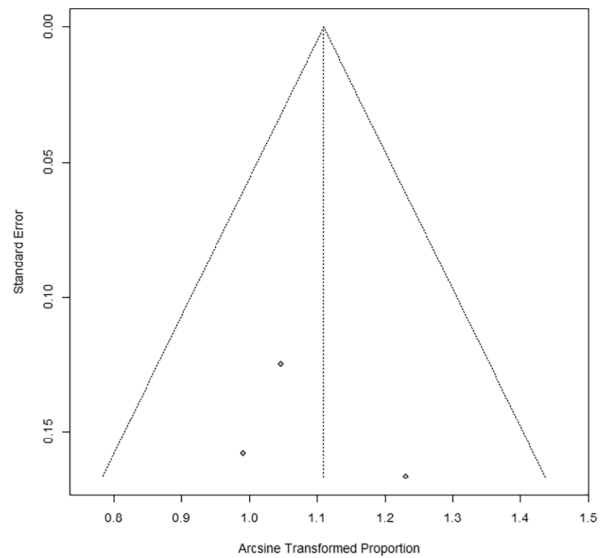
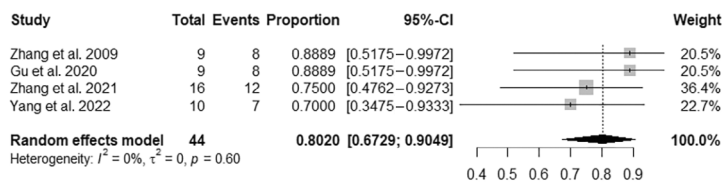


FIGURE 2 Forest plot reporting the pooled proportion of patients affected by Shamblin III MCBTs at the time of diagnosis, and relative funnel plot. No publication bias was detected by Egger's test ($p = 0.408$).

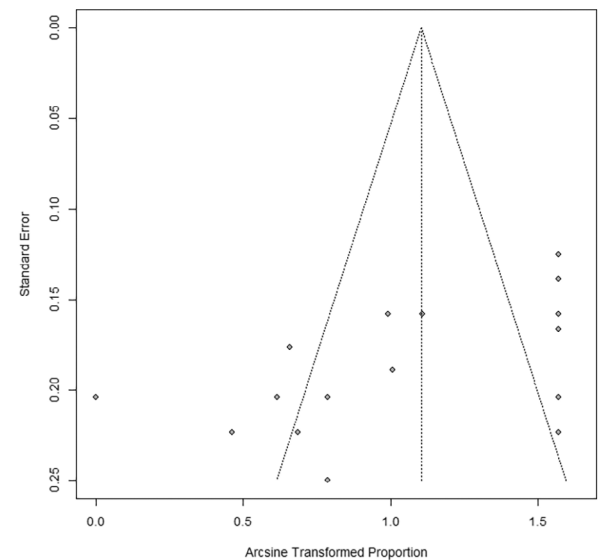
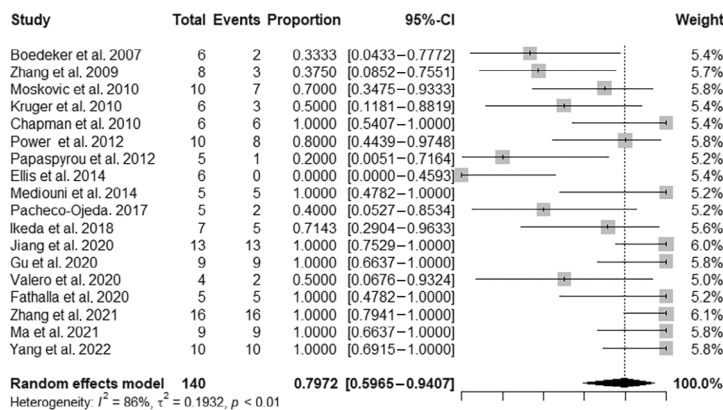


FIGURE 3 Forest plot reporting the pooled proportion of patients with nodal metastasis from MCBTs at the time of diagnosis, and relative funnel plot. Publication bias was detected by Egger's test ($p = 0.031$).

($p = 0.020$). This was also true for the pooled proportion of patients carrying a genetic mutation (17%; 95% CI: 13.2%–45.1%; $I^2 = 85\%$; Egger's test $p = 0.009$).

The majority of MCBTs were classified as Shamblin III (80.2%; 95% CI: 67.2%–90.4%; $I^2 = 0\%$; Egger's test $p = 0.408$) (Figure 2). Data on clinical presentation were heterogenous. The pooled proportion of patients diagnosed with nodal metastasis (79.7%; 95% CI: 59.6%–94%; $I^2 = 86\%$) (Figure 3) and distant metastasis (44.7%; 95% CI: 22.4%–68.1%; $I^2 = 88\%$) (Figure 4) varied widely among studies. A non-negligible proportion of patients presented with both nodal and distant metastasis (6.9%; 95%

CI: 0.7%–18.6%, $I^2 = 78\%$). Regarding location of distant metastasis, bones and lungs were the most commonly reported, followed by liver.

4 | DISCUSSION

4.1 | Epidemiology, clinical features, and proper diagnosis of MCBTs

The pooled proportion of 7.3% of MCBTs found in the present MA is somewhat higher than that described in

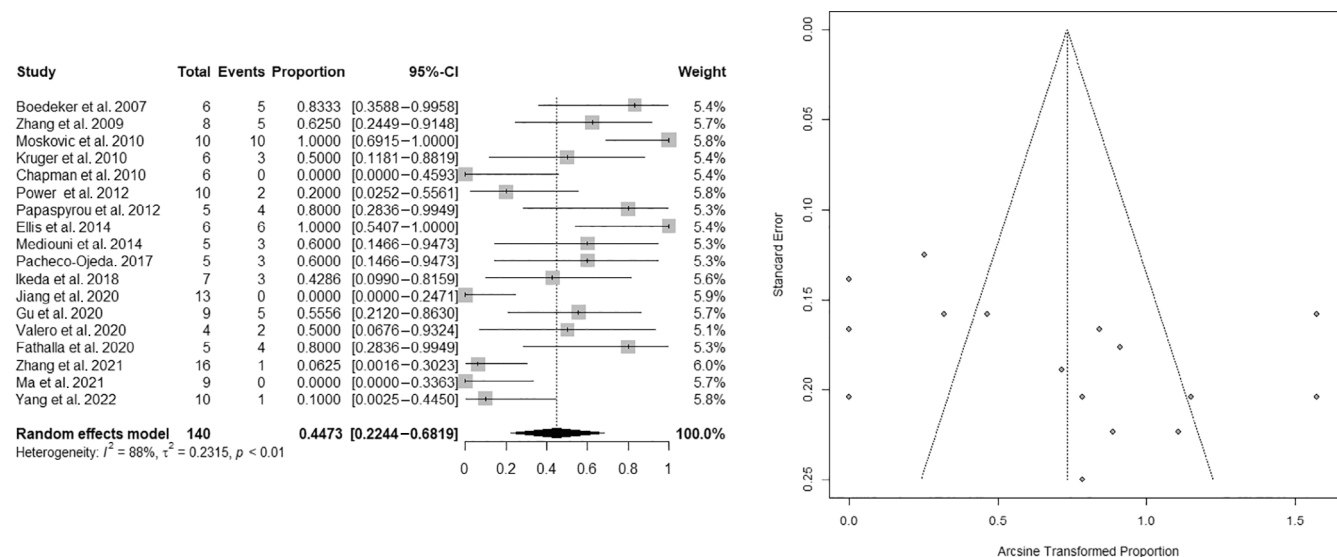


FIGURE 4 Forest plot reporting the pooled proportion of patients with distant metastasis from MCBTs at the time of diagnosis, and relative funnel plot. No publication bias was detected by Egger's test ($p = 0.057$).

