Clinicians' Guides to Radionuclide Hybrid Imaging · PET/CT
Series Editors: Jamshed B. Bomanji · Gopinath Gnanasegaran
Stefano Fanti · Homer A. Macapinlac

Wai Lup Wong *Editor*

PET/CT in Head and Neck Cancer

BNMS
BRITISH NUCLEAR MEDICINE SOCIETY

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PET/CT

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PET/CT series is dedicated to Prof. Ignac Fogelman, Dr. Muriel Buxton-Thomas and Prof. Ajit K Padhy

Foreword

Clear and concise clinical indications for PET/CT in the management of the oncology patient are presented in this series of 15 separate booklets.

The impact on better staging, tailored management and specific treatment of the patient with cancer has been achieved with the advent of this multimodality imaging technology. Early and accurate diagnosis will always pay, and clear information can be gathered with PET/CT on treatment responses. Prognostic information is gathered and can forward guide additional therapeutic options.

It is a fortunate coincidence that PET/CT was able to derive great benefit from radionuclide-labelled probes, which deliver good and often excellent target to non-target signals. Whilst labelled glucose remains the cornerstone for the clinical benefit achieved, a number of recent probes are definitely adding benefit. PET/CT is hence an evolving technology, extending its applications and indications. Significant advances in the instrumentation and data processing available have also contributed to this technology, which delivers high throughput and a wealth of data, with good patient tolerance and indeed patient and public acceptance. As an example, the role of PET/CT in the evaluation of cardiac disease is also covered, with emphasis on labelled rubidium and labelled glucose studies.

The novel probes of labelled choline, labelled peptides, such as DOTATATE, and, most recently, labelled PSMA (prostate-specific membrane antigen) have gained rapid clinical utility and acceptance, as significant PET/CT tools for the management of neuroendocrine disease and prostate cancer patients, notwithstanding all the advances achieved with other imaging modalities, such as MRI. Hence a chapter reviewing novel PET tracers forms part of this series.

The oncological community has recognised the value of PET/CT and has delivered advanced diagnostic criteria for some of the most important indications for PET/CT. This includes the recent Deauville criteria for the classification of PET/CT patients with lymphoma—similar criteria are expected to develop for other malignancies, such as head and neck cancer, melanoma and pelvic malignancies. For completion, a separate section covers the role of PET/CT in radiotherapy planning, discussing the indications for planning biological tumour volumes in relevant cancers.

These booklets offer simple, rapid and concise guidelines on the utility of PET/CT in a range of oncological indications. They also deliver a rapid aide-memoire on the merits and appropriate indications for PET/CT in oncology.

London, UK Peter J. Ell, F.Med.Sci., DR HC, AΩA

Preface

Hybrid imaging with PET/CT and SPECT/CT combines best of function and structure to provide accurate localisation, characterisation and diagnosis. There is extensive literature and evidence to support PET/CT, which has made significant impact in oncological imaging and management of patients with cancer. The evidence in favour of SPECT/CT especially in orthopaedic indications is evolving and increasing.

The *Clinicians' Guide to Radionuclide Hybrid Imaging* (PET/CT and SPECT/CT) pocketbook series is specifically aimed at our referring clinicians, nuclear medicine/radiology doctors, radiographers/technologists and nurses who are routinely working in nuclear medicine and participate in multidisciplinary meetings. This series is the joint work of many friends and professionals from different nations who share a common dream and vision towards promoting and supporting nuclear medicine as a useful and important imaging speciality.

We want to thank all those people who have contributed to this work as advisors, authors and reviewers, without whom the book would not have been possible. We want to thank our members from the BNMS (British Nuclear Medicine Society, UK) for their encouragement and support, and we are extremely grateful to Dr. Brian Nielly, Charlotte Weston, the BNMS Education Committee and the BNMS council members for their enthusiasm and trust.

Finally, we wish to extend particular gratitude to the industry for their continuous support towards education and training.

London, UK

Gopinath Gnanasegaran
Jamshed Bomanji

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Introduction

The monogram on PET/CT of the head and neck (H&N) focuses mainly on the most common H&N malignancies, namely squamous cell cancers (SqCC) of the oral cavity, pharynx and larynx. There is also discussion of other less common malignant tumours, including nasal, paranasal sinus and salivary gland cancers. Notwithstanding a specific monogram for lymphoproliferative disorders, a brief commentary is provided to highlight some of the features specific to head and neck lymphoproliferative disorders in the appendix. Soft tissue, bone and cartilage tumours are not considered.[1] Thyroid cancers and malignant melanoma are considered in another monogram in the series.

[1] Malignant tumours may arise from adipose, muscle, vessels, fibrous tissue and nerves but the scope of malignant soft tissue tumours is too diverse for consideration within this text.

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Clinical Background of Head and Neck Tumours

1

Tom Roques

Contents

1.1 Causes

Long-term exposure to carcinogens, e.g., tobacco smoke, chewed betel nut and alcohol are causative factors in many H&N cancers (H&Nca) [1]. There are other more specific causative agents, e.g., hard wood dust in nasal and ethmoid cavity cancers. Such exposure alone however is not sufficient. Other genetic and environmental factors are necessary but their contributory effect is poorly understood. One notable example is the association between human papilloma virus (HPV), probably from oral sex, and oropharyngeal cancer. Most sexually active adults are exposed to HPV-16, the main virus linked to oropharyngeal cancer[1] [2–4]. Why only a tiny minority do not clear the virus effectively so that it is subsequently a causative factor in cancer is unclear?

Premalignant lesions in the oral cavity, e.g., leukoplakia and erythroplakia and carcinoma-in-situ in the larynx often predate invasive disease [5].

[1] HPV-16, 18, 31, 32 are the usual subtypes of the virus linked to oropharyngeal cancer, with HPV-16 the most common.

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1.2 Epidemiology

There are approximately 9000 new H&N cancers diagnosed each year in England and Wales, the majority being squamous cell cancer (SqCC). Regarding sites of origin, a quarter each are from the oral cavity, oropharynx and larynx and the remaining 25% from the other subsites put together.[2] The incidence of oral cavity and oropharyngeal cancers is rising with approximately 30% more cases than a decade ago: oral cavity cancer because of exposure to smoking decades ago, and oropharyngeal cancer because of HPV-associated disease. The incidence of tumours at other sites is not changing.

1.3 Clinical Presentation

Most H&N cancers are more common in the 50–70 age group. They usually present with the effects of a local tumour in the organ of origin or with enlarged malignant nodes.

Oral cavity cancers, except lip cancers, usually present with a painful, non-healing ulcer or red or white patches in the mouth which may be detected during a routine dental examination. More advanced tumours cause trismus or loose teeth. Some are detected with a neck lump. Lip cancer often presents with a lip ulcer or lump on and enlarged nodes at presentation rare.

Oropharyngeal cancers commonly have already spread to adjacent nodes at presentation and often present with a neck lump though people may also notice a sore throat, dysphagia or referred ear pain.

In *Nasopharyngeal cancers*, one in three people present with nasal symptoms, e.g., epitaxis or nasal obstruction, one in five conductive deafness, one in five a neck lump due to nodal metastases and one in ten people, pain.[3] Some have the combination of conductive deafness, elevation and immobility of the homolateral palate together with pain in the side of the head (due to 5th cranial nerve involvement) which represents symptoms of local tumour invasion (Trotter's triad). Others present with headache, diplopia, facial numbness, hypothesia, trismus, ptosis and hoarseness [6].

[2] DAHNO data. The Data for Head and Neck Oncology (DAHNO) is the UK National Head and Neck Cancer Audit. Focuses on cancer sites within the H&N (excluding brain tumours and thyroid cancers), it is commissioned by the Healthcare Quality Improvement Partnership (HQIP) as part of the National Clinical Audit and Patient Outcomes Programme (NCAPOP), and developed in partnership with the British Association of Head and Neck Oncologists (BAHNO).

[3] Many people with no neck lumps have nodal metastases; almost half will have subclinical metastatic nodes at presentation, about 1 in 3 ipsilateral, 1 in 5 bilateral [6].

Hypopharyngeal cancers usually present with a combination of symptoms which will include dysphagia, pain or discomfort in swallowing referred pain to the ear on the same side as the primary site, hoarseness or a neck nodal mass[4] [7].

Larynx cancers usually present with a hoarse voice. Presentation with nodal enlargement is relatively uncommon for glottic cancers due to the lack of lymphatic drainage of the glottic larynx [8].

Parotid cancers usually present as a lump in the gland. The main challenge is to determine whether the mass is benign or malignant as non-cancerous nodules are common.

Paranasal sinus and nasal cancers. Clinical features of ethmoidal cancers include nasal obstruction, epitaxis, proptosis and diplopia. Maxillary sinus cancers include nasal obstruction, epitaxis, infra-orbital anaesthesia, tooth ache, facial pain and swelling and trismus. Malignant enlarged nodes occur in 5% at presentation [9].

Sometimes, people with SqCC in neck nodes do not have a primary site detectable by clinical or radiological examination though the pattern of nodal spread may favour an occult primary for one particular subsite.[5] In the elderly presenting in this way metastases from a skin cancer should be considered.

Systemic symptoms such as anorexia and weight loss are uncommon in H&Nca unless the location of the tumour directly affects swallowing.

1.4 Diagnosis

People usually present to ENT or oral surgery clinics where examination of suspicious primary lesions can be carried out in clinic by direct examination or naso-endoscopy. Biopsies are then taken to confirm diagnosis, in the clinic, under image guidance (often ultrasound) or under general anaesthesia. An incisional or core biopsy is usually preferred, other than in the investigation of a neck lump where fine needle aspiration may be the first test. Cross sectional imaging is limited to selected people in establishing diagnosis.

Significant morbidity is associated with H&Nca treatment, and it is crucial at presentation to assess the comorbidities of the person and their social circumstances, both of which may have a major bearing on the treatment options considered.

[4] Incidence of enlarged metastatic neck nodes at presentation: piriform sinus, two-thirds to three-quarters in the ipsilateral neck, 5% bilateral; post cricoid 20–30%, ipsilateral, 1 in 20 bilateral; posterior pharyngeal wall, 50% ipsilateral, 5% bilateral [8].

[5] In general, prior to H&N treatment, the pattern of H&Nca nodal spread is fairly predictable and orderly, and the site of nodal disease often provides a good indicator of the location of the primary site.

1.5 Classification and Staging

Staging plays a pivotal role in the care of people with H&Nca. Disease stage influences treatment plan and usually correlates well with outcomes.[6] The Tumour Nodal Metastases (TNM) system is widely used to classify H&Nca.[7] The T classification indicates the size and extent of the primary tumour and differs in detail for each sub-site because of anatomical considerations. The N classification for neck nodes is uniform for all sub-sites except for nasopharynx.[8] M classification is exactly the same as for other body sites.

In common with other body sites, and for similar purposes, inter alia, analysis of care of people with similar prognosis, T, N and M are grouped into anatomical and prognostic groups commonly referred to as stage groups, classified by the Roman numerals from I to IV, with increasing severity of disease. For T classification of more common H&N cancers, see Appendices (1.1.1–1.1.4); N classification, Appendices (1.2.1 and 1.2.2); M classification, Appendix (1.3); stage groups of more common H&N cancers, Appendices (2.1–2.4).

1.6 Outcomes

The chances of cure vary, depending on the tumour site and stage, as well as comorbidity and performance status which may limit treatment options.

Generally, early H&Nca have favourable outcomes. For example, for stage I laryngeal SqCC the relative survival rate is more than 80% 5 years following diagnosis[9] [10]. And stage I oral cavity SqCC, 5 years following diagnosis the relative survival rate is more than 70% [11]. By contrast, more advanced diseases have much higher chance of relapse with significantly lower cure rates. So, by comparison, the relative survival for Stage IV laryngeal SqCC is less than 40%, 5 years from diagnosis [10]. In stage IV oral cavity SqCC, 5 years following diagnosis, the relative survival rate is approximately 30% [11]. Perhaps also deserving note,

[6] This is less true of HPV associated oropharyngeal cancers where stage 4a disease (by virtue of N2 status) is common but outcomes remain excellent.

[7] The TNM classification is a collaboration between the UICC and AJCC. It was developed by Pierrre Denoix and formalized by the International Union Against Cancer (UICC) in 1950s. The American Joint Committee on Cancer (AJCC) was founded to compliment the work of the UICC. Since the 1980s, the work of the UICC and AJCC has been coordinated resulting in the simultaneous publication of the TNM Classification of Malignant Tumours by the UICC and the AJCC Cancer Staging Manual.

[8] The classification is also different for H&N skin cancers and thyroid cancers, which are beyond the scope of the monogram.

[9] Relative survival represents the likelihood that a person will not die from causes specifically associated with the cancer considered, at some specified time after the diagnosis. In other words, adjustments are made, albeit partially, for other causes of death not related to the cancer considered.

HPV-linked oropharynx cancers have significantly better cure rates compared with HPV-negative oropharyngeal cancers [2].

As with many cancers, recurrent disease is often not curable so reducing exposure to known risk factors, early detection and effective initial therapy are the most effective strategies to increase cure rates.

Second primary tumours, usually in the H&N, oesophagus and lungs, are not uncommon because of the exposure of mucosal surfaces to carcinogens and this is another factor which influences outcomes [12–14].

Key Points

- Long-term exposure to carcinogens, e.g., tobacco smoke, chewed betel nut and alcohol are causative factors in many H&N cancers (H&Nca).
- Premalignant lesions in the oral cavity, e.g., leukoplakia and erythroplakia and carcinoma-in-situ in the larynx often predate invasive disease.
- The incidence of oral cavity and oropharyngeal cancers is rising with approximately 30% more cases than a decade ago.
- Most H&N cancers are more common in the 50–70 age group. They usually present with the effects of a local tumour in the organ of origin or with enlarged malignant nodes.
- Oral cavity cancers, except lip cancers, usually present with a painful, non-healing ulcer or red or white patches in the mouth which may be detected during a routine dental examination.
- Sometimes, people with SqCC in neck nodes do not have a primary site detectable by clinical or radiological examination though the pattern of nodal spread may favour an occult primary for one particular subsite.
- The chances of cure vary, depending on the tumour site and stage, as well as comorbidity and performance status which may limit treatment options.
- As with many cancers, recurrent disease is often not curable so reducing exposure to known risk factors, early detection and effective initial therapy are the most effective strategies to increasing cure rates.
- Second primary tumours, usually in the H&N, oesophagus and lungs, are not uncommon.

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Pathology of Head and Neck Tumours

2

Katherine Sisson and Tom Roques

Contents

The neoplastic processes in the H&N are extremely diverse and extensive. For this reason, only the more common malignant neoplasms will be considered.[1] Consideration of the normal structures (epithelial lining, soft tissue, salivary glands etc.) provides a useful guide to the types of tumours encountered.

Morphological features by light microscopy are the mainstay of diagnosis. Other techniques, e.g., immunohistochemistry, and more recently molecular studies, are sometimes required to confirm a diagnosis, e.g. for poorly differentiated tumours that may not demonstrate typical diagnostic features.

2.1 Squamous Epithelium: Squamous Cell Carcinoma (SqCC)

The vast majority of H&N epithelial tumours are SqCC as the normal epithelial lining in the oral, oropharyngeal cavities and larynx is composed of squamous epithelium. Squamous metaplasia occurs readily as a result of injury to the respiratory

[1] Refer to the W.H.O. Classification of Tumours of the H&N for more information [1].

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type epithelium normally present in the nasal cavity, paranasal sinuses and upper aero-digestive tract and pre-neoplastic changes (squamous dysplasia) are well recognised as a result of tobacco smoke and alcohol consumption.

Viruses are important in the pathogenesis of nasopharyngeal and oropharyngeal tumours. Epstein Barr Virus (EBV) manifests as non-keratinising SqCC (nasopharyngeal carcinoma). The causative agent may be highlighted by in-situ hybridisation for EBV encoded RNA (EBER).

More recently, HPV high risk subtypes 16, 18, 31 and 33 have been implicated in the development of palatine tonsil and tongue base SqCC. These tumours cannot be distinguished on their morphological appearance and site, and it is necessary to either perform in-situ hybridisation to demonstrate the presence of HPV 16 and 18 or use immunohistochemistry to detect upregulation of p16 (a cell cycle protein). The latter is more widely used since it is cheaper and easier to perform. However, it is a surrogate marker and not specific to the viral aetiology.

The diagnostic features of SqCC are keratinisation and/or the presence of intercellular bridges. SqCC is broadly categorised into non-keratinising and keratinizing subtypes. The latter may be graded into well, moderately and poorly differentiated according to the amount of keratinization present (Broders classification) although it is worth noting that there is poor correlation between grade and clinical outcomes. SqCC can manifest in a wide range of morphological patterns including papillary, verrucous, spindle cell, basaloid, adenosquamous, lymphoepithelioma-like and acantholytic. Spindle cell and basaloid (non-HPV related) SqCC have a poorer prognosis while the verrucous subtype has a better prognosis.

In addition to grading and subtyping SqCC, the pathologist will include other prognostically relevant detail in excision specimens including the invasive front of the tumour (infiltrative or cohesive), tumour size and invasion depth, presence or absence of perineural and vascular invasion, measurement of excision margins for both invasive and in-situ disease and the presence of extracapsular lymph node spread.

2.2 Respiratory Epithelium: Adenocarcinoma

Respiratory type (pseudostratified columnar ciliated) epithelium which lines the nasal cavity and paranasal sinuses may give rise to adenocarcinomas. These are broadly categorised as intestinal type, which shows morphological and immunohistochemical appearances of colonic adenomatous mucosa, and non-intestinal type.

2.3 Salivary Glands

Normal salivary glands are composed of serous and mucinous acinar cells and ducts with surrounding myoepithelial cells and supporting stroma. Given these different cell types, neoplasia within the salivary glands consists of a diverse group of benign and malignant tumours, some of which show overlapping morphological and immunohistochemical appearances. Therefore, diagnosis can sometimes be difficult and molecular genetics is likely to be of importance in formulating the diagnosis in the future.

In addition to the major salivary glands there are also a number of minor salivary glands throughout the oral cavity and seromucinous glands within respiratory type mucosa, so this category of tumours is not purely confined to the parotid and submandibular glands. That said, the majority occur in the parotid, of which benign pleomorphic adenomas are most common. Minor salivary gland tumours are more likely to be malignant.

Given the extensive list of potential tumours, only the most common and relevant malignant tumours will briefly be discussed. For a more extensive list, see the WHO classification [1].

Mucoepidermoid carcinoma

- It is most frequent malignant primary salivary gland neoplasm.
- It is characterised by goblet (mucous) cells, intermediate and squamoid cells, forming variably solid and cystic patterns.
- It may be low, intermediate or high grade depending on percentage of constituent cell types.

Adenoid cystic carcinoma

- It consists of epithelial and myoepithelial cells with basaloid morphology arranged in a cribriform architecture with punched out spaces. It may show trabecular tubular and solid patterns.
- It often has very infiltrative appearance. It has high propensity for perineural invasion. These features account for the high recurrence rate.

Acinic cell carcinoma

- It is composed of sheets of cells with abundant granular eosinophilic cytoplasm (acinar type cells).

Two other not infrequently encountered carcinomas which behave in a high grade fashion are salivary duct carcinoma and carcinoma ex-pleomorphic adenoma. In addition, some low grade carcinomas can show areas of dedifferentiation and therefore may become high grade.

2.4 Soft Tissues

Benign and malignant tumours may arise from fat, muscle, vessels, fibrous tissue and nerves, but the scope of malignant soft tissue tumours is too diverse for a detailed description within this text. Referral to the WHO classification of soft tissue tumours is recommended [1].

However, there is a specific group of tumours that primarily occur in the nasal cavity and paranasal sinuses, many of which are of soft tissue origin. These are described as small round blue cell tumours, so called since they have small hyperchromatic nuclei with minimal surrounding cytoplasm. There are certain morphological features that may distinguish the different entities, but immunohistochemistry is of paramount importance to confirm a diagnosis. Tumours included in this category are: tumours of neuroectodermal origin; namely, olfactory neuroblastoma and primitive neuroectodermal tumour (PNET), mucosal malignant melanoma,

neuroendocrine tumours i.e. small cell carcinoma, sinonasal undifferentiated carcinoma, lymphoma, and rhabdomyosarcoma.

2.5 Metastatic Disease

Metastases to H&N are rare and usually as a result of primaries originating in the kidney, colon, breast, lung, thyroid, prostate or melanoma. Identification often requires immunohistochemistry as well as a detailed clinical history and radiological correlation.

Key Points

- The neoplastic processes in the H&N are extremely diverse and extensive.
- Morphological features by light microscopy are the mainstay of diagnosis.
- The vast majority of H&N epithelial tumours are SqCC as the normal epithelial lining in the oral, oropharyngeal cavities and larynx is composed of squamous epithelium.
- Viruses are important in the pathogenesis of nasopharyngeal and oropharyngeal tumours. Epstein Barr Virus (EBV) manifests as non-keratinising SqCC (nasopharyngeal carcinoma).
- The diagnostic features of SqCC are keratinisation and/or the presence of intercellular bridges.
- SqCC is broadly categorised into non-keratinising and keratinizing subtypes.
- Respiratory type (pseudostratified columnar ciliated) epithelium which lines the nasal cavity and paranasal sinuses may give rise to adenocarcinomas.
- Normal salivary glands are composed of serous and mucinous acinar cells and ducts with surrounding myoepithelial cells and supporting stroma.
- Neoplasia within the salivary glands consists of a diverse group of benign and malignant tumours, some of which show overlapping morphological and immunohistochemical appearances.
- Metastases to H&N are rare and usually as a result of primaries originating in the kidney, colon, breast, lung, thyroid, prostate or melanoma. Identification often requires immunohistochemistry as well as a detailed clinical history and radiological correlation.

