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FOCUS ON: HEAD AND NECK CANCER

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Multimodality imaging of head and neck cancer

A.D. King

Department of Diagnostic Radiology & Organ Imaging, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR, China

Corresponding address: Dr Ann D. King, Department of Diagnostic Radiology & Organ Imaging, Faculty of Medicine, The Chinese University of Hong Kong, Prince of Wales Hospital, Shatin, New Territories, Hong Kong SAR, China.
Email: king2015@cuhk.edu.hk

Abstract

Imaging has an important role in staging, planning treatment and post-treatment follow up of patients with head and neck cancer. The most commonly utilized imaging modalities are discussed in relation to their relative indications, strengths and weaknesses. This is followed by a brief update on the advances in functional magnetic resonance imaging.

Abstract: *Head and neck; cancer; imaging.*

Introduction

The paper focuses on the use of computed tomography (CT), magnetic resonance imaging (MRI), ultrasound (US) and positron emission tomography (PET) using fluoro-2-deoxy-D-glucose ([^{18}F]FDG PET) for staging and pre-treatment management of patients with head and neck cancer. Each modality is reviewed in relation to imaging the primary tumour, nodal and distant metastases, the emphasis being on head and neck squamous cell carcinoma (HNSCC). This is followed by a brief update on the advances in functional MR imaging for predicting and monitoring cancer treatment response.

Imaging the primary cancer

Primary cancers of the aerodigestive tract, such as HNSCC and non-Hodgkin's lymphoma, are usually staged by MRI or CT. Although MR has lost its multiplanar advantage, it is still superior to CT for demonstrating the primary cancer and relationship of cancer boundaries to normal anatomical structures (Table 1). The advantages of MR affect all T stages; in early T stage disease MR influences the accuracy of staging by determining whether a tumour is confined to the primary site (Fig. 1a–c); in more advanced stage disease it has an impact on surgical resectability and radiotherapy field planning. However, artifacts from swallowing, breathing and coughing limit the quality of MRI and become an increasing problem on moving down the neck. Therefore on descending the head and neck the advantages of MRI decrease and those of CT increase so that in general MRI is preferred in the skull base/nasopharynx and CT in the larynx (Fig. 2).

[^{18}F]FDG PET has a role in the identification of the unknown primary but at present it has no proven additional value in staging patients with a known primary tumour. [^{18}F]FDG PET does not appear to demonstrate more extensive disease at the primary site and anatomical detail is limited by the spatial resolution. However, while [^{18}F]FDG PET does not show greater tumour extent, potentially its role in the future may lie in showing smaller tumour extent. A recent study by Daisne *et al.*[3] showed that CT and MRI overestimate the size of the primary tumour, and [^{18}F]FDG PET provides a smaller but more accurate assessment of volume. In addition, from our experience and that of Quon *et al.*[4] [^{18}F]FDG PET also appears to show less extensive tumour invasion into the bone marrow of the skull base than MRI, which for the reasons shown in Table 1 may be overestimating bone marrow involvement.

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Table 1 Advantages and disadvantages of MRI compared to CT for cancer depiction

	Advantages	Disadvantages
Neural	Tumour extension into the cavernous, dura and perineural tumour spread	
Sinonasal	Delineation of tumour from inflammatory disease	
Bone/cartilage	Superior sensitivity for invasion especially into the bone marrow (MRI is good for excluding invasion)	Inferior specificity leading to more false positive results. MRI is unable to distinguish tumour infiltration from inflammatory changes[1,2]. This is especially a problem in the mandible and maxilla where co-existing dental disease frequently cause abnormalities in the bone marrow (Fig. 2). Chemical shift artifacts may cause problems identifying small cortical erosions in the mandible or erosion of thin plates of bone in regions such the paranasal sinuses and petrous temporal bones
Muscles and facial planes	Delineation of tumour invasion of fascia (e.g. pharyngobasilar fascia) and small muscles (e.g. pharyngeal wall and prevertebral region)	
Nodes	Retropharyngeal nodes	
Vessels	Relationship of tumour to vessels	More flow artifacts in the large veins
Oral cavity and oropharynx	Better delineation of tumour in the tongue. Fewer problems with metallic artifacts from dental amalgam and prosthesis in the oral cavity and spine	
Calcification		Identification of tumour calcification (e.g. sarcomas and thyroid cancer)
Post treatment	Better distinction of scar tissue from recurrent cancer	