the literature,^{10,11} potentially reflecting a couple of combined biases: (1) referral bias (with more experienced centers reporting on such cases being also those with the highest possibility to treat MCBTs); and (2) detection bias (with the highest attention devoted by large-volume centers in performing scrupulous pre-, intra-, and postoperative work-up and thus able to discover a higher incidence of MCBTs, sometimes even after many years of follow-up). This incidence, however, remains significantly lower than that reported for malignant vagal paragangliomas (16%–19%),¹⁵⁸ and higher than that usually quoted for malignant jugulo-tympanic tumors (2%–4%).¹⁵⁹

The wide range of affected ages (from the 4th to the 6th) is not different from previously reported age ranges in the literature, especially considering that the diagnosis of MCBT can be significantly delayed (even decades) after the first treatment of a presumed benign lesion. The slightly higher female preponderance in MCBT is also observed in benign CBT.

In both the MA and SR, MCBTs were most commonly associated with SDHB gene mutations (hallmark of the paraganglioma [PGL] syndrome 4).^{18,160} The second most frequently encountered mutation was in the D subunit of SDH, which is found associated with PGL syndrome 1.¹⁶¹ Of note, such genetic testing had been specifically performed in only 50% of the largest case series considered in the MA, with an increasing frequency only in the most recent years.

Most MCBTs showed a maximal diameter >4 cm and were classified as Shamblin III. This can be an indirect sign of local aggressiveness and potentially malignant biological behavior. Apart from the obvious technical issues concerning CCA, ICA, and cranial nerves

preservation/reconstruction with associated potential complications and neurologic sequelae, a Shamblin III scenario should therefore always prompt more accurate pre- and intraoperative diagnostic evaluations to exclude the risk of malignancy. The cranial extent of MCBTs was not systematically reported in the literature, nor was the related Mehanna's Type,⁹ probably because this classification is too recent to be widely adopted.

MCBTs are more frequently symptomatic at diagnosis (31.3% vs. 12.2% of benign CBTs, with a $p < 0.05$ according to Zhang and coworkers),³⁶ usually for a painful and palpable neck mass, dysphagia, dysphonia, hoarseness, alterations in tongue movements, pulsatile tinnitus, dizziness, headache, and earache. Bilaterality is also more frequently associated with malignant behavior (25% for MCBTs compared with 8.5% for benign CBTs in the Zhang series).³⁶ Biochemical activity was rarely described, even though it reached 20% in the series by Reitz et al.,³⁹ thus roughly paralleling the rate of familial syndromes.

Some authors report a proportion of 2:1 of regional versus distant metastases at diagnosis of MCBTs,¹⁵⁹ while others describe a nearly equal frequency of regional and distant diseases.⁴ Our study seems to confirm a higher prevalence of regional metastasis with a proportion quite similar to those reported by Lee et al.,¹⁵⁹ and a non-negligible simultaneous occurrence of both regional and distant disease. However, of note, it is still not infrequent to find reports on “presumed MCBTs” without regional or distant metastases, based solely on an erroneous definition of aggressive local behavior or abnormal histopathological findings.^{162,163}

Although we agree with Harley et al.¹⁶⁴ on the more likely future malignant behavior of CBT displaying local

aggressive and invasive growth, and we underline the need for more in-depth molecular analysis that could anticipate such a behavior by simply evaluating the surgical specimen, we are still far from such a possibility. To date, in fact, we lack tools that are capable of making a histopathologic diagnosis of MCBT and, as a consequence, we still depend on post hoc detection of tumor cells in regional lymph nodes or distant organs that do not normally contain chromaffin cells, as defined by the World Health Organization.¹⁶⁵

One of the shortcomings in the exact diagnosis and definition of the true incidence of MCBT is represented by the fact that the lymph nodes yield to be considered optimal for its detection is not standardized. As reported by Harley and coworkers,¹⁶⁴ in fact, an associated neck dissection is frequently not performed or carries an insufficient number of lymph nodes to be analyzed. As a consequence, many authors refer a delayed diagnosis of distant metastases months or years later and, in these cases, we cannot really determine whether distant localizations occurred without regional spread or without a correct evaluation of already pre-existent lymph nodes involvement.

Therefore, future directions to anticipate as much as possible the diagnosis of MCBTs should include: (1) at the patient level, in every cervical paraganglioma carrier, systematically addressing possible genetic mutations, testing catecholamine secretion, and intensively searching for possible multifocal disease since these are all well-known risk factors for an increased malignant potential^{166,167}; (2) at the tumor level, continuing the search for possible hallmarks predictive of the malignant potential of such lesions, for example quantifying superoxide anions (whose higher concentration is directly linked to SDHx mutations and ensuing more frequent DNA mutations) within the CBT surgical specimen using a fluorogenic dye as recently described by Kajal and coworkers¹⁶⁸ or evaluating the matrix metalloproteinases-1, -2, and -3 levels in plasma and tissue samples (found to be significantly higher in MCBTs by Serra et al.)⁹¹; (3) at the nodal level, following the recommendations of performing at least a prophylactic level IIA sampling, potentially extended to a selective neck dissection of levels II–III for diagnostic purposes in every CBT^{30,37,70,81,138,159,169,170}; (4) at the metastatic level, applying as much as possible a diagnostic work-up and/or follow-up including Gallium 68 labeled 1,4,7,10-tetraazacycloDodecane-1,4,7,10-Tetraacetic Acid–NaI–Octreotide Positron Emission Tomography/Computed Tomography (Ga-68 DOTANOC PET/CT).¹⁷¹

As a general rule, special attention to exclude MCBT should be given to lesions with presentation at the extremes of age, gross infiltrative and aggressive behavior into the surrounding neck structures, multifocal nature, association with family history (in particular SDHB or SDHD genes mutations), and size >4 cm with Shamblin III classification (Figure 5A,B).



