Neck Carcinoma of Unknown Primary (NCUP)

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Terminology

- Squamous Cell Carcinoma of Unknown Primary (SCCUP)
- Carcinoma of Unknown Primary (CUP)

- **Neck** Carcinoma of Unknown Primary (NCUP)
    - More accurate description

- History
- Introduction
- Anatomy
- Classification
- Diagnosis
- Management

Hayes Martin

- **1950**
- “An adult patient who presents with a palpable lateral neck mass, whether solid or cystic, should be considered to have a metastatic lymph node until proven otherwise”

- The case for branchiogenic cancer (malignant branchioma). Ann Surg (1950) 132(5):867–87. doi: 10.1097/ 00000658-195011000-00002

- Metastatic CA in cervical lymph node
  - suspicious lymph nodes in levels I, II, III, IV and V in the neck
- Without identifiable primary after appropriate investigation .
- Highly curable disease
- Mostly SCC
- 2-4% of head and neck SCCa
- M:F 6:1

- **Important to distinguish between cancers where the 1^0 will be identified after investigation and the true CUP**

- The patient with proven or suspected metastatic cancer in the cervical nodes and no evident primary cancer represents a unique challenge.
- Identification of the primary site allows us to direct appropriate treatment strategies
- Incidence of patients with NCUP is increasing with the increasing numbers of HPV-related oropharyngeal cancers (OPCs)

HYPOTHESIS

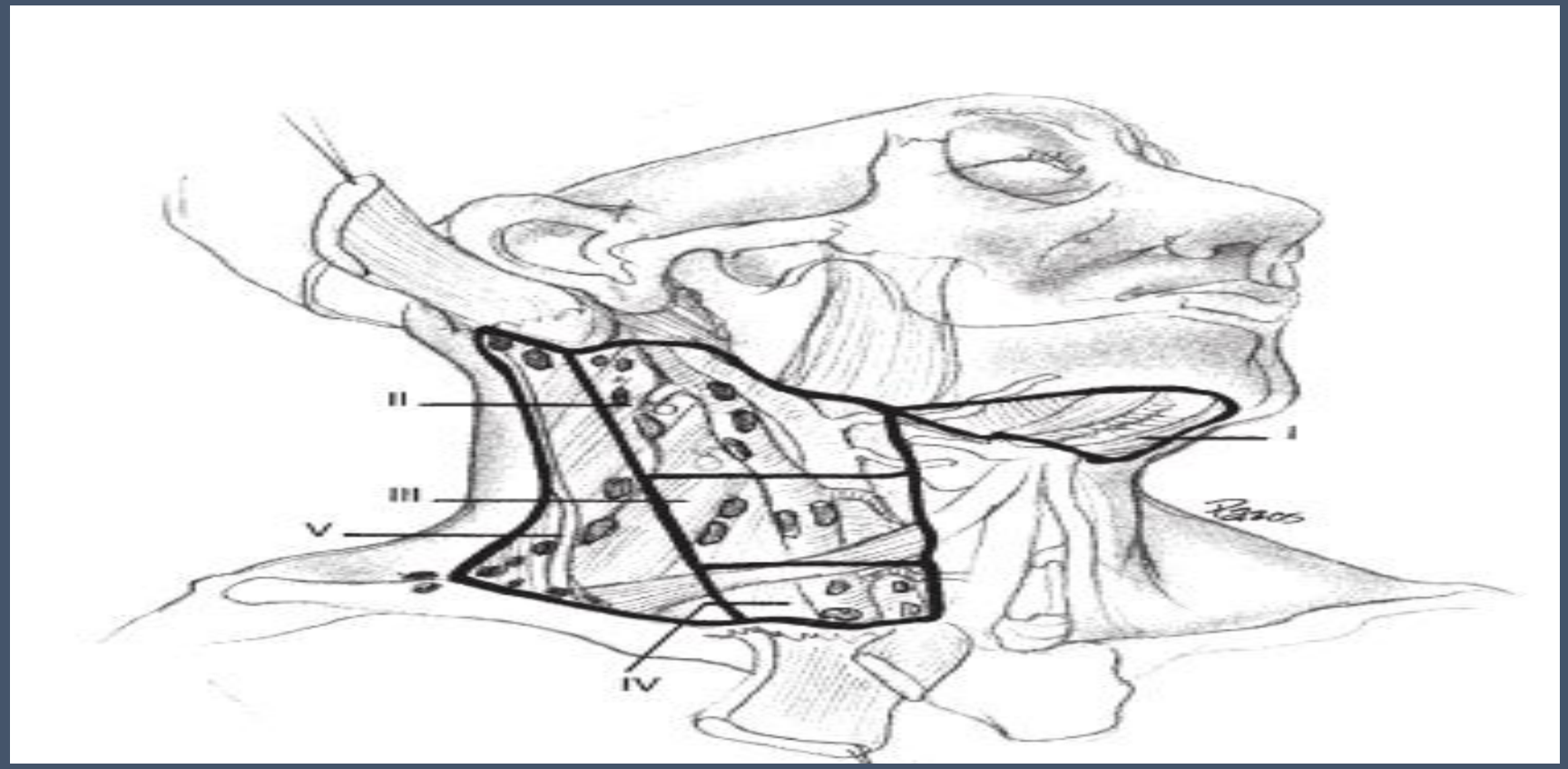
- **Primary tumor has involuted and is not detectable**
- Malignant phenotype favors metastases over primary tumor growth
- Primary lesion can be identified in only 30-80% of cases at autopsy
- **The rate of emerging primary tumour varied from 7% to 20%**
    - within 2 years after treatment

- Perkins SM, Spencer CR, Chernock RD, Haughey BH, Nussenbaum B,Adkins DR, et al. Radiotherapeutic management of cervical lymph node metastases from an unknown primary site. Arch Otolaryngol Head Neck Surg (2012) 138(7):656–61. doi: 10.1001/archoto.2012.1110

NCUP
Pathological subtypes

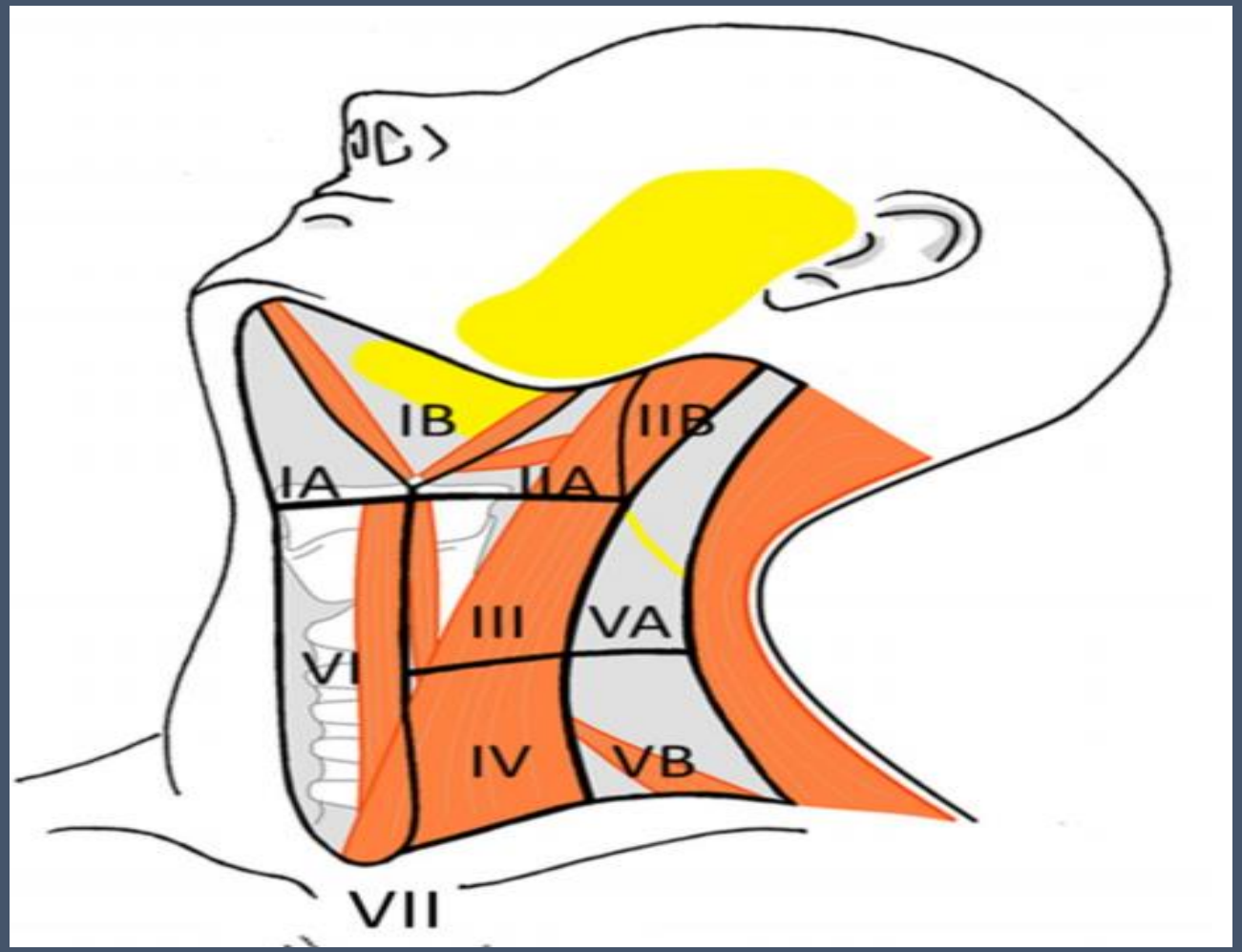
- SCC 75 %
  - 90 % HPV positive
- Undifferentiated carcinoma
- Adenocarcinoma
- Lymphoepithelial carcinoma

