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Diagnostic Accuracy in the Detection of Cervical Lymph Node Metastases in Head and Neck Squamous Cell Carcinoma Patients- a Comparison of Sonography, CT, PET/CT and MRI

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1. Introduction

1.1 Epidemiology

Head and neck cancers are histopathologic cancers targeting the oral cavity, nasal cavity, pharynx, larynx, thyroid, paranasal sinuses and salivary glands (Wheless et al., 2010; Bray et al. 2018). Among all head and neck cancers, more than 90% consist of head and neck squamous cell carcinoma (HNSCC) (Bray et al., 2018). As the 6th most prevalent cancer globally, HNSCC accounted for 250,000 cases and 63,500 deaths in 2012 in Europe (Global Burden of Disease Cancer et al., 2017). This number increased to over 890,000 newly diagnosed patients and 450,000 mortalities in 2018 (Bray et al., 2018). Unlike the female population, male populations are more often affected, with a proportion ranging from 2:1 to 5:1 (Suh & Cho., 2016; Huang et al., 2018). In Asia, cancers located in the oral cavity, particularly tongue cancer, have been reported in the Indian subcontinent. In southern China and Hong Kong, nasopharyngeal cancer is the most prevalent HNSCC, whereas pharyngeal or laryngeal cancers comprise a higher ratio in other populations (Bray et al., 2013; Lambert et al., 2011; DeSantis et al., 2013). These elements contribute to an overall disproportionate cancer burden in parts of Asian countries. The African American male population has a significantly higher (approximately 50%) incidence of laryngeal cancer than white Americans (Settle et al., 2009). Laryngeal and oropharyngeal cancer-related mortalities are also high in African American males (Lubin et al., 2010).

1.2 Etiology and risk factors

Alcohol intake and tobacco use are crucial in the development of HNSCC located in the larynx, hypopharynx, oropharynx and oral cavity (Wyss et al., 2013). One study comparing subjects who intake alcohol of over 50 g per day with those under 10 g/day reported a 5 to 6-fold increase in the hazard ratio of head and neck cancers (De Stefani et al., 1998). The risk of developing head and neck cancer increased to 5 to 25-fold for heavy cigarette smokers compared to non-smokers (Chaturvedi et al., 2013).

The involvement of human papillomavirus (HPV), specifically 16/18 subtype, was also observed in some HNSCC patients, particularly in cancers occurring at the tongue's base and the tonsillar area (Sheikh et al., 2020). In developed countries, the incidence of HPV-related oropharyngeal cancers is significantly greater among male younger population (<60 years) than among female population (Sheikh et al., 2020). In the development of nasopharyngeal carcinoma, which is one of the most common malignancies in South China, Epstein-Barr virus (EBV) acts as the leading etiopathogenesis (Bray et al., 2013).

Although alcohol intake and tobacco use as well as HPV and EBV infection play significant roles in the pathogenesis of HNSCC, their pathological mechanisms vary differently. Tobacco and alcohol-related HNSCC are relevant to p53 gene mutation and TP53 overexpression with an increased proliferative index i.e., Ki-67 immunohistochemistry (IHC) (Stelow et al., 2010). In the pathogenesis and development of HNSCC, particularly oropharyngeal cancer, expressions of HPV E6 and E7 oncogenes inactivate the tumor-suppressor proteins pRb and p53, hence promoting genomic instability (Ghittoni et al., 2010; Schiffman et al., 2016; Gheit, 2019).

Additional associated risk factors include opium use, immunosuppression, betel quid chewing, poor hygiene in oral cavity and periodontal disease, genetic factors, radiation exposure, environmental as well as occupational exposures (Grulich et al., 2007; Guha et al., 2014; Hashim et al., 2016; Lacko et al., 2014; van der Laan et al., 1995; Becher et al., 2005; Leonel et al., 2021).

1.3 Clinical presentation, pathology, and staging

Head and neck cancer's clinical manifestations vary quite differently based on the initial site and different associated risk factors. Otalgia may be an essential symptom for cranial nerves (Suh & Cho., 2016; Bray et al., 2013; DeSantis et al., 2013; Settle et al., 2009) that supply afferents to the middle and external ear, which could indicate the presence of head and neck cancers. Pain travels through cranial nerves (5, 7, 9, and 10) that supply the ear and the referred

area, prompting suspicion of head and neck cancers (Suh & Cho., 2016; Bray et al., 2013; DeSantis et al., 2013; Settle et al., 2009).

Neck mass is a common presenting complaint in roughly 90% of patients with nasopharyngeal carcinoma due to regional nodal metastases (Mehanna et al., 2010; Johnson et al., 2020). Oral cavity cancer patients may have symptoms of mouth pain, dry mouth, halitosis, dysphagia, dysgeusia, weight loss, etc. (Mehanna et al., 2010; Johnson et al., 2020). Oropharyngeal cancer patients could have manifestations including dysphagia, pain, upper-airway obstruction, and neck nodes (Mehanna et al., 2010; Johnson et al., 2020).

Hypopharyngeal cancer patients usually manifest non-specifically for a long duration. Therefore, patients with typical symptoms including dysphagia, otalgia, and neck mass are often found with advanced disease (Mehanna et al., 2010; Johnson et al., 2020). For laryngeal cancer patients, their symptoms widely vary according to the primary origin of the cancer. Patients with glottic cancer might have early complaints of persistent hoarseness and later symptoms such as dysphagia, chronic cough, otalgia, etc (Mehanna et al., 2010; Johnson et al., 2020). Supraglottic cancer patients may reveal symptoms of airway obstacle or palpable nodal metastases of the neck area, which might be later discovered (Mehanna et al., 2010; Johnson et al., 2020).

We use the tumor, lymph node, and metastases (TNM) staging system from the American Joint Committee on Cancer (AJCC) and the Union for International Cancer Control (UICC) for the staging of head and neck cancers. Here, we adopted the 7^{th} edition of AJCC. The 8^{th} edition was published in 2018, but it was not used in this study because it requires the identification of the depth in oral cancer patients, a recommended p16 test in oropharyngeal cancer patients, additionally, both of which were not routinely performed in this study group which enrolled patients between 2010 and 2011. Tables 1-6 present the TNM staging of cancers of the lip, oral cavity, and pharynx below. The AJCC Cancer Staging Manual was referred to classifying other head and neck cancer subtypes.

CLINICAL *Extent of disease before any treatment*	STAGE CATEGORY DEFINITIONS		PATHOLOGIC *Extent of disease during and from surgery*
❒ y clinical– staging completed after neoadjuvant therapy but before subsequent surgery	TUMOR SIZE: _____	LATERALITY: ☐ left ☐ right ☐ bilateral	❒ y pathologic – staging completed after neoadjuvant therapy AND subsequent surgery
	PRIMARY TUMOR (T)		
❑ TX	Primary tumor cannot be assessed		❑ TX
❑ T0	No evidence of primary tumor		❑ T0
❑ Tis	Carcinoma *in situ*		❑ Tis
❑ T1	Tumor 2 cm or less in greatest dimension		❑ T1
❑ T2	Tumor more than 2 cm but not more than 4 cm in greatest dimension		❑ T2
❑ T3	Tumor more than 4 cm in greatest dimension		❑ T3
❑ T4a	Moderately advanced local disease. (lip) Tumor invades through cortical bone, inferior alveolar nerve, floor of mouth, or skin of face, i.e., chin or nose (oral cavity) Tumor invades adjacent structures only (e.g., through cortical bone, [mandible or maxilla] into deep [extrinsic] muscle of tongue [genioglossus, hyoglossus, palatoglossus, and styloglossus], maxillary sinus, skin of face)		❑ T4a
❑ T4b	T4b Very advanced local disease. Tumor invades masticator space, pterygoid plates, or skull base and/or encases internal carotid artery		❑ T4b
	Note: Superficial erosion alone of bone/tooth socket by gingival primary is not sufficient to classify a tumor as T4.		
	REGIONAL LYMPH NODES (N)		
❑ NX	Regional lymph nodes cannot be assessed		❑ NX
❑ N0	No regional lymph node metastasis		❑ N0
❑ N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension		❑ N1
❑ N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2
❑ N2a	Metastasis in single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension		❑ N2a
❑ N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2b
❑ N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension		❑ N2c
❑ N3	Metastasis in a lymph node more than 6 cm in greatest dimension		❑ N3
	DISTANT METASTASIS (M)		
❑ M0	No distant metastasis (no pathologic M0; use clinical M to complete stage group)		
❑ M1	Distant metastasis		❑ M1

Table 1: Cancer of lip and oral cavity TNM staging

(from AJCC Cancer Staging Manual Seventh Edition, page 37)

