

# World Journal of *Otorhinolaryngology*

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# World Journal of Otorhinolaryngology

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*WJO* covers topics concerning endoscopy, rhinology, pharyngology, laryngology, tracheo-esophagology, otology, tracheology, cancer, nasal symptomatology, congenital nasal diseases, inflammatory diseases of the external nose, rhinitis, allergic rhinitis, nasal polyps, nasal septal diseases, nasal bleeding, nasal or sinus foreign bodies, sinusitis, rhinogenic complications, diagnostic imaging, evidence-based medicine, epidemiology and nursing. Priority publication will be given to articles concerning diagnosis and treatment of otorhinolaryngologic diseases. The following aspects are covered: Clinical diagnosis, laboratory diagnosis, differential diagnosis, imaging tests, pathological diagnosis, molecular biological diagnosis, immunological diagnosis, genetic diagnosis, functional diagnostics, and physical diagnosis; and comprehensive therapy, drug therapy, surgical therapy, interventional treatment, minimally invasive therapy, and robot-assisted therapy.

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## Positron-emission tomography/computed tomography imaging in head and neck oncology: An update

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### Abstract

Cancers of the head and neck account for more than half a million cases worldwide annually, with a significant majority diagnosed as squamous cell carcinoma (HNSCC). Imaging studies such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and <sup>18</sup>F-2-fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT) are widely used to determine the presence and extent of tumors and metastatic disease, both before and after treatment. Advances in PET/CT imaging have allowed it to emerge as a superior imaging modality compared to both CT and MRI, especially in detection of carcinoma of unknown primary, cervical lymph node metastasis, distant metastasis, residual/recurrent cancer and second primary tumors, often leading to alteration in management. PET/CT biomarker may further provide an overall assessment of tumor aggressiveness with prognostic implications. As new developments emerged leading to better understanding and use of PET/CT in head and neck oncology, the aim of this article is to review the roles of PET/CT in both pre- and post-treatment management of HNSCC and PET-derived parameters as prognostic indicators.

**Key words:** Positron emission tomography; Staging; Diagnosis; Computed tomography; Head and neck cancer; Management of squamous cell carcinoma; Carcinoma of unknown primary; Second primary malignancy; Surveillance; Recurrence; Prognosis

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**Core tip:** In the pre-treatment phase, positron-emission tomography/computed tomography (PET/CT) is valuable in the evaluation of patients with carcinoma of unknown primary origin, detection of synchronous second primary tumor, staging of cervical lymph node metastasis and assessment for distant metastases. In the post-treatment

phase, PET/CT is helpful in evaluating treatment response, detecting residual or recurrent tumor and excluding distant metastases. Prognostic factors derived from PET/CT metabolic and functional data are useful in predicting tumor aggressiveness with implication on patient's survivability, and facilitate selection of treatment modality and personalized treatment options.

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## INTRODUCTION

Cancers of the head and neck account for more than half a million cases worldwide annually, with a significant majority diagnosed as squamous cell carcinoma (HNSCC). The incidence of head and neck cancer in the United States is approximately 3% of all new cancer cases, accounting for almost 60000 cases each year and 12000 deaths from the disease<sup>[1]</sup>. Tobacco and alcohol abuse, human papillomavirus (for oropharyngeal cancers), and Epstein-Barr virus infection (for nasopharyngeal cancers) are important risk factors for the development of head and neck cancers. Patient's presentation and clinical findings are occasionally nonspecific and can vary depending on the tumor location in the head and neck. Some of these cancers may escape detection despite detailed physical examination, endoscopy and conventional cross sectional imaging, and pose significant challenges in disease diagnosis and management. Imaging studies such as contrast-enhanced computed tomography (CT), magnetic resonance imaging (MRI) and <sup>18</sup>F-2-fluoro-2-deoxy-D-glucose positron-emission tomography/computed tomography (<sup>18</sup>F-FDG PET/CT) are widely used to determine the presence and extent of tumors and metastatic disease, both before and after treatment. Advances in PET/CT imaging have allowed it to emerge as a superior imaging modality compared to both CT and MRI in select situations, such as detection of carcinoma of unknown primary (CUP), cervical lymph node metastasis, distant metastasis, residual/recurrent cancer and second primary tumors, often leading to alteration in management<sup>[2-5]</sup>. Furthermore, PET/CT as an imaging biomarker may provide an overall assessment of tumor aggressiveness with prognostic implications.

With PET/CT imaging, injected positron-emitting radionuclide <sup>18</sup>F-FDG is taken up by metabolically active cells, particularly cancers, in different concentrations depending on their relative metabolic rates. The radionuclide is initially transported into cells through glucose transporters with the same mechanism as for glucose but cannot be further metabolized. PET images are then created by detecting emissions from <sup>18</sup>F-FDG and reconstructed into

a three-dimensional image. CT images are also generated sequentially and coregistered with PET images using fusion software, enabling functional data obtained on PET to be coupled with anatomical CT images. Quantification of FDG uptake is simplified by measurement of the standardized uptake value (SUV), which represents the activity of <sup>18</sup>F-FDG measured over a certain interval after radionuclide injection and normalized to its dose and the patient's body weight<sup>[6]</sup>.

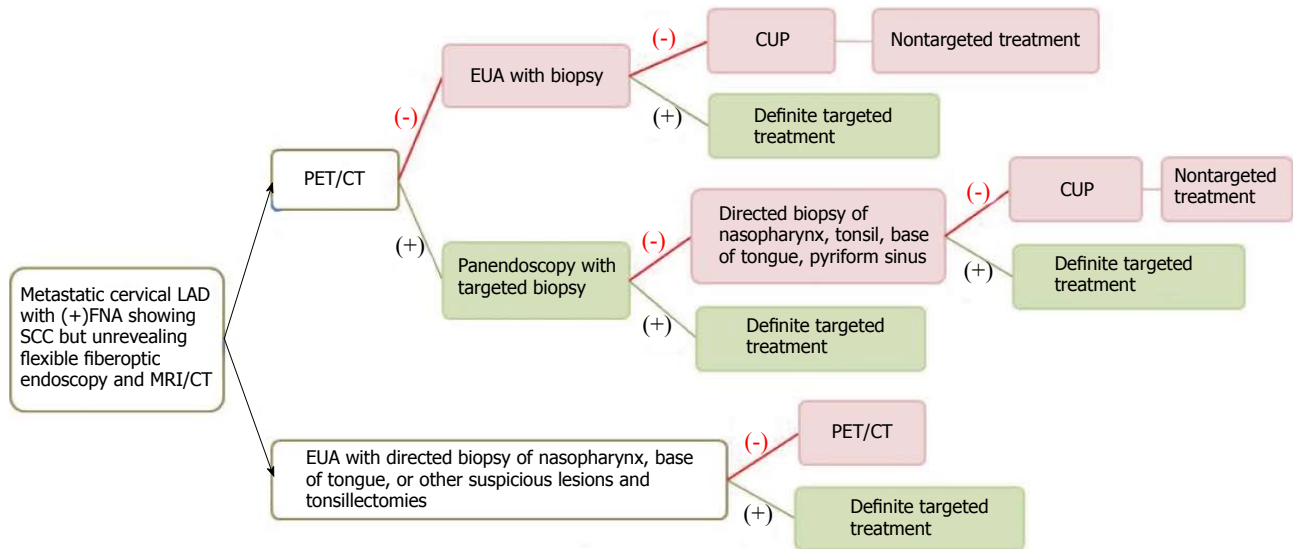
Since the implementation of PET/CT in head and neck oncology over a decade ago with its approval for reimbursement by the Centers for Medicare and Medicaid Services<sup>[7]</sup>, PET/CT has provided high diagnostic accuracy. PET/CT remains especially valuable in detection of regional and distant metastases and evaluation of treatment response. As more patients are cured of their cancers, acute and long-term complications of multimodality approaches including surgery, radiation, and chemotherapy may alter the anatomy and physiology of the head and neck, posing significant challenge in assessing treatment response and detecting residual or recurrent tumor by clinical evaluation and conventional imaging techniques such as CT or MRI. PET/CT may prove helpful with treatment strategy in these patients as well as those with metastatic cervical lymphadenopathy of unknown primary site despite thorough workup.

As new developments emerged leading to better understanding and use of PET/CT in head and neck oncology, this article addresses the roles of PET/CT in both pre- and post-treatment management of HNSCC. PET-derived parameters as prognostic indicators are also discussed.

## PRE-TREATMENT EVALUATION

Proper staging of the head and neck cancer, regional lymph nodes and detection of distant metastasis is critical for developing optimal treatment and determining prognosis. The tumor node metastasis (TNM) staging system of the American Joint Committee on Cancer, 7<sup>th</sup> edition is used to stage HNSCC<sup>[8]</sup>. The extent of the primary tumor (T stage) is site specific, while there is considerable overlap in classifying regional lymph node involvement (N0 to N3 stage) with the exception of thyroid and nasopharyngeal cancers. Metastasis outside head neck regions (*e.g.*, mediastinal and axillary lymph nodes) represents distant metastasis (M stage). Initial evaluation and staging include a combination of physical examination, imaging studies, and direct endoscopy with tissue biopsy or fine needle aspiration.

Imaging exams such as contrast-enhanced CT, MRI and PET/CT are important to assess the extent of local extension, involvement of lymph nodes, and presence of distant metastasis. Multiple studies suggest that PET/CT is superior to conventional imaging (CT or MRI) in initial staging and may alter management, especially when unexpected cervical lymph node or distant metastasis is discovered<sup>[2-5]</sup>. A multicenter prospective study found that PET/CT improved the TNM staging of the primary cancer



**Figure 1 Algorithm in diagnosis and management of carcinoma of unknown primary.** LAD: Lymphadenopathy; FNA: Fine-needle aspiration; SCC: Squamous cell carcinoma; MRI: Magnetic resonance imaging; PET/CT: Positron emission tomography/computed tomography; EUA: Examination under anesthesia; CUP: Carcinoma of unknown primary.

and subsequently altered the management in 13.7% of the patients, mainly due to the ability of PET/CT to detect metastatic or additional disease<sup>[9]</sup>. Furthermore, PET/CT can provide accurate tumor localization with precise metabolic tumor volumetric measurements, cervical lymph node staging, detection of metastases, and finding of synchronous second primary tumors that may alter radiation fields and doses for patients undergoing radiation therapy. The National Comprehensive Cancer Network issued an update in clinical practice guidelines in head and neck cancer and PET/CT imaging in 2013, recommending the use of PET/CT in initial staging of the oral cavity, oropharyngeal, hypopharyngeal, glottic, and supraglottic cancers for stage III-IV disease as well as mucosal melanoma and nasopharyngeal carcinoma (World Health Organization class 2-3 and N2-3 diseases)<sup>[10]</sup>.

The CT portion of the PET/CT examination provides the superior contrast and spatial resolution to detect malignant tumor using morphology (such as ill-defined, infiltrative, ulcerative features), enhancement, and interval growth. The PET portion demonstrates semiquantitative assessment with SUV of malignant tumor typically greater than 2.5-3.0<sup>[11]</sup>. Similarly, a maximum SUV greater than 2.5 is 100% sensitive and a maximum SUV greater than 5.5 is 100% specific for malignant lymphadenopathy<sup>[12]</sup>. However, SUV assessment should be used in conjunction with other clinical data given the overlap between a malignant lesion (high SUV) and a benign inflammatory uptake (low SUV).

Despite the proven efficacy of PET/CT, false negatives of PET/CT may be seen in patients with occult nodal metastases less than 5 mm or metastatic lymph nodes with necrosis<sup>[13-15]</sup>. Cancers with low metabolic activity or decreased FDG uptake may also limit PET/CT sensitivity. Therefore, PET/CT does not have the sensitivity to replace neck dissection and its usefulness is uncertain in evaluating patients with clinically negative (NO) neck<sup>[16]</sup>. In addition,

the utility of PET/CT in determining the resectability of head and neck cancers has not been fully explored to date; CT or MRI remains the mainstay in these patients<sup>[17]</sup>.