FIGURE 5 (A,B) Axial and coronal views of T1-weighted contrast-enhanced MR of a 58-year-old woman with a 4.5 cm Shamblin III CBT of the right side of the neck, symptomatic for pain since 1 year. Both external (ECA) and internal (ICA) carotid arteries, as well as internal jugular vein (IJV) and common (CCA) carotid artery, were anatomically preserved during surgical removal. Levels IIA lymph nodes were dissected and 2 out of 7 were found harboring chromaffin cells metastases. A diagnosis of MCBT was done and SDHB gene somatic mutation was diagnosed. Ga-68 DOTANOC PET/CT scan was negative for multifocal and/or distant metastases. Adjuvant radiotherapy was not performed after multidisciplinary discussion and patient's counseling. She is alive without loco-regional or distant relapse 28 months after surgery.

4.2 | Therapeutic options

The evidence supporting radiotherapy (RT) and/or chemotherapy (CHT) as adjuvant treatments after surgical treatment of MCBT is sparse and does not allow strong recommendations.

However, apart from being increasingly used as an alternative to surgery for selected benign CBTs, RT has been widely applied as adjuvant treatment in more

difficult scenarios such as tumors resected with positive margins (especially at the skull base level) or loco-regional recurrent disease. The issue whether or not to apply it systematically after a diagnosis of MCBT is much more debated. The absence of dedicated guidelines and the inherent diagnostic challenges determine a very heterogeneous application of postoperative (CHT)RT, with different rates of use in the larger series included in the current study. These rates have remained substantially unchanged from the previous National Cancer Data Base analysis performed by Lee et al.¹⁵⁹ Unfortunately, most of proponents of RT as adjuvant treatment after MCBT resection sustain this approach based on similarities with other tumors, more than on a specific solid evidence in favor of such a philosophy.⁴⁰ Lacking animal models of such a disease and considering the impossibility to carry out a prospective randomized control trial with adequate power, shedding light on such a conundrum is probably beyond our possibilities.

A potentially attractive therapeutic option for MCBT is represented by metabolic RT with ¹³¹Iodine-metaiodobenzylguanidine (MIBG, a norepinephrine analog) or ⁹⁰Yttrium- or ¹¹¹Indium-labeled Octreotide based on the capability of MCBT to express somatostatin receptors. The main limits are represented by the fact that roughly half of malignant paraganglioma distant metastases do not take up the tracer and about 30% of potential candidates fail to respond.¹⁷²

Classically, the CHT drugs recommended for MCBTs with distant metastases were cyclophosphamide, vincristine, and dacarbazine (CVD) with rates of complete, partial responses, and stable disease of 4%, 37%, and 14%, respectively, in a MA on malignant paragangliomas including pheochromocytoma by Niemeijer et al.¹⁷³ Use of CHT appears to control symptoms and allows short-term remission, even though without the evidence from randomized trials which are too difficult to perform in such a rare disease.

Targeted molecular therapy, based on the activation and/or deregulation of genes associated to hypoxia observed in SDHx mutations, remains a fascinating concept. Drugs like Sunitinib have been used with apparently promising results.^{174,175}

4.3 | Oncologic outcomes

Clinical presentation and natural history of MCBT (as associated to regional disease only or with distant metastases) directly impact the 5-year survival rate of patients with MCBT, with those presenting distant metastases usually surviving considerably less than those having purely lymph nodes metastasis (11.8% vs. 85%

according to Lee et al.¹⁵⁹ and Goffredo et al.¹⁷⁶). Five-year survival, usually ranging in the literature between 59.5%¹⁵⁹ and 71.6%,⁴ has been confirmed in two large series of the present review in terms of 5- and 10-year distant metastasis free survival of 72.7% and 36.4%, respectively,³³ 5-year overall survival of 60%, and 2-year disease free survival of 30%.³⁵

Unfortunately, regional as well as distant metastases may appear even decades after radical treatment of CBT, thus further complicating more precise epidemiologic and oncologic considerations. Apart from different presentation and clinical history, other factors affect 5-year survival rates of MCBT. For example, lung metastases have a poorer prognosis in comparison to other distant sites like bones, which are easier to be palliatively treated by surgery and RT.¹⁷⁷ However, apart from a general survival advantage in comparison to malignant pheochromocytomas and paragangliomas arising in the trunk, the overall behavior and clinical management of MCBT are still scarcely reported in the literature.

4.4 | Study limitations

Most of the literature on MCBT is from case reports, small series, and long-term retrospective databases in which many genetic, molecular, clinical, therapeutic, and follow-up data are sparsely or incompletely reported. This clearly affects every attempt to comprehensively understand the disease through a MA and reduces the strengths of conclusions to be made on such a rare and elusive tumor.

5 | CONCLUSION

MCBT is an extremely rare disease but a high level of suspicion must be maintained in the diagnostic phase for large (>4 cm), Shamblin III, painful or otherwise symptomatic CBT, especially when encountered in either young or older patients, with bilateral lesions, multifocal disease, and history or genetic evidence of a PGL syndrome. *Neck dissection of levels II-III should be considered part of the diagnostic process and performed together with every CBT resection to detect occult lymph nodes metastases and formulate the diagnosis of malignancy.* Postoperative neck RT can be considered on a case-by-case basis, after proper multidisciplinary evaluation. For MCBTs, life-long follow-up should be continued to detect possible distant metastases by whole body functional imaging. Palliative treatment of distant metastases includes metastasectomy (when feasible) or local photon RT, metabolic RT, CHT, targeted therapy, or a combination of these

approaches. Apart from diseases diagnosed in advanced stages with lung, brain, and liver metastases, MCBTs have usually an indolent course with acceptable 5-year survival rates.

CONFLICT OF INTEREST STATEMENT

The authors have no conflict of interest related to this manuscript.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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REFERENCES

