Management of Metastatic Neck Node: Unknown Primary

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Introduction to Carcinoma of Unknown Primary

- Carcinoma of unknown primary (CUP) is a Heterogeneous clinical syndrome
- Histological diagnosis of metastatic malignant tumor
- WITHOUT the detection of a primary despite
- Standard clinical, laboratory, and radiological investigation

- We will restrict to CUP with metastases to neck nodes

Why is this important?

- Known primary: focussed therapy
- Occult primary: larger treatment volumes to cover the possible sites
- Significant increase in morbidity, more so with radiotherapy & chemotherapy

Incidence

- 4th most commonest cause of cancer death in both sexes
- Annual age adjusted incidence: 7-12/ 100000
- Median age: 60 years
- Little more frequent in males
- Primary may eventually manifest in around 20-30% cases

- NPC: South east Asia
- Oropharynx: North America (esp non- or light smokers)
- Occult cutaneous primary: fair skinned with heavy sun exposure (Australia & southern USA)

Etiology

Upper aerodigestive tract

- Alcohol
- Tobacco products
- Betel nut
- Plummer-Vinson syndrome

- **Potential risk factors -**
  Human papillomavirus,
  Poor oral hygiene
  GERD
  Malnutrition

Nasopharynx

Environmental factors

- Nitrosamines
- Polycyclic Hydrocarbons
- Wood Dust
- Nickel Exposure
- Epstein-Barr Virus

Sinonasal

- Nickel,
- Wood Dust
- Thorotrast Exposure

Cutaneous

- Ultraviolet Light Exposure
- Genetic Disorder Xeroderma Pigmentosum (Autosomal Recessive)

Natural History

Angiogenic incompetence of primary tumor

↓

Marked apoptosis & cell turnover

↓

Phenotype with metastatic potential soon after transformation

- **Remain small, escape clinical detection**
- **Exfoliate for mechanical reasons**
- **Involute/ disappear: defense or growth inhibition**

Pathophysiology

- **Exposure of mucosa or skin to carcinogens → genetic mutations → invasive carcinoma**
- Human Papillomavirus (HPV) in oral and oropharyngeal carcinogenesis. Syrjanen et al (1983)
- The pathophysiology of the unknown primary carcinoma is the same as that of known carcinoma of the head and neck.
- However, the occult primary carcinoma either metastasizes early to the cervical lymphatics or develops in an anatomical site that is not detectable with endoscopy or imaging techniques until it is of considerable size (T3, T4)

Presentation

Symptom	Possible Source
Otalgia/aural fullness	Pharynx, larynx, nasopharynx, or ear
Dysphagia/ odynophagia	Pharynx, esophagus, or oral cavity
Hoarseness	Larynx
Trismus, dysarthria	Oral cavity or oropharynx
Nasal congestion, epistaxis	Sinonasal tract
Aspiration	Oropharynx or larynx

Presentation

- **Painless neck mass: most common presentation**

- Mostly located in level 2 (30–50%)
- Level 1 and 3 (10–20%)
- Level 4 and 5 (5–10%)
- Bilateral involvement of the neck less than 10%

- Node metastases in levels 1-3: primary site is suspected to be in the head and neck region
- Levels 4–5, the primary tumor most likely is located below the clavicles
- Time interval between noting the cervical mass and final diagnosis of HNCUP: 2 to 5 months

Quick Review: Pathology of HPV associated OPC

- 95% of OPC are squamous cell carcinomas
- HPV 16 serotype: 90% of HPV-associated cases

- Overexpression of p16 serves as surrogate marker of HPV integration into DNA

- HPV viral proteins E6 and E7 bind p53 & Rb respectively
- Subsequent loss of tumor suppression

Factors Associated With HPV Status in OPC

HPV+

- Younger
- Non / light smoker / alcohol
- Incidence increasing
- Caucasian
- High-risk sexual behavior
- More likely tonsil / base of tongue
- Poorly differentiated
- Nonkeratinizing
- Basaloid
- p16 upregulated

HPV-

- Older
- Heavy smoking / drinking
- Incidence decreasing
- Non-Caucasian
- Not related to sexual behavior
- No tissue preference
- Keratinizing
- P53 mutation
- EGFR amplified

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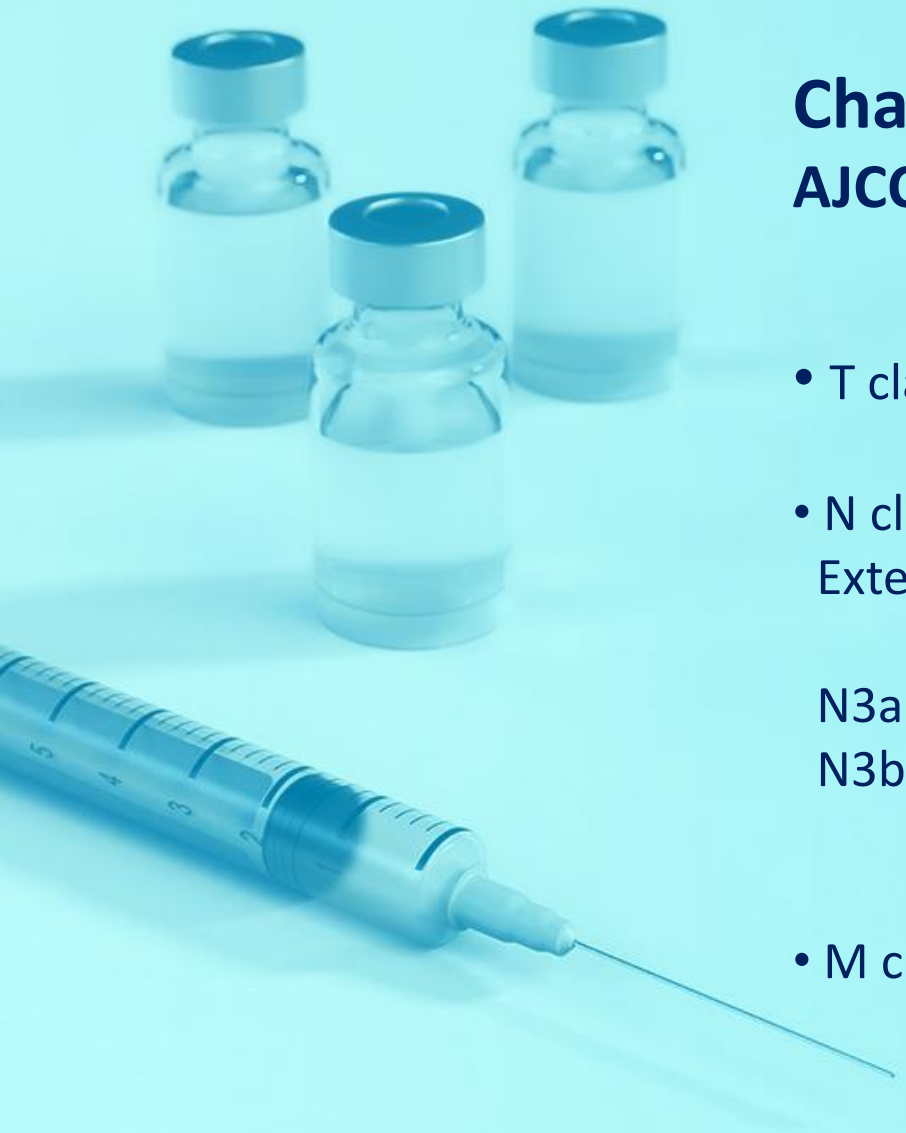
- **EGFR amplified**