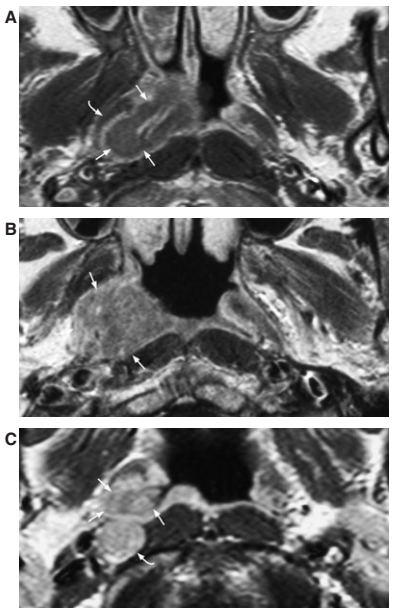

Figure 1 **Axial T1-weighted post contrast MRI of the nasopharynx with a primary tumour in the right lateral wall (arrows) demonstrating how MR depiction of small anatomical structures influences early T staging. (a) Tumour confined to the nasopharynx but displacing the levator palatini muscle (curved arrow) into the parapharyngeal fat space (stage T1); (b) tumour invades through levator palatini into the parapharyngeal fat space (stage T2b); (c) tumour confined to the nasopharynx but separated from an adjacent retropharyngeal node (curved arrow) by the pharyngobasilar fascia (stage T1/N1).**

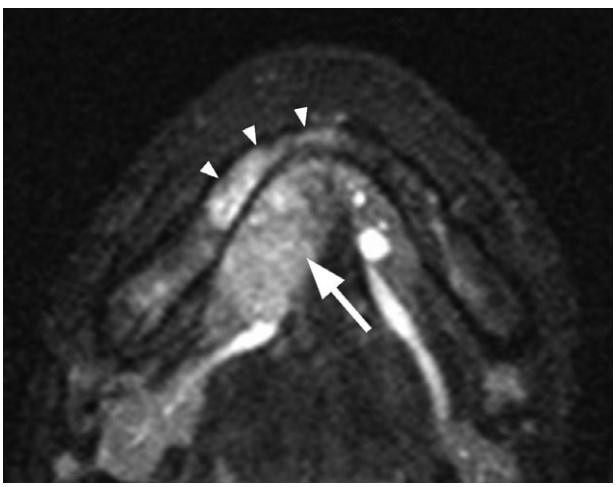

Figure 2 **Pre-operative axial T2-weighted MRI with fat saturation showing a carcinoma in the floor of the mouth (arrows) abutting the mandible which shows mild cortical irregularity and abnormal signal in the bone marrow (arrow heads). Histology showed no tumour invasion of the mandible and the abnormal signal in the marrow was caused by inflammation (case courtesy of Dr KKT Pak and F Lam).**

While MRI or CT are usually the modalities of choice for imaging cancers of the aerodigestive tract, US is the method of choice for detecting cancers arising in superficial organs such as the thyroid and salivary glands. In the thyroid the most common cancer, papillary carcinoma, frequently show punctuate calcification on US (Fig. 3) which allows identification of small tumours that are undetectable on other modalities. US is able to confirm the diagnosis of a thyroid or salivary gland cancer by guided biopsy performed in the same examination and where small tumours are confined to the thyroid

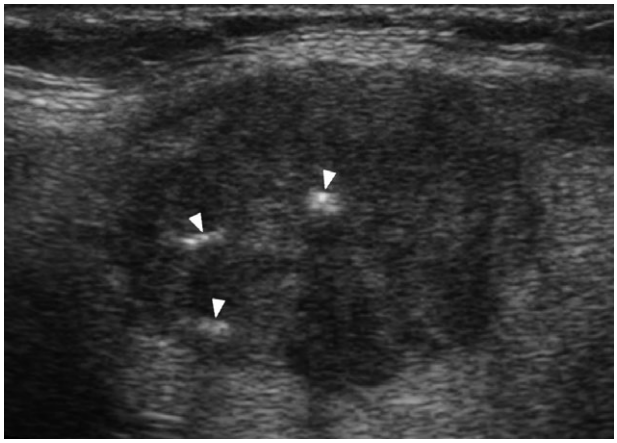

Figure 3 **Ultrasound of a small cancer of the thyroid with punctate calcification (arrows) which is used to identify a papillary carcinoma.**

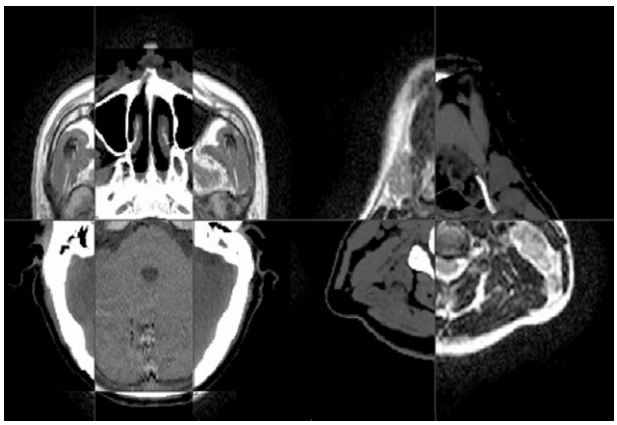

Figure 4 **Successful fusion of MRI onto the CT planning images for IMRT, obtained by performing the MRI scan with the patient inside the radiotherapy cast.**

it may be the only imaging that is required for staging the primary cancer.