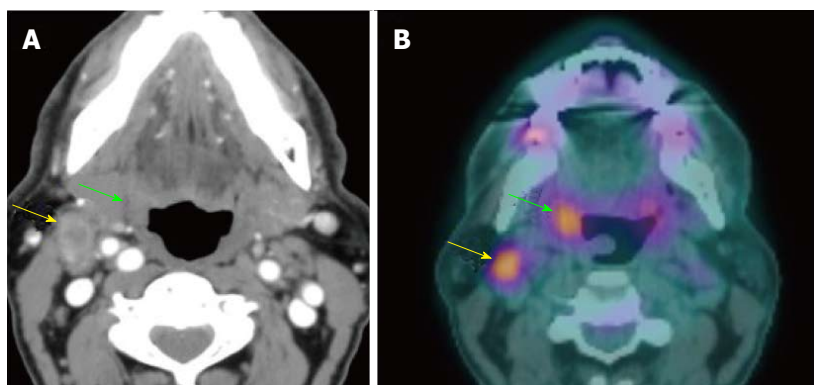
Additional limitations unique to PET/CT include imaging artifacts, lower osseous and soft tissue contrast/resolution (when performed without intravenous contrast) as compared to contrast-enhanced CT and MRI, respectively. PET typically has a resolution of 5 mm<sup>[11]</sup>, while unenhanced CT and MRI have submillimeter resolution<sup>[18]</sup>. The addition of intravenous contrast to CT and MR enhances visibility of the lesions and enable separation of the lesions from adjacent vessels. In this regard, contrast-enhanced CT and MRI are superior imaging modalities for evaluating T stage of HNSCC. There is currently no clear recommendation for routine use of PET/CT in initial T staging, as several studies demonstrated 5.5%-8.5% of patients had T staging upstaged on PET/CT<sup>[2,5]</sup>.

### CUP

Three to five percent of HNSCC patients present with metastatic cervical lymphadenopathy without definite primary site detected<sup>[2,19,20]</sup> despite a thorough history (often with nonspecific symptoms or no symptoms), combination of physical examination with office flexible fiberoptic endoscopy (for small submucosal lesion), or conventional contrast-enhanced CT/MRI performed. The work up algorithm to search for the primary tumor is shown in Figure 1, adapted from Tantiwongkosi *et al.*<sup>[21]</sup> and Schmalbach *et al.*<sup>[22]</sup>.

The choice of treatment depends on staging and histology<sup>[23]</sup>. With locoregionally advanced cervical lymphadenopathy, the goal of treatment is generally directed at cure; whereas, cervical lymphadenopathy from unknown primary originating below the clavicles may represent incurable disease with distant metastasis. Failure to identify the primary tumor leads to nontargeted treatment (bilateral tonsillectomies, bilateral neck dissection, radiation to cover





**Figure 2** Occult squamous cell carcinoma of the right palatine tonsil. The lesion (green arrow) was not appreciated on physical examination, flexible endoscopy and contrast-enhanced CT (A), but demonstrated hypermetabolic activity on PET/CT with maximal SUV: 3.5 (B). Biopsy directed by PET/CT revealed squamous cell carcinoma of the right palatine tonsil. The right level IIA lymphadenopathy also showed increased FDG uptake (yellow arrow). The patient remained disease free for 5 years after treatment. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value; FDG: 2-fluoro-2-deoxy-D-glucose.

the whole pharyngeal mucosa and neck)<sup>[24]</sup> resulting in increased complications, morbidity and mortality.

Several studies support the efficacy of PET/CT in detection of primary cancers in patients with CUP (Figure 2). PET/CT is able to identify the primary cancer in approximately 29% to 54% of cases (62%-93% sensitivity, 33%-93% specificity, 56%-89% positive predictive value and 25%-96% negative predictive value)<sup>[2,25-31]</sup>. A high detection rate of up to 54% can be achieved when the combination of CT, MRI, endoscopy under anesthesia and PET/CT are used. Generally, PET/CT is sensitive and superior for characterizing deep or metastatic cancers, while panendoscopy is more accurate for evaluating smaller or superficial mucosal lesions.

PET/CT is typically performed before panendoscopy to guide the selection of biopsy sites and to avoid erroneous interpretation due to high false positivity (as much as 50%)<sup>[29]</sup> of FDG uptake at sites manipulated during endoscopy. It is still uncertain when PET/CT should be performed after biopsy; therefore, if carcinoma of unknown primary is suspected, it is best to obtain PET/CT prior to endoscopy and biopsy/tonsillectomy. Over 90% of the unknown primary cancers are squamous cell carcinoma found in Waldeyer's ring (lymphoid tissue of the nasopharynx, palatine tonsils or base of tongue)<sup>[22,32]</sup>. Due to variable negative predictive value (25%-96%) of PET/CT, panendoscopy with directed biopsies and bilateral tonsillectomies are considered when PET/CT yields negative result<sup>[3]</sup>. Pattani *et al*<sup>[33]</sup> suggest careful selection of patients for panendoscopy after a negative PET/CT since primary cancer was only found in 9% of CUP cases (1 out of 11 patients).

### Second primary malignancy

HNSCC patients are at increased risk for the development of second primary malignancy (SPM), with synchronous SPM occurring within 6 mo of the index primary cancer or metachronous SPM diagnosed > 6 mo of the index cancer. Approximately 1.4% to 18% of head neck cancer patients have SPMs<sup>[34]</sup>, especially when the index cancers are laryngeal carcinomas. The risk for SPMs remains elevated for at least 10 years<sup>[35]</sup> and are mostly found in the head and neck, lung and esophagus<sup>[36]</sup> with the vast majority being squamous cell carcinoma<sup>[37]</sup>. Since SPM is the second leading cause of non-HNSCC death<sup>[38]</sup>, early detection and

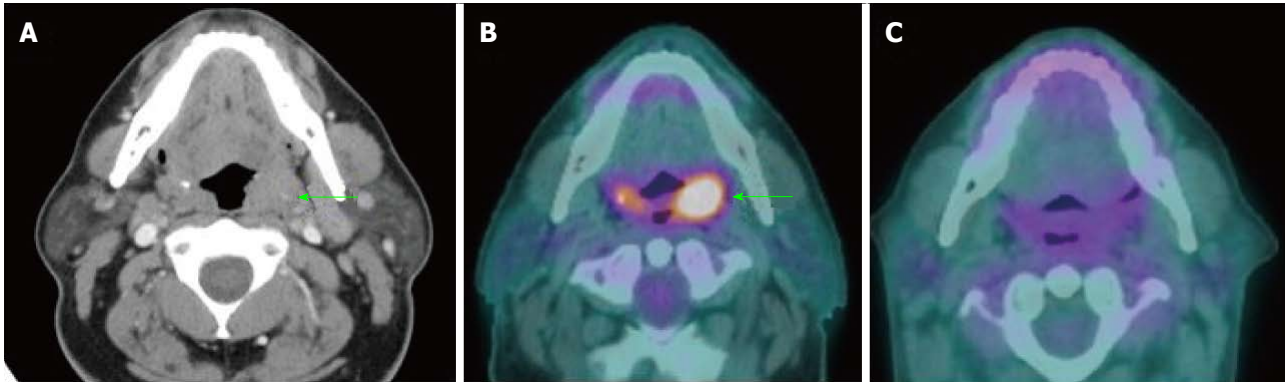
treatment of SPM may alter management and improve patient survival<sup>[34]</sup>. A meta-analysis revealed 87.5% sensitivity and 95% specificity of PET/CT in detection of SPM or distant metastasis, while a negative PET/CT study does not completely exclude the presence of SPM<sup>[39]</sup>. Given the low incidence of synchronous SPMs at initial evaluation of HNSCC patient, several research studies question the cost-effectiveness of panendoscopy<sup>[8]</sup>. Therefore, PET/CT may complement or replace panendoscopy in detecting synchronous SPMs. For patients with localized disease (stage I or II) being treated with either primary surgery or definitive chemoradiation therapy, a thorough physical examination combined with PET/CT may be adequate, obviating the need for panendoscopy unless tissue biopsy under general anesthesia is deemed necessary.

## POST-TREATMENT EVALUATION

### Therapy response assessment and residual tumor detection

Localized disease (stage I or II) comprising approximately 30% to 40% of HNSCC is generally treated with either primary surgery or definitive radiation therapy<sup>[40]</sup>. Locoregionally advanced disease (stage III, IVA, or IVB) associated with high risk of local recurrence and distant metastasis requires a multidisciplinary approach, given the complexity and complications of combined treatment modality that includes surgery, radiation therapy and chemotherapy<sup>[41]</sup>. In select cases, radical concurrent chemoradiation can be used as a definite therapy in preference to surgery to achieve similar cure rates with preserved functional outcome and less morbidity<sup>[42]</sup>.

For patients with locoregionally advanced disease who have undergone treatment, management of residual abnormalities can pose significant challenge. Both surgery and radiation may cause inflammation, fibrosis and distortion of the head and neck anatomy leading to difficulties of interpretation with conventional imaging, especially differentiating between residual cancer and complete response<sup>[43,44]</sup>. Inaccurate post-treatment assessment may result in delayed or unnecessary treatment and increased mortality and morbidity. In this regard, multiple studies have shown that PET/CT is superior to conventional anatomic imaging in assessment of tumor response and detection of residual tumor<sup>[3,45-47]</sup>.



**Figure 3 Complete treatment response at primary tumor site.** Squamous cell carcinoma of the left palatine tonsil (arrows) was seen on contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 11.6. The tumor was no longer hypermetabolic on PET/CT with maximal SUV: 2.8 at 10 wk after treatment (C). PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

The sensitivity, specificity, positive predictive value, and negative predictive value of PET/CT for detection of residual primary tumor have been reported as high as 94%, 82%, 75% and 95%, respectively<sup>[3]</sup>. It is important to note the very high negative predictive value of PET/CT: A negative study highly suggests absence of viable residual disease in both primary site and neck (Figures 3 and 4). The low positive predictive value is due to treatment-related FDG-avid inflammation or infection. A positive PET/CT study in the post-treatment phase needs careful correlation with clinical information and corresponding CT/MRI findings<sup>[48]</sup>. It is suggested that PET/CT should be performed no sooner than 2 mo after completion of treatment to evaluate for residual tumor while avoiding false positive results and to establish a baseline; however, it may be performed sooner if there is clinically suspected recurrent disease<sup>[49]</sup>. We generally recommend performing PET/CT around 3 mo after completion of treatment at our institution (Figure 5).

#### Long-term surveillance and recurrent tumor identification

Patients with complete treatment response, as documented clinically and by structural imaging (CT, MRI, and PET/CT), are generally observed. With advanced chemoradiation therapy, and improving surgical techniques, many patients may have distant metastasis as the first and only sign of treatment failure. PET/CT as a surveillance tool serves the purpose of detecting early recurrent disease, assessing for a metachronous second primary tumor, and excluding interval development of distant metastases. Close interval follow up in the first two to four years following treatment is necessary since 80% to 90% of all recurrences occur within this timeframe<sup>[50,51]</sup>, while the risk of SPM is higher than recurrence beyond three years<sup>[52,53]</sup>.