- Clairmont AA. Carotid body tumor: a review. *Ear Nose Throat J*. 1977;56:380-384.
- Pellitteri PK, Rinaldo A, Myssiorek D, et al. Paragangliomas of the head and neck. *Oral Oncol*. 2004;40:563-575.
- Sajid MS, Hamilton G, Baker DM, Joint Vascular Research Group. A multicenter review of carotid body tumour management. *Eur J Vasc Endovasc Surg*. 2007;34:127-130.
- Suarez C, Rodrigo JP, Mendenhall WM, et al. Carotid body paragangliomas: a systematic study on management with surgery and radiotherapy. *Eur Arch Otorhinolaryngol*. 2014;271:23-34.
- Williams MD, Tischler AS. Update from the 4th edition of the World Health Organization classification of head and neck tumours: paragangliomas. *Head Neck Pathol*. 2017;11:88-95.
- Jansen JC, van den Berg R, Kuiper A, van der Mey AG, Zwinderman AH, Cornelisse CJ. Estimation of growth rate in patients with head and neck paragangliomas influences the treatment proposal. *Cancer*. 2000;88:2811-2816.
- Gonzalez-Urquijo M, Hinojosa-Gonzalez DE, Fabiani MA, et al. High altitude carotid body tumors growth during active surveillance. *Vasc Endovascular Surg*. 2023;57:451-455.
- Shamblin WR, ReMine WH, Sheps SG, Harrison EG Jr. Carotid body tumor (chemodectoma): clinicopathologic analysis of ninety cases. *Am J Surg*. 1971;122:732-739.
- Mehanna H, Mistry P, Golusinski P, et al. Development and validation of an improved classification and risk stratification system for carotid body tumors: multinational collaborative cohort study. *Head Neck*. 2021;43:3448-3458.
- Robertson V, Poli F, Hobson B, Saratzis A, Naylor AR. A systematic review and meta-analysis of the presentation and surgical management of patients with carotid body tumours. *Eur J Vasc Endovasc Surg*. 2019;57:477-486.
- Li Y, Lin B, Liang S, et al. Epidemiology and survival of patients with malignant carotid body tumors in the SEER database. *J Vasc Surg*. 2022;76:973-978.
- Neumann HPH, Erlic Z, Boedeker CC, et al. Clinical predictors for germ line mutations in head and neck paraganglioma patients: cost reduction strategy in genetic diagnostic process as fall-out. *Cancer Res*. 2009;69:3650-3656.
- Pasini B, Stratakis CA. SDH mutations in tumorigenesis and inherited endocrine tumors: lesson from the pheochromocytoma-paraganglioma syndromes. *J Intern Med*. 2009;266:19-42.
- Timmers HJ, Gimenez-Roqueplo AP, Mannelli M, Pacak K. Clinical aspects of SDHx-related pheochromocytoma and paraganglioma. *Endocr Relat Cancer*. 2009;16:391-400.
- Hu K, Persky MS. Treatment of head and neck paragangliomas. *Cancer Control*. 2016;23:228-241.
- Moher D, Liberati A, Tetzlaff J, Altman DG, PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Ann Intern Med*. 2009;151:264-269.
- Centre for Reviews and Dissemination. *Systematic Reviews: CDR's Guidance for Undertaking Reviews in Health Care*. University of York; 2006.
- Boedeker CC, Neumann HPH, Maier W, Bausch B, Schipper J, Ridder GJ. Malignant head and neck paragangliomas in SDHB mutation carriers. *Otolaryngol Head Neck Surg*. 2007;137:126-129.
- Zhang WC, Cheng JP, Li Q, Zhang L, Wang XD, Anniko M. Clinical and pathological analysis of malignant carotid body tumour: a report of nine cases. *Acta Otolaryngol*. 2009;129:1320-1325.
- Moskovic DJ, Smolarz JR, Stanley D, et al. Malignant head and neck paragangliomas: is there an optimal treatment strategy? *Head Neck Oncol*. 2010;2:23.
- Kruger AJ, Walker PJ, Foster WJ, Jenkins JS, Boyne NS, Jenkins J. Important observations made managing carotid body tumors during a 25-year experience. *J Vasc Surg*. 2010;52:1518-1524.
- Chapman DB, Lippert D, Geer CP, et al. Clinical, histopathologic, and radiographic indicators of malignancy in head and neck paragangliomas. *Otolaryngol Head Neck Surg*. 2010;143:531-537.
- Lian LS, Liu CW, Guan H, Zheng YH, Chen XM, Li YJ. Efficacy of surgical therapy for carotid body tumors. *Chin Med Sci J*. 2011;26:241-245.
- Power AH, Bower TC, Kasperbauer J, et al. Impact of preoperative embolization on outcomes of carotid body tumor resections. *J Vasc Surg*. 2012;56:979-989.
- Papaspyrou K, Mewes T, Rossmann H, et al. Head and neck paragangliomas: report of 175 patients (1989-2010). *Head Neck*. 2012;34:632-637.
- Papaspyrou K, Mann WJ, Amedee RG. Management of head and neck paragangliomas: review of 120 patients. *Head Neck*. 2009;31:381-387.
- Ellis RJ, Patel D, Prodanov T, Nilubol N, Pacak K, Kebebew E. The presence of SDHB mutations should modify surgical indications for carotid body paragangliomas. *Ann Surg*. 2014;260:158-162.
- Mediouni A, Ammari S, Wassef M, et al. Malignant head/neck paragangliomas. Comparative study. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2014;131:159-166.
- Pacheco-Ojeda LA. Carotid body tumors: surgical experience in 215 cases. *J Craniomaxillofac Surg*. 2017;45:1472-1477.