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Management of Head and Neck Tumours

3

Tom Roques

Contents

In general, stage I/II cancers are treated with surgery or radiotherapy alone, whilst stage III/IV non-metastatic cancers have better outcomes with combined treatment—either chemotherapy added to radiotherapy, or surgery followed by postoperative radiotherapy, often with concomitant chemotherapy.[1]

The initial treatment decision is often whether surgery or radiotherapy should be the primary treatment. If microscopic complete excision is possible, surgery is the fastest way to remove cancer, offer instant cure, and gives definitive pathology which can guide adjuvant therapy, but removing part of a functional organ necessitates careful rehabilitation and reconstruction.

The theoretical advantage of radiotherapy is target organ preservation and consequent return to normal function. This needs to be balanced against acute side effects which will impact quality of life in the short term, and possible late treatment sequelae, including a nonfunctioning larynx and osteoradionecrosis, which

[1] Chemotherapy at the same time.

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themselves can necessitate surgery. There is also a greater residual uncertainty when a cancer is irradiated but not removed.[2]

The role of the multidisciplinary team in head and neck cancer (H&Nca) cannot be over-emphasised. These tumours and their treatment often have a profound effect on speaking and swallowing. Dieticians, speech and language therapists, restorative dentists and clinical nurse specialists are the key to ensuring people maximise function before, during and after treatment. Incurable disease presents major challenges for similar reasons and the psychosocial effects of advanced local disease have a major impact on quality of life and function. Local recurrence is more common than distant metastases, so H&Nca death is often with advancing local disease and profound functional challenges.

3.1 Surgery

For small cancers, simple excision without reconstruction is often enough and it may be with a knife, transoral laser or robotic surgery depending on site and surgical expertise. One potential advantage of primary surgery over primary radiotherapy is that there is definitive pathological assessment which can aid in prognostication and guide adjuvant treatments for those at higher risk of local recurrence [1]. Adjuvant radiotherapy to the primary site may be recommended with close/involved excision margins when further surgery is not possible.

For larger cancers, the need to aim for complete microscopic excision is counterbalanced by the challenge of functional restoration, particularly when a large excision necessitates reconstruction of bone and/or soft tissue [2]. The type of reconstruction will often depend on comorbidities and functional aims, so a complex free-flap reconstruction may not be appropriate for all people.[3] Meticulous surgical planning and subsequent rehabilitation is very important for best outcomes. Dieticians, speech and language therapists and restorative dentists should meet the person before surgery. Adjuvant radiotherapy to the primary site is usually recommended for T3/T4 tumours, and concomitant chemotherapy in people with positive excision margins.

Neck dissection (ND) is the mainstay for treatment of the neck. Extent of surgery is determined by two main factors. Firstly, nodal levels with involved nodes detected by imaging at staging will be dissected. In addition, ND is recommended for nodal levels at risk of occult metastases predicated by knowledge of tumour biology and routes of spread, even if there is no imaging evidence of node metastases. Adjuvant neck radiotherapy (+/− concomitant chemotherapy) is recommended where adverse pathological features predict higher recurrence rates, e.g. extra-capsular nodal spread or more than one involved node [3, 4].

Types of neck dissections, Appendix (5).

[2] See PET/CT section on the role of FDG PET/CT in the assessment of the neck following chemoradiotherapy in people with advanced neck disease.

[3] See Appendix (4) for different types of reconstruction surgery.

3.2 Radiotherapy

High energy ionising photon radiation can cure most cancers, if they have not spread, and if a high enough dose can be delivered to the tumour without destroying adjacent normal tissues. Many H&N cancers are sensitive to radiation but the challenge has been to deliver dose to the correct site without affecting function. Advances in physics and computing now allow inverse planned treatment: targets that need to be treated or avoided are delineated on a CT image and algorithms find the best arrangement of multiple beams to achieve the conflicting demands of high dose to the tumour but minimal exposure to nearby tissues.

Intensity modulated radiotherapy (IMRT) allows increasing conformal doses to be delivered by moving lead leaves across the beam while treatment is delivered, effectively turning one beam into many smaller ones each able to deliver a different dose depending on how quickly the lead leaves are moved. Different doses can also be delivered to the target volumes, so a lower dose that may be needed to treat nodes at risk from microscopic spread, than to the primary tumour site. See Chap. 4 for further discussion on the topic.

The importance of accuracy of radiation delivery is reflected in the treatment planning process. An immobilisation shell or mask is created from deformable thermoplastics to ensure the person and tumour are in the same position throughout a course of treatment. The person is imaged with CT in the treatment position and these images are used to construct target volumes and critical normal tissues. The treatment itself is fractionated, the treatment delivered over 30–35 daily fractions, five times a week. This maximises recovery of normal tissues, which have a greater capacity than cancer cells to repair some of the daily damage, before the next fraction.

Radiation has significant effects. Acute side effects are to an extent predictable and depend on the site treated. Oropharyngeal irradiation will cause mucositis. It begins 2 weeks into treatment and escalates until it begins to subside about 2 weeks after the end of the course of radiotherapy. This is often severe enough to require opoids and to limit oral intake enough to require nasogastric or gastrostomy tube feeding. Larynx irradiation will produce a hoarse voice whilst salivary gland and oral mucosa radiation disrupts taste and saliva production.

Radiotherapy late side effects can be prevented to some extent by careful treatment planning and excellent support during treatment. Rehabilitation of swallow is easier if less of the pharyngeal mucosa is treated and if dietetic and speech and language therapist support reduces weight loss and maintains some swallowing during treatment. Osteoradionecrosis can be minimised by avoiding radiation dose to the mandible where possible and by good dental care. IMRT now allows routine sparing of the parotid glands for many people, often avoiding long-term xerostomia.

Proton beam therapy utilises the function of protons to deliver their dose at a particular depth in tissue compared to photons which penetrate less selectively. Access and the cost of machines limit their application in H&Nca but they have a particular advantage for some skull base tumours where a high dose is needed to a specific target while trying to avoid dose to brain.

3.3 Curative and Adjuvant Chemotherapy

Concomitant chemotherapy means weekly or three weekly cisplatin during a course of radiotherapy for stage III/IV disease. It potentiates the effect of radiation, increasing cure rates by approximately 6.5% but also increasing acute and late side effects [5]. Other drugs are sometimes used. There is particularly good evidence for cetuximab [6].[4] On-going studies are underway to determine whether cetuximab can substitute cisplatin and whether using combinations of drugs could increase cure rates in more advanced disease.

Neoadjuvant or induction chemotherapy is the use of chemotherapy as the initial treatment, usually before definitive radiation. Response is common but there is a lack of evidence that tumour shrinkage translates into increases in overall cure rates. So, currently, this approach has been particularly used in "organ preservation" techniques where a response to neoadjuvant chemotherapy allows a non-surgical approach to laryngeal and hypopharyngeal cancers to potentially preserve speech and swallowing [7].

3.4 Effects of Age and Comorbidity

Some of the most challenging decisions in cancer treatment are those made with people who have less physiological reserve to withstand treatments either because of co-morbidities or advanced age. This is particularly true in H&Nca where many tumours have not metastasized and so cure is technically possible but where treatment side effects are substantial. Careful discussion of treatment options and aims with the person and their families is vital and must include realistic assessments of function during and after therapy.

3.5 Locoregional Recurrence

Disease recurring after initial treatment poses a significant challenge as it is often at a more advanced stage and because any treatment is more challenging in the context of previous therapy, e.g., complication rates of surgery are higher in an irradiated area and function may already have been compromised by initial therapy. There is evidence that H&Nca sites can be re-irradiated to a curative dose safely as long as there is an interval of at least 3 years and there are no radiation late effects.

[4] Cetuximab belongs to a group of cancer drugs known as monoclonal antibodies. It works by locking into epidermal growth factor receptors [EGFR] on the surface of cancer cells. This stops growth factors from stimulating the cancer cells to divide and grow. It may also make the cancer cells more sensitive to the effects of chemotherapy and radiotherapy.

3.6 Incurable Disease

The cosmetic, social, psychological and functional effects of incurable H&Nca necessitate a multidisciplinary supportive approach to management. Palliative surgery can be useful in selected cases, e.g. debulking tumours that obstruct airways, whilst palliative radiotherapy is particularly useful to improve pain.

Palliative chemotherapy can be used to improve quality of life and perhaps extend survival. Cisplatin, 5-fluorouracil, taxanes and cetuximab all have evidence to support their use but only perhaps 30% of people respond to treatment, so potential benefits must be carefully balanced against the detrimental effects on quality of life. Newer agents targeting genetic abnormalities in cell signalling or modifying the immune system response to cancer are under investigation. They have yet to change management significantly, perhaps reflecting the complex genetics of each tumour which mean that targeting one pathway is not enough to do meaningful harm to the cancer.

Key Points

- In general, stage I/II cancers are treated with surgery or radiotherapy alone.
- Stage III/IV non-metastatic cancers have better outcomes with combined treatment—either chemotherapy added to radiotherapy, or surgery followed by post-operative radiotherapy, often with concomitant chemotherapy.
- The initial treatment decision is often whether surgery or radiotherapy should be the primary treatment.
- If microscopic complete excision is possible, surgery is the fastest way to remove cancer, offer instant cure.
- The theoretical advantage of radiotherapy is target organ preservation and consequent return to normal function.
- For small cancers, simple excision without reconstruction is often enough and it may be with a knife, transoral laser or robotic surgery depending on site and surgical expertise.
- For larger cancers, the need to aim for complete microscopic excision is counterbalanced by the challenge of functional restoration, particularly when a large excision necessitates reconstruction of bone and/or soft tissue.
- Neck dissection (ND) is the mainstay for treatment of the neck. Extent of surgery is determined by the involved and at risk nodal levels.
- Many H&N cancers are sensitive to radiation but the challenge has been to deliver dose to the correct site without affecting function.
- Proton beam therapy utilises the function of protons to deliver their dose at a particular depth in tissue compared to photons which penetrate less selectively.
- Disease recurring after initial treatment poses a significant challenge as it is often at a more advanced stage and because any treatment is more challenging in the context of previous.
- The cosmetic, social, psychological and functional effects of incurable H&Nca necessitate a multidisciplinary supportive approach to management.

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Radiological Imaging in Head and Neck Tumours

4

Julian Kabala and Matthew Beasley

Contents

Imaging has a limited role in diagnosis [1]. Most head and neck (H&N) tumours are referred for imaging after the diagnosis has been confirmed or strongly suspected clinically.[1] That said, with some less common malignancies, magnetic resonance

[1] Especially with the commonest sites of malignancy (oral cavity, oropharynx, larynx).

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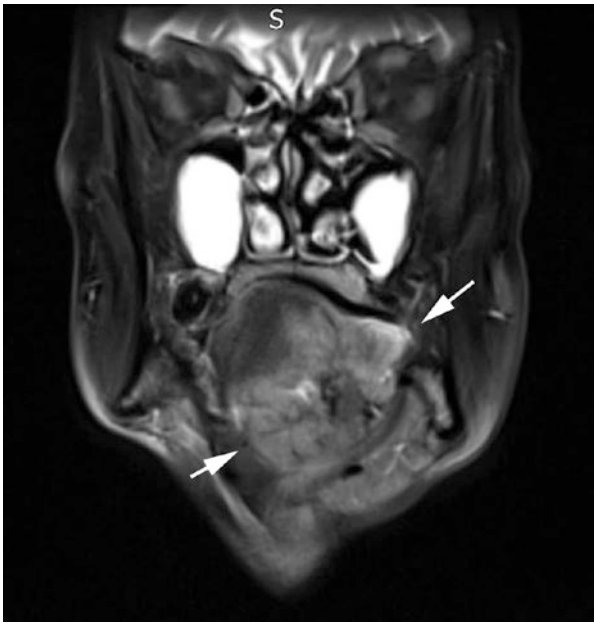

Fig. 4.1 Coronal fat saturated T2W MRI scan showing a very large malignancy originating in the left side of the tongue (*arrows*) and extending into the sublingual space and across the midline

imaging (MRI) has a more significant diagnostic role.[2] Also, in people with squamous cell cancer (SqCC) neck nodes, and no obvious primary site on clinical examination, MRI/CT will demonstrate the primary in approximately one third of cases.

TNM staging system is a clinico-pathological system but it is good practice when reporting scans to apply the principles of the system and offer a radiological stage. The advantage is analysis and description of the scan in a logical manner with appropriate emphasis on features of particular importance for planning treatment.

4.1 Primary Diagnosis/Staging

Primary tumour (T)

MRI, the single most important imaging modality for staging the primary tumour[3] (Fig. 4.1).

Nodes (N)

MR and CT, performed routinely to stage the neck (Fig. 4.2, 4.3, and 4.4). The overall false positive and false negative rates are 15–20% [2]. *Ultrasound* (USS) with fine needle aspiration is currently the most reliable and widely available technique for assessing cervical lymphadenopathy; most often used when there are equivocal nodes on CT/MR.[4]

Metastases (M)

[2] Notably paranasal sinuses, skull base and deep lobe parotid lesions may present non-specifically for example with features of sinusitis, nasal obstruction or cranial nerve symptoms (trigeminal neuropathy, facial or with cavernous sinus involvement, oculomotor palsy).

[3] For MR technique, please see Appendix (8).

[4] For MRI/CT/USS criteria for the diagnosis of nodal involvement, please see Appendix (9).

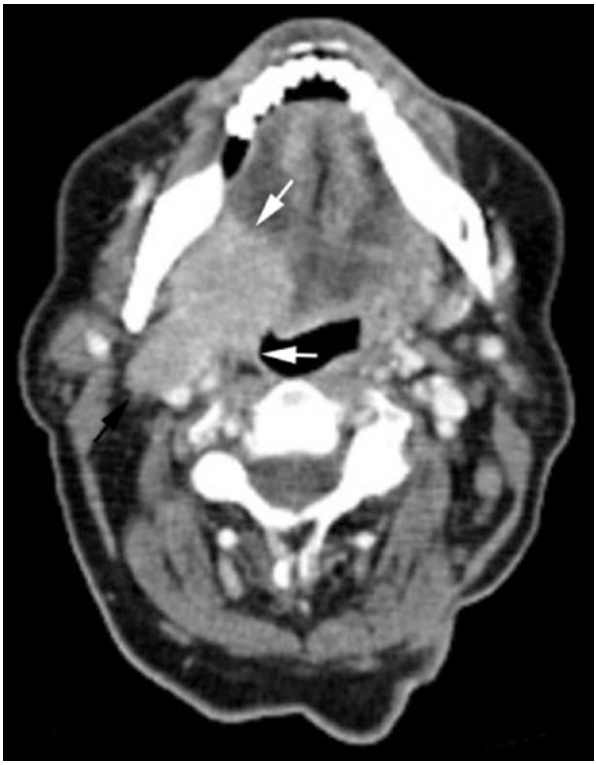

Fig. 4.2 Transverse image from contrast CT scan demonstrating an enhancing tumour of the right tongue base (*white arrows*) extending posterolaterally to abut right level II lymphadenopathy

For all but the smallest tumours, chest computed tomography (CT) is performed, on grounds that the most common site of distant metastases is the lungs.[5] It seems logical to extend the CT to include the extracranial H&N at the same time since this potentially offers additional information about local tumour extension, especially if MRI is equivocal or of poor quality, e.g., if the patient has moved.

Synchronous tumours outside the H&N are demonstrated in around 1%, two thirds carcinoma of bronchus, the remainder mostly oesophageal carcinoma [5–7].

4.2 Post Treatment Assessment

4.2.1 Sequelae of Surgery

Excision of the primary tumor is usually accompanied by repair of the defect with a reconstructive flap and neck dissection.[6] The individual tissue components of the reconstructive surgery, especially bone/fat, are easy to identify on both CT/

[5] CT will demonstrate pulmonary nodules in around 20% of patients. At least half will be benign. The rest will be malignant, mostly metastases, with a higher incidence in advanced H&N cancer (T3 or above and/or local lymph node metastases) [3, 4].

[6] For different types of neck dissection see Appendix (7). For types of surgical reconstruction see Appendix (6).

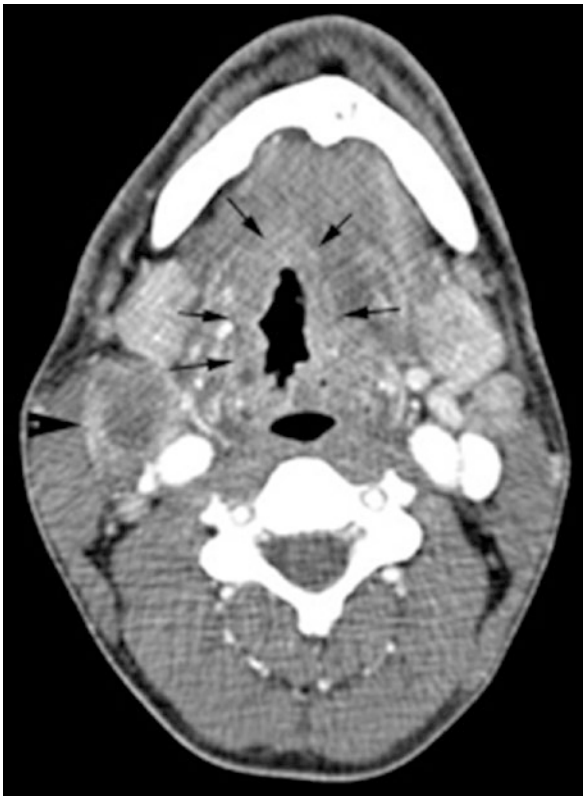

Fig. 4.3 Transverse image from contrast CT scan demonstrating centrally necrotic squamous cell carcinoma of the right tongue base (*small arrows*) and necrotic enlarged right level II lymph node (*large arrow head*) typical of regional nodal metastasis

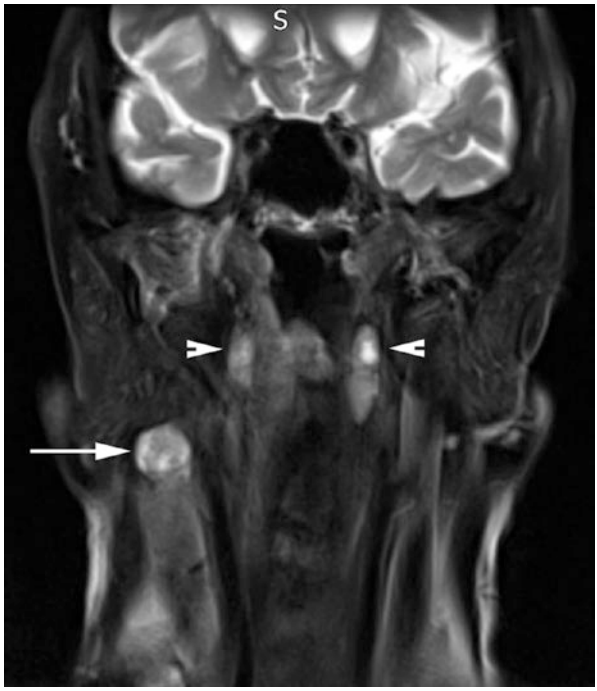

Fig. 4.4 Coronal STIR sequence from MRI scan on patient with tongue base carcinoma demonstrating necrotic right level II (*arrow*) and retropharyngeal (*arrowheads*) lymphadenopathy

MRI. Acute changes post-surgery, e.g., loss of tissue planes, oedema, normal structure distortion/swelling, lymphatic engorgement, seromas and enhancement of damaged tissue following contrast can be identified on CT/MRI; most resolve by 6 weeks.

4.2.2 Sequelae of Radiotherapy

With the exception of structural changes, radiotherapy provokes similar acute appearances, often over a larger area, persisting longer (up to 12 weeks) and with more pronounced and persistent subcutaneous and deep fat oedema (soft tissue stranding) and widespread mucosal swelling, especially in the larynx; usually symmetrical but sometimes surprisingly asymmetrical.

There is usually at least some degree of salivary gland inflammation (associated with high signal on MR and diffuse post-contrast enhancement on MRI/ CT) with subsequent atrophy. Although these features lessen with time there will be some persistence of all of them.

Between 6 weeks and 6 months while granulation tissue evolves into mature stable scar tissue the appearance is quite active on CT and, especially, MRI with post-contrast enhancement. From 6 to 12 months the stereotypical appearance of inert unenhancing scar tissue appears [8]. Although in some cases areas of enhancement persist.

Tumour recurrence, most often locoregional, is characterised by areas of enhancement, increasing bulk or new foci of soft tissue, often irregular and infiltrating, further loss of tissue planes and damage to normal structures, including bone erosion [9]. It is sometimes associated with nodal relapse and/or distant metastases, usually pulmonary. Isolated nodal or distant metastatic disease is less common [10].

