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Metastases from glomus jugulare tumours

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Abstract

This review describes the features of glomus jugulare tumours with metastases. There were 100 sites of metastasis in the 53 cases previously reported. The sites of metastasis may be summarized as bone (33), lungs (23), lymph nodes (19), liver (nine) and other (16). Metastases presented up to 30 years after the initial treatment. The mean age of patients was 45 years and the sex ratio was approximately two females to one male, with no significant difference compared to non-metastatic tumours. There was a significantly higher incidence of pain and a significantly lower incidence of hearing loss at presentation compared to non-metastatic tumours. The commonest treatment was a combination of surgery and radiotherapy. The duration of symptoms before diagnosis was significantly shorter and the rates of persistent or recurrent local disease and death were significantly higher than for non-metastatic tumours. This review highlights the fact that glomus jugulare tumours are not always benign.

Key words: Glomus jugulare tumour; Neoplasm metastasis

Paraganglionic tissue is a widely dispersed neuroendocrine system. Within the head and neck paraganglia are associated particularly with the parasympathetic nervous system, notably along the glossopharyngeal and vagus nerves and their branches. These collections of paraganglionic tissue are commonly referred to as glomus bodies.[1] The largest collections in the head and neck are the carotid bodies which have a chemoreceptor function. Other collections are found in the jugulotympanic, laryngeal and vagal paraganglia.

Tumours derived from paraganglionic tissue are referred to as paragangliomas. Within the head and neck the commonest paraganglioma is the carotid body paraganglioma or chemodectoma but paragangliomas may arise at any of the other sites where paraganglionic tissue is found as well as sites where such tissue is not normally found. The jugulotympanic paragangliomas may arise from paraganglia along the tympanic branch of the glossopharyngeal nerve (Jacobsen's nerve) or the auricular branch of the vagus nerve (Arnold's nerve). Those arising from the jugular fossa are commonly referred to as glomus jugulare tumours and those arising from the middle ear glomus tympanicum tumours. They have been classified as Fisch types A to D.[2]

This review specifically relates to glomus jugulare tumours. The first report of a glomus jugulare tumour was published in 1945.[3] These tumours present most commonly in women and in the fifth decade. Presenting symptoms vary according to the local structures involved and may include hearing loss, tinnitus, vertigo, otalgia, otorrhoea, haemorrhage, headache and symptoms due to lower cranial nerve palsies.[4] Vasoactive substances may be secreted by these tumours.[5] However, testing for catecholamines or their metabolites in the absence of symptoms or signs of 'vasoactivity' has a very low yield and is not routinely indicated. The main treatment modalities are surgery, radiotherapy or a combination of both.[6]

Paragangliomas have similar histological appearances regardless of site. They are typically composed of polygonal neoplastic chief cells arranged in nests (Zellballen) surrounded by a capillary network, as shown in Figure 1a, although several other patterns have been described.[7] The histological pattern of the tumour may be highlighted with a reticulin preparation, as shown in Figure 1b. Nuclei may show considerable atypia but this is not an indication of malignancy. Tumours often show secondary change with stromal fibrosis and haemorrhage. Immunohistochemistry may demonstrate expression of the neuroendocrine markers neuron specific enolase, chromogranin and synaptophysin in the chief cells of the tumour,[8] as shown in Figure 1c. S100 may be used to demonstrate the sustentacular cells which encircle nests of tumour cells,[9] as shown in Figure 1d. Although some studies have suggested that certain features such as large Zellballen, pleomorphic mitotic cells and focal necrosis may suggest malignant behaviour,[10] other studies conflict and

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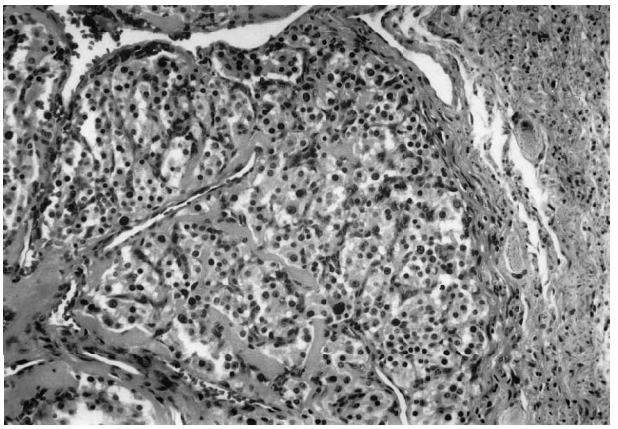

FIG. 1a.

