Newer imaging techniques in head and neck cancer

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Abstract

Computerized tomography (CT), Magnetic Resonance Imaging form the backbone of head and neck cancer imaging. This review describes the role of newer functional imaging techniques like diffusion weighted MR imaging and perfusion imaging in head and neck cancers. A review of the current role of PET-CT in head and neck tumors is also included in this article.

Keywords FDG PET/CT · Diffusion Imaging · Perfusion Imaging · Head neck Cancer

Introduction

In the past few decades, as oncologists and oncosurgeons attempt to cure many types of cancers or atleast provide patients with a longer disease free life, there has been a spectacular parallel and supportive evolution in imaging technology. Currently, imaging plays a pivotal role in the management of all cancers including those of the head and neck. It is used for screening, for preliminary diagnosis, to establish the extent and distribution of disease, for biopsy guidance, staging, prognostication, therapeutic planning, judging response to therapy and restaging. In oncology, the role of imaging is shifting, from merely providing anatomical information to providing insight into tumor biology using techniques such as CT (Computerised Tomography) and MRI (Magnetic Resonance Imaging) perfusion imaging, diffusion MR imaging and PET (Positron Emission Tomography).

CT scan which was introduced way back in the 1970's still remains the backbone of head and neck cancer imaging. It is widely available in all imaging departments, is fast and a relatively inexpensive imaging modality. CT is good at providing information about the size and extent of the primary tumor as well as locoregional lymph nodes. In head and neck cancers it offers an added advan-

tage over clinical examination in assessing disease, thereby affecting patient management.¹

MRI was introduced in the 1980's and since then is competing with CT scan as the imaging modality of choice for head and neck cancers. It provides important information about the primary tumor as regards its deep extension and also detects clinically occult sites of disease.² MRI has inherently better contrast resolution as compared to CT scan and hence is found to be more useful for detection of perineural invasion, marrow infiltration and soft tissue involvement.³

18 Flouride-flurodeoxyglucose (18F-FDG) PET has in the last few years become an established modality in the management of several cancers. It is an imaging technique that provides information about the metabolic changes associated with cancer. PET scanning requires the use of molecules that are labelled with radio nuclides. Numerous such positron emitting radio-isotopes exist and are used in clinical experiments and research. However in clinical PET practice the principal radio-isotope used is the positron emitting 18F-FDG which is a glucose analogue labelled with 18F.

The positron emitters including 18F FDG have short half lives and are produced in cyclotrons. FDG is injected intravenously and is transported from the plasma to the

Fig. 1 DWI in a patient of tongue base squamous cell carcinoma. Mass in the tongue base on axial T2 weighted MR image (arrow **A**) appearing bright on DWI (arrow **B**) and dark on apparent diffusion coefficient (ADC) map (arrow **C**), suggesting a restricted diffusion seen in malignant lesions. Right level II enlarged lymphnode (arrow **C**) appearing bright on DWI (arrow **D**) and dark on ADC map (arrow **E**), suggesting restricted diffusion seen in malignant lymph nodes

cells by glucose transporters (GLUT 1 and GLUT 4). It then undergoes phosphorylation within the cell by the enzyme hexokinase and is converted to FDG-6-phosphate. FDG-6-phosphate is not further metabolised and gets trapped in the cell. Cancer cells demonstrate increased anaerobic glycolysis (Warburg effect)⁴ which is believed to be due to upregulation of glucose transporters and hexokinase and reduced levels of glucose-6-phosphatase thus limiting further metabolism of the tracer in cancer cells.^{4,5} FDG PET and PET-CT plays an important role in the initial diagnosis, staging, response assessment and re-staging of various malignancies including head and neck cancers. PETCT combines the functional information with the anatomic and spatial information provided by CT scan. All PET machines today are sold as integrated PET-CT units. The role of newer imaging techniques like diffusion and perfusion imaging with MRI and CT and metabolic imaging with PET will be subsequently discussed.

Diffusion weighted MR imaging

Diffusion weighted imaging (DWI) using MRI is the simplest form of diffusion imaging. DW sequences are sensitized to detect the Brownian (random) motion of water protons in biological tissues. The apparent diffusion coefficient (ADC) is a mathematical quantification of the extent of free diffusivity of water molecules. The intrinsic

T2 signal changes contributing in the diffusion images are eliminated in ADC maps. In normal tissues and in vasogenic edema where there is unrestricted motion of water protons no restricted diffusion can be measured. However in cytotoxic edema and in tumors with high cellularity there is restricted diffusion of water protons which can be measured quantitatively. This technique is being extensively used in brain for diagnosing acute infarcts⁶ and for differentiating high grade tumors (that display restricted diffusion) from low grade ones. Besides the brain, studies have shown that DWI may be useful to assess transition-zone cancers of the prostate,⁷ to distinguish benign from malignant pulmonary nodules⁸ and to distinguish a malignant vertebral collapse from an osteoporotic vertebral collapse.⁹ Early studies using echoplanar MR imaging have shown that head-neck squamous cancers can show restricted diffusion due to their high cellularity.¹⁰ Non malignant change such as necrosis, fibrosis, inflammation and fibrosis have less cellularity as compared to viable tumor and hence show high ADC values.