A baseline scan around 3–6 months after intervention to demonstrate tumour response and record baseline post intervention changes, followed by surveillance scans for 3–5 years, often yearly, or more frequently, is a commonly used surveillance regime. The accuracy of early tumour detection with this sort of regime remains unclear.[7]

4.3 Radiotherapy Planning

Imaging plays a key role here. Accurate radiological assessment is crucial to radiotherapy planning in the H&N as the distance between tissue containing tumour and critical, radiation sensitive organs is often very small. Most H&N radiotherapy is

[7] In the first year following intervention MRI in particular is prone to false positives, up to 58% between 3 and 6 months following treatment [10]. Subsequently, a wide range of accuracy is reported, with perhaps surprisingly, sensitivity of at least 86% and specificity of 80% for CT compared to 50% and 83% respectively for MRI (admittedly on different study groups) [11, 12]. It remains uncertain how much this improves with diffusion weighted imaging or other specialised MRI techniques [13]. Looking specifically at persistent lymph node disease CT and MRI have similar relatively poor sensitivities and specificities of around 53% and 74% respectively compared to 88% and 66% for ultrasound (rising to a specificity of 96% for ultrasound guided fine needle aspiration cytology) [14].

now planned using a dedicated CT scan with the person immobilised in the treatment position in a thermoplastic shell. CT allows tissue density information which is used to predict radiotherapy dose distribution.

In addition, imaging is increasingly used during radiotherapy to further improve targeting of radiotherapy, image guided radiotherapy. IMRT provides one such example.[8] For people treated radically, to improve accuracy, the original planning CT position is compared with cone beam CT acquired on the treatment day and adjustments of patient position is made if this comparison falls outside predetermined thresholds.[9]

For tumours not easily visualised with CT, incorporation of MRI may reduce the chance of accidentally omitting tissue containing tumour from the high dose area [15]. Diffusion weighted MRI may provide superior information to conventional MRI for radiotherapy planning [16]. The evolving role of PET/CT is considered in the PET/CT chapter.

4.4 Normal Variants and Artefacts

Metal, most commonly dental amalgam, may cause large areas of image distortion or loss (attenuation artefacts).[10]

Prominent normal nodes are often impossible to differentiate from metastatic nodes on CT/MRI, especially in younger adults when normal nodes (especially level II) are relatively large (frequently 10–15 mm, maximum transverse diameter).

4.5 Advantages of MR, CT and USS

4.5.1 MRI

The single greatest advantage is high quality demonstration of soft tissue with good contrast between normal structures, benign and malignant pathology. It is generally the best investigation for delineation of the tumour mass, demonstration of local extension and, in the case of more advanced lesions, into more distant but clinically critical sites, particularly the neural foramina of the skull base and spread into the cranial cavity itself (Fig. 4.5) [17–19].

[8] IMRT is rapidly becoming the standard for radical H&N treatment because it results in more conformal radiotherapy plans which ensure that radiation beams are delivered to follow the shape of the tumour very closely, ensuring all of the tumour is encompassed inside the radiotherapy field and healthy tissue is avoided as far as possible. This allows better sparing of adjacent organs such as salivary glands and facilitates dose escalation with the promise of improved cures rates [20, 21].

[9] Cone beam CT is currently state-of-the-art IGRT. A flat panel detector and a kV radiation source are integrated into a linear accelerator. Multiple projection radiographs are acquired immediately before an RT fraction with short acquisition times, via rotation of the linac gantry. The image obtained [cone beam image] is registered onto the planning CT for calculation of the target position in relation to the planned position.

[10] Iatrogenically positioned material (fixating plates across osteotomy sites) and traumatically acquired foreign bodies cause similar artefacts.

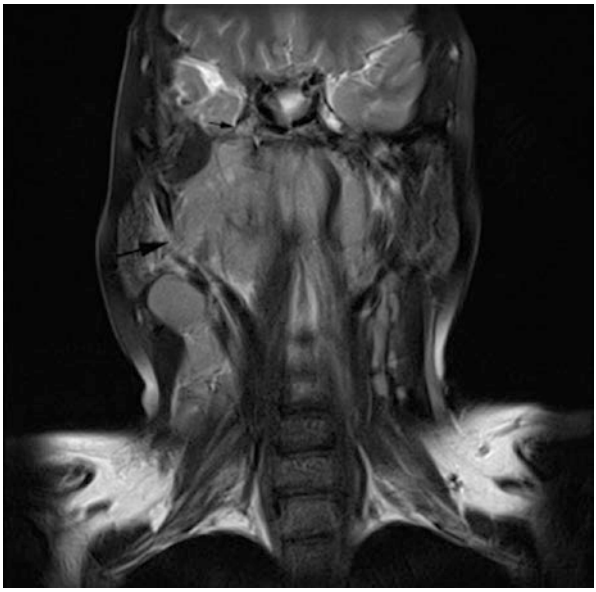

Fig. 4.5 Large right oropharyngeal squamous cell carcinoma invading posterolaterally into the masticator space (*large arrow*) and posterosuperiorly into the preverterbal space and skull base, via the foramen ovale, and into Meckel's cave (*small arrow*)

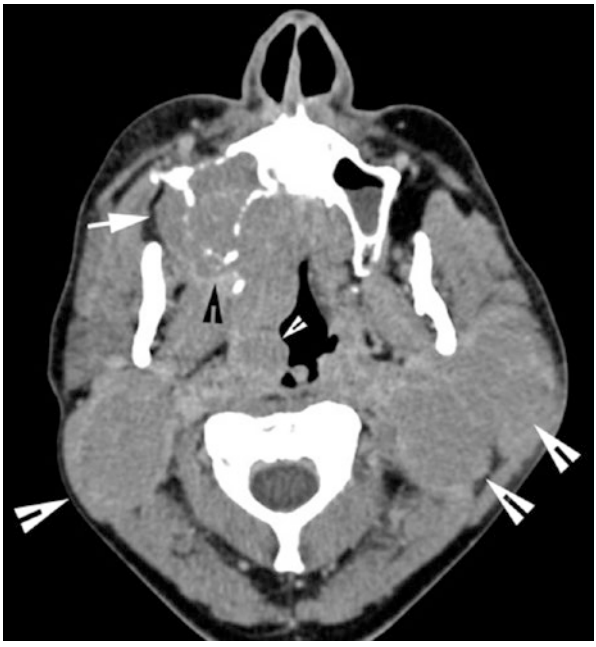

Fig. 4.6 Aggressive malignancy of the right hard palate extending into the maxillary antrum and out through the lateral wall into the cheek (*arrow*). Posterior extension takes the tumour into the pterygopalatine fossa (*black arrowhead*), a critical site of extension since this allows easy access to the cranial cavity and orbit (via the foramen rotundum and inferior oblique fissure). High volume level II (*large white arrowheads*) and right retropharyngeal (*small white arrowhead*) lymphadenopathy is present

4.5.2 CT

Offers complementary information to MRI about the local tumour stage (Fig. 4.6), particularly bone invasion which CT detects with an accuracy in excess of 90%, being marginally less sensitive than MRI but more specific [22–26]. It is currently the only imaging modality able to demonstrate small pulmonary metastases.

4.5.3 Ultrasound

Often combined with Doppler and potentially emerging techniques, e.g., elastography offers excellent characterisation of superficial soft tissue structures, e.g., neck nodes. It can demonstrate the presence, number, size, shape and internal architecture of nodes (all features that may be altered by the presence of metastatic tumour). It is extremely useful for sequential examinations (to monitor equivocal lesions) and to guide biopsies (fine needle and cutting needle).

4.6 Limitations of MR, CT, USS

4.6.1 MRI

People unable to lie flat and/or still for the time involved in scanning and/or tolerate the surface coil, e.g., due to claustrophobia, shortness of breath, pain, marked cervicothoracic scoliosis are unsuitable for MRI.

A minority of metallic foreign bodies constitute a hazard for MRI scanning either because of tissue damage due to heating (spinal nerve stimulaters), movement of metal fragments in the magnetic field (old-style intracranial aneurysm clips, intraorbital foreign bodies) or malfunction (cochlea implants, pacemakers) [27, 28].

4.6.2 CT

A relatively common problem with CT is artefact arising from high-density material in the area of interest [29]. This is a particular problem in the oral cavity, where high-density fillings may degrade large areas of the image. Postoperatively, metal surgical clips may also produce significant streak artifacts.

Renal dysfunction and contrast hypersensitivity constitute respectively relative and absolute contraindications to the administration of intravenous contrast.

Both CT and MRI have particular anatomical sites where accurate tumour staging is difficult, notoriously with respect to invasion of the prevertebral space, still probably best assessed clinically, unless there is marked invasion with obvious muscle/bone changes.

4.6.3 USS

Virtually all ultrasound is reflected at interfaces between soft tissue and air or bone. Consequently, some lesions cannot be visualized, e.g., deep to the mandible or directly through air-filled structures, e.g., behind the trachea. Retropharyngeal nodes therefore cannot be assessed with ultrasound. Also, attenuation of ultrasound rapidly increases with thickness of tissue and therefore there is limited information available about deep lying structures, a problem worsened when there is thick superficial scarring in the neck.

4.7 Pitfalls

1. *Misdiagnosing a cystic neck mass*, most frequently at the mandibular angle, a classical pitfall. The differential usually lies between a SqCC node metastasis and a branchial cleft cyst. Less commonly presentation of metastatic disease from papillary carcinoma of thyroid or cervical nodal tuberculosis. As a general rule, SqCC should be the considered diagnosis; branchial cleft cyst only very cautiously, and especially in people over 40.
2. *Overlooking disease outside the primary area of concern*, e.g., skip lesions of adenoid cystic carcinoma at the skull base, extracranial disease in people with neurological presentations, upper aerogestive tract, thorax, upper abdomen synchronous tumours.
3. In initial staging/assessment of potential recurrent tumour MRI tends to overstage due to associated peritumoral (or post-intervention) oedema and reactive inflammatory changes. Similarly, periodontal infection and recent dental extraction may be misdiagnosed as tumour[11] [22].
4. The distinction of an aggressive-appearing lesion after treatment is between metachronous tumours [6], radiation-induced sarcomas (usually many years post-treatment, average around 9 years, range 3–37 years [30]) and osteroradionecrosis (ORN), where there is bone destruction.

ORN most commonly affects the mandible and demonstrates the typical appearance of osteomyelitis (permeative areas of bone destruction, cortical interruptions, sequestra and pathological fractures) with a surrounding soft tissue inflammatory mass which is often contiguous with swollen and enhancing masticatory muscles. It may appear similar to recurrence but differentiating features include the clinical picture (inflammatory features including the presence of pus and draining sinuses), areas of sclerosis, as the bone attempts healing, and diffuse swelling rather than destruction of adjacent soft tissue structures (particularly the muscles). Most of these features are best seen with CT rather than MRI [31, 32].

Key Points

- Imaging has a limited role in diagnosis
- Most head and neck (H&N) tumours are referred for imaging after the diagnosis has been confirmed or strongly suspected clinically
- MRI, the single most important imaging modality for staging the primary tumour
- MR and CT, performed routinely to stage the neck. The overall false positive and false negative rates are 15–20%

[11] As a general (but not invariable) rule, if there is signal change only on the STIR sequence but not the T1W images, the process is benign; if changes occur on both, it more likely represents tumour invasion.

- Ultrasound (USS) with fine needle aspiration is currently the most reliable and widely available technique for assessing cervical lymphadenopathy; most often used when there are equivocal nodes on CT/MR
- Most H&N radiotherapy is now planned using a dedicated CT scan with the person immobilised in the treatment position in a thermoplastic shell.
- CT allows tissue density information which is used to predict radiotherapy dose distribution.
- Diffusion weighted MRI may provide superior information to conventional MRI for radiotherapy planning
- The single greatest advantage of MRI is high quality demonstration of soft tissue with good contrast between normal structures, benign and malignant pathology.
- CT offers complementary information to MRI about the local tumour stage particularly bone invasion
- Ultrasound (often combined with Doppler and potentially emerging techniques, e.g., elastography) offers excellent characterisation of superficial soft tissue structures, e.g., neck nodes.
- Renal dysfunction and contrast hypersensitivity constitute respectively relative and absolute contraindications to the administration of intravenous contrast.
- Both CT and MRI have particular anatomical sites where accurate tumour staging is difficult, notoriously with respect to invasion of the prevertebral space.

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18F FDG PET/CT: Normal Variants, Artefacts and Pitfalls in Head and Neck Malignancy

5

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Contents

5.1 Introduction

FDG PET-CT is being increasingly used in head-neck cancer for staging, response assessment and detection of disease recurrence. There are several regions in the head and neck like the oral cavity, pharynx, larynx, orbits, salivary glands, each having its own subsites. Each of these subsites demonstrates a standard, symmetric pattern of physiological FDG concentration which enables us to identify pathological lesions. Occasionally, these normal patterns can vary in their standard appearance even in the absence of any intervention or treatment and give an impression of disease. Multi-modality treatment in head-neck cancer leads to loss of anatomical landmarks and symmetry, induces inflammation/infection and causes complications which can result in artefacts and pitfalls during image interpretation.

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5.2 Variants/Alterations in Physiological Uptake

Physiological FDG uptake in the muscles of mastication, extraocular muscles, neck muscles, floor of mouth structures, tonsils, vocal cords can be easily identified due to its bilaterally symmetric nature either side of the midline [1]. When physiological tracer uptake is unilateral and asymmetric in nature, it can be difficult to interpret and lead to errors. Weakness or paralysis of a contralateral muscle due to denervation atrophy (Fig. 5.1), surgical resection leading at alteration of normal mechanics, radiation-induced inflammation and subsequent fibrosis are the common reasons for asymmetric uptake in the head-neck region. Occasionally, such a finding can be seen in individuals without any apparent cause (Fig. 5.2). Localisation of the uptake to a known anatomical structure and absence of a discernible mass or a structural abnormality on the CT can help confirm the physiological nature of tracer uptake [2, 3].

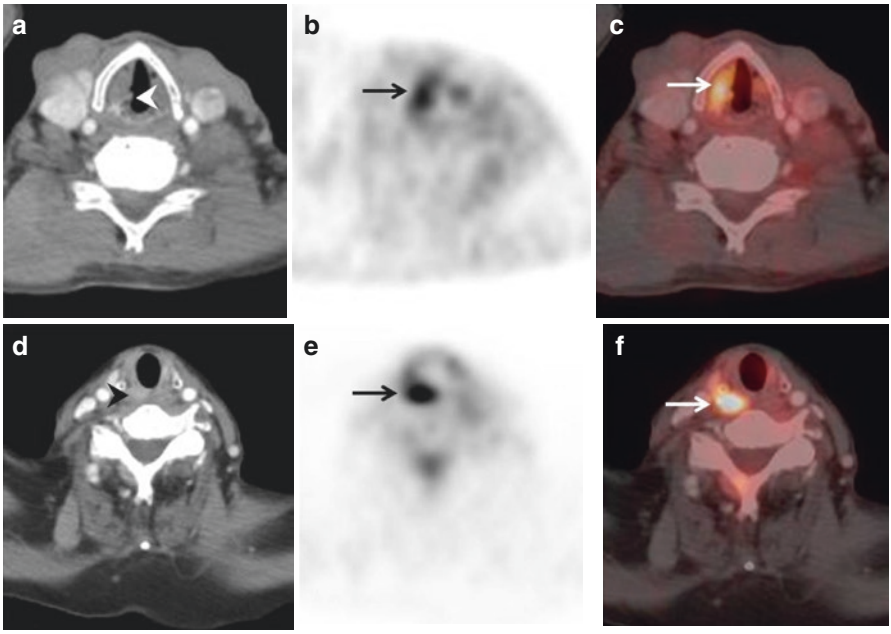

Fig. 5.1 Common presentation and unusual variation of FDG uptake in vocal cord palsy. Axial PET and fused PET/CT show increased physiological FDG uptake in the thyro-arytenoid fibres of the vocal cord (*arrows* in **b** and **c**) because paralysis of the left vocal cord. CT scan shows the free edge of the normal non-paralysed right vocal cord (*arrowhead* in **a**). Axial PET and fused PET/CT of another patient with left vocal cord paralysis shows intense focal FDG uptake on the right, distant from the expected site of physiological uptake (*arrows* in **e** and **f**). This finding is due to physiological uptake in the crico-arytenoid fibres of the vocal cord (*arrowhead* in **d**) and can be erroneously considered disease in the post cricoid region

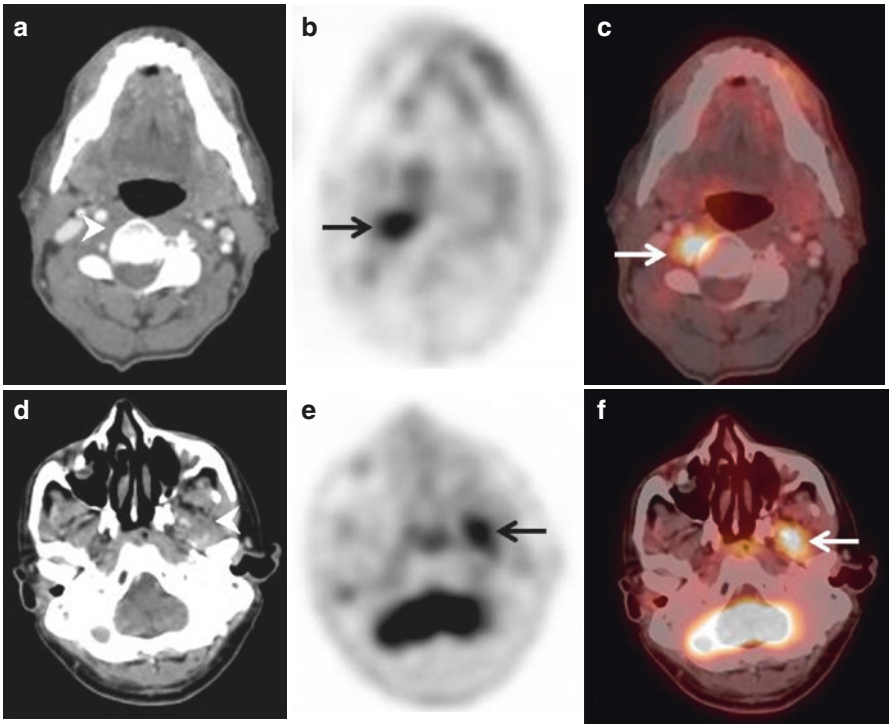

Fig. 5.2 Asymmetric physiological uptake in neck muscles. Axial PET and fused PET/CT show asymmetric intense focal FDG uptake (*arrows* in **b** and **c** and **e** and **f**) which is localised to the longus coli (*arrowhead* in **a**) and the lateral pterygoid (*arrowhead* in **d**) muscles on the CT scan. Note the absence of any abnormal finding on CT images

5.2.1 Surgical Changes

The extent of surgery for head-neck cancer can range from marginal/wide excisions to more extensive resections that involve removal of soft tissue, muscle, bone, vessels and nodal groups along with the tumour itself. Large defects arising due to such surgeries are closed by using muscle flaps and bone grafts. Pectoralis myocutaneous flap is commonly used for reconstruction of large surgical defects in the head neck region [4]. It can be identified by the well-defined muscle and fat density structure at the site of the defect produced by a denervation atrophy and fatty replacement of the muscle [5]. Absence of normal physiological uptake at the site of reconstruction disturbs the normal symmetric nature of uptake (Fig. 5.3). Altered mechanics of mastication, deglutition and other motor functions can produce asymmetric patterns of physiological uptake which can often mimic pathology (Fig. 5.4).