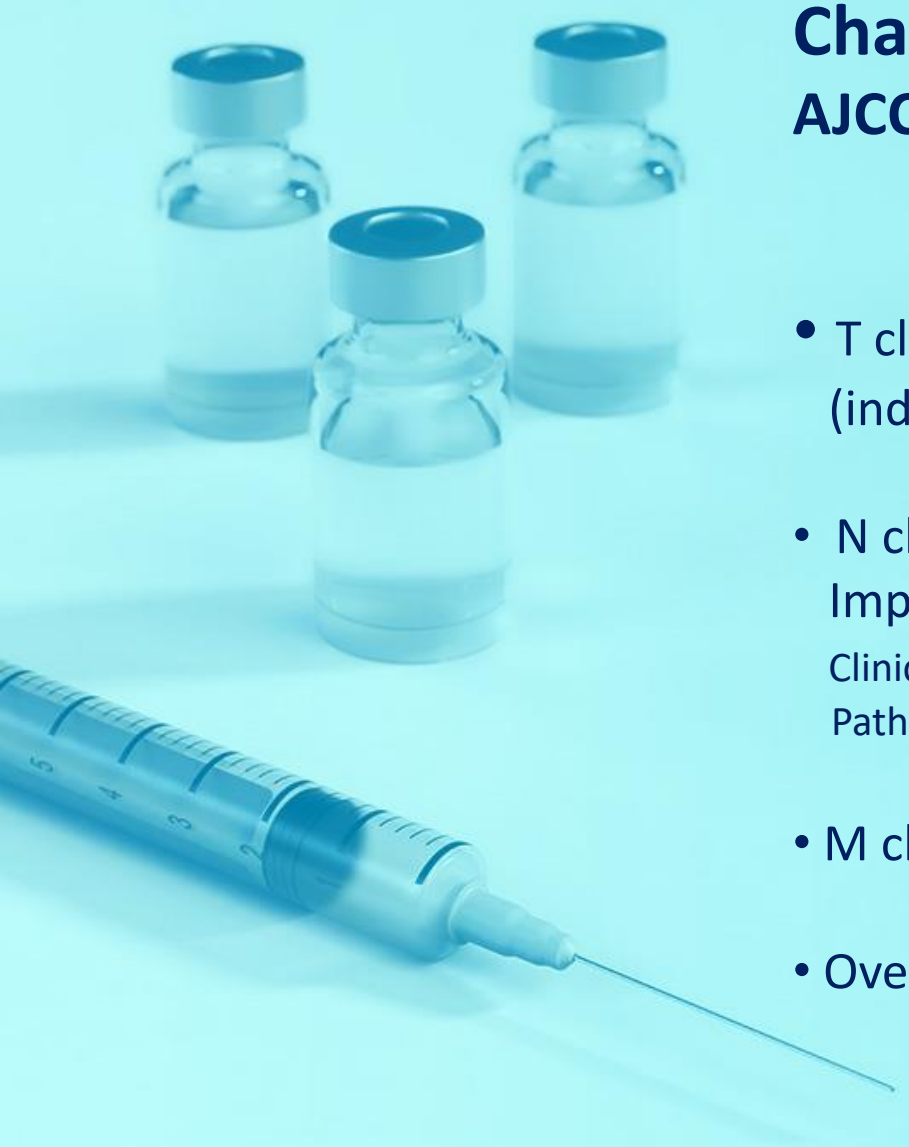
Changes in HPV Neg OPC Staging
AJCC 8th

- T classification: Unchanged except T0 removed

- N classification: Unchanged with the exception of Extra Nodal Extension (ENE: fixed, deep muscle or skin invasion) dividing N3 into

  N3a: Lymph node >6cm in dimension, No ENE
  N3b: any ENE+

- M classification: Unchanged



Changes in HPV Pos OPC Staging
AJCC 8th

- T classification: Unchanged except removal of Tis and T4b (indistinguishable survival curves of T4a and T4b)

- N classification: ENE is not included in HPV positive tumors
  Important difference is between clinical and pathologic staging.
  Clinical staging is based on laterality and size of nodes
  Pathologic staging postoperatively is based on number of nodes (N1: 1-4, N2: ≥5)

- M classification: Unchanged

- Overall stage: Radical change as stage IV is reserved for M1 disease

Why was HPV status included in AJCC 8ed?

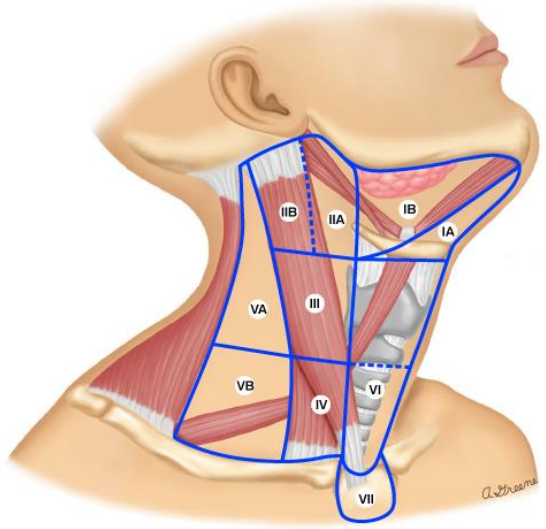
7th ed

- Reflected behavior of tobacco related OPC
- But not HPV+ disease
- Hazard discrimination with loss of ability to differentiate between stages

8th ed

- Two distinct groups depending upon whether or not they overexpress p16 to separate HPV+ or HPV- disease

Neck Node Levels



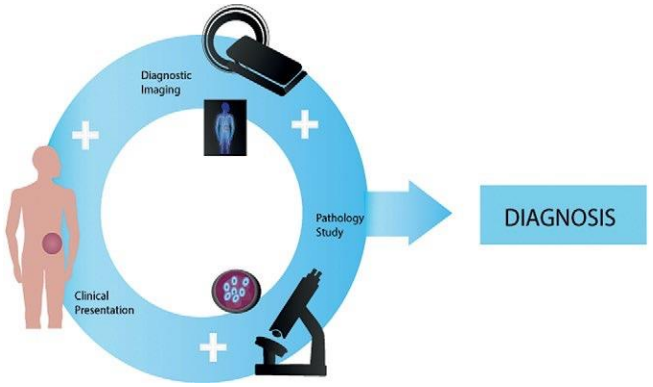
Neck nodes involved	First echelon drainage site
Level I	FOM, Lip, Ant tongue
Level II	NPX, OPX, Tongue, LX, HPX
Level III	SGL, PFS, Post Cricoid
Level IV*	HPX, Subglottic LX, Thyroid, Eso
Level V	NPX, Thyroid
Level VI	NPX, OPX wall, HPX, PNS
Supraclavicular*	Thyroid, Eso, Infraclavicular primary
Level VIII	Skin

