SIMPOSIO: Strategie terapeutiche nelle metastasi laterocervicali da focus ignoto

Neck metastases from unknown primary: role of the H&N surgeon

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NECK MASSES (persisting more than 3-4 wks, no clear infectious causes, no regression with medical therapy): diagnostic work up

- Age Groups
  - Pediatric (0 to 15 years): 90% benign
  - Young adult (16 to 40 years): similar to children
  - Late adult (>40 years): "rule of 80"
- Guidelines (most of the diagnostic work up rely on the technical abilities of the H&N surgeon)

Definition of occult primary

- Neck nodal localization of cancer, in which, after the careful work up no primary site has been found
- The diagnosis must be obtained by an algorithm pivoted on
  - the achievement of the definite histological diagnosis of the neck mass
  - the careful investigation of the potential primary sites
- Both the tasks require a wide range of technical skills and notable clinical experience, which are usually prerogatives of the otolaryngologists/ head and neck surgeon

NCCN Guidelines Version 1.2012
Occult Primary

PRESENTATION

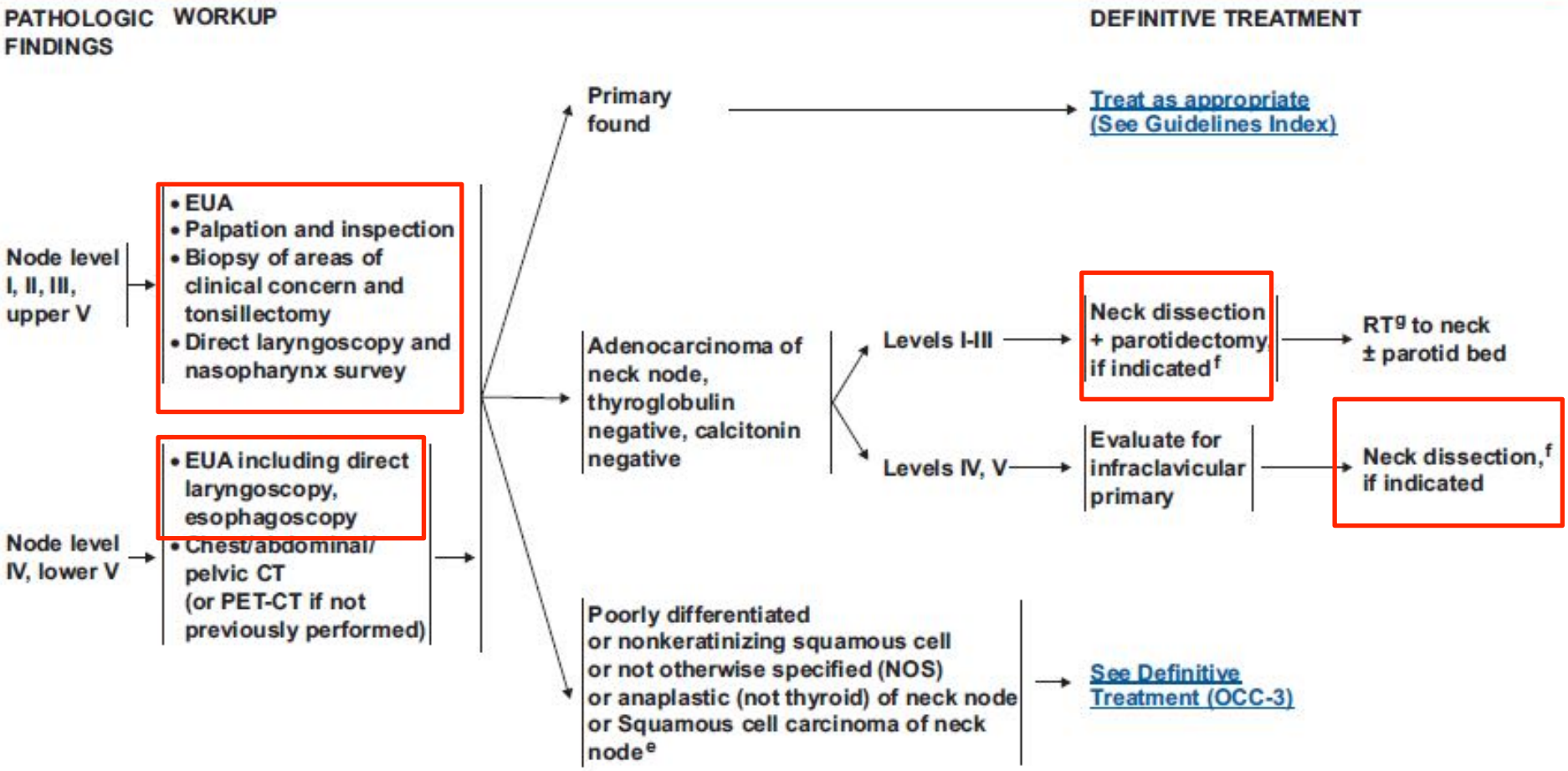
Neck mass → H&P and Complete head and neck exam with attention to skin; palpation of the base of tongue and oropharynx; mirror and fiberoptic examination as indicated to visualize nasopharynx, oropharynx, hypopharynx, and larynx → Fine needle aspiration (FNA)[a]