	Clinical			Pathologic			
Group	T	N	M	Group	T	N	M
❑ 0	Tis	N0	M0	❑ 0	Tis	N0	M0
❑ I	T1	N0	M0	❑ I	T1	N0	M0
❑ II	T2	N0	M0	❑ II	T2	N0	M0
❑ III	T3	N0	M0	❑ III	T3	N0	M0
	T1	N1	M0		T1	N1	M0
	T2	N1	M0		T2	N1	M0
	T3	N1	M0		T3	N1	M0
❑ IVA	T4a	N0	M0	❑ IVA	T4a	N0	M0
	T4a	N1	M0		T4a	N1	M0
	T1	N2	M0		T1	N2	M0
	T2	N2	M0		T2	N2	M0
	T3	N2	M0		T3	N2	M0
	T4a	N2	M0		T4a	N2	M0
❑ IVB	Any T	N3	M0	❑ IVB	Any T	N3	M0
	T4b	Any N	M0		T4b	Any N	M0
❑ IVC	Any T	Any N	M1	❑ IVC	Any T	Any N	M1
❑ Stage unknown				❑ Stage unknown			

Table 2: Cancer of lip and oral cavity anatomic stage

(from AJCC Cancer Staging Manual Seventh Edition, page 38)

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

Table 3: Cancer of pharynx T staging

(from AJCC Cancer Staging Manual Seventh Edition, page 51)

REGIONAL LYMPH NODES (N)

Nasopharynx

The distribution and the prognostic impact of regional lymph node spread from nasopharynx cancer, particularly of the undifferentiated type, are different from those of other head and neck mucosal cancers and justify the use of a different N classification scheme.

Regional lymph nodes cannot be assessed
No regional lymph node metastasis
Unilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa, and/or unilateral or bilateral, retropharyngeal lymph nodes, 6 cm or less, in greatest dimension*
Bilateral metastasis in lymph node(s), 6 cm or less in greatest dimension, above the supraclavicular fossa*
Metastasis in a lymph node(s)* >6 cm and/or extension to supraclavicular fossa
Greater than 6 cm in dimension
Extension to the supraclavicular fossa**

* Midline nodes are considered ipsilateral nodes.
**Supraclavicular zone or fossa is relevant to the staging of nasopharyngeal carcinoma and is the triangular region originally described by Ho. It is defined by three points: (1) the superior margin of the sternal end of the clavicle, (2) the superior margin of the lateral end of the clavicle, (3) the point where the neck meets the shoulder (see Fig. 4.2). Note that this would include caudal portions of Levels IV and VB. All cases with lymph nodes (whole or part) in the fossa are considered N3b.

Oropharynx and Hypopharynx

Regional lymph nodes cannot be assessed
No regional lymph node metastasis
Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension, or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
Metastasis in a lymph node more than 6 cm in greatest dimension

* Metastases at Level VII are considered regional lymph node metastases.

DISTANT METASTASIS (M)

No distant metastasis (no pathologic M0; use clinical M to complete stage group)
Distant metastasis

Table 4: Cancer of pharynx N and M staging

(from AJCC Cancer Staging Manual Seventh Edition, page 52)

CLINICAL				PATHOLOGIC			
GROUP	T	N	M	GROUP	T	N	M
❑ 0	Tis	N0	M0	❑ 0	Tis	N0	M0
❑ I	T1	N0	M0	❑ I	T1	N0	M0
❑ II	T1	N1	M0	❑ II	T1	N1	M0
	T2	N0	M0		T2	N0	M0
	T2	N1	M0		T2	N1	M0
❑ III	T1	N2	M0	❑ III	T1	N2	M0
	T2	N2	M0		T2	N2	M0
	T3	N0	M0		T3	N0	M0
	T3	N1	M0		T3	N1	M0
	T3	N2	M0		T3	N2	M0
❑ IVA	T4	N0	M0	❑ IVA	T4	N0	M0
	T4	N1	M0		T4	N1	M0
	T4	N2	M0		T4	N2	M0
❑ IVB	Any T	N3	M0	❑ IVB	Any T	N3	M0
❑ IVC	Any T	Any N	M1	❑ IVC	Any T	Any N	M1
❑ Stage unknown				❑ Stage unknown			

Table 5: Cancer of nasopharynx anatomic stage

(from AJCC Cancer Staging Manual Seventh Edition, page 53)

CLINICAL				PATHOLOGIC			
GROUP	T	N	M	GROUP	T	N	M
❑ 0	Tis	N0	M0	❑ 0	Tis	N0	M0
❑ I	T1	N0	M0	❑ I	T1	N0	M0
❑ II	T2	N0	M0	❑ II	T2	N0	M0
❑ III	T3	N0	M0	❑ III	T3	N0	M0
	T1	N1	M0		T1	N1	M0
	T2	N1	M0		T2	N1	M0
	T3	N1	M0		T3	N1	M0
❑ IVA	T4a	N0	M0	❑ IVA	T4a	N0	M0
	T4a	N1	M0		T4a	N1	M0
	T1	N2	M0		T1	N2	M0
	T2	N2	M0		T2	N2	M0
	T3	N2	M0		T3	N2	M0
	T4a	N2	M0		T4a	N2	M0
❑ IVB	T4b	Any N	M0	❑ IVB	T4b	Any N	M0
	Any T	N3	M0		Any T	N3	M0
❑ IVC	Any T	Any N	M1	❑ IVC	Any T	Any N	M1
❑ Stage unknown				❑ Stage unknown			

Table 6: Cancer of oropharynx and hypopharynx anatomic stage/prognostic groups

(from ACC Cancer Staging Manual Seventh Edition, page 53)

1.4 Diagnosis and methods of treatment

The diagnosis of HNSCC depends on a comprehensive history combined with palpation, inspection, and/or direct/indirect flexible/rigid endoscopy as well as imaging approaches (Johnson et al., 2020). An inspection is crucial to define the degree of cancer and biopsies for a further pathological examination. Imaging approaches such as sonography, computed tomography (CT), Fluorine-18 fluorodeoxyglucose positron emission tomography/ computed tomography (^{18}F FDG PET/CT), and magnetic resonance imaging (MRI) are critical to assessing the level of tumor penetration, metastases of regional nodes and distant metastases or recurrence (Pfister et al., 2020). PET/CT can be conducted to evaluate local lymph nodes, distant metastases and their viability following treatment (Pfister et al., 2020).

Initial assessment of HNSCC involves a comprehensive history and inspection, palpation, and/or direct/indirect flexible/rigid endoscopy as well as imaging scans (Pfister et al., 2020). Visual and/or palpatory examination of the nasal and oral cavities, as well as the floor of the mouth, anterior two-thirds part of the tongue, tonsillar fossae and tongue base (optimally observed via mirror inspection or flexible laryngoscopy) (Pfister et al., 2020). Also, palate, buccal and gingival mucosa, and posterior pharyngeal wall should be examined as part of the physical evaluation (Pfister et al., 2020).

A metastatic evaluation with appropriate imaging modalities is strongly suggested for newly diagnosed HNSCC patients, specifically at regional lymph node spread (De Bree et al., 2009; Pfister et al., 2020). Imaging scans of lungs are often carried out with locoregionally advanced HNSCC for metastases check. Additionally, patients who have a carcinoma *in situ* with intense smoking, alcohol intake, or family cancer history might as well profit by a more extensive examination for metastatic diseases or a second primary cancer such as chest CT (De Bree et al., 2009; Pfister et al., 2020).

Imaging modalities including sonography, CT, PET/CT, and MRI play an important role in evaluating tumor penetration level, regional nodal metastases, as well as distant metastases or

recurrence (Richards & Peacock, 2007; Zoumalan et al., 2010; De Bree et al., 2009). Notably, PET/CT can be carried out to evaluate regional and distant metastases as well as their viability post-treatment. Cacicedo suggests PET/CT be performed on routine basis as imaging work-up of advanced HNSCC (stage III-IV) (Cacicedo et al., 2015).

Treatment for HNSCC necessitates sufficient consideration of the location and stage of the tumor, also the expected clinical outcomes, morbidity related to different treatment strategies as well as patient-oriented aspects such as their overall health status, comorbidities, and the type of treatment preferred by patients (Marur & Forastiere, 2016). Generally, a multidisciplinary approach including all associated clinicians with adequate expertise is critical in terms of the treatment and management of HNSCC patients. Early-stage (stage I and stage II) HNSCC patients normally undergo treatments such as surgical removal or receiving primary radiotherapy. A multidisciplinary approach of both (chemo-) radiation combined with surgery with functional organ-preservation strategies is suggested for advanced patients (stage III to IVB) (Marur & Forastiere, 2016).

Regarding the treatment of recurrent or metastatic HNSCC patients, the management approach is generally based upon previous treatments, performance status, comorbidities, tissue PD-L1 combined positive score (CPS), the rapidity of tumor progression, related prognostic factors, etc (Cohen et al., 2019). Several systemic agents are actively available, such as chemotherapy, immune checkpoint inhibitors (ICIs), as well as targeted therapies like cetuximab. Clinical trials could also be a good alternative for selected patients during their disease course. Patients who have severe comorbidities and/or poor performance status could consider supportive care, without initiating systemic treatment (Marur & Forastiere, 2016; Cohen et al., 2019).

