MONASH University

Head and Neck Squamous Cell Carcinoma: Improving the Detection of Metastatic Cervical Lymph Nodes on a Combined PET/CT Scan

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Abstract

Objective: The presence of cervical lymph node metastasis is an important prognostic factor for patients with head and neck squamous cell carcinomas (HNSCC). Accurate assessment of lymph node metastasis in these patients is essential for appropriate management and for prognostic and management purposes. Here, we evaluated the effectiveness of the maximum standardized uptake value (SUV_{max}) on positron emission tomography (PET) in assessing lymph node metastasis in head and neck squamous cell carcinomas prior to surgery.

Methods: A retrospective review of 74 patients with HNSCC who underwent PET/CT prior to neck dissection were examined. Pre-operative PET/CT scans were reviewed by a single, experienced nuclear medicine physician and SUV_{max} of the largest node in each nodal basin documented. These were compared with the histology results of the neck dissection.

Results: A total of 364 nodal basins including 86 basins with metastatic nodes were evaluated. A nodal SUV_{max} ≥3.16 yielded a sensitivity of 74.4% and specificity of 84.9% in detecting metastatic nodes. The ratio between nodal SUV_{max} and liver SUV_{max} was found on receiver operating characteristic (ROC) to be effective in detecting metastatic nodes with an area under ROC curve of 0.90. A nodal SUV_{max} /Liver SUV_{max} ratio ≥0.90 yielded a sensitivity of 74.1% and specificity of 93.4%.

Conclusions: Nodal SUV_{max} and nodal SUV_{max}/ liver SUV_{max} are both useful in the pre-operative detection of metastatic nodes. The latter is likely to be more useful as it corrects for inter-scanner variability.

Declaration

This thesis contains no material which has been accepted for the award of any other degree or diploma at any university or equivalent institution and that, to the best of my knowledge and belief, this thesis contains no material previously published or written by another person, except where due reference is made in the text of the thesis.

Signature: 

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Date: 13th November 2016

Publications during enrolment

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2. LIM, R., RAMDAVE, S., BEECH, P., BILLAH, B., KARIM, MN., SMITH, JA., SAFDAR, A. & SIGSTON, E. 2016. Utility of SUVmax on ^{18}F-FDG PET in detecting cervical nodal metastases. *Cancer imaging*, 2016, 16:39.

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Contents

ABBREVIATIONS

BMI: body mass index

CT: computed tomography

END: elective neck dissection

^{18}F-FDG: 18F-fluorodeoxyglucose

GTV: gross tumour volume

HNSCC: head and neck squamous cell carcinoma

HPV: human papilloma virus

IJV: internal jugular vein

MDT: multidisciplinary team

MRI: magnetic resonance imaging

MRND: modified radical neck dissection

NCCN: National Comprehensive Cancer Network

NSCLC: non-small cell lung cancer

PET: positron emission tomography

pRb: retinoblastoma protein

RND: radical neck dissection

ROI: region of interest

SAN: spinal accessory nerve

SCC: squamous cell carcinoma

SCM: sternocleidomastoid muscle

SND: selective neck dissection

SOHND: supra-omohyoid neck dissection

SUV: standardized uptake value

SUV_{max}: maximum standardized uptake value

SUV_{mean}: mean standardized uptake value

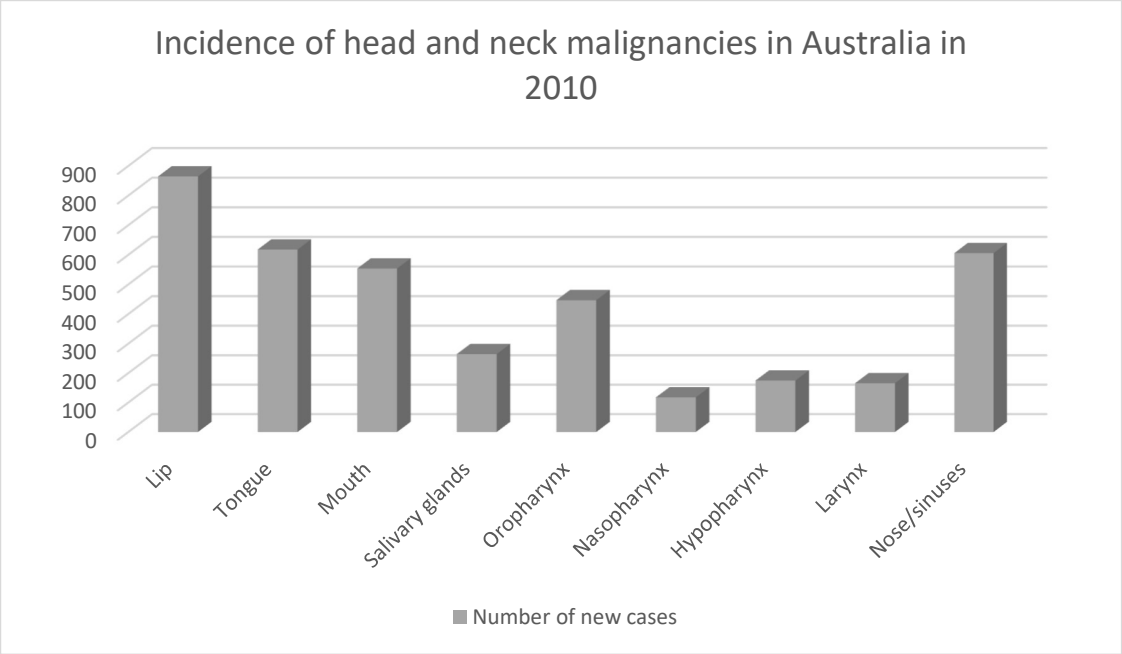
USS: ultrasound

INTRODUCTION

Epidemiology of head and neck cancer

Head and neck squamous cell carcinoma (HNSCC) accounts for approximately 3.2 percent of all malignancies worldwide (Jemal et al., 2010). In Australia, head and neck malignancies constitute about 2.7 percent of all new cancer cases, and accounts for 2.4 percent of all cancer deaths in Australia, the majority of these being squamous cell carcinomas (AIHW, 2012). In 2010, malignancies of the oral cavity, oropharynx and larynx, were responsible for most of the mortality from head and neck malignancies amongst Australians (AIHW, 2012).

Figure 1. Incidence of head and neck malignancies in Australia in 2010



Data adapted from Australian Institute of Health and Welfare & Australasian Association of Cancer Registries 2012. Cancer in Australia: an overview, 2012. Cancer series no. 74. Cat. no. CAN 70. Canberra: AIHW.

Risk factors

Alcohol and tobacco

Alcohol and tobacco use are two of the most important risk factors for developing HNSCC, with approximately 80-85% of patients reporting a significant history of use of these substances (Lenhard et al., 2001, Zhang et al., 2000). However, these risk factors play a smaller role in the development of HNSCC in younger patients (ie. Under 45 years) compared to older age groups, and in women, compared to men (Hashibe et al., 2009).

While alcohol consumption is an independent risk factor for HNSCC, its' synergistic effect with the carcinogenic potential of tobacco, in particular for oral and oropharyngeal malignancies, has been documented (Lenhard et al., 2001, Hashibe et al., 2009, Baan et al., 2007). Daily consumption of approximately 50g of alcohol increases the risk of oral cavity, pharyngeal and laryngeal cancers by two to three times, compared with non-drinkers (Znaor et al., 2003, Talamini et al., 2002, Baan et al., 2007). In addition to the direct carcinogenic effect of alcohol, it increases malignant transformation of mucosa by suppressing the efficiency of DNA repair after exposure to nitrosamine compounds found in cigarette smoke (Lenhard et al., 2001).

Cannabis use has also been found to be an independent risk factor for oropharyngeal cancers (Marks et al., 2014). Tetrahydrocannabinol, the major active cannabinoid in marijuana smoke engages

specific cell surface receptors, including those found on immune cells of the tonsil. Engagement of these receptors enhances anti-inflammatory cytokine production and suppresses pro-inflammatory cytokine production, leading to suppression of anti-tumour immunity (Marks et al., 2014).

A genetic predisposition to HNSCC has been suggested due to the occurrence of some cases of HNSCC in young patients and in those without a history of exposure to the common carcinogens (Lenhard et al., 2001). This genetic predisposition may be the result of reduced metabolism, conjugation and excretion of carcinogens as well as inherited abnormalities of p53 function (Davidson et al., 1993).

Occupational

The role of certain occupational exposures and their role in the development of HNSCC are well documented. Laryngeal cancer is associated with occupational exposures to nickel and asbestos while woodworkers are at risk of nasopharyngeal cancers as a result of the wood dust (Burch et al., 1981, Jayaprakash et al., 2008, Siew et al., 2012). Textile workers, in particular those who work with raw fibres are known to have an increased risk of oral and pharyngeal cancers (Moss and Lee, 1974).

Dietary

Figure 2. Betel quid

Photo adapted from *Betel quid chewing as a source of manganese exposure: total daily intake of manganese in a Bangladeshi population.* (Al-Rmalli et al., 2011)

Betel quid chewing is an ancient practice in many Asian countries. Made from a combination of betel leaf, areca nut and slaked lime, betel quid chewing is practiced by over 250 million individuals in Southeast Asia, the Philippines and the South Pacific Islands (Gupta and Ray, 2004, Stich et al., 1982).

While the chewing of betel quid has been demonstrated to be an independent risk factor for the development of oral cancer, the carcinogenic potential of betel quid chewing is also synergistic with that of alcohol and tobacco (Ko et al., 1995). Indeed, patients with exposure to all three carcinogens

have a 123-fold higher incidence of oral cancer. The risk of oral cancer was also increased amongst patients who chewed betel quid with the betel fruit, and amongst those who swallowed betel juice (Ko et al., 1995).

Viral

The human papilloma virus (HPV) has also been shown to be a risk factor for HNSCC, in particular oropharyngeal, oral cavity and laryngeal cancers. HPV is a ds-DNA virus that has a propensity for infecting squamous epithelial cells (Hennessey et al., 2009). Over 100 HPV subtypes have been identified and these subtypes can be broadly classified into low-risk and high-risk subtypes. Low risk subtypes, such as HPV-6 and 11 are typically associated with benign warts, while high-risk subtypes such as HPV-16, 18, 31, 33 and 45 (Hennessey et al., 2009). The HPV subtypes of interest in HNSCC are HPV-16 and 33 (Attner et al., 2010). HPV is thought to cause HNSCC through the production of two oncoproteins, E6 and E7, that promote the degradation of p53 and retinoblastoma tumour suppressor proteins (Cheng et al., 1995, Hennessey et al., 2009, Munger et al., 2004, Werness et al., 1990). The retinoblastoma protein (pRb) functions as a negative regulator of p16 protein and its degradation in turn leads to an overexpression of the p16 protein, which is a cyclin-dependent kinase inhibitor (Langendijk and Psyrri, 2010, Wittekindt et al., 2005). Therefore, detection of p16 can be used as a surrogate measure for HPV infection, circumventing the need for laborious and expensive HPV DNA detection (Wittekindt et al., 2005).

Compared to HPV-negative HNSCC, HPV-positive patients have been shown to have a better prognosis (Arenz et al., 2014, Fakhry et al., 2008, Friesland et al., 2001, Hennessey et al., 2009, Kumar et al., 2007, Sisk et al., 2002). This is in part due to the higher sensitivity of these tumours to

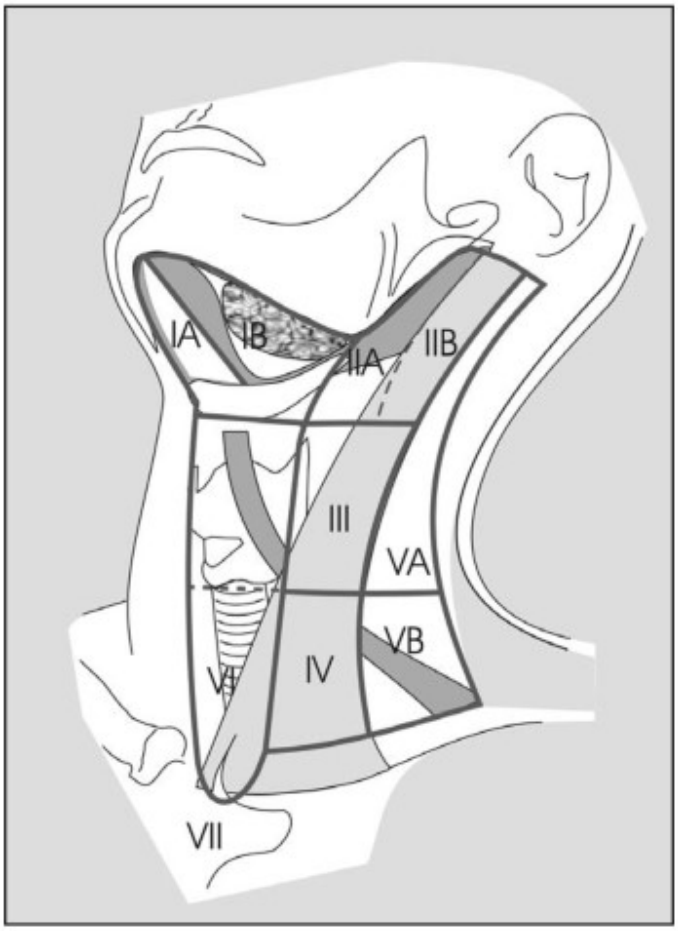
chemoradiotherapy, as shown by a prospective multi-centre study published in 2008 evaluated the association of tumor HPV status with therapeutic response and survival among 96 patients with stage III or IV HNSCC of the oropharynx or larynx. This study found that compared to patients with HPV-negative tumours, HPV-positive tumours had higher response rates after induction chemotherapy (82% vs 55%, CI 9.7% to 44.3%, p = 0.007) (Fakhry et al., 2008).

