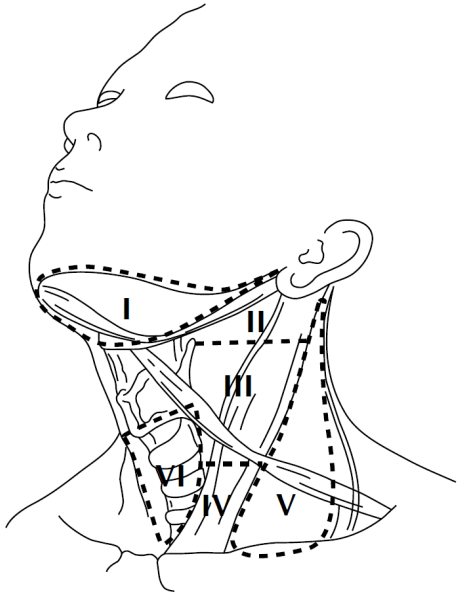
Management of unknown primary with neck node metastasis: Current evidence



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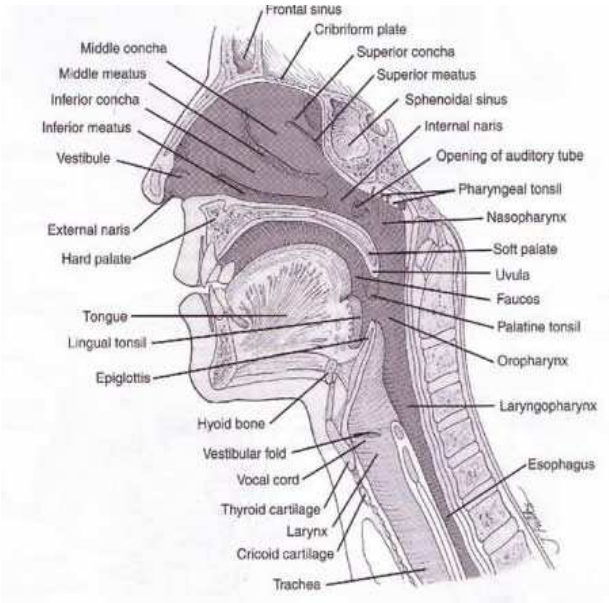
Introduction- Approach to Topic

- What is MUO – different terminologies
- How to diagnose
- How to treat
- Review of literature
- Take home message

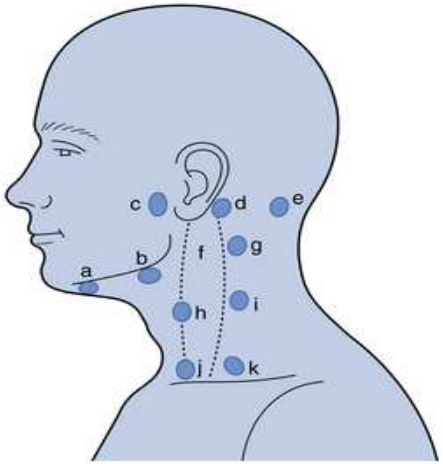
Different terminologies

- CUP: Carcinoma of unknown primary
- PUO: Primary of unknown origin
- MUO: Metastases of unknown origin
- UKP: Unknown primary



A

a Submental
b Submandibular
c Preauricular
d Postauricular
e Occipital
f Jugulo-digastric
g Jugulo-omohyoid
h Mid jugular
i Midposterior cervical
j Lower jugular
k Lower posterior cervical