1.5 Prognosis

The prognosis of HNSCC predominantly depends upon the TNM stage during initial diagnosis, surgical resection margins, and HPV status (Budach & Tinhofer, 2019; Saroul et al., 2022).

Early-stage (stage I and II) HNSCC patients have a better prognosis and overall survival than patients at advanced stage (stage III or stage IV) (Budach & Tinhofer, 2019; Johnson et al., 2020). Additionally, the prognosis of HNSCC patients who are HPV positive appears to be remarkably better than those who are HPV negative. Moreover, according to AJCC, the depth and extent of invasion in oral cancer patients, extracapsular nodal extension, overall health status (e.g., performance status), consumption of tobacco and alcohol, HPV status and EBV status are closely associated with their prognosis (Budach & Tinhofer, 2019; Johnson et al., 2020).

Saroul and team concluded TNM stage was a major prognostic factor (hazard ratio = 3.34, p = 0.002, for stage T3-4). The RTOG 0129 trial demonstrated a significant decrease (58%) in terms of the risk of mortality (HR 0.42; 95% CI 0.27–0.66) among HPV-positive HNSCC patients compared to HPV-negative patients (Ang et al., 2010). Referring to the US National Cancer Database in 2018, Li et al. similarly discovered that HPV status acts as the strongest indicator for prognosis of overall survival in 41950 out of 175,223 patients (Li et al. 2018). Additional studies also suggest that radiomics, which are different attributes extracted from diagnostic radiographic scans including CT, MRI, and PET, could potentially act as non-genetic prognostic indicators for HNSCC (Budach & Tinhofer, 2019). Additionally, depth of tumor invasion, EBV status together with consumption of tobacco and alcohol are related to the prognosis in HNSCC patients (Almangush et al., 2013; Boffetta et al. 2007).

2. Purpose of study

Imaging modalities including sonography, CT, PET/CT, as well as MRI are generally applied in clinical practice, particularly for lymph node analysis and clinical staging. Nevertheless, studies comparing the diagnostic accuracy of these modalities from a cross-sectional perspective are limited. This study was conducted to emphasize evaluating cervical nodal metastases among HNSCC patients through comparing these four radiographic modalities and exploring the imaging modality with better accuracy and could provide clinical value.

We also sought to assess the diagnostic accuracy, sensitivity, specificity of each modality and the Kappa consistency test and ROC Curve utilising histopathology as a gold standard for comparisons.

3. Material and Methods

3.1 Patient enrollment

This retrospective study enrolled 26 patients who were diagnosed with HNSCC at the Department of Otolaryngology-Head and Neck Surgery, Technical University of Munich from 2010 to 2011. All patients were newly diagnosed and had not received any previous anti-cancer treatment approaches including surgery, radiotherapy, and chemotherapy. Before confirming the pathological diagnosis, all patients were subjected to all the radiographic modalities including sonography, CT, PET/CT, and MRI.

3.2 Methods

3.2.1 Morphological methods

This study used imaging studies including sonography, CT, PET/CT, and MRI, which are common in clinical practice.

3.2.1.1 Sonography

Neck sonography, also known as ultrasound (US) is a readily accessible, cost-efficient, secure, and precise modality, which is broadly used for assessing suspected nodal assessment in HNSCC (Heusch et al., 2014). Notably, B-scan as well as color-coded duplex imaging (CCDI) forms the basis of sonography diagnostics for cervical lymph nodes (LNs) (Künzel et al., 2022). The use of sonography has enabled possible assessment of the size of LN, cystic configuration, hyperechoic lesions, the loss of fatty hilum as well as extracapsular extension and peripheral vascularization, which constitutes major criteria for LN malignancy (Wendl et al., 2012; Künzel et al. 2018).

Sonography is important in diagnosing HNSCC for visualizing local nodal metastases and detecting pathological changes as well as lesions of the salivary and thyroid glands (Richards & Peacock, 2007).

Herein, diagnosis with sonography was carried out by specialists in otorhinolaryngology with adequate clinical experience in sonography. Sonography scan was performed in high-resolution B-mode using the Siemens S2000 (linear transducer, 9-14 Mhz, Tissue Harmonic Imaging) (Siemens Medical Solutions, Erlangen, Germany).

3.2.1.2 CT scan

CT scan acts as an extended use of the X-ray procedure and is one of the most important radiological techniques. The X-ray beam scans from several different directions by rotating the X-ray tube. The use of CT scans is important in ear, nose, and throat medicine for evaluating nodal metastases and diagnosing sinusitis and temporal bone fractures. The CT scan analysis description for lymph node contained: the specific volume and size, the existence of central necrosis, and the presence of nodal cluster within cancer region and its drainage pathway (Zoumalan et al., 2010).

A CT scan can help in detecting malignancy based on anatomic distortions or specific tumor enhancement in HNSCC. It allows greater spatial resolution, faster acquisition times, and better evaluation of bone destruction compared to MRI (Feldhaus et al., 2019). Modern multidetector CT machines can be used with slice thickness less than 3mm, even 1 mm (Zoumalan et al., 2010; Feldhaus et al., 2019), hence providing optimal spatial resolution for radiologists. The CT scan analysis description for LN assessment includes specific volume and size, the existence of central necrosis, and the presence of nodal clusters within the cancer region and its drainage pathway (Zoumalan et al., 2010).

For this study, the CT images were evaluated by certified radiologists. Low-dose CT techniques were performed with further administration of an intravenous contrast medium (100ml Imeron 300, Bracco Medical, Germany).

3.2.1.3 PET/CT scan

A PET/CT scan is combined of positron emission tomography (PET) and CT. PET/CT uses injected radionuclides that emit positrons to visualize metabolically or functionally active tissues (Rudmik et al., 2011; Suenaga et al., 2016). Images of PET/CT are generated by detecting positron emissions and subsequent use of reconstruction techniques for constructing a 3-D image. Fluorodeoxyglucose is a commonly utilized agent, with varying uptake levels in cells based on respective tissue metabolism (Rudmik et al., 2011; Suenaga et al., 2016). In PET/CT scans, PET and CT scans are sequentially carried out under the identical imaging session via a hybrid PET/CT scanner, hence product-integrated PET/CT imaging. With the help of fusion software, the PET images are subsequently integrated with the anatomic CT imaging to help localize the physiologic parameters (Abgral et al., 2009). In the HNSCC field, a PET-CT scan plays an important role in evaluating local lymph nodes and remote metastases as well as second primary malignancies (Suenaga et al., 2016).

Assessment of the PET/CT scan images is conducted by specialists in radiology and nuclear medicine. We used a Biograph 64 PET/CT scanner (Siemens Medical Solutions, Erlangen, Germany). Once the venous infusion of ^{18}F FDG (5 MBq/kg body weight) was complete, the PET/CT associated data could be recorded after 90 minutes.

3.2.1.4 MRI scan

MRI offers superior soft tissue definition unlike CT scan and is superior in assessing perineural spread, skull base invasion as well as intracranial extension in HNSCC (Kuno et al., 2018). MRI can bring extra benefits in evaluating the tongue base and parotid glands, too (Pfister et al., 2020). The NCCN guidelines recommend that skull base erosion be evaluated with an MRI scan for nasopharyngeal cancer (Pfister et al., 2020). In HNSCC, an MRI is generally carried out to provide complementary information to a CT scan based on these reasons.

In this work, radiology specialists evaluated the MRI images. A Magnetom Verio 3T scanner

(Siemens Medical Solutions, Erlangen, Germany) was used to create magnetic resonance tomography (MRT) images. We performed T1, T2-weighted short tau inversion recovery (T2-STIR), and contrast agent T1 sequences. The Magnetvist (0.2 ml/kg body weight) (Bayer-Schering, Berlin, Germany) was used as a contrast agent.

3.2.1.5 Imaging template

After obtaining all imaging data, we analysed and compared the same lesions with different modalities from axial, sagittal, and coronal dimensions. In addition to CT, PET/CT, and MRI, we also compared the morphology and positive findings of sonography, which was applicable in a paper format. All patients in this study had available imaging data including sonography, CT, PET/CT, and MRI and pathological reports as gold standards.

For staging and treatment of head and neck malignancies, cervical lymph nodes are often separated into a minimum of six anatomic neck lymph node levels (Robbins et al., 2002; Robbins et al., 2008; Grégoire et al., 2014). Conclusively, Level I is the submental and submandibular area, Level II is the upper internal jugular (deep cervical) chain area, Level III is the middle internal jugular (deep cervical) chain area, Level IV is the lower internal jugular (deep cervical) chain, Level V is the posterior triangle and Level VI is the central (anterior) compartment area (Robbins et al., 2002; Robbins et al., 2008; Grégoire et al., 2014) (Fig. 1). Nonetheless, this study did not enroll patients with level I and level VI nodal metastases; therefore, we modified LNs levels into 4 levels, level II, III, IV and V, either ipsilateral or bilateral. We subsequently compared the nodal positivity detected in these 4 imaging modalities to the histopathological report for statistical analysis.