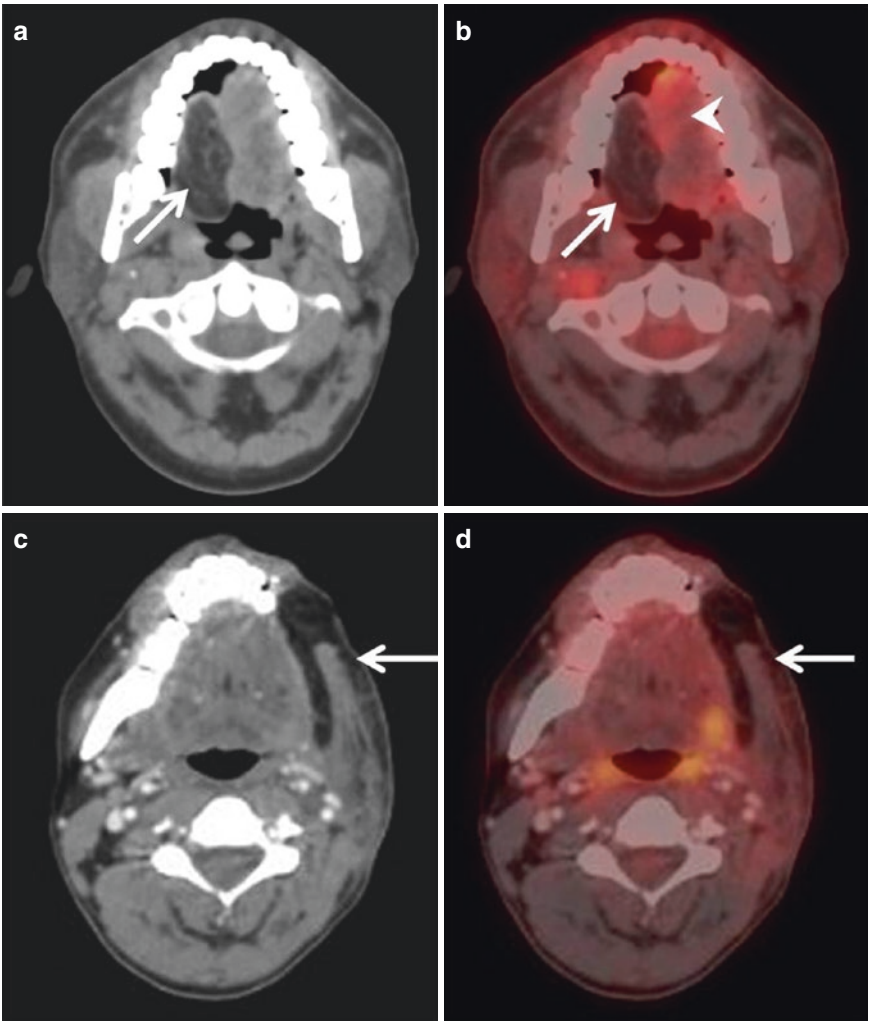

Fig. 5.3 Surgical changes due to flaps and grafts. Axial CT and fused PET/CT show myocutaneous flaps used to close hemiglossectomy and hemimandibulectomy defects seen as fat density structures (*arrows* in **a**–**d**). Physiological FDG uptake is seen in the remnant tongue (*arrowhead* in **b**)

5.2.2 Radiation Changes

Radiotherapy leads to certain acute effects like increased vascularity, edema and inflammation in structures included in the radiation field. After radiation therapy the skin, subcutaneous tissue, neck muscles, salivary glands, pharyngeal and laryngeal mucosa show a pattern of FDG uptake (Fig. 5.5) which is symmetrical and diffuse in nature [6]. This uptake is transient and can be seen in the first few months

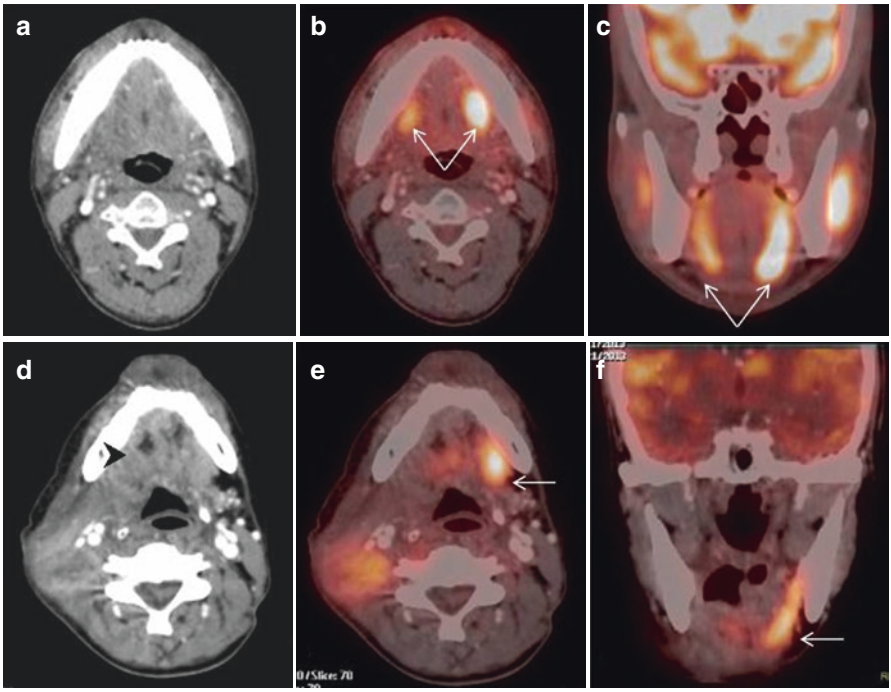

Fig. 5.4 Symmetric and asymmetric uptake in the floor of mouth (FOM). Axial PET and fused PET/CT demonstrate symmetrical FDG uptake in the FOM/mylohyoid muscle (*arrows* in **b** and **c**). Asymmetric focal physiological uptake is seen in the FOM on the left (*arrows* in **e** and **f**) due to surgical excision of right FOM tumour (*arrowhead* in **d**)

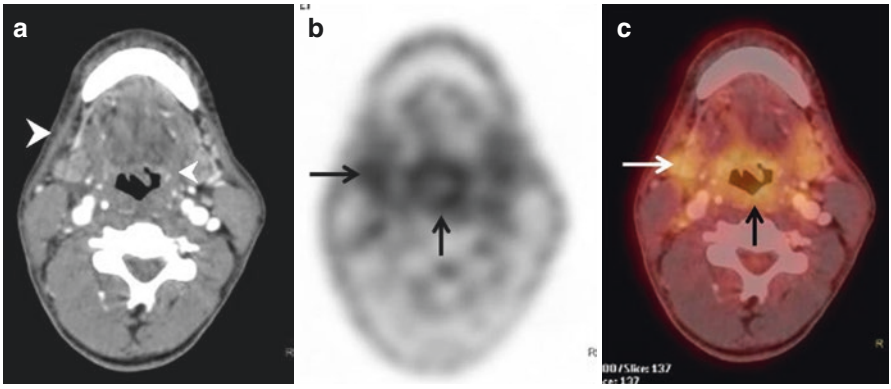

Fig. 5.5 Expected changes after radiation therapy. Axial PET and fused PET/CT images show diffuse low grade uptake in the pharyngeal mucosa and parapharyngeal regions (*vertical arrows* in **b** and **c**) and in the right submandibular gland (*horizontal arrows* in **a** and **c**). CT shows thickened platysma (*arrowhead* in **a**)

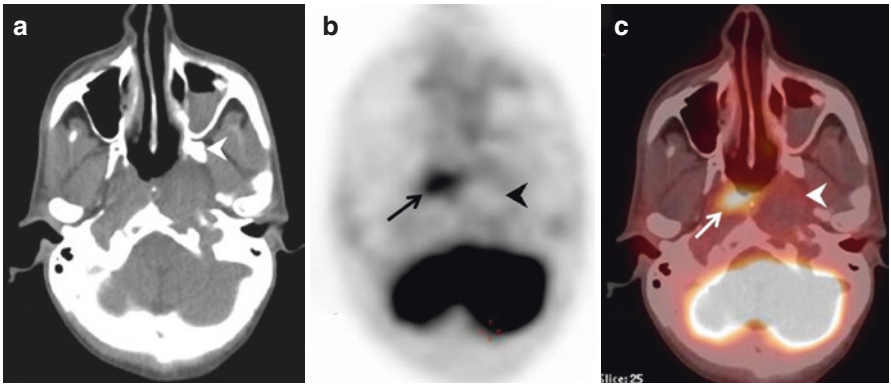

Fig. 5.6 Asymmetric post radiation uptake post mimicking disease. Axial PET and fused PET/CT show asymmetric uptake in the right lateral aspect of the nasopharynx which is normal and physiological in nature but can mimic disease (*arrows* in **b** and **c**). Tumour involving the left lateral wall has been completely irradiated seen as photopenia (*arrowheads* in **a**–**c**)

following radiotherapy. Unilateral and asymmetric inflammatory or physiological uptake can be misleading and wrongly interpreted as disease (Fig. 5.6).

Timing of PET/CT after radiotherapy has been a matter of much debate. Performing PET/CT too soon can produce false positive as well as false negative results. One of the possible mechanisms for false negativity is radiation-induced vascular damage which affects tracer concentration in the viable tumour [7]. Waiting a few weeks longer allows FDG to accumulate in the viable cells leading to a true positive diagnosis of residual disease (Fig. 5.7). Posttreatment inflammation can result in false positives leading to unnecessary interventions and biopsies (Fig. 5.7). Waiting too long after the radiation can result in loss of therapeutic window and a potentially complicated surgery due to setting in of fibrosis. An interval of 8–12 weeks after radiotherapy has been recommended to offset the drawbacks of imaging too early or too late [8, 9].

5.3 Pitfalls Due to Treatment Complications

One of the rare but feared complications of radiation therapy is tissue necrosis, seen months to years after radiotherapy.

Devitalisation of the irradiated bone causes osteoradionecrosis (ORN). Mandible is the commonest site of ORN in the head-neck region. Dental infection or trauma is known to precipitate ORN. Increased FDG uptake is seen in areas of the mandible affected by ORN (Fig. 5.8) and can be mistaken for recurrence. FDG PET is limited in its ability to differentiate viable tumour from ORN [10]. Lysis, cortical erosion and fragmentation of the mandible with air pockets, soft tissue thickening, fistula formation are some of the features seen on CT scan that can help in establishing diagnosis of ORN [11].

Laryngeal necrosis/chondronecrosis is a late effect of radiation therapy for laryngeal cancer. When the perichondrium is breached by the tumour exposing

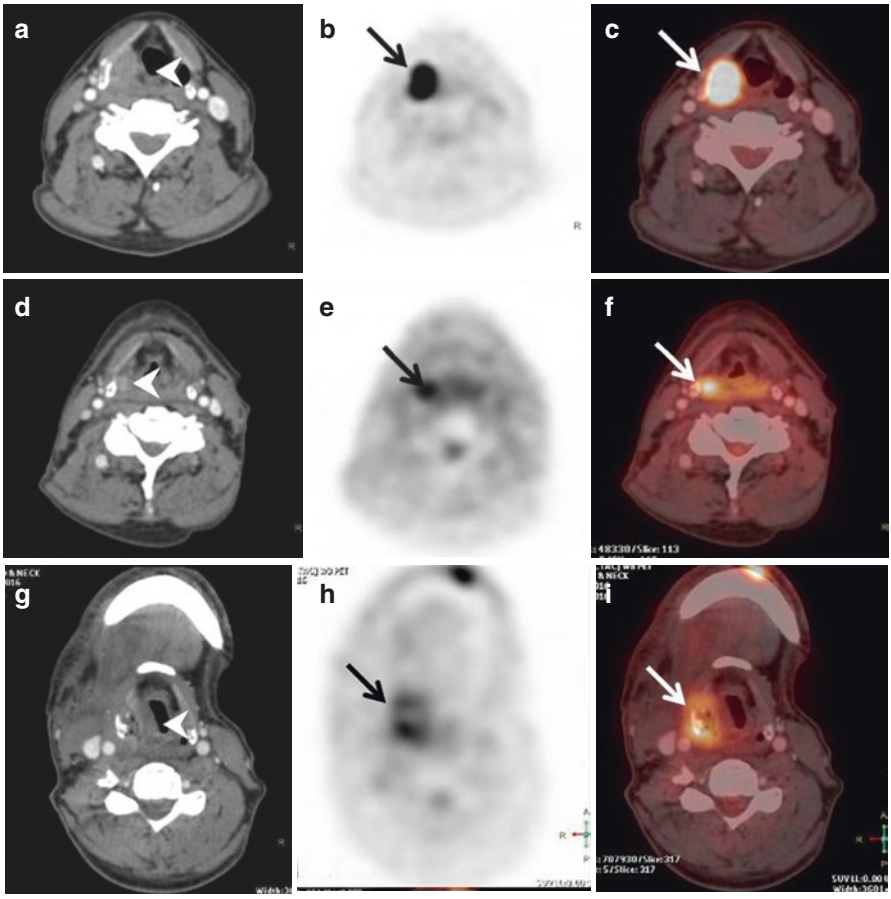

Fig. 5.7 Evaluation after chemo-radio therapy. Axial CT, PET and fused PET/CT show malignancy of the right pyriform sinus (*arrowhead* in **a**, *arrows* in **b** and **c**). Scan done after 8 weeks of chemoradiation treatment shows focal uptake (*arrows* in **e** and **f**) in an enhancing lesion in the pyriform sinus (*arrowhead* in **d**) suggesting residual disease. PET/CT done after 6 weeks of radiation in another patient shows uptake in the pyriform sinus which is more diffuse in nature (*arrows* in **h** and **i**) due to post radiation inflammation and not residual disease

the underlying irradiated cartilage to microorganisms, it can lead to infectious perichondritis and laryngeal necrosis. FDG uptake is seen in the reactive inflammatory rim around the area of necrosis and should not be confused with tumour (Fig. 5.9). Fragmentation of the cartilage, fluid and air bubbles are findings suggesting chondronecrosis on CT [12]. Deep soft tissues of the neck as well as those of the pharynx and larynx can also undergo soft tissue necrosis. Complete photopenia in the necrotic area with rim of FDG uptake in the surrounding inflammed tissues and air bubbles in the necrotic centre suggests the diagnosis of soft tissue necrosis (Fig. 5.10).

Vertebral osteomyelitis/spondylodiscitis in the cervical spine is a rare complication seen after radiation therapy to the head-neck region. Intense FDG uptake in the

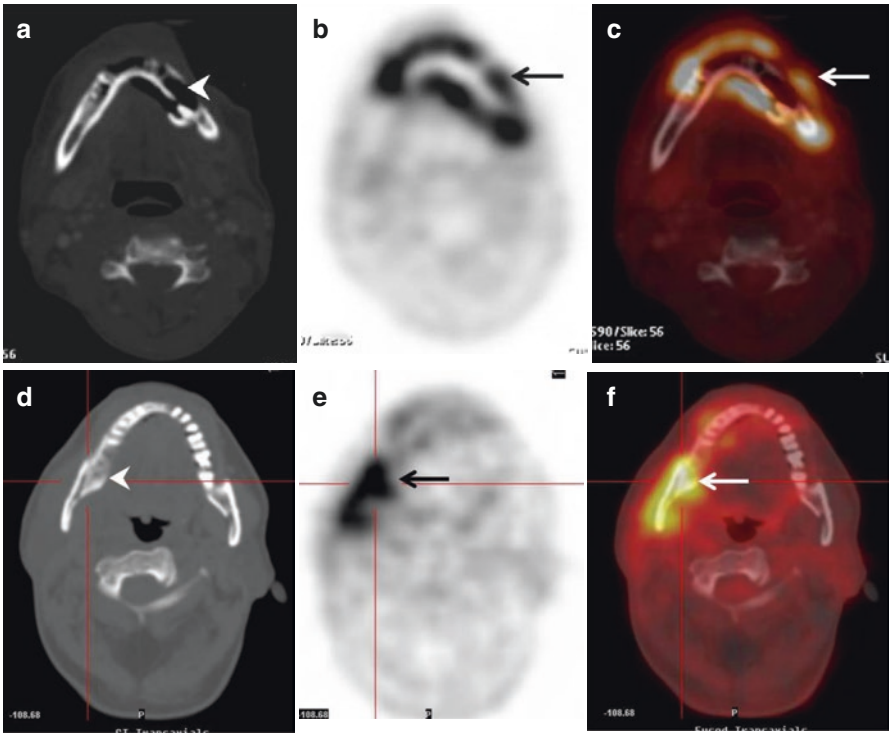

Fig. 5.8 Mandibular Osteoradionecrosis. CT shows lytic defect in the left hemimandible with air pockets (*arrowhead* in **a**) due to ORN. Axial PET and fused PET/CT show peripheral rim of uptake in the surrounding inflammed tissues (*arrows* in **b** and **c**) with photopenia in the central necrotic portion. (**d**–**f**) Another variant of mandibular ORN, with diffuse sclerosis seen on CT (*arrowhead* in **d**) and intense uptake seen on PET (*arrows* in **e** and **f**)

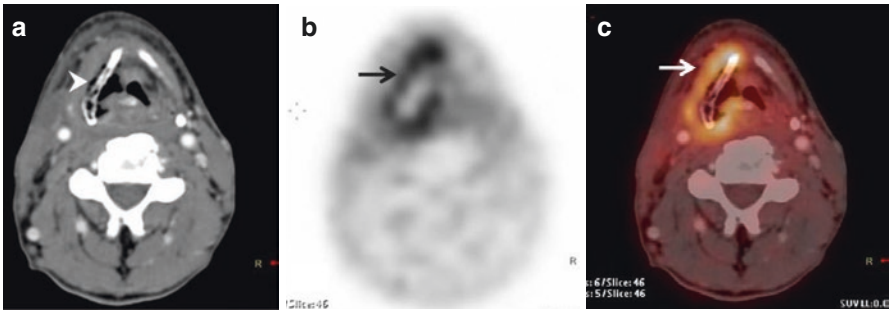

Fig. 5.9 Chondronecrosis. CT shows air bubbles in the fragmented thyroid cartilage (*arrowhead* in **a**). Axial PET and fused PET/CT show peripheral rim of uptake in the surrounding inflammed tissues with central photopenia (*arrows* in **b** and **c**) suggesting chondronecrosis

involved vertebrae with associated erosive changes in the bones can mimic vertebral metastases (Fig. 5.11). Findings restricted to the radiation portal and localised to the intervertebral discs and adjoining end plates indicate the diagnosis of infective spondylodiscitis.

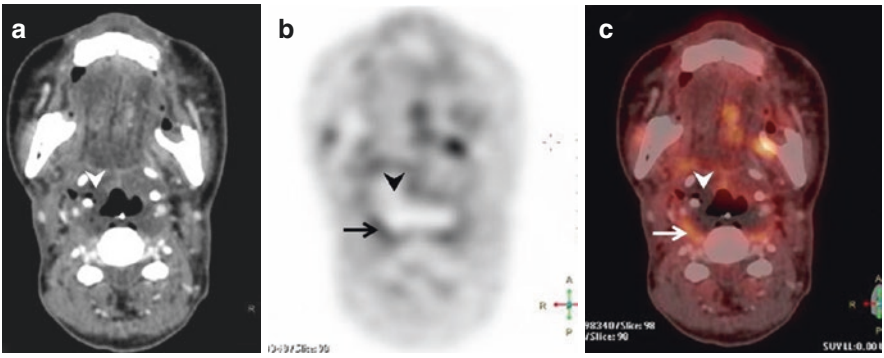

Fig. 5.10 Soft tissue necrosis. CT and PET/CT show a hypodense non-enhancing oropharyngeal wall with air bubbles within (*arrowheads* in **a** and **c**). Axial PET and PET/CT show peripheral rim of uptake in the surrounding inflammed tissues with central photopenia (*arrows* in **b** and **c**) suggesting soft tissue necrosis

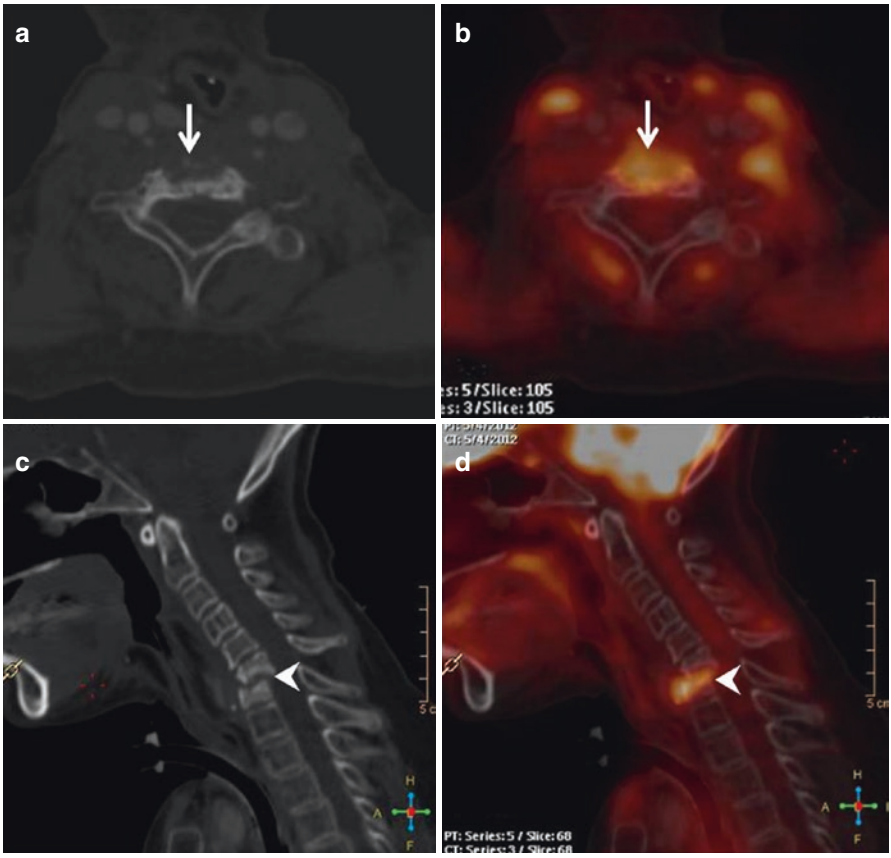

Fig. 5.11 Post radiation Spondylodiscitis. Patient treated with radiation for oropharyngeal cancer. CT shows a lytic defect in the vertebral body (*arrow* in **a**) showing increased FDG uptake (*arrow* in **b**) suggesting the possibility of metastasis. Sagittal PET/CT shows tracer uptake localised to C6–C7 intervertebral disc (*arrowhead* in **d**) with erosive changes in the adjacent end plates (*arrowhead* in **c**) due to post radiation spondylodiscitis

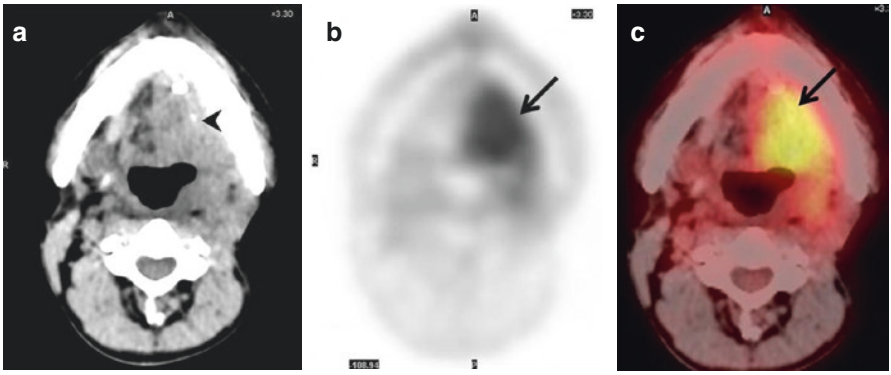

Fig. 5.12 Surgical flap inflammation. CT scan shows a recently operated muscle flap in the left half of the tongue (*arrowhead* in **a**). Axial PET and PET/CT show intense FDG uptake restricted to the flap (*arrows* in **b** and **c**) which has sharp well-defined margins suggesting flap inflammation

Complications due to surgery occur early as compared to radiation and include serous collections, infections, abscess and fistulae, flap inflammation and necrosis. Benign serous collections or seromas are self-limiting and are not FDG avid unless they are infected. Surgical complications occur at the site of resection and reconstructed flaps in the head-neck region. Flap inflammation and necrosis is associated with increased FDG uptake that is diffuse and linear with well-demarcated margins restricted to the region of the reconstructed flap/graft (Fig. 5.12).

