Carcinoma of

Unknown primary

$\bar{C}$ Isolated cervical LN

→ Definition (WHO)

Histological diagnosis of metastasis without a primary after thorough clinico-radiological evaluation.

→ Theories

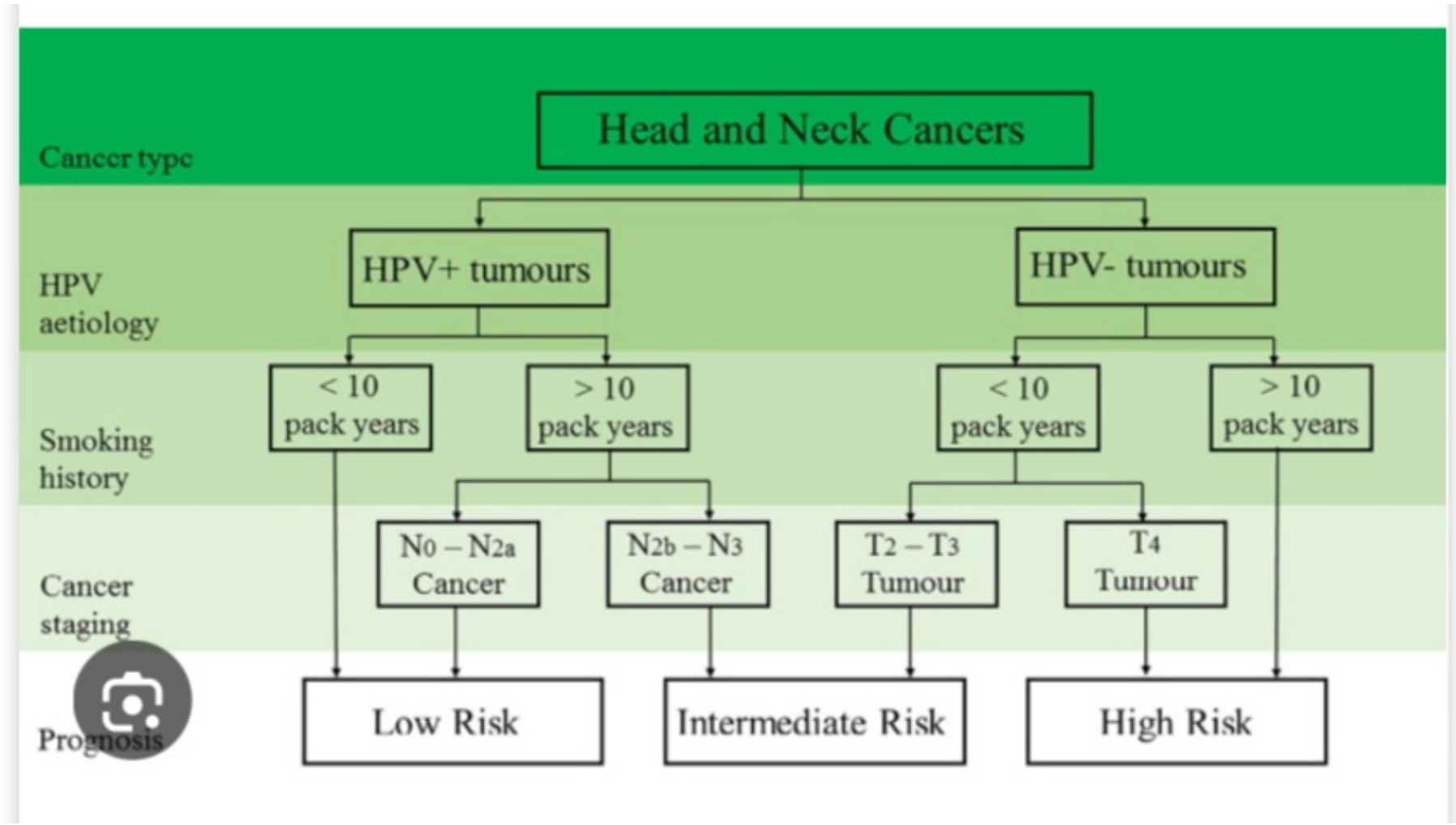
1. Too small primary.
2. Primary looses potential to grow after early metastasis
3. Primary destroyed by vascular | immune mechanisms.
   - mets inhibits growth d/t dysfunctional neo angiogenesis
4. Spontaneous regression of primary.
5. Microscopic primary in the mucosal folds of Waldeyer's ring.