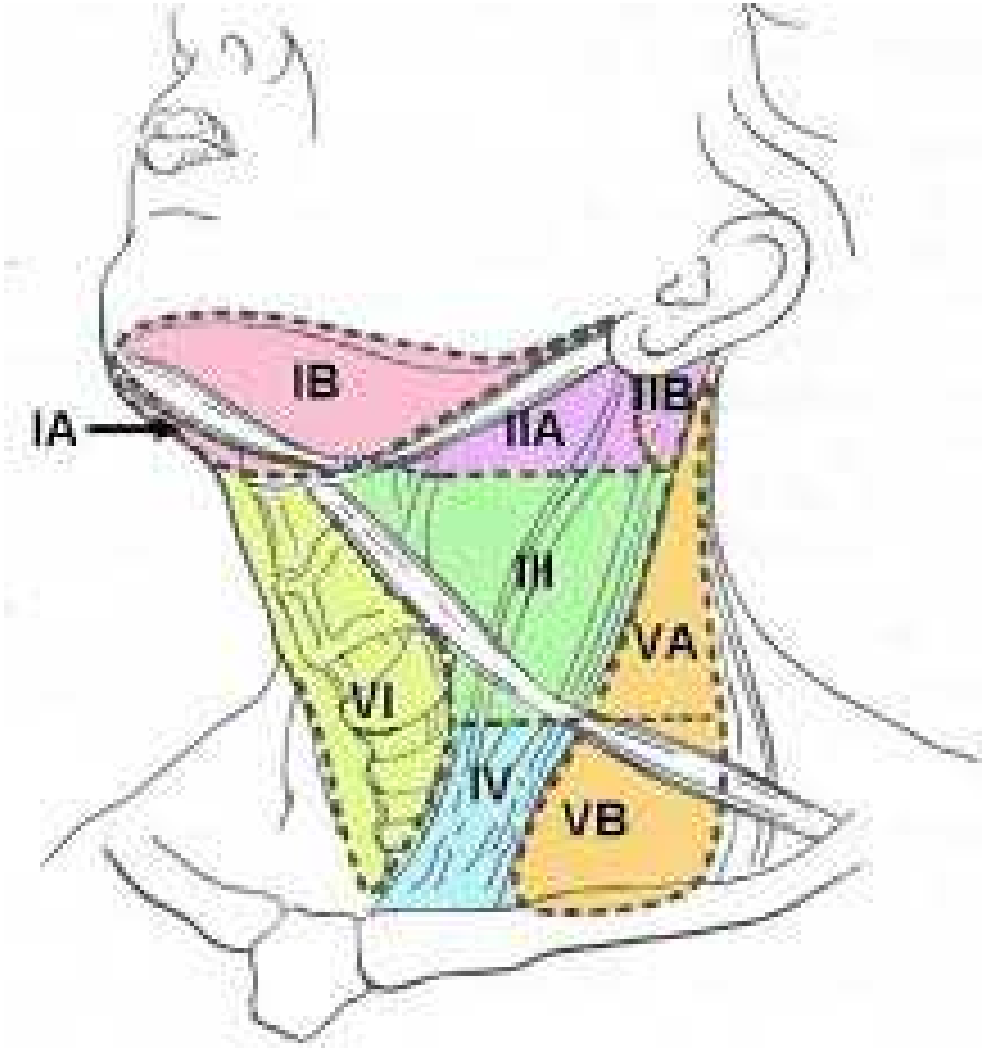
Unknown primary

- A lymph node in the neck with malignant pathology without any obvious primary mucosal origin.

- Head and neck unknown primaries are generally squamous cell carcinomas

- Incidence: 5 % of head and neck cancers

Levels of the Neck



Levels of the Neck

- Level I - This includes the submental and submandibular lymph nodes.
  - The submental triangle (sublevel IA) is bounded by the anterior belly of the digastric muscles (laterally) and the hyoid (inferiorly). The submandibular triangle (sublevel IB) is bounded by the body of the mandible (superiorly), the stylohyoid (posteriorly), and the anterior belly of the digastric (anteriorly).

- Level II - This includes lymph nodes of the upper jugular group and is divided into sublevels IIA and IIB.
  - Level II is bounded by the inferior border of the hyoid (inferiorly), the base of skull (superiorly), the stylohyoid muscle (anteriorly) and the posterior border of the SCM (posteriorly). Sublevel IIA nodes lie anterior to the SAN. Sublevel IIB nodes lie posterior to the SAN.

- Level III - This includes lymph nodes of the middle jugular group.
  - This level is bounded by the inferior border of the hyoid (superiorly) and the inferior border of the cricoid (inferiorly), the posterior border of the sternohyoid (anteriorly) and the posterior border of the SCM (posteriorly).

- Level IV - This includes lymph nodes of the lower jugular group.
  - This level is bounded by the inferior border of the cricoid (superiorly), the clavicle / sternal notch (inferiorly), the posterior border of the sternohyoid (anteriorly) and the posterior border of the SCM (posteriorly).

- Level V - This includes posterior compartment lymph nodes.
  - This compartment is bounded by the clavicle (inferiorly), the anterior border of the trapezius (posteriorly), the posterior border of the SCM (anteriorly). It is divided into sublevels VA (lying above a transverse plane marking the inferior border of the anterior cricoid arch) and VB (below the aforementioned plane).

- Level VI - This includes the anterior compartment lymph nodes.
  - This compartment is bounded by the common carotid arteries (laterally), the hyoid (superiorly), the suprasternal notch (inferiorly).

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- 3-5% of presentation,55-65 years
- 80-85% are tonsil and base of tongue
- Most commonly level II F/B III whereas I, IV and V are less frequent.
- Unilateral more common and B/L 10%
- Metastases in upper neck is mostly from head and neck – SCC, PD (Exception Adenocarcinoma - thyroid, parathyroid and parotid)
- From lower neck below clavicles other than from head and neck - Adenoca

Clinical Presentation

- Patients generally present with a painless, solitary neck mass, most often discovered by the patient.
- Masses are usually at least 3-5 cm
- Patients have usually gone through at least one course of antibiotics
- Benign masses are also often solitary and painless

Differential diagnosis

- Benign
  - Developmental (i.e., thyroglossal duct cyst, branchial cleft cysts or inclusion cysts)
  - Inflammatory (i.e., lymphadenitis, benign reactive hyperplasia, infected sebaceous cyst)
  - Benign Neoplasms (i.e., lipoma, fibroma, hemangioma, neurofibroma, parathyroid adenoma or goiter)

Differential diagnosis

- Malignant
  - Metastatic carcinoma, sarcoma or melanoma
  - Lymphoma, Leukemia
  - Carotid body tumor
  - Primary major salivary gland tumor
  - Thyroid cancer
  - Parathyroid cancer
  - Histiocytosis
  - Carcinoid

Relationship of Node Location to Likely Disease

- Nodes at certain levels more likely certain primaries
- **Upper neck nodes** are the most likely to be head and neck cancer
  - Subdigastric node may be virtually any head and neck primary, or a non-Hodgkin's lymphoma
  - Submandibular node suggests oral cavity, lip, nasal vestibule or salivary gland primary
  - Submental nodes are uncommon

Relationship of Node Location to Likely Disease

- **Mid Neck**
  - Likely primaries include larynx, hypopharynx, and less commonly esophagus, disease below clavicles or lymphoma

- **Lower Neck and Supraclavicular Nodes**
  - Most often metastatic from chest or abdomen, possible esophagus or lymphoma.