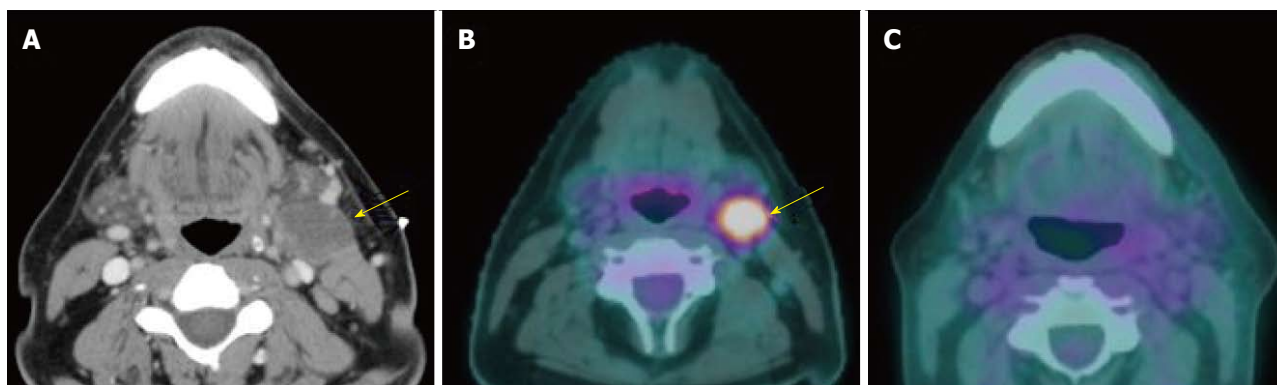
PET/CT has 93%-100% sensitivity and 63%-94% specificity in detection of recurrent tumor in both primary site and the neck, respectively<sup>[48,54,55]</sup> (Figure 6). The negative predictive value of a single PET/CT and double PET/CT (obtained within 6-mo period) are 91% and

98%, respectively. Negative results of two consecutive PET/CT studies could potentially eliminate the need for routine post-treatment imaging if there is no clinical suspicion of tumor recurrence<sup>[56]</sup>. In addition, there are no differences in survival between PET/CT detected and clinically detected recurrence<sup>[57]</sup>. Although there is an appreciable radiation dose and lifetime cancer risk associated with PET/CT, the use of this examination is warranted when utilized in the appropriate clinical setting<sup>[58]</sup>.

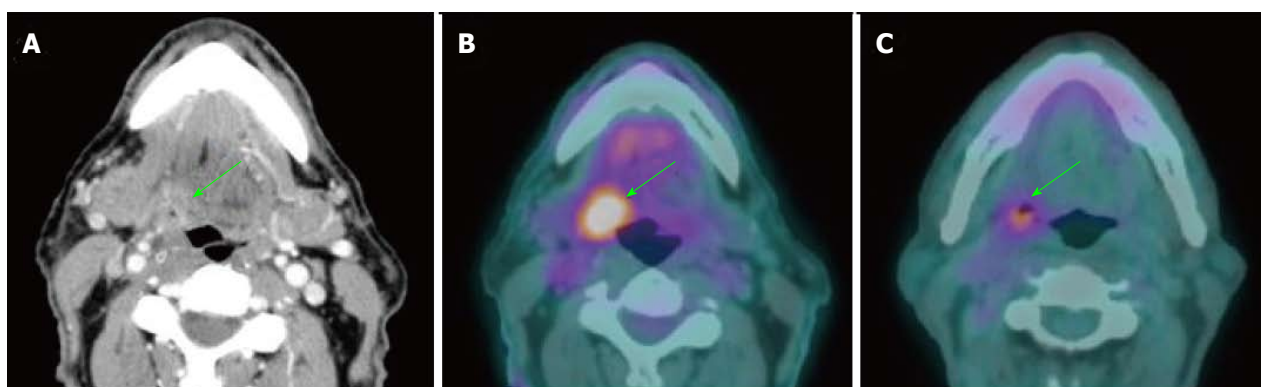
Metachronous second primary tumor may occur after 6 mo of the index primary tumor with 2.8% annual rate<sup>[59]</sup>. The incidence of distant metastasis following definitive treatment is 9% with the risk increased in patients with locally advanced stages<sup>[59,60]</sup> (Figure 7). Overall 17.9% of HNSCC patients develop second primary cancers or distant metastasis, especially in patients with recurrent disease<sup>[39,60]</sup>. The identification of distant metastatic lesions at the time of restaging recurrent tumors may obviate aggressive surgery while focusing on palliative chemoradiation options<sup>[60]</sup>. Therefore, PET/CT has strong utility in detecting second primary tumors or distant metastases with high sensitivity and specificity<sup>[39]</sup>.

#### PROGNOSIS

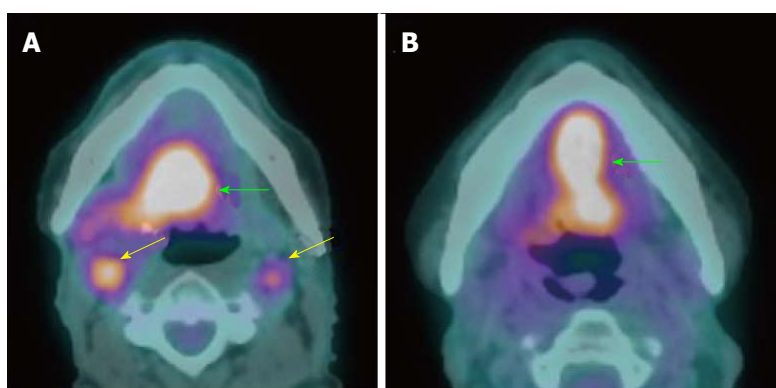
As an invaluable tool in staging cancers of the head and neck, PET/CT imaging provides metabolic and functional data that may serve as quantifiable prognostic factors. The PET-derived parameters, SUV and its various forms, have been shown correlating well with glucose metabolism rate in various cancers, including HNSCC<sup>[61]</sup>, and are useful in predicting tumor aggressiveness and long-term survival of patients<sup>[62]</sup>. They have also been used in selecting treatment modality and personalizing treatments. In a study comparing resectable, advanced HNSCC patients treated with surgery followed by chemoradiation therapy vs those with chemoradiation and salvage surgery, Roh *et al.*<sup>[63]</sup> found that patients with high FDG uptake and treated with surgery first had better disease-free survival (DFS). In addition, Inokuchi *et al.*<sup>[64]</sup> found that high FDG uptake



**Figure 4 Complete response of metastatic cervical lymph node.** Left level IIa metastatic lymphadenopathy (arrows) from the same patient in Figure 3 with squamous cell carcinoma of the left palatine tonsil was identified on both contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 12.1. After treatment, the lymph node was no longer hypermetabolic at 10-wk PET/CT (C) with maximal SUV: 2.5, representing complete response. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.



**Figure 5 Residual primary tumor.** Squamous cell carcinoma of the right base of tongue (arrows) was identified on contrast-enhanced CT (A) and pre-treatment PET/CT (B) with maximal SUV: 10.2. The tumor remained FDG-avid on PET/CT (C) with maximal SUV: 4.8 at 12 wk after treatment, representing residual disease. PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.



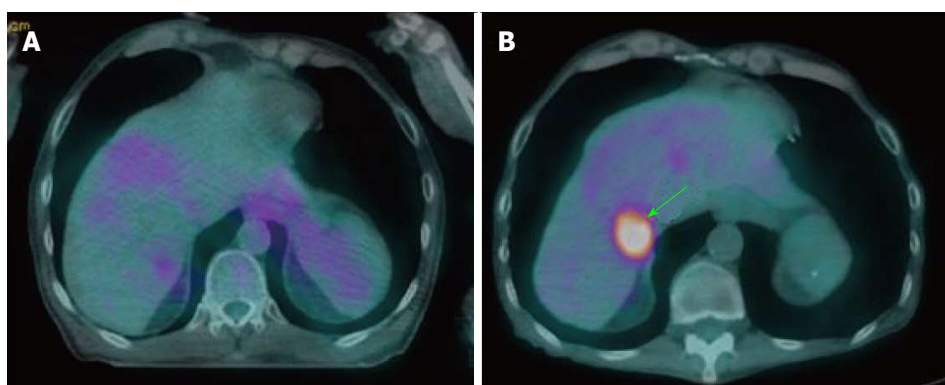
**Figure 6 Recurrent primary tumor detected by positron-emission tomography/computed tomography.** Squamous cell carcinoma of the base of tongue (green arrows) with bilateral level IIa metastatic lymphadenopathy (yellow arrows) was identified on pre-treatment PET/CT with maximal SUV: 13.2 (A). The tumor remained intensely hypermetabolic on PET/CT with maximal SUV: 6 at 13 mo after treatment (B). PET/CT: Positron-emission tomography/computed tomography; SUV: Standardized uptake value.

in HNSCC patients treated with definitive chemoradiation predicted a decrease DFS, nodal progression-free survival, and distant metastasis-free survival. The investigators also suggested using pre-treatment FDG uptake of cervical lymph nodes to select patients for planned neck dissection. They found that patients with high FDG uptake and treated with planned neck dissection had better nodal progression-free survival.

Metabolic tumor volume (MTV), a SUV-based parameter representing the tumor volume that has SUV above a

specific threshold, has been suggested in the literature as a robust measure in predicting treatment outcomes. For example, clinical trials are underway to explore if patients with human papillomavirus (HPV)-associated oropharyngeal cancers, which are known to have better prognosis than those not associated with HPV, would have similar cancer control with less intensified and therefore less toxic treatment options<sup>[65]</sup>. It has been suggested that this patient population could be stratified further based on MTV. Patients with more aggressive HPV-related HNSCC, as suggested





**Figure 7 Failure of treatment due to distant metastasis.** A: Pre-treatment PET/CT of the patient with squamous cell carcinoma of the base of tongue in Figure 6 did not reveal any increased FDG uptake in the liver; B: PET/CT performed at 13 mo after treatment showed new hepatic metastasis (arrow), representing treatment failure. PET/CT: Positron-emission tomography/computed tomography; FDG: 2-fluoro-2-deoxy-D-glucose.

by the increased MTV, had significantly poorer outcomes in one study conducted by Tang *et al*<sup>[66]</sup>. In addition to MTV, total lesion glycolysis (TLG) was first introduced by Larson *et al*<sup>[67]</sup>. It is the product of mean SUV and MTV, combining the volumetric and metabolic information of PET/CT to evaluate treatment response. Recent studies demonstrate the usefulness of TLG for evaluating head and neck cancers, with high TLG correlating to increased risk of adverse events or death<sup>[62,68,69]</sup>.

The PET-derived parameters are also currently used in combination with other prognostic factors. N-stage, T-stage, and pre-treatment SUV of lymph node when used in combination have been shown better at predicting distant metastasis-free survival than individual factors<sup>[70]</sup>. Recently, there has been increased interest in identifying prognostic molecular biomarkers. Moeller *et al*<sup>[71]</sup> incorporated HPV status in addition to post-treatment FDG uptake in their mortality risk assessment. In addition conventional parameters (SUV, MTV, TLG, tumor volume, and diameter) in PET/CT, textural parameters to assess tumor heterogeneity such as coefficient of variation, skewness, and kurtosis may also provide prognostic information but are not fully explored in head and neck oncology.

## CONCLUSION

With wide-spread availability and use, PET/CT imaging maintains an important role in head and neck oncology. In the pre-treatment phase, PET/CT is valuable in the evaluation of patients with carcinoma of unknown primary origin before panendoscopy and biopsy, detection of synchronous second primary tumor, staging of cervical lymph node metastasis and assessment for distant metastases. In the post-treatment phase, PET/CT is helpful in evaluating treatment response, detecting residual or recurrent tumor and excluding distant metastases. Prognostic factors derived from PET/CT metabolic and functional data are useful in predicting tumor aggressiveness with implication on patient's survivability, and facilitate selection of treatment modality and personalized treatment options.

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## Embryology of the nose: The evo-devo concept

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### Abstract

Aim was to gather relevant knowledge in evolution and development to find a rational explanation for the intricate and elaborate anatomy of the nose. According

to classic embryology, the philtrum of the upper lip, nasal dorsum, septum and primary palate develop from the intermaxillary process, and the lateral walls of the nasal pyramid from the lateral nasal processes. The palatal shelves, which are outgrowths of the maxillary processes, form the secondary palate. The median nasal septum develops inferiorly from the roof of the nasal cavity. These valuable embryologic data do not explain the complex intricacy of the many anatomical structures comprising the nose. The evo-devo theory offers a rational explanation to this complex anatomy. Phylogenically, the nose develops as an olfactory organ in fish before becoming respiratory in tetrapods. During development, infolding of the olfactory placodes occurs, bringing the medial olfactory processes to form the septolateral cartilage while the lateral olfactory processes form the alar cartilages. The olfactory fascia units these cartilages to the olfactory mucosa, that stays separated from brain by the cartilaginous olfactory capsule (the ethmoid bone forerunner). Phylogenically, the respiratory nose develops between mouth and olfactory nose by rearrangement of the dermal bones of the secondary palate, which appears in early tetrapods. During development, the palatal shelves develop into the palatine processes of the maxillary bones, and with the vomer, palatine, pterygoid and inferior turbinate bones form the walls of the nasal cavity after regression of the transverse lamina. Applying the evolutionary developmental biology (evo-devo) discipline on our present knowledge of development, anatomy and physiology of the nose, significantly expands and places this knowledge in proper perspective. The clinicopathologies of nasal polyposis, for example, occurs specifically in the ethmoid labyrinth or, woodworker's adenocarcinomas, occurring only in the olfactory cleft can now be explained by employing the evo-devo approach. A full understanding of the evo-devo discipline, as it pertains to head and neck anatomy, has profound implications to the otolaryngologist empowering his skills and abilities, and ultimately translating in improving surgical outcomes and maximizing patient care.

