What the general dental practitioner (GDP) needs to know about HPV related oropharyngeal malignancy

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Abstract:

The rates of oropharyngeal squamous cell carcinoma have continued to rise secondary to the increasing prevalence of the human papillomavirus (HPV). HPV related disease is typically found in younger patients who do not have the traditional risk factors for malignancy. General dental practitioners (GDPs) have the opportunity to examine patients regularly and may therefore have an opportunity to identify oropharyngeal malignancies at an early stage. However, many GDPs are unfamiliar with oropharyngeal anatomy, pathology and clinical examination. This review summaries the key points in identifying patients with oropharyngeal malignancy who necessitate urgent referral.

Key Points:

- Provides an overview of anatomy of the oropharynx
- Provides an anatomical based method of assessment for oropharyngeal malignancy
- Increases awareness of the increasing incidence of HPV related oropharyngeal malignancy, occurring in younger patients without the traditional risk factors for oral cancer
- Increases awareness of the varied clinical presentation of oropharyngeal malignancy
- Recommends that all GDPs extend their routine clinical examination to include the oropharynx and neck in an attempt to improve early malignancy detection rates and reduce potential patient harm and medicolegal claims

Key Words: Oropharyngeal Cancer; Oral Cancer; Mouth Neoplasms; Anatomy; Diagnosis; Physical Examination

Introduction:

The undergraduate dental curriculum requires all graduates to attain core competencies which includes mastering the oral soft tissue examination. Despite the absence of anatomical and pathological boundaries between the oral cavity and oropharynx there is currently no formal training or similar expectation of competency in the examination of the oropharynx as there is for the oral cavity [1]. In 2007 the United Kingdom (UK) National Committee for Undergraduate Oral Surgery reiterated the requirement for a fundamental level of knowledge in the cause and effects of oral diseases, including oral cancer and its management. Surprisingly, these recommendations again failed to extend to the oropharynx [2]. As a result, general dental practitioners (GDPs) at all stages of training have often had little or no formal instruction or assessment of the anatomy and pathology of the oropharynx. This clinical idiosyncrasy has been recognised by the General Dental Council (GDC) noting that many of the oropharyngeal sub-sites are amenable to examination in the routine dental setting (with the notable exception of the base of tongue), and that perhaps incorporating a more general definition of “oral cancer” to include both oral cavity and oropharynx may encourage such examination [3]. Similarly, in the United States of America, the American Dental Association recently amended their policy on early detection and prevention of oral cancer to include oropharyngeal cancer recommending that dentists conduct routine visual and tactile examinations for all patients [4]. Many GDPs however remain unfamiliar or not confident with oropharyngeal assessment leading to potentially missed opportunities in the early diagnosis of malignancy and resulting in patient harm and subsequent medicolegal claims [Local Audit & Personal Communication].

The purpose of this review is to highlight the importance of oropharyngeal assessment and to provide a structured anatomically based guide to examination.

Oral and Oropharyngeal Cancer

In 2016, over 3,700 patients were diagnosed with oral cavity cancer and a further 3,500 were diagnosed with oropharyngeal cancer in the UK [5]. Approximately 70–80% of all new

head and neck SCC (HNSCC) cases are associated with tobacco and alcohol use. However, despite campaigns over the last few decades to reduce smoking related cancers the rates of oropharyngeal SCC (OPSCC) have continued to rise due to an increasing contribution of HPV associated disease [6]. HPV related SCC accounts for around 70-80% of all cases of OPSCC but only 1.3-7% of SCC in other head and neck subsites [6-8]. Approximately 50% of patients with oral or oropharyngeal cancer will present with evidence of tumour in a cervical lymph node, and in many cases this may be the first presentation, particularly in HPV positive SCC [9].

HPV

Human papillomaviruses are non-enveloped DNA viruses belonging to the papillomavirus family with over 200 characterised HPV types, with more being regularly identified [10]. HPV skin infection is very common, and causes common warts and verrucae, which have no malignant potential. The mode of transmission is variable; while anogenital warts are spread by direct person to person contact, common skin and plantar warts can be spread from contaminated surfaces such as floors [11,12]. Although oropharyngeal warts are considered to be sexually transmitted, it is also possible to infect the mouth by direct contact with skin warts (autoinoculation e.g. by biting skin warts) [13]; although, skin warts are not known to be associated with the oncogenic HPV strains 16 or 18.

Recent research has suggested that around 10% of the healthy European population will have oral HPV infection at any given time, with infections being almost twice as likely in men and high risk groups (sex workers, people receiving screening at sexually transmitted infection clinics, and men who have sex with men). The persistence of oral HPV infection ranges from 3.5 to 20.7 months, with the majority of patients clearing the infection by 1 year [14]. The longer that someone has active HPV infection, the greater the likelihood that this will induce malignancy, and it is recognised that about 10% of patients won't naturally clear the virus within 2 years of becoming infected [15,16].

Since 2006 three vaccines targeting HPV have been used worldwide – bivalent vaccine (targeting HPV 16,18) [17], quadrivalent vaccine (targeting 16, 18, 6 and 11) [18], and more recently nonavalent HPV vaccine (targeting HPV 6, 11, 16, 18, 31, 33, 45, 52, 58) [19]. Currently, the UK offers girls and boys aged 12 to 13 years the quadrivalent HPV (16, 18, 6 and 11) vaccine as part of their national HPV vaccination program [20]. HPV 16 and 18 are reported to be responsible for 70% of cervical cancers, and 40–80% of other HPV-related cancers; while HPV 6 and 11 are responsible for 80-90% of anogenital warts [21]. Disease modelling studies have suggested that elimination of HPV 16, 18, 6, and 11 is possible if 80% coverage in girls and boys is reached and if high vaccine efficacy is maintained over time [21]. Current evidence suggests an 85% uptake in eligible girls in the UK, with dramatic reductions already seen in HPV16 and 18 infections; in 2018 these were identified in less than 2% of young sexually active women, compared to 15% in 2008 [22,23]. It remains to be seen exactly what impact this will have on the future of HPV related disease and cancer [24].

HPV positive OPSCC affects three times the number of men than women and has quite unique features of presentation, typically occurring in younger cohorts without the usual oral cancer risk factors [7,8]. HPV associated OPSCC is closely associated with poorly differentiated cancer grade, positive lymph nodes and late-stage disease, which classically are associated with poor prognosis. However, HPV associated OPSCC and other HNSCC patients demonstrate significantly better clinical outcomes when compared to non-HPC related SCC; most notably in their response to chemotherapy and radiotherapy [7,8]. Furthermore, HPV associated OPSCC and HNSCC have a lower risk for second primary cancers [[7]. As a result, HPV tumour status is now included in the WHO classification based on p16 immunohistochemistry (the surrogate marker for HPV), and confers differing TNM staging criteria by the Union for International cancer Control (UICC) [25, 26].

Anatomy of the oropharynx

The oropharynx extends from the junction of the hard and soft palates superiorly to the epiglottis inferiorly. Superior to the oropharynx is the nasopharynx, and inferiorly is the laryngopharynx (also called the hypopharynx) (**Figure 1**).

The tongue is subdivided into an anterior two-thirds which forms the oral (and mobile) tongue, and the base of tongue (posterior one-third) by the circumvallate papillae. The base of tongue is a component of the oropharynx, and contains the lingual tonsils (one of the four components of Waldeyer's ring of lymphoid tissue). The tongue base should not be confused with the "root" of the tongue, which is the region deep to the mobile tongue and anterior to the base of the tongue which includes the lingual septum and bilateral genioglossus and geniohyoid muscles (**Figure 1**).

Inferior to the base of tongue are the paired valleculae. These are separated in the midline by the median glossoepiglottic fold passing from the base of tongue to the lingual surface of the epiglottis. Laterally, each vallecula is bounded by the lateral glossoepiglottic fold.

The anterolateral walls of the oropharynx are formed by two projecting ridges (the two faucial pillars) (**Figure 2**). Anteriorly is the palatoglossal fold (anterior faucial pillar) formed by the underlying palatoglossus muscle passing from the undersurface of the palate to the side of the tongue. Posteriorly the palatopharyngeal fold (posterior faucial pillar) formed by the underlying palatopharyngeus muscle passing downwards and a little backwards from the lower border of the soft palate to the side wall of the pharynx. In the space between the two folds lie the palatine tonsils (a further component of Waldeyer's ring).