30. Pacheco-Ojeda L. Malignant carotid body tumors: report of three cases. *Ann Otol Rhinol Laryngol.* 2001;110:36-40.
31. Ikeda A, Shiga K, Katagiri K, et al. Multi-institutional survey of carotid body tumors in Japan. *Oncol Lett.* 2018;15:5318-5324.
32. Jiang X, Fang G, Guo D, et al. Surgical management of carotid body tumor and risk factors of postoperative cranial nerve injury. *World J Surg.* 2020;44:4254-4260.
33. Gu G, Wang Y, Liu B, et al. Distinct features of malignant carotid body tumors and surgical techniques for challengeable lesions: a case series of 11 patients. *Eur Arch Otorhinolaryngol.* 2020;277:853-861.
34. Valero C, Ganly I, Shah JP. Head and neck paragangliomas: 30-year experience. *Head Neck.* 2020;42:2486-2495.
35. Fathalla AE, Elalfy MA. Clinical outcome of carotid body paraganglioma management: a review of 10-year experience. *J Oncol.* 2020;2020:6081273.
36. Zhang W, Liu F, Hou K, et al. Surgical outcomes and factors associated with malignancy in carotid body tumors. *J Vasc Surg.* 2021;74:586-591.
37. Ma H, Wei M, Wang X, et al. Necessity of intraoperative level IIA lymph node dissection in patients with carotid body tumors: a retrospective study of 126 cases. *ORL J Otorhinolaryngol Relat Spec.* 2022;84:271-277.
38. Yang L, Li W, Zhang H, Yu L, Zheng M. Clinicopathological characteristics of patients with carotid body tumor with cervical lymph node metastasis. A retrospective study of 10 cases and review of the literature. *Medicine.* 2022;101:e30379.
39. Reitz K, Ramos A, Speranza G, et al. Non-functional carotid body tumors in patients without somatic mutations may be considered for non-operative management. *Ann Vasc Surg.* 2022;85:57-67.
40. Mayer R, Fruhwirth J, Beham A, Groell R, Poschauko J, Hackl A. Radiotherapy as adjunct to surgery for malignant carotid body paragangliomas presenting with lymph node metastases. *Strahlenther Onkol.* 2000;176:356-360.
41. Somasundar P, Krouse R, Hostetter R, Vaughan R, Covey T. Paragangliomas – A decade of clinical experience. *J Surg Oncol.* 2000;74:286-290.
42. Mall J, Saclarides T, Doolas A, Eibl-Eibesfeld B. First report of hepatic lobectomy for metastatic carotid body tumor. *J Cardiovasc Surg (Torino).* 2000;41:759-761.
43. Dias da Silva A, O'Donnell S, Gillespie D, Goff J, Shriver C, Rich N. Malignant carotid body tumor: a case report. *J Vasc Surg.* 2000;32:821-823.
44. van der Mey AGL, Jansen JC, van Baalen JM. Management of carotid body tumors. *Otolaryngol Clin North Am.* 2001;34:907-924.
45. Hinerman RW, Mendenhall WM, Amdur RJ, Stringer SP, Antonelli PJ, Cassisi NJ. Definitive radiotherapy in the management of chemodectomas arising in the temporal bone, carotid body, and glomus vagale. *Head Neck.* 2001;23:363-371.
46. Plukker JTM, Brongers EP, Vermey A, Krikke A, van den Dungen JJAM. Outcome of surgical treatment for carotid body paraganglioma. *Br J Surg.* 2001;88:1382-1386.
47. Bomanji JB, Hyder SW, Gaze MN, et al. Functional imaging as an aid to decision-making in metastatic paraganglioma. *Br J Radiol.* 2001;74:266-269.
48. Persky MS, Setton A, Niimi Y, Hartman J, Frank D, Berenstein A. Combined endovascular and surgical treatment of head and neck paragangliomas – a team approach. *Head Neck.* 2002;24:423-431.
49. Patetsios P, Gable DR, Garrett WV, et al. Management of carotid body paragangliomas and review of a 30-year experience. *Ann Vasc Surg.* 2002;16:331-338.
50. Kumaki N, Kajiwara H, Kameyama K, et al. Prediction of malignant behavior of pheochromocytomas and paragangliomas using immunohistochemical techniques. *Endocr Pathol.* 2002;13:149-156.
51. Lazaro B, Klemz M, Steiner Flores M, Landeiro JA. Malignant paraganglioma with vertebral metastasis. *Arq Neuropsiquiatr.* 2003;61:463-467.
52. Koch CA, Rodbard JS, Brouwers FM, Eisenhofer G, Pacak K. Hypotension in a woman with a metastatic dopamine-secreting carotid body tumor. *Endocr Pract.* 2003;9:310-314.
53. Argiris A, Mellott A, Spies S. PET scan assessment of chemotherapy response in metastatic paraganglioma. *Am J Clin Oncol.* 2003;26:563-566.
54. Niemann S, Muller U, Engelhardt D, Lohse P. Autosomal dominant malignant and catecholamine-producing paraganglioma caused by a splice donor site mutation in *SDHC*. *Hum Genet.* 2003;113:92-94.
55. Kohler HF, Carvalho AL, Mattos Granja NV, Nishinari K, Kowalski LP. Surgical treatment of paragangliomas of the carotid bifurcation: results of 36 patients. *Head Neck.* 2004;26:1058-1063.
56. Garcia Franco C, Heili S, Jimenez Hiscock L, Zapatero GJ. Pulmonary metastases in a bilateral carotid body paraganglioma. *Interact Cardiovasc Thorac Surg.* 2004;3:578-580.
57. Carroll W, Stenson K, Stringer S. Malignant carotid body tumor. *Head Neck.* 2004;26:301-306.
58. Uguz MZ, Arslanoglu S, Onal K, Gokce H. Malignant carotid body tumor: a case report. *Kulak Burun Bogaz Ihtis Derg.* 2004;13:38-40.
59. Benn DE, Gimenez-Roqueplo AP, Reilly JR, et al. Clinical presentation and penetrance of pheochromocytoma/paraganglioma syndromes. *J Clin Endocrinol Metab.* 2006;91:827-836.
60. Christie N, Parsons AM, Behrns KE. Metastatic hepatic paraganglioma 6 years after carotid body tumor resection. *Clin Gastroenterol Hepatol.* 2006;4:24.
61. Paris J, Facon F, Thomassin JM, Zanaret M. Cervical paragangliomas: neurovascular surgical risk and therapeutic management. *Eur Arch Otorhinolaryngol.* 2006;263:860-865.
62. Havekes B, Corssmit EPM, Jansen JC, van der Mey AGL, Vriends AHJT, Romijn JA. Malignant paragangliomas associated with mutations in the succinate dehydrogenase D gene. *J Clin Endocrinol Metab.* 2007;92:1245-1248.
63. Zheng JW, Zhong LP, Zhang ZY, et al. Carotid artery resection and reconstruction: clinical experience of 28 consecutive cases. *Int J Oral Maxillofac Surg.* 2007;36:514-521.
64. Zheng JW, Zhu HG, Yuan RT, et al. Recurrent malignant carotid body tumor: report of one case and review of the literature. *Chin Med J (Engl).* 2005;118:1929-1932.
65. Makeieff M, Raingeard I, Alric P, Bonafe A, Guerrier B, Marty-Ane C. Surgical management of carotid body tumors. *Ann Surg Oncol.* 2008;15:2180-2186.
66. van der Bogt KEA, Vrancken Peeters MPFM, van Baalen JM, Hamming JF. Resection of carotid body tumors. Results of an evolving surgical technique. *Ann Surg.* 2008;247:877-884.