WORKUP

- Squamous cell carcinoma, adenocarcinoma, and anaplastic epithelial tumors[b] →
  - Chest imaging
  - CT with contrast or MRI with gadolinium (skull base through thoracic inlet)
  - PET/CT scan as indicated (before exam under anesthesia)
  - HPV, Epstein-Barr virus (EBV) testing suggested for squamous cell or undifferentiated histology[c]
  - Thyroglobulin and calcitonin staining for adenocarcinoma and anaplastic undifferentiated tumors
  - Primary found → Treat as appropriate (See Guidelines Index)
  - Primary not found[d] → See Workup and Treatment (OCC-2)
- Lymphoma → See NCCN Guidelines for Non-Hodgkin's Lymphomas
- Thyroid → See NCCN Guidelines for Thyroid Carcinoma
- Melanoma → Systemic work-up per NCCN Guidelines for Melanoma
  - Skin exam, note regressing lesions
  - → See Primary Therapy for Melanoma (MM-4)

[a] 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.
[b] Determined with appropriate immunohistochemical stains.
[c] Whether HPV or EBV positive status may help to define the radiation fields is being investigated (See Discussion).
[d] 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 cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.



[e]HPV and EBV testing are suggested if not yet done.
[f]See Principles of Surgery (SURG-A).
[g]See Principles of Radiation Therapy (OCC-A).

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Diagnostic work up in suspected occult T: offices of H&N surgeon