The posterior wall of the oropharynx is formed by all three constrictor muscles and the overlying mucous membrane.

Symptoms of oropharyngeal disease.

1. *Persistent sore throat*.

This is an extremely common symptom which is usually short lived (a matter of a few days up to two weeks) and it is clearly important to determine whether there is a serious underlying cause e.g. tumour. The site of the soreness should, if possible, be localised to the

oral cavity, oropharynx or beyond this. It is often caused by inflammation of the pharyngeal mucosa due to either traumatic agents (such as cigarette smoke, alcohol, mucosal scratch, gastro-oesophageal reflux, inhaled particles e.g. hard wood saw dust, or prior radiotherapy), or due to infection. Viruses such as the adenovirus (common cold) cause symptoms of pain, worse when swallowing and associated with a gruff voice, mucosal redness and cervical lymphadenopathy which will usually resolve in a week. In glandular fever the Epstein Barr virus leads to hypertrophy of the whole of the reticulo-endothelial system including the liver and spleen, as well as the tonsils and cervical lymph nodes. The systemic symptoms of headaches, tiredness and muscle pain may continue for some weeks, and other uncommon complications may be severe. Bacterial infections e.g. the Group A beta haemolytic streptococcus in acute tonsillitis, causes “strep throat”, including the tonsils in children <15 years of age, which will appear inflamed and frequently with pus evident, local cervical lymphadenopathy, and fever. Antibiotics shorten the duration of symptoms.

Poorly localised and radiating pain and pain that persists for more than 4 weeks should raise suspicion of more sinister pathology.

2. *Odynophagia*

Pain or soreness which only occurs on swallowing (termed odynophagia) may be more significant, particularly if it has been present for more than 4 weeks. Such pain can often be well localised and the site often remains constant. Pain from the oropharynx may be referred to the ipsilateral ear and associated otalgia should increase the index of suspicion that there is a more serious underlying cause.

3. Dysphagia

Swallowing problems are more commonly seen in hypopharyngeal and upper oesophageal disease but is sometimes seen in oropharyngeal pathology. This is usually related to a ‘mass effect’. Swallowing involves a crossing of the stream of liquid and food with that of breathing and this occurs within the pharynx. Swallowing has two components: the voluntary

passage of the bolus from the oral cavity to the stomach and automated airway protection. The main sphincter mechanisms protecting the airways are the soft palate which closes the nasal passages, and the protection of the larynx from the elevated hyoid bone and epiglottis. As the base of the tongue retracts and the constrictors sequentially contract the food bolus is pushed into the oesophagus. Mass effect or tumour infiltration of these muscles will result in swallowing difficulties.

4. *Change in quality of voice*

Classically hoarseness is related to laryngeal pathology. However, one can see changes in the quality of the voice in relation to oropharyngeal disease. Patients with a mass lesion involving the oropharynx e.g. markedly enlarged tonsils, sometimes develop 'hot potato speech'. This describes a change in the resonance of the voice when speech has a muffled quality (likened to a person speaking with a hot potato in their mouth).

Hypernasal speech is a disorder that causes abnormal resonance in the voice due to increased airflow through the nose during speech. It is caused by an open nasal cavity resulting from incomplete closure of the soft palate. It can arise as a result of a structural abnormality e.g. post radiotherapy fibrosis of the soft palate/tumour of the soft palate or secondary to a neurologic abnormality.

5. *Lump in the throat*

A sensation of a lump in the throat is often an intermittent problem and tends to improve when the patient is swallowing food. The most common diagnosis (of exclusion) is globus pharyngeus when the patient does not experience true dysphagia. However, occasionally pathology involving the oropharynx can present with a sensation of a lump in the throat e.g. markedly enlarged tonsil or a mass in the region of the tongue base.

6. *Neck swelling*

Pathology of the oropharynx can lead to secondary neck swelling. This may take the form of associated cervical lymphadenopathy but can also be related to a parapharyngeal abscess secondary to infection e.g. tonsillitis, peritonsillar abscess (quinsy).

7. *Halitosis*

Objective evidence of halitosis can be associated with infective pathology such as acute tonsillitis and malignant neoplasms with some secondary infection e.g. an advanced tongue malignancy.

Examples of oropharyngeal tumours seen clinically and radiologically are shown in **Figures 3- 5**.

Extended Dental Examination of the Oropharynx and neck

By extending the oral soft tissue examination to include the oropharynx and associated lymph nodes GDPs have the opportunity to potentially identify oropharyngeal malignancy.

It is essential that a systematic approach is taken to the examination and that each step is explained to the patient. Each structure within the oropharynx can be examined using a good light source and two dental mirrors (or a disposable equivalent) to allow the mucosal surfaces to be examined, with the exception of the tongue base/valleculae which can often be challenging to clearly visualise. It is good practice to slide the little finger within the lingual sulcus slowly backwards towards the posterior tongue using the finger pulp to assess (where possible) the muscles of the deeper posterior tongue (**Figure 6**). Palpation of the tonsils and posterior tongue will typically require the use of topical local anaesthetic spray to overcome the gag reflex, and is perhaps beyond the realm of a GDP routine review.

If a macroscopic lesion is identified it should be evaluated by palpation with a finger to try and assess any submucosal spread. Malignancies in general feel firm due to the infiltrative process, and may be associated with a normal mucosal appearance. It should be noted that in healthy individuals there is a very wide variation in the appearance of the oropharynx, particularly the lymphoid tissue.

1. **Soft Palate**

   Visualisation of the soft palate is usually straightforward (even in patients with an active gag reflex). The mucosa is assessed to exclude swelling, ulceration, vesicles,

erythroplakia, leukoplakia, erythroleukoplakia. Normal movement can be assessed by asking the patient to say “Aagh” and one may see reduced movement when there is submucosal infiltration/fibrosis e.g. infiltrating tumours, post radiotherapy, and in certain neuromuscular conditions e.g. motor neurone disease.

2. **Posterior pharyngeal wall**

   Pathology of the posterior wall is relatively unusual. However, ulceration may occur as well as swelling and tumours e.g. retropharyngeal lymph node enlargement, retropharyngeal abscess most commonly seen in children secondary to foreign body penetration, which can be assessed by direct or indirect inspection with a dental mirror.

3. **Tongue base / valleculae**

   It is often not possible to examine the entirety of the tongue base and valleculae in clinical practise due to limited access. It is possible to visualise some of the mucosa of the tongue base and valleculae in a cooperative patient with a dental mirror. The mirror should be warmed or moistened with the patient’s saliva to avoid misting, and the patient informed of the procedure in an attempt to minimise the gag reflex. One is looking for abnormal masses/ulceration. Distinguishing pathology from normal muscular tension will be gained with experience. The key is to look for asymmetry. It is not unusual to see a vallecular cyst (that is often asymptomatic) and hyperplasia of the lingual tonsil in those patients who underwent removal of their palatine tonsils as children.

4. **Lateral wall (tonsil/tonsillar pillars)**

   There is considerable variability in the appearance of the lateral wall. In patients who have undergone previous tonsillectomy there is usually evidence of mucosal scarring and on occasions some residual lymphoid tissue. Inflammatory conditions can give rise to white areas appearing on the tonsils as in acute tonsillitis/glandular fever. There is often a degree of asymmetry and what constitutes ‘significant asymmetry’ (requiring further investigation or removal for histology) can be difficult to determine.

Certainly, if the change in asymmetry is recent or progressive then specialist referral is justified. Rarely asymmetric tonsils may arise because of a parapharyngeal mass displacing the ipsilateral tonsil to the midline e.g. a deep lobe tumour of the parotid gland (**Figure 5**). If there is doubt then imaging (CT and/or MRI) may help to determine whether the asymmetry is a true phenomenon as opposed to secondary to a parapharyngeal mass.

5. Cervical Lymph nodes

Oropharyngeal assessment is completed with examination of the neck for cervical lymphadenopathy. This has become more relevant as HPV positive SCC can present with nodal disease before significant oropharyngeal symptoms. In addition, a small sub-set of patients will present with metastatic cervical lymphadenopathy with a clinically and radiologically occult tumour (primary of unknown origin). The examination of the neck will not be new to GDPs with the inspection preceding the palpation of the nodal areas. The horizontal and vertical chains of nodes should be assessed from behind the patient with the neck slightly flexed, and using the tips of the fingers. The upper deep cervical lymph nodes, including the jugulodigastric at the level of the intersection of the internal jugular vein and posterior belly digastric muscle, are beneath the sternocleidomastoid muscle. The jugulodigastic (Level IIa) lymph nodes are often palpable as the largest of the cervical chain, but these should be symmetrical. Systematic examination of Levels I-V (**Figure 7**) should be completed.