Medium power view of a paraganglioma showing polygonal cells with pale cytoplasm and round nuclei which show some pleomorphism. The tumour has a packeted architecture with groups of cells separated by fine fibrovascular tissue (H & E; × 235).

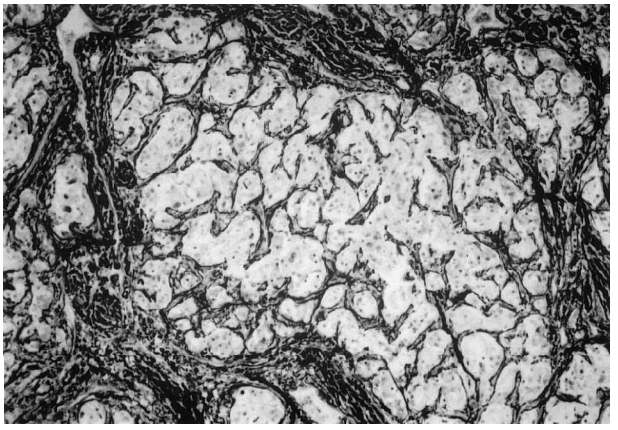

FIG. 1b

The packeted architecture of the tumour is demonstrated most clearly by the use of reticulin preparations which outline the fine connective tissue around the tumour cell lobules (× 59).

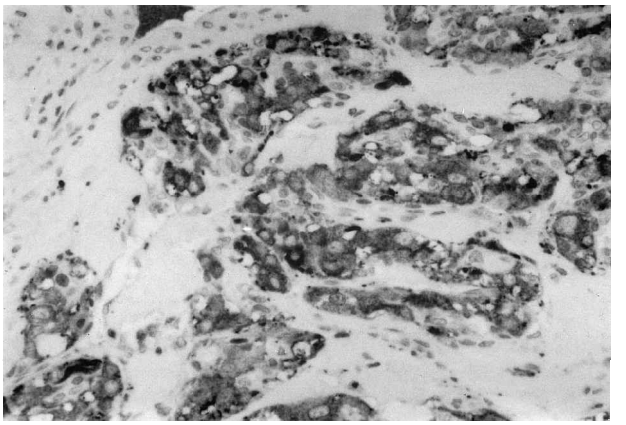

FIG. 1c

Immunocytochemical preparation using an antibody to neuron specific enolase demonstrates expression of this antigen within the cytoplasm of the tumour cells (× 235).

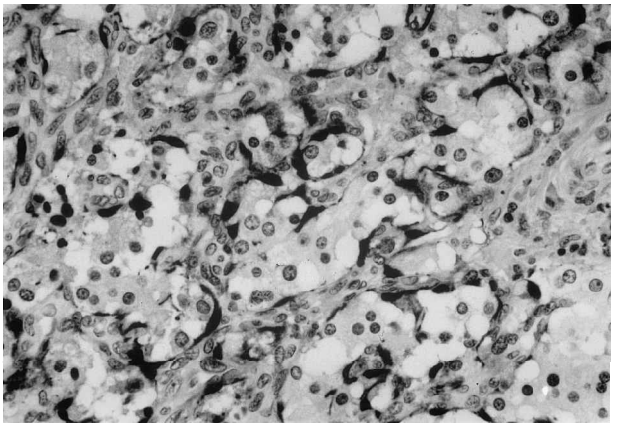

FIG. 1d

Immunocytochemical preparations using an antibody to S100 protein. This labels the cytoplasm and nuclei of sustentacular cells (darkly stained) which are present particularly at the margins of the tumour lobules and have a somewhat elongated structure. The polygonal tumour cells are themselves negative for this protein (× 118).

prediction of behaviour on the basis of histology is unreliable at present.[7] Recent studies have examined the utility of immunohistochemical markers.[11] However, at present the diagnosis of malignancy is made by the presence of metastases.