→ History & physical

f/s/o HPV associated primary
- young age
- No H/o smoking | alcohol
- multiple sexual partners
- Cystic LN mass → A/w in PTC

f/s/o EBV related primary – North east India / Asian ethnicity have nasopharyngeal primary.

→ HPV risk stratification in association ī smoking.



Pack years definition

1 pack in India = 10 ciagrette

1 pack in west = 20

Pack years = No: of Pack per day x
No: of years exposed.

→ Location of LN & drainage sites

Cervical Lymph Node Level	Anatomic Correlation	Location	Primary Site(s) Drained
IA	Submental	Extends from mandible to hyoid bone, between the bellies of the digastric muscles	Anterior oral cavity / lower lip
IB	Submandibular	Bounded by submandibular gland, mandible, and digastric muscles	Oral cavity (upper and lower lip, cheek and nose) and skin (lip, nose, medial canthus)
II	Upper jugular	Deep to sternocleidomastoid muscle Extends from inferior aspect of transverse process of C1 to hyoid	Oropharynx, hypopharynx, oral cavity, larynx, Parotid
III	Middle jugular	Deep to sternocleidomastoid muscle Extends from hyoid to caudal edge of the cricoid cartilage	Oropharynx, larynx, hypopharynx, thyroid cavity
IV	Inferior jugular	Deep to sternocleidomastoid muscle Extends from caudal edge of cricoid cartilage to 2cm above sternoclavicular joint	Larynx, hypopharynx, thyroid, cervical esophagus, trachea
V	Posterior cervical triangle	Anterior to trapezius and posterior to sternocleidomastoid, extending superiorly from hyoid bone to the transverse cervical vessels inferiorly	Nasopharynx, skin of posterior neck, scalp, hypopharynx
VI	Anterior neck compartment	Extends from caudal edge of thyroid cartilage to manubrium	Larynx, thyroid

Level II, V ⇄ B/L mets → Nasopharynx.

Supraclavicular LN → Infraclavicular primary.

→ Tissue diagnosis

FNAC vs → especially in Cystic LN
→ USG guided Core needle Bx

- less invasive
- cost effective
- minimal risk of seeding.
- Sn - 83-97%
- Sp - 90-100%

- must for HPV - p16 IHC
- Routinely done for Level II, III scc up.
- may be done in other levels in high risk individual

P16 IHC [- very high sensitivity
If negative, No other testing required for HPV

↓

testing may be done for EBV

by Ebstein-Barr Encoding Region in-situ Hybridisation (EBER) or

↑ serum EBV DNA titre

* Open | excision Bx - Not recommended in unknown primary neck Node.

→ IHC in unknown primary

" Poorly differentiated Carcinoma " → 1. Lymphoma
2. SCC

- Pancytokeratin – Carcinoma
  - CK 7, CK 20 + – Adeno CA.
  - P 40 – SCC
- CD 45 + - lymphoma.
- Vimentin – Sarcoma.
- S-100 | HMB + → Melanoma.
- Chromogranin | synaptophysin – NET
-

→ Imaging in CUP

- Imaging before scopies always → 20% false positives when performed after Biopsy.

- CECT Head & neck vs PET|CT

  - Identification rate 32-37%
  - 2/o distant mets in same scan, and hence change management.
  - Better sensitivity & specificity compared to CECT

Role of MRI in CUP

X does not detect unknown mucosal primary.

X Has better Sn & Sp for Submucosal soft tissue differentiation in a known primary.

→ Pan endoscopy.

- Complete evaluation of upper aerodigestive tract.

- FOL scopy (including nasopharynx) + oesophagoscopy + Bronchoscopy.

± Narrow band imaging

Detection rate - 35%

Better visualisation of Small superficial mucosal lesions

- Blue light has
  - ↓ depth of penetration
  - ↓ scattering
  - = Absorption spectrum of Hemoglobin.

→ Blind Biopsy

- No role in the current era of IHC & PET/CT.
- Rate of positive yield following blind bx
  - Nasopharynx - 0%.
  - Pyriform fossa - 0%.
  - Tonsillectomy - 39%.
  - Base of tongue - 18%.