Specialist Opinion

GDPs unfamiliar with the appearance and range of symptoms of oropharyngeal disease should have a low threshold for referral. Contact can be made directly with the on-call hospital staff, or by using the Maxillofacial/Head & Neck Two Week Wait referral which will

ensure the patient is examined by a head and neck cancer team member. The following list should prompt urgent referral:

- Erythroplakia, leukoplakia, speckled erythroleukoplakia plaques.
- Unilateral tonsillar enlargement
- Mucosal ulceration >3 weeks
- Mucosal mass without ulceration.
- Asymmetry of the soft palate, posterior tongue, or lateral pharyngeal wall.
- Unexplained unilateral pain which radiates to an ear.
- Unexplained cervical lymphadenopathy

The frequency of routine dental follow-up places the GDP in a privileged position to potentially recognise oropharyngeal pathology and instigate timely referral. This is particularly important in HPV related SCC, where disease is often silent in the early stages. The failure to identify neck lymphadenopathy in the past has left GDPs open to patient dissatisfaction and delayed diagnosis. Misdiagnosis and late diagnosis of oral cancer has been described as having serious consequences for patients and the profession, with litigation and GDC attendance being realistic possibilities [4,27,28] . An awareness of the anatomy and potential clinical presentations of oropharyngeal disease will aid in reducing these potential adverse events.

In conclusion, the differing risk factors and demographics between oral and oropharyngeal cancer support the recommendation that all GDPs should include a neck examination, mucosal examination of the mouth and oropharyngeal region in all patients, not just those with the classic oral cancer risk factors.

Figure Legends:

Figure 1: Annotated sagittal T2 weighted MRI image demonstrating the three components of the pharynx: the oropharynx lying between the nasopharynx and laryngopharynx. The oropharynx includes the base of tongue and valleculae.

Figure 2: Annotated clinical photograph of the oropharynx highlighting the key anatomical sub-sites

Figure 3: Series of clinical photographs demonstrating malignancy of the oropharynx:

A: Intra-oral photograph of a large right tonsillar tumour (black arrows) which is causing displacement of the uvula (red arrow) to the left

B: Intra-oral photograph of a large tumour involving the right tonsillar fossa. The anterior tonsillar pillar is highlighted by the dashed line.

C: Nasendoscopy image of a large ulcerating tumour of the right tonsillar fossa

Figure 4: Imaging examples of oropharyngeal tumours:

A: Axial and sagittal CT imaging demonstrating large tongue base tumour infiltrating the epiglottis (black arrows) with an associated large nodal mass (red arrows)

B: Axial CT imaging showing large cystic level IIa lymph node in a patient with an unknown primary tumour

C: Axial and coronal T1 post contrast and T2W MRI showing large right tonsillar fossa tumour

D: T2W MRI showing large hypopharyngeal tumour involving the posterior pharyngeal wall (black arrows), and left level III nodal mass (red arrows)

Figure 5: This intra-oral clinical photograph and corresponding coronal MRI image demonstrate oropharyngeal asymmetry secondary to a large tumour within the deep lobe of the parotid gland (in this case, histology showed a benign pleomorphic adenoma).

Figure 6: Series of clinical photographs to demonstrate how to perform clinical examination of the oropharynx. Using dental mirrors to retract the cheek and move the tongue inferiorly, inspect the posterior pharyngeal wall, uvula, and tonsillar fossae (A). Confirm that the uvula

is midline and that there is no asymmetry of the tissues or masses. Observe symmetrical movement of the tissues when asking the patient to say “aargh” (B). Examine all surfaces, and run a little finger along the lingual sulcus on both sides, to palpate for any masses or irregularity (C). Finish the examination by palpation of the neck for cervical lymphadenopathy with the neck slightly flexed (D).

Figure 7: Surface anatomy of the cervical lymph node levels. Examination should proceed systematically. Many clinicians opt to commence with the submental (Level Ia) nodes, submandibular (Level Ib), superior to inferior along the sternocleidomastoid (Level II-IV), and finishing with the posterior triangle (Level V).

References:

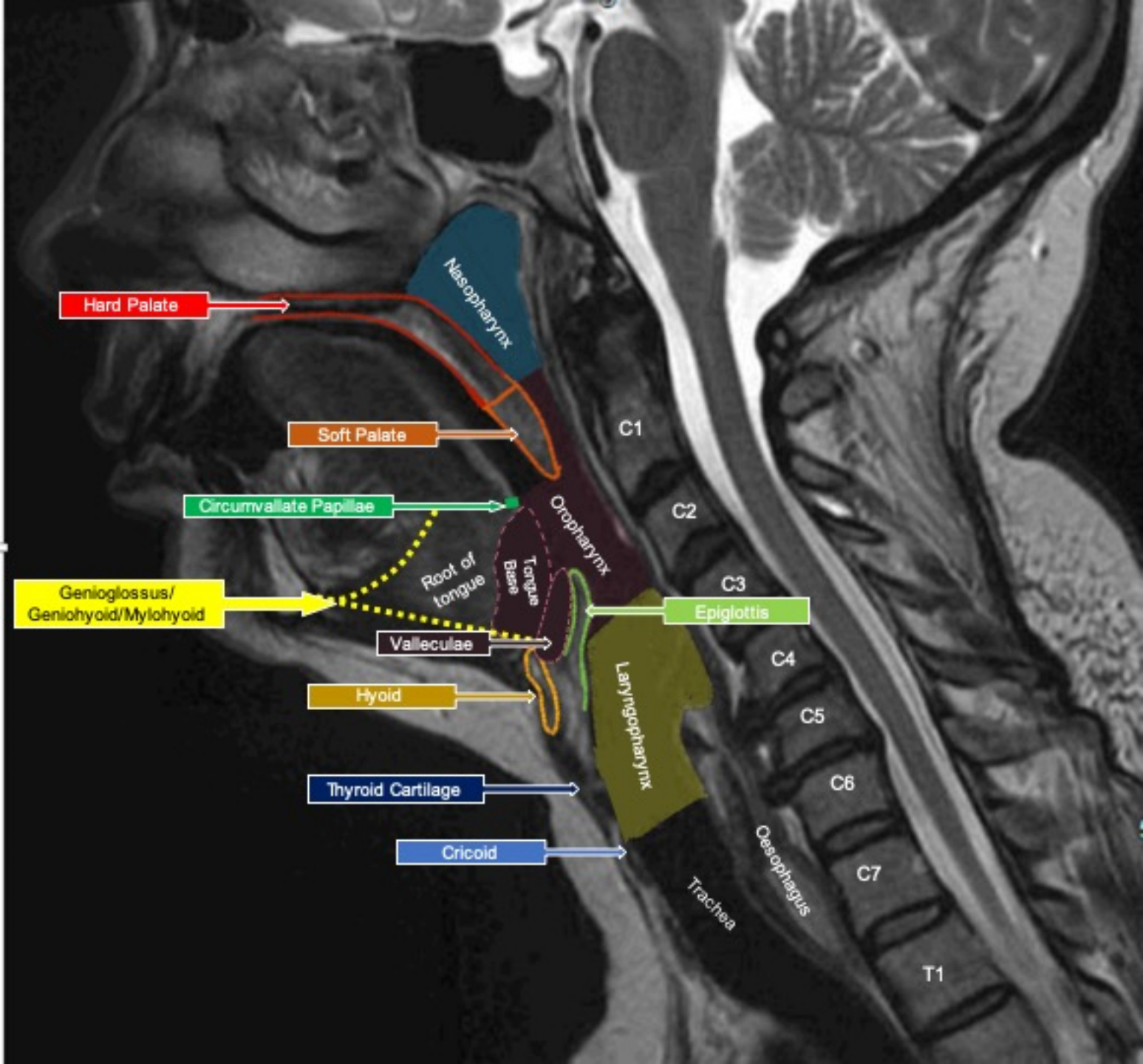
1. Field JC, Cowpe JG, Walmsley AD. The graduating European Dentist: a new undergraduate curriculum framework. Eur J Dent Educ 2017; 21 Suppl 1:2-10.
2. Macluskey M, Durham J, Cowan G, Cowpe J, Evans A, Freeman C et al. UK national curriculum for undergraduate oral surgery subgroup for teaching of the Association of British Academic Oral and Maxillofacial Surgeons. Eur J Dent Educ 2008; 12(1): 48-58
3. Gibson J. Oral cancer – CPD and the GDC. Br Dent J; 2018; 225(9):884-888
4. ADA News: ADA expands policy on oral cancer detection to include oropharyngeal cancer. October 1, 2019. https://www.ada.org/en/publications/ada-news/2019-archive/september/ada-expands-policy-on-oral-cancer-detection-to-include-oropharyngeal-cancer# [Accessed May 4, 2020]
5. Conway DI, Purkayastha M, Chestnutt IG. The changing epidemiology of oral cancer: definitions, trends and risk factors. Br Dent J 2018; 225: 867-873
6. Pan C, Issaeva N, Yarbrough WG. HPV-driven oropharyngeal cancer: current knowledge of molecular biology and mechanisms of carcinogenesis. Cancers Head Neck 2018; 3:12