The reason behind the increased radiosensitivity of HPV-positive tumours is the fact that patients with transcriptionally-active HPV infection are more likely to carry wild-type TP53, which renders the tumour more susceptible to radiation-induced apoptosis (Peltenburg, 2000, Ragin et al., 2006).

Cervical nodal levels

Historically, cervical lymph nodes were described in 10 principal groups – (1) occipital, (2) mastoid, (3) parotid, (4) submaxillary, (5) facial, (6) submental, (7) sublingual, (8) retropharyngeal, (9) anterior cervical, and (10) lateral cervical (Ferlito et al., 2010). With improvements in the understanding of the lymphatic drainage system in the neck, this classification has evolved into 6-level classification of cervical lymph nodes that is widely used today (See diagram below) (Robbins et al., 2008).

Figure 3. Schematic diagram of cervical lymph node levels



Level I

This level is further subdivided into levels IA and IB. Level IA contains submental lymph nodes and is bounded by the midline, anterior belly of the diagastric muscle and the hyoid bone. Level IB contains submandibular lymph nodes and is bounded by the anterior and posterior bellies of the diagastric muscle and the body of the mandible (Ferlito et al., 2010).

Lymphatics from the oral cavity, lower lip, anterior nasal cavity and anterior mandibular alveolar ridge drain to lymph nodes in this level (Deschler and Day, 2008).

Level II

This level has the skull base as the superior border and the inferior border of the hyoid bone inferiorly. The medial border is the anterior border of the sternocleidomastoid muscle and the lateral border is the posterior border of the sternocleidomastoid muscle. Level II is further subdivided into levels IIA and IIB. Level IIA lymph nodes are those which lie anterior, medial or lateral to the internal jugular vein (IJV), or posterior to the IJV and are inseperable from it. Level IIB lymph nodes are those lying posterior to the IJV but are seperated from it by a fat plane (Ferlito et al., 2010, Som et al., 2000).

Lymphatics from the oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx and parotid gland drain to lymph nodes in this level (Deschler and Day, 2008).

Level III

This lymph node level, previously known as the mid-jugular nodes, is bordered by the inferior border of the hyoid bone superiorly, the inferior border of the cricoid cartilage inferiorly, the lateral border of the sternocleidomastoid muscle and the medial aspect of the common carotid artery (Ferlito et al., 2010, Som et al., 2000).

Lymphatics from the oral cavity, nasopharynx, oropharynx, hypopharynx and larynx drain to lymph nodes in this level (Deschler and Day, 2008).

Level IV

This level is bordered superiorly by the inferior border of the cricoid cartilage, inferiorly by the clavicle, medially by the medial aspect of the common carotid artery and laterally by the lateral border of the sternocleidomastoid muscle (Ferlito et al., 2010, Som et al., 2000).

Lymphatics from the hypopharynx, cervical oesophagus, larynx drain to lymph nodes in this level (Deschler and Day, 2008).

Level V

This level, known as the posterior traingle, is bordered superiorly by the skull base and inferiorly by the clavicle. The anterior border is the posterior border of the sternocleidomastoid muscle and the posterior border is the anterior border of the trapezius muscle. It is further divided into levels VA and VB, with the lower margin of the cricoid cartilage dividing the two (Ferlito et al., 2010, Som et al., 2000).

Lymphatics from the nasopharynx, oropharynx and the thyroid gland drain to lymph nodes in this level (Deschler and Day, 2008).

Level VI

The superior border of this level is formed by the hyoid bone and the inferior border by the superior edge of the manubrium. The medial and lateral borders are the common carotid arteries on either side (Ferlito et al., 2010, Som et al., 2000).

Lymphatics from the thyroid gland, glottic and subglottic larynx, apex of the piriform sinus and cervical oesophagus drain to lymph nodes in this level (Deschler and Day, 2008).

The importance of detecting nodal involvement

The presence of cervical nodal metastases is one of the most important prognostic factors in HNSCC (Agarwal et al., 2008, Nguyen et al., 2014, Yongkui et al., 2013). A single nodal metastasis reduces a patient's survival rate by 50% - this is further halved with bilateral lymphadenopathy (Mukherji et al., 2001, Nguyen et al., 2014, Walden and Aygun, 2013). The presence of cervical nodal metastases is strongly associated with the risk of distant metastases – these occur in 50% of patients with more than three lymph node metastases in the neck but in only 7% of patients without cervical nodal metastases (Leemans et al., 1993). The presence of extracapsular spread is also associated with reduced survival (Walden and Aygun, 2013).

The accurate detection of nodal involvement is essential for accurate staging of the patient and influences treatment options. For example, a T1-2, N0 oral cavity primary would not require post-operative radiotherapy but if the neck is upstaged after a neck dissection post-operative radiotherapy should be considered. The dose of radiotherapy to be administered is guided by the presence of adverse risk features. In the neck, thse include N2-3 nodal disease, nodal disease in levels IV of V and the presence of perineural invasion. Patients with these high risk features receive a significantly higher dose (60-66Gy) of radiotherapy for 6 – 6.5 weeks while patients without these advise risk features receive a lower dose (44-50Gy). The latter has a lower incidence of short and long-term side effects.

Management of HNSCC

The management of HNSCC at most centres in Australia is guided by the National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology (Pfister et al., 2015). These guidelines provide a framework within which clinicians and patients can explore treatment options and ultimately select one in accordance with a patients' values. The treatment modality selected is inflenced by patient factors and tumour factors. Patient factors include the general health of the patient, compliance, convenience of treatment and patient preference. Tumour factors include the site, size, TNM stage of the tumour and presence of pathological features known carry a high risk of local and distant metastases. The history of a previously treated head and neck malignancy will also affect the selection of therapy.

The workup and management of head and neck malignancies is complex. After a thorough history and clinical examination, imaging and biopsy of the primary tumour or cervical nodes, patients are staged in accordance with the American Joint Committee on Cancer (AJCC) (Patel and Shah, 2005).

In order for patients to access the full range of support services and specialists for optimal treatment and follow-up, all patients with a head and neck malignancy should be discussed at a multidisciplinary team (MDT) meeting. This team should comprise of representatives from the following departments:

- Head & Neck surgery
- Plastic & Reconstructive Surgery
- Oral & Maxillofacial Surgery

- Radiation Oncology
- Medical Oncology
- Diagnostic Radiology
- Pathology
- Specialized Head & Neck Nursing
- Speech Therapy
- Dietetics

Treatment Modalities

These include:

- Surgery
- Radiotherapy
- Chemotherapy

In general terms, outcome of single modality treatment is equivalent for early-stage tumours. More advanced-stage tumours usually require a combination of these modalities, either with curative or palliative intent (Pfister et al., 2015).

Surgery

The goals of surgical management of head and neck malignanies depend on whether the primary intent is curative or palliative.

If the intent is curative, then the goals of surgery are to achieve surgical clearance of the primary tumour and/ or metastatic disease in the neck, as well as for reconstructive purposes after a major primary tumour resection. Even without preoperative evidence of disease in the cervical lymph nodes, an elective neck dissection is sometimes performed to confirm the absence of disease in the neck, especially if the primary tumour is known to have a high rates of occult neck metastases. This is necessary for accurate staging and therefore, management of the patient. Surgery also has a role in the salvage treatment of patients who have relapsed after undergoing a non-surgical treatment modality as a first-line therapy (Pfister et al., 2015).

On the other hand, surgery with a palliative intent aims to improve quality of life by resecting fungating tumours and debulking those which can cause airway compromise.

Types of Neck dissections and their role

- Classification of neck dissections

  The commonly used classification of neck dissections is that proposed by the Committee for Neck Dissection Classification of the American Head and Neck Society (Robbins et al., 1991). It is as follows:

- Radical neck dissection (RND)

  This form of neck dissection was first described in 1906 by George Crile and popularized by Hayes Martin as standard treatment for the node-positive neck (Shah, 1990a, Ferlito et al., 2010). The procedure involves complete removal of all lymph nodes in levels I to V with sacrifice of the spinal accessory nerve (SAN), IJV, and SCM.

  When an additional lymph node group (ie. Mediastinal, retropharyngeal or occipital nodes) and non-lymphatic structure (ie. Carotid artery, vagus or hypoglossal nerves) is removed, the procedure is termed extended RND (Ferlito et al., 2010).

- Modified radical neck dissection (MRND)

  By the mid-1960s, it was contended that the morbidity of a RND could be reduced without compromize in the rate of local control. This saw the rise in popularity of the MRND led by Suarez and Bocca (Ferlito et al., 2010, Bocca, 1966). The procedure involves complete removal of all lymph nodes in levels I to V, but sparing at least one of three non-lymphatic stuructures – SAN, IJV or SCM. Since the SAN is rarely involved with disease, it can be spared, reducing the significant morbidity associated with its sacrifice.

- Selective neck dissection (SND)

This involves preserving one or more levels typically associated with an MRND. It is further subdivided into a supraomohyoid neck dissection (levels I-III), lateral neck dissection (levels II-IV) and posterolateral neck dissection (levels II-V) (Lau et al., 2011)(Lau et al., 2011).

- Management of clinically positive necks

Traditionally, a RND has been regarded as the gold standard for surgical treatment of clinically apparent cervical nodal metastases (Harish, 2005). This treatment is based on the principal that if one node has clinically apparent metastasis, then other nodes are likely to have micro-metastases (Harish, 2005). However, more recent studies have found that the rates of neck failure are comparable for a nodal stage regardless of whether a RND or MRND was performed (Chu and Strawitz, 1978, Molinari et al., 1980). Thus, high-morbidity RND has been largely replaced by the MRND.

- Management of clinically negative necks

Accurate staging of a clinically negative neck is challenging. Assessment of nodal disease by palpation is known to be highly inaccurate, partly because nodal metastases below 0.5cm in diameter are non-palpable (Sako et al., 1964). Imaging techniques such as ultrasound, CT, MRI and PET are also limited in their ability to detect nodal metastases. Hence, the ability to accurately stage the neck without surgery remains elusive.

An elective neck dissection (END) is considered when the risk of occult cervical nodal metastases is more than 15-20% (Ferlito et al., 2010). Studies have shown that the risk of tumour metastases increases as the location of the primary tumour progresses from the anterior to posterior part of the upper aerodigestive tract, with tongue malignancies having a risk of nodal metastases of 25% compared to 56% with hypopharyngeal malignancies (Byers et al., 1988). Tumours that are poorly differentiated and have greater depth of invasion are also more likely to have nodal metastases (Shah et al., 2012).

Given the high risk of occult nodal metastases of oral cavity cancers, in particular tongue cancers, an elective SND of levels I-III is usually performed (Shah, 1990b). This can be unilateral or bilateral depending on whether the primary tumour is located on one side or in the midline.

Tumours of the oropharynx have a rate of occult nodal metastases of 33-46%, in particular to levels II-IV, thus necessitating a SND of these levels (Byers et al., 1988, Shah, 1990b).

Laryngeal tumours have a risk of harbouring occult nodal metastases of 15-25%, with supraglottic tumours having the highest risk and early stage glottic cances havign the lowest risk (Byers et al., 1988). These tumours also have a high risk of metastatic spread to contralateral nodes, hence a bilateral level II-IV is commonly performed (Byers et al., 1988, Shah, 1990b).

- Salvage neck dissection

A salvage neck dissection refers to a neck dissection performed after chemotherapy or radiotherapy, where there is clinical and/or radiological evidence of residual disease or recurrence of disease. The indications for a salvage neck dissection are still being studied, but at present there is evidence that patients who have incomplete neck control after neoadjuvant therapy benefit from a neck dissection (Clayman et al., 2001, Hehr et al., 2002, Vongtama et al., 2004).

AIMS OF STUDY

Accurate nodal staging of the neck is essential for appropriate management of the patient and their cancer. At present, elective neck dissections are performed for primary tumours with a high risk of occult cervical nodal metastases, even if the neck is clinically negative. This is because, we currently lack a foolproof method for detecting cervical nodal metastases pre-operatively. Should such a method become available, we might be able to drastically reduce the numbers of elective neck dissections performed.