Before leaving primary cancer imaging, one further area that warrants brief discussion is the multimodality imaging for planning three-dimensional conformal radiotherapy and intensity modulated radiotherapy (IMRT). CT is required for dose calculation in radiotherapy planning and therefore other modalities must be fused onto the CT images. Fusion between CT and [^{18}F]FDG PET has shown variable results, but MRI with superior depiction of the tumour boundaries and vital anatomical structures is now used routinely for nasopharyngeal cancers around the skull base. Unfortunately precision image co-registration of CT and MRI cannot be obtained consistently but this problem can be improved by performing the MRI scan with the patient inside the radiotherapy cast, in the same position as the CT planning scan (Fig. 4).

Imaging neck node metastases

The identification of a malignant node using the morphological modalities of CT, MRI and US depends on the criteria of size, shape and internal architecture. All three modalities have similar problems with respect to size and shape, and so their relative strengths and weaknesses depend on the ability to identify abnormalities of internal architecture such as nodal necrosis (Fig. 5a–c), extranodal neoplastic spread (ENS) (Fig. 5c), nodal hilum (Fig. 6a,b), vascularity (Fig. 7a,b) and calcification (Fig. 8) (Table 2). Nodal metastases are staged at the same time as the primary tumour and hence MRI or CT is employed most frequently. However, US has many additional advantages that improve the accuracy of detection of metastatic nodes (Table 2). In addition, US is the best modality for performing imaged guided biopsy, a recent meta-analysis showing that US guided fine needle aspiration cytology is the most accurate modality for detecting cervical lymph node metastases[11]. Therefore the additional use of US/US-guided biopsy appears justified in most patients, but because of resource implications US may be targeted at those patients who are likely to benefit the most, namely those who are candidates for surgery, observation or IMRT.

The routine use of [^{18}F]FDG PET for staging neck node metastases is less well established. While overall, [^{18}F]FDG PET is equal or superior to the morphological imaging[12,13], the results can be variable. In common with all imaging modalities false negative and false positive results are encountered. False negative results are found in nodes that are small, necrotic, or cannot be separated anatomically from the primary tumour. False positive results may arise from a range of causes, the most important of which are reactive nodes. Reactive nodes may have an SUV that overlaps with malignant nodes[14] and where a node is positive on [^{18}F]FDG PET alone, the diagnosis may need to be confirmed by US guided biopsy.

Imaging distant metastases

The incidence of distant metastases from HNSCC is between approximately10 and 25%, being higher in the terminally ill and at autopsy. The majority of metastases occur within the first 2 years of diagnosis and once they have developed, survival is poor. Distant metastases from HNSCC are most commonly found in the lungs, mediastinal nodes, bone and liver. The majority of these distant metastases are in the chest and therefore patients usually undergo a routine chest radiograph; imaging of further sites is dependant on clinical findings or blood tests. However, the chest radiograph misses pulmonary and nodal metastases (Fig. 9)[15] and therefore "high risk" patients undergo a CT of the thorax, which can be extended to include the whole liver. The criteria for