The images (Fig. 2 to 4) below are from a random patient in our study, using a template here for clarification. Red arrows below marked suspicious lesions identified by CT, PET/CT, and MRI scans. Sono report of this patient stated suspicious lymph nodes are in levels I, II, and III right side and level II left side (classification N2c), which was concordant with the other three imaging modality findings.

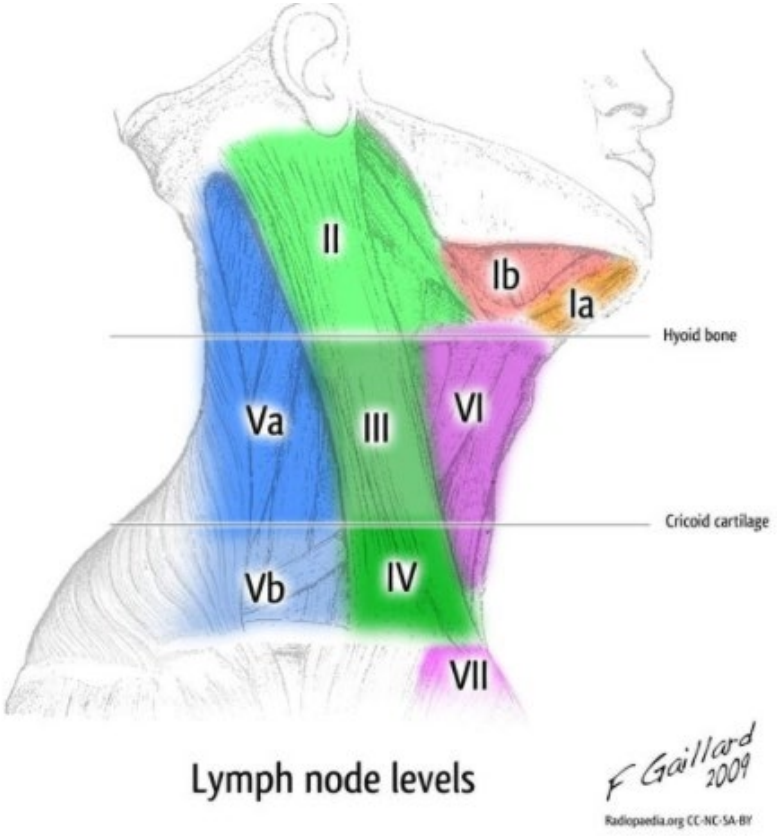

Fig 1: Cervical lymph node levels

(from 20th US. edition of Gray's Anatomy of the human Body)

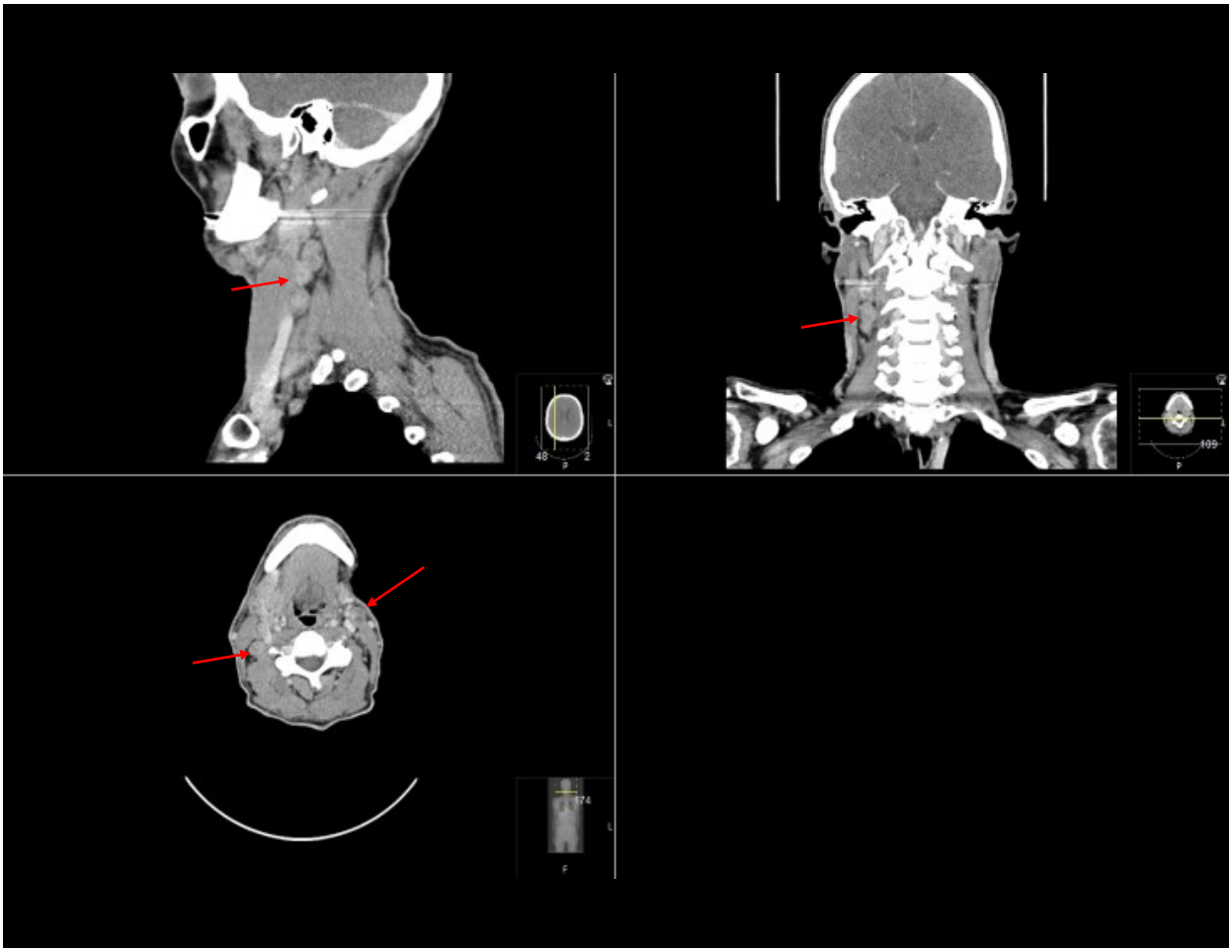

Fig 2: Imaging template acquired by CT
(nodal lesion targeted by red arrow)

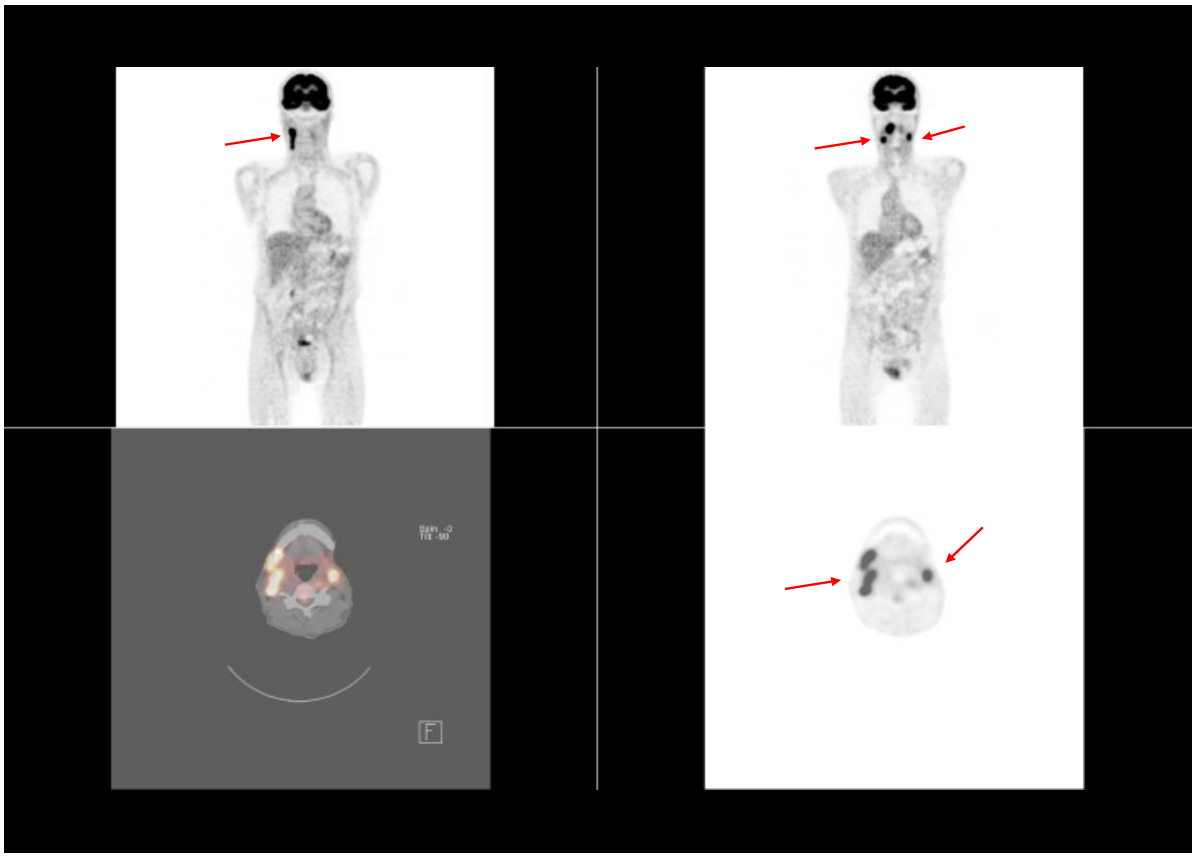

Fig 3: Imaging template acquired by PET/CT
(nodal lesion targeted by red arrow)