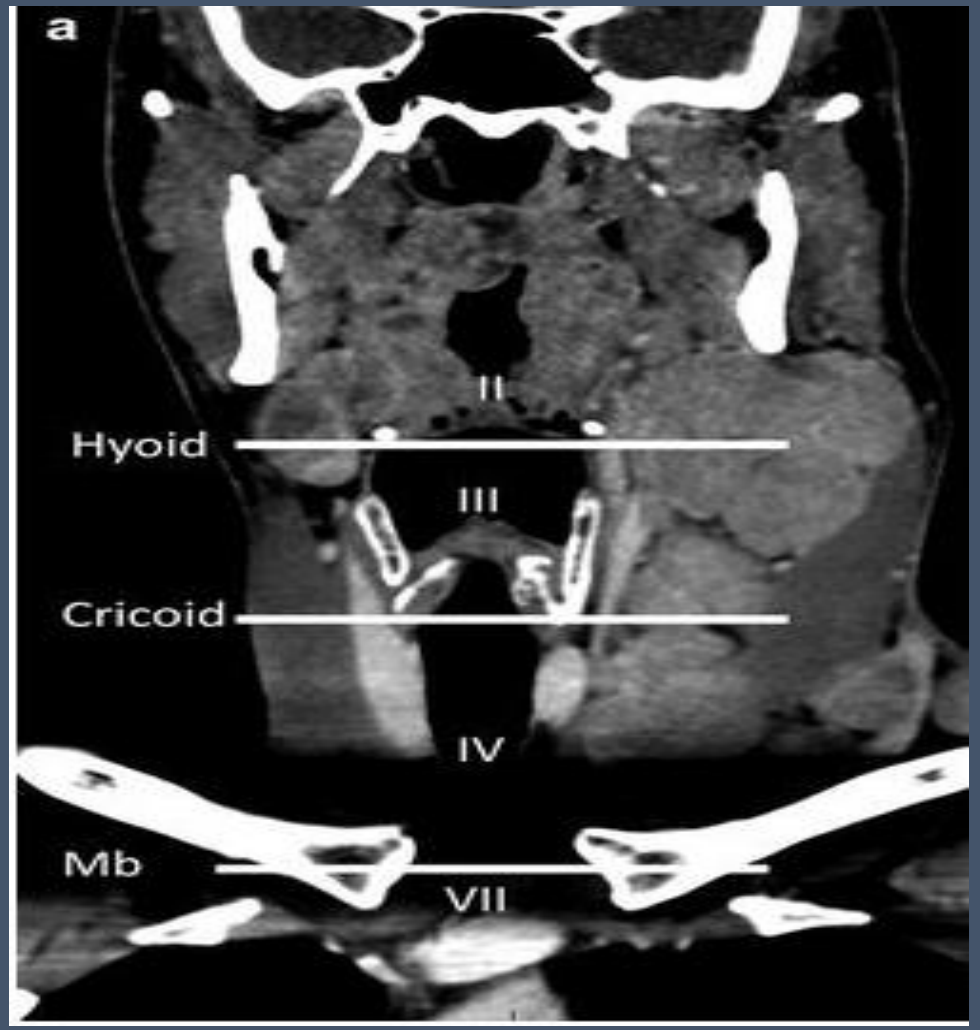
Neck anatomy



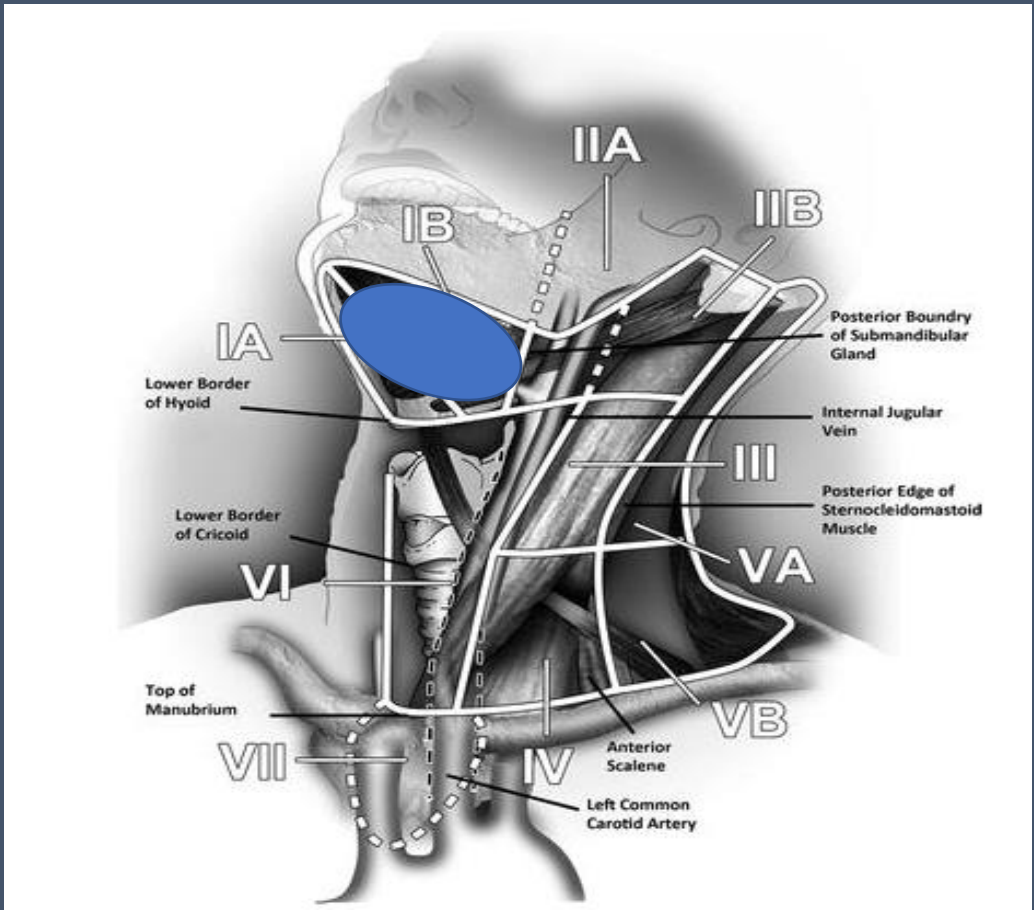
https://radiopaedia.org/cases/lymph-node-levels-of-the-head-and-neck-annotated-ct?case_id=lymph-node-levels-of-the-head-and-neck-annotated-ct

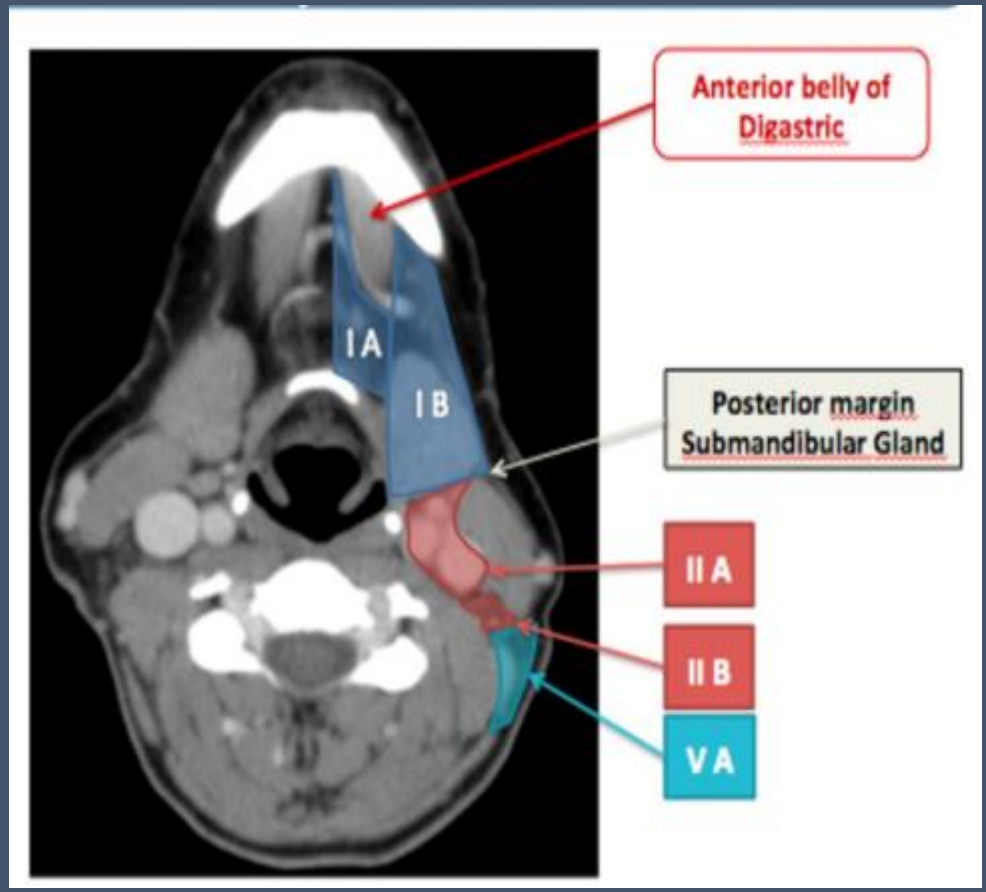
Neck anatomy





Level I


IIA
IB
IIB
IA
Posterior Boundry of Submandibular Gland
Lower Border of Hyoid
Internal Jugular Vein
III
Posterior Edge of Sternocleidomastoid Muscle
Lower Border of Cricoid
VI
VA
Top of Manubrium
VB
VII
IV
Anterior Scalene
Left Common Carotid Artery