- **Parotid lymph nodes**

  Parotid lymph nodes are more likely skin cancer than from a primary parotid tumor

AJCC Nodal Staging

TABLE 9 N Staging for All Head and Neck Sites Except the Nasopharynx and Thyroid

Nx	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis in a single ipsilateral lymph node, more than 3 cm but not more than 6 cm in greatest dimension; or in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension; or in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N2a	Metastasis in a single ipsilateral lymph node more than 3 cm but not more than 6 cm in greatest dimension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension
N2c	Metastasis in bilateral or contralateral lymph nodes, none more than 6 cm in greatest dimension
N3	Metastasis in a lymph more than 6 cm in greatest dimension

Diagnosis

Physical exam

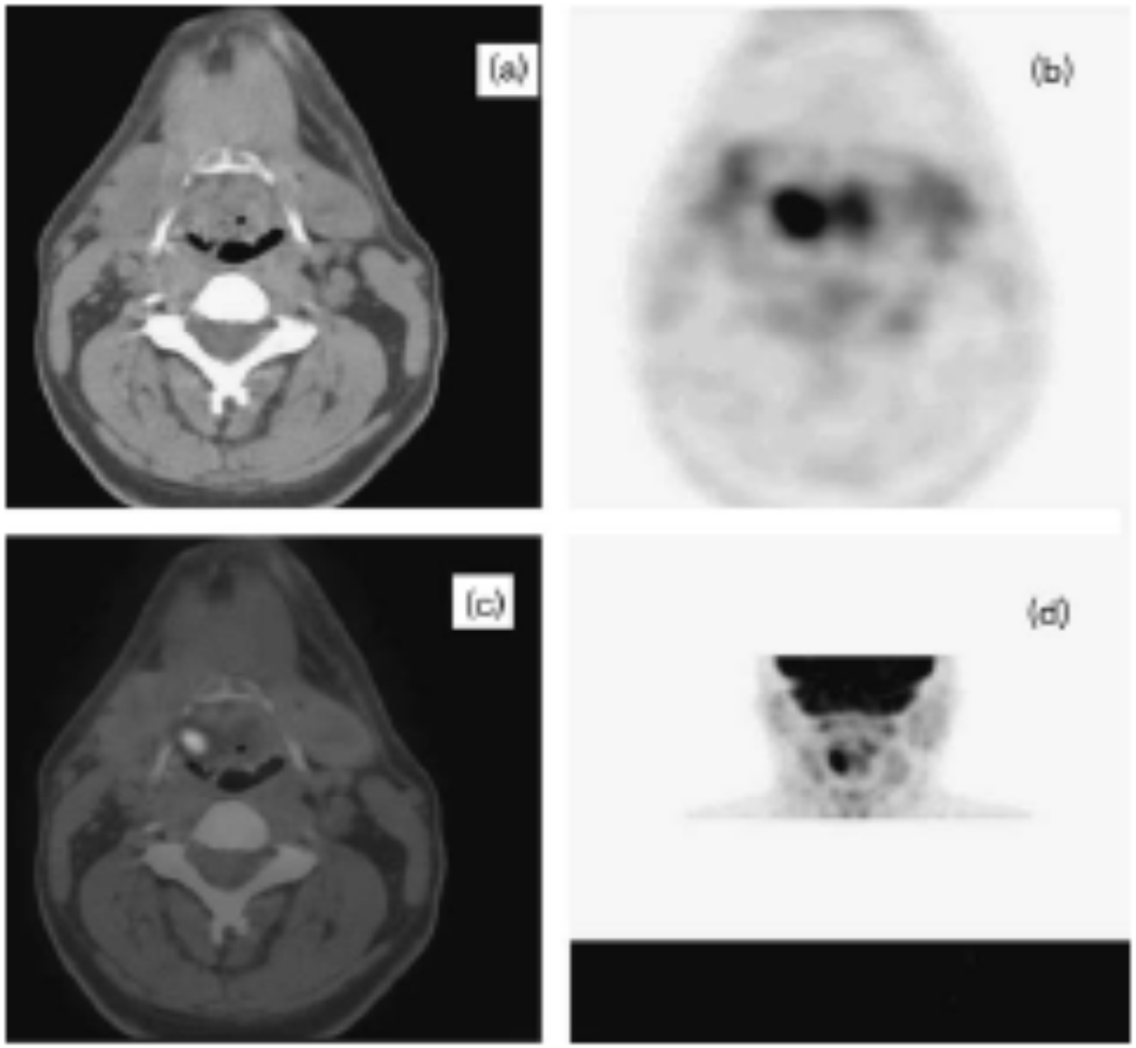
- Soft, rubbery nodules suggest lymphoma and leukemia
- Hard, fixed masses suggest carcinoma
- Indirect examination of oral cavity and oropharynx with mirror and/or fiberoptic endoscopy

Diagnosis

Imaging

- CT followed by an MRI if inconclusive
- If there is still no imaging data for a primary, a PET may be ordered
  - In a meta-analysis of 16 studies looking at the role of PET in 302 patients with cervical node metastases where a primary has yet to be discovered through the work up, **25% of primaries are identified through PET**. Previously unrecognized regional or distant metastases were identified in 27% of patients
    - Rusthoven, KE, Koshy, M, Paulino, AC, The role of fluorodeoxyglucose PET in cervical lymph node metastases from an unknown primary tumor. Cancer 2004; 101:2461

Fig. 2



Axial low-dose CT (a), PET (b), fused PET–CT (c) and maximal intensity projection views (d) showing a focal FDG uptake on the right valleculae, confirmed on biopsies (patient 38).