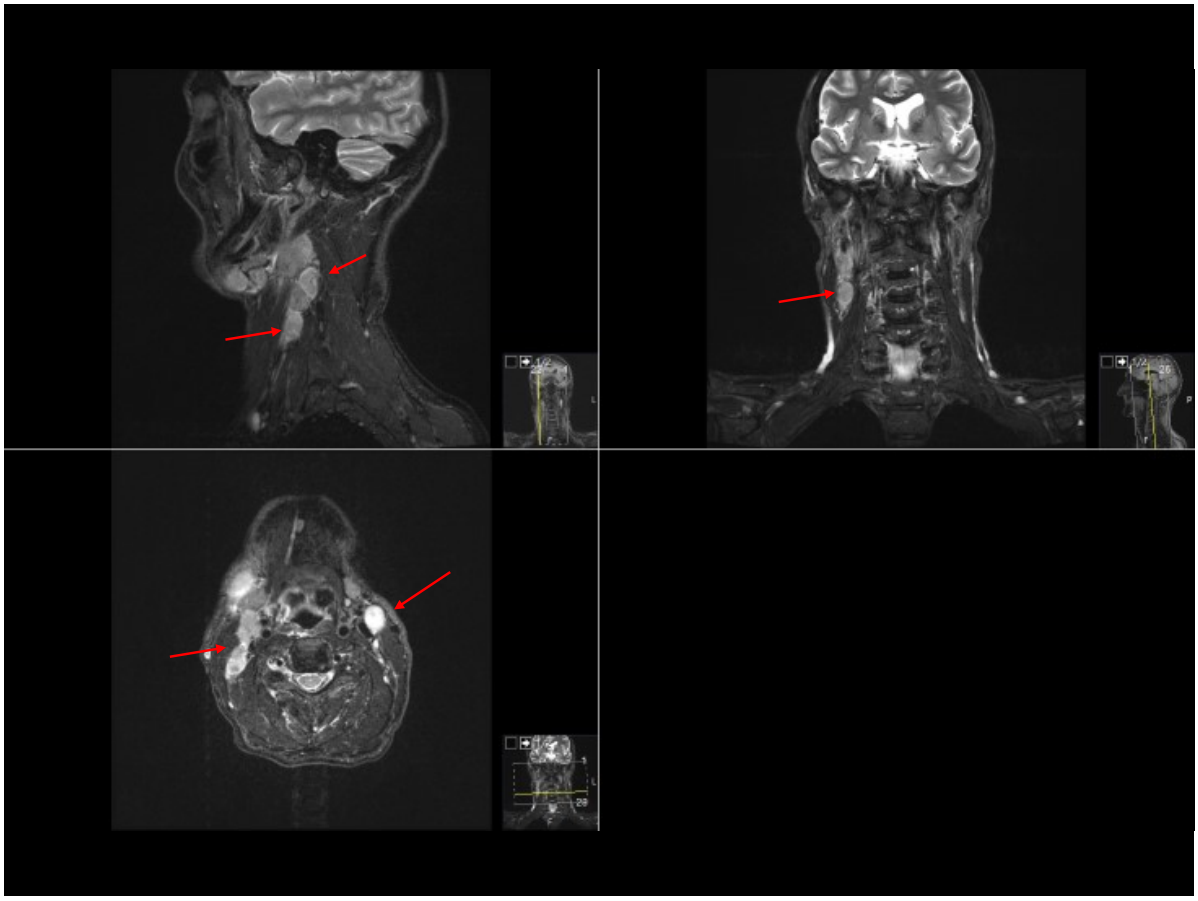

Fig 4: Imaging template acquired by MRI
(nodal lesion targeted by red arrow)

3.3 Histology

A total of 25 out of 26 enrolled patients had histopathological reports from the pathology department. The certified pathologists provided the histopathological results.

3.4 Statistical analysis

As mentioned above, the cervical LN levels were modified into 4 levels, level II, III, IV, and V, either ipsilateral or bilateral. Subsequently, we compared the nodal positivity detected in these 4 imaging modalities based on cervical lymph node levels to the histopathological results (which is the gold standard) for statistical analysis. The MedCalc software was used for data analysis. MedCalc software is a broadly used statistical software package for biomedical research, particularly for diagnostic evaluation tests (MedCalc, 2015). First, we analysed the demographic distribution of patients enrolled. Sensitivity, specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV), and overall accuracy as well as receiver operating characteristic (ROC) curve analysis were computed for each imaging method. Of note, a ROC curve is a plot of the true positive rate (sensitivity) in the function of the false positive rate (100-specificity) for different cut-off points of a parameter; the closer area under the curve (AUC) is to 1, the better the model (DeLong et al., 1988).

McNemar test was also performed using MedCalc to establish if the overall diagnostic accuracy differed between sonography, CT, PET/CT, and MRI in cervical nodal metastases evaluation. The McNemar Test is broadly performed to decide if the proportions of categories in two related groups significantly differ from each other.

Lastly, the kappa statistic through the MedCalc software was utilized to analyse interrater reliability of the 4 imaging modalities. Notably, the kappa statistic is commonly utilized to evaluate interrater reliability in academic research to select and indicate the most accurate representations of the measured variable (McHugh, 2012). For instance, a kappa value with different ranges represents different levels of interrater agreement and consistency, a kappa value of 0-0.2 signifies a poor agreement, a kappa value of 0.2-0.4 signifies a fair agreement,

a kappa value of 0.4-0.6 signifies a moderate agreement, a kappa value of 0.6-0.8 signifies a substantial agreement and a kappa value of 0.8-1.0 signifies a nearly perfect agreement (McHugh, 2012).

4. Results

4.1 Demographic characteristics of enrolled HNSCC patients

As shown in the demographic table (Table7), this study enrolled 26 HNSCC patients. Their median age was 54 years, ranging from 28 to 71 years. More than 70% of patients were male. The primary sites of cancer mainly included cancer of the oral cavity and oropharynx, 5 cases of hypopharyngeal cancer included, too. Based on the 7th edition AJCC staging, nearly half of the patients (46.2%) were early-staged (stage I and II) and another half of patients (53.8%) were at the advanced stage (stage IV) with no patients at initial stage III. Regarding treatments, 42.3% of patients received surgery alone, 53.9% received surgery combined with radiation therapy (RT) or radiochemotherapy (RCT) and one patient received radiation therapy only.

Features	N (%)
Age	54.0 (range: 28-71)
Gender	
Male	20 (76.9%)
Female	6 (23.1%)
Primary Site of Cancer	
Oral cavity	9 (34.6%)
Oropharynx	12 (46.2%)
Hypopharynx	5 (19.2%)
Initial T-stage	
T1	13 (50.0%)
T2	5 (19.2%)
T3	5 (19.2%)
T4	3 (11.5%)
Initial M-stage	
M0	23 (88.5%)
M1	3 (11.5%)
Treatment	
radiation therapy	1 (3.8%)
surgery only	11 (42.3%)
surgery+radiation therapy	8 (30.8%)
surgery+radiochemotherapy	6 (23.1%)

Table 7: Demographic characteristics of HNSCC patients (n=26)

4.2 Diagnostic accuracy and comparison among sonography, CT, PET/CT, and MRI scans in evaluating cervical lymph node metastases in HNSCC patients

4.2.1 Diagnostic accuracy of sonography in detecting cervical lymph node metastases

All the detected cervical lymph nodes were compared through sonography with the lymph node levels confirmed by histopathological results. We used bilateral LN levels II, III, IV, and V of each patient to make final analysis; one patient had a missing histopathological report. We found an overall 96.0% accuracy in the detection of lymph node metastases with sonography. The sensitivity and specificity were 85.7% and 97.7%, respectively, with 85.7% positive predictive value (PPV) and 97.7% negative predictive value (NPV).