**Key words:** Nose; Evo-devo; Embryology; Development; Anatomy

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**Core tip:** The intricate and elaborate anatomy of the human nose can be best understood by gathering knowledge in evolution and development. Phylogenically and ontogenically, the nose results from two distinct entities: The olfactory and respiratory organ. In vertebrates, the olfactory placodes give rise to the fibrocartilaginous nose made of alar and septolateral cartilages, olfactory mucosa and the olfactory fascia; the respiratory nose develops by evolutionary remodeling of the palatal bones under the olfactory nose. In humans, the mammalian olfactory chambers are transformed into olfactory clefts and lateral masses of the ethmoid, and the transverse lamina separating the olfactory and respiratory noses has disappeared.

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## INTRODUCTION

Embryology of the nose is poorly described in classical textbooks, in which full of gaps and controversies are found about the different embryologic origins of the nasal bones, cartilages and soft tissue envelopes.

Embryology of the face is, in fact, a very difficult topic, which becomes more understandable in the evo-devo concept<sup>[1]</sup>. The evo-devo theory links the evolution from simple species to complex human development<sup>[2,3]</sup>.

## CLASSIC EMBRYOLOGY

In classic embryology textbooks<sup>[4,5]</sup>, the first 28 day of gestational life the face develops from five swellings: The paired maxillary and mandibular processes and the unpaired frontonasal process.

During the fifth week, the nasal placodes (*i.e.*, nasal discs and nasal plates) develop as a result of ectodermal thickenings and can be observed on the frontonasal process.

In the sixth week, infolding of the ectoderm at the epicenter of these nasal placodes initiates the formation of an oval pit (see below description of nasal pits) resulting in the division of the raised edge of each placode into medial and lateral nasal processes (Figure 1A).

During the sixth week, the medial nasal processes fuse to form the intermaxillary process (Figure 1B), which is the primordia of the septum and bridge of the nose (Figure 1C).

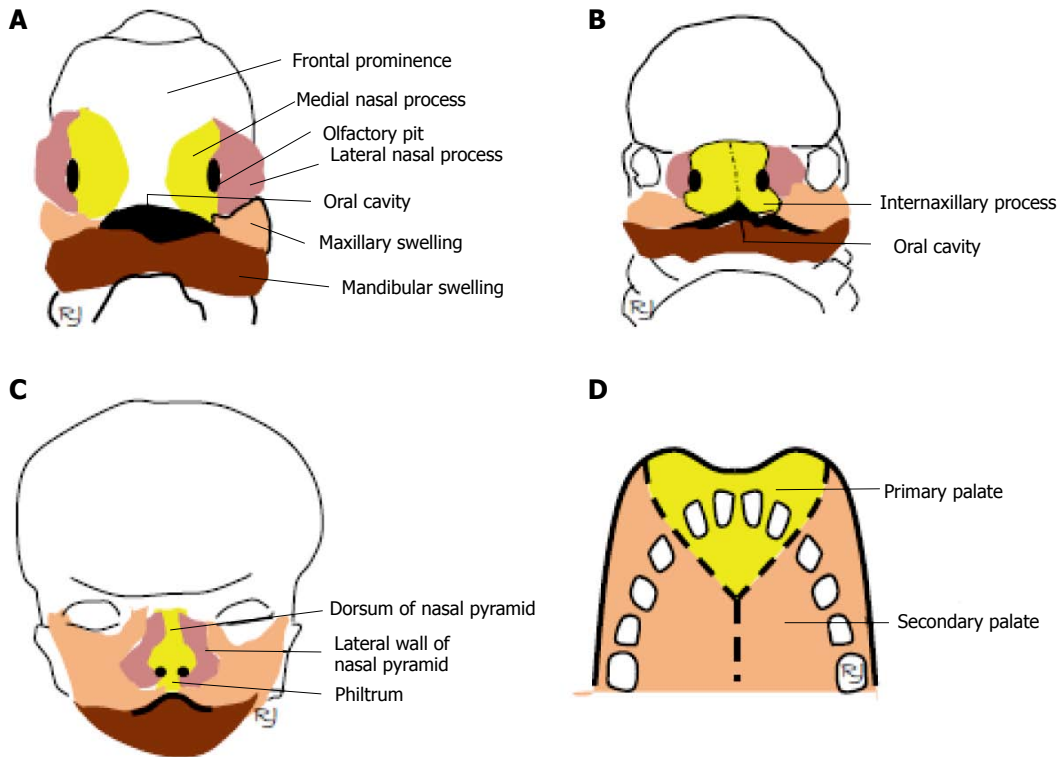
By the end of the seventh week, there is a lateral and inferior expansion of the medial nasal processes at their inferior tips before fusing to form the anterior roof of the oral cavity (Figure 1B). As the poles of the maxillary

swellings continue to develop they come into contact with the intermaxillary process where they fuse with each other. On the superior labial region, the intermaxillary process develops into the philtrum (Figure 1C). Formation of the nasal passages result as the nasal pits deepen penetrating its underlying mesenchyme during week 6 of development. Mesenchyme is loosely organized cells derived from mesodermal embryonic tissue that develops into connective and skeletal tissues. An ectodermally enlarged nasal sac is formed during the last days of the sixth week by the fusion of the deep endings of the nasal pits, which are topographically located superoposterior to the intermaxillary process. During the last days of the sixth week and the first few days of the seventh week, a proliferation of cells occurs at the posterior wall and floor of the nasal sac forming a thickened plate-like fin of ectoderm origin essentially isolating the oral cavity from the nasal sac but still maintaining an epithelial continuity between the regions. This "keel" structure is now referred to as the nasal fin. The nasal sac enlarges as a result of vacuoles developing within the nasal fin and then it fuses with the sac. The nasal fin begins to attenuate to a thin membrane named the oronasal membrane, which demarcates the oral cavity from the nasal sac. Towards the end of the seventh week, the oronasal membrane obliterates creating the opening of the primitive choana. Formation of the nasal cavity floor, or primary palate, occurs by the backward growing of the intermaxillary process.

Throughout the eighth and ninth week, the development of the definitive and secondary palate occurs. The main portion of the definitive palate develops by two shelf-like outgrowths from the maxillary processes. These two thin medial extension outgrowths are called the palatine shelves, which appear during the sixth week of development. While these shelves are directed in a downward manner on either side of the tongue, it is during the ninth week where these shelves rotate and ascend rapidly attaining a horizontal position above the tongue. Fusion of the primary palate and the palatine shelves (along the midline) assists in the formation of the secondary palate (Figure 1D). The order of fusion first begins at the ventral region of the palatine shelves before proceeding dorsally.

Mesenchymal condensations occurs when previously dispersed mesenchymal cells come together to differentiate into a single tissue type and is considered the critical transitional stage that precedes cartilage formation during embryonic development<sup>[6]</sup>. When these mesenchymal cell condensations occur in the ventral region of the secondary palate endochondral ossification ensues to achieve the formation the hard palate. At the dorsal region of the secondary palate, myogenic mesenchymal cells come together to form the muscular layer of the soft palate.

During the formation of the secondary palate, there is a proliferation of cells from the mesoderm and ectoderm region of the medial nasal and frontonasal processes that help form the nasal septum along its midline. As a result,



**Figure 1 Classic embryology of the nose.** A: Formation of the medial and lateral processes of the nose on the raised rim of the olfactory placodes; B: Formation of the intermaxillary process by fusion of the medial nasal processes; C: The intermaxillary process is seen as the primordium of the bridge and septum of the nose and the lateral nasal processes as the primordia of the lateral walls of the nasal pyramid; D: The intermaxillary process is seen as the primordium of the primary palate.

the two nasal passages of the nasal cavity have now been established, communicating with the pharynx located posterior to the secondary palate. This communicating portal is now termed the definitive choana.

According to classical concept, the philtrum of upper lip, the nasal dorsum, septum, and primary palate originate from the development of the intermaxillary process, whereas the lateral walls of the nasal pyramid develop from the lateral nasal processes (Figure 1A-C).

Two major questions which can be addressed to this classic description are why the nose is formed by such a complex intricacy of different anatomical structures, and why the origin and formation of these are not found in the classic embryological description. Examining the formation of the nose in the evolution of species may, actually, give clues to the answers<sup>[1]</sup>.

## THE NOSE IN EVOLUTION

The first vertebrates were jawless fish named agnathans who are classified in the phylum Chordata and sub-phylum Vertebrata and whose fossil ancestors can be traced back to the Cambrian period around 500 million years ago.

Living agnathans display a primitive or rudimentary olfactory organ. This organ consists of a median blind duct that communicates with the environment by means of an external nostril, but there is no posterior opening into the pharynx. The olfactory mucosa lies at the blind end in a chamber of the anterior braincase and is connected

to the brain through olfactory filaments.

Lungfish played a critical role when organisms shifted from an aquatic mode of life to a terrestrial setting representing one of the most dynamic major adaptive shifts during the course of evolution. It was von Bischoff who first described the presence of choanae in lungfishes in 1840 as he considered these organisms excellent models for examining respiratory morphology of early tetrapods (*i.e.*, a four-footed organism) as they appeared intermediate in morphology between amphibians and fishes<sup>[7]</sup>.

The anatomy of lungfish shows that the olfactory passages open posteriorly in the oral region and into the respiratory portion of the organism. These posterior communicating pathways, however, were in all likelihood not used for the purposes of respiration but rather to increase the power of olfaction. The buccopharyngeal pump passes forceful currents of water between the nasal and oral regions as these fishes perform suction feeding and may perhaps serve as the mechanism by which they increase their olfactory sense.

When the first tetrapods arrived, which includes all vertebrates higher than fishes (*e.g.*, amphibians, reptiles, etc.) one can appreciate the remarkable morphological diversity seen in body form of later tetrapods allowing them to utilized an equally broad array of terrestrial ecological niches.

In amphibians, their ability to smell is derived from the superficial oscillatory movements of their buccal floor in order to establish intimate contact to their immediate



surroundings be it a terrestrial or aquatic medium. The nasal respiratory function, however, is secondary as skin respiration is predominant. Amphibians, as a result, recruited the olfactory organ, as an intermittent tool for its respiratory apparatus.

Thus, with the amphibians the primary olfactory nose has evolved towards a nose devoted to olfaction and respiration. The amphibian nose communicates externally *via* the external naris and connects with the oral cavity posteriorly to the primary palate by the internal naris. The nasal cavity of amphibians is lined by olfactory epithelium with the exception of its ventro-lateral wall region.

Rocek and Vesely<sup>[8]</sup> reported on the larval development of the South American toad (*i.e.*, *Pipa pipa*) showing that the anterior skeletal portion of the amphibian snout is already formed by the following cartilaginous structures. First, a cartilaginous septolateral unit whose outgrowths occurs laterally from a "cartilago obliqua" emanating from the "planum internasale"; and two, the distinct formation of a pair of "cartilago alaris". The latter two assemblies appear to be persistent and continuous with the posterior end of the cartilaginous skeleton thereby essentially protecting its olfactory chambers.

In the early fully terrestrial tetrapods, a transverse sheet of dermal bones has developed inferior to the braincase specifically in the roof of the mouth posterior to the internal naris and primary palate (Figure 2A). This dermal portion of the secondary palate consists of four paired bones: The vomer, palatine, ectopterygoid and pterygoid bones, which lie as a flat sheet between the two maxillary bones. Each internal nostril is bounded by the premaxilla of the primary palate anteriorly, the maxilla laterally, the vomer medially, and the palatine bone posteriorly<sup>[9]</sup>. This secondary hard palate configuration was probably the precursor in allowing permanent breathing to travel through the primary nose as inspiratory air would travel through a non-collapsible oral cavity before going to the trachea.