Naturally DWI can aid differentiation of post treatment changes from viable tumor. Residual or recurrent disease harbors regions of increased cellularity and should demonstrate restricted diffusion or low ADC values.¹¹ Clinical studies have demonstrated that DWI can be a very useful additional tool in assessing the post treatment neck. DWI features can allow better tissue sampling which can help in providing correct diagnosis.¹² As

Fig. 2 CT perfusion images in a patient of hypopharyngeal squamous cell carcinoma. White arrows point to the region of interest (ROI) in the hypopharyngeal primary in the CT image (A) and in the colour map that represents the time attenuation curve (B). Arrowheads point to the (ROI) in the neck nodes in the CT image (C) and in the colour map (D). Both the primary and the metastatic node demonstrate increased perfusion

regards cervical lymph nodes low ADC values are seen with metastatic adenopathy¹³ (Fig. 1). Metastatic nodes demonstrate a large number of cells, increased mitosis and cellular polymorphism which probably decrease the extra cellular space causing decreased ADC values.¹⁴ In a recent study DWI showed higher accuracy in detection of malignant nodes as compared to routine MR sequences (76% vs 7%) mainly due to improved detection of sub-centimetre sized metastatic nodes.¹⁵

Experience and expertise is required for interpretation of DWI images. Refining techniques of performing DWI along with standardization of quantitative methods of estimation is required before DWI can be incorporated in widespread routine clinical practice.

Perfusion imaging

Neovascularity is a very important feature of malignant tumors and is required to sustain their rapid growth. Neovascularity in tumors can be studied using perfusion imaging techniques performed using MRI and CT. Changes in tumor signal intensity (on MRI) and attenuation (on CT) are studied during dynamic injection of intravenous contrast. Various perfusion parameters can be generated which can be grouped into two major methods: compartmental analysis and deconvolution-based methods. Various aspects of neovascularity like the blood flow (BF), blood volume (BV), capillary permeability (CP) and mean transit time (MTT) can be studied using deconvolution based methods. Perfusion imaging can have a

wide range of applications in head and neck tumors such as detection of primary, differentiation between benign and malignant tumors (Fig. 2) and assessment of response to treatment. CT Perfusion was found to be of some value in distinguishing between benign and malignant tumors of the head and neck on the basis of the low MTT values of the malignant lesions.^{16,17} Hermans et al. have demonstrated that CT based perfusion values are an independent predictor of local control in squamous cell carcinoma of the head and neck treated with definitive radiation or chemo-radiation.¹⁸ According to this study tumors with a lower perfusion rate had a significantly high local failure rate. Initial results by Gandhi et al have shown that CT perfusion techniques can offer non-invasive monitoring of response to neo-adjuvant treatment in oropharyngeal cancers.¹⁹

Their study demonstrated that percentage reduction of blood volume (BV) correlated well with endoscopic response to induction chemotherapy. Similar results were also published by Zima et al., demonstrating that tumors with elevated BF and BV on CT perfusion were associated with response to induction chemotherapy and it was possible to recognize patients who could successfully respond to induction therapy.²⁰

Dynamic contrast enhanced (DCE) MR imaging

DCE MR imaging has been used to study head and neck cancers.^{21,22} It studies the tumor microenvironment which

Fig. 3 FDG PET-CT study in a case of left pyriform fossa squamous cell carcinoma for pretreatment staging. Intense FDG uptake is seen in the primary site (arrow) and in the left sided neck node (arrowhead). FDG avid metastatic lesion in the vertebrae and the liver

shows increased microvascular permeability and diameter, increased blood flow and blood volume of the microvasculature, increased tissue oxygenation and metabolism.²³ DCE MRI has been found to be useful in differentiating residual tumor from post radiation fibrosis.²⁴ The value of DCE MR has also been demonstrated as a predictor of response in to radiation therapy.²⁵ Tumor blood flow is an important parameter in predicting outcome after RT and tumors which show diminished perfusion at the end of radiotherapy are more likely to respond to radiation. On the other hand tumors which show greater post contrast enhancement after RT are likely to fail locally.