Anterior belly of Digastric
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Posterior margin Submandibular Gland
IIA
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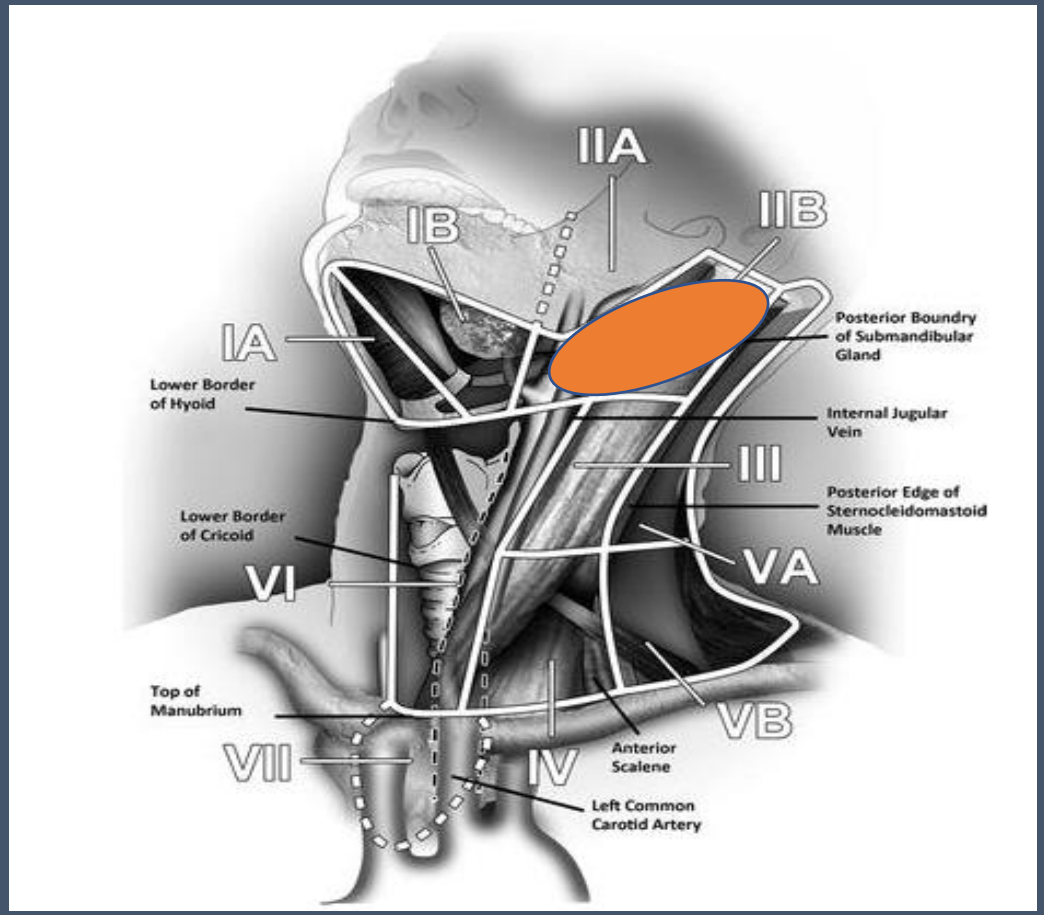
Level II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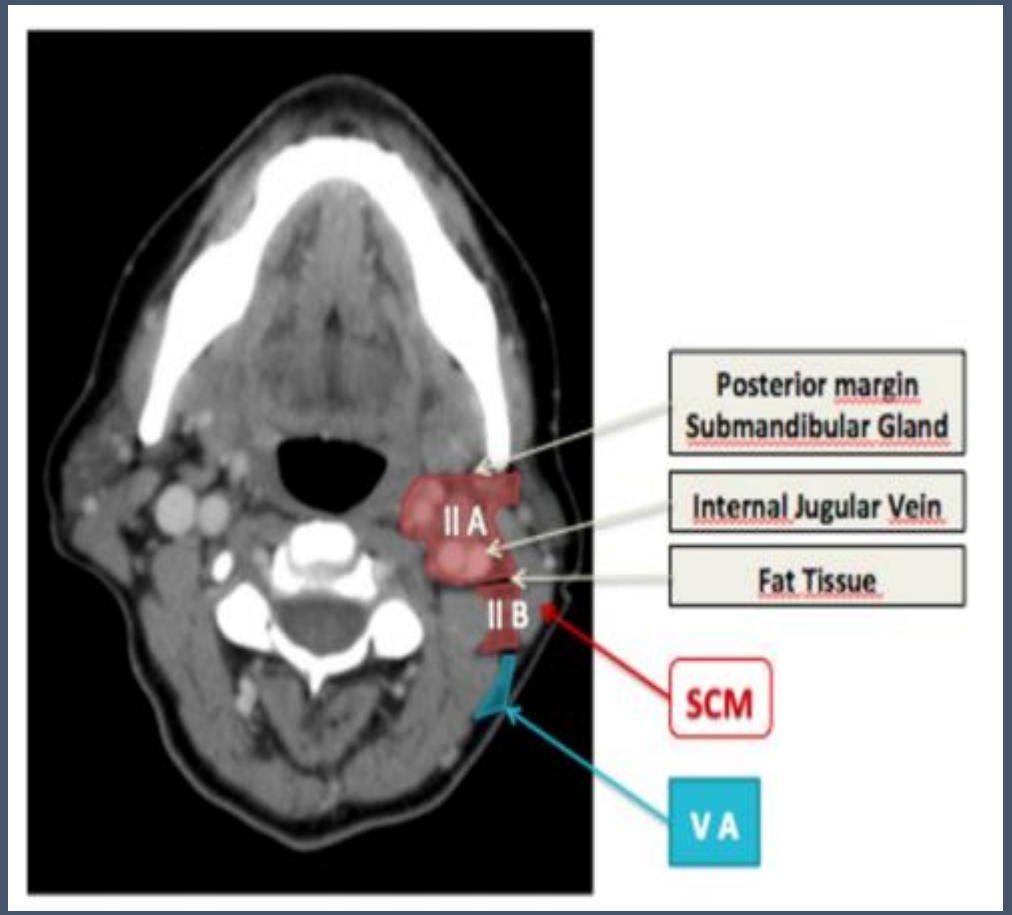
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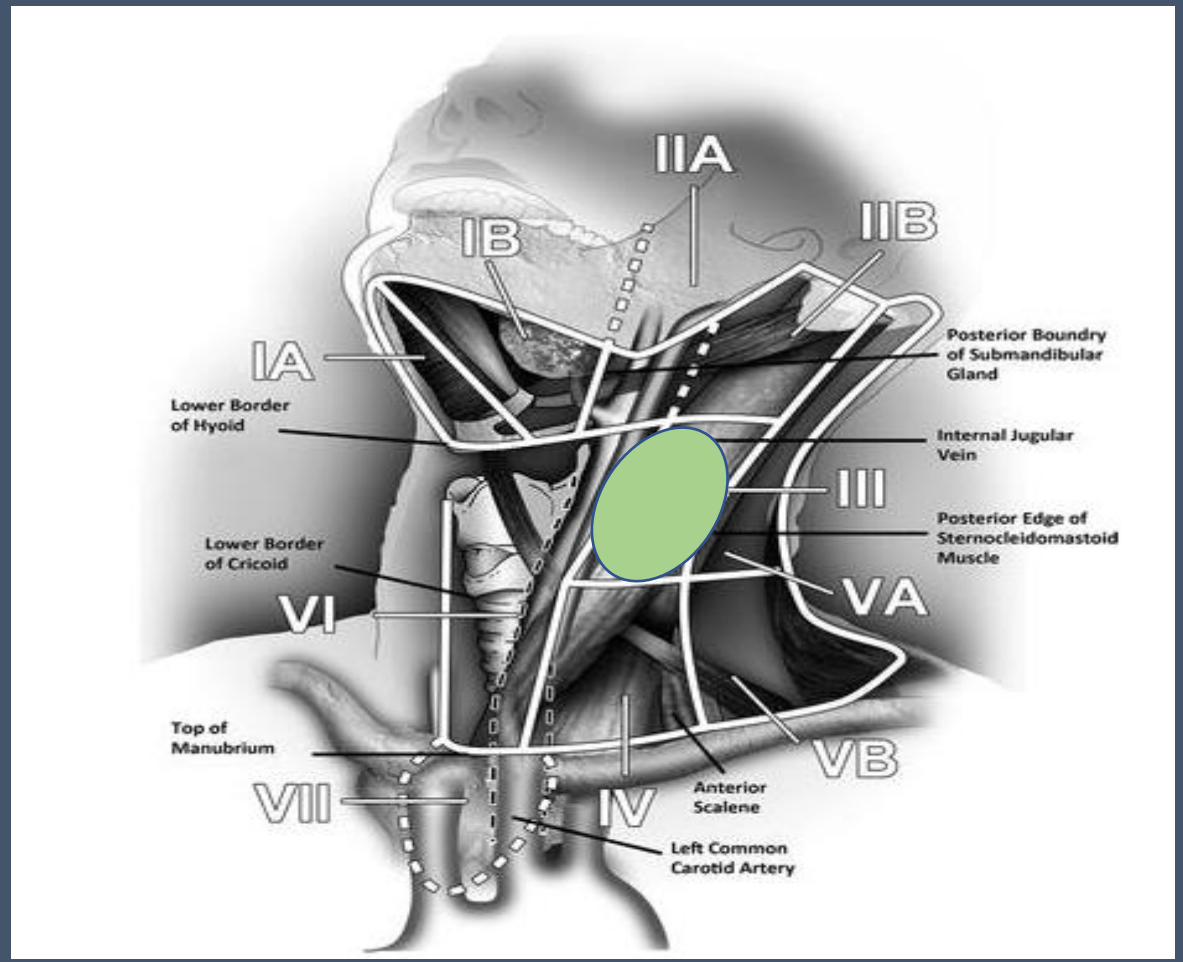
II B
Posterior margin Submandibular Gland
Internal Jugular Vein
Fat Tissue
SCM
VA

Level III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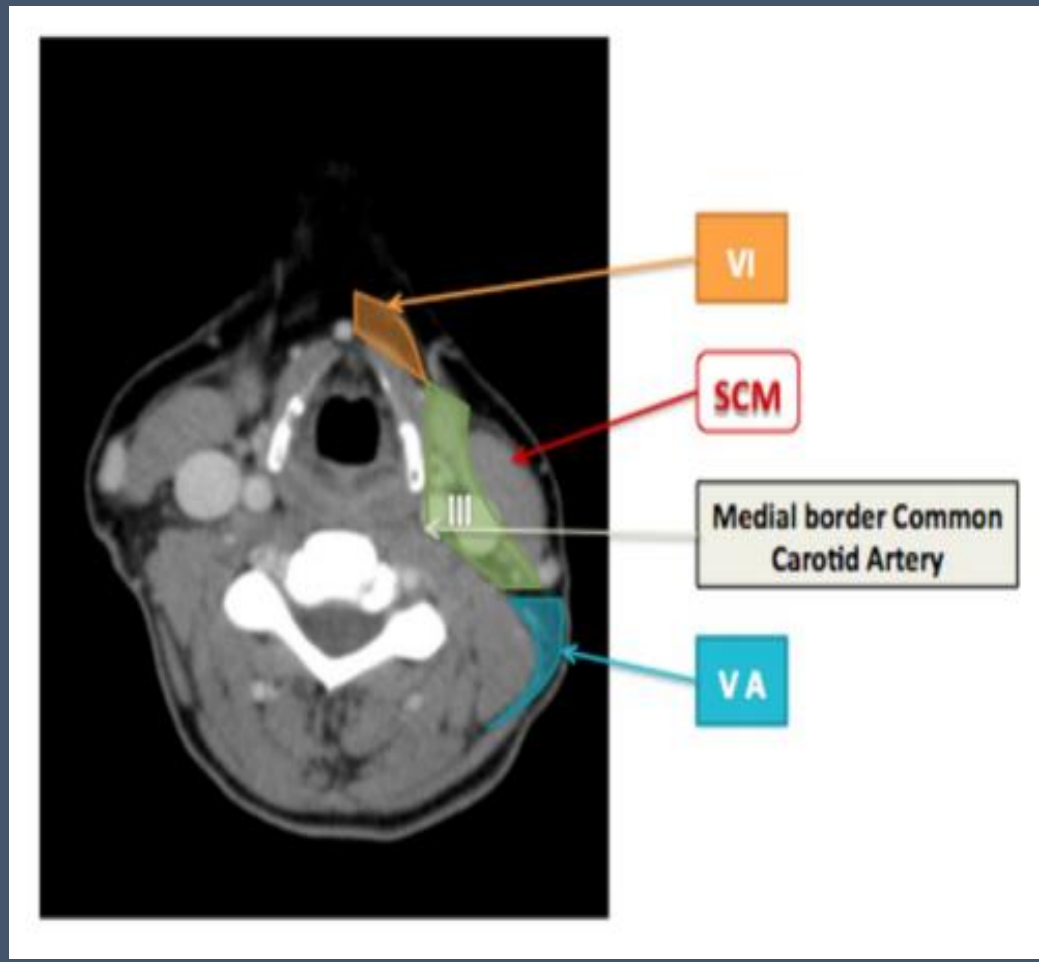
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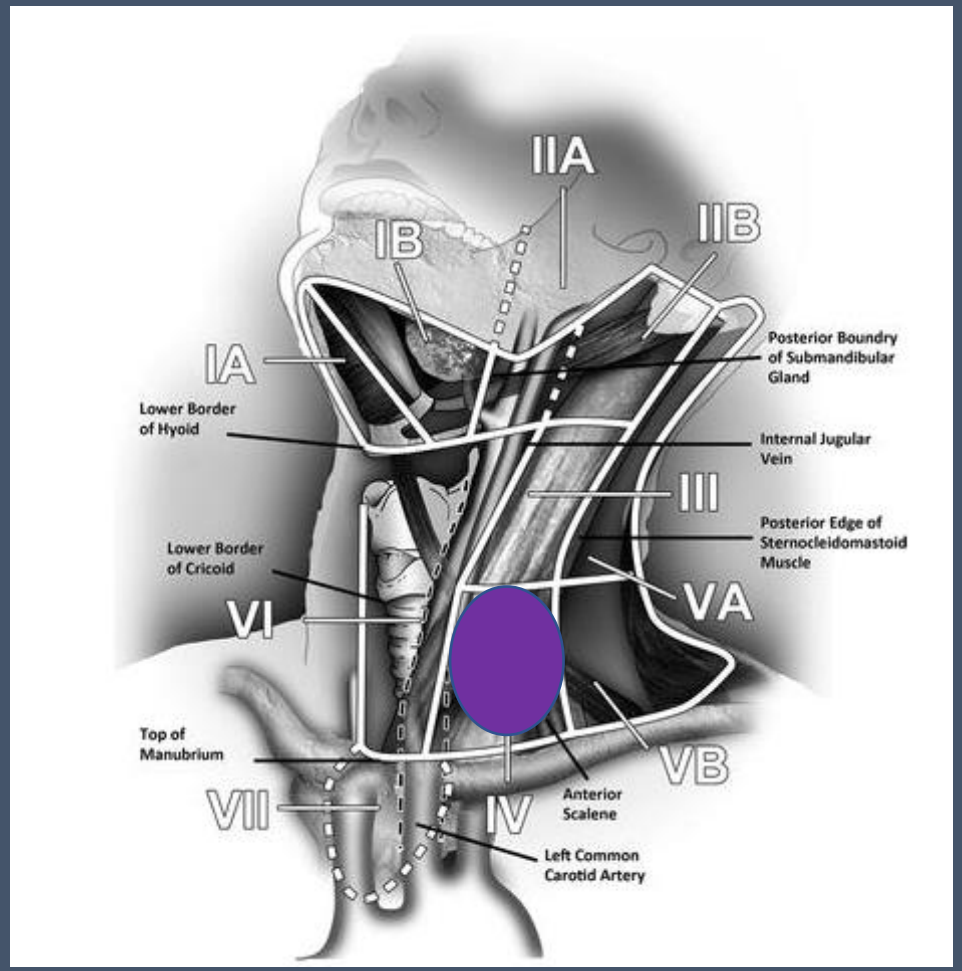
SCM
III
Medial border Common Carotid Artery
VA

