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 $\rightarrow$ genetic mutations $\rightarrow$ invasive carcinoma


- 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

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Possible Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Otalgia/aural fullness</td>
<td>Pharynx, larynx, nasopharynx, or ear</td>
</tr>
<tr>
<td>Dysphagia/ odynophagia</td>
<td>Pharynx, esophagus, or oral cavity</td>
</tr>
<tr>
<td>Hoarseness</td>
<td>Larynx</td>
</tr>
<tr>
<td>Trismus, dysarthria</td>
<td>Oral cavity or oropharynx</td>
</tr>
<tr>
<td>Nasal congestion, epistaxis</td>
<td>Sinonasal tract</td>
</tr>
<tr>
<td>Aspiration</td>
<td>Oropharynx or larynx</td>
</tr>
</tbody>
</table>
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
### Factors Associated With HPV Status in OPC

<table>
<thead>
<tr>
<th>HPV+</th>
<th>HPV-</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Younger</td>
<td>• Older</td>
</tr>
<tr>
<td>• Non / light smoker / alcohol</td>
<td>• Heavy smoking / drinking</td>
</tr>
<tr>
<td>• Incidence increasing</td>
<td>• Incidence decreasing</td>
</tr>
<tr>
<td>• Caucasian</td>
<td>• Non-Caucasian</td>
</tr>
<tr>
<td>• High-risk sexual behavior</td>
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<tr>
<td>• <strong>Poorly differentiated</strong></td>
<td>• <strong>Keratinizing</strong></td>
</tr>
<tr>
<td>• <strong>Nonkeratinizing</strong></td>
<td>• <strong>P53 mutation</strong></td>
</tr>
<tr>
<td>• <strong>Basaloid</strong></td>
<td>• <strong>EGFR amplified</strong></td>
</tr>
<tr>
<td>• p16 upregulated</td>
<td></td>
</tr>
</tbody>
</table>
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

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

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 (EBV Encoded RNA) positivity by ISH is highly suggestive of nasopharyngeal carcinoma
• For other organs, SCC has no specific IHC markers
CUP: IHC

CK7+ CK20+
- Urothelial tumors
- Ovarian mucinous adenocarcinoma
- Pancreatic adenocarcinoma
- Cholangiocarcinoma

CK7+ CK20-
- Lung adenocarcinoma
- Breast carcinoma
- Thyroid carcinoma
- Endometrial carcinoma
- Cervical carcinoma
- Salivary gland carcinoma
- Cholangiocarcinoma
- Pancreatic carcinoma

CK7- CK20+
- Colorectal carcinoma
- Merkel cell carcinoma

CK7- CK20-
- 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 (i.e., 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%
NCCN Guidelines Version 2.2022
Occult Primary

PRESENTATION

PATHOLOGY

WORKUP

- CT with contrast or MRI with contrast (skull base through thoracic inlet)\(^a\)
- FDG PET/CT as indicated (before EUA)\(^b\)
- Chest CT with contrast (if PET/CT not done)\(^b\)
- HPV, EBV testing for squamous cell or undifferentiated histology\(^c\)
- Thyroglobulin, calcitonin, PAX8, and/or TTF staining for adenocarcinoma and anaplastic/undifferentiated tumors

As clinically indicated:
- Dental evaluation\(^d\)
- Nutrition, speech and swallowing evaluation/therapy\(^e\)
- Smoking cessation counseling\(^f\)
- Fertility/reproductive counseling\(^f\)

T0 and p16 (HPV)-positive

T0 and EBV+ or EBER+

Primary found

Primary not found

Treat as oropharyngeal cancer (see ORPH-1)

Treat as nasopharyngeal cancer (see NASQ-1)

Treat as appropriate (See NCCN Guidelines Index)

See Workup and Treatment (OCC-2)

See NCCN Guidelines for Non-Hodgkin Lymphomas

See NCCN Guidelines for Thyroid Carcinoma

Workup and treatment per NCCN Guidelines for Melanoma: Cutaneous

- Skin exam, note regressing lesions

See Workup for Mucosal Melanoma (MM-1)

See Primary Therapy for Mucosal Melanoma (MM-4)

\(^a\) 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.

\(^b\) For additional cessation support, refer to the Patient/Provider Smoking Cessation Resources in the NCCN Guidelines for Smoking Cessation.

\(^c\) 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].
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

<table>
<thead>
<tr>
<th>Prognostic factors</th>
<th>Tumour related</th>
<th>Host related</th>
<th>Environment related</th>
</tr>
</thead>
<tbody>
<tr>
<td>Essential</td>
<td>Histology</td>
<td>Immunosuppression (especially skin cancer)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>N category and number of nodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Extracapsular extension</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Presence or absence of metastatic disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>p16(^{NK_{4}A})/HPV status, or EBV DNA status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additional</td>
<td>Tumour differentiation</td>
<td>Gender</td>
<td>Subsequent discovery of primary</td>
</tr>
<tr>
<td></td>
<td>Location of nodal disease (above vs below clavicle)</td>
<td>Haemoglobin level</td>
<td>Overall treatment time</td>
</tr>
<tr>
<td></td>
<td>Surviving nuclear expression</td>
<td>Smoking history</td>
<td></td>
</tr>
</tbody>
</table>

*New and Promising: TP53*
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 of field cancerization
  - Presence of an intact apoptotic response
# Treatment Recommendations

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

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

Neck dissection

- pN1: Follow up
- pN2a: Follow up or unilateral RT
- pN2b
  - p_{16}+: Unilateral RT
  - p_{16}⁻: Consider bilateral RT
- pN2c-pN3b/cN3a⁺/R1
  - Bilateral RT + platin-based CTX
NCCN Guidelines Version 2.2022
Occult Primary