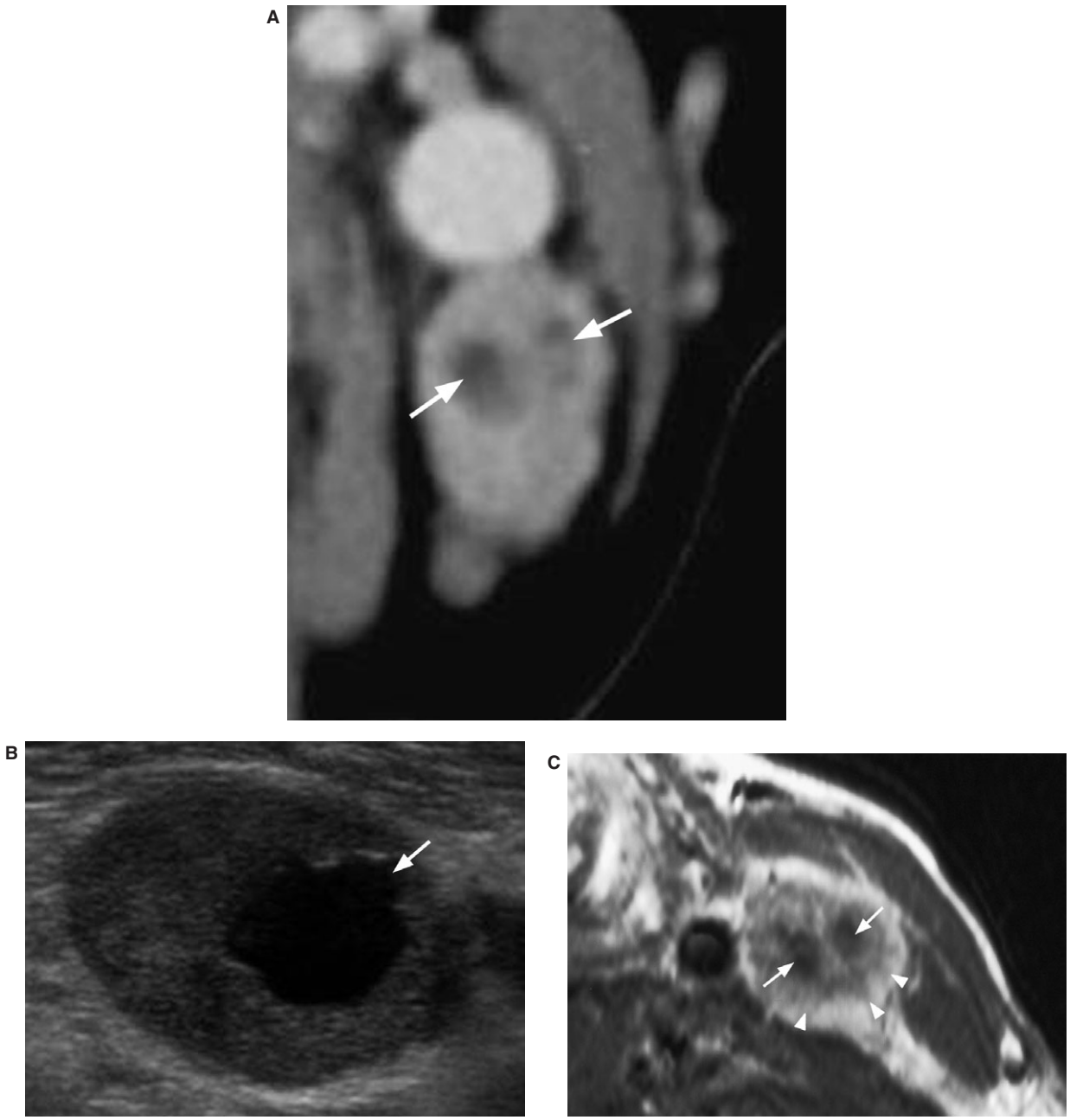

Figure 5 **Nodal necrosis (arrows) on (a) contrast enhanced CT, (b) US and (c) T1W post contrast MRI, the latter also shows early ENS (arrow heads).**

"high risk" are controversial but one of the most important factors appears to be advanced nodal disease (large nodes, multiple nodes and nodes that extend to the lower neck and supraclavicular fossa). Unfortunately over 10% of patients with a negative CT scan of the thorax go on to develop distant metastases in the chest or elsewhere within 12 months, leading Bower *et al.*[16] to propose that a whole body imaging technique such as [^{18}F]FDG PET is required. It appears that for the detection of distant metastases in the chest [^{18}F]FDG PET may have a problem with specificity[19], but a high sensitivity could be valuable for excluding distant metastases especially in those patients in whom extensive surgery is planned. Furthermore, [^{18}F]FDG PET has already proven of value in detecting unsuspected second primary cancers in patients with HNSCC[17,18] and is currently under evaluation in thyroid cancer for identifying ^{131}I-negative distant metastases.

Functional MRI for head and neck cancers

Advances in head and neck imaging are shifting from the morphological to the functional techniques.

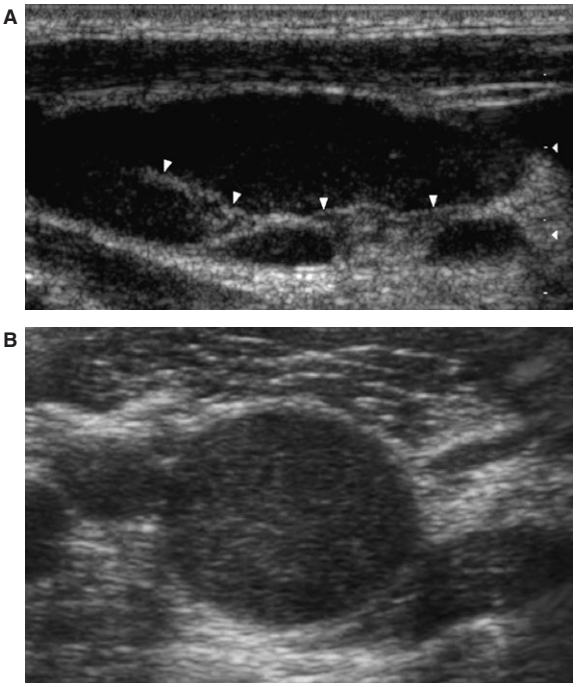

Figure 6 **US demonstrating (a) normal node with a nodal hilus (arrow heads) and (b) a metastatic node with loss of the nodal hilus.**