While we are still some years away from this development, we can work toward improving the detection of metastatic cervical nodes with the best imaging modalities avilable to us, namely the use of PET/CT scans.

This project was conceived to examine how we can better utlize data from the PET/CT scan, in particular, the SUV_{max} of lymph nodes and other anatomical regions, diameter of lymph nodes, presence of nodal extra-capsular spread and presence of nodal entral necrosis, in order to improve the pre-operative detection of metastatic lymph nodes.

Study questions

1. To identify predictive characteristics for metastatic cervical lymph nodes on PET/CT by comparing pathology results with imaging findings

- What absolute nodal SUV_{max} cut-off would yield the highest sensitivity and specificity for the detection of pathological nodes
- Would an SUV ratio, for example
    a. (LN SUV)/(Primary tumour SUV) OR
    b. (LN SUV)/(Aortic SUV) OR
    c. (LN SUV)/ (Liver SUV), be a better indicator of a metastatic node?
- Is there a difference in the size of metastatic nodes and benign ones? What size cut-off would yield the highest sensitivity and specificity?
- Can the presence of a metastatic node be predicted using a combination of
    i. SUV_{max}
    ii. Size
    iii. Presence of nodal extra-capsular spread
    iv. Presence of nodal central necrosis?

2. Was the SUVmax of the primary tumour related to the incidence of lymph node metastases?

REVIEW OF LITERATURE

Imaging modalities used in the workup of head and neck malignancies

Computed tomography (CT)

CT has been a useful clinical imaging modality since the 1970s. Apart from characterizing the primary tumour and assessing for distant metastases, the main use of this imaging modality is in the detection of cervical nodal metastases. This has been done since the early 1980s (Mancuso et al., 1983), and has been clearly shown to be superior to clinical examination in the evaluation of nodal metastasis (Friedman et al., 1993, Stevens et al., 1985).

The diagnosis of lymph node metastases is largely based on measurement of nodal dimensions. These include maximum transverse diameter (Close et al., 1989, Feinmesser et al., 1987, Friedman et al., 1993, Mancuso et al., 1983, Som, 1992) or ratios of maximum longitudinal to maximum transverse diameter (Steinkamp et al., 1995). The shape, grouping and enhancement pattern of lymph nodes are further criteria with less significance.

All of these criteria remain controversial, and recommendations for differentiating between benign and malignant lymph nodes with imaging studies vary widely (Close et al., 1989, Feinmesser et al., 1987, Friedman et al., 1993, Mancuso et al., 1983, Som, 1992, Steinkamp et al., 1994).

To date, even with the use of contrast to enhance the major blood vessels, the complex anatomy and numerous structures in the neck make it challenging to distinguish between lymph nodes and small blood vessels. The differentiation of non-enlarged, borderline-sized metastatic lymph nodes from the enlarged reactive or inflammatory lymph nodes seen in cancer patients still remains challenging. Interpretation of the CT scan is even more challenging in thin patients, where the lack of fat planes compromises the assessment of lymph nodes (Close et al., 1989).

What are PET and PET/CT ?

Positron emission tomography (PET) scans are a non-invasive, quantitative assessment of a tissue by analysing the 3-dimensional distribution of radioactivity based on the annihilation photons that are emitted by labelled tracers (Boellaard et al., 2010). The most common tracer used at present is the fluorodeoxyglucose (FDG), a glucose analogue. Image acquisition after PET/CT is most commonly performed 60 minutes after administration. However, the uptake period has been recognized to be highly variable, with the FDG concentration only reaching a plateau after four to six hours in some tumours (Lowe et al., 1995).

The reason PET scans are better at detecting unknown primaries than CT or MRI is because metabolic changes resulting from malignancies precede structural changes. Malignant cells have a higher metabolic rate than normal tissue, and therefore utilize glucose more rapidly. Since most PET scans employ ^{18}F-FDG, a glucose analogue, they are able to provide information about metabolic events in tissues (Prowse et al., 2013).

While providing metabolic information about tissues, PET scans offer poor visualization of anatomic structures, thereby limiting their use. This shortcoming can be overcome by superimposing the PET images on the images of a non-contrast CT scan, a practice known as image fusion or co-registration. This is done in sequence without having to move the patient. The anatomical information derived from the CT scan can be used to improve the accuracy of localisation and characterisation of lesions detected by the PET scan (Boellaard et al., 2010).

How good is PET/CT at detecting pre-treatment cervical nodal metastases?

The detection of cervical nodal metastasis is an important part of staging HNSCC patients before treatment, and the use of an accurate diagnostic modality is of utmost importance. In order to evaluate the role of ^{18}FDG-PET/CT in the detection of cervical lymph node metastasis, meta-analysis of 14 articles (742 patients), published between 2005 and 2011, was performed by researches in China (Yongkui et al., 2013). This study found that the pooled sensitivity, and specificity with 95% confidence interval for PET/CT on a per-neck-side analysis were 0.84 (0.77-0.89) and 0.84 (0.78-0.89), while on a per-nodal-level analysis, the pooled sensitivity was 0.84 (0.78-0.88) and the specificity was 0.96 (0.94-0.98). These figures were similar to that of a previous meta-analysis by Kyzas et al. published in 2008 (Kyzas et al., 2008). The main limitation of this study included the probable lack of standardization of PET/CT protocols and inter-observer variation.

Large, multicentre prospective studies with standardization of PET/CT protocols are needed to answer this clinical question.

Indications for PET & PET/CT in the head and neck

Detection of unknown primary

An unknown primary head and neck cancer (UPHNC) is one that presents with microscopically confirmed metastatic malignancy in a cervical node but without the primary site being detectable by routine diagnostic procedures (Issing et al., 2003). These include clinical examination with flexible nasoendoscopy and imaging with either CT or MRI in order to detect suspicious areas for biopsy during panendoscopy. Most of these primaries have been shown to originate in the head and neck region, but a small proportion are located in the lung, skin and other regions (Koivunen et al., 2002).

One of the largest prospective studies of the role of PET in UPHNC found that PET successfully identified the primary tumour in 16 out of 71 patients (22.5%) (Scott et al., 2008). Another retrospective study published in 2013 included 32 patients with UPHNC and found that FDG-PET/CT had a detection rate of 50% (Prowse et al., 2013). This study combined their results with that of 10 earlier studies, yielding a detection rate of 37.4% (123 out of 329 patients had their primary tumours identified).

Detection of second primary

The presence of synchronous tumours, defined as tumours detected within 6 months of the initial tumour, can greatly alter management decisions and prognosis in patients with HNSCC. Thus it is important to detect these in the workup of the patient. A study of 1112 patients with HNSCC found that 7% of patients presented with synchronous primaries of the head and neck and 1% presented

with synchronous carcinomas of the lung (Erkal et al., 2001). Another study reported a similar rate of occurrence of synchronous tumours of 7.8% (Schwartz et al., 1994).

The utility of PET in detecting synchronous primaries was investigated by a study by Strobel et al. published in 2009 (Strobel et al., 2009). It included 589 patients with untreated HNSCC and found 56 synchronous primaries (9.5%), 84% of which were detected by FDG-PET/CT, suggesting that this imaging modality is effective at detecting synchronous primaries. However, another study by Hanamoto et al. published in 2013 found FDG-PET or FDG-PET/CT to be able to detect only 33% of the 57 synchronous primaries found on conventional imaging with chest x-rays, contrast-enhanced head and neck CT and panendoscopy (Hanamoto et al., 2013).

This difference in the efficacy of FDG-PET or FDG-PET/CT in detecting synchronous primaries may be the result of the difference in location of these primaries in the 2 studies. In the study by Strobel et al., the majority of the synchronous primaries were in the lung (46%) and head and neck (17%), while in the study by Hanamoto et al., the majority of synchronous primaries were in the esophagus (50%) and stomach (25%), reflecting the high prevalence of gastrointestinal tract tumours in the Japanese population.

The ability of FDG-PET or FDG-PET/CT in detecting synchronous primaries of the gastrointestinal tract, especially early stage ones, has been shown to be poor, thus explaining the difference (Kato et al., 2002, Lim et al., 2006).

Detection of distant metastases

The presence of distant metastases in a patient with HNSCC confers a very poor prognosis. At present, since there is no effective systemic treatment for disseminated HNSCC, these patients usually receive palliative treatment.

There is strong evidence that PET imaging is superior to conventional imaging in detecting distant metastatic disease. Numerous studies have examined the ability of FDG-PET and FDG-PET/CT in detecting distant metastasis. The reported sensitivity of FDG-PET ranges from 53% to 100%, while the specificity ranges from 86.9% to 98% (Chang et al., 2005, Senft et al., 2008, Wang et al., 2009, Yen et al., 2005). The FDG-PET/CT on the other hand, has a reported sensitivity between 86% and 96.8%, and a specificity of between 84% and 100% (Gordin et al., 2007, Haerle et al., 2011, Yi et al., 2012).

Detection of recurrence

Despite aggressive combined-modality therapy, the loco-regional recurrence rate remains as high as 40% (Ang et al., 2001). Therefore, close post-treatment surveillance is essential in order to provide timely salvage therapy.

The detection of loco-regional recurrence is challenging. Radiation and surgery result in tissue distortion that obscures early detection of recurrence on conventional detection methods such as clinical examination, CT and MRI (Lell et al., 2000).

The use of FDG-PET to detect recurrence has become widespread in recent years. However, false-positives on the PET scan can result in post-irradiated tissues because FDG-uptake of tissues can be increased or decreased by radiation treatment (Gordin A., 2006, Greven et al., 1994, Kubota et al., 1992).

A systematic review and meta-analysis by Gupta et al. pooled the results of 51 studies involving 2335 patients (Gupta et al., 2011). The pooled sensitivity, specificity, positive predictive value and negative predictive value of post-treatment FDG-PET/CT for detecting primary site recurrence was 79.9%, 87.5%, 58.6% and 95.1%. With respect to the detection of neck recurrence, the sensitivity was 72.7%, specificity 87.6%, positive predictive value 52.1% and negative predictive value 94.5%.

PET /CT for Radiotherapy Planning

Planning radiotherapy treatment for HNSCC requires the radiation oncologist to define the lesion to be irradiated. This is done by identifying the gross tumour volume (GTV), or the macroscopic tumour seen on the scan. The GTV may vary depending on the imaging technique used to evaluate it. Obtaining an accurate and reproducible GTV is essential to minimize the dose of ionizing radiation applied to non-target organs.

Prior to the advent of PET/CT, a CT scan alone was used for this purpose. However, the lack of differentiation between healthy soft tissue and tumour extension on a CT scan compromises the accuracy of this imaging modality in defining GTV.

The co-registration of PET and CT images has been reported to reduce inter-observer variability in GTV delineation in lung and brain tumours (Ashamalla et al., 2005, Van Laere et al., 2005). Several studies have also investigated the difference in GTV delineation of head and neck tumours with PET and CT respectively – two studies reported a decrease in GTV using PET compared to CT (Heron et al., 2004, Paulino et al., 2005) while one study reported no difference in PET GTV compared with CT (Bellón Guardia et al., 2010).

Numerous studies have attempted to define the role of PET/CT scans in the workup of head and neck malignancies. A systematic review published in 2013 pooled 84 prospective studies published in peer-reviewed journals and made the following recommendations (Yoo et al., 2013):

- PET is recommended in the M and bilateral nodal staging of all patients with head and neck squamous cell carcinoma where conventional imaging is equivocal, or where treatment may be significantly modified

- PET is recommended in all patients after conventional imaging and before, or in addition to, diagnostic panendoscopy where the primary site is unknown

- PET is recommended for the staging and assessment of recurrence in patients with nasopharyngeal carcinoma if conventional imaging is equivocal.

- PET is recommended for restaging patients who are being considered for major salvage treatment, including neck dissection.

How are nodal metastases detected on PET/CT at present?

SUV_{max}

The standardized uptake value (SUV) is the most widely used method for the quantification of FDG uptake (Strauss and Conti, 1991). It is measured by the following formula:

$$SUV = \text{Tissue activity} / (\text{Injected dose/body weight})$$

Where tissue activity is expressed in Becquerels/g, injected dose in Becquerels and body weight in kg. To measure SUV, a 2D or 3D region of interest is positioned centrally within a target (ie. Lymph node or tumour) using an interactive work station (Adams et al., 2010). The SUV of a target can be expressed as SUV_{mean} or SUV_{max}. SUV_{mean} is the average SUV calculated from multiple voxels, while SUV_{max} is the highest voxel SUV reading in the region of interest (Adams et al., 2010). The SUV_{max} is the more common method of reporting SUV, due to the fact that it is more reproducible and less observer-dependent than SUV_{mean} (Adams et al., 2010, Benz et al., 2008). In theory, a greater SUV_{max} of a lymph node would correspond to an increased likelihood of a metastatic deposit in that node, because 18F-flurodeoxyglucose is absorbed by and trapped in tumors in greater concentration than normal tissue. However, this is not always the case in clinical practice as many factors can influence the SUV reading of the primary tumour or lymph node. These include the blood sugar level of the patient at the time of PET scanning, the presence of an inflammatory process near the tumour, patient movement and the interval between injection of FDG and acquisition of PET.