The reptilian vertebrate representative, the crocodilians, exhibit many of the above characteristics as does the mammalian condition, which also shares this bauplan suggesting convergent evolution taking place. Tracking the phylogenetic history of the crocodilian, which spans over two-hundred million years, one can observe its akinetic skull features including the formation of its secondary nose.

Crocodilian evolution has been characterized by the gradual constitution of an akinetic skull and the formation of a secondary nose. Simultaneously with many modifications and reconfigurations of its palatal bones a secondary bony nasal passageway progressively develops, permitting inspiratory airflow to enter through its external naris and exit posteriorly through the internal naris or choana, which gradually shifted posteriorly until they were completely contained by the pterygoid bones.

Current hypotheses state that the evolution of feeding behaviors may have been the driver for the structural modifications of the crocodilian rostrum: The displacement and remodeling of the bones configuring

the crocodilian secondary palate, which may initially have occurred reinforce the snout and skull instead of providing a physical bony partition between the oral and nasal cavities. As a result, the secondary nose could be regarded as an incidental byproduct of the masticatory mechanical forces between the dermal bones of the secondary palate and the skull base. The vacuities that were then occupied with air from the primary nose, were finally recruited to provide for the physiological function of breathing.

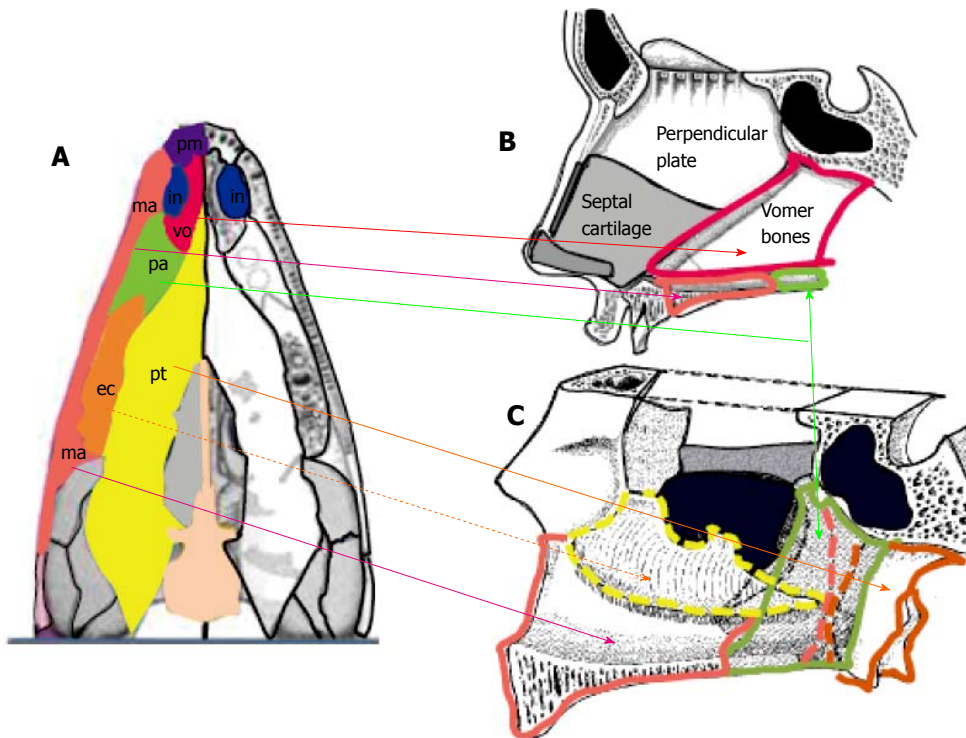
The fundamental configuration of the nasal fossa is a highly conserved region. As one tracks the evolution from crocodilian to the mammalian skull, very little change can be observed in this region with its persistent and constant morphology seen in a great majority of mammalian groups.

In mammalian groups, the palate separates the nasal and oral cavities: Primary, secondary, and soft palate. The primary internal naris remains as a vestigial opening, *i.e.*, the anterior palatine canal, which is topographically positioned between primary and secondary palate.

The primary nose fully opens behind a virtual, coronal plane through the anterior palatine canal, into both the respiratory and olfactory noses. Respiratory and olfactory noses are separated from each other by the transverse lamina, a thin, bony axial structure. Thus, the respiratory nose appears as two paramedian, long axial channels walled in on the inferior, lateral and medial sides by the reconfiguration of the primary palatal bones (vomer, palatine, pterygoid, and inferior turbinate bones) between the two maxillary bones and their palatine processes, and partitioned from the olfactory nose through the transverse lamina. The olfactory nose is completely embedded in the anterior cranial base, that is, the ethmoid bone<sup>[10]</sup>.

The living primates (which include humans) are taxonomically classified in two suborders: *Strepsirrhini* and *Haplorhini*, the latter group includes our human ancestors<sup>[11]</sup>. Through the course of primate evolution, profound changes in the nasal fossa allow one to differentiate the haplorhines from strepsirrhines and all other mammals.

The word haplorhine means "dry nose" whereas strepsirrhine means "wet nose". As a result, strepsirrhine primates exhibit wet noses similarly to dogs and cats. Haplorhine primates have a fused frontal bone suture as well as a fused mandibular symphysis. While both haplorhine and strepsirrhine primates have a complete orbital ring of bone, only the haplorhine exhibit a complete bony enclosure posteriorly separating the periorbital contents from the temporalis muscle as it traverses through the infratemporal fossa on its way to attaching the coronoid process of the mandible<sup>[12]</sup>. The superior portion of the haplorhine nasal fossa is constricted by the orbital cones, which come about from the combined effect of orbital convergence and orbital frontation. Orbital convergence refers to the extent to which the orbital opening faces anteriorly improving stereoscopic vision that include the element of depth perception<sup>[13]</sup>.



**Figure 2** Evo-devo origin of the respiratory nose. A: The palatal bones in the tetrapods (in: Internal naris; pm: Premaxilla; ma: Maxilla; vo: Vomer; pa: Palatine; pt: Pterygoid; ec: Ectopterygoid); B: Anatomy of the nasal septum in human (perpendicular plate of ethmoid and septal cartilage form the septum of the olfactory nose); C: Anatomy of the nasal lateral wall in human (ethmoid bone removed).

Orbital frontation refers to what extent the superior and inferior margins are to the plane of the orbital opening so that more “frontated” organisms tend to view from the orbital socket more horizontally rather than superiorly<sup>[13]</sup>. In most haplorhines, there is a considerable reduction of their snout length when compared to strepsirrhines. There is one more important anatomical distinction between these two subOrders of primates that resides within the nasal fossa and that is an absence of a transverse lamina in haplorhines, which translates in them not having a bony partition separating the respiratory and olfactory region within the nasal cavity proper.

Strepsirrhines, on the other hand, exhibit a partitioned respiratory and olfactory region within the nasal cavity by possessing a transverse lamina coupled by their complex ethmoturbinate system. But while the order of *Primates* is classified within the microsmatic group of mammals (this group shifted from an olfactory mode of existence to a visual reliance of subsistence), carnivores (classified as macrosmatic meaning their whole existence is based on smell) have the most complex and elaborate turbinate system in all of mammalia. Possession of four or more ethmoturbinates is found in strepsirrhines in contrast to the reported range of one to three pairs found in haplorhines. In addition, the haplorhine ethmoturbinates appear more reduced in size and are less intricately scrolled. Moreover, it appears that the tendency is toward a decrease and reconstitution of ethmoturbinate structural reorganization across the different haplorhine primate taxa.

While traditionally primates have been classified as microsmatic as mentioned above, other authors describe primates undergoing a reduction in their olfactory prowess. In 1970, Cartmill<sup>[14]</sup> proposed the visual predation hypothesis of primate origins, which may help to explain this reduction. The visual predation hypothesis explains the adaptive significance of a variety of skeletal features that characterize modern primates as they transitioned to an arboreal mode of life<sup>[14]</sup>. The change in orbital orientation enhanced stereoscopic vision, which was essential in the manually effective capture of food in a three dimensional setting of arboreal life but it may have initiated a cascade of morphological events to occur elsewhere in the craniofacial region particularly in the nasal area. As bony orbital modification and re-orientation occurred in these primates there was a concurrent reduction and re-arrangement of ethmoturbinate complexity to a more simple inferior-to-superior re-organization and, finally, a partial but not complete loss of olfactory mucosal area.

In humans, the evolutionary pattern of the nasal region as seen in the haplorhine non-human primates is continued in our species. The human nose appears as one organ with no morphological evidence distinguishing between the respiratory and olfactory noses. Studies of inspiratory airflow patterns in the nasal cavity, however, show the path of air flowing along the nasal floor and lower medial portion of the cavity (comparable to the inferior and middle meatus region) mimicking the respiratory pathway of an organism that possesses a transverse lamina<sup>[15]</sup>.

The olfactory mucosa has been mapped to a small surface immediately inferior to the cribriform plate and to

the upper portions of the nasal septum<sup>[16]</sup>. The reduction of the olfactory mucosa seen in humans is strongly associated with the adaptive shift of a quadropedal locomotion gait to bipedality. *Homo erectus* is considered the first committed biped in our evolutionary history, which required the repositioning of the foramen magnum (a more anterior inferior placement) in order to balance the skull over the vertebral column and accommodate erect posture. These morphological changes had the effect of changing the orientation of the cribiform plate from a vertical to a more horizontal manner. This resulted in a conversion of the mammalian olfactory nose into the human ethmoid complex, partitioned on each side in two clinically relevant compartments: The olfactory cleft medially and the ethmoid labyrinth laterally (in which the olfactory mucosa has disappeared).

Despite the evolutionary trend towards regression in the sense of smell, the embryologic development of the human nose is best understood when considering its olfactory origin, the subsequent respiratory reorganization, and the constriction of the ethmoid bone imposed by the orbital cones.

## THE EVOLUTION DEVELOPMENT BIOLOGY (EVO-DEVO) OF THE HUMAN NOSE

The evo-devo approach, in comparison to the classical concept, explains why the nose is formed by a complex intricacy of different anatomical structures, and offers a rational explanation to this question<sup>[1]</sup> (the development of the paranasal sinuses, which occurs after birth, is not mentioned in this paper).

Phylogenically, the nose is exclusively an olfactory organ in fish, and the respiratory nose develops in crocodilians. Ontogenically, the growth and development of the olfactory nose precedes the development of the respiratory nose.

### Development of the olfactory nose

**Development of the olfactory capsule:** The first embryologic evidences of the nose appear during the fourth week under the mask of two olfactory placodes on the frontal process of the embryo. Simultaneously, the corresponding wall of the brain undergoes rapid mitotic activity with a small bulge becoming visible and demarcating the olfactory region. Histologically, the future olfactory bulb and structures called the amygdaloid body and hippocampal formation are found in the forebrain<sup>[17]</sup>.

Approximately, at five weeks Carnegie stage (CS) 15, (Carnegie staging is a method for dating embryos), the appearance of an olfactory pit is observed. This occurs with the invagination of the central portion of the placode. The invagination is in the direction of the adjacent brain where an olfactory elevation appears. Crest cells begin to gather together forming cords or filaments that travel within the mesenchyme.

At CS 16, the future olfactory bulb and the olfactory tubercle appear as elevations along the olfactory area of the cerebral hemispheres, or telencephalon. Between these two telencephalic elevated regions and the olfactory pit there is a significant and concentrated area of mesenchyme through which crest cells and olfactory epithelium must penetrate as they migrate to their destinations.

At CS 17 (approximately six weeks), the olfactory pit gives rise to the olfactory sac along with the development of the olfactory fin. The olfactory fin is an important structure as it separates the primitive nasal and oral cavities.

At CS 18 (6 ½ wk), the formation of the superficial fiber layer of the olfactory bulb originates from the fiber contribution of the olfactory nerve. There is an increase in the separation between the floor of the nasal (olfactory) sac and the oral cavity along with the appearance of a primitive olfactory septum between the olfactory sacs. The primordia of the olfactory centers, which represent the highly complex group of neurons, will be located near the juncture of the temporal and parietal lobes where they will continue to develop in the brain.