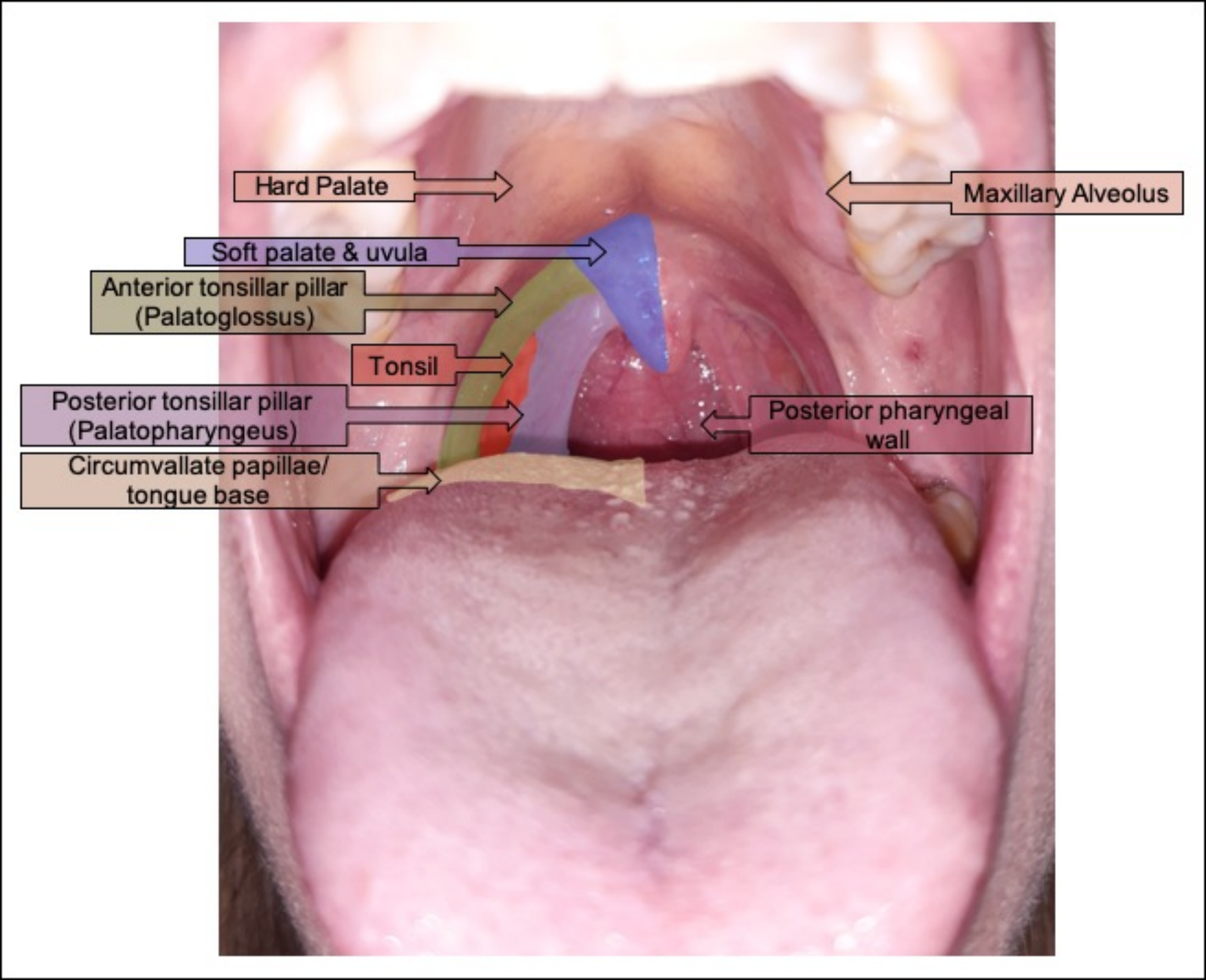
7. Syranen S, Syrjanen K. HPV in head and neck carcinomas: different HPV profiles in oropharyngeal carcinomas – why? Acta Cytol 2019; 63(2):124-142
8. Reid P, Marcu LG, Olver et al. I. Diversity of cancer stem cells in head and neck carcinomas: The role of HPV in cancer stem cell heterogeneity, plasticity and treatment response. Radiother Oncol. 2019 Jun;135:1-12. doi: 10.1016/j.radonc.2019.02.016. Epub 2019 Mar 6.
9. Speight PM, Farthing PM. The pathology of oral cancer. Br Dent J 2018; 225: 841-847
10. Bzhalava D, Guan P, Franceschi S, Dillner J, Clifford G. A systematic review of the prevalence of mucosal and cutaneous human papillomavirus types. Virology 2013; 445(1-2): 224-31
11. Antonsson A, Forslund O, Ekberg H, Sterner G, Hansson BG. The ubiquity and impressive genomic diversity of human skin papilloma viruses suggest a commensalic nature of these viruses. J Virol 2000; 74(24): 11636-41
12. Park IU, Introcaso C, Dunne EF. Human papillomavirus and genital warts: a review of the evidence for the 2015 centres for disease control and prevention sexually transmitted diseases treatment guidelines. Clin Infect Dis 2015; 61 Suppl 8: S849-55
13. Betz SJ. HPV-related papillary lesions of the oral mucosa: a review. Head Neck Pathol 2019; 13(1): 80-90
14. Tam S, Fu S, Xu L, Krause KJ, Lairson DR, Miao H, Sturgis EM, Dahlstrom KR. The epidemiology of oral human papillomavirus infection in healthy populations: a systematic review and meta-analysis. Oral oncol 2018; 82: 91-99
15. Bharti AH, Chotaliya K, Marfatia YS. An update on oral human papillomavirus infection. Indian J Sex Trasnsm Dis AIDS. 2013; 34(2): 77-82.
16. Kim SM. Human papilloma virus in oral cancer. J Korean Assoc Oral Maxillofac Surg. 2016; 42(6): 327-336
17. Crosbie EJ, Kitchener HC. Cervarix--a bivalent L1 virus-like particle vaccine for prevention of human papillomavirus type 16- and 18-associated cervical cancer.