67. Timmers HJLM, Pacak K, Bertherat J, et al. Mutations associated with succinate dehydrogenase D-related malignant paragangliomas. *Clin Endocrinol (Oxf)*. 2008;68:561-566.
68. Rosa M, Sahoo S. Bilateral carotid body tumor: the role of fine-needle aspiration biopsy in the preoperative diagnosis. *Diagn Cytopathol*. 2008;36:178-180.
69. Kakkos SK, Reddy DJ, Shepard AD, Lin JC, Nypaver TJ, Weaver MR. Contemporary presentation and evolution of management of neck paragangliomas. *J Vasc Surg*. 2009;49:1365-1373.
70. Morton RP, Stewart T, Dray MS, Farmilo W. A role for ipsilateral, selective neck dissection in carotid body tumours. *J Laryngol Otol*. 2009;123:934-936.
71. Karaman E, Isildak H, Yilmaz M, et al. Management of paragangliomas in otolaryngology practice: review of a 7-year experience. *J Craniofac Surg*. 2009;20:1294-1297.
72. Ma D, Liu L, Yao H, et al. A retrospective study in management of carotid body tumour. *Br J Oral Maxillofac Surg*. 2009;47:461-465.
73. Li J, Wang S, Zee C, et al. Preoperative angiography and transarterial embolization in the management of carotid body tumor: a single-center, 10-year experience. *Neurosurgery*. 2010;67:941-948.
74. Lehmen JA, Babbel DM, Mikhitarian K, Choma TJ. Paraganglioma presenting as metastatic lesion in a cervical vertebra. A case report and review of the literature. *Spine*. 2010;35:E152-E154.
75. Kimura N, Tateno H, Saijo S, Horii A. Familial cervical paraganglioma with lymph node metastasis expressing somatostatin receptor type 2A. *Endocr Pathol*. 2010;21:139-143.
76. Ayala-Ramirez M, Callender GG, Kupferman ME, et al. Paraganglioma syndrome type 1 in a patient with Carney-Stratakis syndrome. *Nat Rev Endocrinol*. 2010;6:110-115.
77. 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;124:1344-1346.
78. Neskey DM, Hatoum G, Modh R, et al. Outcomes after surgical resection of head and neck paragangliomas: a review of 61 patients. *Skull Base*. 2011;21:171-176.
79. O'Neill S, O'Donnell M, Harkin D, Loughrey M, Lee B, Blair P. A 22-year Northern Irish experience of carotid body tumours. *Ulster Med J*. 2011;80:133-140.
80. Avgerinos ED, Moulakakis K, Brountzos E, et al. Advances in assessment and management of carotid body tumors. *Vascular*. 2011;19:250-256.
81. Liapis CD, Evangelidakis EL, Papavassiliou VG, Kakisis JD, Gougoulakis AG, Polyzos AK. Role of malignancy and preoperative embolization in the management of carotid body tumors. *World J Surg*. 2000;24:1526-1530.
82. Nishijima H, Asakage T, Sugawara M. Malignant carotid body tumor with systemic metastases. *Ann Otol Rhinol Laryngol*. 2011;120:381-385.
83. Barraclough A, Bhamidipaty V, Bray P, Ponosh S. Carotid body tumour. *ANZ J Surg*. 2011;81:934-935.
84. Terzic A, Becker M, Wissmeyer M, Scolozzi P. 18F-DOPA PET/CT unravels malignant paraganglioma mimicking temporomandibular joint disorder. *Dentomaxillofac Radiol*. 2011;40:315-319.
85. Nazari I, Moghaddam FA, Zamani MM, Salimi J. Clinical characteristics and remedies in 45 Iranians with carotid body tumors. *Acta Med Iran*. 2012;50:339-343.
86. Williamson J, Leopold G, Prabhu V, Ingrams D. Successful treatment of a rare metastatic malignant carotid body tumour in a young adult, with conservative surgery and local radiotherapy. *J Laryngol Otol*. 2012;126:428-431.
87. Fruhmenn J, Geigl JB, Konstantiniuk P, Cohnert TU. Paraganglioma of the carotid body: treatment strategy and SDH-gene mutations. *Eur J Vasc Endovasc Surg*. 2013;45:431-436.
88. Sen I, Stephen E, Malepathi K, Agarwal S, Shyamkumar NK, Mammen S. Neurological complications in carotid body tumors: a 6-year single-center experience. *J Vasc Surg*. 2013;57:64S-68S.
89. Luo T, Zhang C, Ning Y-C, Gu Y-Q, Li J-X, Wang Z-G. Surgical treatment of carotid body tumor: case report and literature review. *J Geriatr Cardiol*. 2013;10:116-118.
90. Moris D, Sotiropoulos G, Vernadakis S. Hepatic metastasis of a carotid body paraganglioma 5 years after resection of the primary tumor. *Am Surg*. 2013;79:E194-E196.
91. Serra R, Grande R, Gallelli L, et al. Carotid body paragangliomas and matrix metalloproteinases. *Ann Vasc Surg*. 2014;28:1665-1670.
92. Choi JDW, Tucker KM, Lee TT, Chong GC. Hereditary paraganglioma-pheochromocytoma syndromes associated with SDHD and RET mutations. *Head Neck*. 2014;36:E99-E102.
93. Gad A, Sayed A, Elwan H, et al. Carotid body tumors: a review of 25 year experience in diagnosis and management of 56 tumors. *Ann Vasc Dis*. 2014;7:292-299.
94. Peterson LA, Litzendorf M, Ringel MD, Vaccaro PS. SDHB gene mutation in a carotid body paraganglioma: case report and review of the paraganglioma syndromes. *Ann Vasc Surg*. 2014;28:1321.e9.
95. Oakes A, Witt B, Adler D. Metastatic carotid body paraganglioma detected during evaluation for biliary stone disease. *Diagn Cytopathol*. 2014;42:868-871.
96. Su HK, Urken ML, Khorsandi AS. Growing mass on the right side of the neck. *JAMA Otolaryngol Head Neck Surg*. 2014;140:1085-1086.
97. Gupta SK, Singla S, Karunanithi S, Damle N, Bal C. Peptide receptor radionuclide therapy with ¹⁷⁷Lu DOTATE in a case of recurrent carotid body paraganglioma with spinal metastases. *Clin Nucl Med*. 2014;39:440-441.
98. Gilbo P, Tariq A, Morris CG, Mendenhall WM. External-beam radiation therapy for malignant paraganglioma of the head and neck. *Am J Otolaryngol*. 2015;36:692-696.
99. Leidenz FB, Bastos-Rodrigues L, Oliveira M, et al. Malignant phenotype and two SDHD mutations in a family with paraganglioma syndrome type 1. *Genet Res (Camb)*. 2015;97:e3.
100. Anttila T, Hayry V, Nicoli T, et al. A two-decade experience of head and neck paragangliomas in a whole population-based single centre cohort. *Eur Arch Otorhinolaryngol*. 2015;272:2045-2053.
101. Xiao Z, She D, Cao D. Multiple paragangliomas of head and neck associated with hepatic paraganglioma: a case report. *BMC Med Imaging*. 2015;15:38.
102. Neychev V, Straughan D, Pacak K, Kebebew E. Multidisciplinary management of locally advanced and widely metastatic