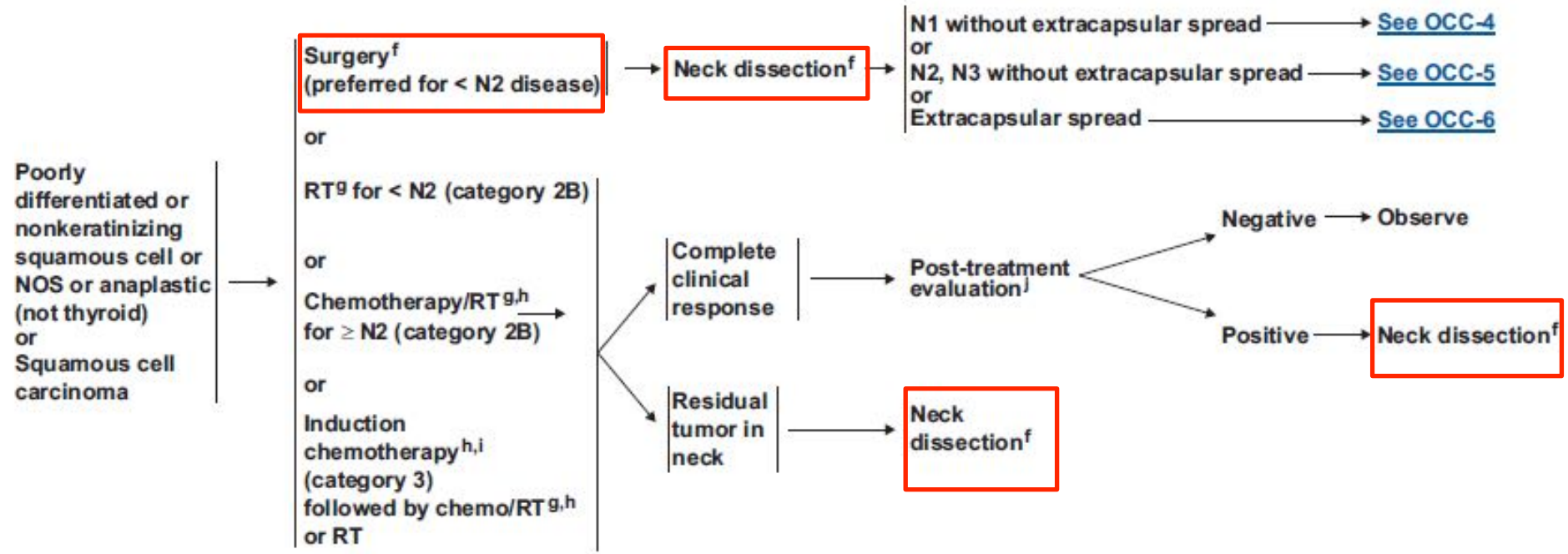
- Hystory (always ask for previous underestimated skin lesions)
- Complete H&N physical exam (including skin) and in particular:
  - Ispection of UADS (mirror and/or fiberoptic)
  - Palpation of the oropharynx
- FNAB (preferably US guided)
- For levels II and Va and, to a lower extent, I and III, biopsies of the areas of clinical concern and random biopsies of rhino-and oropharynx (elective tonsillectomy?! Mono- or bilateral?)
- Open biopsy only if repeated FNAB and previous work up is negative

Offices of H&N surgeon in the diagnostic work up: Pearls .....

- Palpation is the most sensible diagnostic tool for base of tongue masses after CE MRI
- The old-fashioned indirect laryngoscopy is the workhorse for diagnosis of UADs cancers:
  - Extremely low cost
  - Uncomparable one-sight, tridimensional overview of laryngopharyngeal complex, with true colors
  - Possibility for the experienced clinician to biopsy pharyngolaryngeal lesions without general anesthesia (patients with comorbidities)
- Also rhinopharynx can usually be biopsied in local anesthesia if needed (posterior rhinoscopy or with fibroscope assistance)

..... and pitfalls

- IV and Vb nodes always don't forget to check thorax and abdomen
- If a sure histology has not been obtained by FNAB nor a primary site identified by a careful diagnostic work up open biopsy is the "*extrema ratio",* in these cases frozen section is mandatory
- If frozens are positive for a solid malignancy a comprehensive neck dissection must be immediately accomplished, as a previous opening of the cervical fasciae compromises the possibilities of a delayed surgical or non-surgical clearance of the neck
- Never perform an open biopsy of a hard mass in the lateral neck if you cannot have frozen sections or if you are not able/ready to perform a comprehensive neck dissection at the same time



[f] See Principles of Surgery (SURG-A).
[g] See Principles of Radiation Therapy (OCC-A).
[h] See Principles of Systemic Therapy (CHEM-A).
[i] See Discussion on induction chemotherapy.
[j] See Post Chemoradiation or RT Neck Evaluation (SURG-A 7 of 7).