↓

If directed Bx is negative, do

1) Tonsillectomy

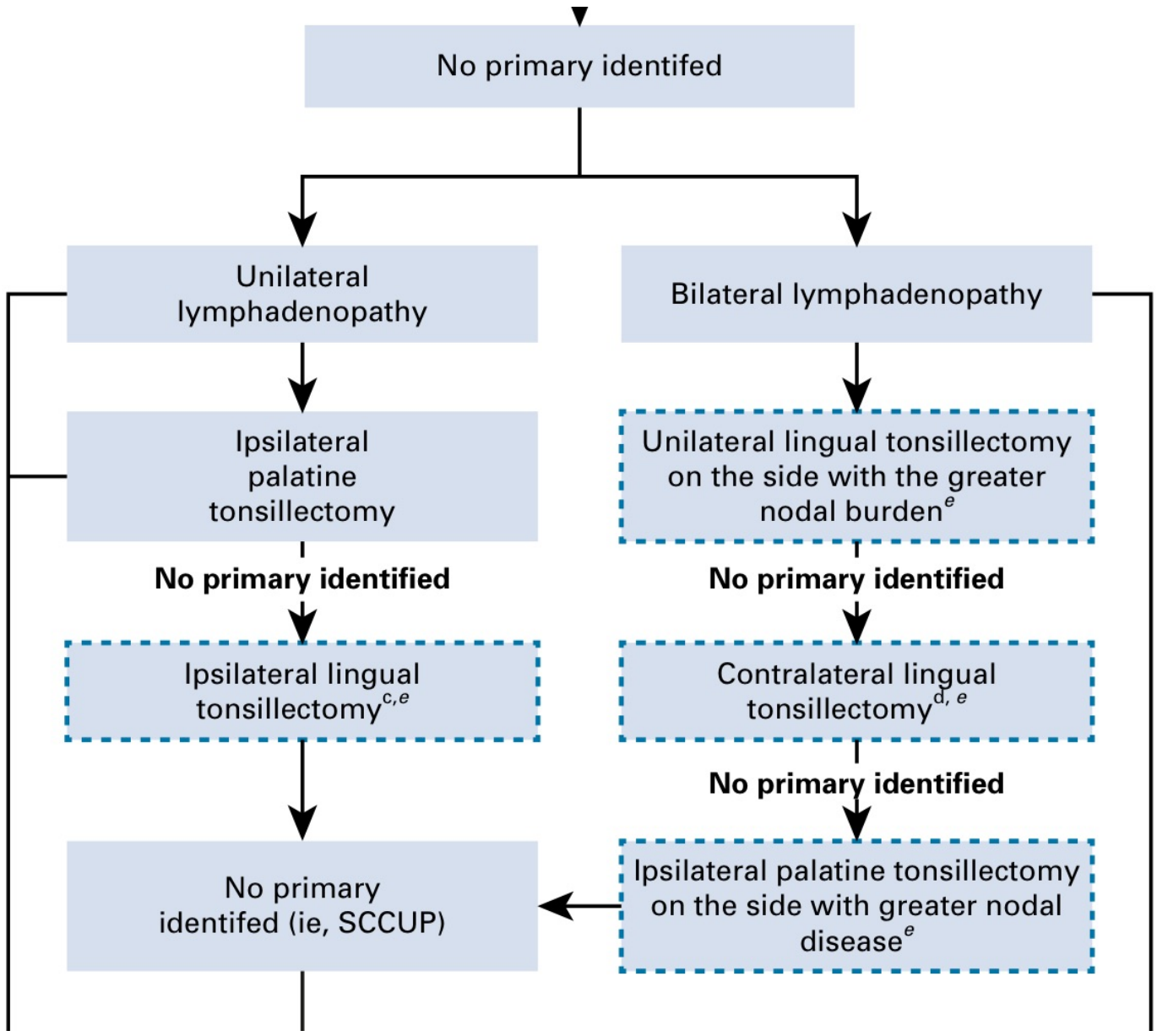
- unilateral - 39-45% detection
- B/L tonsillectomy - less evidence.
- tonsillectomy better than deep tonsillar Bx.

2) TORS guided | Laser guided trans oral Mucosectomy of Base of tongue.

TORS | TLM

- primary identified in 78%.

ASCO guidelines



✓ B/L palatine tonsillectomy not done d/t risk of Oropharyngeal stenosis.

✓ Always do frozen section to negative margins for tonsillectomy / TLM.

As ale western data:

HPV Incidence West - 70%.

India - 20%.

Detection rate of HPV related primary in tonsillectomy / TLM in India - 0-1%.

In India,

Neck Node
↓
Unknown primary
→ PET/CT or LECT (−) → Pan Endoscopy ± NBI (−) → Tonsil CUP.