HISTOLOGY

DEFINITIVE TREATMENT

N1

- Neck dissection
- or
- RT^o (category 2B)

\[ \text{See OCC-4} \]

\[ \text{See Post Systemic Therapy/RT or RT Neck Evaluation (FOLL-A, 2 of 2)} \]

\[ \text{Recurrent or persistent disease (See ADV-3)} \]

N2-3

- Neck dissection
- or
- Concurrent systemic therapy/RT^o,q (category 2B)
- or
- Induction chemotherapy^q,r (category 3) followed by systemic therapy/RT^o,q or RT^o

\[ \text{See OCC-4} \]

\[ \text{See Post Systemic Therapy/RT or RT Neck Evaluation (FOLL-A, 2 of 2)} \]

\[ \text{Recurrent or persistent disease (See ADV-3)} \]

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^ See Principles of Surgery (SURG-A).
^ See Principles of Radiation Therapy (OCC-A).
^ 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.
^ See Principles of Systemic Therapy for Non-Nasopharyngeal Cancers (SYST-A).
^ 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.
NCCN Guidelines Version 2.2022
Occult Primary

TREATMENT

N1 without extranodal extension

RT (target volume determined by tumor size, nodal station, and HPV and EBV status)\(^{f,p}\) or Observe

Follow-up (See FOLL-A, 1 of 2)

Recurrent or persistent disease (See ADV-3)

Post neck dissection

N2, N3 without extranodal extension

RT (target volume determined by tumor size, nodal station, and HPV and EBV status)\(^{f,p}\) or Consider systemic therapy/RT\(^{f,q}\) (category 2B)

Nodal extension

Extranodal extension

Systemic therapy/RT\(^{f,q}\) (category 1) or RT (target volume determined by tumor size, nodal station, and HPV and EBV status)\(^{f,p}\)

\(^{f}\) 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].

\(^{p}\) Treatment for nasopharyngeal (NASO-2) and p16-positive oropharyngeal cancers (ORPHEV-3 and ORPHEV-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).

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.
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
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

<table>
<thead>
<tr>
<th>Risk levels</th>
<th>Comprehensive</th>
<th>Conservative</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High</strong></td>
<td>Involved level</td>
<td>Involved level</td>
<td>66-70 Gy in 33-35 #</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Ipsilateral adjacent level</td>
<td>-</td>
<td>60 Gy in 30 #</td>
</tr>
<tr>
<td>Low</td>
<td>B/l uninvolved levels &amp; potential mucosal sites</td>
<td>+/- Ipsilateral adjacent level</td>
<td>50 Gy in 25 #</td>
</tr>
</tbody>
</table>

### Comprehensive vs Conservative

#### High Risk
- **Comprehensive**: Involved level
- **Conservative**: Involved level
- **Dose**: 66-70 Gy in 33-35 #

#### Intermediate Risk
- **Comprehensive**: Ipsilateral adjacent level
- **Conservative**: -
- **Dose**: 60 Gy in 30 #

#### Low Risk
- **Comprehensive**: B/l uninvolved levels & potential mucosal sites
- **Conservative**: +/- Ipsilateral adjacent level
- **Dose**: 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
Contrast-enhanced CT/MRI of the neck

No primary found

Primary found

FNAB

IHC

Further staging and therapy

<table>
<thead>
<tr>
<th>Marker</th>
<th>Tumor type</th>
<th>Nodal levels commonly involved</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK 5/6</td>
<td>Squamous cell carcinoma</td>
<td>Level I-III</td>
</tr>
<tr>
<td>CK7/CAM 5.2, SOX10, Calponin/SMA/SMMHC</td>
<td>Adenocarcinoma</td>
<td>Salivary Glands</td>
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<tr>
<td>TTF-1, Thyreoglobulin</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TTF-1, CK7+/CK20- PSA, PAP</td>
<td>Thyroid</td>
<td>Level IV-V</td>
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<tr>
<td>GCDFP-15, mammaglobulin, ER</td>
<td>Lung</td>
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<tr>
<td>CDX2, CK20+/CK7- CDX2, CK7+/CK20+ or CK7+/CK20-</td>
<td>Prostate</td>
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<tr>
<td></td>
<td>Breast</td>
<td></td>
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<tr>
<td></td>
<td>Colon</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pancreas/biliary</td>
<td></td>
</tr>
</tbody>
</table>

SCC

No SCC

Contd. to next slide
SCC

Further specifications:
p16+/-, EBV+/-

- Consider tonsillectomy
- Panendoscopy with directed biopsies:
  i.e. p16+ oropharynx, EBV+ nasopharynx

No SCC

PET-CT and/or organ specific diagnostics for non-squamous tumors (e.g. scintigraphy for thyroid markers)

Primary found

HNCUP treatment

No primary found

Primary found

Further staging and therapy
ACKNOWLEDGEMENTS

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  Sarbani Ghosh Laskar, Naveen B Mummudi, Vedang Murthy and Gouri Pantvaidya
- Neck Cancer With Unknown Primary Site, Updated: Mar 04, 2021, Medscape
  Investigation and management of the unknown primary with metastatic neck disease: United Kingdom
  National Multidisciplinary Guidelines
  K Mackenzie,¹ M Watson,² P Jankowska,³ S Bhide,⁴ and R Simo⁵
- Radiation Oncology volume 12, Article number: 82 (2017)
  Diagnostic and treatment modalities for patients with cervical lymph node metastases of unknown primary site
  – current status and challenges
  Jens Müller von derGrün, Aykut Tahtali, Shahram Ghanaati, Claus Rödel & Panagiotis Balermpas

- NCCN Guidelines, Version 2.22
Thank you!

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