

REVIEW

Neuroendocrine tumours of the head and neck: anatomical, functional and molecular imaging and contemporary management

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Abstract

Neuroendocrine tumours (NETs) of the head and neck are rare neoplasms and can be of epithelial or non-epithelial differentiation. Although the natural history of NETs is variable, it is crucial to establish an early diagnosis of these tumours as they can be potentially curable. Conventional anatomical imaging and functional imaging using radio-nuclide scintigraphy and positron emission tomography/computed tomography can be complementary for the diagnosis, staging and monitoring of treatment response. This article describes and illustrates the imaging features of head and neck NETs, discusses the potential future role of novel positron-emitting tracers that are emerging into clinical practice and reviews contemporary management of these tumours. Familiarity with the choice of imaging techniques and the variety of imaging patterns and treatment options should help guide radiologists in the management of this rare but important subgroup of head and neck neoplasms.

Keywords: Neuroendocrine carcinoma; head and neck malignancy; magnetic resonance imaging; positron emission tomography/computed tomography; somatostatin receptor scintigraphy; [¹²³I]meta-iodobenzylguanidine scintigraphy.

Introduction

Neuroendocrine tumours (NETs) of the head and neck region are a rare and diverse group of tumours. A wide range of nomenclature has been used to describe these neoplasms, with limited consensus^[1,2]. NETs arising in the head and neck can be divided into two broad groups: (1) those with epithelial differentiation including typical carcinoid (well differentiated), atypical carcinoid (moderately differentiated, including large cell carcinoma) and small cell carcinomas (poorly differentiated, including composite small cell carcinoma), and (2) neurally derived tumours, including paragangliomas and olfactory neuroblastomas^[3]. Merkel cell carcinoma is an uncommon primary cutaneous small cell cancer, with a predilection for the head and neck region. Rarely, neuroendocrine cancers from non-head and neck sites can metastasize to the head and neck region; this should be considered in the differential diagnosis

particularly if there is a previous history of neuroendocrine cancer^[4]. For the purposes of this article, medullary thyroid cancer and other neuroectodermal tumours, including Ewing sarcoma, primitive neuroectodermal tumours and mucosal melanomas, which have been extensively reviewed elsewhere, are not considered further.

The aim of this article is to discuss current anatomical and functional imaging techniques in head and neck NETs, explore novel molecular imaging techniques, particularly those using highly specific positron-emitting radiopharmaceuticals and the role they may play in the future, describe and illustrate the multimodality imaging appearances of head and neck NETs and review contemporary patient management in each of the different tumour types. Anatomical (cross-sectional) and functional imaging using single photon and positron-emitting radiopharmaceuticals have distinct and complementary roles in the evaluation of head and neck NETs.

An understanding of the range of NETs found in the head and neck with their highly variable natural history, in conjunction with a familiarity with the range of imaging and treatment options available, will be invaluable to help guide radiologists in the management of these rare tumours.

Imaging techniques

Anatomical imaging

Computed tomography (CT) and magnetic resonance imaging (MRI) are the most commonly used techniques when imaging head and neck tumours. Ultrasonography (US) is also widely used as the initial imaging technique in the assessment of neck masses, largely due to its availability and avoidance of ionizing radiation, but it has a relatively limited role in this patient cohort with the exception of patients with head and neck paragangliomas.

Multislice CT facilitates rapid and detailed evaluation of the entire neck with the ability to produce multiplanar reformatted images. A bone algorithm, in addition to a standard soft tissue algorithm, is particularly important for tumours that may involve the skull base. Intravenous contrast administration is essential to delineate the mass, or lymphadenopathy, from adjacent normal structures. Enhancement patterns may be helpful in characterizing some masses, such as paragangliomas.

MRI has superior soft tissue resolution, which makes it an ideal technique for imaging head and neck masses. It is superior to CT in defining intracranial extension of tumours. A head or neck coil is usually required and generally the study should include a combination of axial and coronal T2-weighted fast spin echo (FSE) sequences, T2-weighted fat suppression or inversion recovery sequences and an unenhanced T1-weighted FSE or spin echo (SE) sequence^[5]. Further fat-saturated T1-weighted SE sequences after gadolinium administration often improve characterization of the mass. The addition of contrast-enhanced MR angiography (CE-MRA) has incremental value in patients with head and neck paragangliomas^[6]. There is emerging evidence that diffusion-weighted imaging (DWI) may also be a diagnostic adjunct in this patient cohort but data are inconclusive at present^[7].

Functional Imaging

Functional imaging using single photon radiopharmaceuticals has been used to evaluate head and neck NETs for many years. These techniques are often complementary to anatomical imaging, as a result of their superior specificity and the ability to perform total-body imaging, which can identify multifocal disease or distant metastases that may otherwise evade detection. More recently, advances in imaging hardware technology have led to the development of hybrid scanners capable of performing

anatomical and functional imaging sequentially in the same session. Single photon emission computed tomography (SPECT)/CT has many established clinical applications in the field of oncology, particularly in patients with endocrine malignancies^[8]. The use of SPECT/CT in patients with head and neck NETs provides incremental diagnostic value with convenient and accurate co-registration of anatomical and functional data.

There have also been stepwise advances in the potential range of functional imaging techniques that can be used to evaluate patients with NETs. In particular, there has been significant development of a range of highly sensitive and specific positron-emitting radiopharmaceuticals, which show great promise as highly accurate molecular imaging probes for detection and characterization of NETs^[9]. There have been simultaneous advances in positron emission tomography (PET) scanner technology and combined PET/CT scanners are now widely available.

Tracers used in functional and molecular imaging of head and neck NETs target three distinct cellular aspects:

- (1) Somatostatin receptors: these are frequently overexpressed by NETs and the conventional agent used is [¹¹¹In]DTPA-octreotide ([¹¹¹In]pentetreotide, OctreoScan). PET tracers targeting this receptor include ⁶⁸Ga-labelled somatostatin analogue peptides (⁶⁸Ga-DOTA-TOC, ⁶⁸Ga-DOTA-NOC, ⁶⁸Ga-DOTA-TATE)^[10].
- (2) Catecholamine synthesis and storage pathways: these are relatively unique to neural crest tumours and the conventional scintigraphic technique uses [¹²³I]- or [¹³¹I]-meta-iodobenzylguanidine (MIBG). Novel PET tracers that also target this pathway include [¹⁸F]fluorodopamine (FDA) and [¹⁸F]fluorodihydroxyphenylalanine (FDOPA)^[11].
- (3) Glucose metabolism: [¹⁸F]fluoro-2-deoxy-D-glucose (FDG) is the most widely used PET radiotracer in clinical use today. The metabolism and biodistribution of FDG have been extensively described. FDG is a non-physiologic glucose analogue accumulated in tumour cells with an overexpression of glucose transporters, which undergoes phosphorylation and is trapped intracellularly. Uptake of FDG is inversely related to the degree of tumour differentiation and correlates with biological behaviour. FDG-PET/CT has a specific role in imaging poorly differentiated NETs with more biologically aggressive behaviour.

There is an emerging treatment paradigm for NETs guided by molecular imaging using some of the diagnostic radionuclides described above. In patients with inoperable or metastatic NETs demonstrating receptor positivity, a possible therapeutic option is to replace the diagnostic radionuclide with a therapeutic one. For example, ¹¹¹In or ⁶⁸Ga can be replaced with ⁹⁰Y or ¹⁷⁷Lu (both emit beta radiation) and labelled with the same

peptides. Therefore, molecular imaging and diagnosis of the disease can be effectively followed by personalized treatment using the same molecular imaging vectors, a process referred to as theranostics. Consequently, somatostatin receptor imaging particularly using ^{68}Ga peptide PET tracers shows great promise in guiding individualized patient dosimetry by pre- or posttherapeutic imaging and assessment of therapy response using quantitative imaging^[12]. There is a paucity of data on the use of this treatment in patients with head and neck NETs at present but there is a substantial evidence base on its efficacy in more common NETs^[13].