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Metastatic SCC from occult T: role of H&N surgeon in treatment

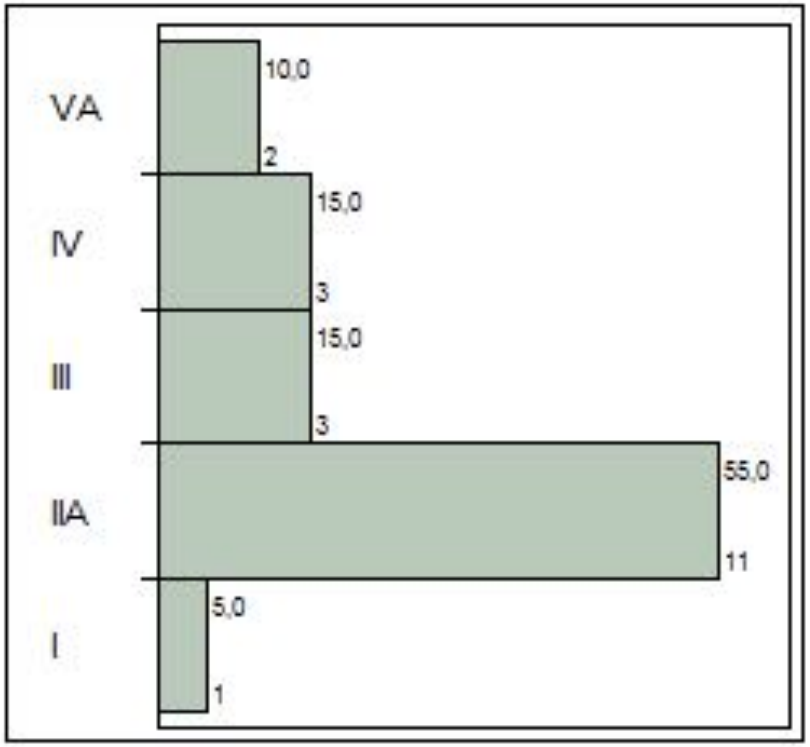
- Neck dissection mainstay of treatment
  - Option for primary treatment
  - Salvage for residual disease
  - Salvage for recurrence
  - Definite staging data

From neck dissection pathological data

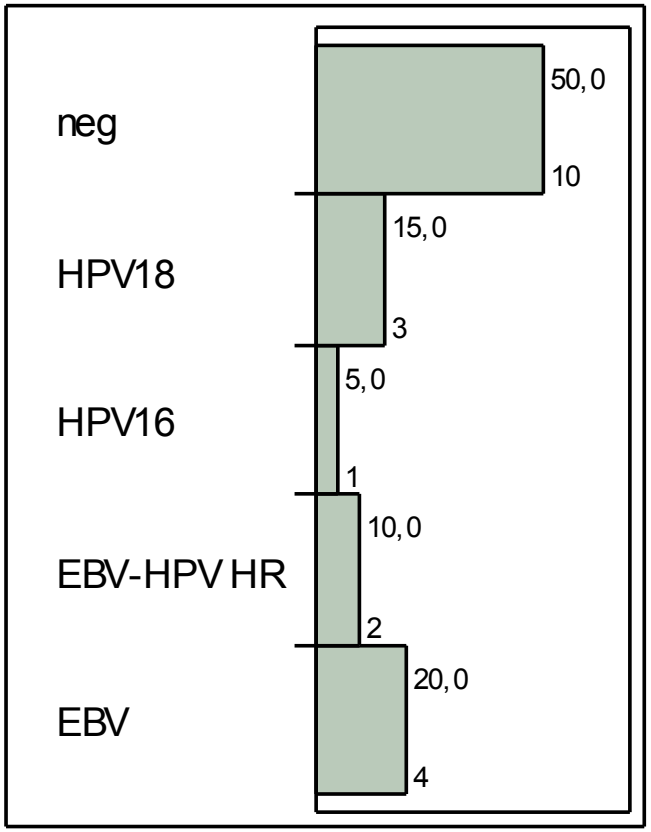
- We evaluated fresh samples from a consecutive series of 20 neck dissections for metastases from unknown primary SCC between 2010 and 2012
- Patients aged between 49 and 75 years (median 62)
- We looked for high risk HPV mRNA and EBV DNA in positive nodes