The use of SUV_{max} to detect nodal metastases has been studied extensively in lung cancers. A study by Bryant et al. included 397 patients with non-small cell lung cancer and found that the median SUV_{max} of metastatic mediastinal lymph nodes was significantly higher than that of benign nodes. Indeed, when a SUV_{max} cutoff of 5.3 was used instead of the traditional value of 2.5, the accuracy of FDG-PET/CT for detecting mediastinal lymph node metastasis increased to 92% (Bryant et al., 2006).

Another study by Ela Bella et al. looked at the ideal SUV_{max} cutoff for identification of metastatic mediastinal lymph nodes and found SUV_{max} of 4.1 to be ideal. This cutoff yielded a sensitivity of 80% and specificity of 92% (Ela Bella et al., 2014). A similar SUV_{max} cutoff for identifying metastatic mediastinal lymph nodes was reported by Vansteenkiste et al. (Vansteenkiste et al., 1998).

As mentioned earlier, the measured SUV_{max} can be affected by a number of factors, one of which is interscanner variability. In order to compensate for this variability, the use of a ratio between the nodal SUV_{max} and primary tumour SUV_{max} has been proposed by Cerfolio et al. in 2007 who studied 239 patients with 335 FDG-PET-positive mediastinal nodes at 14 different PET centres. The authors found that for malignant nodes, the median ratio of the nodal SUV_{max} to primary tumour SUV_{max} was 0.58 (range 0.32 – 1.61) while the median ratio for benign nodes was 0.4 (range 0.21-1.1). Receiver operating characteristics analysis determined the optimal value of the ratio that maximized sensitivity to be 0.56 or greater (sensitivity 94%, specificity 72%) (Cerfolio and Bryant, 2007).

The use of SUV_{max} to detect nodal metastases in the head and neck has only been reported in two studies. In 2012, Matsubara et al. looked at 38 patients with oral SCC and compared their pre-

operative FDG-PET/CT scan results with histopathological findings (Matsubara et al., 2012). The authors reported that nodes with a SUV_{max} of more than 4.5 were all pathologically confirmed as being metastatic, but for nodes with $SUV_{max} \leq 4.5$, it was not possible to distinguish between true positives and false positives. Hence, the long and short axis diameters were measured for those nodes and the long-axis diameter was found to be significantly longer in the true positive nodes. No significant difference between the true positive and false positive nodes were found in the short-axis diameter.

Murakami et al. studied 23 patients with HNSCC and found that SUV_{max} accurately characterized lymph nodes >15mm in diameter, but was not reliable with respect to nodes <15mm, probably because of the partial volume effect attributable to the limited resolution of the PET images. Thus, size based SUV_{max} cutoffs were used in this study: they were 1.9 for nodes less than 10mm in diameter, 2.5 for those 10–15 mm, and 3.0 for nodes more than 15mm. These values yielded 79% sensitivity and 99% specificity (Murakami et al., 2007).

Factors influencing SUV_{max} in a lymph node

As mentioned earlier, the SUV_{max} of a target can be affected by a myriad of factors. These include:

- Tumour volume

  SUV_{max} measurements can be affected by the size of the tumour. Most PET scanners have a spatial image resolution of about 5 to 10 mm (Shankar et al., 2006). For lesions less than 2 times the resolution of the scanner, an underestimation of activity can occur. This effect is

known as partial volume effect and is caused by 3D image blurring resulting from the limited resolution (Soret et al., 2007). This results in small lesions, for instance, metastatic deposits in small lymph nodes, to have lower FDG uptake than expected.

- Nodal necrosis

Lymph node necrosis is highly specific for nodal metastases, and has been reported to occur in up to 32% of metastatic lymph nodes (van den Brekel et al., 1990). When a lymph node becomes centrally necrotic, the number of viable cells that are able to uptake FDG is reduced, resulting in a normal or low SUV on PET scanning.

- Body weight

FDG distribution in the body is weight-dependent. Patients with higher proportions of white fat which is less metabolically active than muscle tissue, will have a higher SUV for a given lesion due to the reduced competition for FDG (Zasadny and Wahl, 1993, Keyes, 1995). It has been suggested that correcting SUV for body surface area is preferable to correcting for body weight, as body weight corrections overestimate FDG uptake in larger patients (Kim et al., 1994).

- Patient movement

Movement artefact could result in a misalignment on co-registration, leading to a spuriously high or low SUV reading. Manual co-registration of structural lesion and PET activity might be able to improve the accuracy of SUV reading.

- Blood sugar level (BSL)

A raised pre-PET BSL can significantly reduce SUV measurements because serum glucose would competitively inhibit FDG uptake (Ling et al., 2013). Thus, most PET protocols require that patients fast for 6-8 hours prior to scanning, and have their BSL measure prior to scanning. For patients whose BSL are above the nominated threshold of the institute performing the PET scan, the PET scan might be postponed to another day when the BSL is within range. The effect of BSL on FDG uptake has been extensively studied. Wahl et al. found that FDG uptake in 6 rodents with mammary carcinoma was significantly reduced by continuous glucose infusion, while Langen et al. investigated 15 patients with bronchial carcinomas and reported markedly decreased tumour FDG uptake when the plasma glucose level was elevated (Langen et al., 1993, Wahl et al., 1992). As such, a protocol for standardisation of whole body FDG-PET studies has been established in the Netherlands, recommending rescheduling a patient if the BSL is greater than 11mmol/L (Boellaard et al., 2008). Some centres have examined the effect of correcting for a high pre-PET BSL on the accuracy of the PET scan with conflicting results (Avril et al., 1997, Stahl et al., 2004, Vriens et al., 2009, Wong et al., 2005).

Attempting to correct a high pre-PET BSL with insulin can potentially affect the FDG uptake of cells. The effect of insulin administration on the effect of FDG uptake is uncertain, with some studies reporting no increase in muscle FDG uptake (Caobelli et al., 2013, Garcia et al., 2014, Song et al., 2013) and others reporting an increase (Busing et al., 2013, Roy et al., 2009).

Similarly, metformin, which increases insulin sensitivity, is known to be associated with increased FDG uptake in the gut, thereby potentially masking gastrointestinal tract tumours (Massollo et al., 2013, Steenkamp et al., 2014). However, its effect on the diagnostic accuracy of FDG-PET in the head and neck is not known.

- Tracer uptake time

The time interval between tracer injection to time of image acquisition can have a significant effect on SUV measurements (Hamberg et al., 1994). Since FDG uptake is time-dependent, the longer the interval between tracer injection and PET scanning, the higher the SUV (Beaulieu et al., 2003, Povoski et al., 2014). Most studies report an interval of approximately 1.5 to 2.5 hours between ^{18}F-FDG injection and PET scanning (Povoski et al., 2014).

- Inter-scanner and intra-scanner variability

The model of PET scanner used for image acquisition can potentially affect SUV measurements due to the differing physical properties and reconstruction options between scanners (Adams et al., 2010). In a study using 101 scanners that were part of the American College of Radiology Imaging Network, inter-scanner variability between the same scanner model was reported to be as high as 6% (Scheuermann et al., 2009).

Even using the same scanner, image acquisition at two different time points can be different. This could be due to the acquisition mode and image reconstruction parameters (Adams et al., 2010). However, using identical image acquisition and reconstruction settings on a single

machine could still result in a difference of SUV_{max}. This was demonstrated by a double-baseline study of ^{18}FDG-PET which showed a SUV_{max} variation of up to 10.7% even though the same scanning equipment was used and the second scans were performed within 7 days of the first (Velasquez et al., 2009).

- Inter-observer variability

Differences in SUV_{max} measurements between observers can result from variation in region of interest (ROI) placement and size. This was demonstrated by a study of 52 tumours in 25 patients which showed inter-observer variability in determining SUV_{max} differences pre and post-treatment to be 16.7% ± 36.2% (Jacene et al., 2009).

Other studies, however, have reported SUV_{max} measurements to be observer-independent (Benz et al., 2008, Huang et al., 2009, Meij-de Vries et al., 2014, Pu, 2007, Varoquaux et al., 2013).

- Use of contrast material for PET/CT

The attenuation of PET images can potentially be affected by the presence of contrast material. This has been suggested by a retrospective study of 20 patients comparing PET images using unenhanced and contrast-enhanced CT scans for attenuation correction, which found SUV differences of up to 5.9% between the two groups (Kinahan and Fletcher, 2010).

- Amount of FDG injected and extent of dose extravasation

The FDG uptake is dependent on the injected dose – a higher injected dose would correspond to a higher SUV on a scan. In practice, a PET scan is performed after intravenous injection of 10-20 mCi of FDG (0.14-0.21 mCi/kg of body weight) (Shankar et al., 2006, Yamamoto et al., 2007). After tracer injection, the residue in the syringe should be measured and subtracted from the original dose in the syringe to accurately determine the net amount of FDG administered.

Occasionally, extravasation of the tracer into the subcutaneous tissues occurs, resulting in a reduction of the dose available for distribution (Osman et al., 2011). This can lead to spuriously low tissue FDG uptake.

- Scanner calibration

The conversion of the PET image to SUV requires an estimation of the scanner calibration factor (Kinahan and Fletcher, 2010). This is performed every 3-4 months using a phantom, which is a known volume filled with substance of a known activity (ie. $^{68}Ge/^{68}Ga$), provided by the PET system manufacturer (Kinahan and Fletcher, 2010).

- Miscellaneous factors affecting SUV

The presence of co-morbid conditions such as sarcoidosis can increase nodal uptake (Asad et al., 2004).

Use of Liver and Aortic SUV_{max} as measurement of background SUV

As elucidated above, the SUV of a target can be affected by a myriad of factors. In order to control for some of these factors, it could be argued that the use of the ratio between the target SUV and 'background' SUV is more meaningful than the target SUV alone. The rationale behind this is that all tissues in the body should theoretically be exposed to the same factors that could influence SUV measurements.

Tissues most commonly used for background SUV measurements include the liver, aortic blood pool, lung and resting muscle (Wahl et al., 2009). This ratio is dimensionless and is meaningful whether voxel measurements are recorded in SUV or using other units.

One way in which the ratio of tumour to background SUV has been shown to be useful is in the detection of adrenal malignancies. A study by Perri et al. reported that mean adrenal lesion-to-liver SUV ratio was 3.8 ± 1.9 (median, 3.3; range, 1.5–9.6) for malignant lesions and 1.1 ± 0.5 (median, 0.8; range, 0.4–2.5) for benign lesions, suggesting that the ratio is a meaningful tool for distinguishing benign from malignant (Perri et al., 2011). This view is corroborated by other studies (Chong et al., 2006, Yun et al., 2001).

The utility of node/liver SUV and node/aortic arch SUV in the detection of mediastinal metastases in patients with NSCLC has been demonstrated by Kuo et al (Kuo et al., 2012). The areas under the receiver-operating characteristic curves in this study were 0.674, 0.693, and 0.715 for node SUV, node/aorta SUV ratio, and node/liver SUV ratio, respectively ($P < .05$). With cutoff values of 3.15, 1.37, and 1.02 for node SUV, node/aorta SUV ratio, and node/liver SUV ratio, respectively, the

sensitivity of ^{18}F-FDG PET/CT for N2 (Nodal metastasis in ipsilateral mediastinal/subcarinal lymph nodes) staging was 57.1%, 85.7%, and 71.4%, and specificity was 74.2%, 50.5%, and 61.9%. This is the only study published that investigated the utility of the SUV ratio between lymph node and aortic blood pool. To the best of my knowledge, no studies have examined the use of node/liver SUV or node/aortic blood pool SUV in the detection of cervical nodal metastases.

A possible caveat regarding the use of liver SUV as a proxy for background SUV is the fact that the liver has an abundance of glucose-6-phosphatase, which could cause continuous glycolysis and reduce its measured SUV more rapidly compared to other tissues. However, a prospective study by Laffon et al. performed PET acquisition at 2 time points on the same day and reported that the decay-corrected SUV of the liver remains nearly constant if the time delay between tracer injection and PET acquisition is in the range of 50–110 min (Laffon et al., 2011). This suggests that in clinical practice, liver SUV can be used for comparison with SUV of suspected malignant lesions, if comparison is made within this timeframe.