Laryngeal neuroendocrine carcinoma

Epithelial malignancies with neuroendocrine differentiation can occur in the larynx, as in any other organ^[14]. True laryngeal NETs are a rare and heterogeneous group. Laryngeal NETs originate from laryngeal mucosal pluripotent cells and account for less than 1% of laryngeal tumours. There is a male predilection (male/female ratio of 3:1)^[14-16]. As with squamous cell carcinoma of the larynx, smoking is a recognized risk factor^[17]. The typical clinical presentations of these tumours are hoarseness of voice and dysphagia.

Histological identification of different tumour types is important to understand the tumour behaviour, prognosis and treatment planning^[18]. Atypical carcinoid is the most frequent type^[14,19]. Both typical and atypical carcinoid tumours commonly involve the supraglottic compartment of the larynx, whereas small cell neuroendocrine carcinoma typically has a more homogeneous involvement of the larynx^[20,21]. Paragangliomas are of neural origin and rarely arise in the larynx; they are discussed later in this review.

Anatomical imaging of laryngeal NETs typically demonstrates an enhancing mass arising from the vocal cords (Fig. 1). CT and MRI are useful to demonstrate local extension of the disease. The findings are non-specific and cannot lead to a definitive diagnosis. Small primary NETs may only be localized by endoscopic assessment and not by conventional anatomical imaging.

Due to the rare nature of laryngeal NETs, there is a paucity of data on the value of functional imaging with conventional scintigraphic agents and no data to guide the use of emerging PET tracers described above. There may be a role for FDG-PET/CT in patients with small cell carcinoma of the larynx to facilitate more accurate staging of the disease and assessment of prognosis^[22,23].

The management of laryngeal NETs is determined by histological type along with clinical and radiological staging. The preferred treatment options for localized disease are:

- (1) Carcinoid tumours of the larynx: surgical excision is the treatment of choice for localized carcinoid tumours of the larynx; a subtotal laryngectomy



Figure 1 Supraglottic neuroendocrine carcinoma. Axial contrast-enhanced CT demonstrates asymmetrical thickening and enhancement of the right supraglottic soft tissues (white arrow). Oedema within the prelaryngeal subcutaneous tissues is secondary to recent radiotherapy.

may be suitable depending on tumour size. Lymph node metastases are not usually seen, and hence a neck dissection is not required^[19]. Radiotherapy is not considered an effective modality of treatment^[1].

- (2) Atypical carcinoid tumours of the larynx: surgical excision is the treatment of choice for atypical carcinoids. By contrast with carcinoid tumours, the incidence of neck node metastases is high^[19,24] and an elective neck dissection is justified. Radiotherapy and chemotherapy have not been considered as effective treatment modalities^[1,24] although this has been challenged by a small more recent series^[25].
- (3) Small cell tumours of the larynx: the prognosis of these tumours is very poor, with over 90% of patients developing distant metastatic disease^[26]. It can be considered a systemic disease in a similar manner to small cell lung cancer. Treatment is with a combination of chemotherapy and radiotherapy.

Non-laryngeal neuroendocrine carcinoma

In the head and neck region, NETs are most commonly found in the larynx. Non-laryngeal NETs of the head and

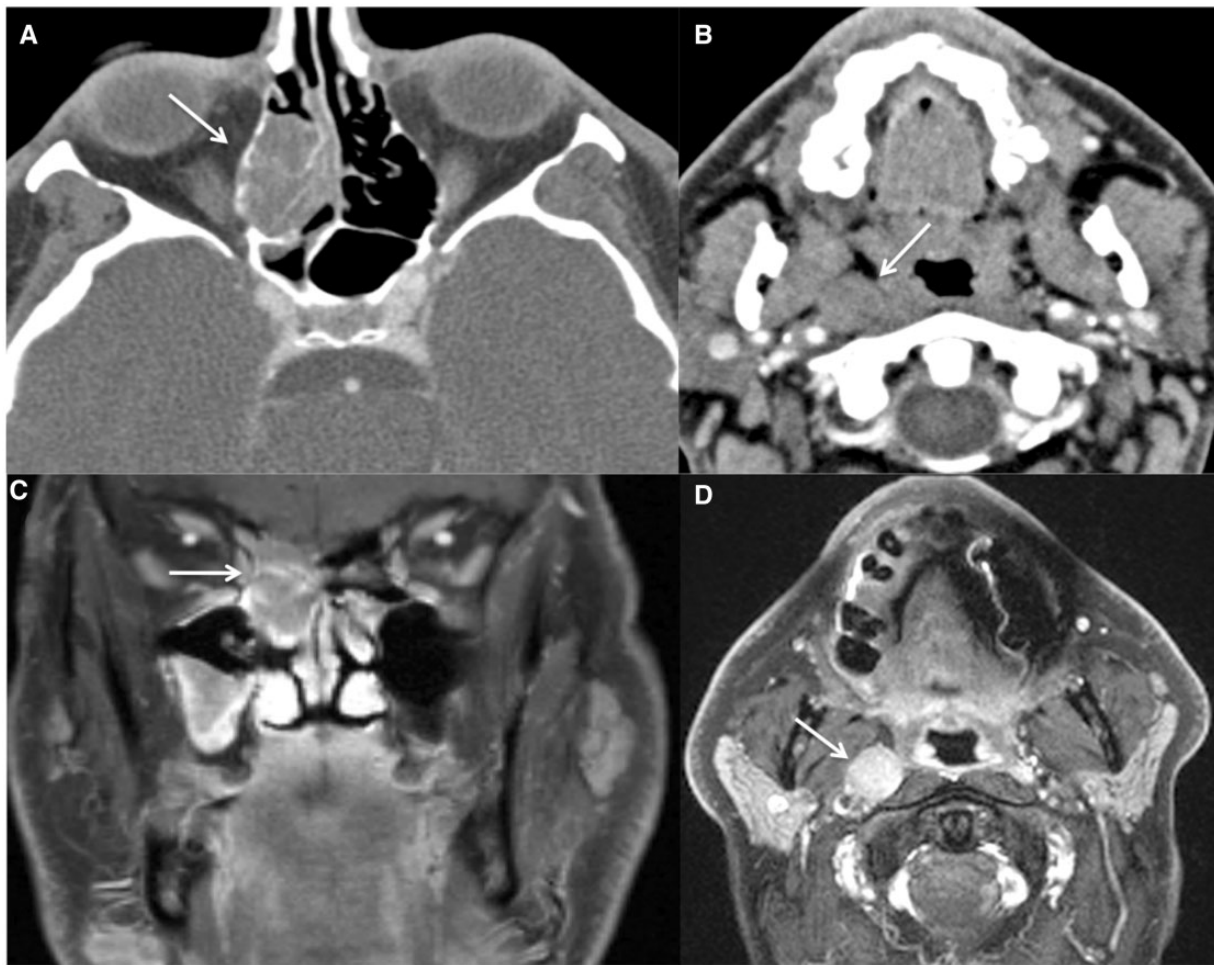


Figure 2 Right ethmoid sinus neuroendocrine carcinoma with nodal spread. (A) Axial contrast-enhanced CT and (C) coronal short tau inversion recovery MRI demonstrates the NET (white arrows) centred in the right ethmoidal complex without tumour extension outside the ethmoidal air cells; there is associated expansion of the sinus and bony erosion best appreciated on CT. (B) Axial contrast-enhanced CT and (D) axial fat-suppressed T1-weighted image on Ga MRI showing a right retropharyngeal lymph node (white arrows), which is much more conspicuous on MRI.

neck are sparsely reported in the literature, occurring most commonly in the paranasal sinuses^[27]. NETs can rarely arise in other sites, including the salivary glands and mucosa^[2]. Like laryngeal NETs, classification is based on the degree of tumour differentiation. Correct pathological classification is challenging; for example in the paranasal sinuses, sinonasal neuroendocrine cancers of epithelial origin must be differentiated from sinonasal undifferentiated carcinomas and olfactory neuroblastomas. Large cell neuroendocrine cancers, with pathological features similar to those arising in the lung, have been reported in salivary glands and arising from the mucosa^[2].