Level VI: Ant Cervical (prelaryngeal (Delphian), pre/paratracheal, Tracheoesophageal

* Lower neck involvement is often associated with primaries below clavicle

Diagnostic Work-up

- **Complete history and clinical examination** is mandatory
- **Imaging studies** should be done prior to any procedure
- **Tissue Diagnosis**
- **Pan-endoscopy & directed biopsies**
- **Molecular studies** for predictive & prognostic information



Diagnostic Work-up: Clinical Examination

- Past history of malignancy or radiation
- History of skin lesions
- Examination of skin, thyroid, breast, abdomen, and other nodal regions)
- Targeted selected biopsies (BOT, Tonsil, PFS, NPX)
- Tonsillectomy?
- Thyroglobulin & calcitonin if adenocarcinoma

Diagnostic Work-up: Tissue Diagnosis

- **Fine needle aspiration (FNA):** first step to establish histology
- May be unreliable to address diagnostic tumor markers

- **Core biopsy/ excisional biopsy:** useful for IHC and molecular biomarker studies

- **Specific IHC markers** in addition to routine H&E staining

IHC in solid tumors

- Technique based on antigen-antibody reaction
- Diagnostic & Theranostic* Utility

Most important role is in the characterization of:

- Undifferentiated neoplasm/ tumor of uncertain origin
- CUPs
- Predictive role for therapeutic implications

The term **theranostic** is the combination of two words, *therapeutic* (thera) and *diagnostic* (nostic), which allows the combination of diagnosis, treatment, and continuous follow up of a disorder

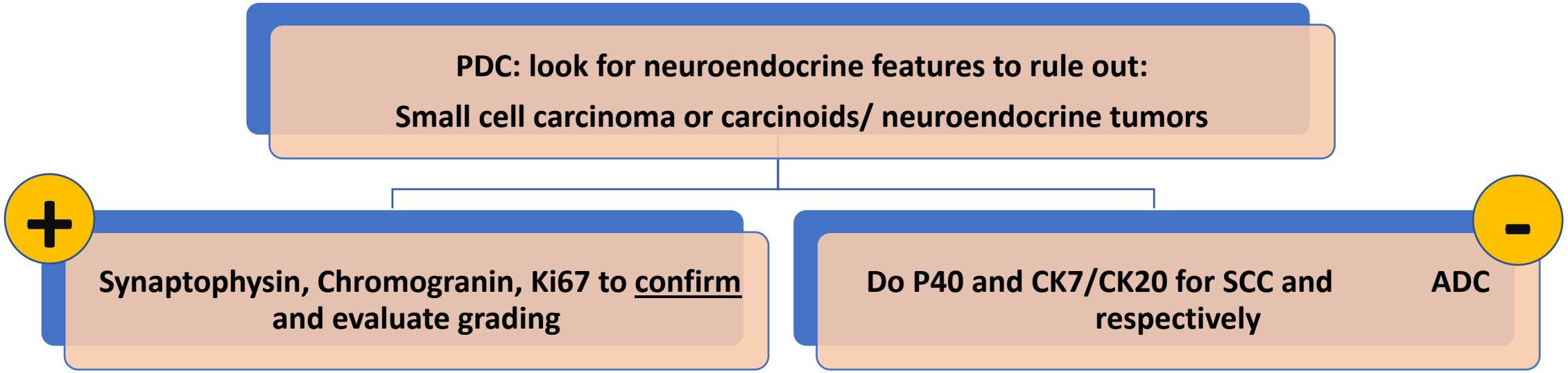
IHC: CUP

- Adenocarcinoma (ADC)
- Poorly differentiated carcinoma (PDC)
- Squamous cell carcinoma (SCC)

Two panels of antibody (IHC) markers for assistance in the workup of CUP

- Cytokeratin (provides direction or clue)
- Organ specific IHC markers

IHC: CUP



- Upto 50% of small cell carcinomas are TTF-1+ irrespective of primary origin site while synaptophysin can be positive in PDC; hence histomorphology trumps IHC here
- **Once neuroendocrine carcinoma is ruled out, evaluate P40 to rule out SCC**

IHC: CUP

P40 is diagnostic of SCC

(P40 is also positive in urothelial carcinoma (UC), but frequency of UC presenting as CUP is very less as compared to SCC)

Specific positive markers for UC: GATA3 & uroplakin II/III

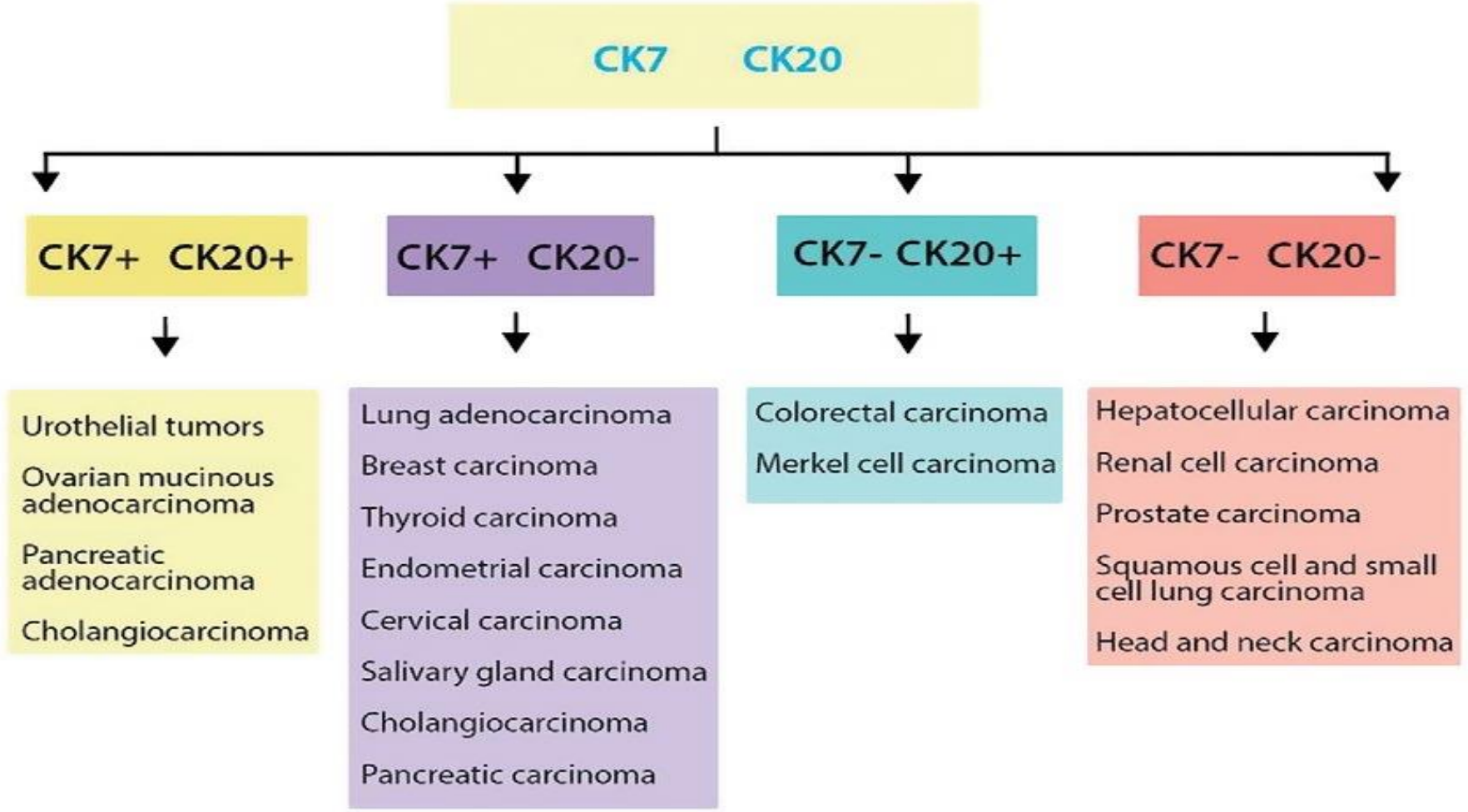
If the tumor expresses both P40 and CK7:

- Emphasis of P40 immunoexpression should supersede that of CK7
- SCC can show CK7 expression especially in cervix & lung origin

Once SCC is confirmed, these two IHC markers can further determine the primary:

- **P16** (surrogate of HPV): highly suggestive of oropharyngeal primary, also in cervix
- **EBER** (**EB**V **E**ncoded **R**NA) positivity by ISH is highly suggestive of nasopharyngeal carcinoma
- For other organs, SCC has no specific IHC markers

CUP: IHC


CK7 CK20
CK7+ CK20+
CK7+ CK20-
CK7- CK20+
CK7- CK20-
Urothelial tumors
Ovarian mucinous adenocarcinoma
Pancreatic adenocarcinoma
Cholangiocarcinoma
Lung adenocarcinoma
Breast carcinoma
Thyroid carcinoma
Endometrial carcinoma
Cervical carcinoma
Salivary gland carcinoma
Cholangiocarcinoma
Pancreatic carcinoma
Colorectal carcinoma
Merkel cell carcinoma
Hepatocellular carcinoma
Renal cell carcinoma
Prostate carcinoma
Squamous cell and small cell lung carcinoma
Head and neck carcinoma

Imaging for CUP

- Chest radiograph
- CECT
- MRI & Magnetic Resonance Angiography
- Positron emission tomography imaging with 2-fluoro-2-deoxyglucose

Imaging: Chest Radiograph

- Screening for lung mets: obviates the need for surgical intervention if mets present
- May detect concurrent lung neoplasm: synchronous primary or a source of cervical nodal mets
- Suspicious lesion: further workup with CECT

Imaging: CECT

- Availability,
- Cost effectiveness,
- Quick (allow dynamic manoeuvres)
- Puffed cheek and modified Valsalva techniques can help to open opposed mucosal surfaces in the oral cavity, oropharynx, and hypopharynx. This may allow the easier detection of unknown mucosal primaries
- Patient compliance
- critical evaluation of the CT scan helps in the location of directed biopsies
- assessing the involvement of vital structures (surgical evaluation)

Imaging: CECT- Pathological Node

- **Short-axis diameter in axial plane ≥10 mm, except**
  - ≥11 mm in level II (subdigastric region)
  - ≥5 mm in the lateral retropharyngeal group
  - Any visible in the medial retropharyngeal group
- **Longest axial diameter cut-off criteria depend on which performance characteristic is of most interest (the following applies to level II and III nodes):**
  - Maximize the sum of sensitivity and specificity: ≥12-15 mm
  - Maximize sensitivity (98%) and negative predictive value: ≥5 mm
- **Cluster of three or more borderline nodes (each ≥8 mm short-axis diameter, except >9 mm in the level II/ subdigastric region)**
- **Long-to-short axis ratio <2 (i.e. Rounder)**
- **Necrotic/cystic areas**
- **Evidence of extranodal extension, including indistinct nodal margins, irregular nodal capsular enhancement, and infiltration into adjacent fat or muscle**

Imaging: MRI

- Superior anatomic details
- Helpful in iodine-allergic patients
- Useful in the evaluation of the superior extent of metastatic cervical lymphadenopathy (ie, intracranial extension)
- MRI is ideal for a patient with cancer on the base of the tongue or of the sinonasal tract
- MRI is slower than a CT acquisition
- Some patients may not be able to tolerate the physical constraints of the scanner
- Magnetic resonance angiography (MRA) is a less-invasive procedure and can provide useful information (resectability)

Imaging: PET-CT

- Detects ~25-37% of primary tumors not detected with other modalities
- Not better than conventional imaging for local disease staging
- Significant false positive/ false negative rates: sensitivity of 84-88% & specificity of 75-84%
- To be done when complete head & neck examination (including pan-endoscopy) and neuroradiological review of CT/MRI fail to detect occult primary
- Prebiopsy PET increases the specificity & positive predictive value; helps in directed biopsy
- Negative PET does not eliminate the need for a careful endoscopy or suspected biopsy: false negative rates are seen in up to 16%

National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2022
Occult Primary

NCCN Guidelines Index
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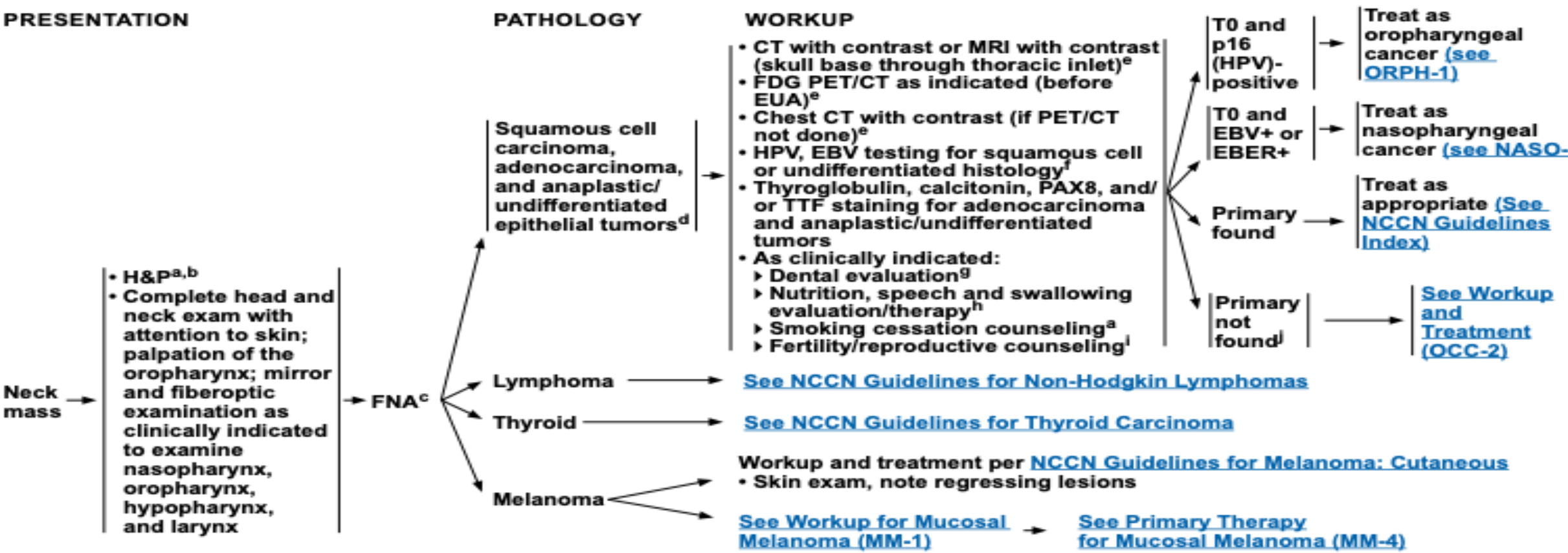
Discussion