Another caveat of using liver SUV is in the presence of fatty liver. This has been suggested to result in a slightly decreased metabolic activity (Qazi et al., 2008), while another study reported no significant difference in SUV_{max} (Abele and Fung, 2010). The presence of liver tumours or metastatic disease would also give spurious liver SUV readings (Wahl et al., 2009). The question of whether chemotherapy affects liver SUV readings remains unanswered, with conflicting reports in the existing literature (Bouckaert et al., 2010, Groheux D, 2013).

Size

The size criteria for detecting a metastatic lymph node on CT was proposed in 1990 by van den Brekel et al. who studied the characteristics of 2719 lymph nodes in 71 neck dissection specimens. This paper concluded that a minimal axial diameter of 10mm was the most effective size criterion, while that of sub-diagastric nodes was 11mm. The authors also reported radiologically detectable necrosis (3mm or larger) to be present in 74% of the positive neck dissection specimens (van den Brekel et al., 1990). Similar results were reported in other studies using a nodal diameter of >10mm as cut-off (Close et al., 1989, Friedman et al., 1993, Yuasa et al., 2000). Friedman et al. found that considering nodes >10mm as malignant yielded a sensitivity of 95% and specificity of 77% (Friedman et al., 1993). Close et al. had a similar result for nodes >10mm, with a sensitivity of 92% (Close et al., 1989). However, their reported specificity was much lower at 35%.

Some studies used a size threshold of 15mm as a cut-off for malignant nodes. Stevens et al. reported a sensitivity of 97% and specificity of 82%, while Close et al. had a sensitivity of 60% and specificity of 85% (Close et al., 1989, Stevens et al., 1985).

However, using size criteria alone does not help differentiate between metastatic and reactive nodes because the latter can reach the same dimensions so false positive results occur (Geetha et al., 2010). More recently, it has been suggested that using a 1cm cutoff for detection of cervical nodal metastases might cause radiologists to miss smaller metastatic nodes (Don et al., 1995). This study found that 68 out of 102 (67%) of metastatic nodes had a longitudinal diameter smaller than 1cm (Don et al., 1995). A study of sonographic criterion for cervical lymph node metastases suggested that different size criterion be used for different levels of the neck. This study suggested that for a

clinically N0 neck, a minimal diameter of 7mm was the optimal criterion for level 2 nodes, while 6mm should be the cutoff for the rest of the neck (van den Brekel et al., 1998).

Necrosis

The presence of central nodal necrosis on CT or MRI has a high specificity for nodal metastases (Close et al., 1989, Som, 1992, van den Brekel et al., 1990). In these lymph nodes, the medulla of the node is replaced by tumour cells, eventually causing necrosis. The necrotic area of a lymph node appears of low attenuation, while the cortical portions of the node appear to be of higher attenuation. The use of contrast material further enhances the nodal cortex, causing the necrotic portion to become more evident.

On a PET scan, the presence of central necrosis could lead to falsely low FDG uptake, due to the smaller number of viable cells to take up FDG. Interestingly, a series by Ng et al. found that the nodes with gross nodal necrosis in their study were not always associated with false-negative findings on ^{18}FDG PET - of the 16 necrotic nodal groups, only 3 were responsible for the false negative results on ^{18}FDG PET, whereas the remaining 13 still exhibited positive FDG uptake with nodular or rim configurations (Ng et al., 2005).

The detection of central necrosis on a CT scan can be complicated by the presence of a fatty hilum, which appears as an area of low attenuation within the lymph node, and could be mistaken for central necrosis. A blood vessel with plaque formation can masquerade as a node with central necrosis (Close et al., 1989).

Extra-capsular spread

Extra-capsular spread or extension of a metastatic deposit beyond the capsular confines of the lymph node is seen on CT as an enhancement of the nodal capsule and poorly defined margins around the node (Som, 1992). This appearance might not be accurate if the patient has had prior surgery, radiotherapy or infection in the area (Mancuso et al., 1983, Som, 1992).

The detection of extra-capsular spread is important due to the significant impact its presence has on treatment decisions. If extracapsular spread can be accurately detected pre-operatively, a clinician might recommend primary chemoradiotherapy rather than primary surgery plus adjuvant chemoradiotherapy.

Prior to the advent of PET/CT scans, CT alone was commonly used to evaluate the presence of nodal extra-capsular spread. The detection of extra-capsular spread on CT is operator dependent. Studies have described the sensitivities of CT in detecting extra-capsular spread between 60-100%, with much higher specificities (Carvalho et al., 1991, King et al., 2004, Som, 1992, Souter et al., 2009).

In 2014, Chun et al. evaluated the use of FDG PET/CT for the identification of extra-capsular spread in 89 patients with laryngeal cancer, and reported significant differences in the SUV_{max} between cervical lymph nodes with and without extra-capsular spread (6.39 ± 4.53 vs. 1.21 ± 1.70, $p < 0.001$) (Chun et al., 2014). The ideal cut-off value for differentiating nodes with extra-capsular spread from those without was 2.8, yielding a sensitivity of 85.7% and specificity of 85.6%. Similar results were reported in 2013 by Joo et al., who described significant SUV_{max} differences between

nodes with extra-capsular spread and those without (6.73±3.78 vs 3.02±2.24,p<0.001). The authors recommended a SUV_{max} cut-off value of 3.85 for differentiating between the two (Joo et al., 2013).

Shape

The shape of a lymph node can be useful in conjunction with nodal size. Most hyperplastic lymph nodes are "lima-bean" shaped, while spherical nodes have been suggested to be more likely to harbor metastasis (Close et al., 1989, Som, 1992). This helps distinguish between benign hyperplastic lymph nodes and metastatic ones.

Visual determination of the shape of a lymph node is subjective. Some authors have proposed a more objective method, by using the long/short axis diameter (Matsuoka et al., 2009, Steinkamp et al., 1995). Steinkamp et al. performed ultrasound examination on 730 lymph nodes in 285 patients, noting specifically the long and short axis diameters. This study reported that round nodes with a long/short ratio of less than 2 were correctly diagnosed as metastases with 95% accuracy (Steinkamp et al., 1995).

Clustering of benign-appearing lymph nodes

The presence of multiple benign-looking lymph nodes of less than 15mm in diameter was found by Close et al. to be a sign of malignancy, with nodal metastasis found in 61% of cases meeting this criteria (Close et al., 1989). Similar results were also reported by Stevens et al (Stevens et al., 1985).

Limitations of PET

While PET scans provide excellent information regarding the metabolic activity of a tissue, they do have inherent limitations. The most obvious would be their inability to depict the anatomical structure of pathological tissues, which restricts its use in the detection of nodal metastases. However, the poor spatial resolution of PET can be greatly compensated by integrating CT with PET – CT provides anatomical detail while PET provides metabolic information. By co-registering the two in a PET/CT scan, clinicians are able to tap the strengths of each imaging modality. Most PET centres, including Monash Health, use a non-contrast enhanced CT for the co-registration due to concerns regarding the effect of contrast material on the PET image quality. This, however, compromises the ability of the PET/CT to detect nodal necrosis and extra-capsular spread.

The diagnostic capability of PET/CT is also affected by tumour volume. Most occult nodal metastases have deposits extending over only 1-2mm while most PET scanners have a spatial image resolution of about 5 to 10 mm (Stoeckli et al., 2002, Shankar et al., 2006). ^{18}FDG uptake by small deposits of tumour cell is often poorly depicted due to the partial volume effect as described earlier (Takei et al., 2013). Hence, occult cervical nodal metastases can be missed by a PET/CT scan. Improving the special resolution of PET scans and the development of tumour-specific tracer could potentially improve the detection of these lesions.

Finally, the SUV_{max} of a primary head and neck tumour or cervical lymph node does not give an indication of its histological grade. This was demonstrated by a large study of 262 patients with HSNCC which reported no significant correlation of SUV and tumour grading after adjustment for T-stage and anatomical localization of the tumour (Haerle et al., 2010). Similar findings were made

by a more recent study by Varoquax et al. (Varoquaux et al., 2013). An association between SUV and histological grade has, however, been reported in other cancers such as lung (Zhao et al., 2013) and endometrial cancers (Nakamura et al., 2010).

Significance of Primary Tumour SUV_{max}

The significance of the primary tumour SUV has been studied in lung, gastric and endometrial malignancies amongst others. In patients with clinically N0 non-small cell lung cancer, the primary tumour SUV_{max} was a significant indicator of pathological nodal involvement ($p = 0.016$) (Miyasaka et al., 2013). Primary tumours with a SUV_{max} of 10 or more had a sensitivity of 49% and specificity of 83.2% for mediastinal nodal involvement. Similar results have been reported in other studies of patients with lung malignancies (Nambu et al., 2009, Sachs et al., 2005, Downey et al., 2004). In patients with endometrial malignancies, a higher primary tumour SUV_{max} was reported to be associated with a significantly lower disease-free survival rate and overall survival than those with a lower SUV_{max} (<12.7; $p = 0.00042$) (Kitajima et al., 2012, Walentowicz-Sadlecka et al., 2014). A study of patients with gastric cancer has shown that a primary SUV_{max} of greater than 3.75 was associated with a higher rate of nodal metastases (Choi et al., 2014).

In patients with HNSCC, a meta-analysis of 6 clinical trials which included 453 patients reported that increase in the primary tumour SUV was found to be a poor prognostic marker (Zhang et al., 2014). At least two other studies reached a similar conclusion (Chan et al., 2009, Higgins et al., 2012).

How will improving the detection of nodal metastases on PET/CT impact patient management?

The management guidelines of head and neck malignancies laid out by the NCCN hinge on the accurate TNM staging of patients. Improving the pre-operative detection of nodal metastasis is important as it has the potential to alter surgical management. In patients for whom an elective dissection is not planned based on the site and histological grade of the primary tumour, nodal staging is based mainly on clinical examination and radiological imaging. In these cases, being able to detect a metastatic node with a high degree of sensitivity could lead to some patients being spared a neck dissection and the potential morbidity with the procedure.

METHODS

Ethics approval

Ethics approval was granted by Monash Health on 12th March 2014 (Research Project application No. 14073Q)

Study Protocol

This research project involved patients from January 2011 to December 2014 who had:

- Histology results confirming head and neck squamous cell carcinoma
- A pre-operative staging PET/CT scan performed at Monash Health
- Neck dissection of at least three cervical lymph node levels, at a single operation, performed at Monash Health

Patients who met the above criteria were included in the study, regardless of whether their PET scans were suspicious of nodal metastasis or not.

Exclusion criteria:

- Patients whose neck dissection specimen was not divided up into the individual levels prior to being sent to pathology
- All salvage neck dissections (ie. those who have had neoadjuvant chemotherapy/radiotherapy) or any form of previous chemotherapy or radiotherapy
- All patients who have had <3 cervical lymph node levels removed at a single operation

Data collection

Basic demographic information of the patients were collected:

- Age
- Gender
- Location of primary tumour
- Type of neck dissection
- Date of neck dissection

A senior nuclear medicine physician and this author carried out a retrospective review of patients at Monash Health who had staging PET/CT scans performed before neck dissection. In each of these scans, the largest lymph node in each of the five cervical lymph node levels was identified and the following characteristics documented for each nodal level:

- largest and smallest diameter of the lymph node
- maximum SUV uptake
- the presence of central necrosis within the lymph node
- presence of extracapsular extension of tumour within the node

Other features of the PET/CT were also documented. These included:

- date of the scan
- SUV_{max} of primary tumour
- SUV_{max} of aortic
- SUV_{max} of liver

The purpose of documenting the SUV_{max} of the liver and aorta was to utilize these as background tissue SUV_{max} measurements.

The pathology results of all these patients were collected. The number of lymph nodes removed from each cervical level during neck dissection was documented. A nodal basin with at least one metastatic node was deemed to be a 'metastatic basin', regardless of the number of metastatic nodes within the basin or the size of the metastatic deposit(s).

The PET/CT features of each nodal basin was then compared with the pathology results.

PET /CT imaging protocol

Preparing for the PET/CT scan

Patients were given a PET scan information sheet and advised of the following:

- No vigorous exercise (ie. running, lifting weights, bike riding) for 24 hours prior to the scan
- Have a high-protein, low-carbohydrate/low sugar diet for 24 hours prior to the scan
    - Acceptable foods: meat, eggs, leafy vegetables
    - Foods to avoid: breads, pastas, cereals, potatoes, corn, sweets, soft drinks, alcohol
- Fast for a minimum of 6 hours prior to the scan
- Drink at least 6 glasses of plain water while fasting

- Regular medications that can be administered on an empty stomach should be taken, except hypoglycaemic agents
- Dress warmly in the lead up to the scan

In cases where the patient was an inpatient, the ward nurse looking after the patient was instructed of the above, and also told not to administer any parenteral nutrition and any intravenous fluids containing glucose should be discontinued at least four hours before the PET/CT examination

For patients with type II diabetes, the following instructions were given:

- Alert the nuclear medicine department to schedule PET scan in the morning
- Cease Metformin 48 hours prior to scan
- Other oral diabetic medications, including insulin, should not be taken on the day prior to the scan
- The scan will be performed in the morning
- Blood sugar should be equal to or below 10 mmol/L. Patients travelling from rural areas should check their BSL before leaving home and inform the nuclear medicine department if it is above 8mmol/L
- A BSL reading of more than 10mmol/L might result in the scan being rescheduled

Patients with type I diabetes mellitus had their scans scheduled in the late morning and were told to eat a normal breakfast at 7.00 a.m. and inject their usual amount of morning insulin. They were then instructed to fast until their scan was performed.