Paranasal sinus neuroendocrine cancer represents only about 5% of malignancies arising in this site, and demonstrate aggressive behaviour with a propensity for regional and distant metastases^[28]. The ethmoid sinuses and nasal cavity are the most common sites of origin within

the paranasal sinuses^[29]. Presenting symptoms overlap with those of benign sinus disease, including epistaxis and nasal obstruction. Partly as a result, presentation is typically with advanced disease^[28,29]. Defining an optimal treatment strategy is currently impossible due to the lack of data, with surgery, radiotherapy and chemotherapy all potential options. The use of imaging to define adverse features including skull base involvement helps guide an individualized choice of treatment. Regional recurrence rates, reported to be in the order of 25%^[28], mandate careful imaging assessment and consideration of prophylactic treatment of the node-negative neck.

Anatomical imaging typically demonstrates a heterogeneously enhancing mass within one of the paranasal sinuses with underlying bony destruction and extension into the adjacent anatomical spaces (Fig. 2). Appearances are often non-specific but the presence of expansion as well as erosion of sinus walls is more

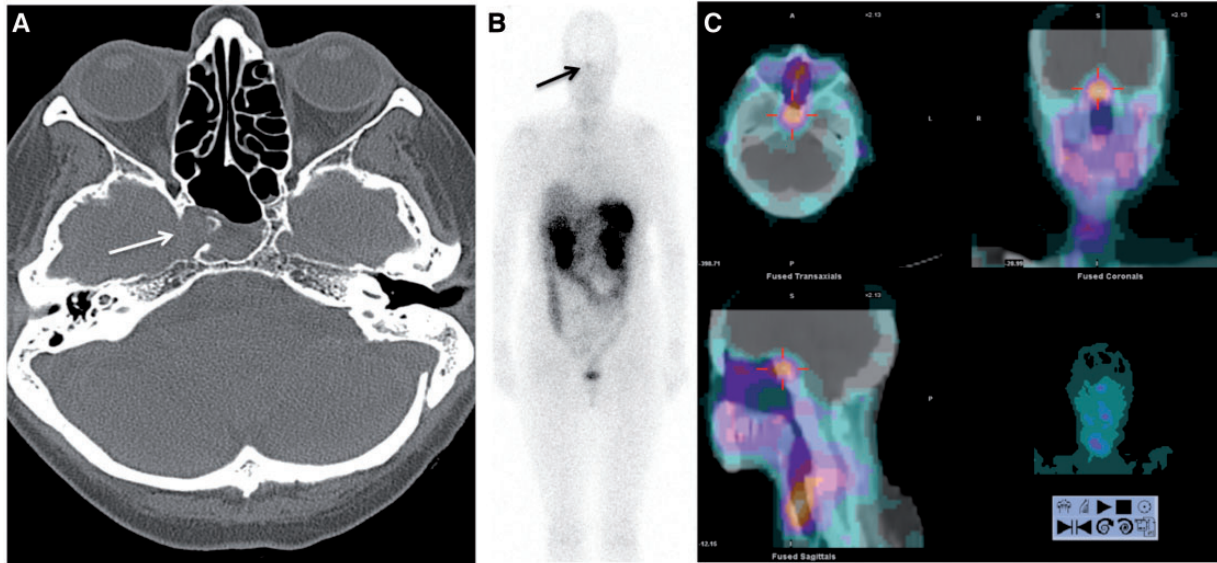


Figure 3 Sphenoid sinus neuroendocrine carcinoma. (A) Axial CT (bone windows) demonstrates an expansile soft tissue mass within the right side of the sphenoid sinus causing erosion of the right lateral wall of the sphenoid sinus (white arrow) extending into the petrous temporal bone. (B) Anterior view from a whole-body planar [^{111}In]DTPA-octreotide scintigram showing low-grade tracer uptake in the region of the right sphenoid sinus (black arrow). (C) Axial, coronal and sagittal fused SPECT/CT images from the same study confirm that there is abnormal octreotide uptake within the sphenoid sinus NED (red cross-hairs).

suggestive of a NET than the altogether more common squamous cell carcinoma^[27]. Somatostatin receptor scintigraphy (SRS) improves specificity and positive cases are usually well-differentiated/moderately differentiated tumours and have better clinical outcome with treatment (Fig. 3). Conversely, lack of uptake on octreotide scintigraphy does not exclude the diagnosis. There are no data in the literature on the use of other functional imaging techniques in this rare subtype of head and neck NETs.

Paragangliomas of the head and neck

Paragangliomas are rare vascular tumours accounting for less than 1% of head and neck tumours^[30]. These neuroectodermal origin tumours arise from a group of tissues (paraganglia), which in the head and neck region migrate along the branchiomeric (of the branchial mesoderm) distribution. Paragangliomas within the head and neck arise mainly from four primary sites: the carotid body at the common carotid artery bifurcation (carotid body tumours), the jugular foramen (glomus jugulare), along the vagus nerve (glomus vagale), and from the tympanic branch of the ascending pharyngeal artery within the middle ear (glomus tympanicum). Other sites, including the larynx^[1], are rare. Median age at diagnosis is around 50 years, although paragangliomas can present at any age. Most paragangliomas are sporadic, with only 7–9% having a familial cause^[31]. Presenting symptoms are typically due to cranial nerve dysfunction and/or a slowly enlarging neck mass. Only 2–5% of paragangliomas

secrete catecholamines^[32] and less than 5% of paragangliomas are malignant^[33]. Malignancy is defined by the presence of regional or distant metastases and cannot be predicted histologically^[34]. Biopsy is not usually advised due to the risk of bleeding, and appropriate radiology is essential for diagnosis.

Paragangliomas demonstrate early neural or blood vessel involvement and a propensity for skull base invasion and intracranial involvement. CT is the study of choice to investigate bone involvement, whereas MRI defines soft tissue detail, intracranial, neural and dural involvement. On MRI, all paragangliomas exhibit a high signal on T2-weighted imaging and a low signal on T1-weighted imaging (Fig. 4). As with CT, they demonstrate avid contrast enhancement. The classic salt and pepper appearance seen on MRI relates to the presence of hyperintense foci (salt) interspersed with multiple areas of signal void (pepper) due to high flow in vascular channels (Fig. 4)^[35]. This feature is only reliably seen in tumours over 1 cm in size^[36].