5.4 Pitfalls Due to False Negative Findings

Unlike the numerous known causes of false positive studies, pitfalls due to false negative PET are relatively fewer. Necrotic lymph nodes harbor less number of viable cells and often show poor or no FDG concentration [13] (Fig. 5.13). Certain malignancies like those of the salivary glands and spindle cell neoplasms also show poor FDG concentration and can be missed. The ability of PET to detect perineural spread of disease (commonly encountered in adenoid cystic carcinomas) is inferior to MRI (Fig. 5.14). Careful attention should be given to the subtle FDG uptake along the pathways of perineural spread and corresponding CT findings to diagnose this condition.

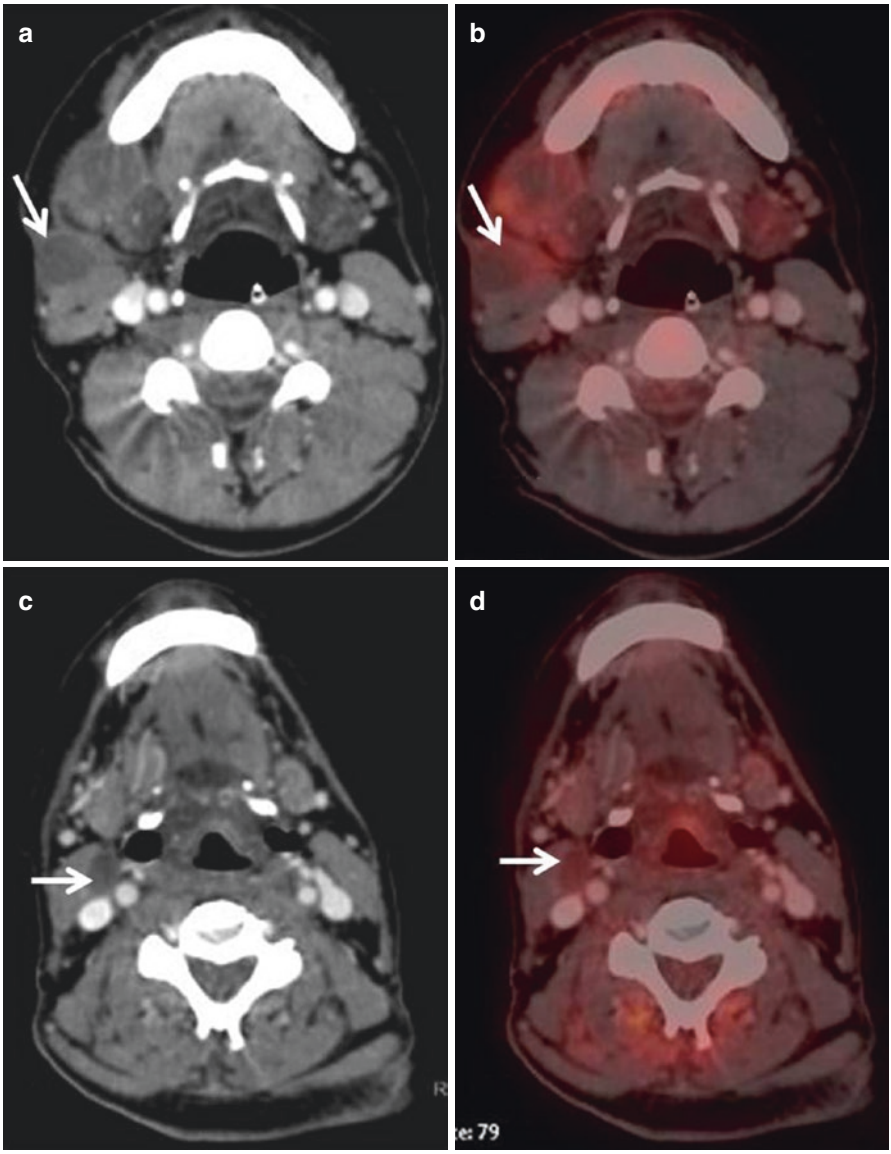

Fig. 5.13 False negative PET due to necrotic nodes. CT scan shows necrotic right sided neck nodes in two different patients (*arrows* in **a** and **c**) which had metastatic foci on cytology. No FDG uptake is seen on fusion PET/CT images (*arrows* in **b** and **d**)

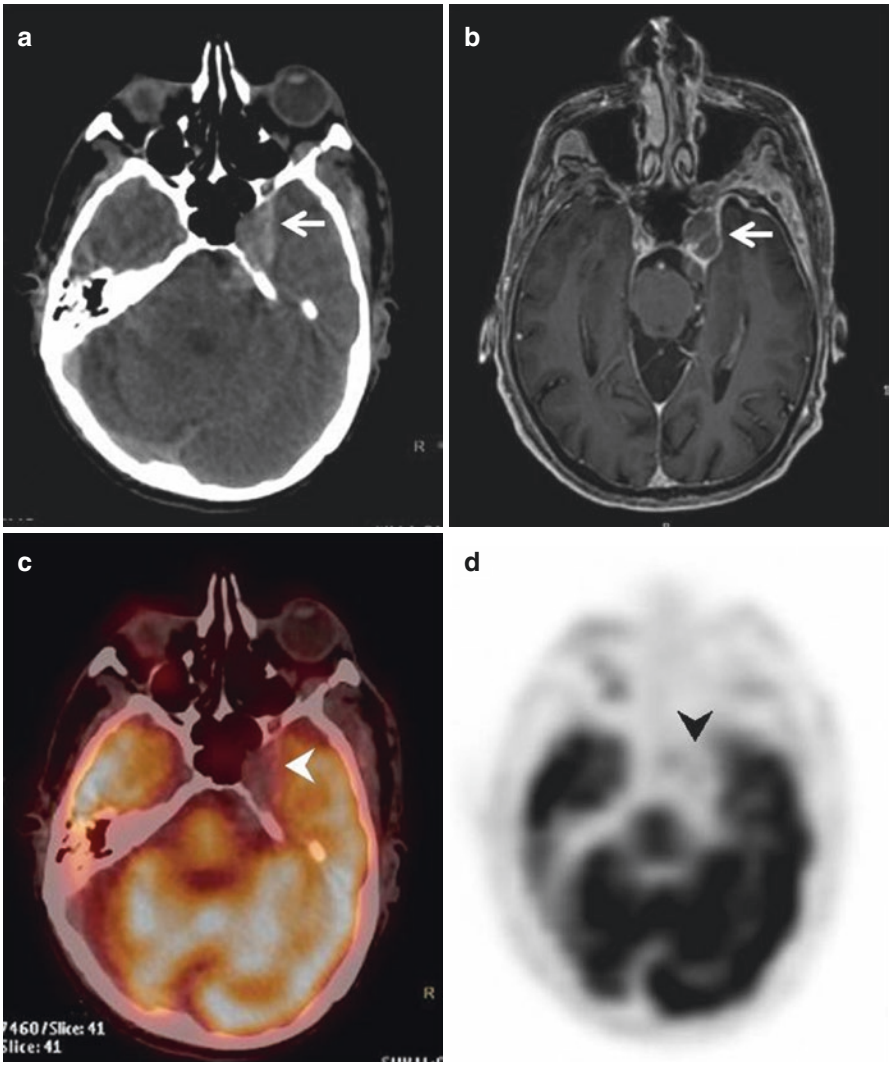

Fig. 5.14 False negative PET in perineural disease. CT scan and axial T1 W MRI show perineural disease spread in the region of the cavernous sinus (*arrows* in **a** and **b**) in patient of adenoid cystic carcinoma of the hard palate. Axial PET and PET/CT show no metabolic activity in the lesion (*arrowheads* in **c** and **d**)

Conclusion

The complex anatomy of the head-neck region and its various subsites gives rise to pattern of physiological uptake that can be highly variable. Normal variations in the pattern of physiological uptake as well as alterations produced by surgical and radiation therapy can produce errors in interpretation. Pitfalls can also arise

because of treatment-related complications, which simulate disease. Knowledge of physiological variations of tracer uptake, Artefacts and treatment complications is essential in avoiding diagnostic pitfalls.

Key Points

- FDG PET-CT is being increasingly used in head-neck cancer for staging, response assessment and detection of disease recurrence.
- FDG concentration enables us to identify pathological lesions.
- Multi-modality treatment in head-neck cancer leads to loss of anatomical landmarks and symmetry, induce inflammation/infection and cause complications which can result in Artefacts and pitfalls during image interpretation.
- Physiological FDG uptake in the muscles of mastication, extra-ocular muscles, neck muscles, floor of mouth structures, tonsils, vocal cords can be easily identified due to its bilaterally symmetric nature either side of the midline
- When physiological tracer uptake is unilateral and asymmetric in nature, it can be difficult to interpret and lead to errors.
- Altered mechanics of mastication, deglutition and other motor functions can produce asymmetric. FDG uptake in the head-neck region. Complications of surgery and radiation therapy can lead to false positive findings and pitfalls.

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PET/CT in Head and Neck Tumours

6

Wai Lup Wong

Contents

FDG PET/CT has an established role in the assessment of head and neck squamous cell cancer (H&N SqCC). As such, the focus of the chapter will be on FDG PET/CT and H&N SqCC. Separate short commentaries are provided on the role of FDG PET/CT for other tumours and on the evolving role of radio-tracers beyond FDG. Specific comments relevant to H&N haematolymphoid disorders is included in the appendix.[1]

[1] Please see Appendix 9.

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to Radionuclide Hybrid Imaging, https://doi.org/10.1007/978-3-319-61440-3_6

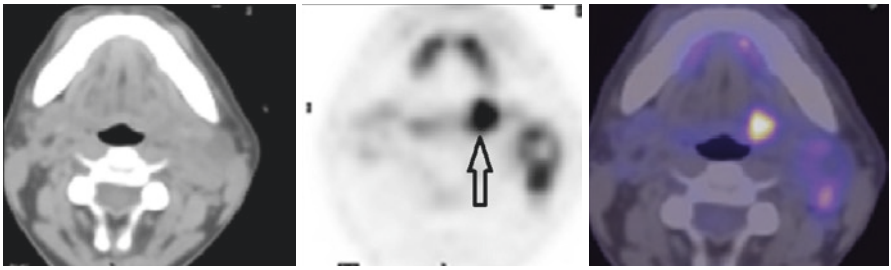

Fig. 6.1 60 year old man presented with an enlarged node in the LT neck. USS with FNAC showed SqCC. Usual assessment including CT and MR shows no primary site. FDG PET/CT shows the neck node and intense focal FDG uptake in the left tongue base (*hollow arrow*). EUA and biopsies confirm a primary malignancy in left tongue base

6.1 Primary Diagnosis

There is universal agreement for using FDG PET/CT in people with malignant neck nodes and no primary site identified on usual assessment [1]. FDG PET/CT influences management plan primarily, by increasing detection of the primary site [2, 3]. The diagnostic rate to an extent depends on the investigations prior to FDG PET/CT, and the more the investigations the lower the detection rate. In addition, FDG PET/CT improves diagnosis of nodal disease, detects unexpected distant metastases, albeit infrequently.[2] Finally, occasionally but importantly, FDG PET/CT detects occult synchronous cancers, most often silent colon and lung cancers [2, 3]. Currently, many centres offer people FDG PET/CT after clinical assessment and CT/MR shows no primary site, and prior to EUA and biopsy. Increase in confidence in the use of FDG PET/CT and availability of scanners is leading to the view that FDG PET/CT should be considered the initial investigation reserving CT/MR only if necessary for treatment planning [5] (Fig. 6.1).

6.2 Staging

FDG PET/CT plays two important roles here: firstly, for staging people with high risk of disseminated disease [1]. In a significant number in this group, FDG PET/CT detects metastases not diagnosed on usual assessment [6–8]. There is however divergence in guidance as to whom should be offered FDG PET/CT. Perhaps for three reasons. Firstly, there is no consensus with regard to definition of "high risk" amongst clinicians. Second, there is the further variation influenced by cost-benefit considerations. The decision as to who should have FDG PET/CT, is made on balancing the probability of detecting metastases against the cost of detection. In other words, the number of FDG PET/CTs required to detect one person with metastases

[2] A retrospective cohort study of 78 people, one of the largest studies in this area, FDG PET/CT detected primary tumours in 30 people not identified on usual assessment including flexible fibre-optic nasoendoscopy and CT/MR/both, unexpected contralateral neck nodal disease in 2, and mediastinal nodal disease 1, and liver metastases 1 [4].

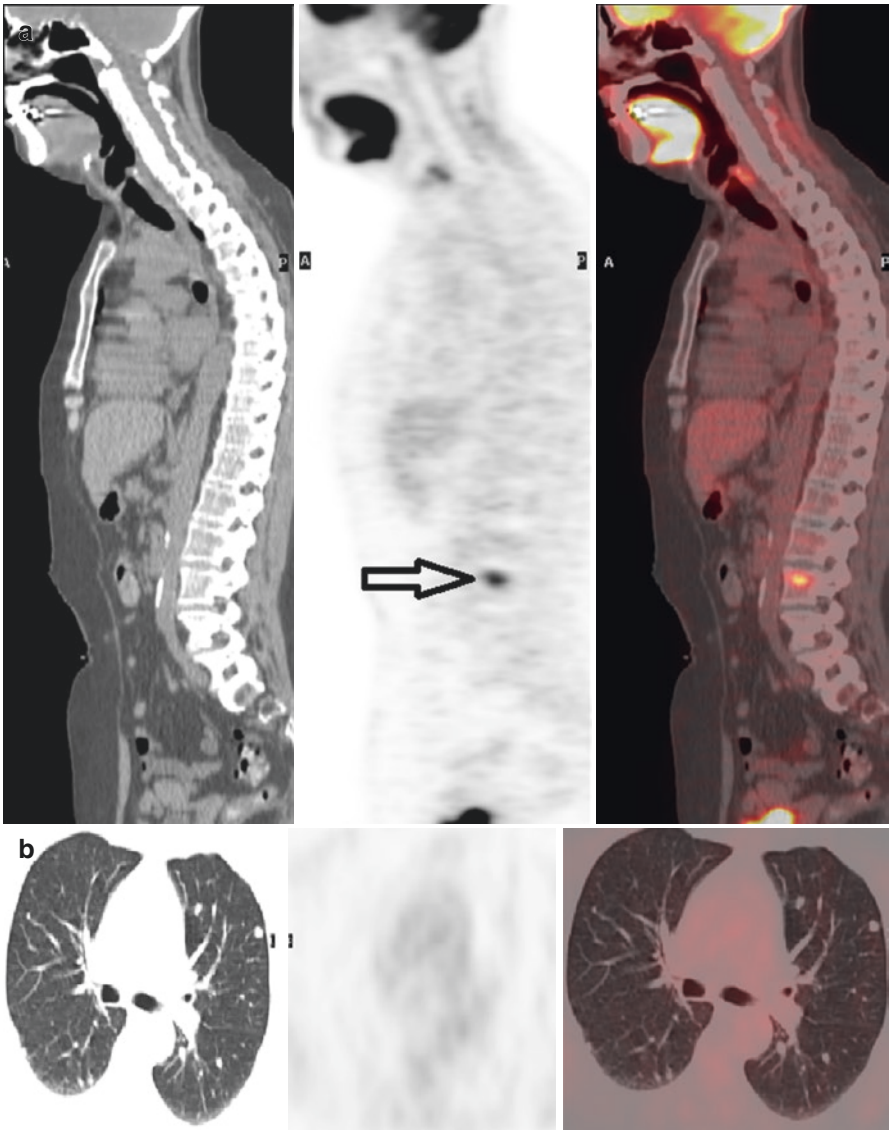

Fig. 6.2 (**a**) FDG PET/CT confirms the primary site in the tongue and neck nodal disease. It also shows a bone metastasis (*hollow arrow*). (**b**) FDG PET/CT also shows small non FDG avid lung metastases

balanced against the cost of false positive results. The tipping point applied varying between guideline making groups. And thirdly, the increasing view was that guidelines should be flexibly implemented.[3] Recent NICE guidelines recommend offering FDG PET/CT only to people with T4 nasopharyngeal and hypopharyngeal cancer and for people with advanced neck disease (N3) [5]. Other guidelines recommend FDG PET/CT more extensively [1] (Figs. 6.2a and 6.2b).

[3] Please see Appendix 8.

Secondly, in common with other cancers, FDG PET/CT has a key role in the investigations of lesions indeterminate on usual assessment including in lung, liver, and adrenal glands, when improved characterisation can change the treatment plan [1].

6.3 Response Assessment

The role of FDG PET/CT in this area is evolving. With revived enthusiasm in chemotherapy for H&N SqCC, there is interest in non-invasive imaging which can distinguish responders from non-responders early during treatment.[4] FDG PET/CT has been shown to predict early-on response to neo-adjuvant chemotherapy in a variety of solid tumours including oesophageal carcinoma.[5] There is currently one published study for H&N SqCC. In 15 patients, an FDG response after two cycles of chemotherapy predicted event-free survival [9].

6.4 Post-treatment Assessment

FDG PET/CT is misleading before 8 weeks post-chemo-radiotherapy. On the other hand, FDG PET/CT has a high negative predictive value, greater than 90%, 8 weeks or more after [10–17]. A recent study perhaps provides convincing evidence of the value of FDG PET/CT in this area.[6]

FDG PET/CT has two main roles in people suspected of recurrence: first, to confirm the diagnosis. FDG PET/CT is superior to CT/MR for distinguishing recurrence from treatment sequlae [19, 20] (Figs. 6.3 and 6.4). However, state-of-the-art MR techniques have not been included in this comparison. That said, in a significant number of people the recurrence is obvious on clinical assessment or standard CT/MR and does not require PET/CT. Secondly, the role is to accurately delineate the extent of disease dissemination. Here, for a significant number of people, FDG PET/CT is of limited relevance as the decision to take a palliative approach has already been made, prior to FDG PET/CT.[7]

[4] Please see Chap. 3.3 for further details on the role of chemotherapy in the treatment of H&N SqCC.

[5] Please see monogram on oesophageal cancer.

[6] In 564 H&N SqCC people with advanced neck nodal disease following chemoRT, 282 were recruited into the ND arm, 282 had FDG PET/CT 8–12 weeks following chemoRT and ND only if FDG PET/CT showed residual disease. 54 NDs were performed in the surveillance arm with 22 surgical complications; 221 NDs in the ND arm with 85 complications. FDG PET/CT surveillance was cost effective compared to planned ND with a £1, 415 per person saving and an additional gain of 0.07 QALY [18].

[7] Please see Chap. 3.4 and 3.6.

Fig. 6.3 FDG PET/CT shows appearance consistent with recurrent disease in the tongue base (*arrowhead*). Initial biopsies showed inflammation only. Deeper re-biopsies focussing on the FDG avid area confirmed active disease. Results of the initial biopsy are not surprising, as the recurrence is under the surface of the tongue base

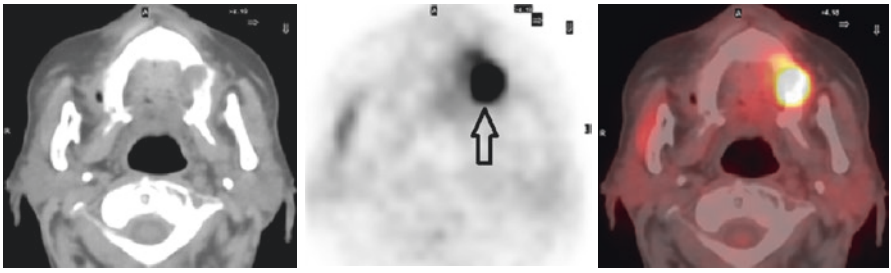

Fig. 6.4 A 76-year-old man with previously treated H&N cancer represents with trismus. FDG PET/CT shows recurrence in the left floor of mouth extending into the maxilla (*hollow arrow*), a difficult site to biopsy. It also shows FDG uptake in the normal right masseter muscle abutting the mandible due to trismus

6.5 Radiotherapy (RT) Planning

FDG PET/CT is increasingly used for radiotherapy target volume delineation [21]. Benefits include inter-observer variability in gross tumour volume (GTV) delineation reduction, GTV size reduction and identification of tumour that would not otherwise have been treated but for PET/CT, reducing geographical misses. However, two major challenges prevail. Firstly, inflammation leads to tumour margin overestimation. Secondly, there is presently no reliable, universally accepted, standardised method of identifying tumour margins. Notwithstanding, two small retrospective studies show significantly better overall survival and event-free survival applying FDG PET/CT-based IMRT, compared with the control group. More studies are needed to clarify the benefits of FDG PET/CT in this area.