Diagnosis

- Fine needle biopsy of LN

- Incisional or excisional biopsy before definitive treatment

✓ neck recurrence

✓ distant metastasis

✓ wound necrosis

- SCC and UD- EBV and p16
- EBV in situ hybridization – Nasopharyngeal malignancy
- SCC Polymerase chain reaction – Oropharyngeal malignancy
- Treat accordingly

Diagnosis

- Staging surgical endoscopy – panendoscopy (triple endoscopy) – direct laryngoscopy to evaluate oropharynx, larynx and hypopharynx, nasopharyngoscopy and upper esophagoscopy

Diagnosis

Screening Tonsillectomy

- If a primary site has not been discovered by this point, an ipsilateral screening tonsillectomy may be performed
  - This is of greatest benefit in patients with subdigastric, submandibular or midjugulocarotid lymph nodes
  - In a study of 87 patients with unknown primaries, 26% were discovered to have a tonsillar primary after tonsillectomy
    - Lapeyre, M, Malissard, L, Peiffert, D et al. Cervical lymph node metastasis from an unknown primary: Is a tonsillectomy necessary? Int J Radiat Oncol Biol Phys; 39: 291
  - Literature for bilateral tonsillectomy not convincing (no chance of missing contralateral tonsil and greater symmetry on PE after B/L tonsillectomy

Treatment

- Treat as aggressive disease

- Treat based on staging
- N1- neck dissection OR radiation
- N2, N3- combined neck dissection AND radiation

Basic guidelines

cN1: Options include radical neck dissection alone, neck dissection followed by adjuvant radiotherapy, or radiotherapy alone. Modified radical dissection likely confers similar survival as radical with appropriate adjuvant therapy, when final pathology reveals >N1 disease.[11]

Clear indications for adjuvant radiotherapy (+/- chemotherapy) after neck dissection include:

- ≥N2 disease
- ECE
- positive margin
- previous neck violation

ECE and positive margins will warrant the addition of chemotherapy to PORT unless otherwise contraindicated

≥cN2: Combined chemo + radiation therapy is recommended. Surgical management is an option though not preferred upfront. Adjuvant radiotherapy improves locoregional control. For very large nodes, consideration can be made for neck dissection first to remove bulk of disease, followed by adjuvant radiotherapy or chemoradiation.

Example RT prescription dosing is as follows:

- 66-70Gy to gross nodal disease,
- 60-63Gy to high risk nodal levels and likely mucosal primary sites
- 54-56Gy to elective nodal levels

Persistent or progressive nodal disease after radiotherapy should warrant surgical consultation for salvage neck dissection.

M1: Patients will metastatic disease should be referred to medical oncology for discussion of systemic therapy. Palliative radiotherapy for symptom control may be indicated or best supportive care.

- **Poorly Differentiated**
- Most frequent site is pharynx especially NP
- RT to neck and Waldeyer's ring including NP
- Neck dissection for residual
- **Adenocarcinoma**
- Node at level I-III could be salivary gland tumor
- Excision biopsy indicated and if clinical and pathological cannot find primary then consensus on neck dissection (I-V) including parotidectomy if indicated followed by RT