[a] H&P should include documentation and quantification (pack years smoked) of tobacco use history. All current smokers should be advised to quit smoking, and former smokers should be advised to remain abstinent from smoking. For additional cessation support, refer to the Patient/Provider Smoking Cessation Resources in the NCCN Guidelines for Smoking Cessation.

[b] Screen for depression (See NCCN Guidelines for Distress Management).

[c] Repeat FNA, core, or open biopsy may be necessary for uncertain or non-diagnostic histologies. Patient should be prepared for neck dissection at time of open biopsy, if indicated.

[d] Determined with appropriate immunohistochemical stains.

[e] See Principles of Imaging (IMG-A).

[f] Whether HPV or EBV positive status may help to define the radiation fields is being investigated [See Principles of Radiation Therapy (OCC-A) and Discussion].

[g] See Principles of Dental Evaluation and Management (DENT-A).

[h] See Principles of Nutrition: Management and Supportive Care (NUTR-A).

[i] See fertility and reproductive endocrine considerations in the NCCN Guidelines for Adolescent and Young Adult (AYA) Oncology.

[j] Strongly consider referral to a high-volume, multidisciplinary cancer center.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

UICC TNM Staging

- **Staging of unknown primary is according to clinical suspicion of primary tumor**
- **T- category classified as T0**
- **N- category and stage grouping are as per clinical suspicion of primary**

- F/S/O NPX primary (endemic regions, elevated blood EBV DNA titre, poorly differentiated/ undifferentiated histology, non-smoker): preferred N category is in the line of NPX primary and stage grouped accordingly
- Smoker with squamous cell carcinoma when smoking related oro/hypo-pharyngeal or laryngeal mucosal primary is suspected: N- category and stage grouping accordingly

Prognostic Factors

Prognostic factors	Tumour related	Host related	Environment related
Essential	Histology N category and number of nodes Extracapsular extension Presence or absence of metastatic disease $p16^{INK4A}$/HPV status, or EBV DNA status	Immunosuppression (especially skin cancer)	
Additional	Tumour differentiation Location of nodal disease (above vs below clavicle)	Gender Haemoglobin level Smoking history	Subsequent discovery of primary Overall treatment time
New and Promising	*TP53* Surviving nuclear expression		

Prognostic Factors

- Most important factor for treatment outcome and survival is N- stage N1 & N2 disease has a significantly better prognosis than N3
- Disease without ECE have a superior 5-year disease specific survival
- Gender (F>M)
- Haemoglobin (higher is better)
- Tumor differentiation

- p16- positive tumor have significantly higher 5-year OS and DFS

Absence od field cancerization

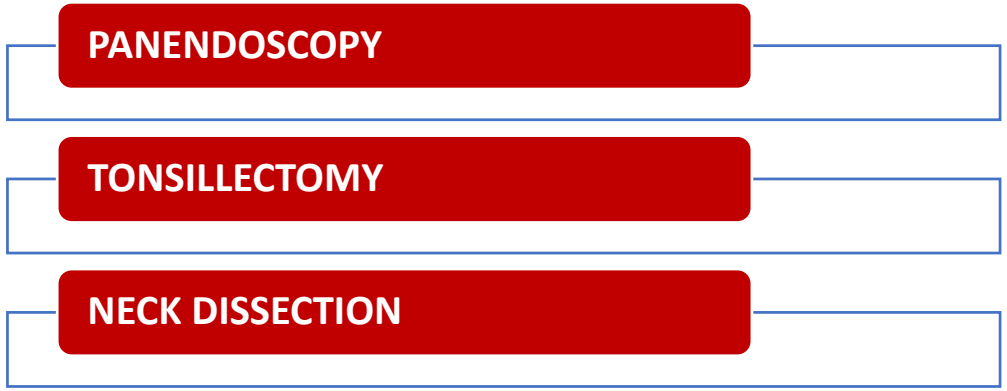
Presence of an intact apoptotic response

Treatment Recommendations

Stage	Surgery	Radiotherapy	Chemotherapy
T0N1 (no ECS)	SND or MRND	No unless for mucosal sites	No
T0N1 (ECS)	SND or MRND	Yes – either involved lymph nodes or ipsilateral neck and boost to involved lymph nodes	Should be considered
T0N2a, N2b, N2c	SND or MRND± contralateral SND or MRND	Yes – ipsilateral but bilateral should be considered	Should be considered
T0N3	Radical or type I MRND	Yes – ipsilateral but bilateral should be considered	Should be considered

Investigation and management of the unknown primary with metastatic neck disease: United Kingdom National Multidisciplinary Guidelines

Surgical Therapy



PANENDOSCOPY

- **Step I is nasal endoscopy**: Examine nasopharynx and take generous biopsies -> Frozen section
- Positive: halt the procedure & proceed with chemo-irradiation
- Negative: proceed to step II

Why nasal endoscopy first?