→ Nodal staging

1) HPV positive Node staging

N classification	N criteria
cN1	One or more ipsilateral lymph nodes, none larger than 6 cm
cN2	Contralateral or bilateral lymph nodes, none larger than 6 cm
cN3	Lymph node(s) larger than 6 cm

} with/without ENE

N classification	N criteria
pN1	Metastasis in 4 or fewer nodes
pN2	Metastasis in >4 lymph nodes

2) HPV Negative node staging

N classification	N criteria
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE-negative
N2a	Metastasis in a single ipsilateral lymph node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE-negative
N2b	Metastasis in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N2c	Metastasis in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE-negative
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE-negative
N3b	Metastasis in any node(s) and clinically overt ENE-positive

→ Management

① Unilateral N_1 < 3cm

Surgery VS Definitive RT

Equal outcomes

- Accurate staging
- Decision making for adjuvant therapy.
- tailoring RT target volumes.

★ selective neck dissection ⇒ ↓ morbidity for U/L < 3cm LN definitely spares one Radical RT

→ Surgery alone option in N1 ? → No prospective RCT.

DAHANCE Study ⇒ Equal outcomes OS/DFS.
Costes et al

↳ But only in HPV positive (stage I patients)

HPV Negative N_1 → Stage III → Sx + Adj RT.

staging	HPV +	EBV +	HPV −
$T_x N_1$	I	II	III

② u/L Large operable nodes

Radical CT/RT
Hb salvage Sx
if persistent disease → PET/CT guided surveillance
12 weeks after CT/RT

VS

Sx Hb PORT
(50-60 Gy)

PET-NECK trial

↓

Avoids Trimodality therapy and associated morbidity

- IMRT ± photons based
- 70 Gy to gross Nodes
+ 50 Gy (2 Gy/#) to mucosal site at risk
+ 40-50 Gy (2 Gy/#) to nodes at risk of harbouring micrometastasis
+ Concurrent chemo ± cisplatin

↓

Comprehensive RT

↓

Locoregional control rate = 100%

③ B/L Nodes

↓

Radical Ct/RT

→ Unilateral VS Bilateral RT

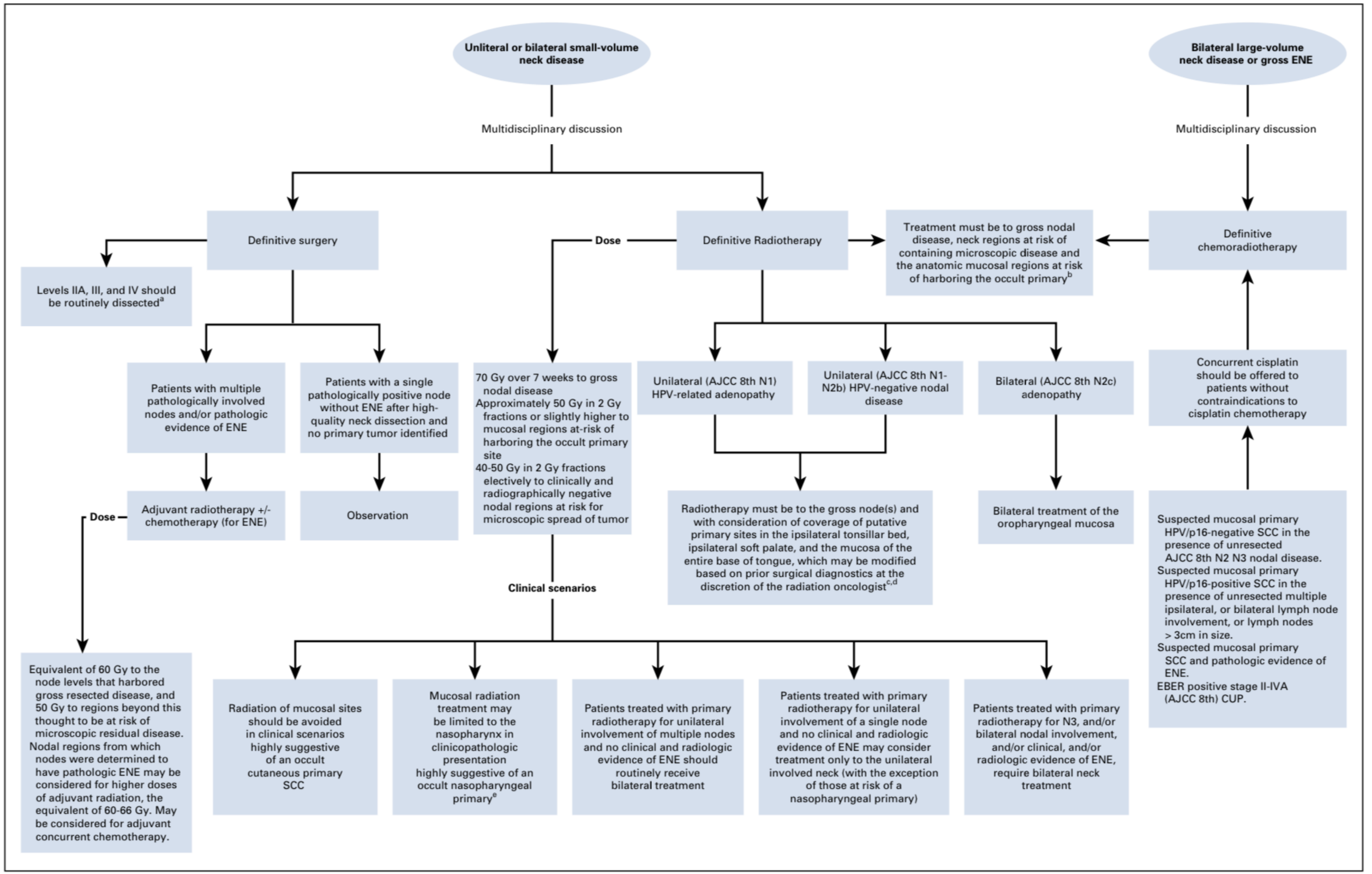
U/L single Node
& clinical / Radiological → Unilateral RT.
ENE