Despite early reports of the excellent diagnostic performance of MIBG scintigraphy in the evaluation of paragangliomas, the sensitivity of this technique has sequentially decreased over time as more experience has been accumulated^[37]. The reported sensitivity varies between 55% and 85%, although the specificity is much higher at 95%. MIBG scintigraphy remains useful in the diagnostic work-up of patients with paragangliomas due to the wide availability of the technique and the ability to identify patients who may be potential

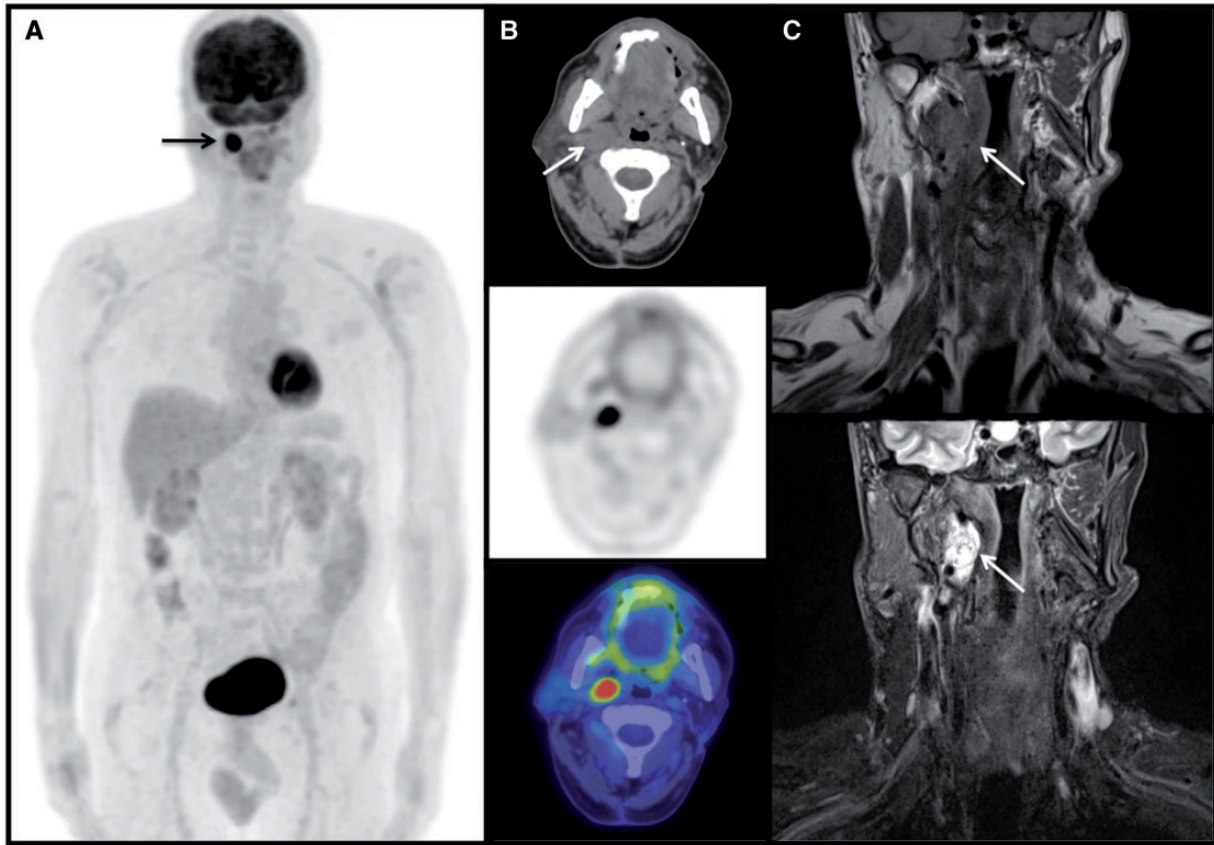


Figure 4 Glomus vagale in a patient with SDHD genetic mutation. (A) Maximum intensity projection PET image from a half-body FDG-PET/CT scan demonstrates avid FDG uptake within the right parapharyngeal region (black arrow). (B) Axial images from the same study: CT (top), PET (middle) and fused PET/CT (bottom) showing an FDG-avid paraganglioma within the right posterior parapharyngeal space (white arrow). (C) Coronal T1 (top) and short tau inversion recovery (bottom) images from an MRI examination in the same patient demonstrates a 2.5-cm mass situated immediately posterior to the carotid vessels in the right parapharyngeal space consistent with a glomus vagale tumour (paraganglioma). The bottom image shows a heterogeneous signal within the lesion with high signal interspersed with signal void, the so-called salt and pepper appearance.

candidates for radionuclide therapy with [^{131}I]MIBG^[38]. As a cautionary note, however, a recent study reported a high incidence of false-negative MIBG scans in patients with malignant head and neck paragangliomas that subsequently metastasized; this was particularly prevalent in patients with the familial form of the disease^[39].

SRS with [^{111}In]DTPA-octreotide has been reported to have a higher sensitivity than MIBG imaging in head and neck paragangliomas^[40]. Sensitivity is reduced when there is lack of somatostatin receptor type 2 expression, such as that seen in poorly differentiated malignant paragangliomas, which are less common in the head and neck and usually familial rather than sporadic in nature. A pitfall of this technique is the potential for false-positive uptake related to inflammation or infection, which can lead to interpretative errors^[13]. Newer ^{68}Ga -labelled somatostatin analogue peptides (^{68}Ga -DOTA-TOC, ^{68}Ga -DOTA-NOC, ^{68}Ga -DOTA-TATE) have shown favourable characteristics in PET/CT imaging, with a high affinity for somatostatin receptors and a stable

process of labelling^[13]. They have shown promising results in imaging of non-head and neck NETs compared with conventional SRS but there are no data on their usefulness in paragangliomas. Imaging can be completed within 2 h with no need for delayed imaging on a subsequent day, as opposed to SRS, which routinely requires imaging at 4 h and at 24 h. However, despite the obvious strengths, this technology has been slow to be adopted into clinical routine in the United Kingdom due to a combination of financial considerations, regulatory hurdles and logistical challenges. It is hoped these issues can be addressed in the near future and, if so, these agents may gradually replace the older agents for functional imaging of NETs^[9].

There has been sustained development and evaluation of several PET ligands with the goal of providing a more holistic molecular fingerprint of neural crest tumours that encompasses other biomarkers such as tumour aggressiveness and molecular differentiation, which may have an important prognostic and therapeutic significance

particularly when combined with genetic and biochemical features. FDOPA-PET/CT is a promising, highly specific imaging technique for evaluation of head and neck paragangliomas. A recent study in patients with non-familial paragangliomas reported a sensitivity of 98% (62/64 lesions) and specificity of 100% for FDOPA-PET/CT, compared with MIBG sensitivity of only 53% (34/64 lesions) and specificity of 91%^[41]. Patients with negative MIBG studies were found not to express vesicular monoamine transporter expression (VMAT-1) likely as a consequence of the poorly differentiated nature of these tumours. Another study reported that FDOPA-PET had a superior sensitivity of 90%, compared with MIBG-SPECT (65%) and CT and MRI (67%)^[42]. However, more limited sensitivity of FDOPA-PET for familial and metastatic paragangliomas has also been reported^[43].