- paraganglioma in a patient with life-threatening compressive symptoms. *Head Neck*. 2015;37:E205-E208.
103. Lamblin E, Atallah I, Reyt E, Schmerber S, Magne J-L, Righini CA. Neurovascular complications following carotid body paraganglioma resection. *Eur Ann Otorhinolaryngol Head Neck Dis*. 2016;133:319-324.
 104. Mourad M, Saman M, Stroman D, Brown R, Ducic Y. Evaluating the role of embolization and carotid artery sacrifice and reconstruction in the management of carotid body tumors. *Laryngoscope*. 2016;126:2282-2287.
 105. Davila VJ, Chang JM, Stone WM, et al. Current surgical management of carotid body tumors. *J Vasc Surg*. 2016;64:1703-1710.
 106. Feyissa AM, Kenney-Jung DL, Shin C, Cheville JC, So EL. Clinical reasoning: an unusual cause of indeterminate spells. *Neurology*. 2016;87:e275-e280.
 107. Smith JD, Harvey RN, Darr OA, et al. Head and neck paragangliomas: a two-decade institutional experience and algorithm for management. *Laryngoscope Investig Otolaryngol*. 2017;2:380-389.
 108. Darouassi Y, Alaoui M, Mliha Touati M, et al. Carotid body tumors: a case series and review of the literature. *Ann Vasc Surg*. 2017;43:265-271.
 109. Niemeijer ND, Rijken JA, Eijkelenkamp K, et al. The phenotype of SDHB germline mutation carriers: a nationwide study. *Eur J Endocrinol*. 2017;177:115-125.
 110. Lopez A, Papouchado B, Brumund KT. Slowly growing right-sided neck mass with progressive dysphagia. *JAMA Otolaryngol Head Neck Surg*. 2017;143:419-420.
 111. Tyagi R, Munjal M, Kaur P, Kaur H, Sood N. Parotid or carotid? Misled by site. *Diagn Cytopathol*. 2017;45:569-573.
 112. Chen L, He S, Zhang Z, Liu D. Diagnostic pitfalls in fine-needle aspiration of metastatic carotid body paraganglioma: a case report. *AJSP Rev Rep*. 2017;22:225-229.
 113. Hinojosa CA, Anaya-Ayala JE, Olivares-Cruz S, Laparra-Escareno H, Trolle-Silva A, Angeles-Angeles A. Malignant Shamblin III carotid body tumors resected with use of the retrocarotid dissection technique in 2 patients. *Tex Heart Inst J*. 2018;45:92-95.
 114. Liu J, Li Y, Yang L, Cai H. Surgical resection of carotid body tumors with versus without preoperative embolization: retrospective case-control study. *Head Neck*. 2018;40:2590-2595.
 115. Zhang J, Fan X, Zhen Y, et al. Impact of preoperative transarterial embolization of carotid body tumor: a single center retrospective cohort experience. *Int J Surg*. 2018;54:48-52.
 116. Chmiel J, Loska P, Brzywczy A, et al. Carotid body paragangliomas – clinical variety and management (RCD code: I-O). *J Rare Cardiovasc Dis*. 2018;4:9-14.
 117. McCrary H, Babajanian E, Calquin M, et al. Characterization of malignant head and neck paragangliomas at a single institution across multiple decades. *JAMA Otolaryngol Head Neck Surg*. 2019;145:641-646.
 118. Bobadilla-Rosado LO, Garcia-Alva R, Anaya-Ayala JE, et al. Surgical management of bilateral carotid body tumors. *Ann Vasc Surg*. 2019;57:187-193.
 119. Rijken JA, de Vos B, van Hest LP, et al. Evolving management strategies in head and neck paragangliomas: a single-centre experience with 147 patients over a 60-year period. *Clin Otolaryngol*. 2019;44:836-841.
 120. Hassanein AG, Hassanein KA-AM, Fadle KN, Al-Eslam AS, Al Qahtani FN. The outcome of multidisciplinary management of carotid body tumors: retrospective cohort study. *J Maxillofac Oral Surg*. 2019;18:610-616.
 121. Wang X, Zhu X, Chen J, Liu Y, Mao Q. Metastatic brain carotid body paraganglioma with endocrine activity: a case report and literature review. *Br J Neurosurg*. 2019;33:269-271.
 122. Lin B, Yang H, Yang H, Shen S. A rare case of bilateral malignant paragangliomas. *World Neurosurg*. 2019;124:12-16.
 123. Tripathy S, Damle NA, Naranje P, Shamim SA, Tripathi M, Bal C. Leptomeningeal metastasis in carotid body paraganglioma. *Clin Nucl Med*. 2019;44:e583-e585.
 124. Amorosi NM, Dann A, White A. Case of a malignant carotid body tumor with systemic metastases: the utility of multimodal imaging. *J Vasc Ultrasound*. 2019;43:193-197.
 125. Lozano FS, Munoz A, De Las Heras JA, Gonzalez-Porras JR. Simple and complex carotid paragangliomas. Three decades of experience and literature review. *Head Neck*. 2020;42:3538-3550.
 126. Contrera KJ, Yong V, Reddy CA, Liu SW, Lorenz RR. Recurrence and progression of head and neck paragangliomas after treatment. *Otolaryngol Head Neck Surg*. 2020;162:504-511.
 127. Li X, Zhang W, Shu C, Li Q, Zhang L, Zhu J. Diagnosis and outcomes of surgical treatment of carotid bifurcation tumors. *J Int Med Res*. 2020;48:1-12.
 128. Sevil FC, Tort M, Kaygin MA. Carotid body tumor resection: long-term outcome of 67 cases without preoperative embolization. *Ann Vasc Surg*. 2020;67:200-207.
 129. Kang J, Heo S-H, Park Y-J, Kim D-I, Kim Y-W. Differential diagnosis and treatment outcomes of tumors at the carotid bifurcation. *Vasc Specialist Int*. 2020;36:128-135.
 130. Roll W, Muther M, Sporns PB, et al. Somatostatin receptor-targeted radioligand therapy in head and neck paraganglioma. *World Neurosurg*. 2020;143:E391-E399.
 131. Han T, Wang S, Wei X, et al. Outcome of surgical treatment for carotid body tumors in different Shamblin type without preoperative embolization: a single-center retrospective study. *Ann Vasc Surg*. 2020;63:325-331.
 132. Alshamsan B, Atallah JP. Durable response to Pazopanib in recurrent metastatic carotid body paraganglioma. *Case Rep Oncol*. 2020;13:1227-1231.
 133. Xing J, Cheng Y, Ying H, Guan M, Jia N, Bai C. Systemic treatment of a metastatic carotid body tumor. A case report and literature review. *Medicine (Baltimore)*. 2020;99:e22811.
 134. Patchana T, Fan J, Jiganti M, Gnass RD. Metastatic acetabular fracture: a rare disease presentation of recurrent head and neck paraganglioma. *Cureus*. 2020;12:e7596.
 135. Mohebbali J, Edwards HA, Schwartz SI, Ergul EA, Deschler DG, LaMuraglia GM. Multispecialty surgical management of carotid body tumors in the modern era. *J Vasc Surg*. 2021;73:2036-2040.
 136. Javidiparsijani S, Brickman A, Murro Lin D, et al. Is regional lymph node metastasis of head and neck paraganglioma a sign of aggressive clinical behavior: a clinical/pathologic review. *Ear Nose Throat J*. 2021;100:447-453.
 137. Illuminati G, Pasqua R, Nardi P, Fratini C, Minni A, Calio FG. Results of resection of carotid body tumors with and without lymphnodes' dissection. *Surg Oncol*. 2021;37:101555.