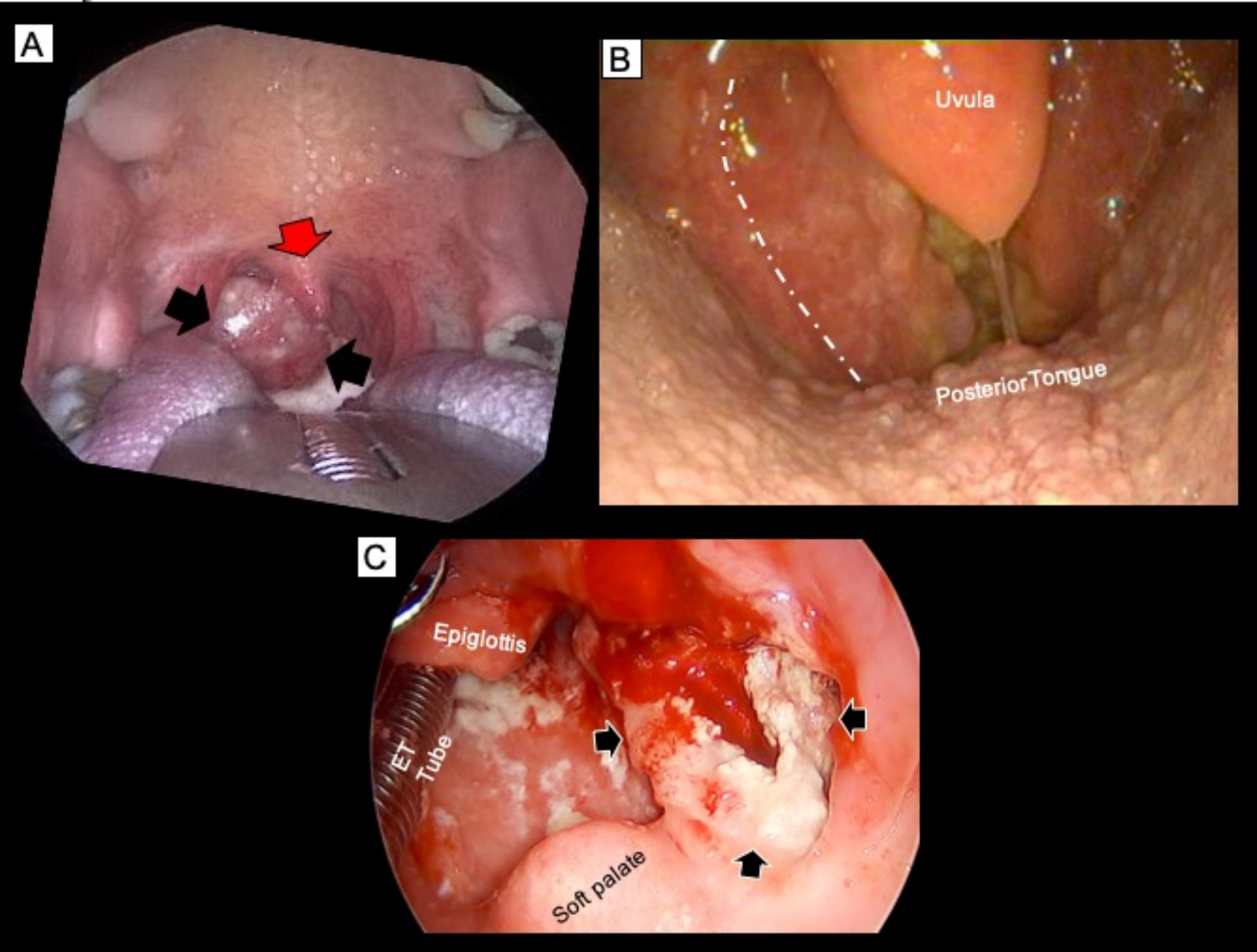
Expert Opin Biol Ther. 2007 Mar;7(3):391-6. PMID: 17309330

18. Shi L, Sings HL, Bryan JT et al. GARDASIL: prophylactic human papillomavirus vaccine development--from bench top to bed-side. Clin Pharmacol Ther. 2007 Feb;81(2):259-64. Review. PMID: 17259949
19. Huh WK, Joura EA, Giuliano AR et al. Final efficacy, immunogenicity, and safety analyses of a nine-valent human papillomavirus vaccine in women aged 16-26 years: a randomised, double-blind trial. Lancet. 2017 Nov 11;390(10108):2143-2159. doi: 10.1016/S0140-6736(17)31821-4. Epub 2017 Sep 5. PMID: 28886907
20. HPV Vaccine overview [Internet]. United Kingdom: NHS [accessed 24 April 2020] Available at: https://www.nhs.uk/conditions/vaccinations/hpv-human-papillomavirus-vaccine/
21. Brisson M, Benard E, Drolet M, Bogaards JA et al. Population-level impact, herd immunity, and elimination after human papillomavirus vaccination: a systematic review and meta-analysis of predictions from transmission-dynamic models. Lancet Public Health 2016; 1(1): e8-e17
22. Public Health England. HPV vaccination programme. GOV.UK (2019)
23. Public Health England. Press release: HPV vaccine drives cancer causing infections down to very low levels. 22 January 2020. www.gov.uk
24. de Oliveira CM, Fregnani JHTG, Villa LL. HPV vaccine: Updates and highlights. Acta Cytol 2019; 63(2): 159-168
25. International Agency for Research on Cancer. WHO classification of Head and Neck tumours (World Health Organisation Classification of Tumours) 4th Edition 2017. ISBN 9283224388
26. AJCC Cancer Staging Manual. 8th Edition. Springer 2017. ISBN 3319406176
27. Dave B. Why do GDPs fail to recognise oral cancer? The argument for an oral cancer checklist. Br Dent J. 2013; 214(5): 223-5

28. McGurk M, Scott SE. The reality of identifying early oral cancer in the general dental practice. Br Dent J. 2010; 208(8): 347-51


Hard Palate
Nasopharynx
Soft Palate
C1
Circumvallate Papillae
Oropharynx
C2
Root of tongue
Tongue Base
Genioglossus/ Geniohyoid/Mylohyoid
C3
Epiglottis
Valleculae
C4
Hyoid
C5
Laryngopharynx
C6
Thyroid Cartilage
Oesophagus
Cricoid
C7
Trachea
T1