The growth of glomus jugulare tumours is usually slow and one case has been reported as surviving for 60 years without treatment.[12] However, local invasion is common and spread upwards into the cranial cavity or downwards into the neck may occur.[13] Metastases from glomus jugulare tumours are relatively rare with an estimated incidence of between one and four per cent.[14,15] Because metastatic glomus tumours may be preferentially reported and because some reports may be multicentric rather than metastatic tumours, this may be an overestimate.[16]

A malignant glomus jugulare tumour with cervical lymph node metastases is presented elsewhere in this issue.[17] This case stimulated a review of the literature relating to metastatic glomus jugulare tumours which is to our knowledge the most comprehensive such review in the literature. The purpose of this review was to determine the characteristics of metastatic glomus jugulare tumours (including sites of metastasis, age and sex distribution, presenting features, treatments used, natural history of disease, local recurrence rate and death rate) and to compare the characteristics of metastatic and non-metastatic glomus jugulare tumours.

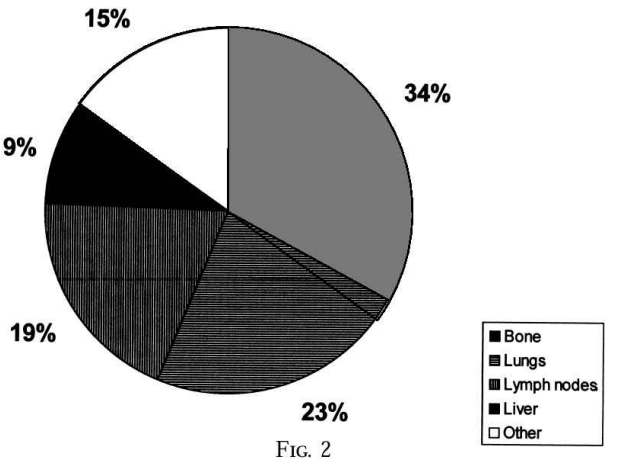

FIG. 2

Metastasis sites.

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TABLE I
REPORTS OF METASTATIC GLOMUS JUGULARE TUMOURS

Author	Site of metastasis	Tumour histology	Metastasis histology
Anthanassopoulou *et al.*,[20] 1993	Lungs, pleura	yes	yes
Brown,[15] 1985	Lungs		
Brown,[15] 1985	Liver		
Bundgaard *et al.*,[21] 1989	Lungs		
Davis *et al.*,[22] 1980	Lungs	yes	yes
El Fiky and Paparella,[23] 1984	Lymph nodes, bone marrow, epicardium, liver, pancreas, ribs, vertebrae, skull, pelvis	yes	yes
Gabriel *et al.*,[24] 1995	Lungs, liver, sacrum	yes	yes
Harrison,[25] 1974	Cervical spine (C5)		
Hassan,[26] 1957	Neck of femur	no	no
Henson *et al.*,[13] 1953	Liver, spleen, lungs	yes	yes
Hoople *et al.*,[27] 1958	Cervical lymph node, lungs	yes	yes
Johnston and Symon,[28] 1992	Mediastinal lymph nodes	yes	no
Johnstone *et al.*,[29] 1990	Cervical lymph nodes; cervical/thoracic/lumbar spine	yes	yes