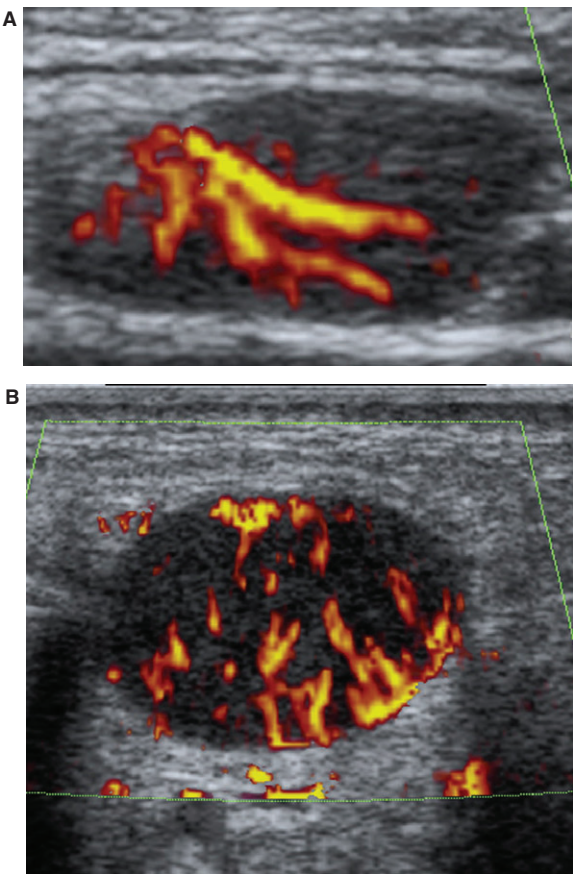

Figure 7 **US demonstrating (a) a normal node with hilar vascularity and (b) a metastatic node with peripheral vascularity.**

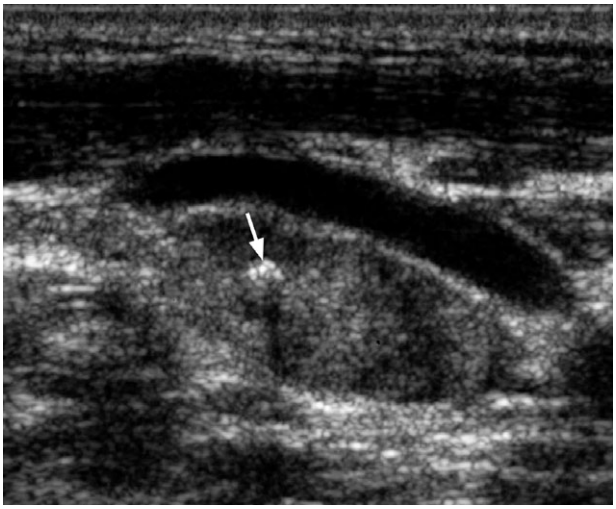

Figure 8 **US of a small metastatic node with punctate calcification (arrow) from papillary carcinoma of the thyroid.**

Table 2 Comparison of MRI, CT and US for the diagnosis of metastatic cervical nodes

Node	MRI, CT and US
Necrosis	Common in metastatic nodes from HNSCC, one of the most accurate signs of a malignant node (provided prevalence of infection in patient population is low). CT and MRI have a similar high sensitivity (92%), US has a high sensitivity for hypoechoic necrosis but isoechoic necrosis may be missed leading to lower overall sensitivity (77%)[5]
Extranodal neoplastic spread	ENS occurs even in small nodes and early ENS can be used as a diagnostic sign of a malignant node. Diagnostic accuracy is similar on MRI and CT[6] but is unknown on US
Hilum	The hilum is a good sign of a normal or reactive node and is identified in 90% of normal nodes >5 mm in size by US[7], but is identified inconsistently by MRI and CT. The hilum is lost in over 90% of metastatic nodes[8] but in cases where the hilum is retained it may be displaced and narrowed by the hypertrophied cortex (especially lymphoma)
Vascularity	Identified by US. Normal nodes have a vascular supply from the hilum while malignant nodes often have a vascular supply from the periphery with or without hilar vascularity[9]
Calcification	Punctate calcification is a sign of a metastatic node from papillary carcinoma of the thyroid on US[10]. Poorly assessed by MRI

These techniques are being used to assess the complex interrelated processes in the cancer microenvironment, such as hypoxia, angiogenesis, pH and metabolism. These techniques have the potential to: (1) improve prediction of the cancer behaviour and response to treatment; (2) evaluate new drugs such as the anti-vascular agents; (3) monitor early cancer response during treatment; and (4) identify residual/recurrent cancer. As the primary treatment for HNSCC shifts from surgery to organ-preserving chemoradiotherapy, these issues are becoming more important. [^{18}F]FDG PET is one functional technique that is used already in clinical practice in some centres to evaluate the response of cancers 3–4 months after treatment. At present functional MRI is a research tool but this non-invasive versatile modality is showing great promise in head and neck cancer and a brief update of some of the potential applications are discussed below.