6.6 Normal Variants and Artefacts

Brown adipose tissue FDG uptake can be difficult to distinguish from adjacent small FDG avid nodes, especially when there is slight mis-registration of PET to CT.

Skeletal muscle FDG uptake is usually linear and symmetrical and does not pose a diagnostic quandary. Occasionally, pre-vertebral muscle FDG uptake and especially when asymmetrical, needs separating from pre-vertebral nodal FDG uptake, and this may not be possible without resorting to correlation with MR or post-intravenous contrast CT.

Dental amalgam causes FDG uptake in the anterior two thirds of the mouth. In practice this rarely poses a clinical dilemma. If there is doubt as to the cause direct inspection will often provide reassurance.

Detecting an occult primary site can be challenging as it requires distinguishing normal Waldeyer's ring lymphoid tissue FDG uptake in nasopharynx, tongue base (lingual tonsil) and palatine tonsils from FDG uptake from an occult primary tumour arising at these sites, these being common sites for an occult primary tumour. That said, the role of FDG PET/CT is not to make the diagnosis but to increase the number of malignancies diagnosed at EUA and biopsy. In this setting a low threshold for diagnosing abnormality should be adopted and any asymmetrical FDG uptake at these sites reported. SUV is of limited use because of the overlap of values between tumour and normal lymphoid tissue [22] (Fig. 6.5).

Thyroid FDG uptake is considered in another monogram in the series. But beware of a node adjacent to thyroid mimicking a thyroid nodule. Rarely parathyroid adenomas can cause confusion.

6.7 Limitations/Pitfalls

As on CT/MR, branchial cysts can be challenging to distinguish from necrotic nodes. No FDG uptake in the wall of the lesion favours the diagnosis of a branchial cyst. On the other hand, presence of FDG uptake in the lesion wall does not assist, as both pathologies can show this appearance, necrotic node due to tumour and inflammation and branchial cyst due to inflammation.

Benign and malignant parotid gland lesions cannot be distinguished. Both pathologies show intense FDG uptake.

Interpretation of FDG uptake in H&N nodes deserves comment. Firstly, nodes with mild and moderate FDG uptake in the H&N. In this group, PET/CT analysis on grounds of FDG avidity to distinguish between malignant and benign is of limited value. That said, FDG PET/CT can be useful by highlighting possible unexpected nodal disease. In some people highlighting possible additional nodal disease will justify further neck assessment, most often initially with ultrasound and fine needle aspiration cytology. In others, treatment may be modified to include the suspicious node/nodes. Determining which nodes are potentially significant is largely influenced by the probability of nodal disease at the location. In other words, if the node lies in the nodal drainage area for the primary site and there is a moderate to high probability for nodal disease at this site then the node notwithstanding its relatively small size and mild FDG uptake requires reporting. On the other hand, if a node lies outside the drainage area and there is low probability for disease at this site then it

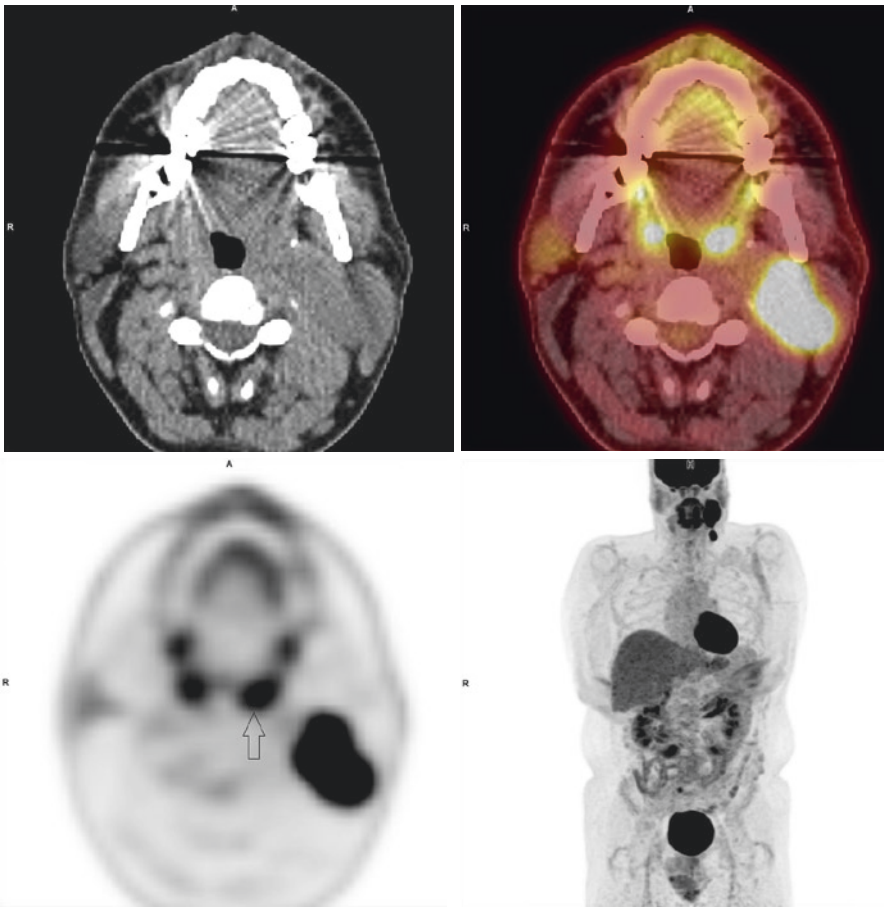

Fig. 6.5 A person with squamous cell cancer in the left neck. Indirect laryngoscopy, CT and MR shows no primary site. FDG PET/CT identified slightly more prominent FDG uptake in the left palatine tonsil compared with the right palatine tonsil and with left glosso-tonsillar sulcus narrowing. Endoscopic biopsies confirm a left palatine tonsil primary site

is unlikely that the node contains tumour. For example, a right level II node, 8 mm, mildly FDG avid, SUVmax 3.0, in a person with nasopharyngeal cancer must be viewed with much more suspicion that such as node in a person with a left maxillary antral cancer. Secondly, with regard to FDG uptake in chest nodes careful distinction needs to be made between those due to sarcoid-like reaction and cancerous nodes. The pattern of FDG uptake assists. FDG uptake in normal sized nodes which include those in paratrachea, both hila and subcarina, would favour sarcoidosis. Especially if there are no FDG avid neck nodes, but even when there is neck nodal disease (Fig. 6.6).

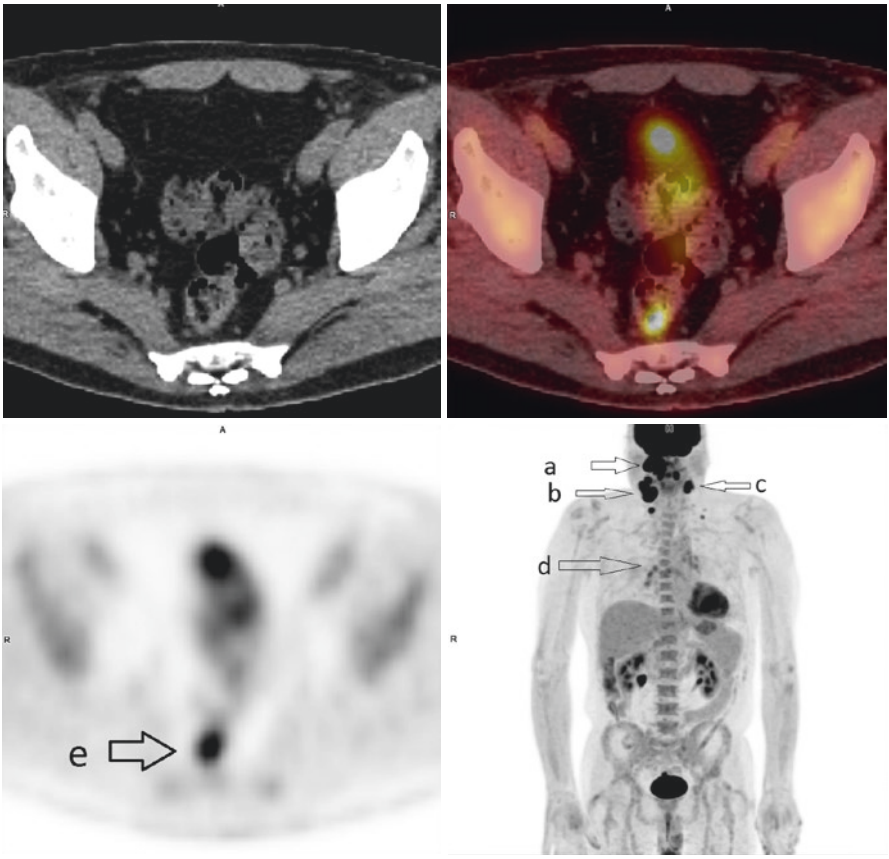

Fig. 6.6 A person with a tongue base cancer (*a*), right neck nodal disease (*b*), left neck nodal disease (*c*), intense FDG uptake in normal size nodes in the chest in the right paratrachea, both hila and subcarina due to sarcoid-like reaction (*d*), unexpected synchronous rectal cancer (*e*)

Post treatment, before making the diagnosis of residual or recurrent disease FDG uptake due to treatment sequelae needs careful consideration. Please see chapter on "18F FDG PET-CT: Normal Variants, Artefacts and Pitfalls in Head and Neck Malignancy".

There is a commonly held view that recent biopsies cause focal FDG uptake in the H&N. This concern is probably overestimated as biopsies usually are tiny and limited to the mucosa.

6.8 FDG PET/CT for H&N Non-SqCC

There is limited evidenced guidance for the use of FDG PET/CT here, beyond anecdotal reports, as these tumours are extremely rare. Notwithstanding, FDG PET/CT is often done prior to treatment and for several reasons: firstly to demonstrate

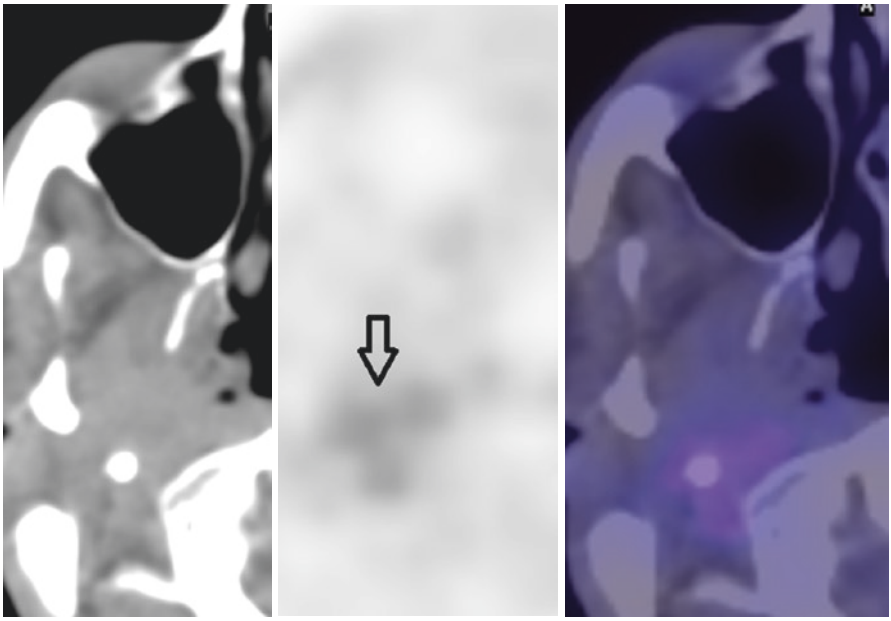

Fig. 6.7 A person with recurrent mucoepidermoid cancer in the skull base with bone destruction locally. FDG PET/CT shows only mild FDG uptake, SUVmax 3.2 (*hollow arrow*)

that the tumour is FDG avid. And if so, FDG PET/CT is considered for pre-treatment staging, and subsequently to detect residual/recurrent disease.[8]

6.9 PET Radiotracers Beyond FDG

6.9.1 Thymidine 3-Deoxy-3-^{18}F-Fluorothymidine (FLT)

Currently, its only potential role is in more accurately distinguishing lung metastases and from benign lesions, compared with FDG [23–25]. However, if it is confirmed that FLT is only taken up by malignant cells, then this may of value on the rare occasion when more information on extent of disease at the primary site is required after usual assessment for treatment planning. Also, FLT may be effective for detecting residual disease following RT and chemotherapy and for predicting outcome to RT and chemo-RT [26–28].

[8] Specific caution: salivary gland cancers and especially muco-epidermoid and adenoid cystic cancers can show paucity of FDG avidity, and especially when they recur (Figs. 6.7 and 6.8).

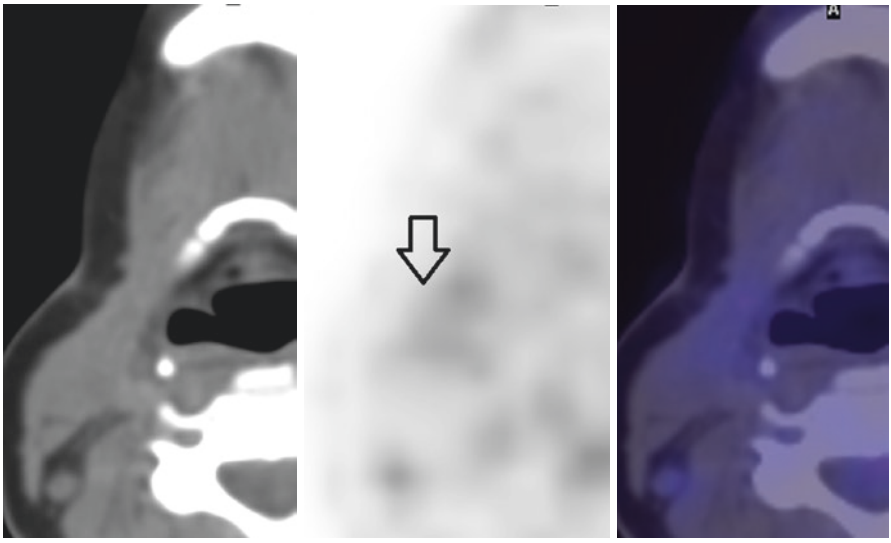

Fig. 6.8 A person with recurrent adenoid cystic cancer. FDG PET/CT shows only very mild FDG uptake, SUVmax 2.9 (*hollow arrow*)

6.9.2 Radiotracers for Detecting Hypoxia

There has been considerable interest in PET tracers which can detect hypoxia in H&N SqCC, because inadequate treatment of hypoxic cells is one of the main causes of failure to effectively treat the primary site. Hypoxic cells require three times more radiation to kill compared with non-hypoxic cells; often it is not possible to deliver the required dose because of the damage it will cause to surrounding to normal tissue. Imaging of hypoxia would provide the opportunity to apply RT to the sub-volume of hypoxic cells only [29, 30].

Fluorinated nitromidazole compounds, including 1-[2-nitro-1-imidazolyl-3[^{18}-F] fluoro-2-propanol ([^{18}F]FMISO), have been used of imaging hypoxia in H&NSqCC.[9] Copper isotopes of varying half-life, including ^{60}Cu, ^{61}Cu, ^{62}Cu and ^{62}Cu labelled to copper-diacetyl-bis(N^4-methylthiosemicabazone) [Cu-ATSM] and copper-pyruvaldehyde-bis(N^4-methylthiosemicarbazone [Cu-PTSM], have also been studied. There is as yet no one clear front runner. [^{18}F]FMISO is the most commonly used and best validated tracer and most studies have shown correlation between hypoxia and [^{18}F]FMISO uptake [31]. But it is only slowly cleared from the blood compartment and the radiotracer passively diffuses into the cell which takes a relatively long time. This means that for imaging to be effective it has to be done between 2 and 3 h post-injection [32] There are as yet inadequate data to recommend the other tracers as superior.

[9] Other florinated nitromidazole compounds that have been studied include 1-(5-[^{18}F]fluoro-5-deoxy-α-D-arabinofuranosyl)-2-nitro-imidazole ([^{18}F] FAZA), ^{18}F-2-(2-Nitro-imidazol-1-yl)-*N*-(3,3,3-trifluropropyl)-Acetamide [^{18}F–EF3] and ^{18}F–Fluoroerythronitromidazole [^{18}F–FETNIM].

6.9.3 11C–Choline PET/CT

In a pilot study ^{11}C–choline improved the delineation of orbital and skull involvement compared with FDG PET/CT in people with nasopharyngeal cancer [33]. This is because physiological ^{11}C–choline uptake in brain and extra-ocular eye muscles is minimal compared with FDG. The advantage of 11C–choline beyond this specific scenario has been questioned [34].

Key Points

- FDG PET/CT has an established role in the assessment of head and neck squamous cell cancer.
- There is universal agreement for using FDG PET/CT in people with malignant neck nodes and no primary site identified on usual assessment.
- In people with malignant neck nodes and no primary site identified on usual assessment, FDG PET/CT influences management plan primarily by increasing detection of the primary site.
- Increase in confidence in the use of FDG PET/CT and availability of scanners, is leading to the view that FDG PET/CT should be considered the initial investigation people with malignant neck nodes and no primary site identified on usual assesment, reserving CT/MR only if necessary for treatment planning.
- In people with primary head and neck squamous cell cancer, FDG PET/CT detects metastases not diagnosed on usual assessment
- FDG PET/CT is misleading before 8 week's post-chemo-radiotherapy. On the other hand, FDG PET/CT has a high negative predictive value, greater than 90%, 8 weeks or more after.
- Post treatment, before making the diagnosis of residual or recurrent disease FDG uptake due to treatment sequelae needs careful consideration.
- There is a commonly held view that recent biopsies cause focal FDG uptake in the head and neck. This concern is probably overestimated as biopsies usually are tiny and limited to the mucosa.
- There is limited evidenced guidance for the use of FDG PET/CT for head and neck non squamous cell cancer.
- There is divergence in guidance as to whom should be offered FDG PET/CT.

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PET/CT in Head and Neck Tumours: Treatment Sequelae Mimicking Active Disease—A Pictorial Atlas

7

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Contents

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to Radionuclide Hybrid Imaging, https://doi.org/10.1007/978-3-319-61440-3_7

7.1 Case 1: Residual Tongue Mimicking Recurrent Disease

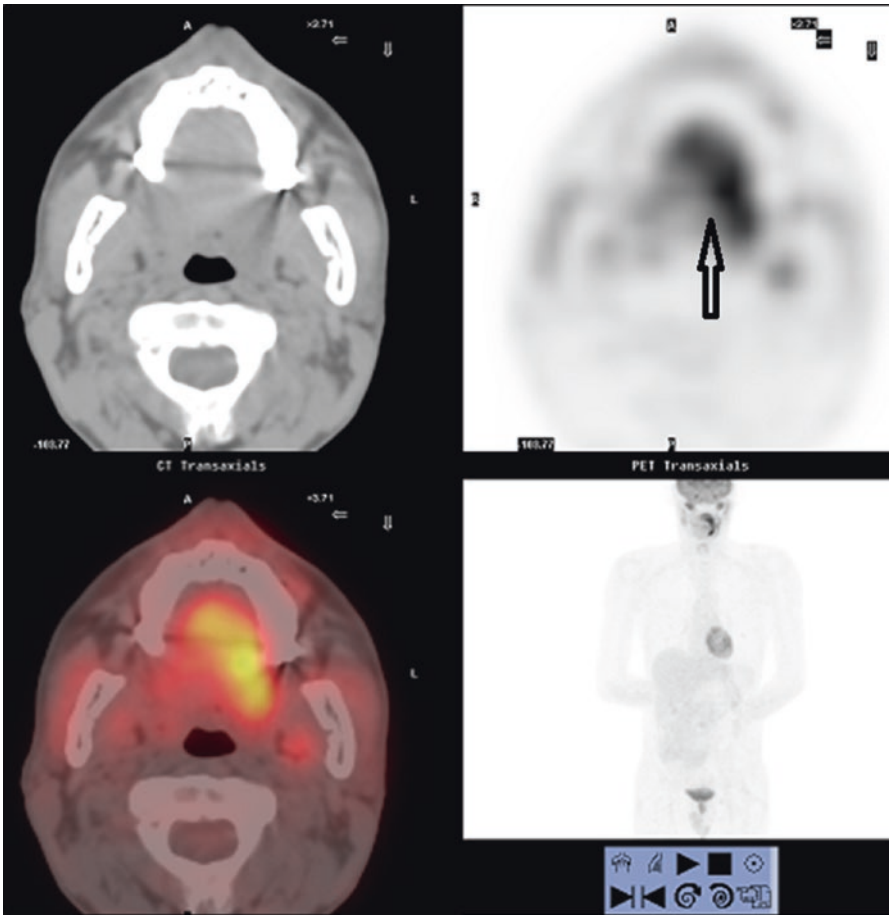

Fig. 7.1

A 56-year-old person following H&N radiotherapy which included the right half of tongue. FDG PET/CT shows normal FDG uptake of the left half of tongue (hollow arrow); not to be confused with recurrent disease. The right half of tongue has atrophied following radiotherapy and is not FDG avid. Similar changes are seen following partial tongue resection.