Hard Palate
Maxillary Alveolus
Soft palate & uvula
Anterior tonsillar pillar
(Palatoglossus)
Tonsil
Posterior tonsillar pillar
(Palatopharyngeus)
Posterior pharyngeal
wall
Circumvallate papillae/
tongue base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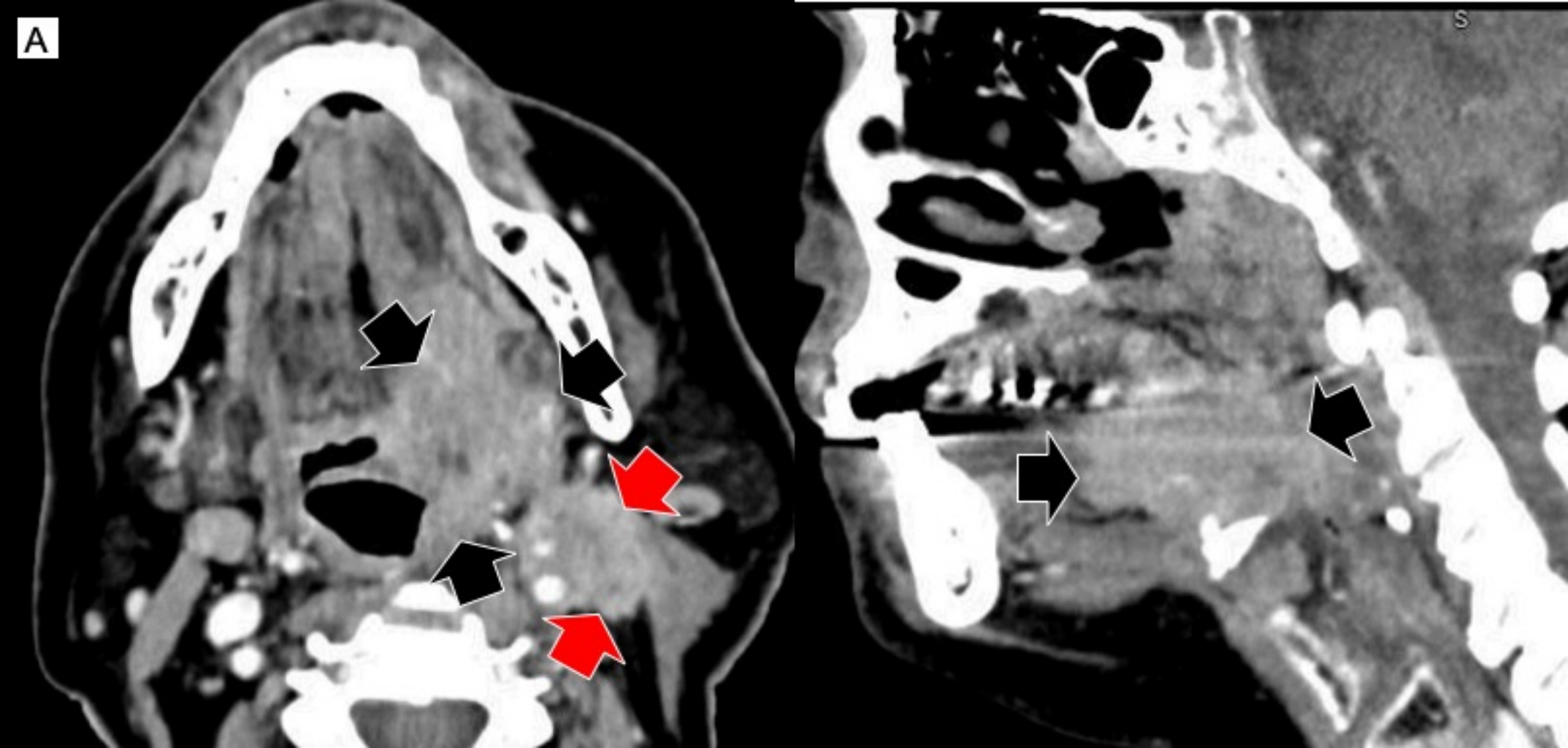