Tracer dosage

For a standard whole-body PET scan, 300MBq of ^{18}FDG is administered through an IV cannula. Image acquisition is performed approximately 60 -90 minutes after tracer injection.

Scanning Protocol

The patients were collected from the waiting room or ward and identified in accordance with hospital protocol. Informed consent was obtained, a brief relevant medical history was taken, height and weight were measured, and patient was asked to change into a hospital gown removing all metal items. An intravenous (IV) cannula was inserted if the patient did not already have one. The patient's BSL was measured before FDG was administered via the indwelling cannula.

In the period between injection of FDG tracer and image acquisition, the patient was instructed to remain seated or recumbent and silent in order to minimize muscular FDG uptake. Patients were kept warm 30-60 minutes prior to tracer injection and throughout the uptake period in order to minimize FDG accumulation in brown fat.

Image acquisition is performed approximately 60 -120 minutes after tracer injection by using integrated PET-CT scanner (Siemens Biograph™ TruePoint™). A standard scan for suspected HNSCC covers vertex to upper thighs. The CT images are acquired without contrast and comprised of a topogram and the helical CT scan.

Post-procedure instructions

Inpatients will have a 'Nursing Patients Post PET Procedure' information sheet and a 'Nuclear Medicine Radiation' label with date / dose and scan type inserted into the current notes. This is to identify to all Monash Health staff that the patient has been administered radiation and that pregnant staff and visitors, and visitors with young children should avoid prolonged close contact with the patient during the designated time period.

Verbal instructions given to outpatients regarding avoiding prolonged close contact with pregnant women and young children for a period of 6 hours post injection.

Patients who have been administered a sedative for the procedure are sent home with post sedation instructions / precautions and should be monitored post procedure for appropriateness of discharge from the department.

Interpretation of PET/CT

After the acquisition, relevant data was sent to MMWP and Syngo.via for viewing by a single nuclear medicine physician, and to PACS and PLAZA for archiving.

Determination of SUV_{max} values

SUV_{max} was determined by manually placing a cylindrical region of interest (ROI) over the primary tumour site, the descending aorta and liver, as well as the largest lymph node in each nodal basin of

interest. This was done on trans-axial images by an experienced nuclear medicine physician on a dedicated workstation.

Determination of node/aorta and node/liver SUV ratios

Node SUV_{max} values were divided by the SUV_{max} of the descending aorta and liver to calculate the node/aorta and node/liver SUV ratios

Histological Analysis

Neck dissection specimens were processed by dedicated head and neck pathologists at Monash Health, in accordance with the guidelines issued by the Royal College of Pathologists in the United Kingdom. The specimens were inspected and palpated and each discrete palpable node was dissected out with attached pericapsular adipose tissue. These nodes were then placed in a cassette which was then stained and serially sliced prior to being loaded onto pathology slides for viewing under the microscope. On occasions when the pathologist was unable to yield an adequate number of nodes by palpation, the specimen was placed in Carnoy's solution and left overnight. This is a mixture of ethanol, chloroform and acetic acid that aids in enhancing the differentiation between fat and lymph nodes and thus allows smaller lymph nodes to be seen more easily.

Statistical analysis

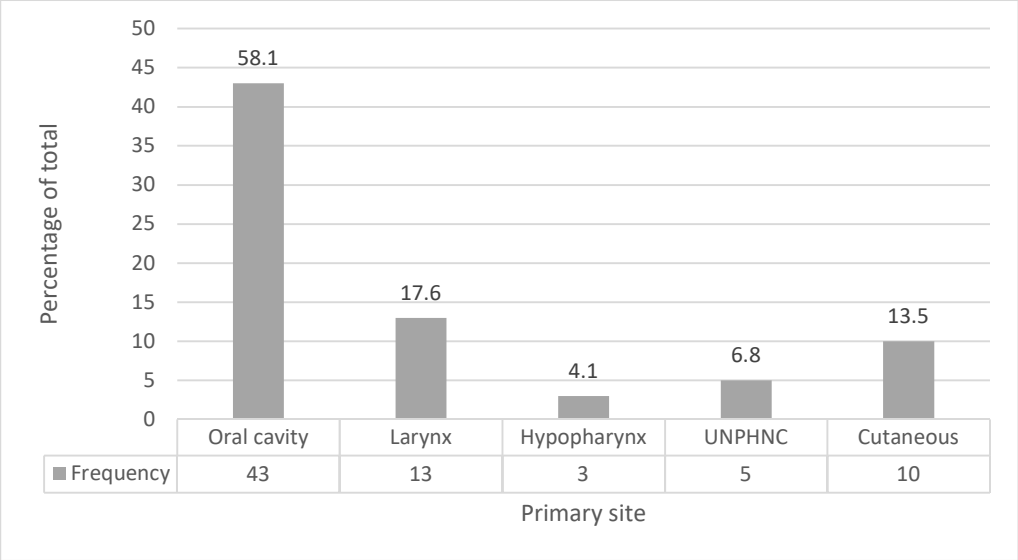
All statistical analyses were performed using IBM SPSS version 22. The pathological interpretation was taken as the reference standard. The node SUVmax, node/aorta SUVmax, and node/liver SUVmax ratio were taken as continuous variables. On a per-cervical level analysis, these variables were compared between pathologically positive and negative lymph node basins.

RESULTS

Patient Demographics

The study cohort consisted of 74 patients with HNSCC, including 57 males and 17 females. The median patient age was 64 (range 35-89). Primary sites included the oral cavity, hypopharynx, larynx and skin (Figure1).

Figure 1. Primary Sites



5 patients had no primary site found. A total of 95 neck-sides, including 364 nodal basins, were dissected (Table 1).

Table 1. Nodal Basins Dissected

			Level with metastatic nodes	
Nodal basin	Frequency	%	*f*	%
Level I	70	19.23	18	25.71
Level II	95	26.37	33	34.73
Level III	95	26.37	21	22.11
Level IV	74	21.25	10	12.99
Level V	25	7.42	4	14.81
Total	359	100	86	23.62

Out of the 359 nodal basins removed, only 321 were able to be analysed. This is because the remaining 38 nodal basins had lymph nodes which were too small to be detected on a PET/CT. None of these nodal basins harboured pathological nodes.

149 patients who fit all other inclusion criteria had to be excluded because their neck dissection specimens were sent en-bloc (ie. Not divided into the individual nodal levels), because less than three cervical lymph node levels were removed in the neck dissection or because they had PET/CT scans performed at a nuclear medicine centre external to Monash Health.

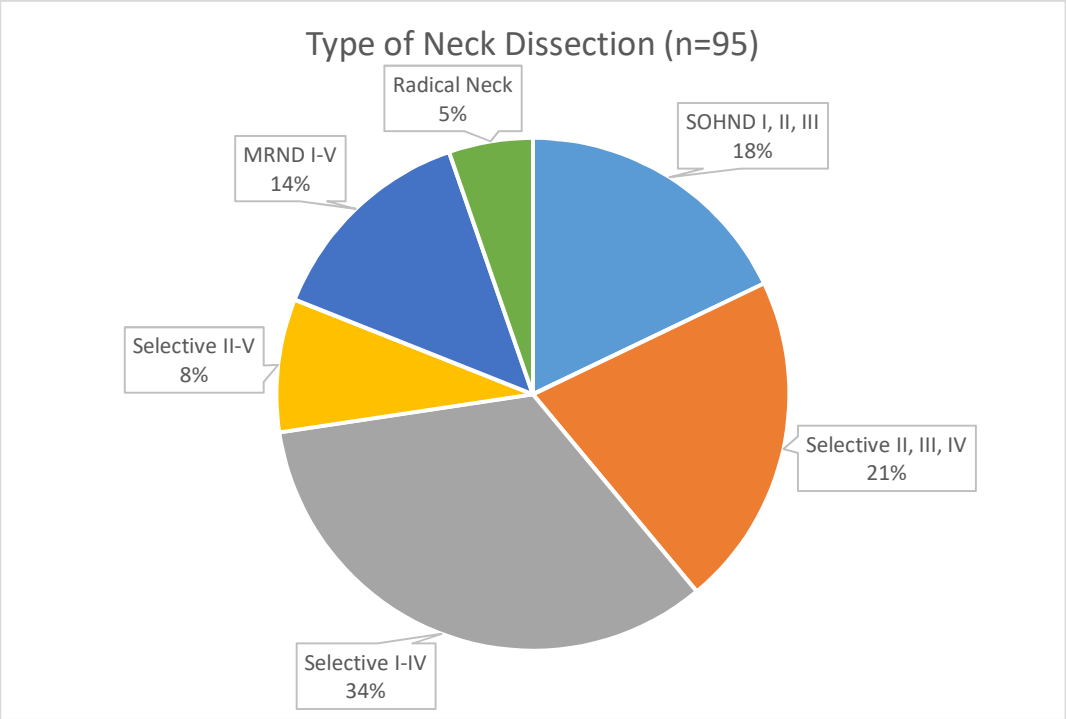
Metastatic nodes

Metastatic nodes were found in 86 of 359 levels (24.0%). The nodal basins with the highest likelihood of having a histologically-confirmed metastatic node were levels 1 and 2 (Table 1). The percentage of each dissected nodal basin having at least one metastatic node is shown in Table 1.

Type of neck dissection

The most common neck dissection performed was a selective neck dissection of levels I to IV (33.7%) followed by a selective neck dissection of levels II to IV (21.1%), supra-omohyoid neck dissection (SOHND) (17.9%) modified radical neck dissection (MRND) (13.7%), selective neck dissection of levels II to V (8.4%) and radical neck dissection (5.3%)(Figure 2).

Figure 2. Type of Neck Dissection



Days between PET/CT scan and neck dissection

The median time between a patient in our study having the PET/CT scan and the neck dissection was 27 days (range 1-62).

SUV_{max}

The mean primary tumour SUV_{max} was 14.42, median was 14.26 (range 3.89 – 36.69). The mean aortic SUV_{max} was 2.82 and the median was 2.70 (range 1.79 – 4.68). The mean liver SUV_{max} 3.41

and the median was 3.38 (range 2.27 – 5.51). The summary statistics of SUV_{max} for each nodal level is shown in Table 2.

Table 2 Summary statistics of PET nodal SUV_{max}

Node	N	Mean	SD	Minimum	Maximum	Median	IQR	
							Q1	Q3
RLv1	32	3.63	4.09	0.58	17.7	2.23	1.37	3.48
RLv2	45	4.60	5.28	1.29	25.0	2.70	1.90	3.86
RLv3	43	3.24	4.18	0.74	23.5	1.89	1.45	2.70
RLv4	25	1.76	0.89	0.90	5.40	1.58	1.27	2.02
RLv5	10	1.28	0.80	0.67	3.50	1.09	0.97	1.20
LLv1	32	3.53	3.10	0.62	13.3	2.24	1.55	4.78
LLv2	49	3.98	3.58	1.60	20.3	2.63	2.11	4.38
LLv3	45	2.94	3.69	0.82	22.5	1.63	1.33	2.41
LLv4	31	2.11	1.56	0.84	7.20	1.49	1.32	2.02
LLv5	9	1.86	1.19	0.91	4.10	1.32	1.01	2.92

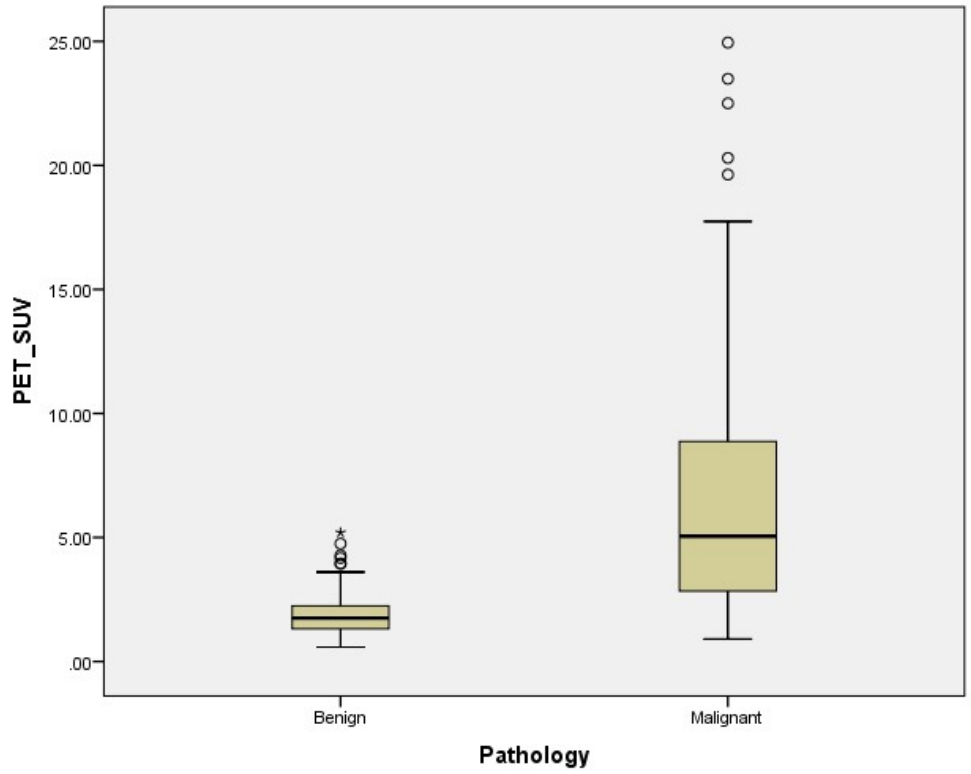
The summary statistics of SUV_{max} for each nodal level stratified by presence or absence of nodal disease is shown in Table 3. A box-plot comparing PET nodal SUV_{max} between benign and malignant nodes is shown in Figure 3.