Level IV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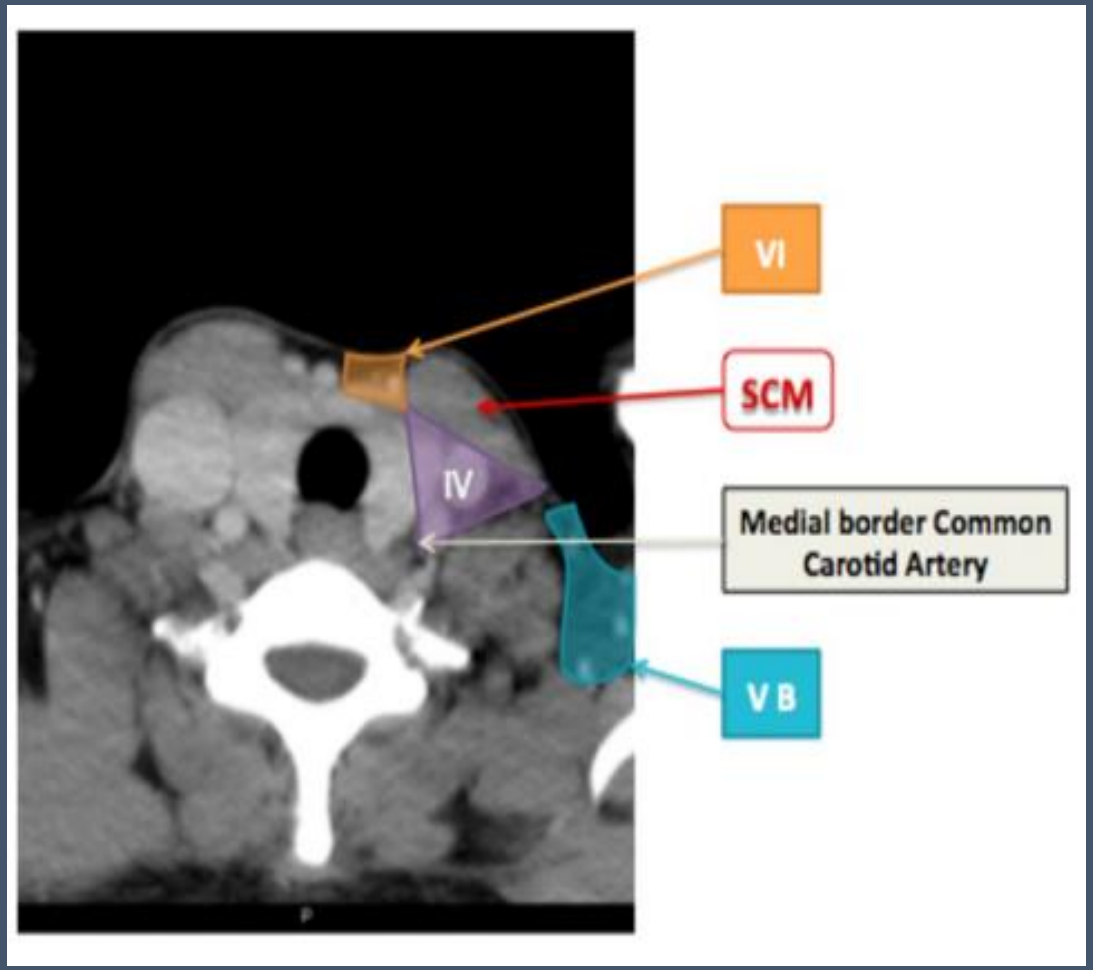
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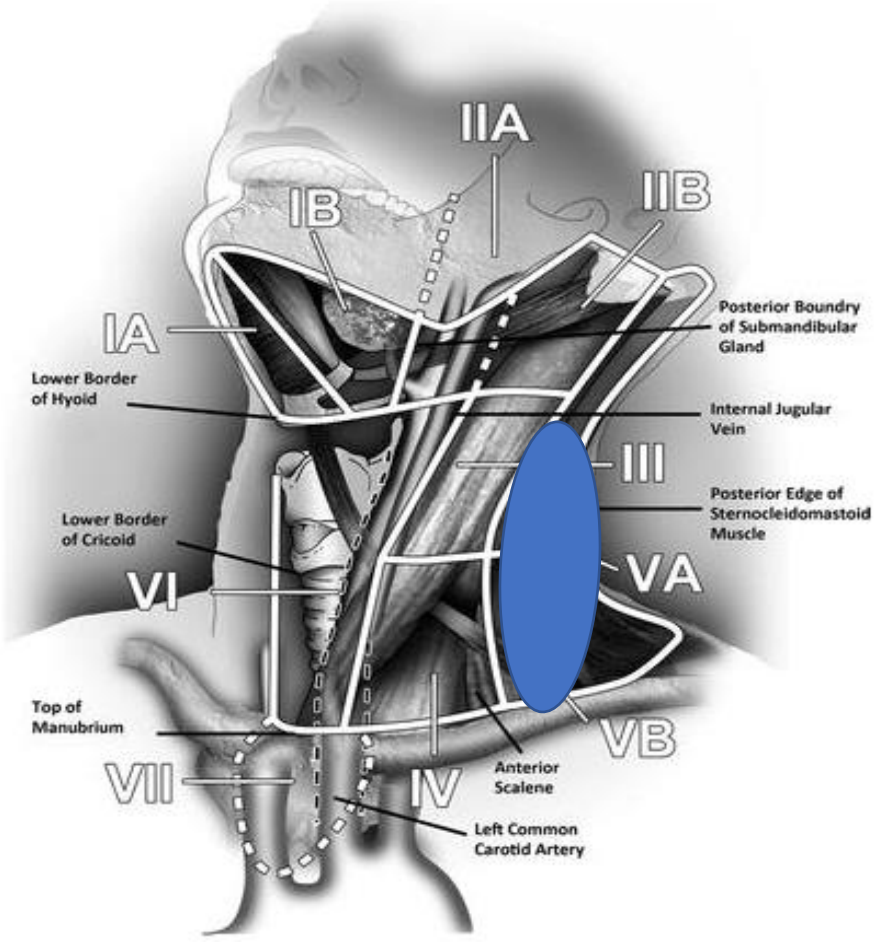
Medial border Common Carotid Artery
VB

Level V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Left Common Carotid Artery


VI
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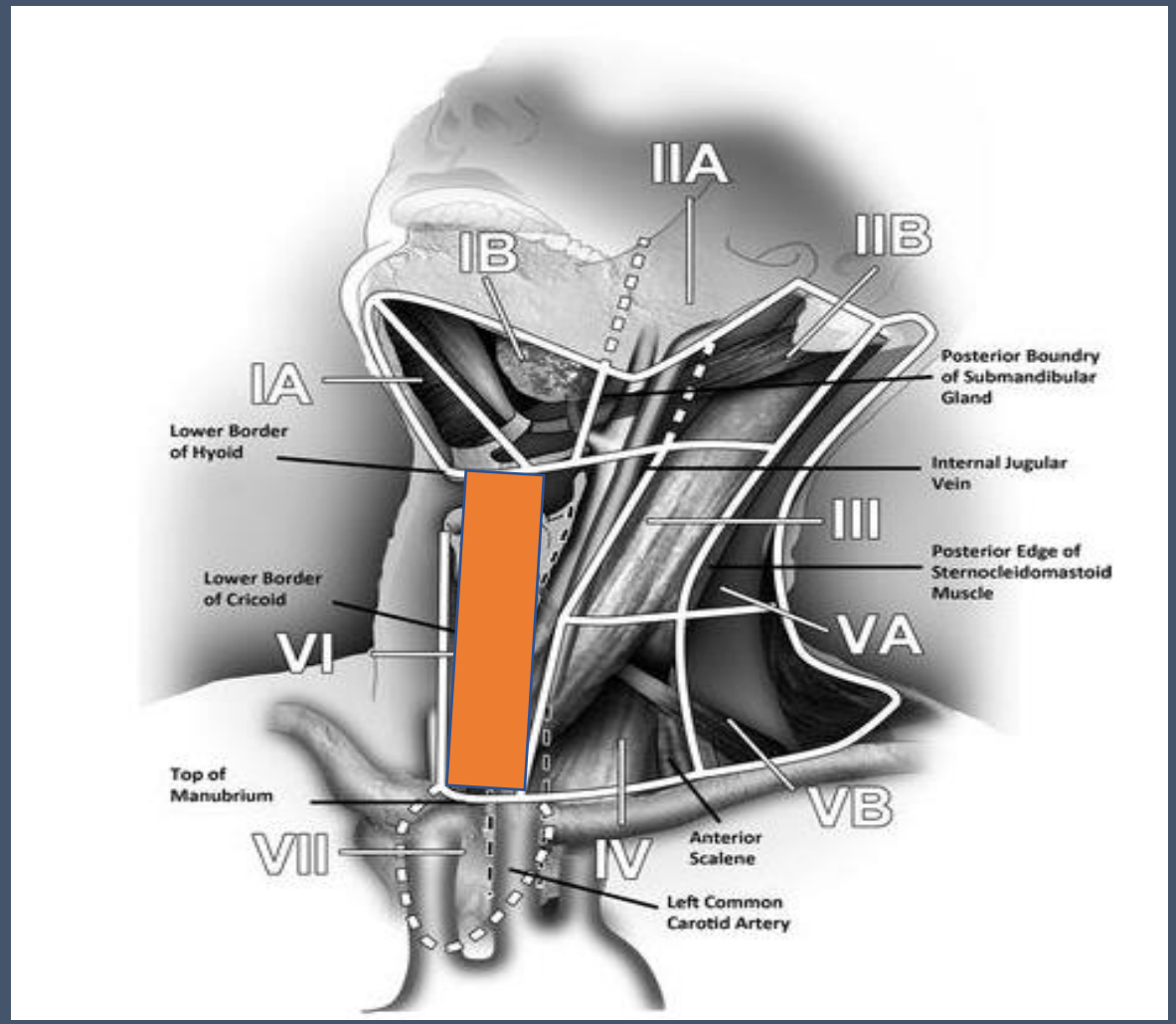
SCM
VA
Trapezius