NCCN Guidelines Version 1.2015
Occult Primary

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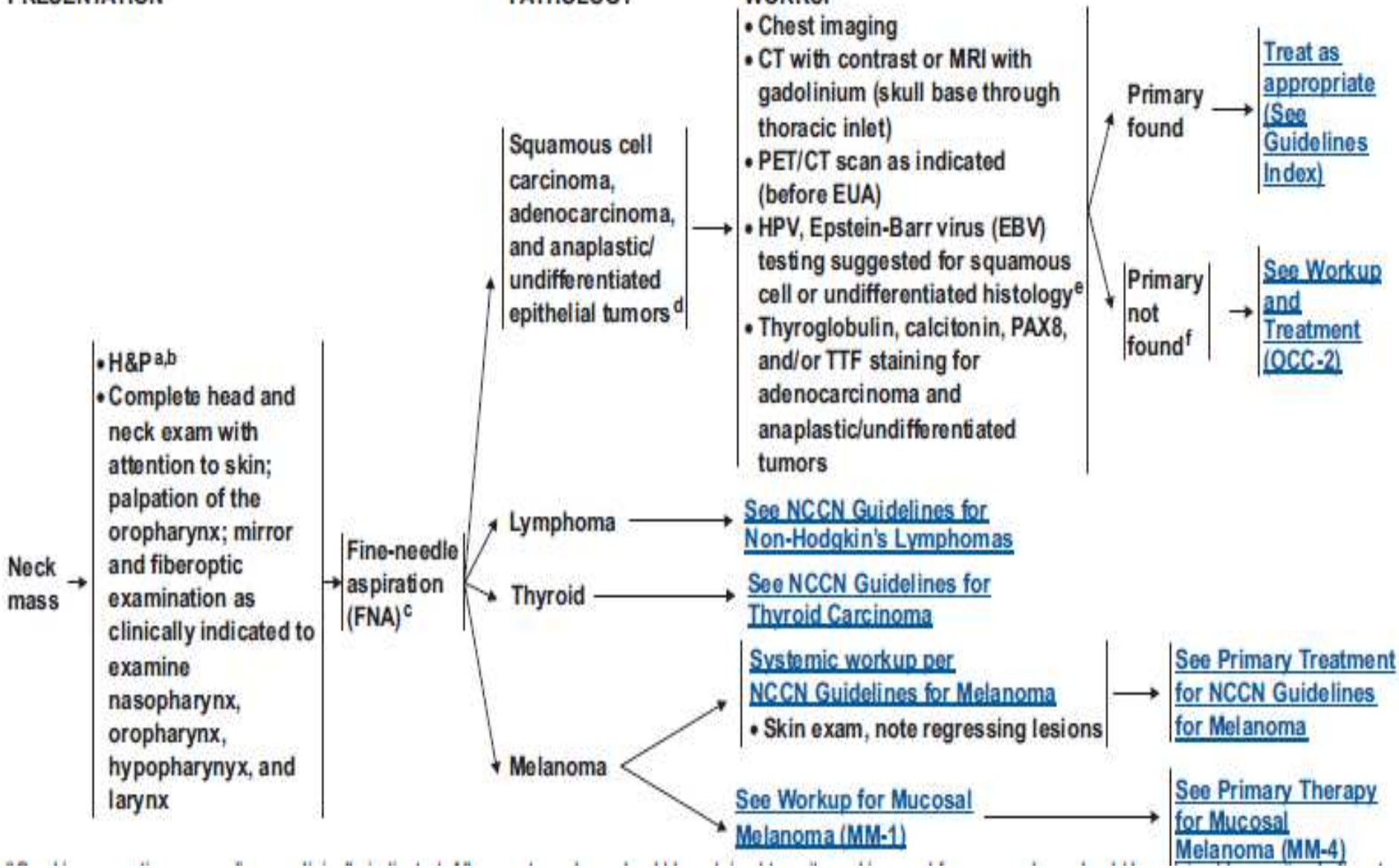

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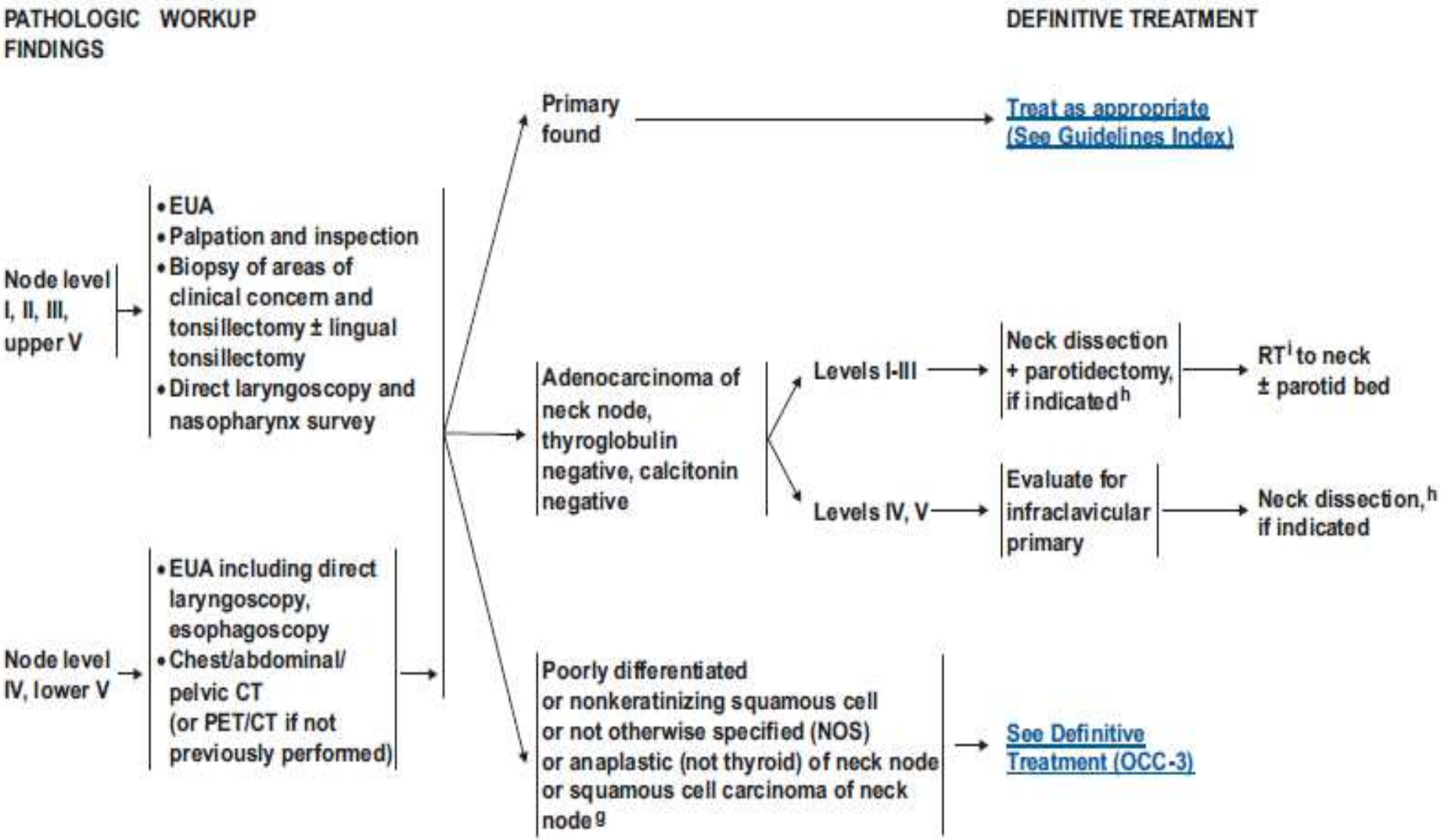