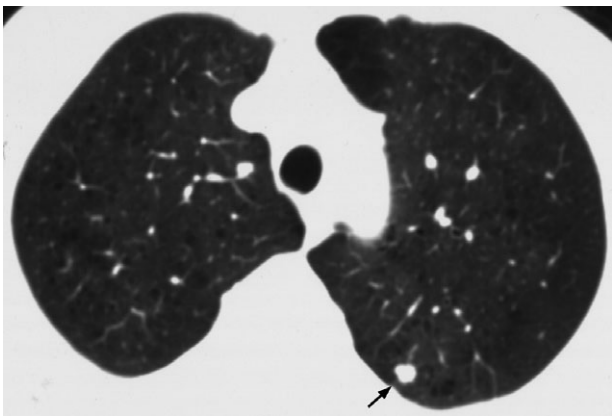

Figure 9 **Small pulmonary metastases (arrow) from a HNSCC identified on CT thorax but missed on the chest radiograph.**

Diffusion-weighted imaging (DWI)

DWI is a quick, easy and widely available functional MR technique. DWI evaluates the mobility of water in different tissues to generate diffusion weighted images and apparent diffusion coefficient (ADC) maps. Diffusion-weighted images are being used to identify a range of cancers and the ADC value improves characterisation of head and neck tumours[20–23]. The ADC values can also be used to monitor cancer treatment. During treatment the ADC value of cancer increases as a result of an increase in cell permeability and swelling, cell destruction, leakage of water into the extravascular extracellular space (EES) and necrosis (Fig. 10). These changes may occur early in treatment, preceding volume changes. At the end of treatment, DWI has the potential to detect residual cancer. A recent study by Vandecaveye *et al.*[24] has shown the ADC value of non-tumoural post therapeutic tissue was significantly higher than that of persistent/residual HNSCC and could be used to distinguish between the two with an accuracy of 95%. In addition, DWI had less false positive results than [^{18}F]FDG PET for persistent tumour in this study.

Dynamic contrast enhanced MRI (DCE-MRI)

In order for cancers to grow they need to increase their vascularity. The increase in vessels produces an increase in the vascular surface area, the vascular walls are more permeable and are susceptible to periodic collapse leading to acute hypoxia, and the chaotic arrangement of vessels leads to areas of increased vascular density, as well as decreased vascular density and chronic hypoxia. DCE-MRI uses low molecular weight paramagnetic contrast agents such as gadolinium to assess this microvasculature as well as the EES of cancers. In the head and neck region rapid serial imaging is performed using T1-weighted gradient echo images as the intravenous contrast passes through the cancer microvessels, into the

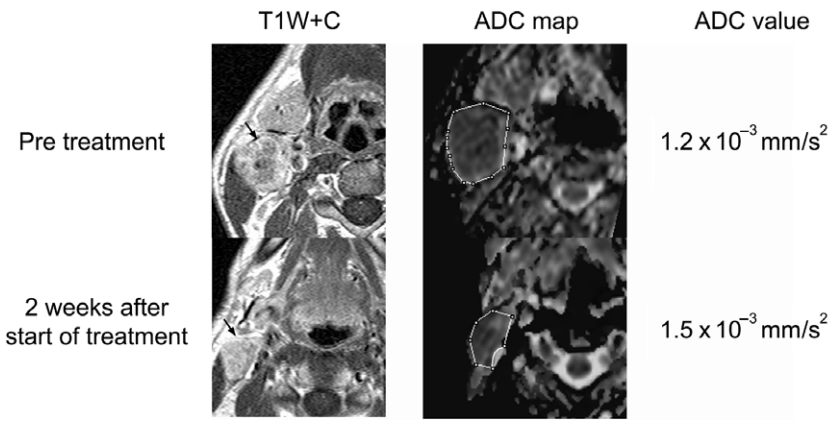

Figure 10 **DWI showing an increase in the ADC value of a node (arrows) from HNSCC that responded to treatment.**