Table 3. Summary statistics of PET SUV stratified by Pathology

Node	N	Mean	SD	Minimum	Maximum	Median	IQR	
Benign nodes (n = 235)							Q1	Q3
RLv1	25	2.08	1.11	0.58	5.20	1.84	1.22	2.76
RLv2	30	2.32	0.74	1.29	3.94	2.18	1.67	2.81
RLv3	31	1.74	0.55	0.74	3.00	1.79	1.34	2.12
RLv4	22	1.59	0.50	0.90	2.64	1.48	1.21	1.93
RLv5	9	1.03	0.18	0.67	1.28	1.08	0.94	1.15
LLv1	21	1.84	0.67	0.62	2.90	1.80	1.24	2.41
LLv2	31	2.33	0.51	1.60	3.24	2.27	1.84	2.72
LLv3	36	1.72	0.71	0.82	4.75	1.55	1.30	2.02
LLv4	24	1.64	0.82	0.84	4.17	1.43	1.17	1.78
LLv5	6	1.37	0.52	1.00	2.37	1.21	1.02	1.65
Pathological nodes (n = 86)								
RLv1	7	9.19	5.96	2.82	17.74	6.52	3.41	16.00
RLv2	15	9.16	7.29	1.90	24.95	5.11	2.84	16.73
RLv3	12	7.11	6.58	1.33	23.49	4.48	2.71	11.34
RLv4	3	3.03	2.04	1.58	5.37	2.15	1.58	-
RLv5	1	3.50	-	3.50	3.50	3.50	3.50	3.50
LLv1	11	6.76	3.40	1.82	13.30	6.18	4.73	8.53
LLv2	18	6.82	4.72	1.83	20.30	5.62	3.04	9.25
LLv3	9	7.83	6.27	1.62	22.50	6.28	3.08	10.00

LLv4	7	3.72	2.36	1.49	7.16	2.68	1.62	6.02
LLv5	3	2.83	1.70	0.91	4.13	3.46	0.91	-

Figure 3: Box plot comparing PET nodal SUV_{max} between benign and malignant nodes



Multi-variable analysis of various indicators of metastatic nodes

Multivariable logistic regression was conducted with plausible indicators of metastatic nodes. Adjusting for all possible confounders and indicators entered in the model nodal SUV_{max} appeared as significant indicator of metastatic nodes. (OR 3.275; 95%CI: 2.018-5.317; P<0.000). None of the other factors 'primary tumour SUV_{max}' (p>0.05), 'extra-capsular spread' (p>0.05), 'nodal necrosis'

(p>0.05), largest nodal diameter (p>0.05) and smallest nodal diameter (p>0.05) appeared to be significant indicators of metastatic nodes.

Table 4. Binary logistic regression illustrating indicators of metastatic nodes

Indicators	B	OR	95% C.I. for OR		P Value
Nodal SUV_{max}	1.186	3.275	2.018	5.317	**<0.000***
Primary tumour SUV_{max}	-0.052	0.949	0.877	1.027	0.194
Extra-capsular spread	-1.595	5.50	0.14	2.900	0.240
Nodal necrosis	-0/718	1.104	0.056	4.245	0.515
Largest nodal diameter	-0.079	1.082	0.824	1.402	0.571
Smallest nodal diameter	-0.104	0/901	0.643	1.263	0.545
Constant	0.546	1.726	-	-	0.799

*Statistically significant at P < 0.001

Optimal nodal SUV_{max} cut-off for discriminating between pathological and benign nodes

Since Table 4 showed that nodal SUV_{max} was the only statistically significant predictive factor for nodal metastases, an ROC analysis was employed to generate the optimal nodal SUV_{max} cut-off for this purpose.

A Youden's Index was generated considering every possible cut-off point. The value that generates the highest Youden's Index for the particular ratio is considered as the optimal cut-off for that ratio, as it provides highest discrimination between pathological and benign nodes.

The optimal nodal SUV_{max} cut-off was found to be 3.16. This means that if nodal SUV_{max} is >3.16, there is 74.4% chance that the node is pathological. If a node has a SUV_{max} <3.16, then there is a 84.9% chance that the node is benign (Table 5). Also, if nodal SUV_{max} >3.16, then the likelihood of disease is 14.57 times more likely than if nodal SUV_{max} <3.16.

Table 5: ROC analysis for generating nodal SUV_{max} Cut-off with maximum sensitivity and specificity

	Highest Youden's Index	Cut-off*	Sensitivity	Specificity	Likelihood Ratio Pos. Test	Likelihood Ratio Neg. Test
Nodal SUV_{max}	0.693	3.16	0.744	0.849	14.57	0.270

* Positive if Greater Than or Equal To

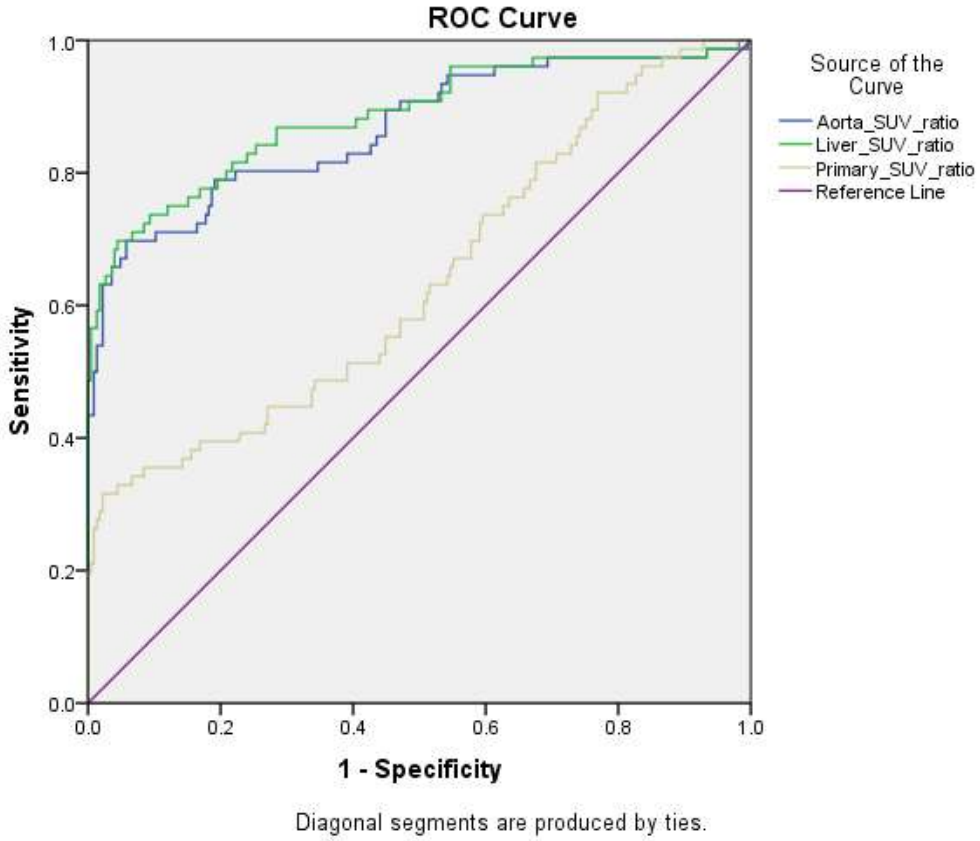
Utility of SUV_{max} ratios in detecting pathological nodes

A Receiver Operating Characteristic (ROC) analysis was employed to evaluate the statistical significance of differences in the accuracy of three different ratios in determining pathology:

- nodal SUV_{max}/primary tumour SUV_{max}
- nodal SUV_{max}/aortic SUV_{max}
- nodal SUV_{max}/liver SUV_{max}

In this analysis, the SUV_{max} ratio for each of primary tumour SUV_{max}, aortic SUV_{max} and liver SUV_{max} was calculated by dividing the nodal SUV_{max} by primary tumour SUV_{max}, aorta SUV_{max} and liver SUV_{max} respectively. The results are shown in Figure 4 and Table 6.

Figure 4. Receiver operative characteristics curves of Nodal SUV_{max}/Primary SUV_{max} Ratio, Nodal SUV_{max}/Aorta SUV_{max} Ratio and Nodal SUV_{max}/Liver SUV_{max} Ratio



ROC analysis of Nodal SUV_{max}/Primary SUV_{max} ratio, Nodal SUV_{max} /Aorta SUV_{max} ratio and Nodal SUV_{max} /Liver SUV_{max} ratio confirms that all three ratios are good predictors of nodal metastasis. (Fig 4). To choose the best predictor of nodal metastasis adjusting for all possible confounding factors a stepwise backward elimination multi-variable logistic regression analysis was performed on all the potential PET predictors of nodal metastasis. After each step, the predictor with the lowest p-value was removed. By the end of the analysis, nodal SUV_{max} / liver SUV_{max} ratio was found to be the best predictor for nodal metastasis (Table 6).

Table 6. Stepwise multi-variable logistic regression analysis

Predictor	B	S.E.	P Value	OR	95% C.I. for OR	
					Lower	Upper
Nodal SUV_{max}/ Liver SUV_{max}	4.114	0.556	**.000***	61.1	20.2	185.6
Constant	-4.642	0.496	.000	0.010		

*Statistically significant

Optimal cut-off value for Nodal SUV_{max}/ Liver SUV_{max} ratio for discriminating between pathological and benign nodes

The optimal cut-off value for nodal SUV_{max}/ liver SUV_{max} ratio is 0.903. This means that a node with a nodal SUV_{max}/ liver SUV_{max} of greater than or equal to 0.903 is considered metastatic with a sensitivity of 74.1% and specificity of 93.4% (Table 7).