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HISTOLOGY

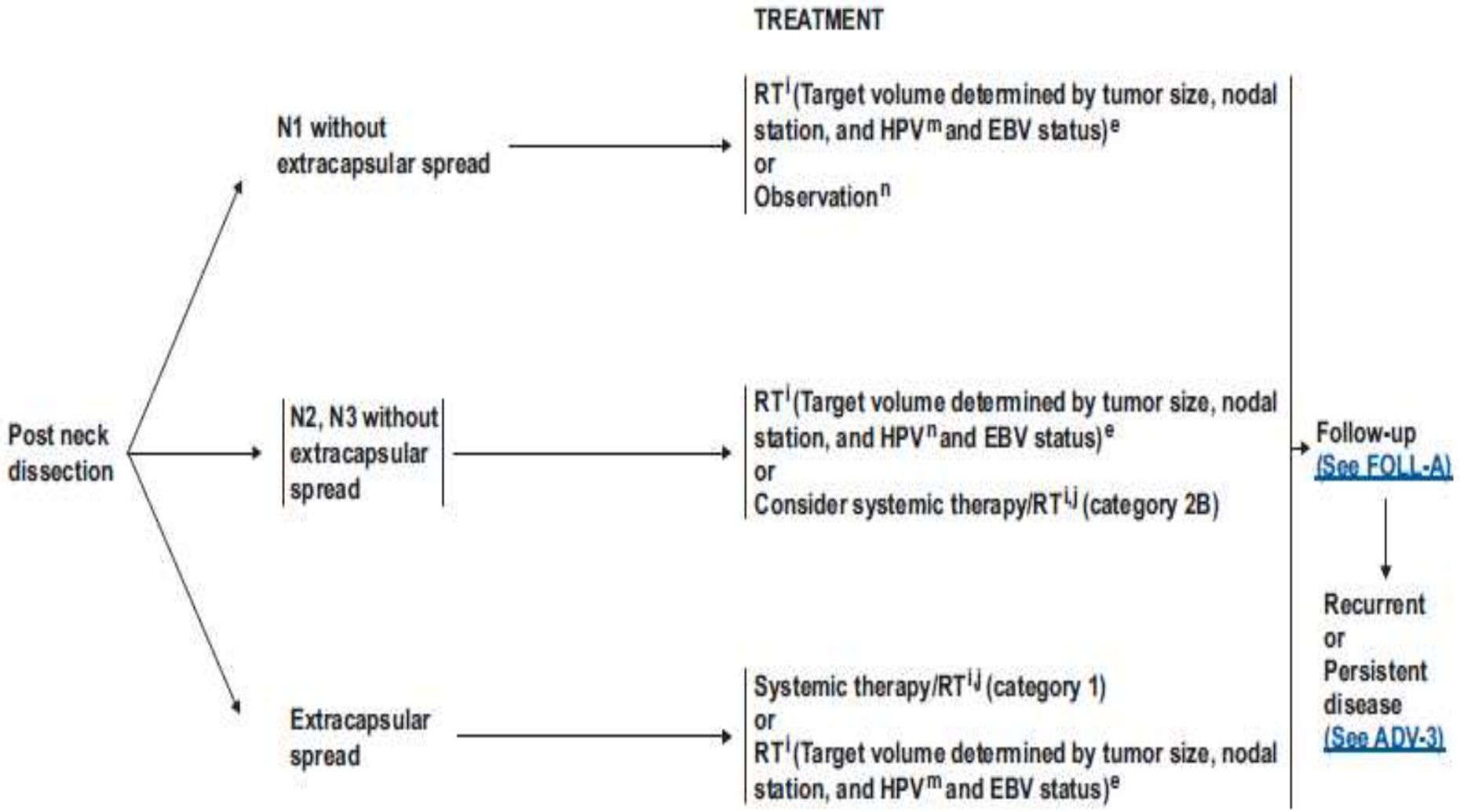
Poorly differentiated or nonkeratinizing squamous cell or NOS or anaplastic (not thyroid) or Squamous cell carcinoma

DEFINITIVE TREATMENT

- Surgery[h] (preferred for < N2 disease) → Neck dissection[h] → See OCC-4
- or
- RT[i] for < N2 (category 2B)
- or
- Systemic therapy/RT[i,j] for ≥ N2 (category 2B)
- or
- Induction chemotherapy[j,k] (category 3) followed by systemic therapy/RT[i,j] or RT[i]