At CS 19, as vacuoles cultivate within the nasal fin they fuse with the nasal sac resulting in the sac's enlargement. The nasal sac's enlargement thins the nasal fin to a slender membrane before rupturing and forming the primitive choanae.

At CS 20 and 21, the various olfactory centers maintain their development within the brain while the olfactory epithelial fibers penetrate the sea of mesenchyme to establish connections.

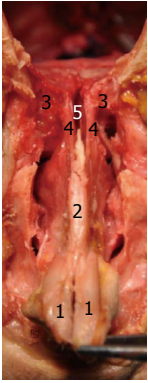
At CS 22, the lateral walls of the olfactory sacs begin to fold over to form furrows and ridges, that increase the surface of olfactory epithelium.

At CS 23 (around the eighth week), the mesenchymal olfactory septum between the olfactory sacs has become cartilaginous and is now part of the olfactory capsule, which in itself is cartilaginous based. The olfactory capsule presents with its typical "M" shape morphology enveloping and separating both olfactory conduits from the brain.

During human foetus development from the ninth to tenth weeks, six major furrows develop along with their corresponding ridges or folds called ethmoturbinals (*i.e.*, turbinates arising from the ethmoid) arising from the lateral aspect of the cartilaginous olfactory capsule. This cartilaginous precursor will undergo mineralization forming the ethmoid bone.

**Development of the olfactory conduits:** The olfactory placodes are ectodermal thickenings. Infolding occurs at the epicenter of each olfactory placode and, as the placodes deepen, a raised rim on each placode results dividing the medial and lateral olfactory processes. The intermaxillary process is formed when the medial olfactory processes fuse at the midline.

In the images of the Wistar rat fetus<sup>[18,19]</sup>, the primary



**Figure 3 Anatomy of the olfactory nose.** The alar (1) and septolateral (2) cartilages are united to each other and to the ethmoidal skull base (3) by the olfactory fascia (4) (the perpendicular plate of the ethmoid (5) has been partially removed).

nose becomes evident through the gap between the vertical palatal processes, after removal of the tongue. The histologic coronal sections of the snout of these rats clearly show that, the septum of the primary nose is already present and complete, before the flip up and development of the respiratory nose and secondary palate.

Additionally, from a phylogenic perspective, the cartilaginous skeleton of the amphibian snout is already comprised of a cartilaginous septolateral unit and an independent pair of "cartilago alaris", and precedes the appearance of the secondary palate and respiratory nose in crocodilians.

From these observations, it seems logical to hypothesize the following: The invagination movement of the center of the olfactory placodes could also pull in the raised rim of each placodes resulting in bringing the medial olfactory processes to fuse at the midline. Formation of the septolateral cartilage ensues before bringing the lateral olfactory processes in front of the septolateral cartilage, giving origin to the alar cartilages. The quadrangular plate of the septolateral cartilage connects to the perpendicular plate arising from the cartilaginous nasal capsule (*i.e.*, the forerunner of the ethmoid bone) to form the septum of the olfactory nose, which is visible in the Wistar rat fetus study<sup>[18,19]</sup>.

Thus, the olfactory placodes and their derivative pits give rise by differentiation to the following: (1) The olfactory mucosa; (2) The septolateral and alar cartilages; and (3) The connecting tissues lying in between these structures, *i.e.*, the olfactory fascia<sup>[20]</sup>.

The different fibrous portion of the olfactory fascia may be described as ligaments that unit the nasal cartilages to each other and to the olfactory mucosa, and the fibrocartilaginous nose to the facial and skull base skeleton.

These elements form the olfactory nose (Figure 3), which in humans stay separated from the braincase by the ethmoid bone, and largely communicates with the respiratory nose at the expense of the disappearance of the transverse lamina, a bony plate phylogenically separating the olfactory and respiratory nose until the stage of early

primates.

### Development of the respiratory nose

Phylogenically, the respiratory nose first appears in crocodilians. Based on paleontological data, the vomer bones are two plates of bone staying horizontal between the internal naris of early tetrapods which fused as a distinct plate located in the sagittal plane dividing the air passages of crocodilians<sup>[21]</sup>.

Some evidence of a similar rearrangement in mammals has been published in a study of the Wistar rat secondary palate development<sup>[18,19]</sup>. The flip up of the palatal processes leads to their fusion behind the primary palate, leaving a gap between the upper surface of the secondary palate and the inferior border of the septum of the olfactory nose, which is progressively closed by a structure growing from the fused palatal shelves towards the septum of the olfactory nose. This growing structure, in the evo-devo concept, is believed to be the fused vomer bones<sup>[1]</sup>.

The principle influence in palatal formation within crocodilians and other mammals appears to be in the significant development of the so-called palatine processes of the maxillae, the bones that give rise to the dentition, which push back the dermal palatal bones and is at the origin of their morphological changes and anatomical rearrangement. Applying the evo-devo perspective, the human respiratory nose appears as two paramedian, long axial conduits walled in on their inferior, lateral and medial sides by the rearranging of the dermal palatal bones (vomer, palatine, pterygoid, and inferior turbinate bones) between the two maxillary bones and their palatine processes (Figure 2). The transverse lamina, a bony structure which phylogenically was the floor of the ethmoidal chambers and the roof of the respiratory nose probably disappeared in the haplorhine ancestor of humans secondary to the constriction of the nasal fossae by the frontation and convergence of the orbital cones and the retraction of the snout.

The soft palate has evolved from the crocodilian basihyal valve, a significant gular fold that arches across the pterygoids immediately in front of the internal choana allowing crocodilians to have efficient respiratory function during submerged aquatic conditions. The basihyal valve consists of the following two flaps: The upper flap descends from the palate and gives rise to the mammalian soft palate, and the lower flap, located at the back of the tongue, is stringently reinforced by the hyoid cartilage (or the hyoid-epiglottic complex).

## CONCLUSION AND FINAL THOUGHTS

The development of the nose can be seen as the invagination of the olfactory organ between the two maxillae towards the anterior cranial base, with its floor being secondarily disturbed by the onset of nasal respiratory development at the expense of the oral cavity. Application of the evo-devo perspective provides new insight not only to the development of the nose,



its complex nasal physiology and anatomy but more importantly, may explain the predisposition, direction and spread of various diseases in otorhinolaryngology. Armed with this knowledge, the otorhinolaryngologist will better understand the clinical issues permitting modification of standard diagnostic, surgical and therapeutic management of the different diseases afflicting the craniofacial and neck regions. As a result, employing the evo-devo concept to our already pool of knowledge on Ear, Nose and Throat institutes will generate favorable surgical outcomes and, in effect, maximize patient care.

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## Retrospective Study

# Use of Holmium:Yag laser in early stage oropharyngeal squamous cell cancer

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**Author contributions:** Virk JS drafted the manuscript and performed literature searches; Dilkes M performed, collated and analysed all data.

**Institutional review board statement:** This study was registered with the clinical governance and ethics team. This study was approved and ratified by the ethics board.

**Informed consent statement:** All patients agreed to undergo this surgery after a multi-step consent process in keeping with GMC guidelines (United Kingdom).

**Conflict-of-interest statement:** We have no financial relationships to disclose.

**Data sharing statement:** There is no further data to share.

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## Abstract

**AIM:** To evaluate the efficacy of Holmium:Yag laser resection for oropharyngeal squamous cell cancer.

**METHODS:** A prospectively collected case series of all patients with oropharyngeal squamous cell carcinoma undergoing laser resection using the Holmium:Yag laser technique only over a 15 year period at a tertiary referral centre. All patients underwent long term follow up with regular clinical and radiological surveillance, when indicated. All patients were operated on under general anaesthetic with a laser-safe endotracheal tube. Typically laser resection was performed first using an operating microscope, followed by neck dissection. The tumour was held with a Luc's forceps or Allis clamp. The Holmium:Yag laser was implemented *via* a fibre delivery system. The Holmium:Yag laser fibre, of 550 micron diameter, was inserted through a Zoellner sucker and attached *via* steri-strips to a second Zoellner suction to provide smoke evacuation. The settings were 1J/pulse, 15 Hz, 15 W in a continuous delivery modality *via* a foot pedal control. The procedure is simple, bloodless, effective and quick. All surgeries were performed as day cases.

**RESULTS:** Twenty-seven oropharyngeal squamous cell cancer patients were identified, at the following subsites: 23 lateral pharyngeal wall/tonsil, 2 anterior faucal and 2 tongue base. Of the 23 tonsil tumours, 19 required no further treatment (83% therefore had negative histopathological margins) and 4 required chemoradiotherapy (17% were incompletely excised or had aggressive histopathological features such as discohesive, perineural spread, vascular invasion). The 2 patients with anterior faucal pillar neoplasia needed no further treatment. Both tongue base cancer cases required further treatment in the form of chemoradiotherapy (due to positive histopathological margins). Postoperatively, patients complained of pain locally, which resolved with regular analgesia. There were no postoperative haemorrhages. Swallowing and speech were normal

after healing (10-14 d). There was one case of fistula when neck dissection was carried out simultaneously; this resolved with conservative management. All patients were followed up with serial imaging and clinical examination for a minimum of five years. Median follow up was 84 mo.

**CONCLUSION:** Holmium:Yag lasers are a safe and effective treatment for Stage 1 and 2 squamous cell carcinoma of the oropharynx, excluding the tongue base.

**Key words:** Holmium:Yag; Laser; Human papillomavirus; Oropharyngeal; Squamous cell carcinoma; Cancer; Squamous cell cancer

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**Core tip:** Oropharyngeal squamous cell carcinoma is increasing in incidence. Management is controversial due to the large human papillomavirus cohort. The gold standard remains single modality therapy for early stage disease, either primary surgery or radiotherapy. Laser resection is one of the viable surgical options. We present a series of patients treated with Holmium:Yag laser resection. Holmium:Yag lasers are a safe and effective treatment for Stage 1 and 2 squamous cell carcinoma of the oropharynx, excluding the tongue base. Its uses could be extended within the speciality and elsewhere, particularly with a robotic arm.

Virk JS, Dilkes M. Use of Holmium:Yag laser in early stage oropharyngeal squamous cell cancer. *World J Otorhinolaryngol* 2016; 6(2): 41-44 Available from: URL: <http://www.wjgnet.com/2218-6247/full/v6/i2/41.htm> DOI: <http://dx.doi.org/10.5319/wjo.v6.i2.41>

## INTRODUCTION

Oropharyngeal squamous cell carcinoma (SCC) is increasing in incidence. This has been confirmed in large epidemiological studies both in the United States and the United Kingdom recently<sup>[1]</sup>. This is principally due to the human papilloma virus (HPV) infected cohort of patients, particularly subtype HPV-16. HPV-associated oropharyngeal SCC comprises the vast majority of oropharyngeal SCC<sup>[1]</sup>.

All patients undergo cross-sectional imaging and biopsy for pathological and radiological staging (Table 1)<sup>[2]</sup>. The gold standard of management remains single modality therapy for early stage disease (T1-2 NO-2a MO)<sup>[3]</sup>, either primary surgery or radiotherapy, with both reported to be equally successful<sup>[4]</sup>. Decisions are based upon patient choice and co-morbidities (*i.e.*, ability to undergo general anaesthetic), size and position of the tumour (less than 4 cm and preservation of superior pharyngeal constrictor) and the functional deficit<sup>[5]</sup>.

Early stage disease incorporates N1 and N2a neck disease. Hence, neck dissection should also be considered if there are positive nodes (with no radiological evidence

of extra capsular spread). Ipsilateral selective level II-IV neck dissection may be warranted even with negative imaging.

Laser resection is one of the viable surgical options. Many modalities have been described but fall into two broad groups of trans-oral carbon dioxide laser surgery or trans-oral robotic surgery. Other options, apart from radiotherapy, include photodynamic therapy, diathermy excision or through open approaches with reconstruction (such as transmandibular with free flap reconstruction)<sup>[2,5]</sup>.