Familial paraganglioma is associated with mutations in the succinate dehydrogenase (SDH) gene-mitochondrial complex involved in electron transfer and the Krebs cycle^[44]. There are four subunits (A to D) that form the enzyme complex, and these are associated with different geno-phenotypic expressions of disease. Patients with SDHB mutations are prone to malignant head and neck paragangliomas with a high propensity for metastasis, whereas SDHD mutations typically manifest with multiple, benign head and neck paragangliomas with very rare occurrence of metastatic disease^[45]. Up to 10% of head and neck paragangliomas are reported to be related to these hereditary mutations^[46]. Limited data exist concerning the clinical and imaging features that distinguish sporadic from familial paragangliomas. A recent study reported that young age, large tumour volume, greater rate of metastatic and multifocal paragangliomas, higher intralesional metabolic activity on FDG-PET, and increased CT enhancement were observed in SDHB-related head and neck paragangliomas^[47]. The authors suggested that these findings may warrant genetic screening for SDH mutations and because SDHB-positive patients demonstrate more supradiaphragmatic lesions, whole-body functional imaging may be of particular value in these patients. In another study that evaluated 30 patients with SDHB germline mutation-related metastatic neural crest tumours, FDG-PET had a sensitivity of 100%, which exceeded that of FDOPA (88%), MIBG (80%), and SRS sensitivity (81%). A large proportion (90%) of the lesions negative on FDOPA and MIBG were localized with FDG-PET suggesting it to be the imaging study of choice in patients with SDHB germline mutations^[43]. Others have reported that FDA-PET had the highest sensitivity (90%) for detection of bone metastases in patients with metastatic pheochromocytomas and paragangliomas, followed by bone scintigraphy (82%), CT or MRI (78%), FDG-PET (76%) and MIBG (71%). However, in the subgroup with SDHB mutation, the optimal imaging approaches for bone metastases were CT and MRI (96%), bone

scintigraphy (95%), and FDG-PET (92%)^[48]. It is not possible to predict the best combination of anatomical and functional imaging in individual patients with head and neck paragangliomas but, in general, FDG;PET/CT should be considered in the diagnostic work-up of SDHB mutation carriers to provide the most accurate staging (Fig. 5). FDOPA- or FDA-PET may provide the highest accuracy in non-SDHB patients although there are no cost-effectiveness data available and these tracers are limited to highly specialized centres at present.

The presentation and imaging characteristics of each of the different sites of head and neck paraganglioma are summarized below:

Carotid body tumours

The most common type arises from the carotid body and accounts for over 60% of head and neck paragangliomas^[49]. The epicentre of this tumour is typically the posteromedial wall of the carotid bifurcation but growth along the wall of the external or internal carotid arteries has also been reported^[49]. They typically splay the internal and external carotid arteries. On further disease extension, these tumours encase the carotid arteries and extension into the skull base/intracranial cavity is recognized^[30]. The most common clinical presentation of a carotid body paraganglioma is an insidiously enlarging lateral neck mass often associated with bruit. Other symptoms include hoarseness, stridor, tongue paresis, vertigo, and mild dysphagia^[30]. The typical CT appearance of a carotid body tumour is an avidly enhancing soft tissue mass located in the infrahyoid neck splaying the internal and external carotid arteries (Fig. 6).

Glomus jugulare tumours

Glomus jugulare paragangliomas arise from the jugular bulb, the tympanic branch of the glossopharyngeal nerve (Jacobson nerve), or the auricular branch of the vagal nerve (Arnold nerve). The tumour spreads along the path of least resistance including mastoid air cells^[50], vascular channels^[50,51], Eustachian tube^[52], and neural foramina. The prevalence of these tumours is uncertain; some authors believe they are more common than carotid body paragangliomas, whereas others believe carotid body tumours are more common. Nonetheless, about 80% of all paragangliomas are either carotid body tumours or glomus jugulare tumours^[53]. Typically, patients present with pulsatile tinnitus. Less common manifestations include conduction deafness, vertigo, hoarseness, and aural pain or discharge. Cranial nerve palsies occur late in the disease progression. High-resolution CT early on in the disease process typically shows an irregular/enlarged jugular foramen. Progressive growth of the tumour causes a moth-eaten pattern of erosion of the jugular foramen and mastoid (Fig. 7). Ossicular chain destruction is common.

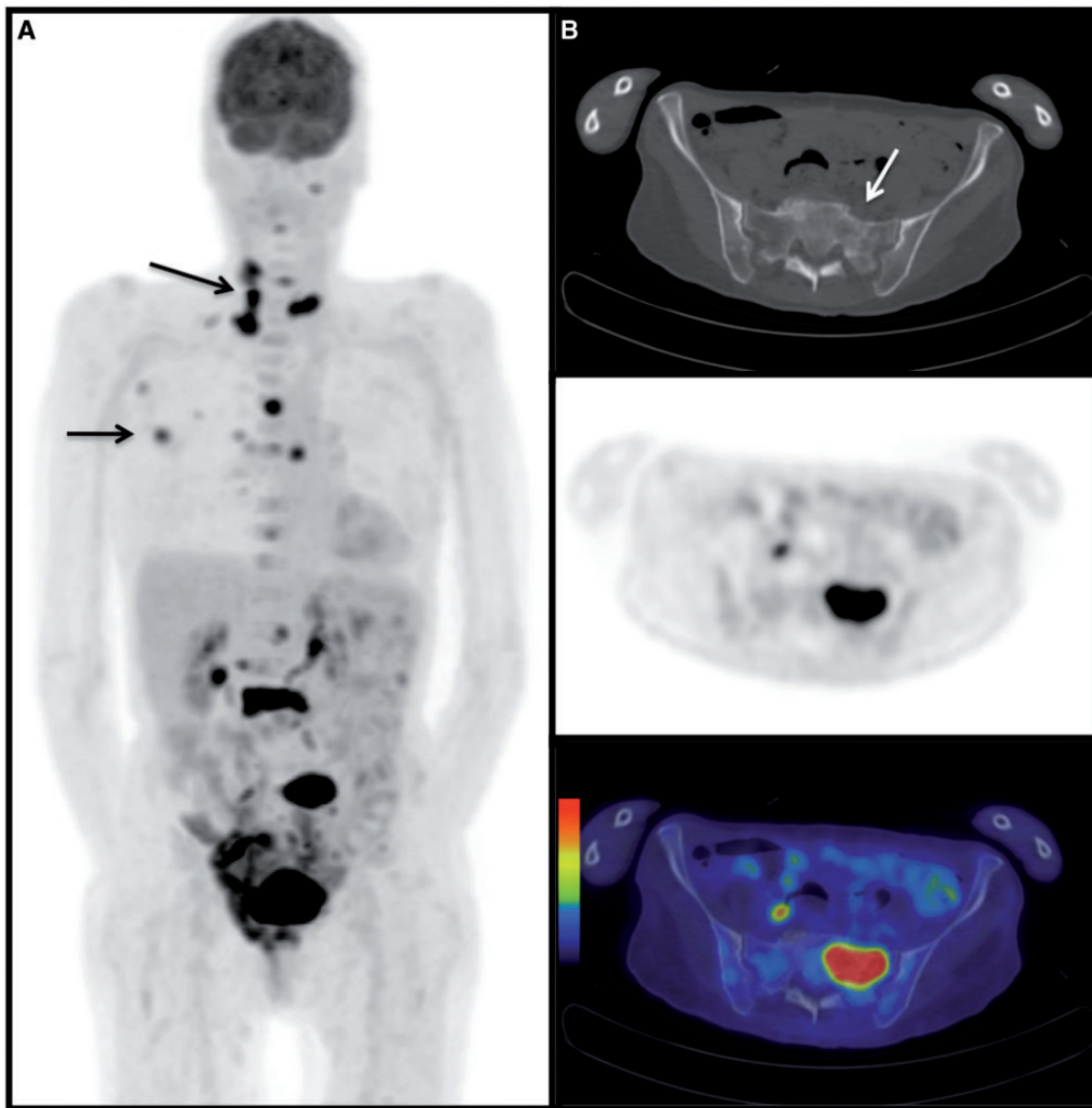


Figure 5 Metastatic head and neck paraganglioma in SDHB genetic mutation. (A) Maximum intensity projection PET image from a half-body FDG-PET/CT scan demonstrates a plaque-like area of extremely intense FDG uptake in the right neck around the carotid sheath (top black arrow). There are multiple foci of abnormal uptake elsewhere including the lungs (lower black arrow) and axial skeleton, including the right scapula, ribs, sternum and numerous vertebrae. (B) Axial images from the same study: CT (top), PET (middle) and fused PET/CT (bottom) showing a large FDG-avid bone metastasis within the left side of the sacrum; there is little evidence of structural abnormality on the CT component (white arrow, top).