Systemic therapy/RT[i,j] for ≥ N2 (category 2B) or Induction chemotherapy[j,k] (category 3) followed by systemic therapy/RT[i,j] or RT[i]:

- Complete clinical response → Post-treatment evaluation[l]
  - Negative → Observe
  - Positive → Neck dissection[h]
- Residual tumor in neck → Neck dissection[h]


TREATMENT
Post neck dissection
N1 without extracapsular spread
N2, N3 without extracapsular spread
Extracapsular spread
RT[i] (Target volume determined by tumor size, nodal station, and HPV[m] and EBV status)[e]
or
Observation[n]
RT[i] (Target volume determined by tumor size, nodal station, and HPV[n] and EBV status)[e]
or
Consider systemic therapy/RT[i,j] (category 2B)
Systemic therapy/RT[i,j] (category 1)
or
RT[i] (Target volume determined by tumor size, nodal station, and HPV[m] and EBV status)[e]
Follow-up
(See FOLL-A)
Recurrent
or
Persistent
disease
(See ADV-3)

PRINCIPLES OF RADIATION THERAPY[1,2]

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]

Either IMRT or 3-D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures, especially the parotid glands.

PRINCIPLES OF RADIATION THERAPY[1,2]

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]

Either IMRT or 3-D conformal RT is recommended when targeting the oropharynx to minimize the dose to critical structures, especially the parotid glands.

IMRT

- Part of the purpose of using IMRT is to decrease dose to the parotid, in order to decrease the grade of xerostomia and improve dose homogeneity
- Bhide, S et al. Intensity modulated radiotherapy improves target coverage and parotid gland sparing when delivering total mucosal irradiation in patients with squamous cell carcinoma of head and neck of unknown primary site. 2007; 32(3):188-95

- Can also keep dose off of the larynx

Radiation

- Ipsilateral neck vs. bilateral neck, Bilateral favored
- Some studies show increase risk of neck disease or emergence of primary with ipsilateral treatment compared to bilateral without overall survival being affected
- Alternate studies show extensive radiation of mucosa and bilateral neck improve survival compared to ipsilateral neck radiation
  - Study of 352 patients with squamous cell or undifferentiated cancer of the cervical lymph nodes with no evident primary, the patients who received ipsilateral neck radiation compared to those receiving bilateral had a 1.9 relative risk of recurrence in the head and neck and lower 5 year disease free survival
    - Grau, C Johansen, LV, Jakobsen, J et al. Cervical lymph node metastases from unknown primary tumours. Results from a national survey by the Danish Society for Head and Neck Oncology. Radiother Oncol 2000;55:121.

Largest experience with primary RT – Danish Society of Head and Neck Oncology over a 20 year period

- 352 patients with CUP
- 277 were managed with bilateral neck irradiation and elective irradiation of sites in the nasopharynx, hypopharynx and larynx
- 26 received ipsilateral nodal irradiation only
- Patients treated with ipsilateral neck radiation compared to those receiving bilateral neck radiation had a 1.9-fold higher risk of recurrence in the head or neck (51 versus 27 percent, p = 0.05)
- Ipsilateral nodal irradiation also had a trend toward lower five year disease-specific survival (28 versus 45 percent).

Grau et al., Radiotherapy and Oncology: 2000 (55)

Radiation by Node location

- Upper nodes
  - Naso-, oro- and hypopharynx and supraglottic larynx. Oral cavity not included
- Junctional or lateral retropharyngeal node
  - Naso- and oropharynx
- Submandibular- solitary node
  - Neck only because of the major morbidity of irradiating the entire oral cavity
- Midjugular
  - Oro-, hypopharynx and supraglottic larynx
- Supraclavicular
  - Large portal to include apex of axilla

Metastatic Cervical LNs

- Cervical node metastases of **squamous cell carcinoma** from occult primary constitute about 2-5% of all patients with CUP

- **Mets in upper & mid neck**
  - attributed to H&N cancers

- **Lower neck (SCF)**
  - associated with 1^0 below the clavicles e.g. lung or GI tract