- If results are positive, the patient is spared of

1. Additional morbidity of further biopsies &
2. Probable surgical treatment of cervical lymphadenopathy

Surgical Therapy

Step II is laryngoscopy

- Oral cavity, oropharynx, hypopharynx, and larynx are inspected and palpated

Step III is rigid cervical Esophagoscopy

- Suspicious area biopsy

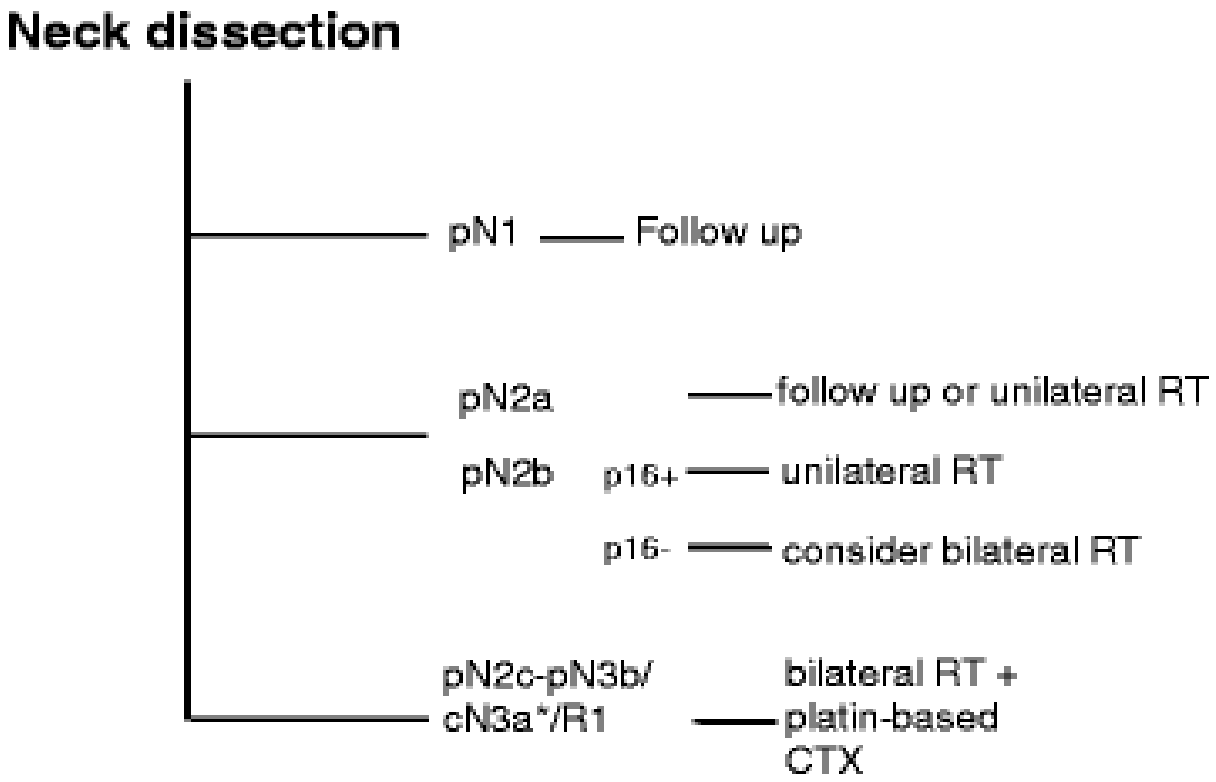
- Base of tongue
- Tonsils
- TORS (trans oral robotic surgery) may identify up to 70 % of unknown primary

Surgical Therapy

Role of Tonsillectomy

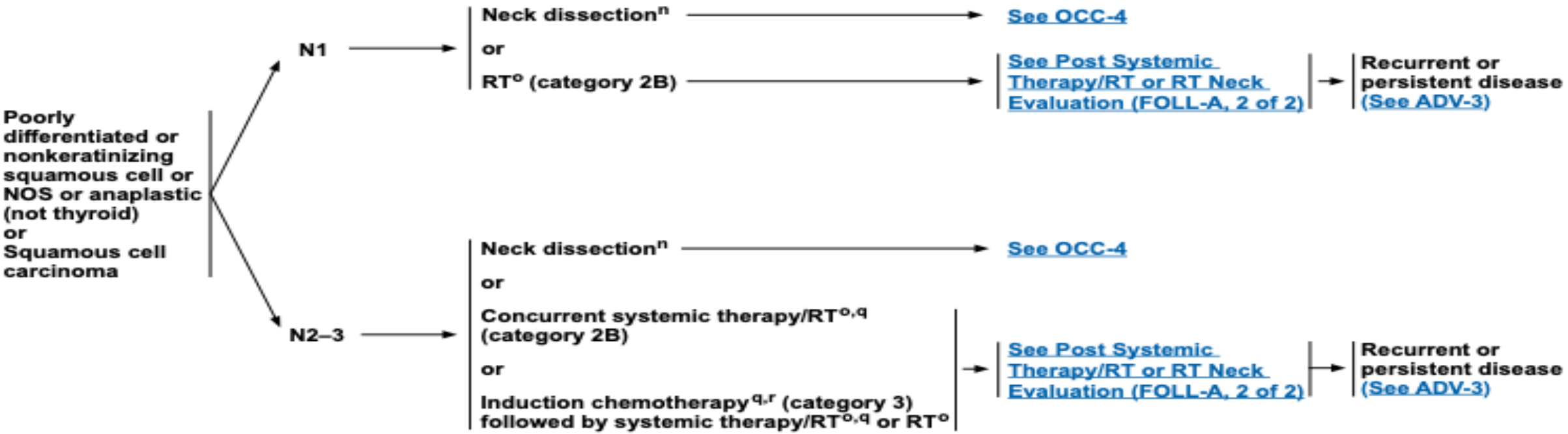
- Tonsillar fossa is often found to harbour occult primary cancers
- Higher likelihood of finding occult tumors with a tonsillectomy than a deep biopsy
- Tonsillectomy better than conventional imaging for detection of small primary
- Ipsilateral tonsillectomy: sufficient for single node involving level IB/II/III
- Bilateral tonsillectomy: in presence of bilateral level II cervical nodes
- Controversial in the FDG-PET-CECT era, little data evaluating the two

Surgical Therapy



NCCN Guidelines Version 2.2022
Occult Primary

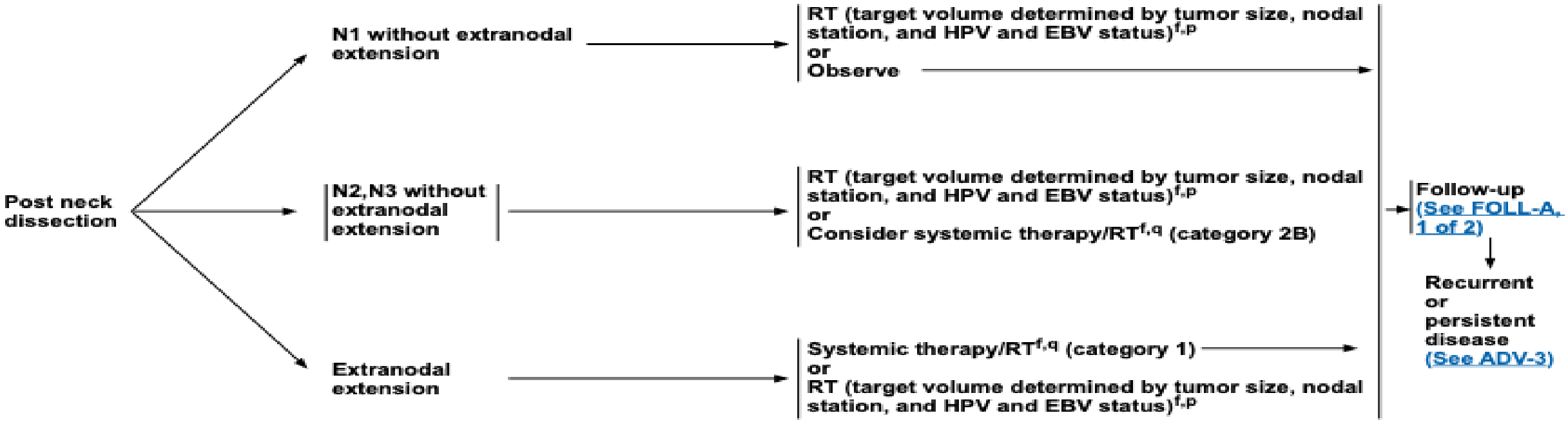
HISTOLOGY **DEFINITIVE TREATMENT[p]**



[n] See Principles of Surgery (SURG-A).
[o] See Principles of Radiation Therapy (OCC-A).
[p] Treatment for nasopharyngeal (NASO-2) and p16-positive oropharyngeal cancers (ORPHPV-3 and ORPHPV-4) may guide management of EBV-positive and p16-positive occult primary tumors.
[q] See Principles of Systemic Therapy for Non-Nasopharyngeal Cancers (SYST-A).
[r] See Discussion on induction chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.
Clinical Trials: NCCN believes that the best management of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