Glomus vagale tumours

Vagal paragangliomas typically occur within or below the inferior ganglion (nodose ganglion) or within the superior ganglion (jugular ganglion)^[54]. These are the third most common type of paragangliomas in the head and neck. Typically, patients present with a painless insidious lateral neck mass behind the angle of the mandible. Lower cranial nerve palsies occur late in the disease process^[55]. On CT, vagal paragangliomas appear similar to carotid body tumours but displace both internal and external carotid arteries anteromedially (Fig. 4). In addition, extension into the suprahyoid carotid space is

seen in approximately two-thirds of vagal paragangliomas.

Glomus tympanicum tumours

The glomus tympanicum tumour is typically a small discrete lesion of the cochlear promontory confined within the tympanic cavity^[56,57]. Unlike with glomus jugulare, ossicular chain destruction is unusual^[56]. These tumours, however, may spread to the mastoid air cells, Eustachian tube and nasopharynx^[58]. Pulsatile tinnitus is a common clinical manifestation of this tumour.

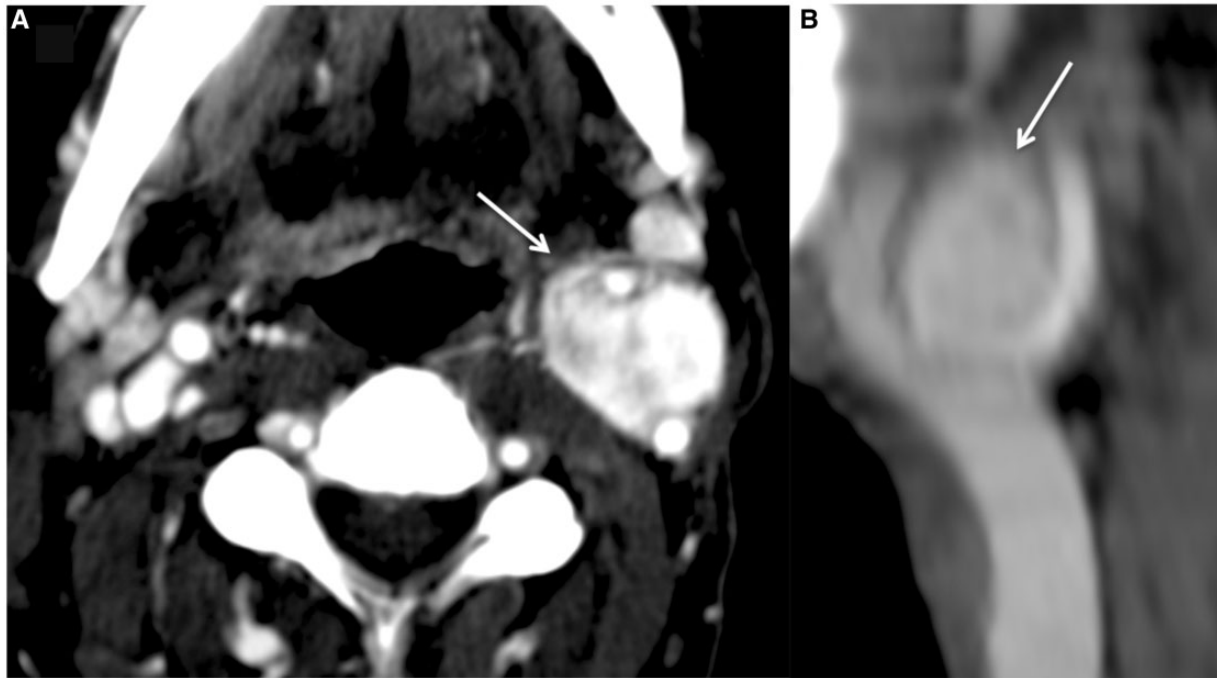


Figure 6 Carotid body tumour. (A) Axial maximum intensity projection image from a contrast-enhanced CT of the neck showing a heterogeneous, hypervascular mass in the left carotid space (white arrow). (B) Sagittal reformat of the same study shows that the lesion is positioned between the bifurcation of the common carotid artery (white arrow); this is the typical appearance of a carotid body tumour (paraganglioma).

Management of paragangliomas

Most head and neck paragangliomas demonstrate an indolent growth pattern. One imaging study demonstrated a median growth rate of 1.0 mm/year with a median tumour doubling time of 4 years^[59]. Death from paraganglioma is rare^[60] and the aim of treatment is to minimize/reduce morbidity rather than to improve survival. Options for treatment include observation for selected cases, surgery or radiotherapy. Traditionally, surgery has been the preferred method of primary treatment, with radiotherapy reserved for unresectable disease or less fit patients. The vascularity and skull base location of many paragangliomas make surgical management very challenging. Preoperative embolization has been used to reduce intraoperative blood loss and facilitate complete resection^[61]. High local control rates of series of external beam radiotherapy and radiosurgery has challenged this approach. A recent systematic literature review^[62] suggested that external beam radiotherapy or stereotactic radiosurgery offered similar tumour control compared with surgery, with lower risks of morbidity. Similarly, a meta-analysis^[63] of tumour control rates and treatment-related morbidity for glomus jugulare tumours found that radiosurgery offered superior local control with a lower rate of cranial nerve palsy compared with surgery. Laryngeal paragangliomas are generally treated by local excision or partial laryngectomy^[1].

Radiological investigations are key to planning both surgical and non-surgical approaches. Choosing the

correct surgical approach requires knowledge of the extent of invasion of adjacent structures. Similarly, the location of steep dose gradients provided by modern highly conformal radiotherapy or stereotactic radiosurgery allowing sparing of adjacent normal structures requires excellent definition of the soft tissue and bony extent of disease. Radiotherapy is routinely planned on CT imaging in the treatment position. CT/MRI co-registration can be used to directly incorporate the soft tissue definition offered by MRI into the radiotherapy planning process^[64].

Olfactory neuroblastoma

Olfactory neuroblastoma (ONB) (also known as esthesioneuroblastoma) is a rare malignant neuroectodermal tumour arising from the olfactory epithelium of the olfactory ring of the superior nasal mucosa. Neuroepithelial sensory cells found in the upper nasal cavity are thought to be the cellular origin of these tumours^[65]. Neuroectodermal carcinoma of the sinonasal tract is also thought to arise from these specialized sensory cells of the nasal mucosa. ONB accounts for about 2% of all sinonasal tract tumours^[66]. A bimodal age distribution in the 2nd and 6th decades of life has been described, although ONB may occur at any age. No gender predilection has been found^[66].

The presenting features of ONB relate to the pattern of local spread. The origin of ONB is usually unilateral^[67]



Figure 7 Glomus jugulare tumour. Coronal (A), sagittal (B) and axial (C) images from a contrast-enhanced CT scan demonstrate a bilobed, expansile, hypervascular mass (white arrows) within the right base of the skull extending through the jugular foramen into the right cerebellopontine angle. On the axial image (C), there is clear evidence of involvement of the adjacent bones. (D) Axial T2-weighted image from an MRI scan in the same patient showing heterogeneous signal within the lesion (white arrow) with high signal interspersed with signal void, the so-called salt and pepper appearance that is typical of a paraganglioma (glomus jugulare).

and hence unilateral nasal obstruction and epistaxis can occur in the early stage of the disease. However, patients often present with locally advanced disease, due to local spread through the cribriform plate into the skull base. Symptoms of more advanced disease include headache, rhinorrhea or visual disturbances. Occlusion of the ipsilateral nasolacrimal duct may lead to epiphoria. There are isolated cases reports of ONB presenting with Cushing syndrome^[68]. Clinical assessment may reveal a reddish-grey pedunculated mass.