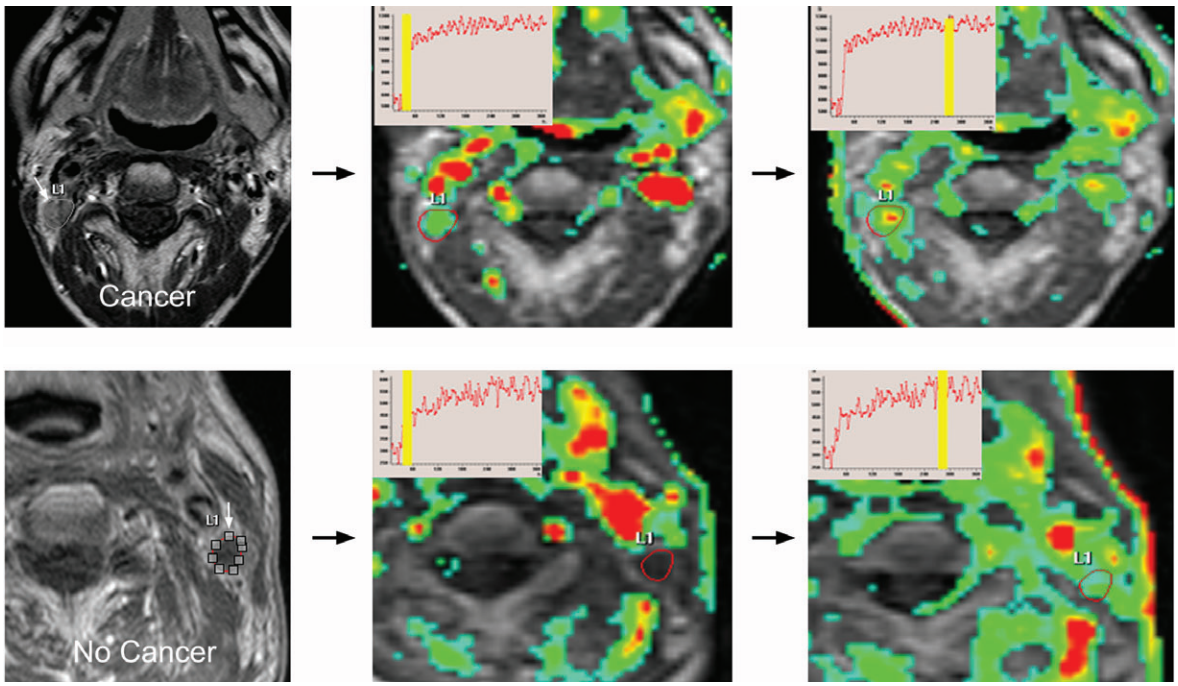

Figure 11 **DCE for monitoring response in a nodal metastasis: (a) residual cancer tends to show earlier and more intense enhancement than (b) post treatment scar tissue.**

EES, and back into the vasculature. The results may be analysed using time-signal intensity plots to acquire relative signal intensity data, such as the initial area under the gadolinium curve (IAUGC), or may be analysed using sophisticated pharmacokinetic models to give more quantitative and reproducible measurements, such as the volume transfer constant between the blood plasma and EES (the K^{trans})[25]. DCE-MRI is currently under evaluation for assessment of new anti-vascular agents and cancer hypoxia. It has also been used to identify persistent/recurrent cancer. Cancers appear to show greater and earlier contrast enhancement compared to fibrotic scar tissue[26] (Fig. 11) and the enhancement pattern shows promise in predicting local control in head and neck cancers[27–29].

MR spectroscopy (MRS)

MRS demonstrates chemicals or metabolites within cancers that can be used as biomarkers to identify cancer and explore changes associated with hypoxia and cancer treatment. Proton (^{1}H) and phosphorus (^{31}P) spectroscopy have been most widely evaluated, ^{1}H MRS has the advantage of being more sensitive so enabling it to analyse smaller tumours (1 cm^3). In common with cancers elsewhere in the body ^{1}H MRS is able to demonstrate choline (Cho) at 3.2 ppm in cancers of the head and neck including HNSCC, lymphoma and thyroid cancer[30,31]. Changes in Cho are currently under interrogation for monitoring cancer treatment (Fig. 12) and have been shown already to be of value in the breast. Lactate is another biomarker that has been found in metastatic nodes from HNSCC and has the potential to be used in the assessment of cancer hypoxia[32]. MRS is a promising technique for the future but at present MRS is limited by technical difficulties.

Blood oxygen level dependent MRI (BOLD)

Hypoxic cancers are more resistant to radiotherapy and chemotherapy. Currently there is interest in improving the therapeutic response of hypoxic cancers to radiotherapy by using radiosensitisers such as carbogen (95% oxygen mixed with 5% carbon dioxide to decrease oxygen induced vasoconstriction)[33]. Therefore, there is a need for a non-invasive test that can identify hypoxic cancers which are likely to respond to this kind of treatment. BOLD uses a T_2^*-sensitive sequence during oxygen inhalation to detect an increase in signal resulting from the reduced paramagnetic effect of a reduction in the blood deoxyhaemoglobin within a cancer. As with all functional MR techniques, BOLD presents challenges; the signal is not purely the result of oxygenation, the effects are short lived, and signal changes are small and may be difficult to reproduce. However, despite these difficulties BOLD has been used successfully to detect decreases in the blood deoxyhaemoglobin in human cancers during carbogen inhalation[34,35] and shows promise for tailoring treatment for hypoxic cancers in the future (Fig. 13).