138. Ding Y, Li L, Han D, Wang S, Chen X. Head and neck malignant paragangliomas: experience from a single institution. *Ear Nose Throat J*. 2021. doi:10.1177/01455613211052338
139. Yasan H, Kumbul YC, Ciris IM, Sivrice ME, Okur E. The importance of prostate-specific membrane antigen expression in carotid body paragangliomas. *Turk Arch Otorhinolaryngol*. 2021;59:203-209.
140. Basel H, Bozan N. Cervical paraganglioma: experience of 114 cases in 14 years. *Braz J Otorhinolaryngol*. 2021;87:127-131.
141. Greenberg SE, Holman R, Kohlmann W, Buchmann L, Naumer A. Paraganglioma and other tumour detection rates in individuals with SDHx pathogenic variants by age of diagnosis and after the age of 50. *Clin Endocrinol (Oxf)*. 2021;95:447-452.
142. Tang H, Jiang X, Xue S, Fu W, Tang X, Guo D. Long-term surgical outcomes of carotid body tumors with pathological fibrosis: a cohort study. *Front Oncol*. 2021;11:684600.
143. Yamada H, Fukushima T, Kobayashi T, Kanda S, Koizumi T, Iwaya M. Successful response to cyclophosphamide, vincristine, and dacarbazine chemotherapy in a patient with metastatic carotid body paraganglioma. *Case Rep Oncol*. 2021;14:1827-1833.
144. Pavlov V, Snezhkina A, Kalinin D, et al. Case report: genetic alterations associated with the progression of carotid paraganglioma. *Curr Issues Mol Biol*. 2021;43:2266-2275.
145. Abolfotouh S, Back L, Aro K, et al. Carotid interposition in patients with head and neck tumors: clinical experience of 13 cases reconstructed with a great saphenous vein autograft. *Acta Otolaryngol*. 2022;142:419-424.
146. Tajibayev TK, Chormanov AT, Matkerimov AZ, et al. Carotid body tumors: case series of extremely rare head and neck paragangliomas. *NAMJ*. 2022;1:29-34.
147. Mikoshiba T, Yoshihama K, Ito F, et al. Carotid body tumor with neck metastasis due to germline SDHB variant: a case report and literature review. *Int Cancer Conf J*. 2021;11:6-11.
148. Jedrzejko N, Berg KB, Gurung A, MacKenzie S. Tumour to tumour metastasis: case of a carotid body paraganglioma metastatic to a hepatocellular adenoma. *BMJ Case Rep*. 2022;15:e248527.
149. Ihne S, Kircher M, Papagianni A, et al. AA amyloidosis in inflammatory active malignant paraganglioma. *Amyloid*. 2022;29:137-138.
150. Alfawaz A, Albloushi D, Quttaineh D, Alsafran S, AlQabandi O, Albader M. Malignant carotid body tumor: a report of two cases. *Ann Med Surg*. 2023;85:1857-1862.
151. Luna-Ortiz K, Bautista-Perez JJ, Luna-Peteuil Z, Martinez-Hernandez HJ. Carotid artery resection and reconstruction due to benign and malignant head and neck tumors. *Indian J Otolaryngol Head Neck Surg*. 2023;75:4216-4222.
152. Tabb JN, Maas JA, Earla BP, Fallon KB, McDonald AM, Dobelbower MC. Carotid body paraganglioma metastatic to spine causing cord compression: a case report. *Diagn Pathol*. 2023;18:31.
153. Munn Z, Barker TH, Moola S, et al. Methodological quality of case series studies: an introduction to the JBI critical appraisal tool. *JBI Evid Synth*. 2020;18:2127-2133.
154. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials*. 1986;7:177-188.
155. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med*. 2002;21:1539-1558.
156. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;327:557-560.
157. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;315:629-634.
158. Mottie L, Meulemans J, Vander Poorten V. Vagal paragangliomas. *Curr Opin Otolaryngol Head Neck Surg*. 2023;31:146-154.
159. Lee JH, Barich F, Hynds Karnell L, et al. National Cancer Data Base report on malignant paragangliomas of the head and neck. *Cancer*. 2002;94:730-737.
160. Astuti D, Latif F, Dallol A, et al. Gene mutations in the succinate dehydrogenase subunit II SDHB cause susceptibility to familial pheochromocytoma and to familial paraganglioma. *Am J Hum Genet*. 2001;69:49-54.
161. Baysal BE, Ferrell RE, Willett-Brozick JE, et al. Mutations in SDHD, a mitochondrial complex II gene, in hereditary paraganglioma. *Science*. 2000;287:848-851.
162. Por YC, Lim DTH, Teoh MK, Soo KC. Surgical management and outcome of carotid body tumours. *Ann Acad Med Singapore*. 2002;31:141-144.
163. Ahuja A, Kumari S. A rare case of malignant metastatic tumor diagnosed on fine-needle aspiration of cervical lymph node. *Cytojournal*. 2019;16:15.
164. Harley RJ, Lee JH, Ostrander BT, et al. Local tumor behavior associated with survival among patients with paraganglioma of the head and neck. *OTO Open*. 2022;6:1-12.
165. Lloyd RV, Osamura RY, Kloppel G, Rosai J, eds. *WHO Classification of Tumours of Endocrine Organs*. IARC Press; 2017.
166. Amar L, Pacak K, Steichen O, et al. International consensus on initial screening and follow-up of asymptomatic SDHx mutation carriers. *Nat Rev Endocrinol*. 2021;17:435-444.
167. Taieb D, Wanna GB, Ahmad M, et al. Clinical consensus guideline on the management of pheochromocytoma and paraganglioma in patients harbouring germline SDHD pathogenic variants. *Lancet Diabetes Endocrinol*. 2023;11:345-361.
168. Kajal S, Kairo AK, Quadri JA, et al. Can superoxide anions predict the malignant potential of carotid body tumor? A pilot study. *Indian J Otolaryngol Head Neck Surg*. 2023;75:1819-1825.
169. Zbaren P, Lehmann W. Carotid paraganglioma with metastases. *Laryngoscope*. 1985;95:450-454.
170. Netterville JL, Reilly KM, Robertson D, Reiber ME, Armstrong WB, Childs P. Carotid body tumors: a review of 30 patients with 46 tumours. *Laryngoscope*. 1995;105:115-126.
171. Naswa N, Kumar A, Sharma P, Bal C, Malhotra A, Kumar R. Imaging carotid body chemodectomas with ⁶⁸Ga-DOTA-NOC PET-CT. *Br J Radiol*. 2012;85:1140-1145.
172. Plouin P-F, Fitzgerald P, Rich T, et al. Metastatic pheochromocytoma and paraganglioma: focus on therapeutics. *Horm Metab Res*. 2012;44:390-399.
173. Niemeijer ND, Alblas G, Van Hulsteijn LT, Dekkers OM, Corssmit EPM. Chemotherapy with cyclophosphamide, vincristine and dacarbazine for malignant paraganglioma and pheochromocytoma: systematic review and meta-analysis. *Clin Endocrinol (Oxf)*. 2014;81:642-651.

174. Joshua AM, Ezzat S, Asa SL, et al. Rationale and evidence for sunitinib in the treatment of malignant paraganglioma/pheochromocytoma. *J Clin Endocrinol Metab.* 2009;94:5-9.
175. O'Kane GM, Ezzat S, Joshua AM, et al. A phase 2 trial of sunitinib in patients with progressive paraganglioma or pheochromocytoma: the SNIPP trial. *Br J Cancer.* 2019;120:1113-1119.
176. Goffredo P, Sosa JA, Roman SA. Malignant pheochromocytoma and paraganglioma: a population level analysis of long-term survival over two decades. *J Surg Oncol.* 2013;107:659-664.
177. Fitzgerald PA, Goldsby RE, Huberty JP, et al. Malignant pheochromocytomas and paragangliomas: a phase II study of therapy with high-dose ^{131}I -metaiodobenzylguanidine (^{131}I -MIBG). *Ann N Y Acad Sci.* 2006;1073:465-490.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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