Cross-sectional imaging with CT to assess the extent of bone destruction and MRI are recommended to define the local extent of disease^[69]. Anatomical imaging classically reveals a dumbbell-shaped mass centred at the cribriform plate containing intracranial and nasal cavity components (Fig. 8). Speckled calcification and bone erosion are often seen on CT; the tumour exhibits intense contrast enhancement. MRI demonstrates the local extent of the soft tissue component. These tumours are hypointense on T1 and hyperintense on T2 with marked

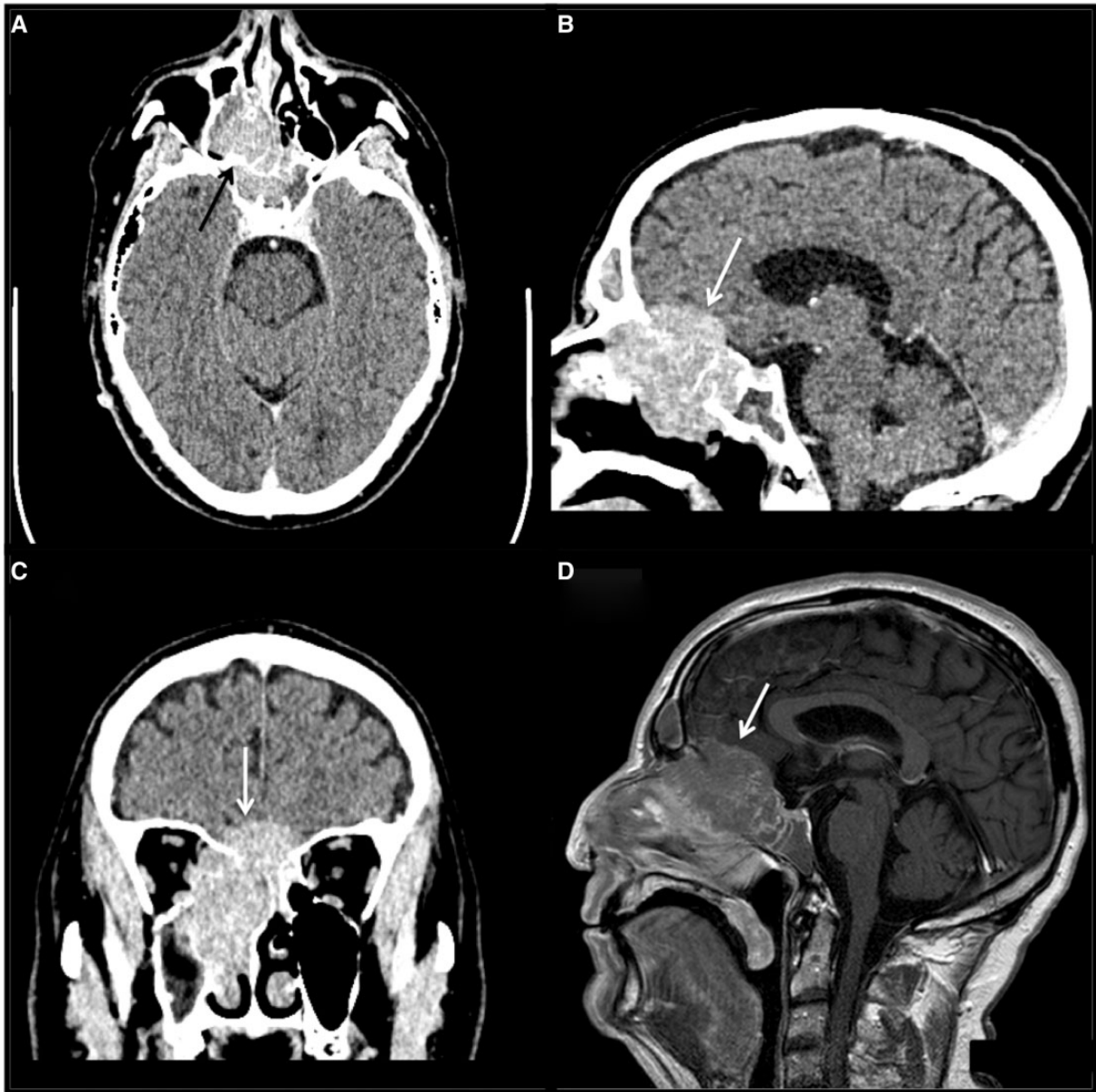


Figure 8 Olfactory neuroblastoma (esthesioneuroblastoma). Axial (A), sagittal (B) and coronal (C) images from a contrast-enhanced CT examination demonstrate an enhancing mass lesion centred on the right cribriform plate extending intracranially (white arrows) into the anterior cranial fossa and the right nasal cavity. (D) Sagittal T1-weighted image from an MRI scan in the same patient showing the right nasal cavity mass extending into the anterior cranial fossa. Biopsy confirmed an olfactory neuroblastoma.

homogeneous contrast enhancement. Both obstructed secretions in the adjacent sinuses and areas of cystic degeneration appear hyperintense^[70]. Anatomical imaging cannot reliably differentiate these tumours from other more common sinonasal tumours, including sinonasal undifferentiated carcinoma and squamous cell carcinoma^[65].

ONB usually expresses somatostatin receptors and SRS can be used as a diagnostic adjunct^[71]. However, several brain tumours including meningiomas, gliomas and pituitary adenomas also express somatostatin

receptors and demonstrate octreotide uptake^[72]. This radionuclide imaging is therefore not ideal for the definitive diagnosis of ONB. By contrast, MIBG scintigraphy has superior accuracy due to specific uptake and storage mechanisms in neuroblastomas^[72]. The sensitivity and specificity of MIBG scintigraphy is very high in assessment of extracranial neuroblastomas^[73-76]. At present, there are no data available on the use of novel PET agents for assessment of ONB.

Accurate imaging assessment of the local extent of disease including intracranial and orbital involvement is

essential for planning treatment. The most widely recognized staging system is the Kadish classification; stage A is confined to the nasal cavity, stage B extends into the sinuses and stage C includes skull base and intracranial involvement and distant disease. Limited retrospective series are the best evidence to guide the management of these rare tumours. Outcomes have improved with the advent of craniofacial resections^[77]. Craniofacial resection with clear margins may be adequate treatment for early-stage disease^[67]. Adjuvant radiotherapy seems to improve local control and is routinely used for more advanced tumours^[78]. Recent case reports suggest a potential role for neoadjuvant chemoradiotherapy before craniofacial resection for advanced disease^[79].

ONB can spread to the regional lymph nodes either at presentation or as a site of relapse. The first echelon lymph nodes are in the lateral retropharyngeal region, levels Ib and II^[80]. In a recent report of 26 patients treated without elective neck radiotherapy, 7 (27%) relapsed in the neck after a median time of 74 months; half of these neck recurrences were associated with distant disease^[80]; the authors recommended elective neck treatment for Kadish stages B and C. Therefore, careful radiological assessment of regional lymph nodes is essential at diagnosis; any additional role of octreotide or MIBG-based imaging in this assessment is uncertain.

Merkel cell carcinoma

First described by Toker in 1972^[81], Merkel cell carcinoma (MCC) is an uncommon neuroendocrine (small cell) tumour of the dermis that is characterized by aggressive regional nodal invasion, distant metastases, and a high rate of recurrence. Although it remains controversial, the widely accepted origin of the tumour is the Merkel cell, which is within the basal layer of the epidermis usually functioning as a chemoreceptor^[82,83].

MCC commonly occurs in sun-exposed skin with over half of these involving the head and neck region, often in elderly whites with no reported sex predilection^[84,85]. It commonly manifests as a rapidly growing non-tender nodule in a sun-exposed area.