Kupper and Heuber,[30] 1970	Liver, pleura, vertebral bodies	yes	yes
Lahey and Warren,[31] 1951	Cervical lymph node		
Lattes and Waltner,[32] 1949	Liver	yes	yes
Lederer *et al.*,[33] 1958	Liver, lungs	yes	yes
Lennert,[34] 1964	Cervical lymph nodes	yes	yes
Lennert,[34] 1964	Cervical lymph nodes	yes	yes
Marshall and Horn,[35] 1961	Cervical lymph nodes	yes	
McCabe and Fletcher,[36] 1969	Lung, skeletal		
McCabe and Fletcher,[36] 1969	Lung, skeletal		
McCabe and Fletcher,[36] 1969	Lung		
McMeekin *et al.*,[37] 1969	Lungs, hilar lymph nodes	yes	yes
Meessen,[38] 1963	Cervical lymph nodes, lungs, liver, bowel	yes	yes
Monroe and Lore,[39] 1977	Chest wall, back, neck of femur, head of femur	yes	yes
Moore *et al.*,[40] 1973	Lungs	yes	no
Osborn and Mojtahedi,[41] 1986	Cervical spine (C7)	yes	yes
Poppen and Riemenschneider,[42] 1951	Cervical lymph nodes	yes	yes
Powell *et al.*,[43] 1992	Cervical lymph nodes		
Pryse-Davies *et al.*,[44] 1964	Cervical lymph node	yes	yes
Rauch,[45] 1968	Parotid lymph nodes	yes	no
Rauch,[45] 1968	Brain	yes	
Rosenwasser,[46] 1958[47] 1968	Thoracic spine (T7), rib, floor of nose	yes	yes
Rosenwasser,[46] 1958,[47] 1968,[48] 1969,[49] 1973	Thoracic spine (T10), rib	yes	no
Rosenwasser,[47] 1968,[48] 1969	Spine, rib		
Rosenwasser,[47] 1968,[48] 1969	Lung		
Rosenwasser,[47] 1968,[49] 1969,[49] 1973	Spine, rib		
Rosenwasser,[47] 1968,[48] 1969,[49] 1973	Lungs		
Rosenwasser,[47] 1968,[49] 1973	Spine, rib		
Rosenwasser,[50] 1974	Lung, retroperitoneal space, spine		
Sakakura *et al.*,[51,] 1986	Lung, pancreas, spinal epidural space, bone	yes	yes
Saldana *et al.*,[52] 1973	Ribs		
Schwartz and Israel,[53] 1983,[54] Bojrab *et al.*,[54] 1991	Lungs, cervical lymph nodes	yes	yes
Shambaugh,[55] 1955	Cervical lymph nodes		
Shapiro and Neues,[56] 1964	Cervical lymph nodes, lung	no	no
Shepard *et al.*,[57] 1988	Lungs, thoracic spine (T6), sacrum, ileum	yes	yes
Spector *et al.*,[58] 1973	Posterior neck, nasopharynx	yes	
Sykes and Ossoff,[58] 1986	Cervical spine	yes	
Takahashi *et al.*,[60] 1987	Cervical lymph node	yes	yes
Tamari *et al.*,[61] 1951	Liver, lungs	yes	
Taylor *et al.*,[62] 1965	Lungs	yes	yes
Winship *et al.*,[63] 1948,[64] 1952[62]	Cervical lymph nodes	no	no