Level VI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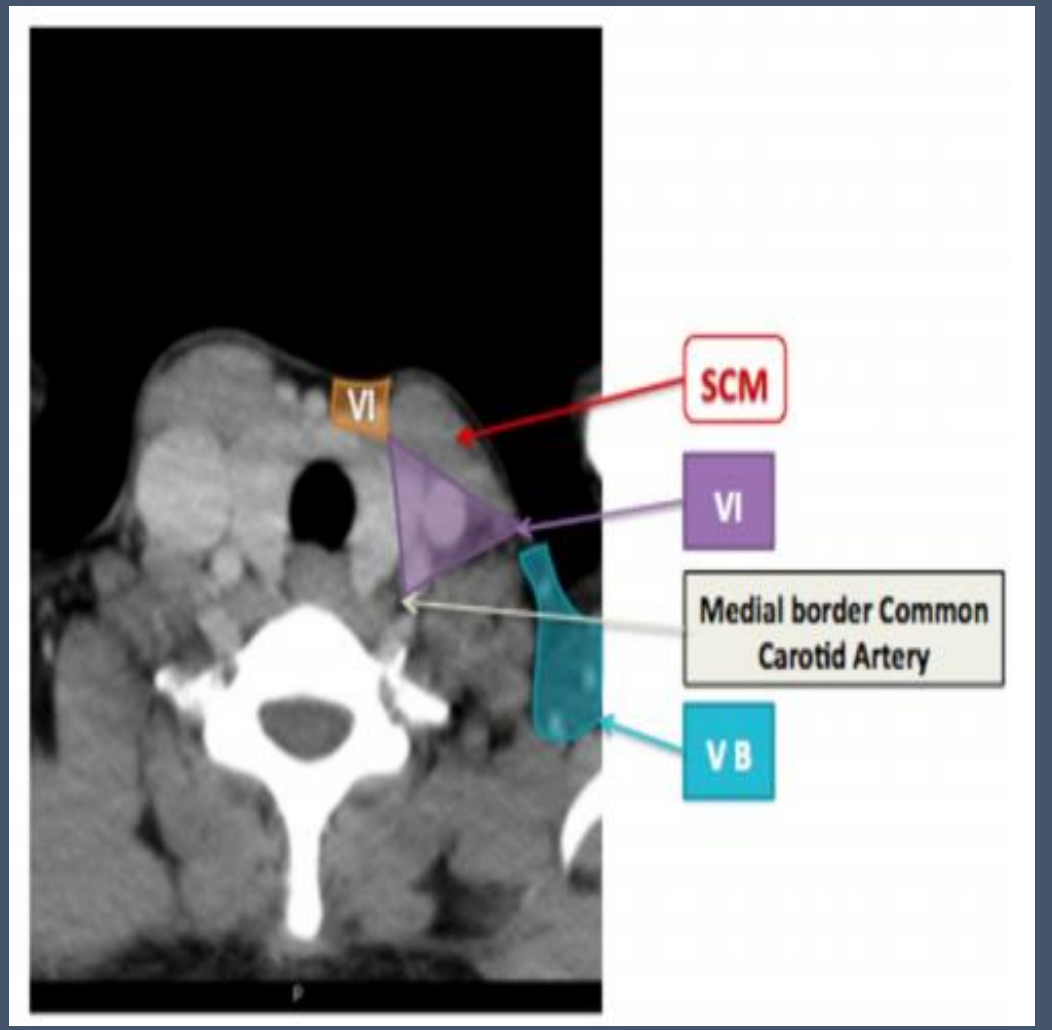
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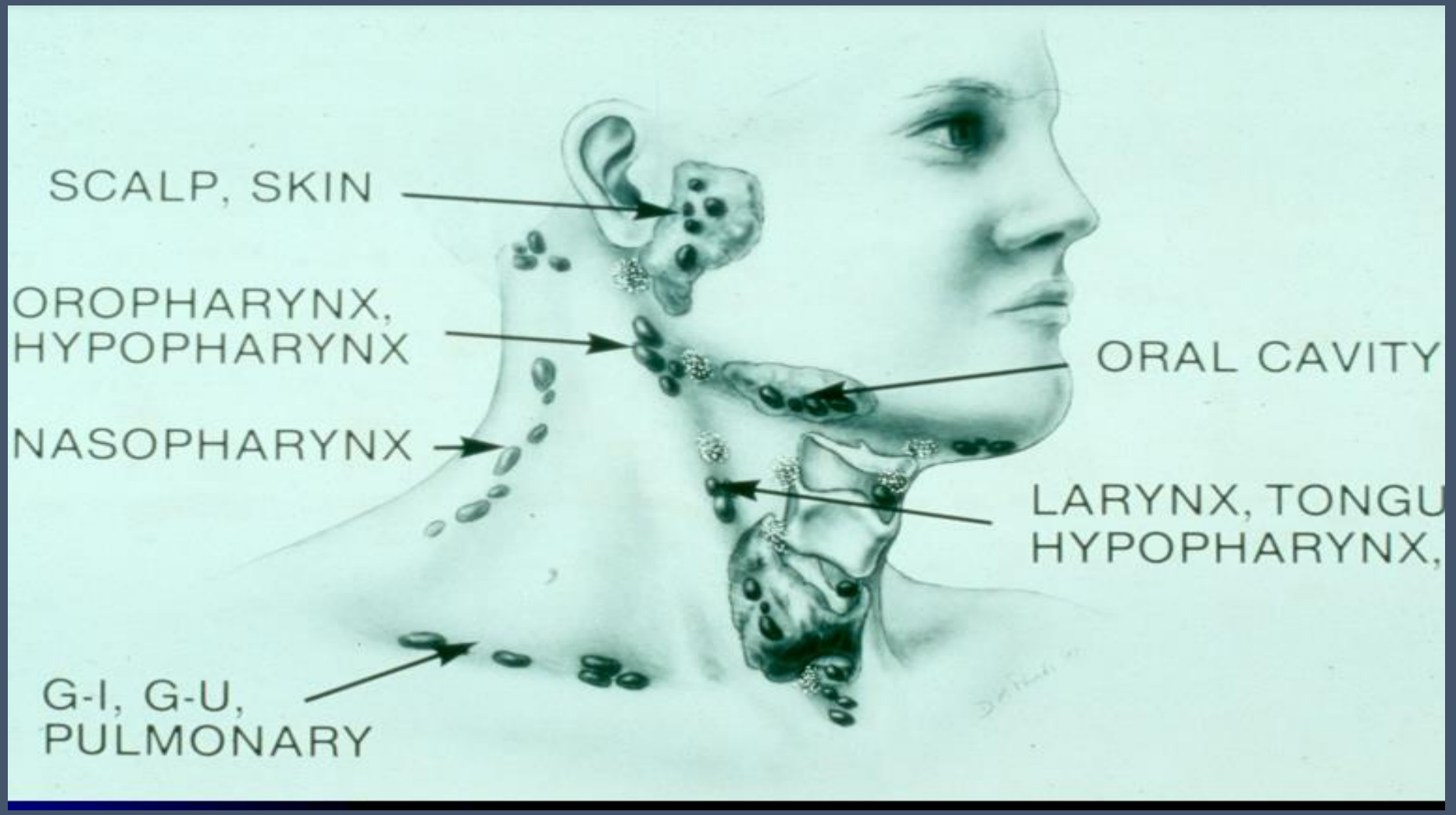
SCM
VI
Medial border Common Carotid Artery
V B

Lymphatic drainage



Level of the involved lymph nodes may offer insight into the location of the primary site and may also guide the diagnostic evaluation

Clinical presentation
History

- Neck mass
  - Painless
  - Weeks – months
- Weight loss
- Risk factors :
  - Tobacco Smoking
  - Alcohol
  - Radiation therapy @ childhood
  - Sun exposure

Clinical presentation
Examination

- Palpation of the neck
    - All the levels
    - **Salivary glands**
    - **Thyroid**

- Meticulous physical examination of the **upper aerodigestive tract**
    - Fiberoptic nasopharyngoscopy and laryngoscopy

- Inspection of the **skin**
- Cranial nerve function

ENDOSCOPIC PROCEDURES
Narrow band imaging

- The obvious limitations of random biopsies led to the development of technologies.

- Help the head and neck surgeon identify the proper site to biopsy
    - Find a primary tumour that is imperceptible to the eye.

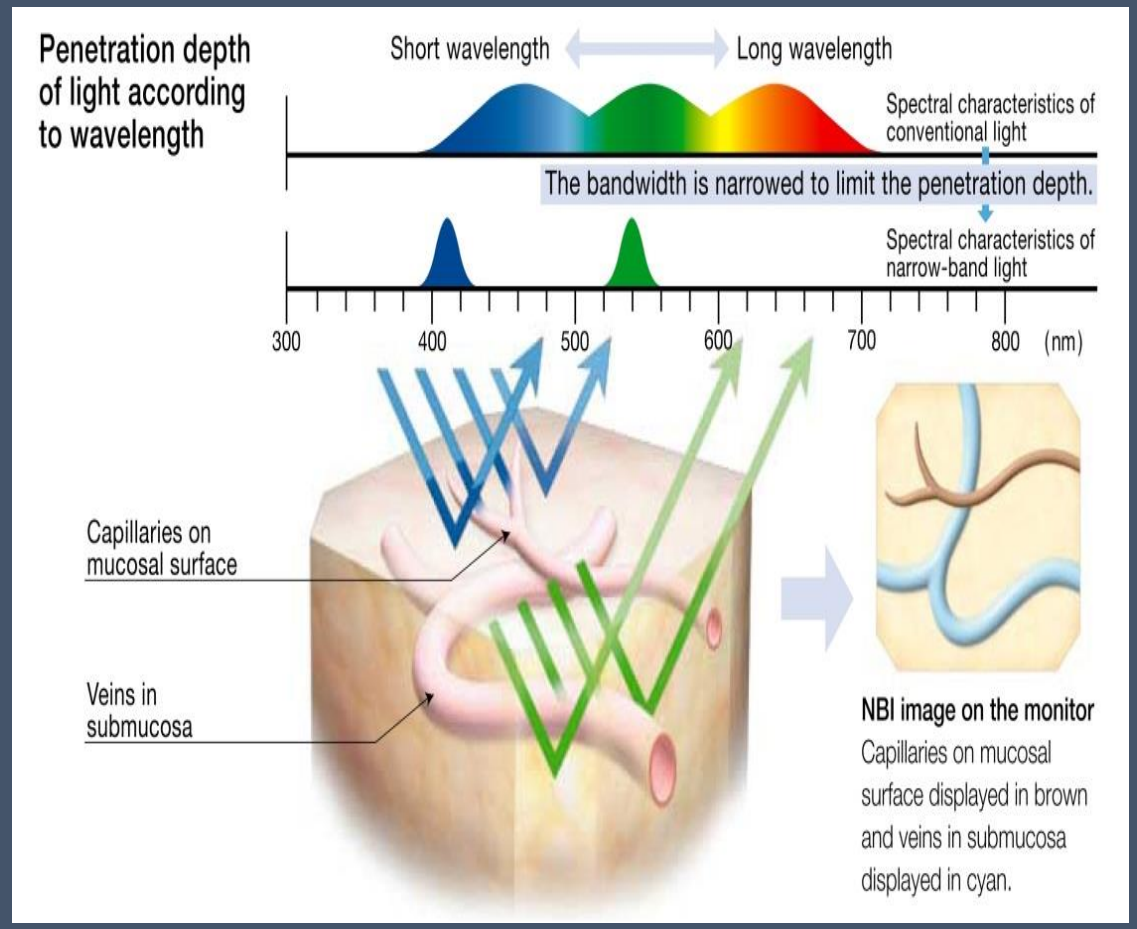
- MOA : works by restricting light to two spectral wavelengths, **the blue (400-430nm)** and **green (525-555 nm).**
    - The blue enhances capillaries and green enhances deeper blood vessels
    - Allow lesion easier to be detected

