Diffusion-weighted MRI versus combined positron emission tomography and computed tomography (PET/CT) in evaluation of N0 neck in patients with Head and neck squamous cell carcinoma (HNSCC).

A meta-analysis study
Submitted for Partial Fulfillment of Master Degree in Science of OtoRhinoLaryngeology

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بسم الله الرحمن الرحيم

وقُلِ اعْمَلُوا فَسَيَرَى اللَّهُ عَمَلَكُمْ
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List of abbreviations

18F-FDG	:	18F-Fluorodeoxyglucose.
ADC	:	Apparent diffusion coefficient.
cN+	:	Clinical node positive.
cN0	:	Clinical node negative.
CT	:	Computed tomography.
DWI	:	Diffusion weighted Imaging.
false +ve	:	False positive.
false –ve	:	False negative.
FDG-PET	:	Fluorodeoxyglucose positron emission tomography.
HNSCC	:	Head and neck squamous cell carcinoma.
LN	:	Lymph nodes.
Mbq	:	Megabecquerels.
MRI	:	Magnetic resonance imaging.
NPC	:	Nasopharyngeal carcinoma.
PET	:	Positron emission tomography.
PET/CT	:	Combined positron emission tomography and computed tomography.
QUADAS	:	Quality assessment for studies of diagnostic accuracy.
SCC	:	Squamous cell carcinoma.
SLN	:	Sentinel lymph node.
SND	:	Selective neck dissection.
true +ve	:	True positive.
true –ve	:	True negative.
US	:	Ultrasound.
USgFNAC	:	Ultrasound guided fine needle aspiration cytology.

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Introduction

Head and neck squamous cell carcinoma (HNSCC) develops from the mucosal linings of the upper aerodigestive tract, comprising 1) the nasal cavity and paranasal sinuses, 2) the nasopharynx, 3) the hypopharynx, larynx, and trachea, and 4) the oral cavity and oropharynx. Squamous cell carcinoma (SCC) is the most frequent malignant tumor of the head and neck region. HNSCC is the sixth leading cancer by incidence worldwide about 5% (**Kamangar et al., 2006 and Mack et al., 2008).**

Lymphatic metastasis is an important prognostic factor in patients with HNSCC. Regardless of the primary tumor site, the presence of a single metastatic lymph node in HNSCC reduces the 5-year survival rate by approximately 50%. The presence of bilateral metastatic lymph nodes in the neck reduces the survival rate to about 25% of that of patients without nodal metastasis. Cervical lymph node metastases influence not only the risk of local recurrence but also the risk of distant metastases, making lymph node status one of the most important predictors of prognosis.Therefore, accurate assessment of the lymph node status is important for the choice of treatment (**Mack et al., 2008).**

The clinically negative (cN0) neck is defined by absence of palpable or radiographically suspicious lymph nodes. Patients who are cN0 may still harbor occult metastases that, unrecognized, may cause treatment failure. The incidence of nodal metastases presents a wide variation from 10 to 50%, depending on the clinical, imaging and histopathological methods that are used (**Goudakos et al., 2009).**

Lymph node staging by physical examination is not accurate in discriminating metastatic from benign lymph

nodes. Even in superficial areas such as the cervical regions, a physical evaluation of lymph nodes cannot reliably detect metastases. Thus, imaging techniques are often used to enhance the preoperative assessment of cervical lymph node status. Radiological imaging modalities, such as combined positron emission tomography (PET) and computed tomography (CT) [PET/CT] and diffusion weighted imaging (DWI) can be used to detect nodal metastasis and determine the treatment decisions (**WU et al., 2012).**

The combination of PET/CT has been reported to be more accurate than CT or PET alone in a preoperative setting(**Roh et al., 2007).** PET/CT shows additional information for anatomic localization with regard to metastatic lymph node level and result in correct differentiation between malignant nodes and benign lesions. Overall, addition of CT fusion led to a 15% increase in accuracy of nodal staging compared with PET alone (**Mark et al., 2011).**

Despite reasonably high overall accuracy, however, the clinical application of PET/CT in N0 neck may be limited by the combination of limited sensitivity for small metastatic deposits and a relatively high number of false-positive (false +ve)findings resulting from limited ability of PET to discriminate inflammatory process from tumor infiltration**(Schöder et al., 2006).**False negative (false –ve) findings were likely related to either the presence of microscopic metastases not detected by PET/CT, or by the proximity of nodal metastases to the primary tumor which might have obscured their detection (**Akram et al., 2009).**

DWI is a non-invasive technique which analyzes the structure of a biologic tissue at a microscopiclevelandmaythereforebeapotentialtoolfor evaluating the micro structural differences between vital tumor tissue, and tumor-free tissue. The principle of DWI is to exploit the translational motion of water protons in biologic

tissues, which is caused by the Brownian motion. On DWI, translational motion causes phase dispersion of excited water protons, which consecutively leads to a signal loss on DWI. Signal loss can be quantified by calculating the "apparent-diffusion-coefficient" (ADC), which refers to the specific diffusion capacity of biologic tissue (**Schafer et al., 2011).**

The main advantage of magnetic resonance imaging (MRI) is the lower interobserver variation, and these techniques are, in general, less time consuming (**WU et al., 2012).**

Meta-analysis would be the statistical method used in this study to determine the overall diagnostic value of DWI versus PET/CT in evaluation of cN0 neck in patients with HNSCC.Meta-analysis is a quantitative statistical procedure that synthesizes finding across many studies, overcoming the problems of small samples and diverse outcomes and programs (**Tobler, 1986).**

Aim of The Work

The Aim of this work is to assess:

The overall diagnostic value of DWI versus PET/CT in evaluation of cN0 neck in patients with HNSCC.