Review of the literature revealed 53 previous reports of glomus jugulare tumours with metastasis. Not included is a series which reported metastasis to liver, lung, spleen or bones in six out of a series of 167 cases but gave no further details[18] and a report of a glomus jugulare tumour with multiple central nervous system metastases which was subsequently re-interpreted as meningeal sarcomatosis.[19] The information given in these reports is summarized in Table II, in which an empty box denotes that an item of information was not given.

There were 100 sites of metastasis in the 53 cases. These may be summarized as: bone (33), lungs (23), lymph nodes (19), liver (nine) and other (16), as shown in Figures 2 and Table II. Further details of the sites of metastasis are given in Tables III, IV and V.

Where information was given, the diagnosis of glomus jugulare tumour was histologically confirmed in 92 per cent (33 of 36 cases) and the diagnosis of metastasis was histologically confirmed in 77 per cent (24 of 31 cases). In other cases these diagnoses were made on clinical or radiological grounds.

A comparison was made between the characteristics of cases in this series of metastatic glomus jugulare tumours and in the largest reported series of non-metastatic glomus jugulare tumours.[4] It should be noted that these are the characteristics of

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TABLE I (contd)
REPORTS OF METASTATIC GLOMUS JUGULARE TUMOURS

Age	Sex	Surgery	Radio-therapy	Interval between onset of symptoms and start of treatment	Interval between start of treatment and presentation of metastasis	Persistent or recur-rent local disease	Death	Follow up (after Rx)
43	F	yes	yes	2 years	9 months	yes	no	9 months
		yes	yes			yes	yes	2 years
38	M	yes	yes	6 months	18 months	yes	no	5 years 9 months
40	M	yes	yes	5 years	immediate	yes	yes	3 years 7 months
47	F	no	yes		17 years	yes	yes	20 years
50	F	yes	yes	2 years	11 years	yes	no	12 years 6 months
17	F	yes	no	9 months	3 years 3 months	yes	yes	3 years 3 months
49	M	yes	yes	4–5 months	4 months	yes	yes	5 months
49	F	yes	yes	6 months	7 years	yes	yes	7 years
38	F	yes	yes	2 years 6 months	immediate	yes	no	21 years
23	M	yes	no	6 weeks	6 weeks	yes	yes	6 weeks
71	F	no	yes	3 months	9 months	yes	yes	9 months
73		yes	no		9 days	yes	yes	9 days
61	F							
51	F	yes	no	7 years		yes	no	5 years
30	M	yes	yes				yes	1 year
18	M	yes	yes				yes	9 months
11	F	yes	yes				yes	1 year
34	F	yes	yes	8 years	6 months	yes	yes	6 months
72	F	yes	yes	10 years	30 years	yes	yes	30 years
45	M	no	yes	2 months	immediate	yes	yes	2 months
63	F	yes	no		22 years	yes	yes	23 years
47	F	yes	no		4 years	yes	no	4 years
63	F	yes	no	3 years	immediate	yes	yes	2 months
51	F	no	yes	12 months	1 month	yes	yes	1 month
25	M	yes	yes	12 months	12 months	yes	no	15 months
26	M	yes	no		4 months		no	4 months
53	F	no	yes		3 years	yes	no	3 years
55	M	no	yes	2 months	immediate	yes	yes	6 months
57	F	no	yes			yes	yes	14 years
61	F	no	no			yes	yes	8 years
57	M	no	yes				yes	6 months
21	F	yes	no			yes	yes	2 years
48	F	yes	yes				yes	14 years
	F						yes	25 years
37	M	yes	yes		6 years	yes	yes	10 years
46	M							
25	F	yes	no	2 years	3 years	yes	no	13 years
45	F	yes	no	1–2 years	9 months	yes	yes	12 months
8	M	yes	yes	6 months	13 months	yes	yes	18 months
42	F	yes	yes	2 years	6 years 9 months	no	no	11 years
		no	yes	12 months				12 months
		no	no			yes	no	
60	F	yes	no	4 years	immediate		no	
73	F	yes	no	4 months	9 days		yes	9 days
52	F	yes	yes	3 years	12 years	yes	yes	12 years
54	F	no	yes	17 years	12 years	yes	no	17 years

reported metastatic and non-metastatic glomus jugulare tumours and may not be representative of glomus tumours in the general population. Fisher's Exact Test was used for statistical analysis and, in view of the number of statistical tests performed (22), a p value of less than 0.01 was taken as significant. The results are shown in Table IV.

The mean age of patients in this series of metastatic tumours was 45 (range eight to 73) as compared with 49 (range 17 to 85) in the largest reported series of non-metastatic tumours. It was not possible to compare these figures statistically because no measure of spread was given for the non-metastatic group.

TABLE II
SITES OF METASTASIS

Site	Number of cases
Bone	33
Lungs	23
Lymph nodes	19
Liver	9
Other	16
Total	100

TABLE III
SITES OF BONE METASTASIS

Site	Number of Cases
Vertebrae	17
Ribs	7
Pelvis	1
Ileum	1
Head of femur	1
Neck of femur	2
Skull	1
Unspecified	3
Total	33

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TABLE IV
SITES OF LYMPH NODE METASTASIS

Site	Number of Cases
Cervical	15
Parotid	1
Mediastinal	1
Hilar	1
Unspecified	1
Total	19

TABLE V
SITES OF OTHER METASTASIS

Site	Number of Cases
Back	1
Bone marrow	1
Bowel	1
Brain	1
Chest wall	1
Epicardium	1
Floor of nose	1
Nasopharynx	1
Pancreas	2
Pleura	2
Posterior neck	1
Retroperitoneal space	1
Spinal epidural space	1
Spleen	1
Total	16

There were 29 females and 14 males (sex not stated in 10 cases) in this series. A female predisposition is also seen in non-metastatic tumours with 209 females and 59 males (sex not stated in 48 cases) in the largest series. There was no statistically significant difference between the sex ratios in the two groups.

Symptoms, signs and investigations at presentation were compared to those of the non-metastatic tumours, as shown in Table VI. Sufficient information for analysis was given in 16 of the 53 metastatic cases and 277 of the 316 non-metastatic cases. The only statistically significant differences between the two groups were a higher incidence of pain and a lower incidence of hearing loss in the metastatic cases compared to the non-metastatic cases (p values 0.000 and 0.009 respectively). In the metastatic cases the higher incidence of pain may be due to the fact that they are more invasive and the lower incidence of hearing loss may be due to the fact that cases with hearing loss present at an earlier stage, before the development of metastases.