Categories	Histopathology +	Histopathology -	Total cervical lymph nodes
Sonography +	24	4	28
Sonography -	4	168	172
Total	28	172	200

Table 8: Number of lymph node levels detected by sonography and histopathology

Metrics	Sonography
Sensitivity	85.7%
Specificity	97.7%
PPV	85.7%
NPV	97.7%
Accuracy	96.0%

Table 9: Diagnostic accuracy of sonography

4.2.2 Diagnostic accuracy of CT scan in detecting cervical lymph node metastases

Similarly, all the detected cervical lymph nodes were compared through a CT scan with the lymph node levels (bilateral LN level II, III, IV) confirmed by histopathological results. One patient had a missing histopathological report. The overall accuracy of the CT scan was 93.5%. The sensitivity, specificity, PPV, and NPV were 85.7%, 94.8%, 72.7%, and 97.6%, respectively, for CT scans.

Categories	Histopathology +	Histopathology -	Total cervical lymph nodes
CT +	24	9	33
CT -	4	163	167
Total	28	172	200

Table 10: Number of lymph node levels detected by CT and histopathology

Metrics	CT
Sensitivity	85.7%
Specificity	94.8%
PPV	72.7%
NPV	97.6%
Accuracy	93.5%

Table 11: Diagnostic accuracy of CT

4.2.3 Diagnostic accuracy of PET/CT scan in detecting cervical lymph node metastases

Further, all the detected cervical lymph nodes were compared through PET/CT scans with the lymph node levels (bilateral LN level II, III, IV) confirmed by histopathological results for statistical analysis. With one patient missing a histopathological report, the overall accuracy for a PET/CT scan was 97.0%. The sensitivity, specificity, PPV, and NPV were 92.3%, 97.7%, 85.7% and 98.8%, respectively.

Categories	Histopathology +	Histopathology -	Total cervical lymph nodes
PET/CT +	24	4	28
PET/CT -	2	170	172
Total	26	174	200

Table 12: Number of lymph node levels detected by PET/CT and histopathology

Metrics	PET/CT
Sensitivity	92.3%
Specificity	97.7%
PPV	85.7%
NPV	98.8%
Accuracy	97.0%

Table 13: Diagnostic accuracy of PET/CT

4.2.4 Diagnostic accuracy of MRI scan in detecting cervical lymph node metastases

Furthermore, all the detected cervical lymph nodes by MRI with the lymph node levels (bilateral LN level II, III, IV) were compared with histopathological results. We had 4 subjects with missing MRI data and 1 subject with missing histopathological reports. The overall accuracy of MRI detection was 72.0%. The sensitivity, specificity, PPV, and NPV were 96.0%, 67.8%, 34.3%, and 99.0%, respectively.

Categories	Histopathology +	Histopathology -	Total cervical lymph nodes
MRI +	24	46	70
MRI -	1	97	98
Total	25	143	168

Table 14: Number of lymph node levels detected by MRI and histopathology

Metrics	MRI
Sensitivity	96.0%
Specificity	67.8%
PPV	34.3%
NPV	99.0%
Accuracy	72.0%

Table 15: Diagnostic accuracy of MRI

4.2.5 Diagnostic accuracy and comparison of sonography, CT, PET/CT, and MRI scans in detecting cervical lymph node metastases

4.2.5.1 Diagnostic test results comparison of sonography, CT, PET/CT, and MRI scans in detecting cervical lymph node metastases

Furthermore, we compared the diagnostic accuracy of sonography, CT, PET/CT, and MRI. Sensitivity was highest for MRI (96.0% compared to 92.3% for PET/CT and 85.7% for sonography and CT). Specificity was comparable with 94.8 % for CT, and 97.8 % for sonography and PET/CT, but only 67.8% for MRI. Whereas the MRI showed the least PPV (34.3%) unlike all other methods (85.7% for sonography and PET/CT, and 72.5% for CT), the NPV was comparable in all methods (97.6-99.0%). The overall accuracy of detecting cervical lymph node metastases was comparable for sonography, CT, and PET/CT with 96.0%, 93.5%, and 97.0%, respectively, whereas MRI had only 72.0% accuracy (Table 16).

Metrics/Modalities	Sonography	CT	PET/CT	MRI
Sensitivity	85.7%	85.7%	92.3%	96.0%
Specificity	97.7%	94.8%	97.7%	67.8%
PPV	85.7%	72.7%	85.7%	34.3%
NPV	97.7%	97.6%	98.8%	99.0%
Accuracy	96.0%	93.5%	97.0%	72.0%

Table 16: Diagnostic accuracy of sonography, CT, PET/CT and MRI

4.2.5.2 ROC curve analysis of sonography, CT, PET/CT, and MRI scans in detecting cervical lymph node metastases

Through ROC curve analysis by the MedCalc software, we calculated the AUC of sonography, CT, PET/CT, and MRI were 0.896, 0.920, 0.933, 0.819. In the assessment of cervical nodal metastases, all four imaging modalities had a good performance.

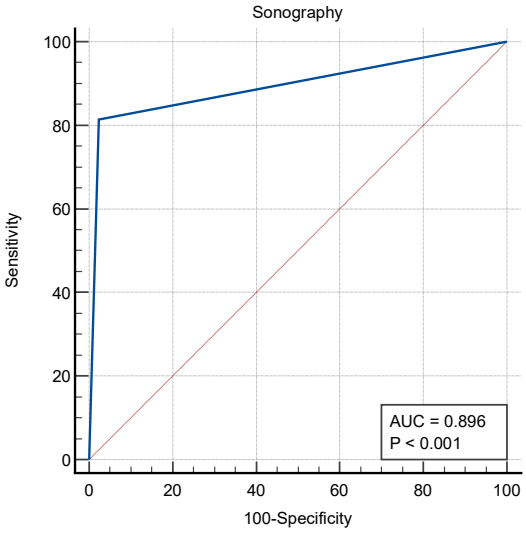

Fig 5: ROC curve of sonography

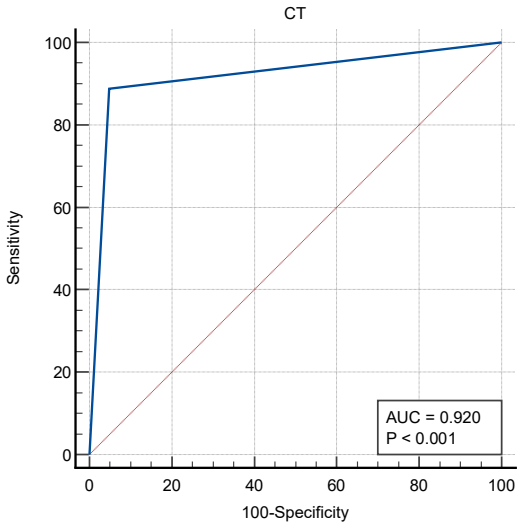

Fig 6: ROC curve of CT

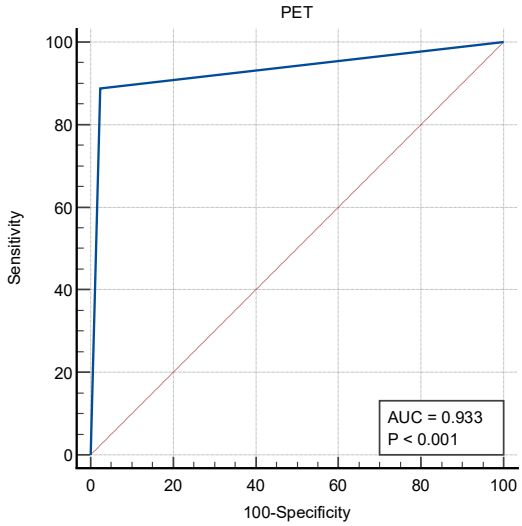

Fig 7: ROC curve of PET/CT

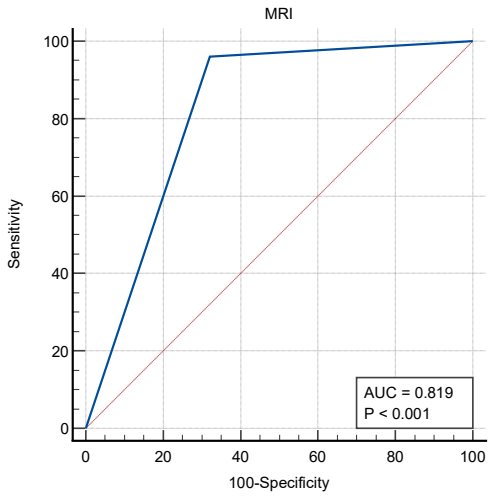

Fig 8: ROC curve of MRI

4.2.5.3 Significant difference in comparison of diagnostic accuracy of sonography, CT, PET/CT, and MRI scans in detecting cervical lymph node metastases

We found no statistical difference between sonography and CT, sonography and PET/CT, as well as CT and PET/CT in evaluating cervical nodal metastases. Nonetheless, sonography and MRI (p<0.001), CT and MRI (p<0.001) as well as PET/CT and MRI (p<0.001) had remarkable differences in cervical lymph node metastases assessments.