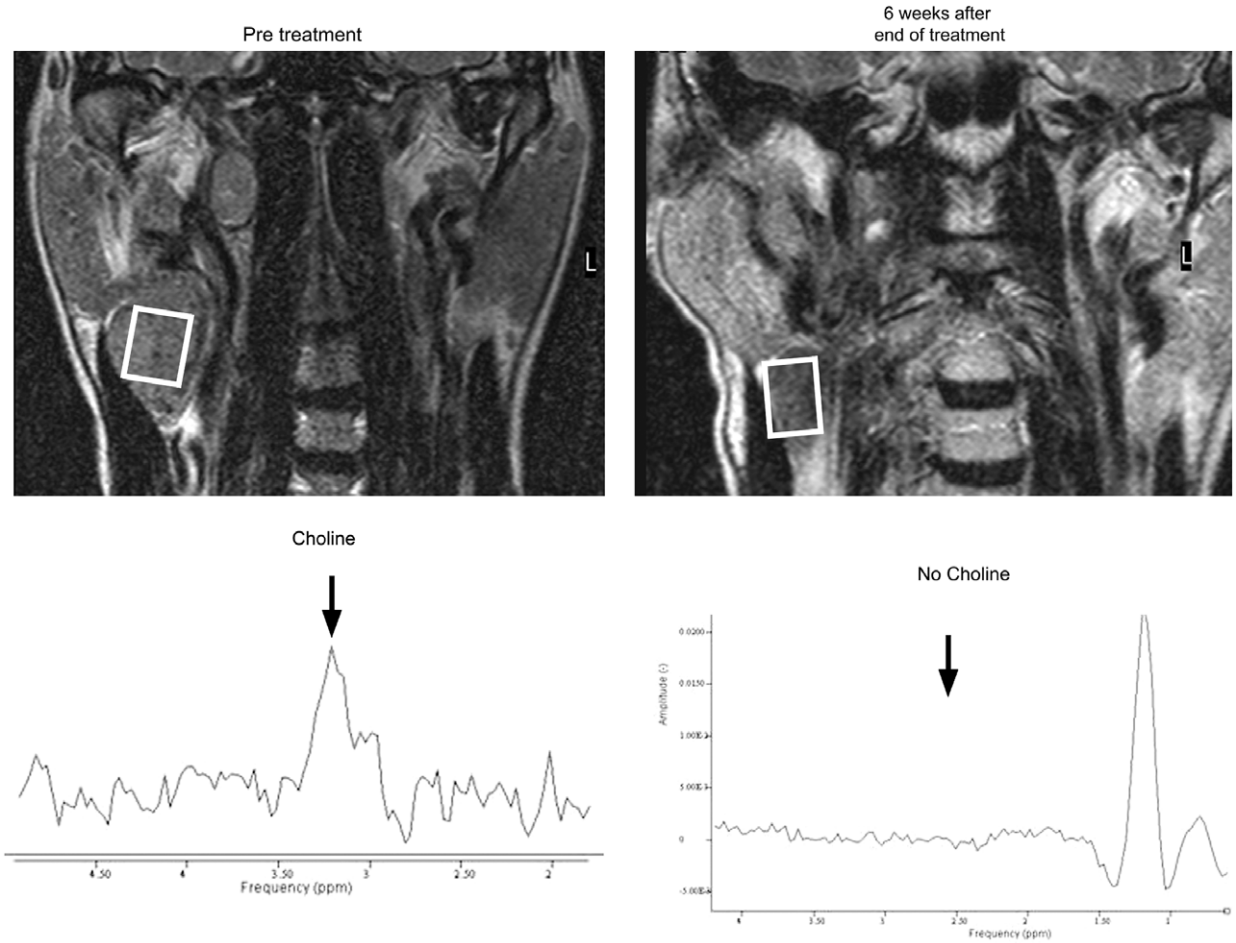

Figure 12 **^{1}H MRS showing loss of the Cho peak at 3.2 ppm in a node from HNSCC that responded to treatment.**

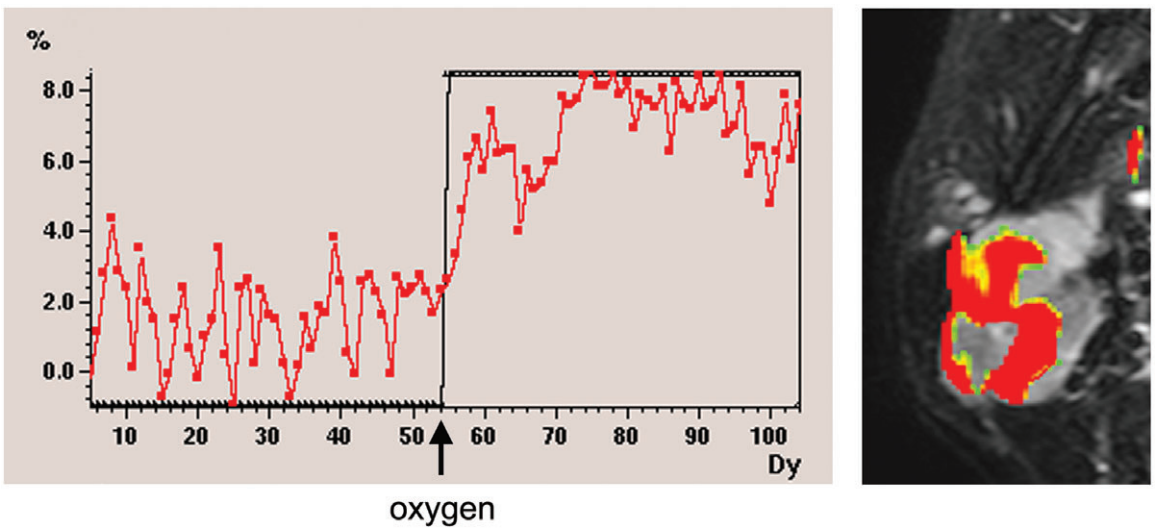

Figure 13 **BOLD imaging showing an increase in signal in a nodal metastasis during oxygen inhalation.**

Conclusion

Imaging head and neck cancer requires a multimodality approach and the strengths and weakness of each modality need to be understood in order to obtain the best results for staging and planning treatment. Future advances for improving prognostic indicators and monitoring of cancer treatment are likely to come from developments in functional imaging such as the functional MR techniques using higher field magnets.

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