In contrast to the commonly used carbon dioxide laser resections, we present a series of patients treated with Holmium:Yag laser resection in the oropharynx for these squamous cell carcinomas. We believe that the properties of the Holmium:Yag laser system is well suited to implementation in the oropharynx in view of its unique ability to vaporize, ablate (due to its longer wavelength of 2100 nm), coagulate soft tissues, a relatively low depth of thermal penetration (0.4 mm), excellent haemostasis and a wide range of tissue effects.

## MATERIALS AND METHODS

A prospectively collected case series of all patients with oropharyngeal squamous cell carcinoma undergoing laser resection using the Holmium:Yag laser technique only over a 15 year period at a tertiary referral centre. The hospital ethics committee approved this study as it did not affect the standard of care offered to the patients.

### Surgical technique

All patients were operated on under general anaesthetic with a laser-safe endotracheal tube. Typically laser resection was performed first using an operating microscope, followed by neck dissection. The tumour was held with a Luc's forceps or Allis clamp. The Holmium:Yag laser was implemented *via* a fibre delivery system. The Holmium:Yag laser fibre, of 550 micron diameter, was inserted through a Zoellner sucker and attached *via* steri-strips to a second Zoellner suction to provide smoke evacuation. The settings were 1J/pulse, 15 Hz, 15 W in a continuous delivery modality *via* a foot pedal control. The procedure is simple, bloodless, effective and quick. All surgeries were performed as day cases.

## RESULTS

Twenty-seven oropharyngeal squamous cell cancer patients were identified, at the following subsites: Twenty-three lateral pharyngeal wall/tonsil, 2 anterior faucal and 2 tongue base. Of the 23 tonsil tumours, 19 required no further treatment (83% therefore had negative histopathological margins) and 4 required chemoradiotherapy (17% were incompletely excised or had aggressive histopathological features such as dis cohesive, perineural spread, vascular invasion). The

**Table 1 Oropharyngeal squamous cell carcinoma staging**

Tx	Primary tumour could not be assessed; information unknown
T0	No evidence of primary tumour
Tis	Carcinoma in situ
T1	Tumour less than 2 cm
T2	Tumour between 2 and 4 cm
T3	Tumour larger than 4 cm (or affecting epiglottis)
T4	(1) Moderately advanced local disease growing into local structures (larynx, tongue, palate, medial pterygoid) (2) Advanced local disease, affecting internal carotid, lateral pterygoid, nasopharynx
Nx	Lymph nodes cannot be assessed or information unknown
N0	No lymph nodes affected
N1	One ipsilateral lymph node, less than 3 cm
N2	(1) One ipsilateral lymph node between 3 and 6 cm (2) Two or more ipsilateral lymph nodes, less than 6 cm (3) Contralateral lymph nodes, less than 6 cm
N3	Any lymph node greater than 6 cm
M0	No distant spread
M1	Distant site affected

2 patients with anterior faucal pillar neoplasia needed no further treatment. Both tongue base cancer cases required further treatment in the form of chemoradiotherapy (due to positive histopathological margins).

Postoperatively, patients complained of pain locally, which resolved with regular analgesia. There were no postoperative haemorrhages. Swallowing and speech were normal after healing (10-14 d). There was one case of fistula when neck dissection was carried out simultaneously; this resolved with conservative management.

All patients were followed up with serial imaging and clinical examination. Median follow up was 84 mo. At this longer term follow up, there were no recurrences in the 19 patients who received laser resection alone. Of the remaining 6 patients who had multimodality therapy in the form of surgery and chemoradiotherapy, there was nodal recurrence in one of the tongue base cancers.

## DISCUSSION

Over the last 20 years, the applications of lasers in otolaryngology have increased exponentially. Holmium:Yag lasers have the unique ability to vaporize, ablate (due to its longer wavelength of 2100 nm) and coagulate soft tissues alongside extremely hard materials, such as calculi, making it the laser of choice for a range of interventions for not only otolaryngologists but also in the fields of urology, orthopaedics, gastroenterological and general surgeons<sup>[6,7]</sup>. Holmium:Yag has a relatively low depth of thermal penetration (0.4 mm), excellent haemostasis and a wide range of tissue effects, allowing use for urological stone surgery, urethral strictures, benign prostatic hypertrophy, biliary stones, nephrectomy, laryngeal lesions, nasal polyposis, turbinoplasty and orthopaedic procedures<sup>[6]</sup>. We present a novel role for the Holmium:Yag laser.

The Holmium:Yag system, in its role for orophary-

ngeal SCC, is particularly useful as it allows a bloodless field, a lateral thermal necrosis of 2 mm (thus generating an extended clearance margin from tumour) and, when used in conjunction with an operating microscope, permits magnification and closer inspection of these margins. The latter precision inspection is particularly important with regard to the superior pharyngeal constrictor, as tumours are often adjacent or partially involving this muscle and, magnification can allow at least partial preservation, which is important to prevent exposure of parapharyngeal fat and the vital structures within. A further advantage of the Holmium:Yag system is that, as a result of the pulsed effects, no laser tip cooling is necessary<sup>[7,8]</sup>. In addition, these operative procedures are quick, with each taking around 20 min, and can be performed as day cases with the associated lower costs. These features make this type of laser system preferable to the standard carbon dioxide laser.

Disadvantages reported include post-operative oedema in comparison with standard techniques and pain. To avoid the potential for fistula formation, some centres recommend staged procedures, with the neck dissection performed a few weeks after the initial laser resection<sup>[6]</sup>.

Overall the Holmium:Yag laser was safe and effective for lateral pharyngeal wall, tonsil and faucal pillar tumours. Only a small proportion required any further treatment at long term follow up. The main group of failures were tongue base tumours as they were too difficult to access and identify. This is confirmed in recent literature and so, radiotherapy remains an important treatment regime<sup>[9]</sup>. However, transoral robotic surgery or lateral pharyngotomy are better surgical options at this subsite and have shown comparable outcomes to radiotherapy in experienced centres<sup>[10-12]</sup>. In addition, minimally invasive surgical techniques are associated with superior quality of life, as compared to the historically extensive open procedures and are cost-effective due to the short stays<sup>[11-13]</sup>. Further research (ECOG-3311, NTC01898494) is currently underway to ascertain the best options for these patients, particularly in the context of HPV-16 associated outcomes<sup>[14]</sup>.

We recommend the addition of the Holmium:Yag laser into the armamentarium of the otolaryngologist, particularly in cases of oropharyngeal SCC, where it has been shown to be safe, cost-effective with comparable outcomes to standard therapies.

## COMMENTS

### Background

Oropharyngeal squamous cell carcinoma is increasing in incidence. Management is controversial due to the large human papilloma virus (HPV) cohort. The gold standard remains single modality therapy for early stage disease, either primary surgery or radiotherapy.

### Research frontiers

Laser resection is one of the viable surgical options. Currently carbon dioxide laser is favoured but further research is warranted in different modalities.

### Innovations and breakthroughs

In this study, the authors demonstrated through a series of patients that, Holmium:Yag laser is safe, cost-effective with comparable outcomes to standard therapies in the treatment of oropharyngeal squamous cell carcinoma (SCC).

### Applications

Hol:Yag laser should be added to the head and neck surgeon's armamentarium for consideration for use on oropharyngeal SCC, excluding the tongue base.

### Peer-review

All relevant current literature was studied and referenced.

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## Randomized Controlled Trial

# Word perception in noise at different channels in simulated cochlear implant listeners

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**Author contributions:** Kumar P conceived the study; Kumar P and Sanju HK designed the study; Sanju HK and Kumar S analyze the data; Sanju HK, Kumar S and Singh V performed the data collection; Kumar P, Sanju HK and Singh V wrote the manuscript; all authors critically reviewed the manuscript and reviewed it.

**Institutional review board statement:** The study was reviewed and approved by All India Institute of Speech and Hearing, Mysuru-6, Karnataka, India.

**Clinical trial registration statement:** This study is registered at All India Institute of Speech and Hearing, Mysuru-6, Karnataka, India.

**Informed consent statement:** Written consent taken from all participants.

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**Data sharing statement:** We are ready to share data.

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## Abstract

**AIM:** To find out effect of different signal-to-noise ratios (SNRs) on word perception at different number of channels.

**METHODS:** Thirty participants with normal hearing in the age range of 18-25 years (mean age 23.6 years) were involved in the study. For word perception test, there were 28 key-words embedded in sentences comprises of four lists processed for different channels (4, 8 and 32 channel) using AngelSim program at -5, 0 and +5 SNRs. The recorded stimuli were routed through audiometer connected with computer with CD player and presented in free field condition with speakers kept at 0° azimuth in a sound treated room.

**RESULTS:** Repeated measure ANOVA showed significant main effect across different SNRs at 4 channel, 8 channel and at 32 channel. Further, Bonferroni multiple pairwise comparisons shows significant differences between all the possible combinations (4, 8 and 32 channel) at +5 dB SNR, 0 dB SNR and -5 dB SNR.

**CONCLUSION:** Present study highlights the importance of more number of channels and higher signal to noise ratio for better perception of words in noise in simulated cochlear implantees.

**Key words:** Cochlear implants; Perception; Signal-to-noise ratio; Speech; Noise

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**Core tip:** Present study highlights the effect of different signal-to-noise ratios (SNRs) on word perception at different number of channels. Thirty young adults with normal hearing were involved in the study. Word perception test were carried out at different channels with multiple SNRs. Result showed significant main effect across different SNRs at 4, 8 and 32 channel. Further, Bonferroni multiple pairwise comparisons shows significant differences between all the possible combinations (4, 8 and 32 channel) at +5, 0 and -5 dB SNR. The present study highlights the significance of more number of channels and higher SNR for better word perception in noise in simulated cochlear implantees.

Kumar P, Sanju HK, Kumar S, Singh V. Word perception in noise at different channels in simulated cochlear implant listeners. *World J Otorhinolaryngol* 2016; 6(2): 45-49 Available from: URL: <http://www.wjgnet.com/2218-6247/full/v6/i2/45.htm> DOI: <http://dx.doi.org/10.5319/wjo.v6.i2.45>

## INTRODUCTION

Earlier studies in cochlear implant has revealed that performance in speech recognition enhanced with increase in number of channels<sup>[1-5]</sup>. Previous studies have shown that speech perception improves with increase in number of channels in quiet listening condition up to 4 to 7 channels<sup>[6,7]</sup>. Fishman *et al.*<sup>[2]</sup>, in 1997 assessed speech recognition in subjects using Nucleus-22 speech processing strategy with increase in number of electrodes. Result showed that speech perception score was poor for all subjects with single electrode cochlear implant listeners and they also observed improvement in speech perception with increase in number of electrodes from 1 to 4 with all test materials. They also found no significant difference in speech perception when number of electrodes increases to 7, 10 and 20. In a similar way, Friesen *et al.*<sup>[8]</sup> in 2001 assessed speech perception with vowel, consonant, word and sentence in listener with Nucleus-22 and Advanced Bionics Clarion cochlear implant and compared scores with normal hearing individual. In that study, speech perception was measured as a function of number of electrodes and signal to noise ratios (+15, +10, +5, 0 dB). Outcomes of the study showed that speech perception improves with increase in number of channels (up to 7 or 8) at all signal to noise ratios. It was also observed that with SPEAK speech processor there was no improvement in speech perception for vowel and consonant recognition with greater than seven electrodes at all noise levels. However, for individuals with normal hearing, performance continued to increase up to at least twenty electrodes. For difficult speech materials like word and sentences, marginal significant increase in speech perception with increase in number of electrodes, *i.e.*, 7 to 10 in Nucleus-22 listeners. In a similar line, Verschuur<sup>[4]</sup>

in 2009 compared patterns of consonants features recognition as a function of channel number in users of Nucleus 24 device with normal hearing subjects listening to acoustic model which mimics similar to that device. They reported that the large changes to channel number had no substantial changes in performance. Similarly, Friesen *et al.*<sup>[5]</sup> in 2009 done speech perception test with CVC stimuli at 2, 4, 8, 12, and 16 spectral channels on 10 normal hearing subjects. They observed that performance with CVC stimuli enhanced with increase in number of spectral channels. Perreau *et al.*<sup>[9]</sup>, in 2010 also investigated speech perception test in spatially separated noise with different number of channels. They reported that the performance was affected for all subjects as the number of electrodes was reduced. A study done by Zeitler *et al.*<sup>[10]</sup>, in 2009 examined speech recognition outcome with reduction in the number of functional channel after post-implantation. The result showed that even though reduction in number of channels does not have a direct influence on performance of speech recognition, the reduction of five or more number of channels can suggest impending device failure. From the above literature it can be observed that most of these studies done in quiet listening situation, whereas everyday listening situation contains background noise in our day-to-day life. So, there is a need to study the effect of different signal-to-noise ratio (SNR) on word perception at different number of channels of cochlear implant in simulated conditions. The aim of the study is to find out effect of different SNRs on word perception at different number of channels.