7.2 Case 2: Post-tonsillectomy

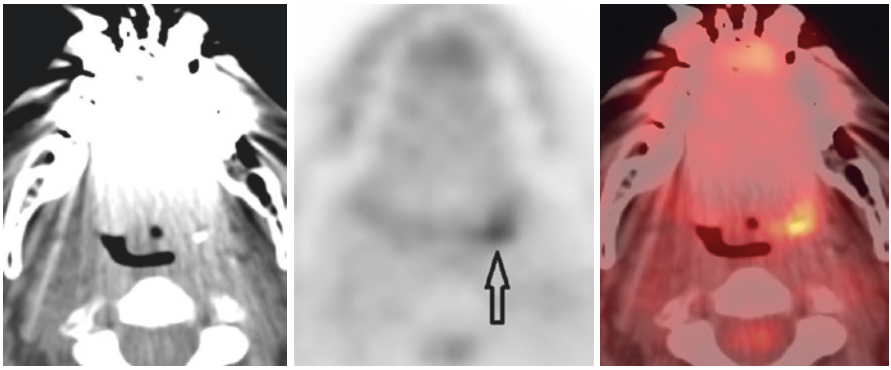

Fig. 7.2

Post RT tonsillectomy. FDG uptake in normal LT tonsil (hollow arrow).

7.3 Case 3: Osteonecrosis

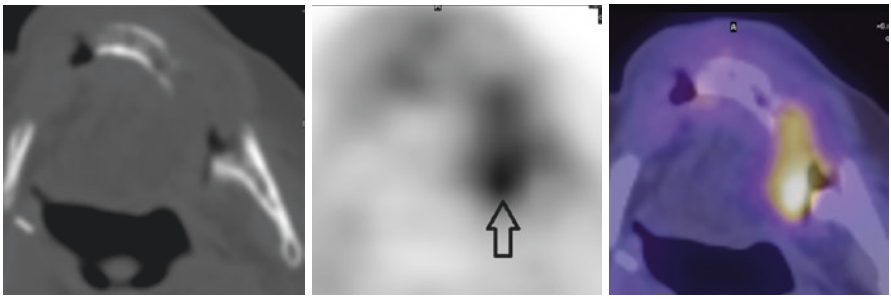

Fig. 7.3

Following surgery, osteonecrosis in LT mandible (hollow arrow).

7.4 Case 4: Radio-osteonecrosis

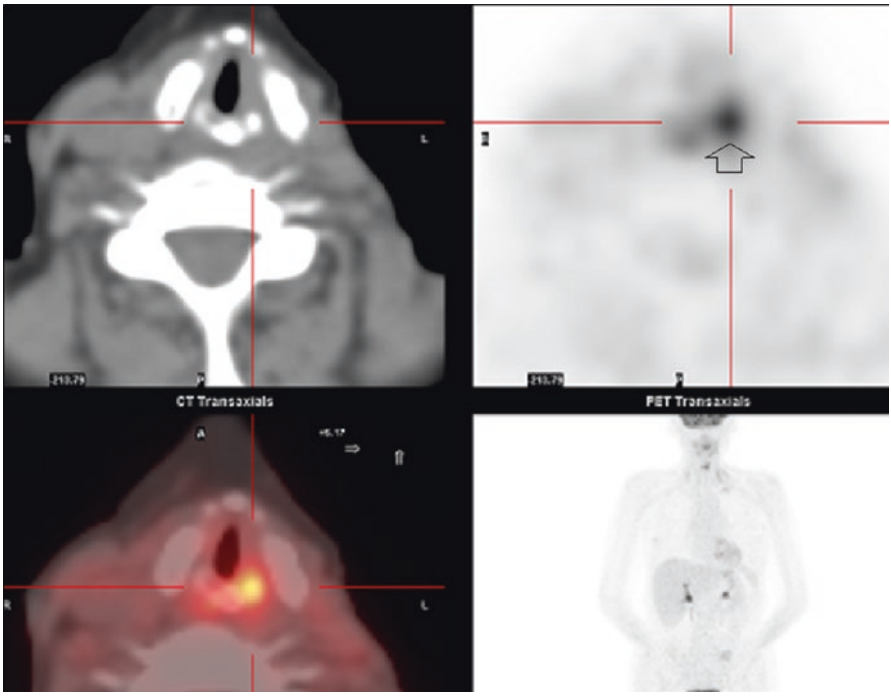

Fig. 7.4

A 65-year-old person developed dysphagia and severe pain in the throat 6 months following laryngeal radiotherapy. FDG PET/CT showed cricoid cartilage radionecrosis (hollow arrow). Symptoms and FDG uptake resolved following conservative treatment.

7.5 Case 5: Radiation Myelitis

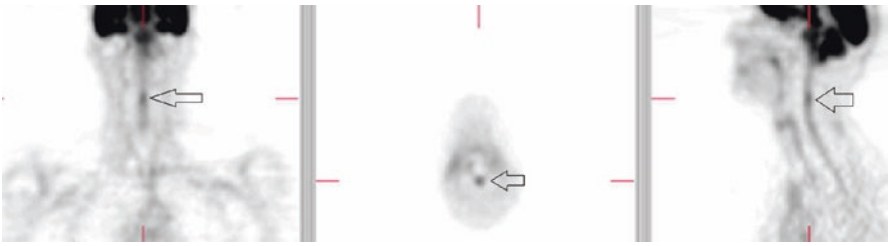

Fig. 7.5

A 59-year-old woman who developed parathesia of both arms following radiotherapy for a post-cricoid cancer. FDG PET/CT shows focal increased FDG uptake due to cervical cord due to radiation myelitis (hollow arrow); Symptoms and FDG changes resolved 6 months later following conservative treatment.

7.6 Case 6: Recent Neck Dissection: Cylous Collection

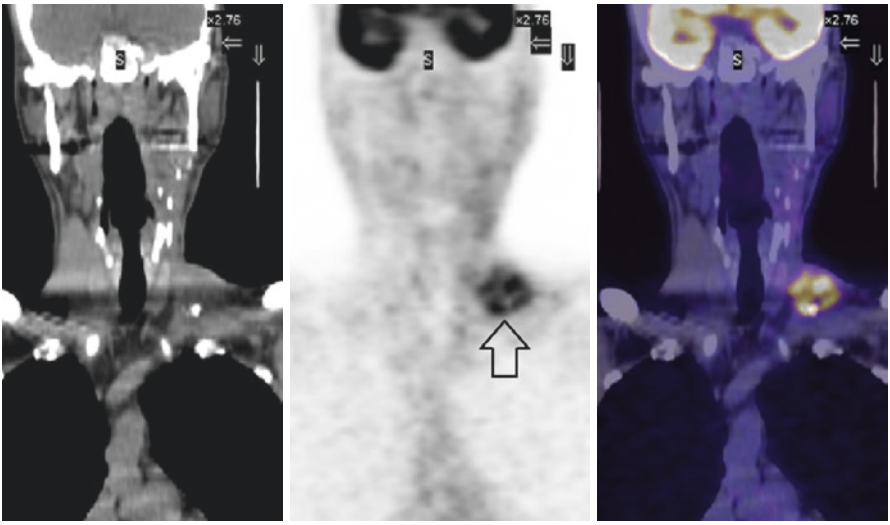

Fig. 7.6

FDG uptake in a left supraclavicular fossa mass following a recent "difficult" neck dissection due to a cylous leak.

7.7 Case 7: Granulomas

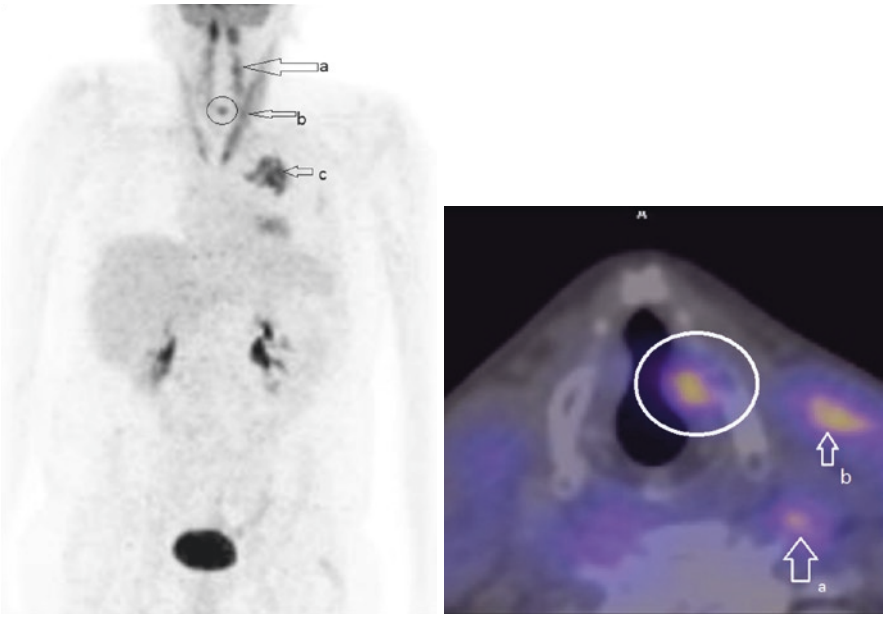

Fig. 7.7

A 76-year-old person with intense FDG uptake in the LT vocal cord due to a granuloma following vocal cord injection for LT vocal cord palsy due to LT recurrent nerve paralysis caused by a left upper lobe cancer invading into mediastinum (circled); a, FDG uptake in normal prevertebral muscle; b, FDG uptake in normal sternocleidomastoid muscle; c, intense FDG uptake in the LT upper lobe cancer invading the mediastinum locally.

7.8 Case 8: Post-chemoradiotherapy Neck

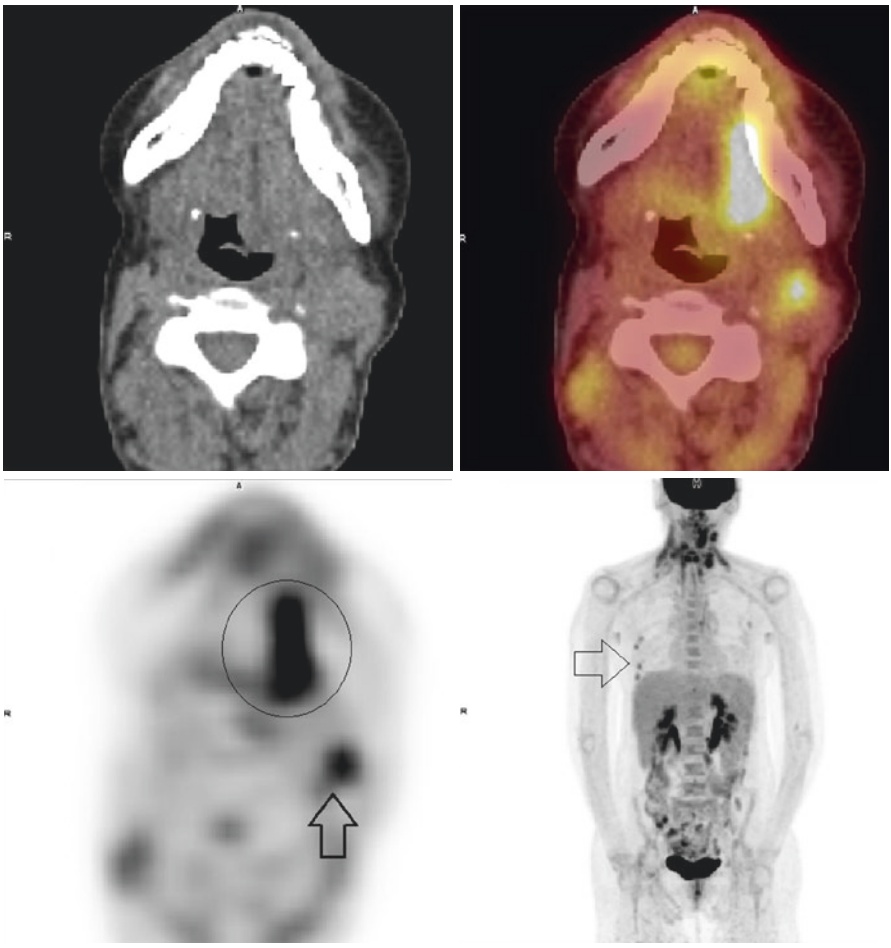

Fig. 7.8

A 56-year-old man with a left tongue cancer and left neck nodal disease treated with chemo-radiotherapy. FDG PET/CT 12 weeks following completion of treatment shows persistent intense FDG uptake at the primary site (circled) and persistent intense FDG uptake in the left post treatment neck nodes (hollow arrow) in keeping with persistent active disease at the primary site and in the left neck. There is also increased FDG uptake in the right chest wall due to healing traumatic rib fractures (hollow arrows).

7.9 Case 9: Post-chemoradiotherapy Neck

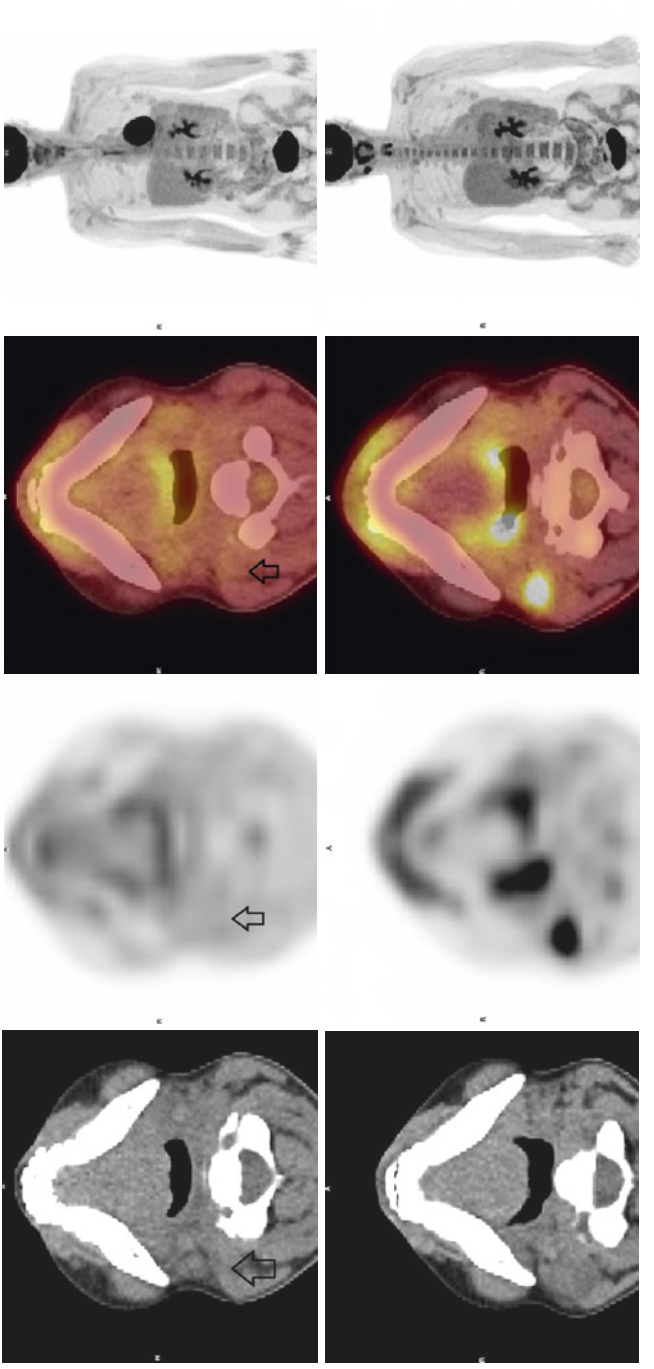

Fig. 7.9

A 70-year-old woman with a right tonsil cancer with right neck nodal disease. *Pre-treatment FDG PET/CT* (lower row) intense FDG uptake of the right tonsil cancer and intense FDG uptake in an enlarged right neck node. *Post-treatment FDG PET/CT* 12 weeks following completion of treatment (upper row) shows resolution of FDG uptake at the primary site and in sub-centimeter residual right neck node (hollow arrow), in keeping with no residual active disease at the primary site and the right post-treatment neck.

7.10 Case 10: Post-chemoradiotherapy Neck

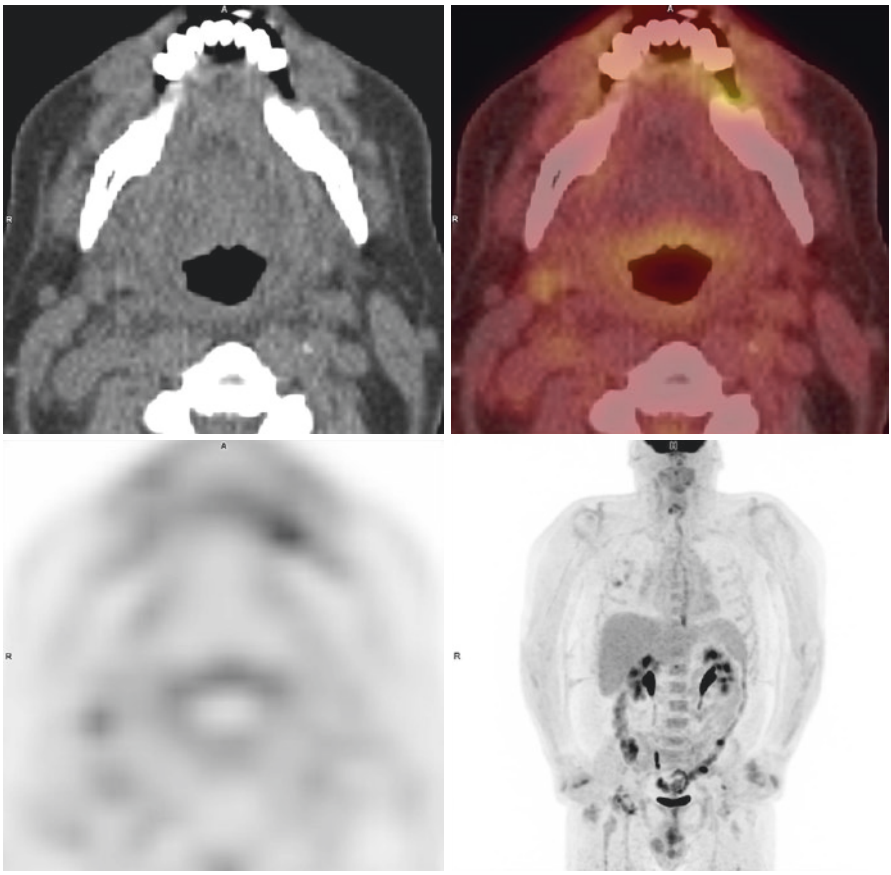

Fig. 7.10

A 56-year-old HPV+ man with a right tonsil cancer and right level II nodal disease. *Post-treatment FDG PET/CT* 12 weeks following completion of chemo-radiotherapy treatment shows resolution of FDG uptake at the primary site, in keeping with no

residual active disease. Indeterminate appearance in the right post treatment neck (hollow arrow) with FDG uptake in the right neck node (SUVmax 3.0), between that of internal jugular vein (SUVmax 1.9) and cerebellum (SUVmax 7.1). Follow-up FDG PET/CT 6 weeks later showed complete resolution of FDG uptake in the left neck node.

7.11 Teaching Points

Treatment sequelae that mimic active disease include (Cases 1–10):

- *Residual tongue mimicking recurrent disease*. Atrophy of the treated portion of the tongue and hypertrophy of the normal residual tongue, resulting in asymmetric FDG uptake in the oral cavity and oro-pharynx (Case 1).
- *Post-tonsillectomy*. The normal palatine tonsil mimics a palatine tonsil lesion, this a particular pitfall when searching for the occult primary site (Case 2).
- *Osteonecrosis*. following surgery (Case 3).
- *Radio-osteonecrosis*. Following radiotherapy, it occurs in bone and laryngeal cartilage (Case 4).
- *Radiation myelitis*. Thankfully a rare complication (Case 5).
- Tracheostomy site. FDG uptake due to inflammation needs consideration as an alternative to recurrence around the tracheostomy stoma site (Case 6).
- *Recent neck dissection* (Case 7).
- *Cylous collection* (Case 8).
- *Granulomas*. Specifically, vocal cord injection with Teflon needs distinction from a primary vocal cord cancer. Stitch granuloma following neck dissection very rarely causes increased FDG uptake and needs distinction from a neck node containing disease (Case 9).
- *Post chemoradiotherapy neck*, especially in HPV positive people mild FDG uptake (FDG uptake between that seen in the jugular vein and cerebellum) can persist in post treatment neck nodes beyond 8 weeks[1] (Case 10).

Reference

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[1] Recent reports suggest HPV+ nodal disease make take longer to involute. One of the largest studies to date which specifically considered FDG PET-CT response in HPV+ oropharyngeal cancer, FDG PET-CT at 12 weeks post-chemo-radiotherapy demonstrated high NPV for loco-regional failure though with disappointing PPV and sensitivity [1].