TABLE VI
CHARACTERISTICS OF METASTATIC AND NON-METASTATIC GLOMUS JUGULARE TUMOURS

	Metastatic tumours	Non metastatic tumours	p value (Fisher's Exact Test)
General			
Number of cases	53	316	NA
Mean age	45	49	NA
Female : male ratio	29 : 14	209 : 59	0.173
Symptoms			
Hearing loss	38%	91%	0.000*
Tinnitus	25%	52%	0.041
Otalgia	63%	28%	0.009*
Otorrhoea	25%	33%	0.595
Haemorrhage	25%	16%	0.309
Vertigo	25%	25%	1.000
Facial weakness	44%	33%	0.417
Signs			
Normal eardrum	0%	3%	1.000
Red or bulging eardrum	13%	30%	0.165
Polypoid mass in ear canal	44%	67%	0.063
VII nerve palsy	44%	34%	0.428
IX nerve palsy	25%	21%	0.753
X nerve palsy	44%	26%	0.147
XI nerve palsy	31%	19%	0.328
XII nerve palsy	31%	22%	0.368
Investigations			
Hearing loss – sensorineural	19%	44%	0.067
Hearing loss – conductive	13%	22%	0.536
Hearing loss – mixed	0%	2%	1.000
Hearing loss – unspecified	25%	32%	0.324
Natural history of disease			
Mean interval between onset of symptoms and start of treatment	2 years 10 months	6 years	NA
Mean interval between start of treatment and presentation of metastases	4 years 6 months	NA	NA
Prognosis			
Rate of persistence or recurrence of local disease	97%	51%	0.000*
Death rate	68%	10%	0.000*
Mean duration of follow up	6 years 2 months	NI	NA

NA = not applicable.
NI = no information
* = p value less than 0.01.

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In the 44 metastatic cases where information was given, the main treatment was surgery and radiotherapy in 43 per cent (19 cases), surgery alone in 30 per cent (13 cases), radiotherapy alone in 23 per cent (10 cases) and no treatment in five per cent (two cases).

The mean interval between the onset of symptoms and the start of treatment was two years 10 months (range six weeks to 17 years) in the metastatic cases compared to six years (range two weeks to 42 years) in the non-metastatic cases. It was not possible to compare these figures statistically because no measure of spread was given for the non-metastatic group. The mean interval between the start of treatment and the presentation of metastasis was four years six months (range 0 to 30 years). Where information was given, 19 per cent (six of 32 cases) of metastases were diagnosed at the time of treatment and 31 per cent (11 of 36 cases) were diagnosed at post mortem.

Where information was available, the rate of persistence or recurrence of local disease was 97 per cent (34 of 35 cases) in the metastatic cases compared to 51 per cent (105 of 204 cases) in the non-metastatic cases. The death rate was 68 per cent (30 of 44 cases) compared to 10 per cent (32 or 316 cases) in the non-metastatic cases. Both of these differences were statistically significant (p values 0.000). The mean duration of follow-up was six years two months after treatment (range nine days to 30 years) in the metastatic cases and was not given in the non-metastatic cases.

In summary, this review describes the features of glomus jugulare tumours with metastasis. Metastases have presented in a wide variety of sites, the commonest of which include lungs, cervical lymph nodes, vertebrae, ribs and liver, and have presented up to 30 years after initial treatment. No significant difference between the age and sex distribution of metastatic and non-metastatic tumours was demonstrated. The commonest presenting features of metastatic tumours are otalgia, hearing loss, otorrhoea, haemorrhage, vertigo, a polypoid mass in the ear canal and lower cranial nerve palsies. There is a significantly higher incidence of pain and lower incidence of hearing loss in metastatic compared to non-metastatic tumours. The commonest treatment is a combination of surgery and radiotherapy. Metastatic tumours are a more aggressive subset with a shorter duration of symptoms before diagnosis and higher rates of persistent or recurrent local disease and death. This review highlights the fact that glomus jugulare tumours are not always benign.

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