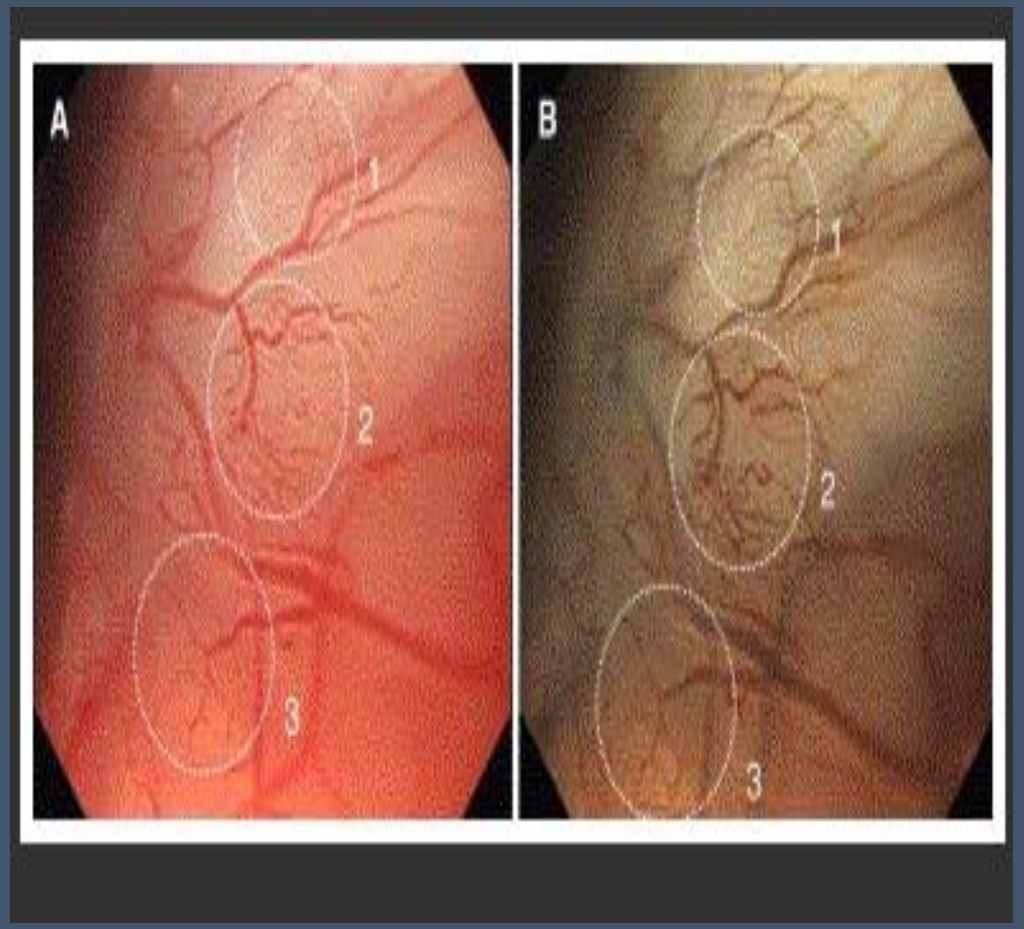
- It can be used during office fibreoptic nasopharyngoscopy or at the time of pan endoscopy under anaesthesia

- Sensitivity : 74 % , specificity : 86%

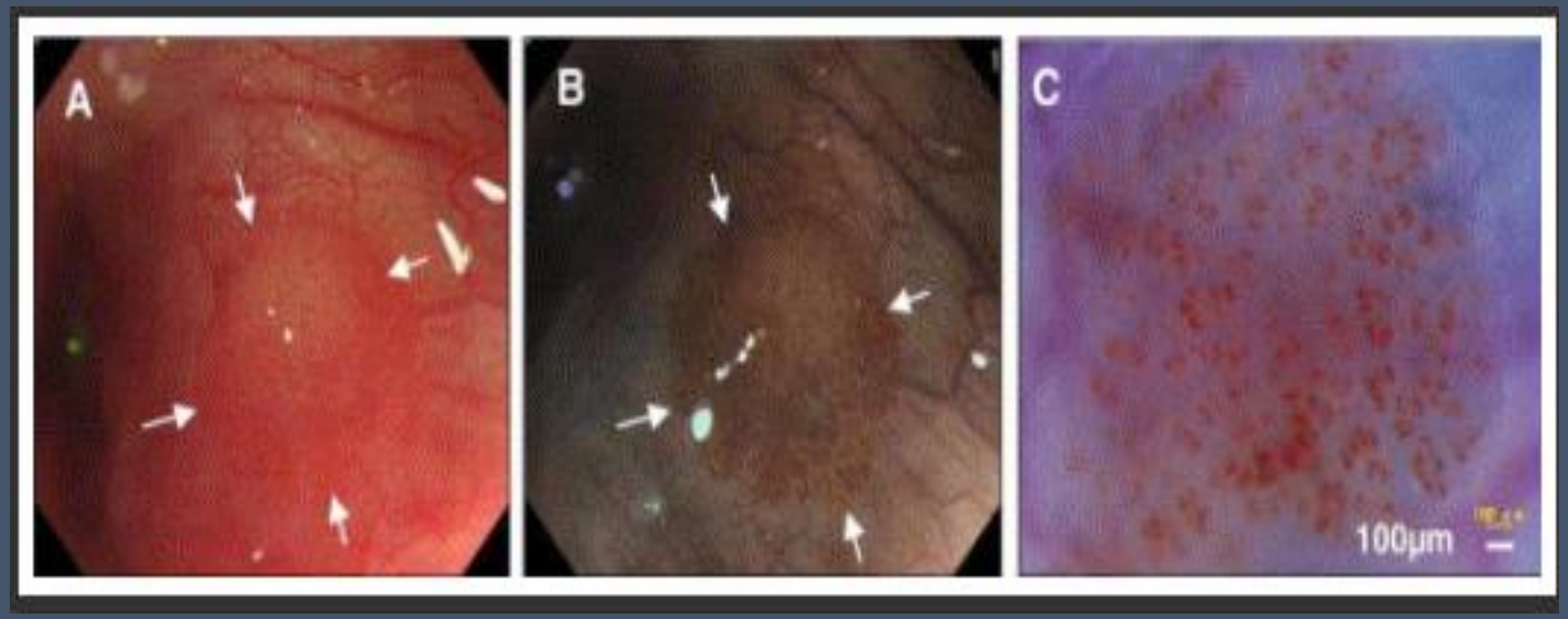
**Zhou H, Zhang J, Guo L, Nie J, Zhu C, Ma X. The value of narrow band imaging in diagnosis of head and neck cancer: a meta-analysis. Sci Rep(2018) 8(1):515. doi: 10.1038/s41598-017-19069-0

ENDOSCOPIC PROCEDURES
Narrow band imaging





ENDOSCOPIC PROCEDURES
Narrow band imaging



Work up
Imaging

- U/S
- CT
- MRI
- PET
- **Narrow band imaging (NBI)**

from the skull base to the thoracic inlet

U/S

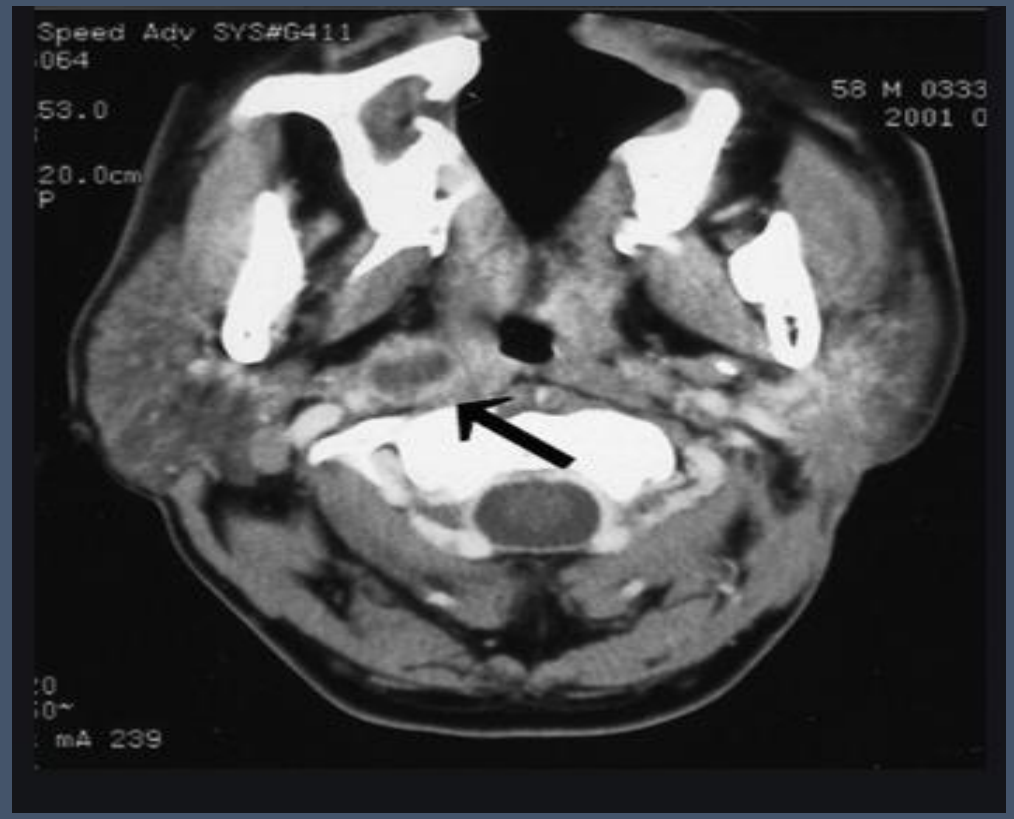
- Distinguish solid from cystic masses
- Details regarding Thyroid nodules
  - Pathological features in nodules and nodes that are not enlarged
  - (Microscopic Thyroid CA with pathological LNs)