TREATMENT



[f] Whether HPV or EBV positive status may help to define the radiation fields is being investigated [See Principles of Radiation Therapy (OCC-A) and Discussion].
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Medical Therapy
including Radiation Therapy

- Patients without an identifiable primary lesion of the head and neck after a thorough examination of the head and neck, a panendoscopy, and possible neck dissection
- Patients with metastatic cervical lymphadenopathy (N1-N3) had a locoregional failure rate of 13-32% when treated with surgery alone
- 0-18% associated with primary surgery (neck dissection) followed by adjuvant external beam radiotherapy

Medical Therapy

- Value of radiation therapy is confirmed
- Field to be covered is controversial
- Patients treated with ipsilateral irradiation had a relative risk of recurrence in the head and neck of 1.9 compared with patients treated with bilateral irradiation
- bilateral cervical irradiation with surgical therapy improves locoregional control of cancer and is accepted as the standard of care for patients with advanced cervical disease (>N2)
- The entire pharyngeal axis is generally accepted as the mucosal sites to be included in the radiation field in patients with occult primary lesions
- In order to decrease the morbidity of radiation induced xerostomia, the nasopharynx may be excluded from the radiation field if the results of the endoscopy and the findings on imaging studies are negative

Role of Radiotherapy

Definitive Radiotherapy

- If excisional biopsy alone: definitive EBRT
- Stage N1 neck disease with no extracapsular extension: RT alone

Adjuvant Radiotherapy

- Stage N2a-c and N3 disease: definitive CRT
- May consider planned neck dissection
- Pre-op RT: avoids delay in RT, tumor cells are better oxygenated
- Post-op RT: accurate pathological evaluation available

Radiotherapy Treatment Volumes
Risk factors/ patient characteristics

Factors suggesting nasopharyngeal primary

- Lymphoepithelioma/undifferentiated carcinoma
- Younger age (<40 years)
- Non-smoker
- Asian, Inuit, Polynesian ancestry, Mediterranean littoral, including North Africa
- Isolated or dominant level V disease; retropharyngeal (RPN) lymph node disease
- EBV positive

Radiotherapy Treatment Volumes
Risk factors/ patient characteristics

Factors suggesting skin primary

- Squamous cell histology
- Non-smoker/no history of excess alcohol consumption
- Fair complexion (e.g. Northern European ancestry)
- Sun exposure with actinic changes/history of skin SCC
- Immunocompromised
- Periparotid/parotid involvement

Radiotherapy Treatment Volumes
Risk factors/ patient characteristics

Factors suggesting HPV-positive OPC primary

- Squamous cell histology, especially basaloid subtype
- Non-smoker/ no history of excess alcohol consumption
- History of marijuana use
- Cystic nodal disease

RT Treatment Volume
Comprehensive & Conservative approaches

Comprehensive approach

- Extensive prophylactic irradiation of all potential mucosal sites, as well as on both sides of the neck
- Achieves effective neck control
- Reduced incidence of subsequent emergence of mucosal primary
- High morbidity: xerostomia, dysphagia and aspiration, osteoradionecrosis

RT Treatment Volume
Comprehensive & Conservative approaches

Conservative approach

- Limited field of irradiation to I/L neck only after thorough work-up to detect the primary tumour
- Especially relevant for patients at high risk for skin cancer
- Not suited for those at high risk for NPC or HPV-related OPC

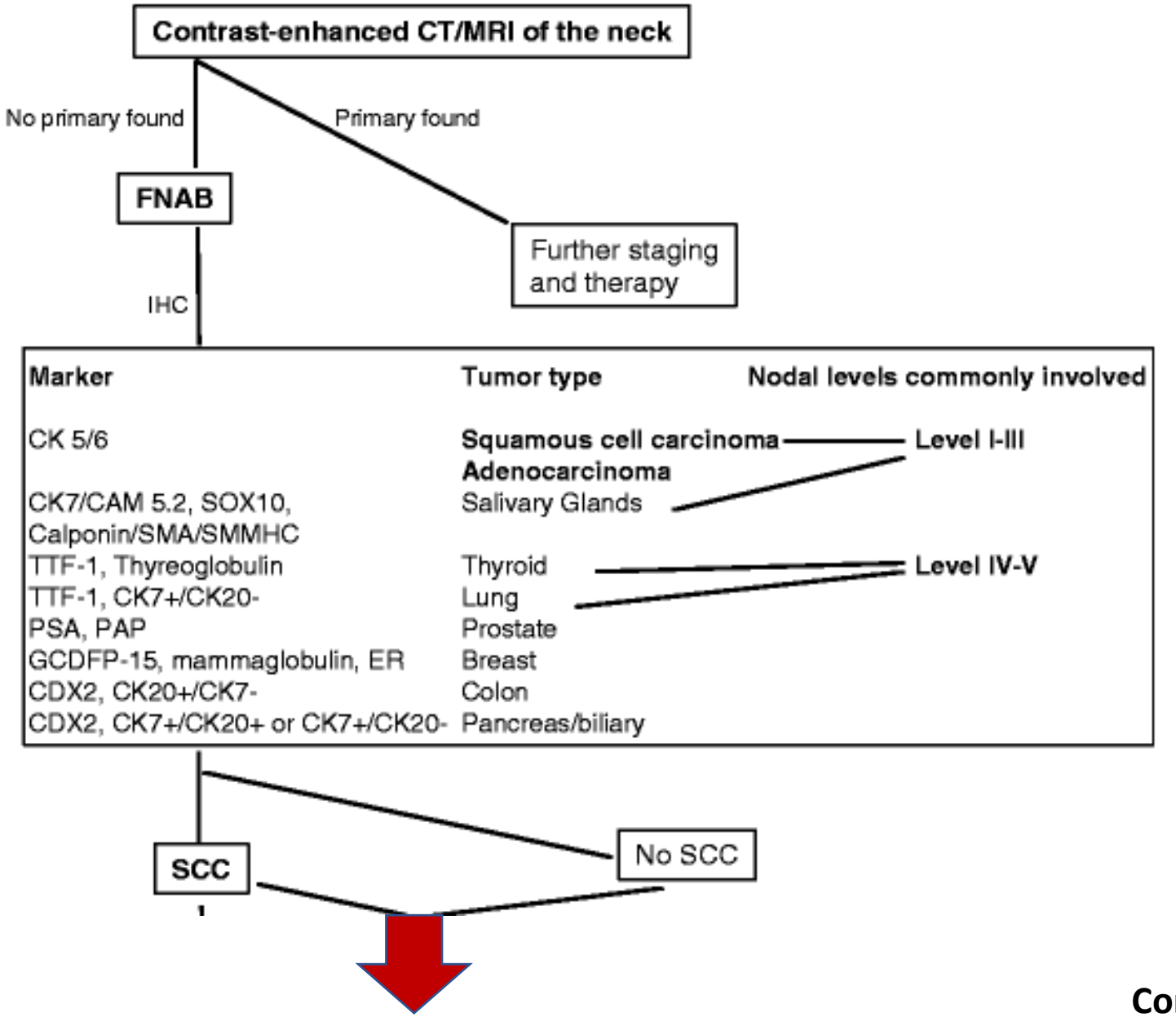
- Limited field of irradiation to potential mucosal sites according to risk factors may be considered:
  - High possibility for HPV-positive OPC: nasopharyngeal mucosa may be spared
  - High possibility for skin carcinoma: contralateral mucosal sites and neck may be spared
  - For adenocarcinoma histology, a submandibular or submental node (low probability of a primary along the pharyngeal axis)