4.2.5.4 Interrater agreement (kappa) statistical analysis of sonography, CT, PET/CT, and MRI scans in detecting cervical lymph node metastases

The level of interrater agreement was good between sonography and CT, sonography and PET/CT, and CT and PET/CT, with a kappa rate of 0.68, 0.74, and 0.83, respectively. However, kappa value was lower in sonography and MRI (0.37), CT and MRI (0.49), and PET/CT and MRI (0.35). This indicates a lesser level of interrater agreement between these groups.

Modalities	Kappa value
sonography and CT	0.68
sonography and PET/CT	0.74
sonography and MRI	0.37
CT and PET/CT	0.83
CT and MRI	0.49
PET/CT and MRI	0.35

Table 17: Kappa value of different imaging modalities

4.3 Overall diagnostic accuracy comparison between sonography, CT, PET/CT, and MRI scans in detecting cervical lymph node metastases

To further investigate the differences in diagnostic accuracy between sonography, CT, PET/CT, and MRI in cervical nodal metastases identification, also to determine the preferred imaging methodology in clinical practice, the McNemar test via the MedCalc software was performed to compare the diagnostic significance between 4 imaging modalities.

In summary, our statistical analyses reported significant differences in overall accuracy in detecting cervical lymph node metastases between MRI and CT, MRI and PET/CT as well as MRI and sonography. Based on these statistics, only the accuracy of MRI in evaluating cervical lymph node metastases was significantly different compared to other modalities; we found no significant difference among other groups.

Modalities/MRI	CT	PET/CT	Sonography
Difference	-20.67%	-25.60%	-26.19%
95% CI	-27.4% to -13.93%	-32.59% to-18.6%	-33.04% to -19.34%
P value	p<0.001	p<0.001	p<0.001
No significant difference among sonography, CT and PET/CT (p>0.05).			

Table 18: Comparison of diagnostic accuracy among different imaging modalities

5. Discussion

5.1 Comparison of the diagnostic accuracy of sonography, CT, PET/CT, and MRI scans in the detection of cervical lymph node metastases in HNSCC patients

5.1.1 Diagnostic accuracy of sonography in the assessment of cervical lymph node metastases in HNSCC patients

Nodal metastases are one of the most relevant prognostic factors for HNSCC patients and could influence the choice of treatments. In addition, post-operative follow-up examination of cervical lymph nodes ought to be conducted for assessment of prognosis (Pfister et al., 2020). Sonography is the first-line method for thyroid disease assessment and also commonly used for paediatric neck malignancies being motionless and avoiding radiation (Künzel et al. 2022; Junn et al., 2020). Several factors have made ultrasound a preferred alternative for detecting cervical lymph nodes in clinical practice. Ultrasound offers distinct advantages: it's readily available, cost-effective, and non-invasive. This combination makes it a highly valuable tool for doctors (Heusch et al., 2014).

The application of sonography can detect and evaluate the metastatic status of cervical lymph node efficiently and precisely (Künzel et al. 2022). This spotlights the necessity to assess the diagnostic accuracy of sonographic evaluation in clinical practice.

A prior study involving 100 surgical patients compared physical exams, ultrasound, and histology to assess cervical lymph nodes. This study highlighted the value of ultrasound in detecting subclinical disease. Ultrasound achieved an impressive sensitivity of 92.6% and specificity of 91% for identifying lymph node metastases (Bruneton et al. 1984). In 1993, Baatenburg de Jong et al. explored the performance of ultrasound and its combination with ultrasound-guided fine-needle aspiration biopsy (UGFNAB) during the evaluation of nodal metastases. They also compared the diagnostic accuracy among patients who have metastatic neck diseases including HNSCC (Baatenburg de Jong et al. 1993). They reported a sensitivity of 96%, specificity of 32%, PPV of 84%, NPV of 72%, and accuracy for lymph node

metastases of 83% (Baatenburg de Jong et al. 1993).

In 2007, Richards et al. investigated the accuracy of ultrasound to assess local nodal metastases in clinically N0 HNSCC. They obtained a sensitivity of 63% and specificity of 92% when the minimum axial diameter (mm) as measured on ultrasound was set as 10 mm (Richards & Peacock, 2007). However, the study by Richards et al. only included clinically N0 HNSCC patients, this implies that when combing all N level HNSCC patients, sonography might exhibit better sensitivity and specificity in assessing cervical lymph node metastases.

Shetty et al. evaluated the accuracy of palpation, ultrasound, and CT in assessing metastatic cervical lymph nodes in oral squamous cell carcinoma patients. They reported that the sensitivity, specificity, PPV, NPV, and overall accuracy for lymph node metastasis detection were 54.5%, 85.71%, 60.0%, 82.75%, and 76.92% by ultrasound, respectively (Shetty et al., 2015). Comparably, Wang et al. compared the diagnostic capability of palpation and ultrasound for cervical nodal metastases among hypopharyngeal cancer patients and obtained a sensitivity of 86.76% and specificity of 80.95%, with 93.65% PPV and 65.38% NPV. Based upon these studies, we summarize that the sensitivity of ultrasound was significantly higher than palpation (Wang et al., 2019).

This study obtained an overall accuracy of 96.0% for lymph node metastases detection by sonography, with a sensitivity of 85.7%, specificity of 97.7%, PPV of 85.7% and NPV of 97.7%, which were moderately higher than those reported in previous studies. This discrepancy might be associated with variations in clinicians' experience in specialized head and neck cancer center and also the small patient number.

5.1.2 Diagnostic accuracy of CT scan in the detection of cervical lymph node metastases in HNSCC patients

CT scans are a mainstay in clinical practice for cervical lymph node status evaluation. There're several reasons for this preference: CT scans can image all the tissues in the neck in a single

scan, CT scanners are readily available in most hospitals and clinics, and compared with MRI scans, CT scans are generally less expensive (Zoumalan et al., 2010; Junn et al., 2020). The CT diagnostic accuracy is a key factor affecting diagnosis and treatments. The following discussion focuses on the CT diagnostic accuracy in terms of cervical nodal metastases evaluation.

Early in 1996, Wong et al. validated the clinical significance of CT among 30 HNSCC patients (Wong et al., 1996). They found a 97% tumor detecting rate for CT. However, they did not investigate cervical lymph node metastases status.

Several researches have investigated the effectiveness of different imaging modalities in detecting lymph node metastases in HNSCC. Yoon et al. compared four methods: ultrasound, CT, PET/CT, and MRI. They found CT scans to be highly specific (99.4%) for identifying cervical lymph nodes. More recently, Kim investigated the use of CT, MRI, and PET/CT to detect metastases in retropharyngeal lymph nodes in 123 HNSCC patients (Kim et al., 2020). Sensitivity, specificity, PPV, NPV, and overall accuracy in detecting RPLN metastases of CT were 65%, 94%, 85%, 83%, and 84% in their study, respectively (Kim et al., 2020). Another study suggested that CT should be applied together with MRI or PET/CT due to its limited sensitivity (Kim et al., 2020).

Salman et al. enrolled 200 HNSCC patients between 2015 and 2016 to assess the detection accuracy in occult cervical nodal metastases using multislice CT scan (Salman et al., 2017). They found a % sensitivity of 100, specificity of 93%, NPV of 93%, PPV of 100%, and overall diagnostic accuracy of 96.2% (Salman et al., 2017).

In this study, we concluded that the sensitivity, specificity, PPV, NPV, and overall accuracy were 85.7%, 94.8%, 72.7%, 97.6% and 93.5%, respectively for CT. Our findings align well with aforementioned studies (Wong et al., 1996; Yoon et al., 2009; Kim et al., 2020; Salman

et al., 2017). This further confirms the established role of CT scans as a valuable morphological imaging technique in clinical practice.

5.1.3 Diagnostic accuracy of PET/CT scan in the detection of cervical lymph node metastases in HNSCC patients

PET/CT is a crucial functional and morphological approach for cancer staging and evaluating cervical lymph node metastases. Several researchers have proved that PET/CT may be more effective than CT and MRI for regional nodal metastases assessment, second primary malignancies, and distant metastases (Johnson & Branstetter, 2014; Escott, 2013; Xu et al., 2012; Lonneux et al., 2010).

While previous studies showed promising results for this technique in detecting nodal metastases, with high sensitivity ranging from 92% to 98%, their specificity varied considerably (77% to 93%). We, however, note that these studies primarily focused on uterine cervical cancer and breast cancer. Our understanding of this technique's effectiveness in other cancer types, like head and neck cancer, may be limited (Monteil et al., 2011; Song et al., 2012). Yutaka et al. enrolled 26 HNSCC patients to investigate the diagnostic capability of PET/CT in assessing cervical nodal metastases compared to CT (Yamazaki et al., 2008). They obtained sensitivity, specificity, PPV, NPV, and overall accuracy of 74%, 92%, 94%, 65%, and 80% for PET/CT, while those of CT were 78%, 58%, 78%,58%, and 71%, respectively (Yamazaki et al., 2008). Moreover, PET/CT could detect all lymph nodes with metastases ≥10 mm, intranodal tumor deposits with a percentage>75% and also intranodal tumor deposits ≥9 mm (Yamazaki et al., 2008).