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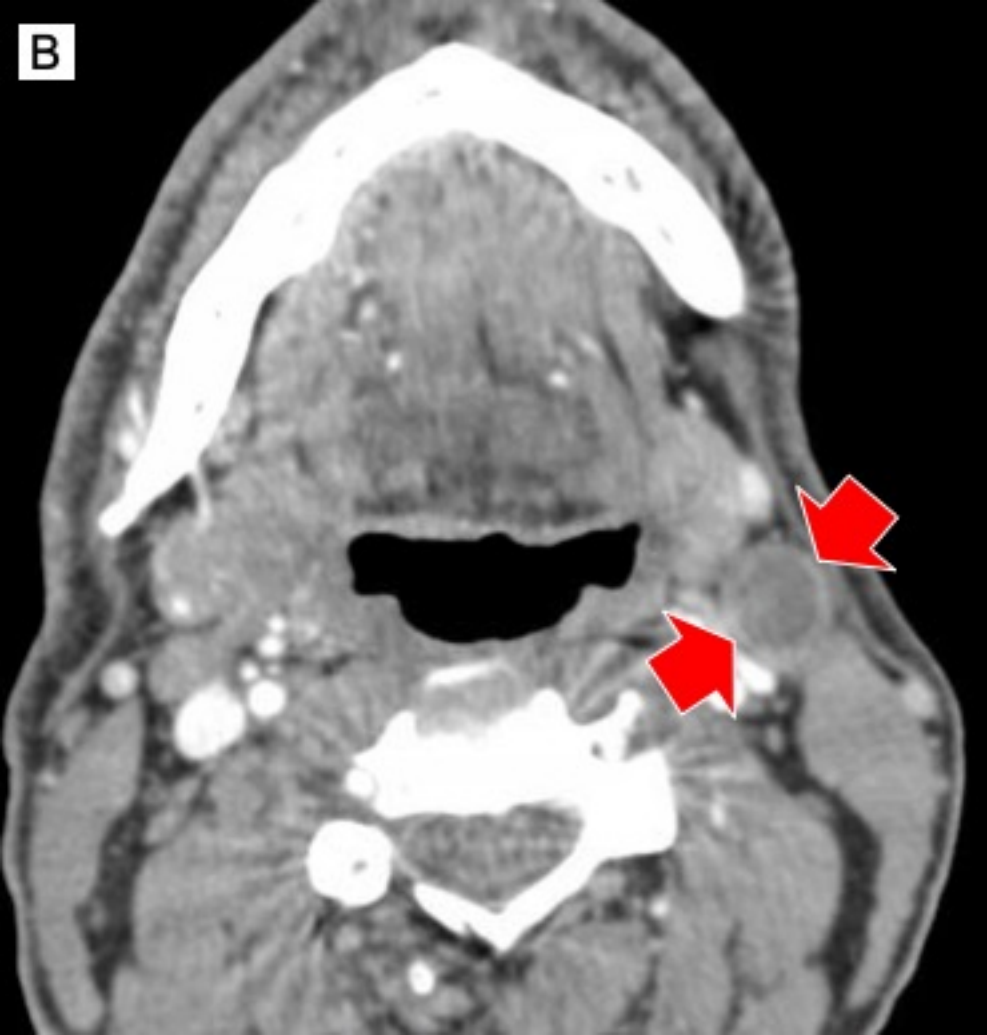
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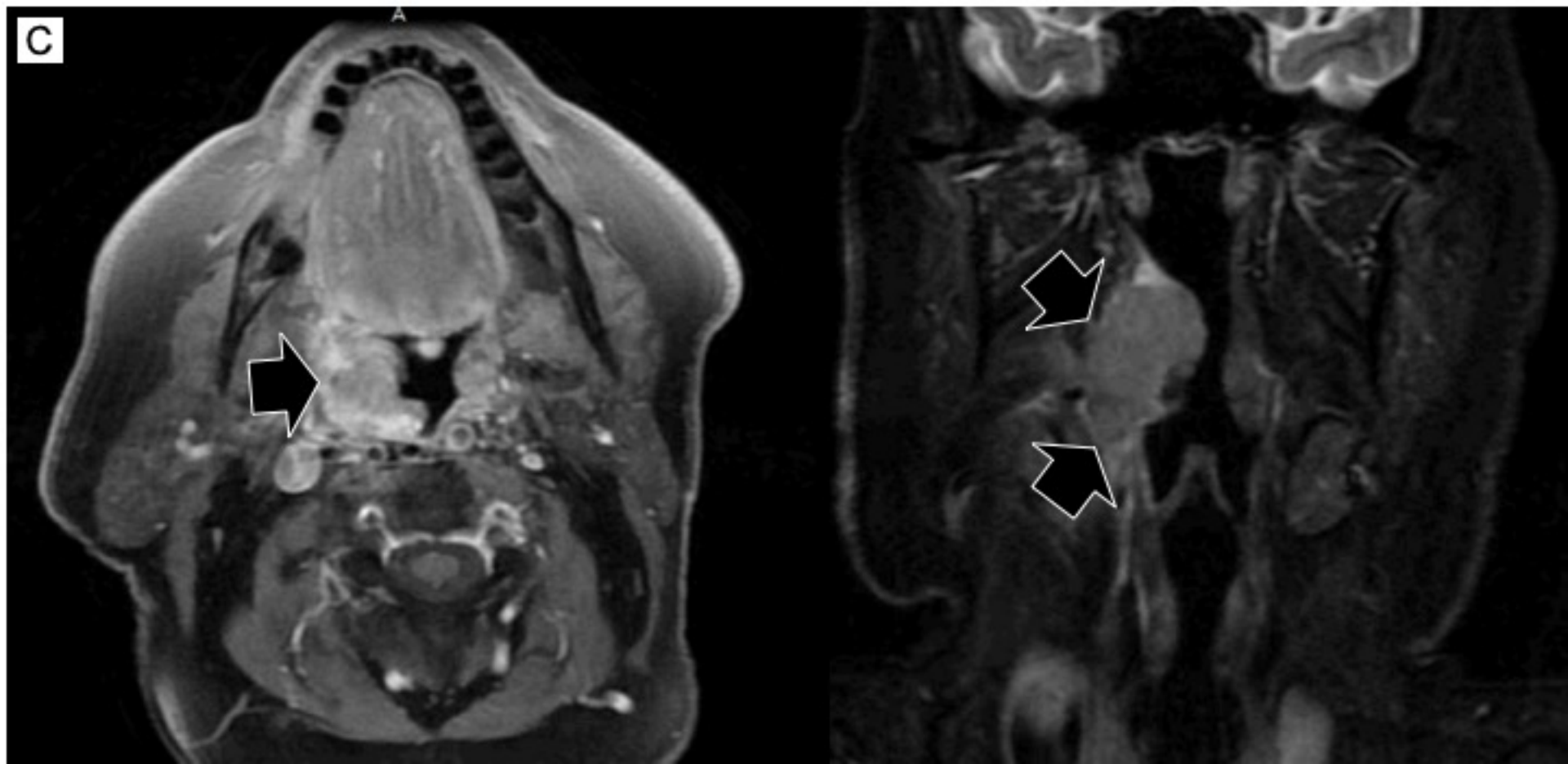
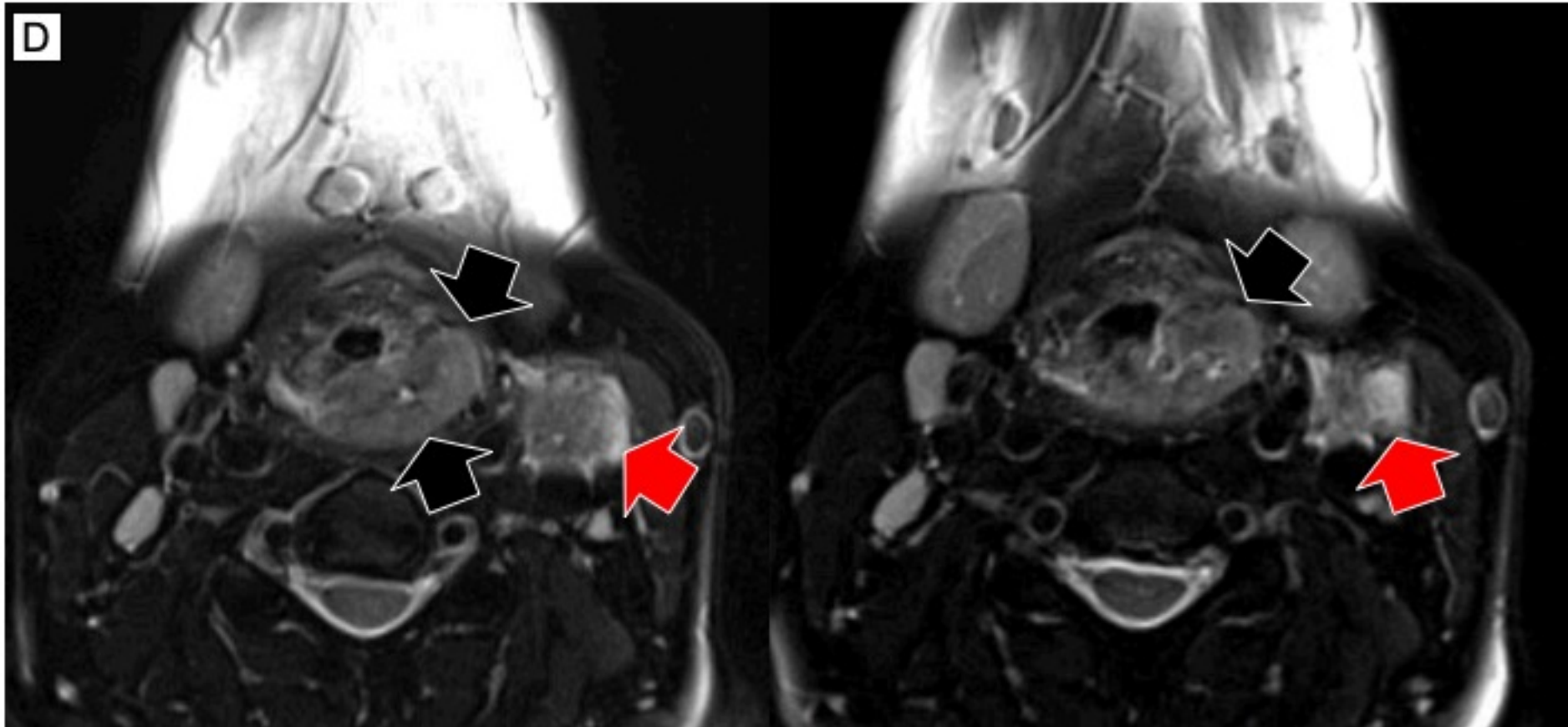