CT

- Anatomy of the cervical adenopathy,
- Relationship to vascular and visceral structures
- Additional non-palpable but suspicious nodes
  - parapharyngeal, retropharyngeal, paratracheal, and mediastinal areas.
- The presence of additional hidden nodes might point to a primary site
  - Retropharyngeal
  - Paratracheal
- Detecting asymmetries of the mucosal surfaces
- Sensitivity : 49% and 94%
- Specificity : 78% and 98%

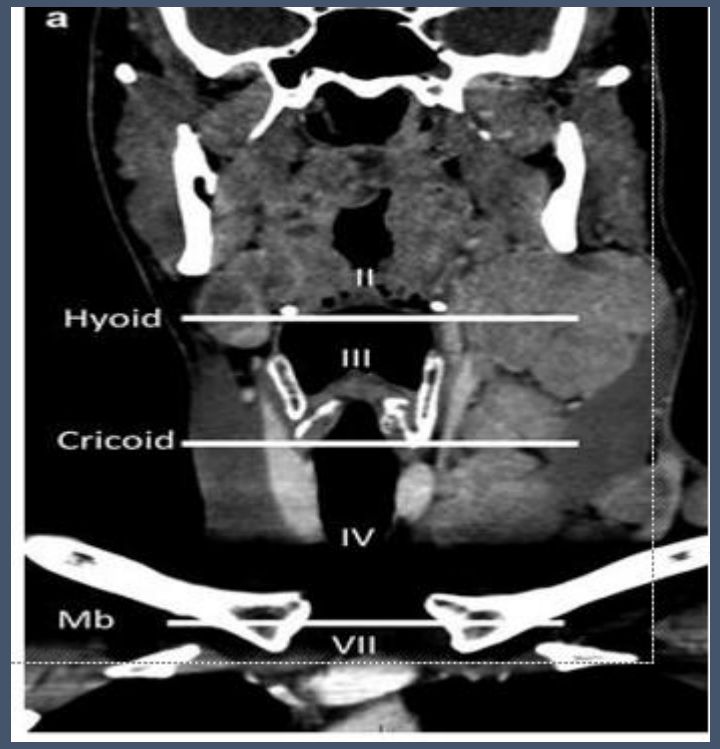
CT neck

- Retropharyngeal LN



CT neck

- Relationship to vascular and visceral structures



MRI

- Iodine allergy
- Renal failure
- Pregnancy

PET/CT

- Direct the head and neck surgeon to a potential primary site (biopsy) in situations where other imaging modalities have failed
    - Sensitivity : 73%
    - Negative predictive value : 69%
    - Allow the diagnosis prior to EUA : 44 %
- False negative , tumour < 5 mm
- False positive ,
    - Physiological uptake
    - Post operative (6 weeks)

Staging Clinical (C)
AJCC 8th edition

N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2		Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension, ENE(-)
	N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
	N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
	N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3		Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in any node(s) with clinically overt ENE(+) $(ENE_c)^2$
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
	N3b	Metastasis in any node(s) with clinically overt ENE(+) $(ENE_c)^2$

Staging Pathological (P) AJCC 8th edition

N1		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(-)
N2		Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-); *or* metastases in multiple ipsilateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(-); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
	N2a	Metastasis in a single ipsilateral node 3 cm or less in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(-)
	N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(-)
	N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(-)
N3		Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(-); *or* metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; *or* a single contralateral node of any size and ENE(+)
	N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
	N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral, or bilateral nodes any size and ENE(+) in any node; *or* a single contralateral node of any size and ENE(+)

Staging Pathological (P) AJCC 8th edition

	N1	N2a	N2a	N2b	N2c	N3a	N3b	N3b
Multiplicity	Single	Single	Single	Multiple	Any	Any	Single	Any
Size (cm)	<3	3- 6	< 3	< 6	< 6	> 6	>3	Any
Laterality	Ipsilateral	Ipsilateral	Ipsilateral	Ipsilateral	Bilateral / contralateral	Any	Ipsilateral	Bilateral / contralateral
ENE	Negative	Negative	Positive	Negative	Negative	Negative	Positive	Positive

Extra nodal extension(ENE)

- (C)
    - Invasion to Skin , muscle , nerves and adjacent structure
- (P)
    - Microscopic vs major

Cyto/histopathology

- Fine needle aspiration (FNA)
- Core biopsy
- Open biopsy

FNA

- U/S guidance
- Positive in 80 % (solid masses)
    - SCC
    - Less accurate if cystic mass

- **Repeated FNA** can yield an additional increment
    - Cystic mass

- Immunocyto/histochemistry(IHC) and molecular techniques
    - Non SCC
    - Infraclavicular primary

    **20 gauge aspiration core device

FNA

- Review of 30 studies and then presented 2,702 aspirates from their own institution:
    - Sensitivity, 89.5%,
    - Specificity, 98.5%,
    - PPV, 97.3%,
    - NPV, 94.0%,
    - Accuracy rates , 95.1%

**Tandon S, Shahab R, Benton JII, Ghosh SK, Sheard J, Jones TM. Fine-needle aspiration cytology in a regional head and neck cancer center: comparison with a systematic review and meta-analysis. Head Neck (2008) 30(9):1246–52. doi: 10.1002/hed.20849

FNA Immunocyto/histochemistry(IHC)

- In situ hybridization (ISH) for HPV
- Epstein Barr Virus (EBV),

Allow diagnosis if suspected SCC (FNA equivocal)

- P53 mutations
- Cytokeratin
- Thyroglobulin levels (wash out)
- Calcitonin,
- Thyroid transcription factor-1
- Paired-box gene 8 (PAX8),
- S100 protein,
- (HMB 45)

Poorly differentiated CA

HPV testing in FNA

- Prove the malignancy
- Confirm and guide the diagnosis of primary tumour
- De-escalating the treatment approach
- Prognostic indicator

** P16 : false positive

** **HPV-RNA , improve accuracy by 88 %**

FNA

Non diagnostic :

- **Low cellularity** of the fluid within a cystic metastasis,
- Sampling of an area of **necrosis,**
- Sampling of **peritumoral inflammation,**
- Excessive vascularity resulting in a **bloody specimen**

Core biopsy

- **When initial fine needle aspiration fails to produce a diagnosis and cancer is strongly suspected**
    - Cystic
    - Suspected lymphoma
- Justify the expense of a **PET-CT** before **panendoscopy**
- Sensitivity (cystic mass) : 87 %
- False negative : 13 %

** Primary not identified during pand endoscopy

** Non surgical therapy is planned

Open biopsy

- Primary not identified or diagnosis cannot be obtained:
  - Negative PET scan
  - Non diagnostic core biopsy

- Frozen section should be done
  - Lymphoma
  - Primary treated by non surgical modality (NPC , infraclavicular)

- planned same setting **neck dissection**

- The “gold standard” is to enter radiation or chemoradiation treatment based on **histology** rather than **cytology**

ADVANCED **PATHOLOGICAL AND MOLECULAR DIAGNOSIS** FOR IDENTIFYING PRIMARY SITES

FNA / core biopsy (IHC) :

Suspicious of SCC

- Positive : P16 ,HPV RNA (ISH) → OPSCC
- P16 negative → upper aerodigestive tract
- EBER positive → NPC

** Directed pan endoscopy and biopsy

ADVANCED **PATHOLOGICAL AND MOLECULAR DIAGNOSIS** FOR IDENTIFYING PRIMARY SITES

FNA / core biopsy (IHC) :

Suspicious of poorly differentiated malignancy

- Thyroglobulin → Papillary thyroid CA
- Calcitonin, → Medullary thyroid CA
- Thyroid transcription factor-1 → Thyroid
- S100 protein , HMB 45 → Melanoma
- CD 20 , PAX 8 → Lymphoma (flow cytometry)
- Chromogranin , Synaptophysin → Neuroendocrine

Next Generation Sequencing

- DNA sequencing
- Produce gene profiles associated with ultraviolet light damage
- Identify the origin:
    - Skin CA or upper aerodigestive SC
- Utilization of **liquid biopsy**
    - Circulating cancer cells
- May affect decisions regarding **irradiation** of the upper aerodigestive tract or the **contralateral side of the neck postoperatively**

ENDOSCOPIC PROCEDURES

Pan endoscopy :

- Direct **laryngoscopy,**
- Rigid or flexible **bronchoscopy,**
- Rigid or flexible **esophagoscopy**

second primary

- Random biopsies of the nasopharynx, oropharynx, hypopharynx and tongue base
  - Absence of abnormal endoscopic findings
  - Yield is very low,
  - Largely been abandoned

**Tanzler ED, Amdur RJ, Morris CG, Werning JW, Mendenhall WM. Challenging the need for random directed biopsies of the nasopharynx, pyriform sinus, and contralateral tonsil in the workup of unknown primary squamous cell carcinoma of the head and neck. Head Neck (2016) 38 (4):578–81. doi: 10.1002/hed.23931

ENDOSCOPIC PROCEDURES
Tonsillectomy

- Bilateral palatine tonsillectomy is recommended
  - Primaries are found in the tonsil contralateral to the lymphatic metastases 10% (1)

- Lingual tonsillectomy
  - 36 lingual tonsillectomies in NCUP using laser microsurgery with identification of the primary tumor in 86% (2)

(1) Koch WM, Bhatti N, Williams MF, Eisele DW. Oncologic rationale for bilateral tonsillectomy in head and neck squamous cell carcinoma of unknown primary source. Otolaryngol Head Neck Surg (2001) 124(3):331– 3. doi: 10.1067/mhn.2001.114309

(2) Nagel TH, Hinni ML, Hayden RE, Lott DG. Transoral laser microsurgery forthe unknown primary: role for lingual tonsillectomy. Head Neck (2014) 36 (7):942–6. doi: 10.1002/hed.23372

ENDOSCOPIC PROCEDURES
Tonsillectomy

- Palatine and lingual tonsillectomy will locate a primary tumor in approximately **70%** of patients with NCUP who have **completely negative** office evaluations and imaging, including PET-CT, particularly in the **HPV+ setting**

- Fu TS, Foreman A, Goldstein DP, de Almeida JR. The role of transoralrobotic surgery, transoral laser microsurgery, and lingual tonsillectomy in the identification of head and neck squamous cell carcinoma of unknown primary origin: a systematic review. J Otolaryngol - Head Neck Surg = Le J d'oto rhino laryngologie chirurgie cervico-faciale (2016) 45(1):28. doi: 10.1186/s40463-016-0142-6

Anatomic stage / prognostic group

Stage III	T0	N1	M0
Stage IVA	T0	N2	M0
Stage IVB	T0	N3	M0
Stage IVC	T0	Any N	M1

Any N upgrade the Stage by adding 2

Management

- Treatment of NCUP is based on :
    - N stage
    - Location of involved LN
    - Primary tumour site,
    - HPV/EBV status of the tumour.