Lee et al. in 2011 reported a sensitivity, specificity, PPV, NPV, overall accuracy of 69%, 89%, 62%, 92% and 85% for PET/CT in assessing cervical nodal metastases in HNSCC patients (Lee et al., 2012). A meta-analysis published in 2018 comprising 18 studies (1044 patients) investigated the diagnostic capability of PET/CT in evaluating nodal metastases in clinically node negative HNSCC, presenting a sensitivity of 58% and specificity of 87% (Kim et al.,

2019). Elsewhere, Veit-Haibach et al. reported an improved diagnostic accuracy of 76% (CT alone) as well as 84% for PET/CT among HNSCC patients (Veit-Haibach et al., 2007).

A meta-analysis, involving 2247 PET/CT scans from 23 studies (Sheikhbahaei et al., 2015), investigated the effectiveness of detecting recurrence of head and neck cancer after definitive treatment. These findings suggested PET/CT scans were highly accurate, with a combined sensitivity of 92% and specificity of 87%.

In this study, we obtained a sensitivity, specificity, PPV, NPV, and overall accuracy of 92.3%, 97.7%, 85.7%, 98.8% and 97%, respectively, for PET/CT, which were comparable to findings in previous studies. Considering previous studies and our results, we infer that PET/CT can not only facilitate primary tumor staging but aid in evaluating regional nodal metastases in HNSCC patients.

5.1.4 Diagnostic accuracy of MRI scans in the detection of cervical lymph node metastases in HNSCC patients

MRI, similar to CT scans, is frequently used to assess cervical nodal status. MRI offers two key advantages over CT scans. First, it can bring detailed messages about the morphology of the lymph nodes. Second, MRI is more effective at visualizing soft tissues and detecting cancer metastasis into the bone marrow, which can be challenging for CT scans (Vishwanath et al., 2020).

Vandecaveye et al. analysed diffusion-weighted (DW) magnetic resonance (MR) images and compared with those from turbo spin-echo MR imaging in detecting nodal metastases in HNSCC patients (Vandecaveye et al., 2009). The study found that the technique was very effective in detecting lymph node spread (metastasis) at each individual lymph node level. The results showed 84% sensitivity, 94% specificity, and 91% accuracy. Similarly impressive results were obtained when examining all the lymph nodes in the neck together (each neck level in total). In this case, the sensitivity was 94%, specificity was 97%, and accuracy was

97% (Vandecaveye et al., 2009). Yoon et al. in 2009 compared the diagnostic performance among four morphological methods - sonography, CT, PET/CT and MRI in evaluating cervical nodal metastases with a sample of 67 HNSCC patients (Yoon et al., 2009). The study exhibited a sensitivity of 77.0%, specificity of 99.4%, and an overall accuracy of 95.3% for MRI, indicating that MRI's diagnostic value was quite comparable to CT's diagnostic value (Yoon et al., 2009).

A previous meta-analysis analysed 12 studies to compare different imaging modalities (sonography, CT, PET/CT and MRI) to assess cervical nodal metastases in clinically N0 HNSCC patients. Their pooled estimates showed a sensitivity of 65% and specificity of 81% (Liao et al., 2012). This meta-analysis found no statistical difference in sensitivity or specificity between the different approaches used to assess lymph node status. However, it's critical to notice that the results may be lower in comparison to previous studies (Yoon et al., 2009; Liao et al., 2012). This is likely because this study focused specifically on head and neck cancer patients with clinically N0 status. Evaluating lymph node metastases among these patients is inherently more challenging.

In 2020, Kim et al. assessed the diagnostic accuracy of MRI, CT and PET/CT in assessing PRLN metastases (Kim et al., 2020). The study exhibited a sensitivity, specificity, PPV, NPV, and overall accuracy of 74%, 94%, 87%, 87%, and 87%, respectively, for MRI (Kim et al., 2020).

In this study, we found a sensitivity, specificity, PPV, NPV, and overall accuracy of 96.0%, 67.8%, 34.3%, 99.0% and 72.0%, respectively, for MRI. Our study identified lymph node metastases with high accuracy (96.0% sensitivity and 99.0% NPV). However, the test also produced a substantial number of false positives (indicated by a lower positive predictive value of 34% and specificity of 68%). This could be due to two limitations. First, our study might have identified more lymph nodes as cancerous (positive) that actually were not (false positives). Second, the relatively small sample size (n=26) might not be sufficient to draw

generalizable conclusions. Our findings could also be interpreted by the fact that no newer imaging protocols such as DWI imaging based on the ADC map were employed to classify the lymph nodes.

5.2 Advanced imaging techniques in HNSCC

In addition to the aforementioned imaging modalities, more and more advanced imaging techniques are under development to satisfy the needs of clinical practice.

Among recent advancements in CT technology, multidetector CT (MDCT) scans using thinner slices can significantly reduce artifacts caused by metal implants. This makes MDCT a strong candidate for becoming a standard CT scan option depending on the specific clinical needs (Junn et al., 2020). Some postprocessing techniques based on CT, including the iterative metal artifact reduction technique, can outperform conventional filtered back-projection in facilitating oral cavity tissue assessment (Diehn et al., 2017).

Among MRI methods, diffusion-weighted imaging (DWI) which's routinely applied to conduct brain scans can also help to differentiate malignancies in staging as well as residual or recurrent disease assessment by employing the apparent diffusion coefficient (ADC) map (Choure et al., 2019). An ADC value cutoff of $0.9*10^{-3}$ mm^2/s was proposed to differentiate malignant lymph nodes from benign ones on a 1.5T magnet (Vincent et al., 2009). Moreover, Perfusion-weighted imaging (PWI), a quantitative decisive technique of delivering blood to tissue, carries high potential for identifying subtle tumor recurrences from granulation or scar tissue due to increased blood flow (Davis et al., 2018).

Researchers have been exploring other relatively innovative techniques such as multi-modality network learning machines in HNSCC (Liao et al., 2020).

The rapid development of advanced imaging technologies offers promise for more accurate and earlier detection of HNSCC. However, the impact on the overall accuracy of detecting

lymph node metastases remains to be fully established due to limitations in the current study, such as a small sample size and the need for more clinical evidence.

5.3 Summary and limitations

This study retrospectively compared and assessed the diagnostic accuracy of four imaging approaches including sonography, CT, PET/CT and MRI in the detection of cervical lymph node metastases in HNSCC patients. The results showed that the modalities except MRI exhibited good diagnostic accuracy (>90%) in assessing cervical lymph node metastases among HNSCC patients while MRI only presented a 72.0% accuracy. MRI was the only imaging technique that demonstrated a difference of statistical significance in accuracy for detecting lymph node metastasis in the neck in comparison with other methods. There were no significant differences in accuracy among ultrasound, CT scans, and PET/CT scans.

This study has some limitations that should be acknowledged. Firstly, we enrolled a small sample size with only 26 patients involved, which may cause bias in the results. Secondly, the imaging machines used for examination from 2010 to 2011 might be outdated and may not reflect the most updated detection efficacy of modern imaging modalities, especially in MRI imaging. Thirdly, this was a retrospective study which may carry some inherent bias. Therefore, prospective studies with a large sample size should be advocated, thus increasing the robustness of our findings.

6. List of Abbreviations

HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus
EBV	Epstein-Barr virus
IHC	immunohistochemistry
TNM	tumor, node, metastases
AJCC	American Joint Committee on Cancer
UICC	Union for International Cancer Control
CT	computed tomography
18F-FDG PET/CT	Fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography
MRI	magnetic resonance imaging
EUA	examination under anesthesia
EGFR	epidermal growth factor receptor
PD-1	programmed cell death protein 1
PD-L1	programmed cell death-ligand 1
CPS	combined positive score
ICI	immune checkpoint inhibitor
US	ultrasound
CCDI	color-coded duplex imaging
LN	Lymph node
PET	positron emission tomography
MRT	magnetic resonance tomography
T2-STIR	T2-weighted short tau inversion recovery
PPV	positive predictive value
NPV	negative predictive
ROC	receiver operating characteristic
AUC	area under the curve

RT	radiation therapy
RCT	radiochemotherapy
RT	radiation therapy
RCT	radiochemotherapy
PRLN	retropharyngeal lymph node
DWMRI	diffusion-weighted magnetic resonance imaging
MDCT	multidetector computed tomography
DWI	diffusion-weighted imaging
ADC	apparent diffusion coefficient
PWI	Perfusion-weighted imaging

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8. List of Tables and Figures

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