C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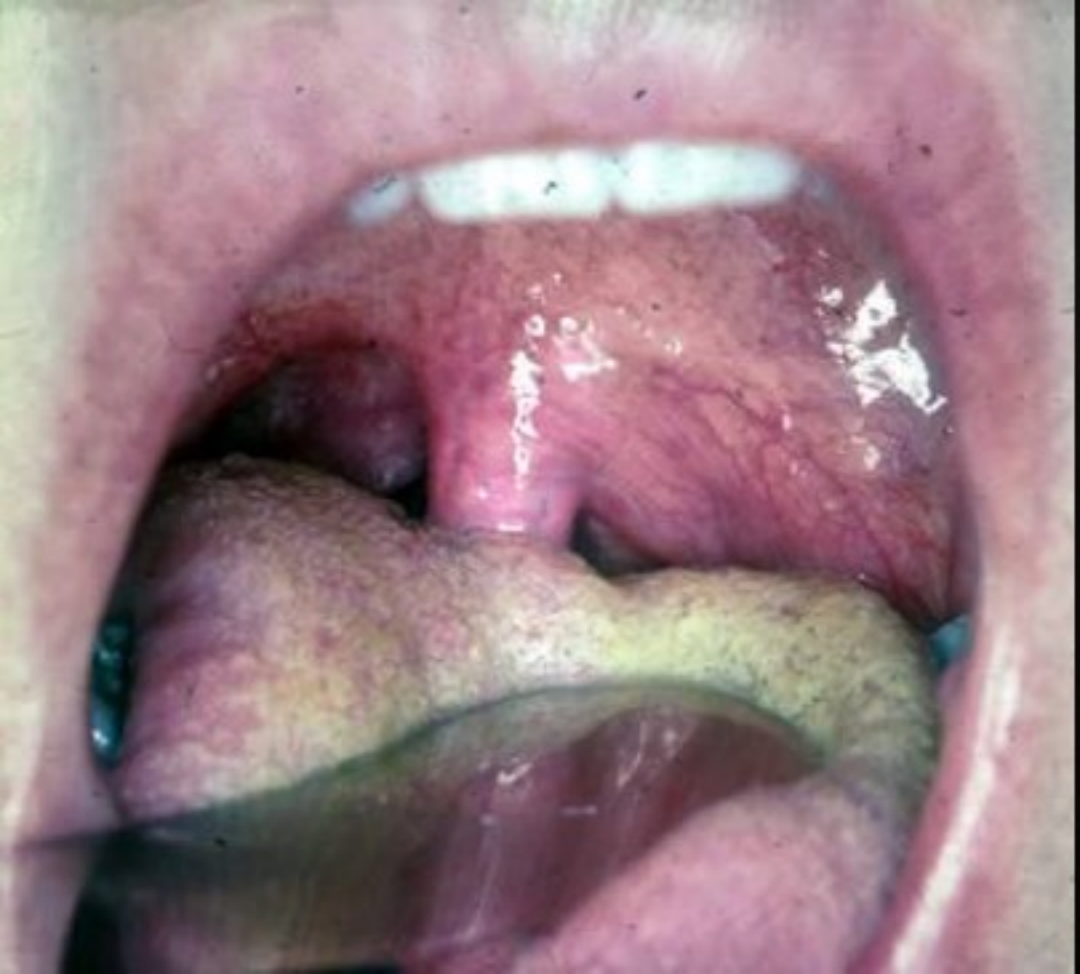
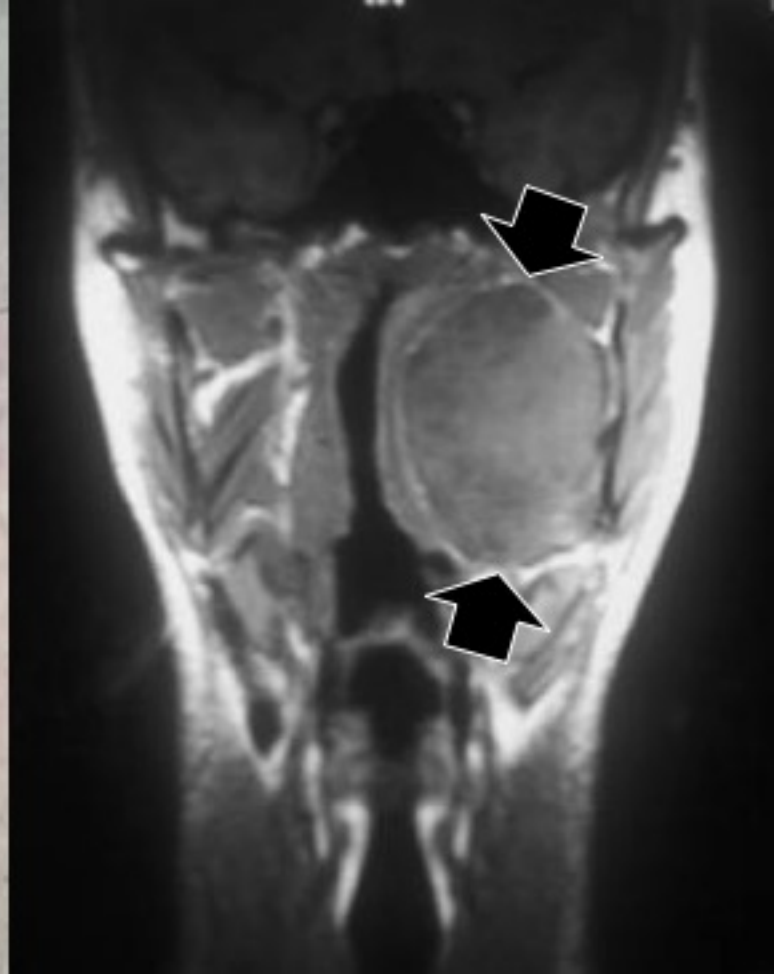
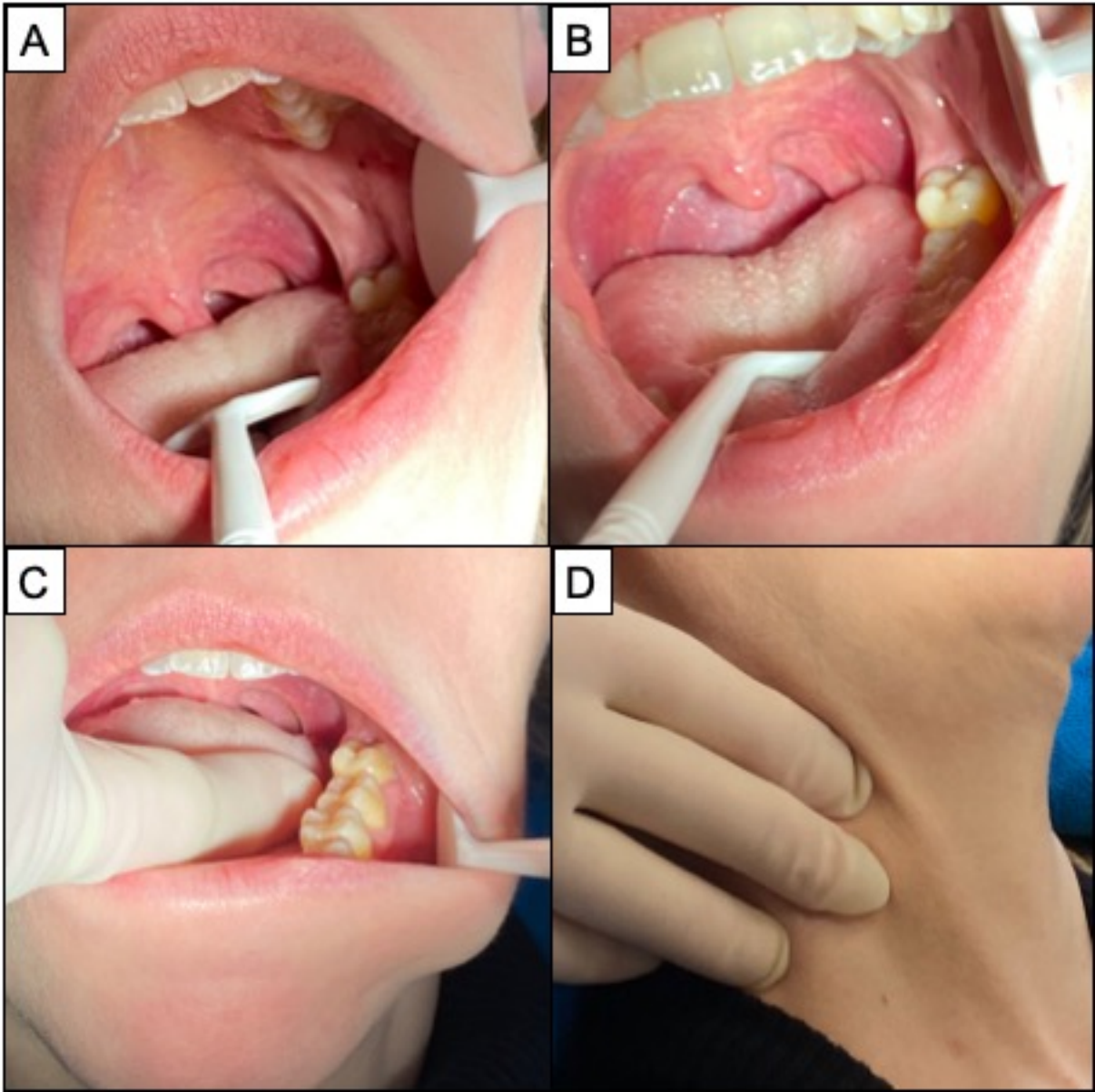
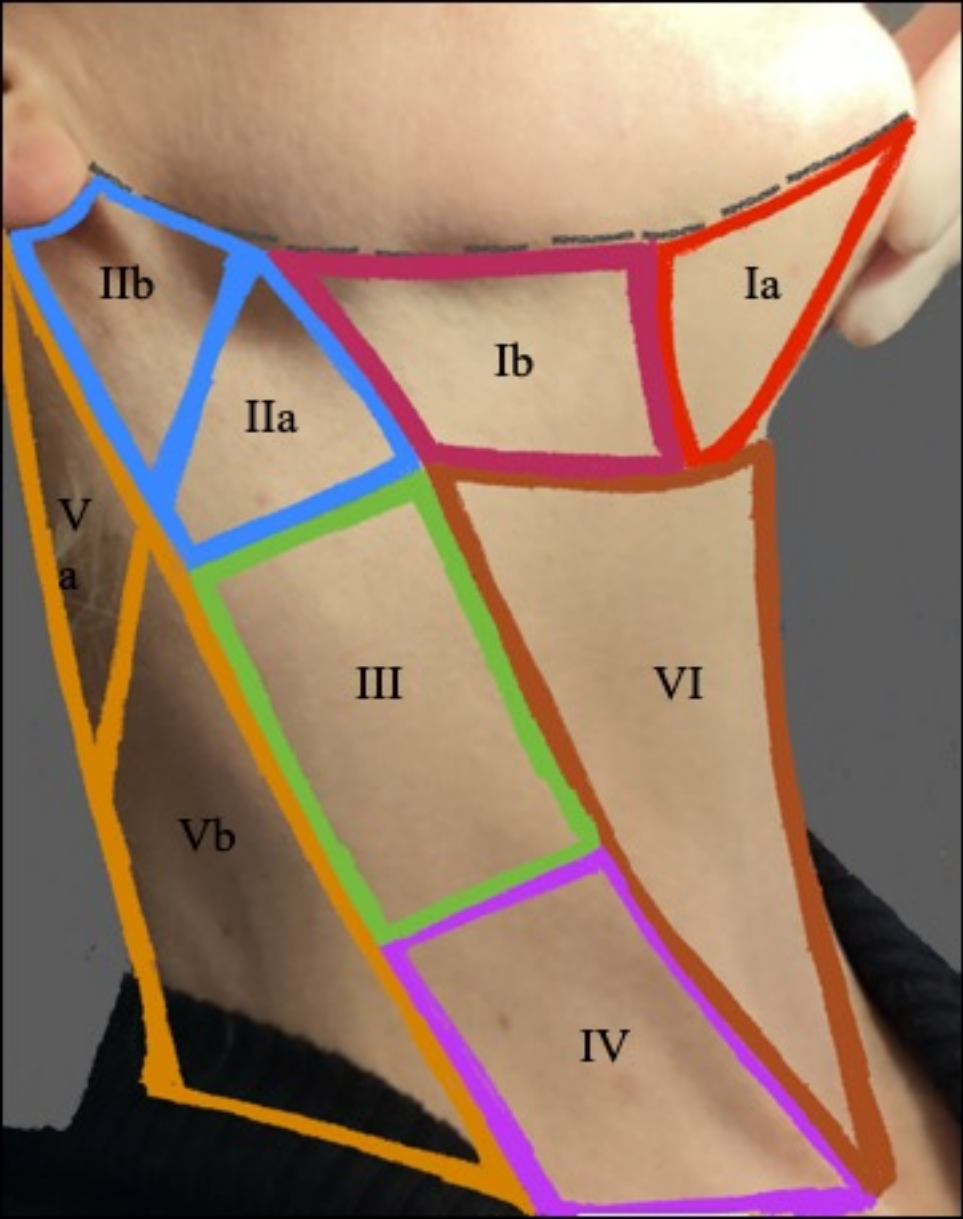





A
B
C
D


IIb
Ia
Ib
IIa
V
a
III
VI
Vb
IV