- Primary tumour regression prior to therapy

- Possibility of primary tumour emerging post completion of therapy
    - Treatment of potential primary tumour side (initial therapy)

Management

N1 (Single modality):

- Neck dissection or
- Irradiation**

- **N2/3 (Dual modality)**
- Neck dissection , post operative radiotherapy**
- Chemoradiotherapy **

** **Radiation therapy**

- Neck
- High risk primary site

Management Adenocarcinoma

- Level I/II/III
  - Neck dissection +/- parotidectomy

- Level IV/V
  - Evaluate for infraclavicular primary
  - Neck dissection if primary not identified

Management
Non keratinizing SCC , NOS , SCC

N1

- Neck dissection (preferred) **or**
- Primary RT

>N2

- Concurrent Chemoradiotherapy (preferred) **or**
- Induction chemotherapy then RT **or**

planned or salvage ND

- Neck dissection , post op RT

Management SC CUP
Post Neck dissection

N1

- Observation or
- RT

N2/3 or ENE

- Chemo and radiotherapy

Management SC CUP
Principle of **primary** RT

DEFINITIVE

RT Alone

- **PTV**
  - **High risk: Involved lymph nodes (this includes possible local subclinical infiltration at the high-risk level lymph node(s)**
    - **Fractionation:**
      - **66 Gy (2.2 Gy/fraction) to 70 Gy (2.0 Gy/fraction); daily Monday–Friday in 6–7 weeks[3]**
      - **Mucosal dosing: 50–66 Gy (2.0 Gy/fraction) to putative mucosal sites, depending on field size. Consider higher dose to 60–66 Gy to particularly suspicious areas**
  - **Low to intermediate risk: Sites of suspected subclinical spread**
    - **44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[4]**

CONCURRENT CHEMORADIATION:[5,6]

- **PTV**
  - **High risk: typically 70 Gy (2.0 Gy/fraction)**
  - **Mucosal dosing: 50–60 Gy (2.0 Gy/fraction) to putative mucosal primary sites, depending on field size and use of chemotherapy. Consider higher dose to 60–66 Gy to particularly suspicious areas**
  - **Low to intermediate risk: 44–50 Gy (2.0 Gy/fraction) to 54–63 Gy (1.6–1.8 Gy/fraction)[4]**

** Consider treating both neck if >N2 or midline occult primary lesion

** Field involve : Nasopharynx , Oropharynx and hypopharynx

Management SC CUP
Principle of post operative RT

POSTOPERATIVE:

RT

- Preferred interval between resection and postoperative RT is ≤6 weeks
- PTV
  - High risk: Adverse features such as extracapsular spread (See OCC-4)
    - Mucosal dose: 50–66 Gy (2.0 Gy/fraction) to putative mucosal sites, depending on field size. Consider higher dose to 60–66 Gy to particularly suspicious areas
  - Low to intermediate risk: Sites of suspected subclinical spread
    - 44–50 Gy (2.0 Gy/fraction) to 54-63 Gy (1.6–1.8 Gy/fraction)[4]

POSTOPERATIVE CHEMORADIATION

- Concurrent single-agent cisplatin at 100 mg/m^2 every 3 weeks is recommended.[7-10]

Prognosis

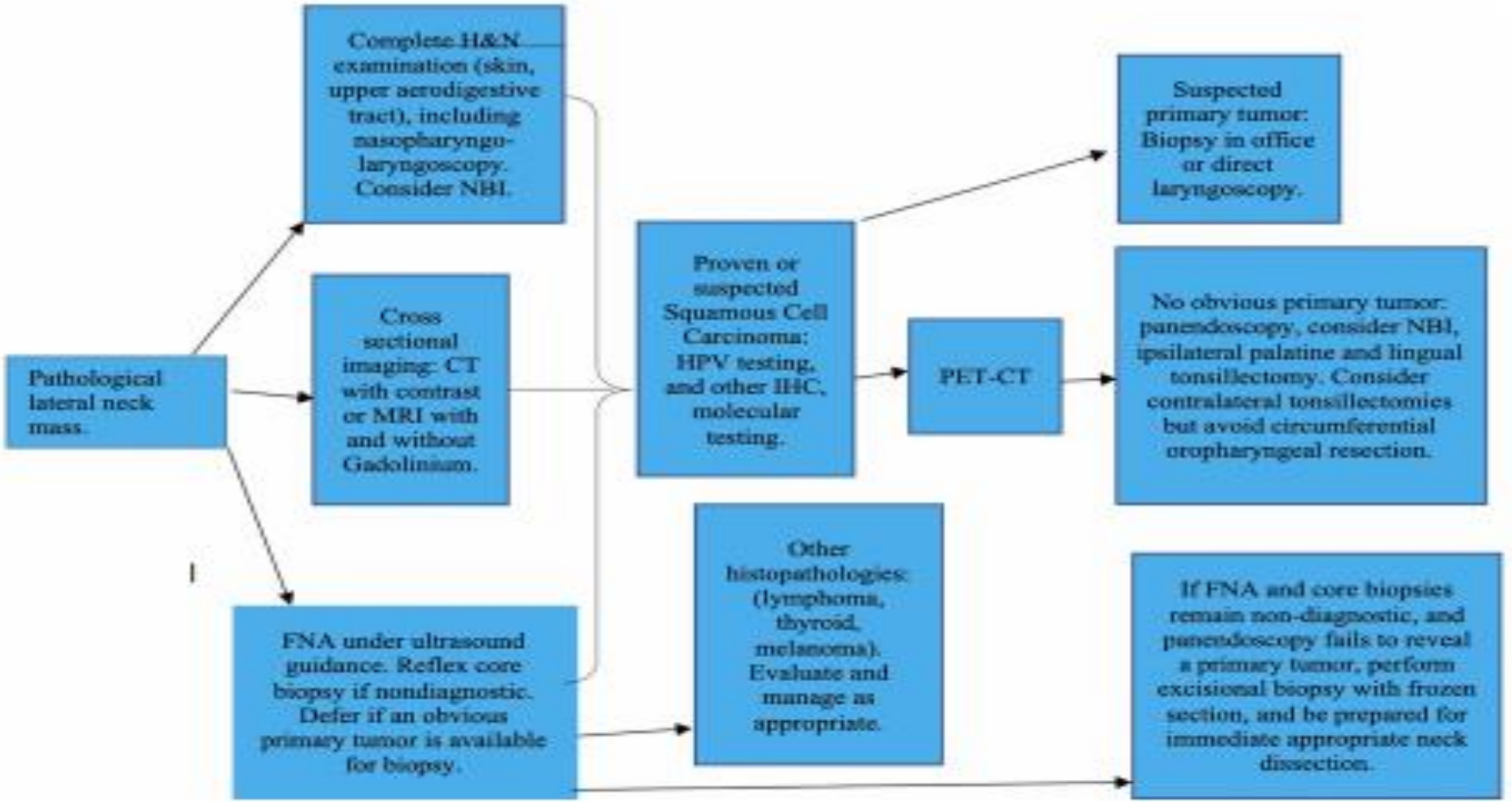
- Age > 70 years,
- patients with N3-stage tumours
- P16 negative tumours ,

worse prognosis

- The overall 5-year survival rate for patients with
  - P16-positive tumours 88%
  - P16-negative tumours 61%

- The 5-year DSS rate of curative intent varied from 20% to 74%

Management algorithm



Follow up / surveillance

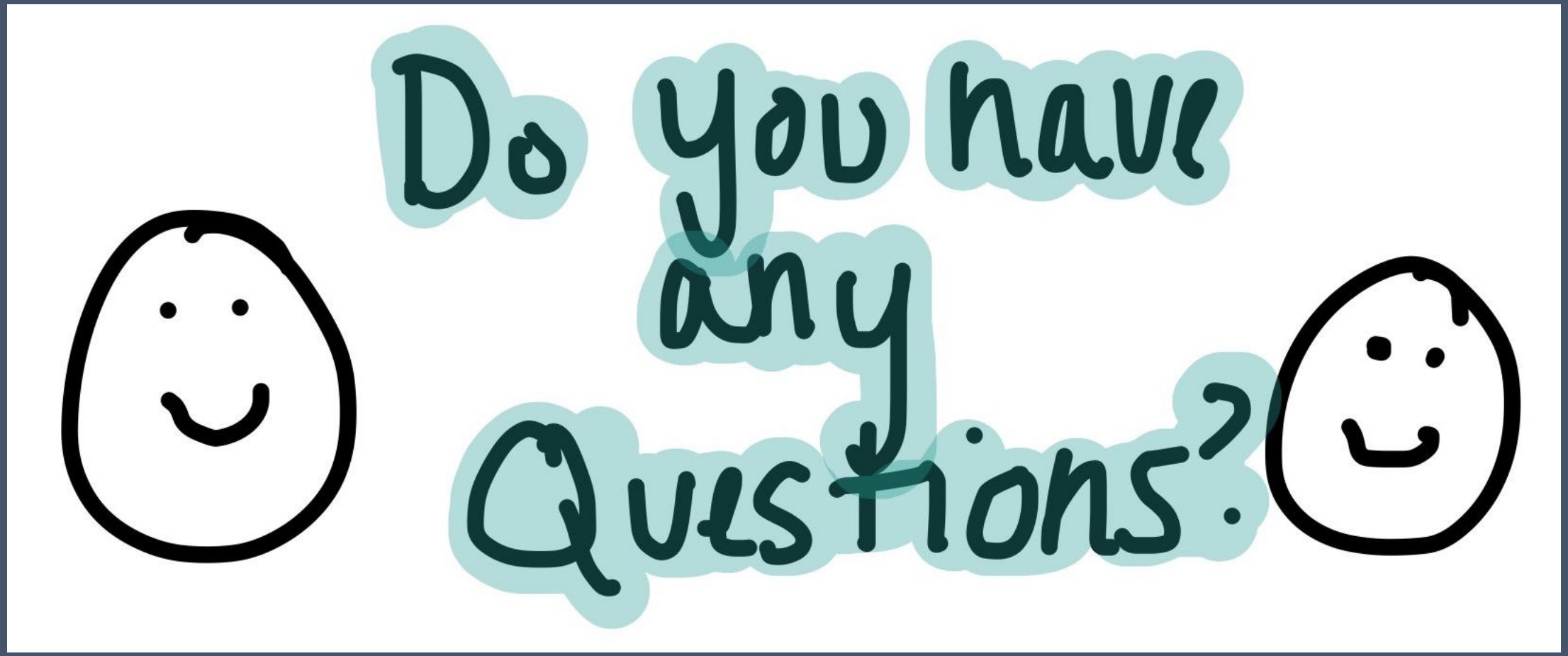
- 4 to 8 weeks for 1st 2 years,
- 3 months for the third year,
- 6 months for years 4 and 5,
- Annually for life

    - Physical examination , outpatient laryngoscopy
    - CT/MRI neck
    - PET/CT
    - Annual chest radiograph
    - Annul TSH

** **Possible emerging of primary tumour after completion of therapy**

Conclusion

- Modern management of metastatic neck cancer with an unknown primary site requires proper recognition of the typical **clinical presentation**, and **avoidance of diagnostic pitfalls** that can lead to **inappropriate interventions**.
- Patients should receive a complete examination of the mucosal surfaces of the upper aerodigestive tract, preferably enhanced by the use of **NBI**
- Histological biopsy should be obtained, preferably from the occult primary site even FNA is diagnostic
- **Next generation gene sequencing** can guide us to probable primary sites.
- Decisions regarding therapy are based on the primary tumour site, if identified, the stage of the neck disease, and the HPV/EBV status of the tumour.


Do you have any Questions?