Review of literature

Anatomy of Cervical Lymph Node Groups:

The patterns of spread of cancer from various primary sites in the head and neck to the cervical lymph nodes (LN) have been documented by retrospective analysis of large series of patients undergoing neck dissection. The nodal groups at risk for involvement are widespread throughout the neck, extending from the mandible and skull base superiorly to the clavicle inferiorly and from the posterior triangle of the neck laterally to the midline viscera and then to the contra lateral side of the neck. It is now recommended that the lymph node groups in the neck be categorized according to the level system originally described by the Memorial Sloan-Kettering Group **(Fig. 1).**

The 2001 report of the American Head and Neck Society's Neck Dissection Committee recommended the use of sublevels for defining selected LN groups within levels I, II, and V on the basis of the biologic significance, independent of the larger zone in which they lay. These are outlined in **(Fig. 1)** as sublevels IA (submental nodes), IB (submandibular nodes), IIA and IIB (together composing the upper jugular nodes), VA (spinal accessory nodes), and VB (transverse cervical and supraclavicular nodes). The boundaries for each of these sublevels are defined in (**Table 1)**.

The risk of nodal disease in sublevel IIB is greater for tumors arising in the oropharynx as compared with the oral cavity and larynx. Thus in the absence of clinical nodal disease in sublevel IIA, it is likely not necessary to include sublevel IIB for tumors arising in these latter sites. The dissection of the node-bearing

tissue of sublevel IIB (submuscular recess) creates a risk of morbidity. Adequate exposure necessitates significant manipulation of the spinal accessory nerve and may account for trapezius muscle dysfunction observed in a significant minority of patients after a selective neck dissection (SND). Sublevel IA is a zone from which many surgeons do not remove lymph nodes unless the primary cancer involves the floor of the mouth, the lip, or structures of the anterior midface or there is obvious lymphadenopathy. Level V is the third region that has been subdivided, into levels VA and VB. The superior component, level VA, primarily contains the spinal accessory lymph nodes, whereas level VB contains the transverse cervical nodes and the supraclavicular nodes, which carry a more ominous prognosis when positive in cases with upper aerodigestive tract malignancies (**Thomas et al., 2010).**

Table (1): Lymph Node Groups Found within the Six Neck Levels and the Six Sublevels.

Lymph NodeGroup	Description
Submental (sublevel I_A)	LN within the triangular boundary of the anterior belly of the digastric muscles and the hyoid bone; these nodes are at the greatest risk of harboring metastases from cancers arising from the floor of the mouth, anterior oral tongue, anterior mandibular alveolar ridge, and lower lip (see Fig.1).
Submandibular (sublevel I_B)	LN within the boundaries of the anterior belly of the digastric muscle, the stylohyoid muscle, and the body of the mandible, including the preglandular and postglandular nodes and the prevascular andpostvascular nodes. The submandibular gland is included in the specimen when the lymph nodes within this triangle are removed. These nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, the anterior nasal cavity, and the soft tissue structures of the midface and the submandibular gland (see Fig. 1).
Upperjugular (sublevels II_A and II_B)	LN located around the upper third of the internal jugular vein and the adjacent spinal accessory nerve, extending from the level of the skull base above to the level of the inferior border of the hyoid bone below. The anterior (medial) boundary is the stylohyoid muscle (the radiologic correlate is the vertical plane defined by the posterior surface of the submandibular gland), and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. Sublevel II_A nodes are located anterior (medial) to the vertical plane defined by the spinal accessory nerve. Sublevel II_B nodes are located posterior (lateral) to the vertical plane defined by the spinal accessory nerve. The upper jugular nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, nasal cavity, nasopharynx, oropharynx, hypopharynx, larynx, and parotid

Lymph NodeGroup	Description
	gland (see Fig. 1)
Middlejugular (level III)	LN located around the middle third of the internal jugular vein, extending from the inferior border of the hyoid bone above to the inferior border of the cricoid cartilage below. The anterior (medial) boundary is the lateral border of the sternohyoid muscle, and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. These nodes are at greatest risk for harboring metastases from cancers arising from the oral cavity, nasopharynx, oropharynx, hypopharynx, and larynx (see Fig. 1).
Lowerjugular (level IV)	LN located around the lower third of the internal jugular vein, extending from the inferior border of the cricoid cartilage above to the clavicle below. The anterior (medial) boundary is the lateral border of the sternohyoid muscle, and the posterior (lateral) boundary is the posterior border of the sternocleidomastoid muscle. These nodes are at greatest risk of harboring metastases from cancers arising from the hypopharynx, thyroid, cervical esophagus, and larynx (see Fig. 1).
Posteriortriangle (sublevels V_A and V_B)	This group is composed predominantly of the LN located along the lower half of the spinal accessory nerve and the transverse cervical artery. The supraclavicular nodes are also included in the posterior triangle group. The superior boundary is the apex formed by the convergence of the sternocleidomastoid and trapezius muscles; the inferior boundary is the clavicle, the anterior (medial) boundary is the posterior border of the sternocleidomastoid muscle, and the posterior (lateral) boundary is the anterior border of the trapezius muscle. Sublevel V_A is separated from sublevel V_B by a horizontal plane marking the inferior border of the anterior cricoid arch. Thus sublevel V_A includes the spinal accessory nodes, whereas sublevel V_B includes the nodes that follow the transverse cervical vessels and the