RT Dose & Volumes per Approach

	Risk levels	Comprehensive	Conservative	Dose
COMP	High	Involved level	Involved level	66-70 Gy in 33-35 #
	Intermediate	Ipsilateral adjacent level	-	60 Gy in 30 #
	Low	B/l uninvolved levels & potential mucosal sites	+/- Ipsilateral adjacent level	50 Gy in 25 #
CONS	**Risk levels**	**Comprehensive**	**Conservative**	**Dose**
	High	Involved level	Involved level	60 Gy in 30 #
	Low	B/l uninvolved levels & potential mucosal sites	+/- Ipsilateral adjacent level	50 Gy in 25 #

UK Guidelines

- All patients presenting with confirmed cervical lymph node metastatic squamous cell carcinoma and no apparent primary site should undergo: (1) PET-CT whole-body scanning, (2) panendoscopy and directed biopsies, and (3) bilateral tonsillectomy
- Tongue base mucosectomy can be offered if facilities and expertise exist
- Concomitant chemotherapy with radiation should be considered in patients with an unknown primary
- Concomitant chemotherapy with radiation should be offered to suitable patients in the postoperative setting, where indicated
- Neoadjuvant chemotherapy can be used in gross “unresectable” disease
- Patients should be followed up to a minimum of 5 years, with a prolonged follow-up for selected patients
- PET-CT scanning at 3-4 months after treatment is a useful follow-up strategy for patients treated by chemoradiation therapy



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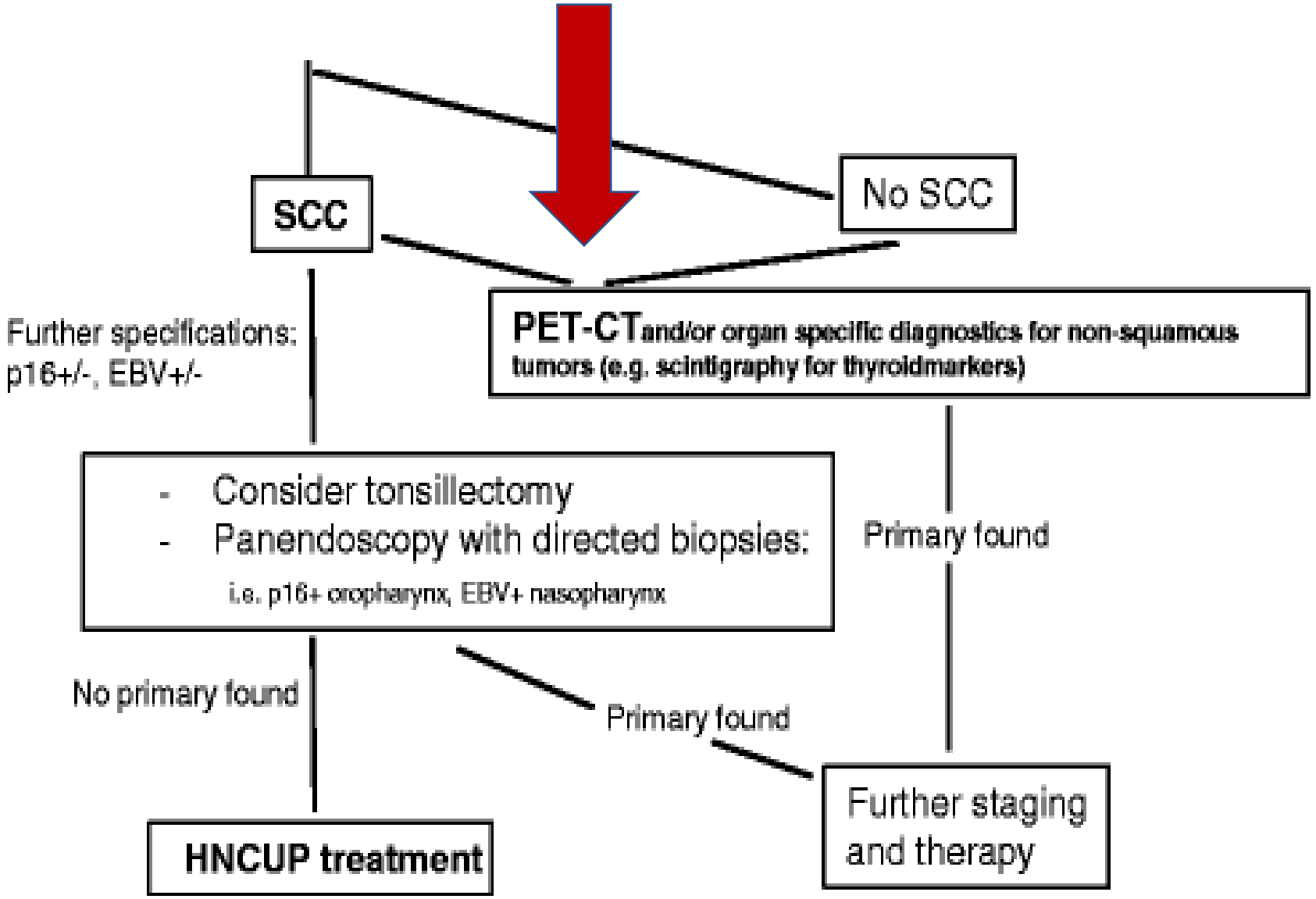
SCC
No SCC
Further specifications:
p16+/-, EBV+/-
PET-CT and/or organ specific diagnostics for non-squamous tumors (e.g. scintigraphy for thyroidmarkers)
- Consider tonsillectomy
- Panendoscopy with directed biopsies:
i.e. p16+ oropharynx, EBV+ nasopharynx
Primary found
No primary found
Primary found
HNCUP treatment
Further staging and therapy

ACKNOWLEDGEMENTS

- **UICC Manual of Clinical Oncology, 9th ed, WILEY Blackwell,**

  Sarbani Ghosh Laskar, Naveen B Mummudi, Vedang Murthy and Gouri Pantvaidya
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Thank you!

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