It is important to note that technical standardization along with skill, expertise and experience in imaging interpretation need to be acquired before these imaging techniques become accepted as standard of care in head and neck malignancies.

FDG PET and PET-CT

The use of FDG PET in head and neck neoplasm has been studied more extensively in squamous cell carcinomas and also to an extent in malignancies of the salivary gland and thyroid. For head and neck squamous cell cancers (HNSCC), PET can be used for initial staging, monitoring response to therapy, restaging and long term surveillance.

Initial staging

PET and PET-CT have a limited role in defining the T stage of the primary. MRI and contrast enhanced CT scan

due to their better resolution and ability to depict local soft tissue and bony anatomy in detail are preferred over PET scan. However in recent times with the advent of integrated PET-CT systems, the study can be performed with intravenous contrast thus combining the functional/metabolic information of PET and the excellent spatial resolution of a dedicated contrast enhanced CT scan. Thus, PET-CT performed with intravenous contrast can be a reasonable alternative for assessing the primary tumour extent at initial presentation.²⁶ The value of PET for assessing cervical nodal metastases at initial staging has been studied extensively. Studies have shown that PET is comparable or superior to conventional imaging in detection of neck node metastases at initial staging. According to a review, the sensitivity and specificity of PET for neck node metastases was 87–90% and 80–93% and that of MRI was 61–97% and 21–100%.²⁷ Another study showed better sensitivity for MRI (93%) than PET (85%), with comparable specificities.²⁸ A more recent study which evaluated ultrasound, CT, MRI and FDG PET-CT showed no statistically significant difference in the sensitivity, specificity and accuracy between these modalities.²⁹ In patients with advanced locoregional disease PET can detect occult distant metastatic disease in up to 10% of patients.³⁰ The inherent whole body coverage of PET as compared to the more loco-regional approach of CT and MRI scanning makes it more suitable to uncover sites of unexpected distant metastases (Fig. 3). At many institutes including ours, PET is suggested for initial evaluation if there is a concern of distant metastatic disease on the basis of the loco-regional extent of disease.

Fig. 4 FDG PET-CT study in a case of unknown primary with metastatic neck nodes. Arrows show FDG avid bilateral metastatic nodes. Arrowhead demonstrates FDG avid disease in the nasopharynx suggesting the site of primary. Note. No obvious morphological change seen on the CT image

In the setting of clinically N0 (nodes not palpable at initial presentation) PET has not been found to be very useful as per recent literature.³¹ This is because of the limited resolution of PET for lesions less than 5 mm and its inability to detect microscopic disease. Selective neck dissection and sentinel node biopsy is more useful in this regard. It is conceivable that in the near future sentinel node biopsy might become the modality of choice in N0 neck owing to its very high reported sensitivity and specificity.

Unknown primary

In patients presenting with cervical nodal metastases detection of primary tumour site is important as it may define the site and extent of surgery and also delineate the field of radiotherapy (Fig. 4). Multiple studies have evaluated the role of PET in detecting occult primary with variable results. The sensitivity of PET to detect the primary site of tumour varied from 10–60% according to recent review of 11 studies.²⁷ The high variability in the results was attributed to differences in inclusion criteria and clinical verifications. Another meta-analysis analysed studies that included patients who had initially negative clinical examination and MRI findings.³² According to this analysis FDG PET was able to detect the primary site in 27% cases (40–150%). There are two schools of thought about unknown primary and FDG PET. As per conventional thinking, the diagnostic evaluation of unknown primary should include a thorough physical examination, CT scan/MRI of the head-neck and panendoscopy with directed biopsies.

FDG PET should be reserved for those cases with indeterminate findings on physical examination and/or head-

neck CT/MRI.³³ More recent thinking suggests using PETCT as the initial imaging modality followed by directed biopsies from the PET positive sites.

Assessment of response to therapy

Assessment of response to therapy is challenging because tissue changes after radiation therapy and surgery obscures the detection of residual/recurrent disease by clinical examination and by conventional imaging modalities. Several studies have shown that FDG PET can detect residual tumor after chemoradiation more accurately than conventional imaging. In a study of 108 patients, residual disease after chemoradiation was detected with a sensitivity of 82%, specificity of 92%, positive predictive value of 64%, negative predictive value of 97% and overall accuracy of 90%.³⁴

According to a recent study the negative predictive value of PET to exclude residual disease is about 97% when it is performed about 8–12 weeks after completion of treatment.³⁵ The study recommended that in patients without residual lymphadenopathy, neck dissection may be withheld safely (Fig. 5). In patients with residual lymphadenopathy, a lack of abnormal ¹⁸F-FDG uptake in these nodes also excludes viable tumor with high certainty. A systematic review and meta-analysis³⁶ of 27 studies evaluating the role of PET in follow up of patients after chemo-radiation revealed that the pooled sensitivity and specificity of PET for detecting residual or recurrent head and neck squamous cell carcinoma were 94% [95% confidence interval (CI), 87–97%] and 82% (95% CI, 76–86%) respectively. Positive and negative predictive values were 75% (95% CI, 68–82%), and 95% (95% CI, 92–97%) respectively.