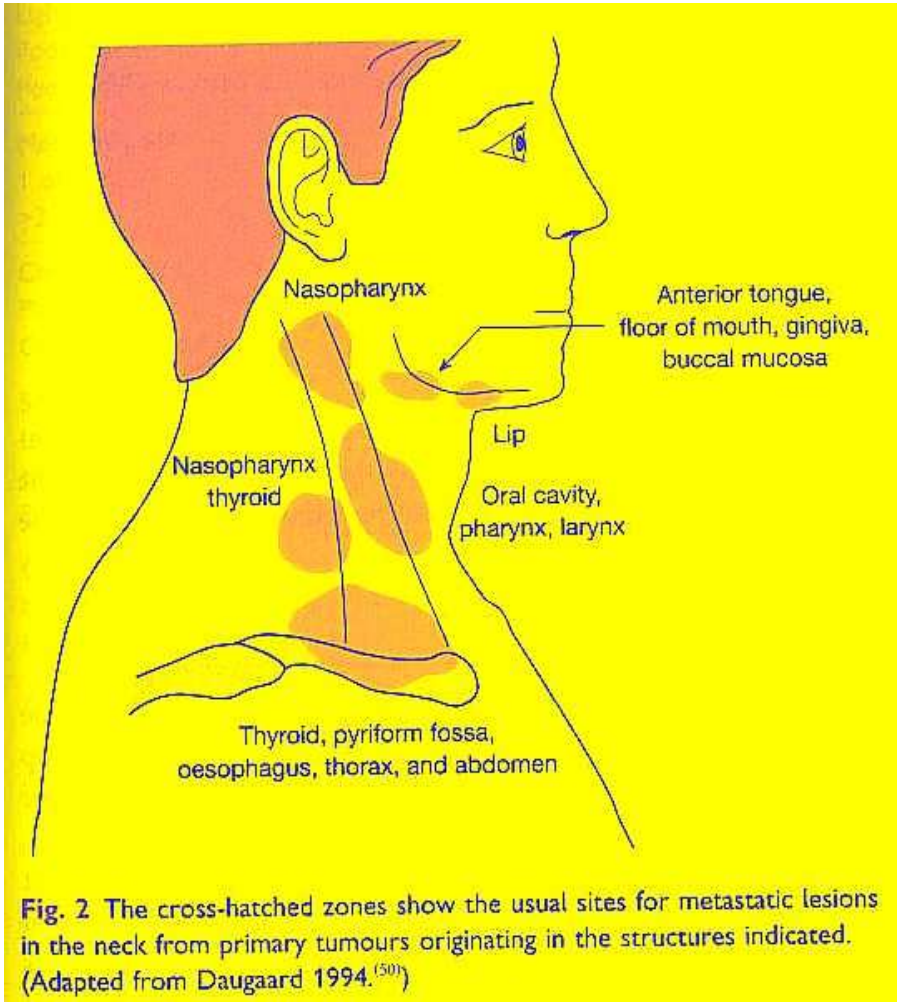


Fig. 2 The cross-hatched zones show the usual sites for metastatic lesions in the neck from primary tumours originating in the structures indicated. (Adapted from Daugaard 1994.[50])

Results

- Emergence rate of primary is 25%
- Medial nodal recurrence rate 35%
- 5 year overall survival rate 66%
- Estimated actuarial risk of emergence of head and neck primary after extensive irradiaton reaches 20% at 10 years.
- Median time to occurrence of subsequent primaries is about 21 months

Complications of Radiation Therapy

- Most common complication is xerostomia (dry mouth due to decreased saliva production)
- Fatigue
- Mucositis
- Altered taste sensations
- Red and irritated skin
- Occasional nausea
- Esophageal stricture

Chemotherapy

- Platinum-based chemotherapy in combination with radiation recommended for N3 patients by European Society of Medical Oncology (ESMO)
- Consider concurrent chemo/RT with supraclavicular LN or undifferentiated tumors, though no strong data to support
- Chemo/ RT is an option for palliation, unresectable local disease, distant metastatic spread

Follow up

- TFT should be monitored if the patient received radiation to the lower neck since upto 30% of patients may develop subclinical or overt radiation induced hypothyroidism
- Clinical and fibrescopic check every two months in the first year, every four months for second an third every year then every six months.
- PET once a year, additional examination at discretion

Recurrence

- Comparing subsequent mucosal primary lesions in patients with unknown primaries to head and neck cancer with a known primary site shows the incidence of a subsequent mucosal recurrence was similar for both groups.

Recurrence

- Location (primary site, new primary site, neck or distant), the histology, time since initial diagnosis and prior therapies.
- surgical management is favored for patients previously treated with radiotherapy, and likewise those previously having undergone surgery alone should be considered for radiotherapy (+/- chemotherapy).
- Some patients - for repeat radiotherapy even to high doses.
- Small localized recurrences may be managed surgically in some cases.
- Recurrence at the base of skull or other difficult-to-access locations can benefit from external consultation at centers equipped with gamma knife or SBRT technologies.
- Other options include palliative radiotherapy or best supportive care.

Prognosis

- The best indicator of prognosis is N stage at presentation
- Also, the presence of extracapsular extension is associated with a poorer prognosis
- Prognosis is similar between patients with a known vs. an unknown primary with the same nodal stage.

Future Research

- Phase III Randomized Study of Selective Irradiation Versus Extensive Irradiation in Patients With Cervical Lymph Node Metastases of Squamous Cell Carcinoma From an Unknown Primary- Opened 2002, now closed awaiting for results
- EORTC-24001, EORTC-22005, DAHANCA-EORTC-24001, CAN-NCIC-EORTC-24001, RTOG-EORTC-24001, NCT00047125

- Depends on whether source is found during workup
- If primary site identified treat accordingly, ND followed by PORT to neck and mucosal sites
- Distinct advantages for different options – Surgery/RT/CT+RT
- Mucosal irradiation decrease primary emergence but at cost
- Tailoring of therapy according to HPV, EBV, Nodal level, history prevent unwarranted toxicity

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Comprehensive neck dissection	
Radical neck dissection	All ipsilateral lymph nodes from level I-V are removed along with the spinal accessory nerve, internal jugular vein and sternocleidomastoid muscle.
Modified radical neck dissection	As for radical neck dissection with preservation of one or more non-lymphatic structures. This is sometimes referred to as a "functional" neck dissection.
Selective neck dissection	
One or more of the lymphatic groups normally removed in the radical neck dissection is preserved. The lymph node groups removed are based on patterns of metastases which are predictable for each site of the disease.	
Extended neck dissection	
Additional lymph node groups or non-lymphatic structures are removed.	

- **Although in politics you cover the known, in medicine you uncover the unknown**