Appendices

Appendix 1.1.1: TNM Classification for the Primary Tumour

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Supraglottis	
T1	Tumor limited to one subsite of supraglottis with normal vocal cord mobility
T2	Tumor invades mucosa of more than one adjacent subsite of supraglottis or glottis or region outside the supraglottis (e.g., mucosa of base of tongue, vallecula, medial wall of pyriform sinus) without fixation of the larynx
T3	Tumor limited to larynx with vocal cord fixation and/or invades any of the following: Postcricoid area, preepiglottic space, paraglottic space, and/or inner cortex of thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the thyroid cartilage and/ or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Glottis	
T1	Tumor limited to the vocal cord(s) (may involve anterior or posterior commissure) with normal mobility
T1a	Tumor limited to one vocal cord
T1b	Tumor involves both vocal cords
T2	Tumor extends to supraglottis and/or subglottis, and/or with impaired vocal cord mobility
T3	Tumor limited to the larynx with vocal cord fixation and/or invasion of paraglottic space, and/or inner cortex of the thyroid cartilage
T4a	Moderately advanced local disease Tumor invades through the outer cortex of the thyroid cartilage and/or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscle of the tongue, strap muscles, thyroid, or esophagus)

W.L. Wong (ed.), *PET/CT in Head and Neck Cancer*, Clinicians' Guides to Radionuclide Hybrid Imaging, https://doi.org/10.1007/978-3-319-61440-3

T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures
Subglottis	
T1	Tumor limited to the subglottis
T2	Tumor extends to vocal cord(s) with normal or impaired mobility
T3	Tumor limited to larynx with vocal cord fixation
T4a	Moderately advanced local disease Tumor invades cricoid or thyroid cartilage and/ or invades tissues beyond the larynx (e.g., trachea, soft tissues of neck including deep extrinsic muscles of the tongue, strap muscles, thyroid, or esophagus)
T4b	Very advanced local disease Tumor invades prevertebral space, encases carotid artery, or invades mediastinal structures

Appendix 1.1.2: TNM Classification for the Primary Tumor

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Lip and oral cavity	
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension
T4a	Moderately advanced local disease* (lip) tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, that is, chin or nose (oral cavity) tumor invades adjacent structure only (e.g., through cortical bone (mandible or maxilla) into deep (extrinsic) muscle of tongue (genioglossus, hyoglossus, palatoglossus, and styloglossus), maxillary sinus, skin of face)
T4b	Very advanced local disease Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery

Appendix 1.1.3: TNM Classification for the Primary Site

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Nasopharynx	
T1	Tumor confined to the nasopharynx, or tumor extends to oropharynx and/or nasal cavity without parapharyngeal extension*
T2	Tumor with parapharyngeal extension*
T3	Tumor involves bony structures of skull base and/ or paranasal sinuses
T4	Tumor with intracranial extension and/or involvement of cranial nerves, hypopharynx, orbit, or with extension to the infratemporal fossa/masticator space
*Note: Parapharyngeal extension denotes posterolateral infiltration of tumor.	
Oropharynx	
T1	Tumor 2 cm or less in greatest dimension
T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension
T3	Tumor more than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4a	Moderately advanced local disease Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible*
T4b	Very advanced local disease Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery
*Note: Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of larynx.	
Hypopharynx	
T1	Tumor limited to one subsite of hypopharynx and/or 2 cm or less in greatest dimension
T2	Tumor invades more than one subsite of hypopharynx or an adjacent site, or measures more than 2 cm but not more than 4 cm in greatest dimension without fixation of hemilarynx
T3	Tumor more than 4 cm in greatest dimension or with fixation of hemilarynx or extension to esophagus
T4a	Moderately advanced local disease Tumor invades thyroid/cricoid cartilage, hyoid bone, thyroid gland, or central compartment soft tissue*
T4b	Very advanced local disease Tumor invades prevertebral fascia, encases carotid artery, or involves mediastinal structures
*Note: Central compartment soft tissue includes prelaryngeal strap muscles and subcutaneous fat.	

Appendix 1.1.4: TNM Classification for the Primary Tumor

Primary tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ
Maxillary sinus	
T1	Tumor limited to maxillary sinus mucosa with no erosion or destruction of bone
T2	Tumor causing bone erosion or destruction including extension into the hard palate and/or middle nasal meatus, except extension to posterior wall of maxillary sinus and pterygoid plates
T3	Tumor invades any of the following: Bone of the posterior wall of maxillary sinus, subcutaneous tissues, floor or medial wall of orbit, pterygoid fossa, ethmoid sinuses
T4a	Moderately advanced local disease Tumor invades anterior orbital contents, skin of cheek, pterygoid plates, infratemporal fossa, cribriform plate, sphenoid, or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than maxillary division of trigeminal nerve (V_2), nasopharynx, or clivus
Nasal cavity and Ethmoid Sinns	
T1	Tumor restricted to any one subsite, with or without bony invasion
T2	Tumor invading two subsites in a single region or extending to involve an adjacent region within the nasoethmoidal complex, with or without bony invasion
T3	Tumor extends to invade the medial wall or floor of the orbit, maxillary sinus, palate, or cribriform plate
T4a	Moderately advanced local disease Tumor invades any of the following: anterior orbital contents, skin of nose or cheek, minimal extension to anterior cranial fossa, pterygoid plates, sphenoid or frontal sinuses
T4b	Very advanced local disease Tumor invades any of the following: orbital apex, dura, brain, middle cranial fossa, cranial nerves other than (V_2), nasopharynx, or clivus

Appendix 1.2.1: TNM Classification for Regional Nodal Metastases (Nasopharynx)

Regional lymph nodes (N)	
Nasopharynx	
The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Unilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension*
N2	Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
N3	Metastasis in a lymph node(s)* >6 cm and/or to supraclavicular fossa*
N3a	Greater than 6 cm in dimension
N3b	Extension to the supraclavicular fossa**

*Midline nodes are considered ipsilateral nodes

**Supraclavicular fossa is defined by three points

[1] The superior margin of the sternal end of the clavicle

[2] The superior margin of the lateral end of the clavicle

[3] The point where the neck meets the shoulder

Note that this would include caudal portions of level IV and VB. And all cases with nodes (whole or part) in the fossa are considered N3b

Appendix 1.2.2: TNM Classification for Regional Nodal Metastases (for All H&N Subsites Except for Skin, Thyroid, and Nasopharynx)

Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension

Appendix 2.1: Stage Grouping (the Larynx, All Subsites)

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Appendix 2.2: Stage Grouping (Lip and Oral Cavity)

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	Any T	N3	M0
	T4b	Any N	M0
Stage IVC	Any T	Any N	M1

Appendix 2.3: Stage Grouping (Pharynx)

Anatomic Stage/Prognostic Groups

Nasopharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T1	N1	M0
	T2	N0	M0
	T2	N1	M0
Stage III	T1	N2	M0
	T2	N2	M0
	T3	N0	M0
	T3	N1	M0
	T3	N2	M0
Stage IVA	T4	N0	M0
	T4	N1	M0
	T4	N2	M0
Stage IVB	Any T	N3	M0
Stage IVC	Any T	Any N	M1
Oropharynx, hypopharynx			
Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Appendix 2.4: Stage Grouping (Nasal Cavity and Paranasal Sinuses)

Anatomic Stage/Prognostic Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T4a	N0	M0
	T4a	N1	M0
	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Appendix 3: Reconstructive H&N Surgery

Magdalene Foo

H&N reconstructive surgery poses a uniquely difficult challenge as there is a need not only to restore facial aesthetics, but also to restore the complex functions of the upper aerodigestive tract. Resection of H&Nca results in tissue deficits which require tissue repair. Tissue transfer can be divided into non-vascularized, pedicled, and free vascularized flaps.

Non-vascularized Tissue Transfer

Non-vital grafts must gain a blood supply from the recipient bed to maintain viability. This limits the three-dimensional graft size. Non-vascularized skin grafts can be used to cover superficial buccal and floor of mouth defects. Iliac crest free bone graft is most commonly used as an interpositional graft to replace continuity defects in the mandible, which are not more than 6 cm.

Pedicled Tissue Transfer

In pedicled tissue transfer, the blood supply is via a single dominant vessel or a soft tissue bridge between the donor site and the grafted tissue. Pedicled flaps have a limited arc of rotation and tethering effect in peripheral defects in the H&N.

Pedicled muscle flap e.g. temporalis muscle flap is rotated into the mouth and can reach most operative sites in the mouth, from anterior mandible through floor of mouth up to hard and soft palate. The pedicled pectoralis myocutaneous flap is the 'work horse' of oral cavity reconstruction. It provides skin and muscle or muscle alone, in large volume adequate to fill all oral cavity and most cutaneous defects. It is reliable and carries minimum donor site morbidity. The latissimus dorsi myocutaneous flap though not often used as a pedicled pectoralis myocutaneous flap for H&N surgery provides a large surface area, suitable for covering the side of a face and neck and scalp. It has a long pedicle through the axilla and neck to reach the orofacial cavity.

Myocutaneeous composit or pedicled bone in conjunction with muscle flaps, rely on adequate vascular supply through the periosteal perforators of the muscle to the attached bone.

Free Vascularized Tissue Transfer

Microvascular surgery has revolutionized the management of H&Nca. It is a versatile and reliable method of reconstruction with a variety of soft tissue and bone flaps and overcomes the design constraints of distant pedicled flaps. Free flaps are selected to match the properties of the resected tissue and tailored to the surgical defect. The soft tissue flaps most useful for oral maxillofacial reconstruction are the radial forearm, scapular and parascapular, rectus abdominis and latissimus dorsi flaps.

Fasciocutaneous radial forearm flaps, are used in oropharyngeal reconstruction. The main advantage is the relatively hairless thin skin and long vascular pedicle, ideal for replacing mobile mucosal areas such as mouth, tongue, cheek, soft palate, and lateral pharyngeal wall.

Scapular and parascapular flap, used for larger cheek defects or scalp replacement. In midface reconstruction after tumour ablation, the scapula flap is the flap of choice, providing flat cortical bone, together with an independent skin paddle.

Inferior rectus abdominis flap, a myocutaneous flap, useful for obliterating volume defects after resection of the paranasal sinuses or skull base.

Latissimus dorsi flap, large myocutaneous able to cover extensive head and neck defects. Following subtotal or total glossectomies, it is important to combine replacement of mucosal tissue with replacement of tissue volume. Rectus abdominis or latissismus dorsi muscle with overlying skin for the mucosal defect provides plenty of soft tissue. However, this is only tissue bulk but no mobility, and postoperative soft tissue function is poor.

Jejunal flaps are used in oesophageal reconstruction. The benefits are outweighed by intra-abdominal surgery for harvesting, considerably increasing perioperative morbidity and mortality.

Appendix 4: Classification of Neck Dissection

Radical Neck Dissection

Removal of node-containing levels in the neck [levels I–V] and spinal accessory nerve, stenocleidomastoid muscle and the internal jugular vein

Modified Radical Neck Dissection

Removal of node-containing levels in the neck [levels 1–V]. The internal jugular vein and /or stenoceidomastoid muscle spared.

Selective neck dissection, as specified by the surgeon

- supraomohyoid neck dissection d*issection of levels I–III, excision of submandibular gland*
- postero-lateral neck dissection *dissection of levels IIA, IIB, III, IV, V*
- lateral neck dissection *dissection of levels II-IV*
- central compartment neck dissection *dissection of level VI, including nodes in the perithyroid, Delphian,*[1] *trachea-oesophageal and antero-superior mediastinum*
- others, *extended neck dissection, as specified by the surgeon*

Source: Neck Dissection. In Stell and Maran's Head and Neck Surgery. 4th ed. Eds. JC Watkinson, MN Gaze, JA Wilson. Publ Butterworth Heinemann 2000; Upper Aerodigestive Tract (including salivary glands) American College of Pathologists Protocol. January 2005

[1] Delphian nodes: midline prelaryngeal nodes, i.e., superficial midline nodes in the neck.

Appendix 5: MR Scanning

The patient should be scanned from the skull base down to the upper border of the manubrium sterni in order to demonstrate the primary tumour, potential sites of local invasion and the regional lymph nodes. A dedicated surface (neck) coil is employed in order to obtain the necessary high resolution. Scans should be obtained in multiple planes and will usually include coronal T1 W and STIR (short TI/Tau inversion recovery) or fat suppressed T2 W, transverse T2 W and post contrast (Gadolinium) transverse and coronal fat saturated T1 W sequences. A transverse T1 W is preferred by some radiologists instead of T2 W. At least one sagittal sequence (especially following contrast) is often useful, particularly for the assessment of lesions involving the tongue base. Some centres are also routinely performing diffusion-weighted imaging.

Appendix 6: MRI, CT, and USS Diagnosis of Nodal Involvement

MRI/CT

Size of Node

The simplest criterion for tumor involvement is increased maximum tranverse diameter of a node. However, normal nodes vary in size, 2–19 mm, and metastatic nodes may measure significantly less than 10 mm. Therefore, the higher the upper limit of normal diameter the greater the specificity but the lower the sensitivity. Widely accepted normal upper limits are 11 mm in the jugulodigastric, 8 mm in the retropharyngeal, and 10 mm in all other regions.

Number of Nodes

A cluster of three or more nodes in the tumour drainage pathway increases the index of suspicion and allows the normal maximum to fall to 9 mm in the jugulodigastric and 8 mm elsewhere.

Shape of Node

A change in shape of the lymph node from elliptical to round is also suggestive of tumour infiltration.

Appearance of Node

The presence of necrosis in lymph nodes of any size is highly suggestive of squamous cell carcinoma metastases. On CT (Fig. 3) this is seen as irregular, low-density, unenhancing areas and on MRI (Fig. 3) as irregular high-signal areas on STIR and T2 W sequence and low-signal, unenhancing areas on the T1 W sequence. On both modalities extranodal tumour extension may be seen as nodes with

ill-defined margins, irregular peripheral enhancement, engorged surrounding lymphatics and (on MRI) a halo of ill-defined high signal on the STIR sequence [1].

Ultrasound

This identifies lymph nodes down to 3 mm diameter and is sensitive for the early detection of loss of normal architecture, tumor-induced necrosis and extralymphatic spread. Tumour disruption of normal nodal vascularity is detectable at an early stage with Doppler ultrasound. It is useful to guide fine-needle aspiration of suspicious nodes and relatively cheap and easy to follow up equivocal nodes.

Combining grey scale appearances with colour Doppler criteria[2] ultrasound demonstrates a sensitivity of 87% (compared to 81% for MRI and CT, rising to 86% for MRI with the addition of diffusion-weighted imaging) and a specificity of 86% (compared to 63% for MRI and 76% for CT) [2]. The addition of ultrasound-guided fine needle aspiration biopsy achieves a specificity of 98% [3]. Currently therefore ultrasound is the most reliable widely available technique for assessing cervical lymphadenopathy and may become more accurate in combination with emerging techniques such as elastography (using ultrasound to assess the elasticity of tissues) [4].

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[2] Presence of peripheral or chaotic intranodal vascularity).

Appendix 7: Applying Clinical Guidelines: A Synthesis of Evidence and Practice in Guideline Adoption

Peter Ross

Guidelines including those from NICE help shape the evidence base for decision making by providing clinicians with a set of scientifically developed statements with regard to which diagnostic test to use and when. However, although guidelines are regarded as an important part of the quality assurance process, research shows that adherence to their recommendations is sometimes variable among physicians. For example, one study in the Netherlands showed that GP compliance with national guidelines for drug prescription was only followed in 61% of cases [1].

In general, there is little understanding of the reasons for the variation in rates of guideline adoption among physicians. A systematic review of the literature identified seven disparate categories of barriers that affected physician guideline adoption including a lack of awareness, a lack of agreement, as well as other external barriers [2]. However, while such reviews are helpful in identifying the factors that influence guideline adoption, they do not expand on the how and why of non-adherence to guideline recommendations. Further, the general innovation literature tells us that guideline adoption is unlikely to be a binary decision. Instead, guideline adoption is likely to follow a complex and iterative trajectory of diffusion and contingent engagement so that "cookbook" approaches to their implementation are unlikely to work [3, 4].

So should we be worried about a lack of convergence in guideline adherence? The answer probably depends on the reason for the divergence of practice. If for example the lack of adherence is due to a lack of awareness or familiarity with the guideline, then intervention strategies to improve adoption rates would surely be beneficial. If, on the other hand, the barrier to adoption, as one qualitative study found, stems from a lack of agreement due to a perceived lack of applicability, then interventions to promote guideline adherence may be counter-productive [5].

National guidelines can only be fully embraced if they are aligned with the values and conditions pertaining to patients and clinicians at a local level. To understand how and why physicians adopt clinical guidelines further qualitative research is needed as factors beyond robustness of evidence will inevitably influence the individual adoption decision. These may include among other things; clinical experience, the power of local opinion leaders and champions, as well as the state of healthcare budgets [6].

In practice rationality is likely to be 'bounded' by resource constraints so that the decision to adopt a guideline will be the result of a process of 'satisficing' whereby the best possible decision in the circumstance is made [7–8]. As a result, we should not perhaps be surprised if the same guidelines are interpreted and implemented in different ways in different contexts. After all, in a post-positivist world achieving a consensus is always going be a contentious process and guideline development and implementation is no exception. Guidelines should not be viewed as tramlines because in the final analysis their diffusion will always depend on the integration of best clinical evidence, local clinical expertise and patient centred consultation [9].

Gone are the days of a 'one best way' approach to healthcare provision. Patient advocates increasingly expect to be a part of the decision process and want guidelines that will help them to choose the intervention that best fits their needs and values.

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Appendix 8: Haemato-lymphoid Tumours

Katherine Sisson, Tom Roque

Extranodal lymphoma accounts for 25–50% of lymphoma within the H&N. Nodal lymphoma is often an extension of systemic disease. Within the paranasal sinuses and Waldeyers ring (tonsils, base of tongue and oropharynx) the most frequent lymphoma is diffuse large B-cell lymphoma. Within the nasal cavity, primary lymphoma is the second most common malignant neoplasm after SqCC and the most frequently encountered is the extranodal NK/T–cell lymphoma. This tumour has a strong association with EBV. Within the paediatric population, Burkitt's lymphoma is the most common lymphoid neoplasm.

Extranodal MALT (mucosa associated lymphoid tissue) marginal zone B-cell lymphoma is not uncommonly encountered in the salivary glands, thyroid and occular adnexal structures. There is a strong association with the autoimmune disorders Sjogren's disease and Hashimoto's thyroiditis.

The main aim of diagnostic imaging, including FDG PET/CT in people presenting with lymphoma in the H&N, is to establish the extent of disease. The role of FDG PET/CT is considered in the monogram which discusses lymphoma.

Addendum

Since the preparation of the text there is published the eighth AJCC classification, and with substantial changes made with regard to the TNM staging of head and neck cancer compared with the seventh edition. One of the most significant updates is a separate classification for HPV associated oropharyngeal cancer [OPC], distinguishing it from the staging of HPV negative OPC. This is in recognition of the differences in pattern of disease, treatment approaches and clinical outcomes between people with HPV positive and HPV negative OPC. With regard the T classification, for HPV positive OPC, in contrast to HPV negative OPC, there is no Tx [primary cannot be assessed] and no Tis [carcinoma in situ] classification, justified on grounds of the non-aggressive nature of p-16 positive OPC and the lack of distinct basement membrane in the epithelium of Waldeyer's ring. There is also no stage T4b, because there is no difference in curves between T4a and T4b HPV associated OPC. The N stage is also different for HPV positive cancers, specifically for HPV associated OPC: N1 one or more ipsilateral nodes none larger than 6 cm, N2 contralateral or bilateral nodes none larger than 6 cm, N3 node or nodes larger than 6 cm. T and N classification of HPV negative OPC remains unchanged in the eighth edition.

There are also important changes with regard the classification of nasopharyngeal cancer [NPC], sufficiently so as to justify a separate chapter for NPC. In addition to refinements in T classification there are key alterations in the N staging of the nasopharynx. Specifically, the supraclavicular fossa is no longer included as a relevant landmark. Instead it is replaced by the caudal border of the cricoid cartilage. For example in the eighth edition, N2 is classified as bilateral metastasis in cervical node [s] 6 cm or smaller in greatest dimension, above the caudal border of cricoid cartilage compared with previously N2 classified as bilateral metastasis in cervical node [s] and unilateral or bilateral metastases 6 cm or less in greatest dimension, above the supraclavicular fossa; N3 in the eighth edition classified as unilateral or bilateral metastasis in cervical node [s] larger than 6 cm in greatest dimension, and or extension below the caudal border of cricoid cartilage compared with N3 previously, which was defined as metastasis in a lymph node[s] >6 cm and/or to supraclavicular fossa. Also in the new classification there is no longer N3a and N3b categories and no distinction is made for nodes greater than 6 cm in dimensions [N3a] and extension into the supraclavicular fossa [N2b]. In addition, for NPC, in common with all sites, extra-nodal extension has been added to the N classification,

other than viral related cancer and mucosal melanoma. This feature now forms an important aspect of staging non HPV positive non Epstein Barr virus positive head and neck cancers.

Other modifications in the eighth edition include: the reorganizing of skin cancer [other than melanoma and Merkel cell carcinoma] from a general chapter for the whole body to a specific chapter for head and neck cutaneous skin cancers, division of pharyngeal cancer into three separate chapters; change to the T categories in nasopharynx, oral cavity and skin.

Bibliography

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Glossary and Abbreviations

ChemoRT	Chemoradiotherapy
CT	Computed tomography
ENT	Ear nose and throat
EUA	Examination under anaesthesia
FDG	2-Deoxy-2-[fluorine-18]fluoro-D-glucose
H&N	Head and neck
H&Nca	Head and neck cancer
H&N SqCC	Head and neck squamous cell cancer
HPV	Human papillo-virus
IMRT	Intensity modulated radiotherapy
MRI	Magnetic resonance imaging
ND	Neck dissection
PET	Positron emission tomography
QALY	Quality adjusted life years
RT	Radiotherapy
SqCC	Squamous cell carcinoma
SUV	Standardised uptake value
SUVmax	Standardised uptake value (maximum)
USS	Ultrasound scanning

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W.L. Wong (ed.), *PET/CT in Head and Neck Cancer*, Clinicians' Guides to Radionuclide Hybrid Imaging, https://doi.org/10.1007/978-3-319-61440-3