Fig. 5 Pre and post chemo-radiotherapy FDG PET-CT study in a case of right sided tonsillar squamous cell carcinoma Block arrow in figure A shows FDG avid disease in the primary site. Thin arrow (A) shows the FDG avid metastatic right level II node. Post treatment study (B) performed 8 weeks after chemoradiation shows complete metabolic response at the primary site (block arrow) and residual disease in the neck node (thin arrow)

Sensitivity was greater for scans performed 10 weeks or more after treatment. The metaanalysis suggested that an appropriately performed PET may reduce the requirement for check endoscopies and planned neck dissections.

Surveillance and detection of recurrence

Numerous studies have shown that PET has a very good accuracy in detecting local and regional nodal recurrences during surveillance.^{37–39} A very recent study of surveillance of patients of head and neck cancer who were negative on clinical examination showed that PET-CT was more accurate than conventional clinical follow up examination and could be proposed systematically at 12 months of regular follow up.⁴⁰ It is of particular value in detecting sites of distant failure before a definitive salvage therapy is planned for locoregional recurrence thus changing the intent of treatment to a systemic or palliative one.

Radiotherapy planning

For radiation therapy planning several publications have shown that target volumes can be altered in as much as 20% cases when FDG PET-CT is used over CT alone.^{41,42} Hence PET-CT is used as an adjunct to CT and MRI for target definition. Long term outcome data identifying pat-

terns of treatment failure related to PET-CT based target volumes are needed to define a standardized approach, before it can be included in routine clinical practice.

Thyroid malignancy

In well differentiated thyroid cancers FDG PET-CT plays an additive role and is used to detect sites of metastatic disease which are scintigraphically negative on radioiodine studies.⁴³ Persistently high thyroglobulin levels with a negative whole body iodine scan is now a recognised indication for FDG PET-CT. Similarly for patients of medullary cancers who show persistently high calcitonin levels post total thyroidectomy, PET-CT has been found to be useful to detect sites of disease recurrence.⁴⁴ PET technology using ⁶⁸Ga-labeled 1,4,7,10-tetraazacyclododecane-N,N9,N99,N999-tetraacetic acid-D-Phe1-Tyr3-octreotide (⁶⁸Ga-DOTA-TOC) has shown promising results in patient studies.⁴⁵ It has been shown to have a much higher diagnostic accuracy for detection and staging of neuroendocrine tumors (NET) including medullary carcinomas (MTC) as compared to somatostatin scintigraphy and CT scan. In another study performed using ⁶⁸Ga-DOTA-NOC for various NET's including MTC, it was shown to be more effective than conventional imaging techniques.⁴⁶ The role of PET in other thyroid cancers like the anaplastic variety are to define the local extent of disease and to look for distant metastases.⁴⁷

Thus FDG PET-CT is increasingly playing a standard role in the management algorithm of various head and neck malignancies.

Potential application of non-FDG PET tracers

Hypoxia imaging and FMISO PET: Squamous cell carcinomas of the head-neck region are known to undergo hypoxic changes. Hypoxic cells are resistant to the effects of chemo and radiation therapy and require thrice the radiation doses as compared to normoxic conditions to get the same degree of cytotoxic effect.⁴⁸ Hypoxia in tumor cells is strongly associated with treatment failure independent of the tumor stage and the treatment modality

used.⁴⁹ The most common compound available for hypoxia imaging is 18F-Fluormisonidazole (18F-FMISO). Newer treatment strategies can be applied to overcome the resistance to conventional RT by using hypoxic PET tracers in head and neck cancers.

18F-FLT PET: The uptake of 18F-FLT and its retention is related to the activity of thymidine kinase and the fraction of cells in the S-phase of the cell cycle. Reduction in FLT uptake and thymidine kinase activity are noted within a day of irradiation. In head and neck cancers FLT imaging could potentially allow a earlier and a more accurate estimation of treatment response than imaging with FDG PET and CT/MRI.⁵⁰

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