The clinical manifestation determines the classification of the disease: stage 1, cutaneous involvement; stage 2, regional nodal invasion; stage 3, systemic metastases. The definitive diagnosis of this tumour is based on histopathology. Imaging has been shown to be beneficial in staging, surgical guidance, therapeutic management, and follow-up^[86,87]. Clinically it is difficult to differentiate stage 1 and 2 disease as up to two-thirds of patients have regional lymphadenopathy at presentation and only 7–31% of patients with stage 2 disease present with palpable lymphadenopathy^[88,89].

The role of lymphoscintigraphy to localize the sentinel nodes that may be involved due to micrometastases from MCC has been examined^[90-92]. The sentinel node is the first node to drain ^{99m}Tc-filtered sulphur colloid,

0.25–0.50 mCi (9.25–18.5 MBq) of which is injected intradermally around the MCC site. As in melanoma; the presence of sentinel nodes seems to be a strong indicator of regional MCC disease^[89,93,94]. These studies indicate a high rate of subclinical metastases; in a small meta-analysis, 33% of patients had a positive sentinel node biopsy^[90]. The outcome of sentinel node-negative patients managed without adjuvant therapy seemed favourable in this meta-analysis, although with very limited follow-up^[90]. Due to the very limited size of the studies in this area, larger prospective studies are required to establish the role of sentinel node biopsy in the routine management of MCC^[95].

The use of imaging to exclude distant metastases is essential before aggressive locoregional treatment with curative intent. When pathology demonstrates a cutaneous small cell carcinoma, all patients should undergo chest imaging to determine whether this is a manifestation of a metastatic small cell carcinoma of the lung or to identify lung metastases. About one-third of patients present with distant metastases^[86]. The metastases can be evaluated with cross-sectional imaging, which may show hypervascular lesions with avid contrast enhancement but the findings are non-specific (Fig. 9). SRS can be used with greater reported sensitivity compared with anatomical imaging^[96] but may be limited in assessing metastases in organs with physiological uptake of octreotide such as the liver, kidneys and spleen.

The additional benefit of FDG-PET/CT compared with conventional imaging has not yet been clearly defined in patients with MCC. However, emerging evidence has suggested that FDG-PET/CT may be more accurate in staging disease compared with conventional imaging methods including functional imaging with SRS^[97-99]. The reported sensitivity and specificity of FDG-PET/CT is as high as 89% and 100%, respectively^[97]. FDG-PET/CT may be particularly useful in restaging patients with recurrent disease and in patients with possible metastases at presentation^[100].

For locoregionally confined disease, treatment is with surgical excision. Achieving the recommended wide margins of 2–3 cm is particularly difficult in the head and neck region^[101]. This does not appear to be necessary with the use of adjuvant wide-field radiotherapy^[102]. There is a high risk of subclinical nodal disease. In the case of MCC in the head and neck region, adjuvant radiotherapy can be used to encompass the primary site, potential in-transit dermal metastases, and regional lymph node beds^[95].

Conclusion

In summary, the diverse tissues of the head and neck can give rise to a wide assortment of rare NETs. Anatomical and functional imaging is often complementary in this patient group and has a key role in diagnosis, staging and guiding management decisions. With the advent of

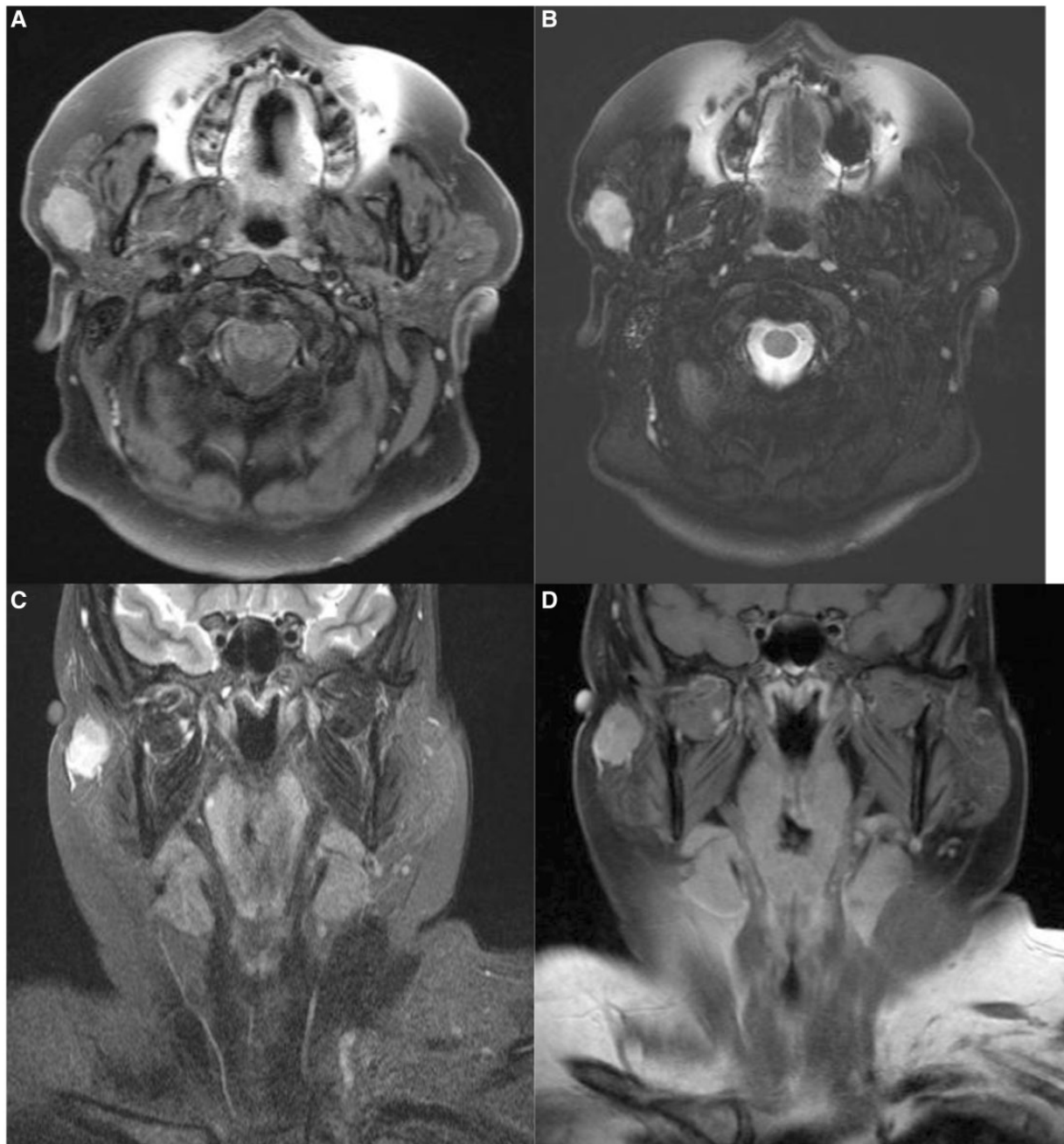


Figure 9 Merkel cell carcinoma. Axial fat-suppressed T1-weighted image after Ga (A), axial (B) and coronal (C) fat-suppressed T2-weighted images and coronal fat-suppressed T1-weighted image after Ga (D) demonstrate a high-signal/enhancing lesion within the right parotid gland, which has a non-specific appearance. This was histologically confirmed to be a nodal deposit from a Merkel cell carcinoma. The primary tumour was subcentimetre in size and located within the skin of the right neck (not seen on imaging).

innovative techniques and novel tracers, the role of functional and molecular imaging in this patient cohort is likely to expand.

Conflict of interest

The authors have no conflicts of interest to declare.

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