↓

- If suspected nasopharyngeal primary
- Bulky U/L nodes
- Suspected ENE
- B/L Nodes

→ Bilateral RT.

→ Summary


Unliteral or bilateral small-volume neck disease
Multidisciplinary discussion
Definitive surgery
Levels IIA, III, and IV should be routinely dissected[a]
Patients with multiple pathologically involved nodes and/or pathologic evidence of ENE
Adjuvant radiotherapy +/- chemotherapy (for ENE)
Patients with a single pathologically positive node without ENE after high-quality neck dissection and no primary tumor identified
Observation
Dose
Definitive Radiotherapy
70 Gy over 7 weeks to gross nodal disease
Approximately 50 Gy in 2 Gy fractions or slightly higher to mucosal regions at-risk of harboring the occult primary site
40-50 Gy in 2 Gy fractions electively to clinically and radiographically negative nodal regions at risk for microscopic spread of tumor
Clinical scenarios
Unilateral (AJCC 8th N1) HPV-related adenopathy
Unilateral (AJCC 8th N1-N2b) HPV-negative nodal disease
Radiotherapy must be to the gross node(s) and with consideration of coverage of putative primary sites in the ipsilateral tonsillar bed, ipsilateral soft palate, and the mucosa of the entire base of tongue, which may be modified based on prior surgical diagnostics at the discretion of the radiation oncologist[c,d]
Bilateral (AJCC 8th N2c) adenopathy
Bilateral treatment of the oropharyngeal mucosa
Treatment must be to gross nodal disease, neck regions at risk of containing microscopic disease and the anatomic mucosal regions at risk of harboring the occult primary[b]
Bilateral large-volume neck disease or gross ENE
Multidisciplinary discussion
Definitive chemoradiotherapy
Concurrent cisplatin should be offered to patients without contraindications to cisplatin chemotherapy
Suspected mucosal primary HPV/p16-negative SCC in the presence of unresected AJCC 8th N2 N3 nodal disease.
Suspected mucosal primary HPV/p16-positive SCC in the presence of unresected multiple ipsilateral, or bilateral lymph node involvement, or lymph nodes > 3cm in size.
Suspected mucosal primary SCC and pathologic evidence of ENE.
EBER positive stage II-IVA (AJCC 8th) CUP.
Dose
Equivalent of 60 Gy to the node levels that harbored gross resected disease, and 50 Gy to regions beyond this thought to be at risk of microscopic residual disease.
Nodal regions from which nodes were determined to have pathologic ENE may be considered for higher doses of adjuvant radiation, the equivalent of 60-66 Gy. May be considered for adjuvant concurrent chemotherapy.
Radiation of mucosal sites should be avoided in clinical scenarios highly suggestive of an occult cutaneous primary SCC
Mucosal radiation treatment may be limited to the nasopharynx in clinicopathologic presentation highly suggestive of an occult nasopharyngeal primary[e]
Patients treated with primary radiotherapy for unilateral involvement of multiple nodes and no clinical and radiologic evidence of ENE should routinely receive bilateral treatment
Patients treated with primary radiotherapy for unilateral involvement of a single node and no clinical and radiologic evidence of ENE may consider treatment only to the unilateral involved neck (with the exception of those at risk of a nasopharyngeal primary)
Patients treated with primary radiotherapy for N3, and/or bilateral nodal involvement, and/or clinical, and/or radiologic evidence of ENE, require bilateral neck treatment