## MATERIALS AND METHODS

### Participants

Thirty participants with normal hearing in the age range of 18-25 years (mean age 23.6 years) were involved in the study. All the subjects were having hearing threshold within normal limits revealed by pure tone thresholds of  $\leq 15$  dBHL at 250 to 8000 Hz. Further, ipsilateral and contralateral reflexes were checked at 500, 1000, 2000 and 4000 Hz for all subjects and tympanometry with 226 Hz probe tone with middle ear analyzer was used to confirm normal middle ear functioning for all subjects. Those participants who were having any other otological, neuromuscular and neurological problem were excluded from the study.

### Testing environment

All the behavioural tests were carried out in a sound treated room. The permissible noise level was as per the guidelines in ANSI S3.1 (1999). Laboratory room were well illuminated and air conditioned for the comfort of the researcher as well as subjects.

### Instrumentation

For pure tone audiometry and word perception test, calibrated dual channel clinical audiometer (PIANO Inventis) was used for all participants. For tympanometry

**Table 1** Mean and standard deviation of correct raw score (words) with different number of channels at various signal-to-noise ratios

	-5 dB SNR		0 dB SNR		+5 dB SNR	
	Mean	SD	Mean	SD	Mean	SD
4 channels	4.00	3.25	5.26	3.27	8.63	5.14
8 channels	15.10	5.84	18.00	4.84	19.86	4.04
32 channels	23.90	5.17	25.63	3.71	26.93	1.70

SNR: Signal-to-noise ratio.

and reflexometry, calibrated GSI-Tympstar Immittance meter was used for all participants.

### Procedure

Modified version of Hughson and Westlake procedure was used for pure-tone audiometry (Carhart and Jerger<sup>[11]</sup>, 1959) across octave frequencies from 250 to 8000 Hz for air conduction and frequencies from 500, 1000, 2000 and 4000 Hz for bone conduction. To carry out tympanometry and reflexometry middle ear analyzer was used using a probe tone frequency of 226 and 500 Hz, 1000, 2000, and 4000 Hz stimuli were used for ipsilateral and contralateral reflex. For word perception test, there were 28 key-words embedded in sentences comprises of four lists processed for different channels (4, 8 and 32 channel) using AngelSim program at -5, 0 and +5 SNRs. The subjects were instructed to write the sentences. They were encouraged and motivated to predict the sentence. No repeat presentation and feedback were provided. All the subjects were asked to sit comfortably without excessive head movement. Testing was done from most adverse listening condition (4 channels, -5 dB SNR) to least adverse listening condition (32 channels, +5 dB SNR). Rest period was provided after completion of each channels condition. The recorded stimuli were routed through audiometer connected with computer with CD player and presented in free field condition with speakers kept at 0° azimuth in a sound treated room. During testing the listener was seated at 1 meter distance in front of loudspeaker (Grason-stadler audio monitors) in a sound treated room. The stimuli presented at three different SNRs (-5 dB, 0 dB and +5 dB) by varying the level of speech noise (generated by PIANO Inventis double channel audiometer), keeping signal constant at 40 dB SL at different number of simulated channels, *i.e.*, 4, 8 and 32 channels. The subjects were supposed to write the sentence heard from loudspeaker. Raw scores were calculated for keywords (number of correct keywords in each sentence).

### Statistical analysis

The statistical analysis of the study was performed by a biomedical statistician. Data of the study was analyzed using SPSS 17.

## RESULTS

Descriptive statistics, repeated measure ANOVA and

bonferroni multiple pairwise comparisons were done using SPSS 17 to analyze the data collected from all subjects. Descriptive statistics was done to find out mean and standard deviation of score at different channels with different SNRs. Repeated measure ANOVA was done to find out any significant main effect across different SNRs at 4, 8 and 32 channels. Further, Bonferroni multiple pairwise comparisons was done to find out any significant differences between all the possible combinations (4, 8 and 32 channel) at +5 dB SNR, 0 dB SNR and -5 dB SNR.

Descriptive statistics showed that mean score increased (better) with increase in number of channels for words (Table 1). Similarly, descriptive statistics also revealed that mean score increases (better) with increase in SNR, *i.e.*, -5, 0 to +5 dB for words (Table 1). Repeated measure ANOVA showed significant main effect across different SNRs at 4 channel [ $F(2, 87) = 125.05$ ;  $P < 0.05$ ;  $\chi^2 = 0.742$ ]; 8 channel [ $F(2, 87) = 198.09$ ;  $P < 0.05$ ;  $\chi^2 = 0.820$ ]; and at 32 channel [ $F(2, 87) = 167.85$ ;  $P < 0.05$ ;  $\chi^2 = 0.794$ ]. Further, Bonferroni multiple pairwise comparisons shows significant differences between all the possible combinations (4, 8 and 32 channel) at +5 dB SNR, 0 dB SNR and -5 dB SNR (Table 2 and Figure 1).

## DISCUSSION

The aim of the present study was to find out effect of different number of channels on word perception at different SNRs. The result showed significant improvement in word perception with increase in number of channels. This study also revealed significant improvement in word perception with increase in signal to noise ratio at different number of channels. Present study also quantified the deteriorating effect on word perception with decrease in SNR at different channels. Finding of present study is in consonance with previous literature<sup>[1,3,5,8-10]</sup>. However, there are few studies not in agreement with present findings<sup>[2,4]</sup>. In general, performance increases with increase in number of channels (4 channels < 8 channels < 32 channels) and of favorable SNR (+5 dB SNR > 0 dB SNR > -5 dB SNR). However, minimum 8 channels are required to achieve at least more than 50% performance irrespective of adverse listening condition (-5 dB SNR). Probably at lesser numbers of channels, information is spectrally sparse and hence poorer performance which further deteriorates in adverse listening condition (-5 dB SNR). The outcome of present study also showed that deteriorating effect of noise persists even at 32 channels condition. Similarly, the outcome of present study revealed that effect of number of channels on word perception in noise and showed that most individuals with CI are unable to fully utilize the spectral information given by the more number of channels in noisy condition. Friesen *et al.*<sup>[8]</sup>, in 2001 measured speech perception with various number of electrodes at different signal to noise ratios of +15, +10, +5, 0 dB, and in quiet. The outcome of the study showed speech recognition score

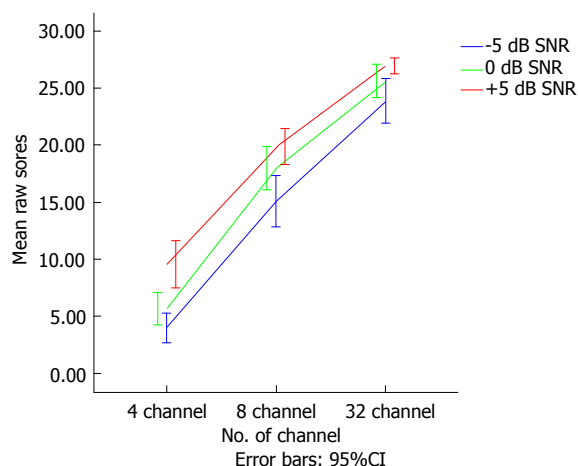
**Table 2** Bonferroni multiple pairwise comparisons at all the possible combinations for words (4, 8 and 32 channel) at +5 dB signal-to-noise ratio, 0 dB signal-to-noise ratio and -5 dB signal-to-noise ratio ( $^bP < 0.001$ )

SNR	Channels	8 channels (mean difference)	32 channels (mean difference)
+5 dB SNR	4 channels	-11.23 <sup>b</sup>	-18.3 <sup>b</sup>
	8 channels		-7.06 <sup>b</sup>
0 dB SNR	4 channels	-12.73 <sup>b</sup>	-20.36 <sup>b</sup>
	8 channels		-7.63 <sup>b</sup>
-5 dB SNR	4 channels	-11.1 <sup>b</sup>	-19.9 <sup>b</sup>
	8 channels		-8.8 <sup>b</sup>

SNR: Signal-to-noise ratio.

improved with increase in number of electrodes (up to seven or eight). They also found that on administration of difficult speech material like words and sentences, performance was increased (marginally significant) with increase in number of electrodes, *i.e.*, 7 to 10 in nucleus-22 cochlear implant listeners. Liu *et al.*<sup>[12]</sup>, in 2004 assessed effects of number of electrodes on Mandarin tone perception in children using Nucleus CI 24 cochlear implant. They reported significant decrease in Mandarin tone perception score with decrease in number of electrodes in children using CI 24 implants. Similarly, Perreau *et al.*<sup>[9]</sup>, in 2010 also investigated speech-in-noise test at different numbers of electrodes in individuals with bilateral cochlear implant. The result revealed that 3 to 4 electrodes is sufficient to get maximal performance on speech-in-noise tests in individuals with bilateral cochlear implant. However, few individuals with cochlear implant shows gradual decrement in speech recognition in noise with decrease in number of functional electrodes. Zeitler *et al.*<sup>[10]</sup>, in 2009 showed that although deactivation does not have direct impact on speech perception score, the reduction of 5 or more electrodes can suggest impending device failure. The finding of the current study is in contrast with the study done by Fishman *et al.*<sup>[2]</sup>, in 1997 reported no differences in speech perception score on any test in the 7-, 10-, and 20-electrode conditions. They also showed no difference in speech perception score with 4 and 20 electrodes processor on sentence and consonant test. The outcome of present study is in contrast with the study done by Verschuur<sup>[4]</sup> in 2009 also showed that large changes in number of channels in the Advanced Combination Encoder signal processing strategy revealed no significant changes in speech perception score. However, the present study was done on simulated cochlear implantees, audiologist or clinical specialist needs to be cautious before implementing present finding on individuals with cochlear implant.

The outcome of the present study highlights the significance of more number of channels and higher SNR for better word perception in noise in simulated cochlear implantees. Present study also quantified the deteriorating effect on word perception with decrease in SNR at different channels. Current study also showed



**Figure 1** Error bar graph of mean score for words with 4, 8 and 32 channels at +5 dB, 0 dB and -5 dB signal-to-noise ratio.

that minimum 8 channels are required to achieve at least more than 50% performance irrespective of adverse listening condition (-5 dB SNR).

## COMMENTS

### Background

Earlier studies in cochlear implant have revealed that performance in speech recognition enhanced with increase in number of channels. Previous studies have shown that speech perception improves with increase in number of channels in quiet listening condition up to 4 to 7 channels.

### Research frontiers

From the above literature it can be observed that most of these studies done in quiet listening situation, whereas everyday listening situation contains background noise in the authors day-to-day life. So, there is a need to study the effect of different signal-to-noise ratio (SNR) on word perception at different number of channels of cochlear implant in simulated conditions. The aim of the study is to find out effect of different SNRs on word perception at different number of channels.

### Innovation and breakthroughs

The authors compares word perception score at three different SNRs (-5 dB, 0 dB and +5 dB) by varying the level of speech noise (generated by PIANO Inventis double channel audiometer), keeping signal constant at 40 dB SL at different number of simulated channels, *i.e.*, 4, 8 and 32 channels. The result showed significant improvement in word perception with increase in number of channels. This study also revealed significant improvement in word perception with increase in signal to noise ratio at different number of channels.

### Applications

The outcome of the present study highlights the significance of more number of channels and higher SNR for better word perception in noise in simulated cochlear implantees.

### Terminology

Signal to noise ratio is signal-to-noise ratio (abbreviated SNR or S/N) is a measure used in science and engineering that compares the level of a desired signal to the level of background noise. It is defined as the ratio of signal power to the noise power, often expressed in decibels.

### Peer-review

Well written paper with good language and grammar.

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