Table 7. Optimal nodal SUV_{max}/ liver SUV_{max} ratio for generating Cut-off with maximum sensitivity and specificity

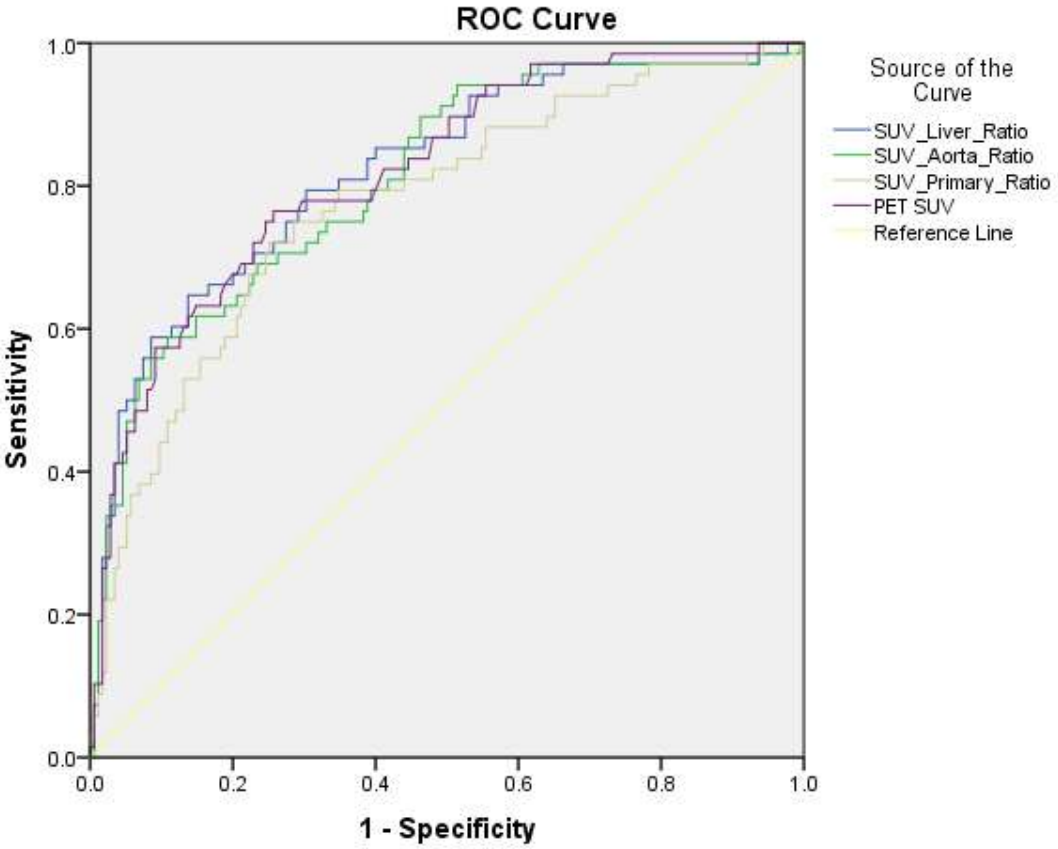
	Highest Youden's Index	Cut-off*	Sensitivity	Specificity	Likelihood Ratio Pos. Test	Likelihood Ratio Neg. Test
Nodal SUV_{max}/Liver SUV_{max} ratio	0.675	0.903	0.741	0.934	11.266	0.277

* Positive if Greater Than or Equal To

Nodal SUV_{max} vs Nodal SUV_{max} /Primary SUV_{max} Ratio, Nodal SUV_{max} /Aorta SUV_{max} Ratio and Nodal SUV_{max} /Liver SUV_{max} Ratio

ROC analysis was employed to evaluate the statistical significance of differences in the accuracy of PET nodal SUV_{max} and the three different ratios in detecting nodal metastasis. This showed that nodal SUV_{max} and nodal SUV_{max} /Liver SUV_{max} ratio were similar predictors of nodal metastasis. Neither was better that the other.

Figure 5. Receiver operative characteristics curves of Nodal SUV_{max}, Nodal SUV_{max}/Primary SUV_{max} Ratio, Nodal SUV_{max}/Aorta SUV_{max} Ratio and Nodal SUV_{max}/Liver SUV_{max} Ratio



Diagonal segments are produced by ties.

DISCUSSION

The introduction of ^{18}F-FDG PET/CT has greatly improved preoperative staging of HNSCC. Compared with ^{18}F-FDG PET alone, ^{18}F-FDG PET/CT allows assessment of regional metabolism non-invasively with metabolic tracers. Integration with non-contrast CT also facilitates anatomic localization of a lymph node. These features have resulted in improved preoperative staging of HNSCC patients using ^{18}F-FDG PET/CT. (Branstetter et al., 2005, Schoder et al., 2004, Syed et al., 2005)

The presence of nodal metastases is one of the most important prognostic factors for patients with HNSCC. (Agarwal et al., 2008, Nguyen et al., 2014, Yongkui et al., 2013) A single nodal metastasis reduces a patient's survival rate by 50% - this is further halved with bilateral lymphadenopathy. (Mukherji et al., 2001, Nguyen et al., 2014, Walden and Aygun, 2013) Therefore, accurate nodal staging of a patient with HNSCC is essential for appropriate management and for prognostic purposes.

At present, a node on a PET/CT is determined to be metastatic or benign based on a combination of factors: the size of the node, the SUV_{max} and the presence or absence of central necrosis. The SUV is the most widely used method for the quantification of FDG uptake. (Siddiqui et al., 2012) The SUV of a target can be expressed as SUV_{mean} or SUV_{max}. SUV_{mean} is the average SUV calculated from multiple voxels, while SUV_{max} is the highest voxel SUV reading in the region of interest. (Adams et al., 2010) The SUV_{max} is the more common method of reporting SUV, due to the fact

that it is more reproducible and less observer-dependent than SUV_{mean}.(Adams et al., 2010, Lee et al., 2000) The SUV_{max} is used at our institution for this reason.

The use of SUV_{max} to detect nodal metastases has been studied extensively in lung cancers, but not in head and neck malignancies. A study by Bryant et al. included 397 patients with non-small cell lung cancer and found that the median SUV_{max} of metastatic mediastinal lymph nodes was significantly higher than that of benign nodes. Indeed, when a SUV_{max} cutoff of 5.3 was used instead of the traditional value of 2.5, the accuracy of FDG-PET/CT for detecting mediastinal lymph node metastasis increased to 92%. (Bryant et al., 2006) Another study by Ela Bella et al. looked at the ideal SUV_{max} cutoff for identification of metastatic mediastinal lymph nodes and found SUV_{max} of 4.1 to be ideal. This cut-off yielded a sensitivity of 80% and specificity of 92% (Ela Bella et al., 2014). A similar SUV_{max} cut-off for identifying metastatic mediastinal lymph nodes was reported by Vansteenkiste et al.(Vansteenkiste et al., 1998)

The use of SUV_{max} to detect nodal metastases in the head and neck has only been reported in two studies. In 2012, Matsubara et al. looked at 38 patients with oral SCC and compared their pre-operative FDG-PET/CT scan results with histopathological findings (Matsubara et al., 2012). The authors reported that nodes with a SUV_{max} of more than 4.5 were all pathologically confirmed as being metastatic, but for nodes with $SUV_{max} \leq 4.5$, it was not possible to distinguish between true positives and false positives. Hence, the long and short axis diameters were measured for those nodes and the long-axis diameter was found to be significantly longer in the true positive nodes. No significant difference between the true positive and false positive nodes were found in the short-axis diameter.

Murakami et al. studied 23 patients with HNSCC and found that SUV_{max} accurately characterized lymph nodes >15mm in diameter, but was not reliable with respect to nodes <15mm. Thus, size based SUV_{max} cut-offs were used in this study: they were 1.9 for nodes less than 10mm in diameter, 2.5 for those 10–15 mm, and 3.0 for nodes more than 15mm. These values yielded 79% sensitivity and 99% specificity (Murakami et al., 2007).

The limitations of these studies are the small sample sizes and the lack of accounting for other variables that could influence SUV readings. These include the blood sugar level of the patient at the time of PET scanning, the presence of an inflammatory process near the tumour, patient movement and the interval between injection of FDG and acquisition of PET.

In this study, nodal SUV_{max} was found to be a statistically significant indicator of metastatic nodes ($p<0.001$), and that a nodal SUV_{max} cut-off of ≥ 3.16 yielded a sensitivity of 74.4% and specificity of 84.9%. It was then hypothesized that a ratio of SUV_{max} values (ie, nodal SUV_{max}/background SUV_{max}) may be one way to negate these inherent differences between PET centres and standardize the measurement. Thus the SUV_{max} of the liver parenchyma, aortic blood pool and primary tumour were measured to see if these ratios could improve the detection of metastatic nodes. Multi-variable logistic regression analysis found the nodal SUV_{max}/liver SUV_{max} ratio to be able to distinguish, with statistical significance, between metastatic and benign nodes. This ratio offered a similar sensitivity as nodal SUV_{max} alone (74.1% compared to 74.4%).

While the sensitivities of these two cut-offs are similar, the use of a nodal SUV_{max}/liver SUV_{max} ratio is able to negate inherent differences between patients and PET centres and therefore standardize

the measurement. This also allows comparisons this ratio between PET scans performed at different centres or on different machines. This is not possible when using nodal SUV_{max} alone.

The use of nodal size to detect metastatic nodes is limited. It is common practice to use a cut-off of 1cm in discriminating between metastatic and benign nodes on a CT scan. However a significant proportion of metastatic nodes are sub-centimetre (Don et al., 1995, van den Brekel et al., 1998). This is in keeping with this study's finding that nodal size is not a significant indicator of a metastatic node.

The presence of nodal central necrosis and extra-capsular spread were not found to be significant predictors of nodal metastasis in this study. This is likely due to the fact that these indicators are poorly seen on a non-contrast CT, and suggests that a contrast CT scan should be done after the PET/CT scan.

Clinical implications

This is the first study to propose using a SUV ratio to detect metastatic cervical nodes. Currently, the lack of literature on this matter means that arbitrary SUV_{max} cut-off values are used. These vary significantly between institutions and the evidence for their use is lacking. However, despite this, PET/CTs are still able to detect cervical lymph node metastasis with reasonable sensitivity and specificity; a meta-analysis on the detection of regional nodal metastasis in patients with head and neck cancers examined 14 articles and found that on a per-nodal-level analysis, the pooled sensitivity was 0.84 (0.78-0.88) and the specificity was 0.96 (0.94-0.98).(Yongkui et al., 2013) Using the SUV_{max} cut-off proposed in this study, in addition to the usual methods of detecting a nodal metastasis,

might improve the overall sensitivity and specificity of PET/CT for the detection of metastatic nodes.

Improving the pre-operative detection of nodal metastasis is important as it has the potential to alter surgical management. In patients for whom an elective dissection is not planned based on the site and histological grade of the primary tumour, nodal staging is based mainly on clinical examination and radiological imaging. In these cases, the use of nodal SUV_{max} alone or nodal SUV_{max}/liver SUV_{max} can aid in distinguishing between metastatic and benign nodes, and thus in deciding whether an elective neck dissection should be undertaken.

Using a nodal SUV_{max}/liver SUV_{max} ratio also allows comparison of nodal tracer uptake between PET scans performed using different scanners. Currently, a comparison is not meaningful due to differences in scanner calibration and thus SUV readings. However, a ratio would negate inherent differences between scanners, making it possible to compare a pre-treatment PET scan with a post-treatment PET scan performed at a different centre to assess treatment response.

Limitations of the study

The main limitations of this study include its retrospective nature, as well as the time lapse between the PET/CT scan and surgery. The median time between a patient in our study having the PET/CT scan and the neck dissection was 27 days (range 1-62). Disease progression could have occurred during this time and what was initially a benign node at the time of scanning could have turned malignant by the time of surgery.

Every effort was made to accurately match radiological nodal levels to pathological ones, however there would have been subtle differences in the delineation of nodal level on the PET/CT and on the actual specimen. For instance, a node straddling levels 2 and 3 could have been considered a level 2 node on the scan but recorded as a level 3 node on the histology report. This is a challenging problem to resolve, even if the study was undertaken in a prospective manner.

There are also inherent limitations to the use of nodal SUV_{max}. These include the blood sugar level of the patient at the time of PET scanning, the presence of an inflammatory process near the tumour, patient movement, the interval between injection of FDG and acquisition of PET and scanner calibration, as mentioned in detail earlier. As such, direct comparisons between nodal SUV_{max} measurements is not possible between scans performed with different scanners. Also, nodal SUV_{max} measurements might be spuriously low in necrotic nodes. In these cases, correlation with CT findings is essential.

Another limitation in this study was the exclusion of 38 nodal basins due to the fact that these basins harboured nodes that were too small to be seen on a PET/CT. Hence we could not record a SUV_{max} for these nodes and therefore excluded them from the statistical analysis. However, the exclusion of these nodes are unlikely to pull the association towards null. These 38 nodes were true negative nodes, and inclusion of these nodes would increase the specificity of the detection and further strengthen support toward the hypothesis of the study. In future studies, investigators could consider drawing a region of interest over a nodal basin in which nodes are too small to be seen, and use the background SUV_{max} as the nodal SUV_{max} for analysis purposes.

While the use of nodal SUV_{max}/liver SUV_{max} ratio appears promising, there are a few caveats in the use of liver SUV as a proxy for background SUV_{max}. The first is that the liver has an abundance of glucose-6-phosphatase, which could cause continuous glycolysis and reduce its measured SUV more rapidly compared to other tissues. However, a prospective study by Laffon et al. performed PET acquisition at 2 time points on the same day and reported that the decay-corrected SUV of the liver remains nearly constant if the time delay between tracer injection and PET acquisition is in the range of 50–110 min. (Laffon et al., 2011) This suggests that in clinical practice, liver SUV can be used for comparison with SUV of suspected malignant lesions, if comparison is made within this timeframe.

Another caveat of using liver SUV is in the presence of fatty liver. This has been suggested to result in a slightly decreased metabolic activity (Qazi et al., 2008), while another study reported no significant difference in SUV_{max}. (Abele and Fung, 2010) The presence of liver tumours or metastatic disease would also give spurious liver SUV readings. (Wahl et al., 2009)

CONCLUSION

In summary, more accurate staging of patients at the time of diagnosis helps guide more appropriate treatment strategies. This preliminary study has identified two indicators of metastatic nodes on PET scans – nodal SUV_{max} and nodal SUV_{max} /liver SUV_{max} ratio. It is the first study examining the utility of a SUV ratio in detection of metastatic cervical lymph nodes. More data are needed from a larger

number of patients from multiple centres. Further research could examine prospectively which of these is a better indicator.

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