Our findings

Primarily involved nodal level

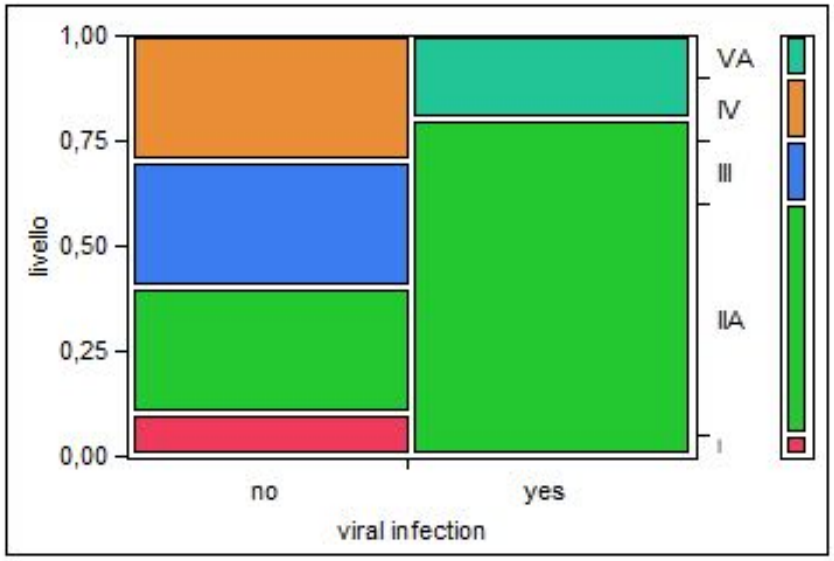


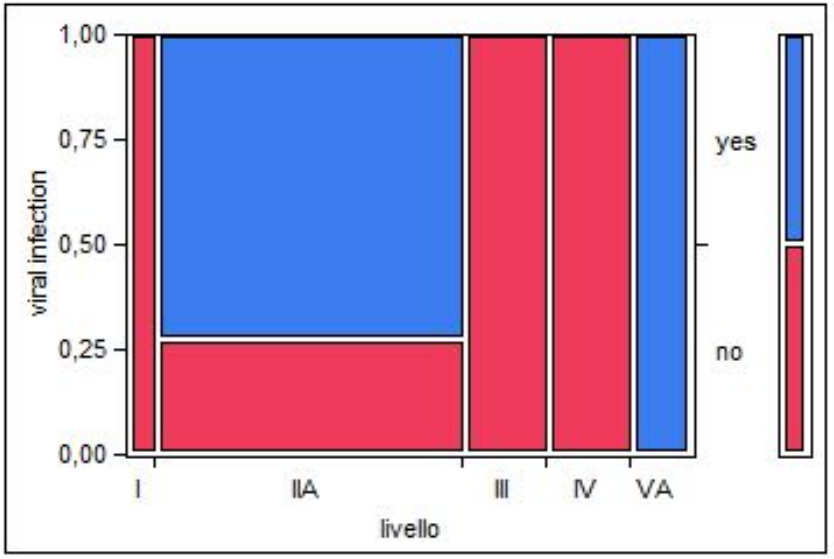
Presence of viruses in neck metastases



Our findings

Viruses are most often present in level IIA (73%) and VA (100%) metastases (p=0,0051)





Viruses in occult T

- Neck metastasis from unknown primary SCC can be a manifestation of virus related head and neck carcinogenesis as rhinopharyngeal and oropharyngeal carcinoma

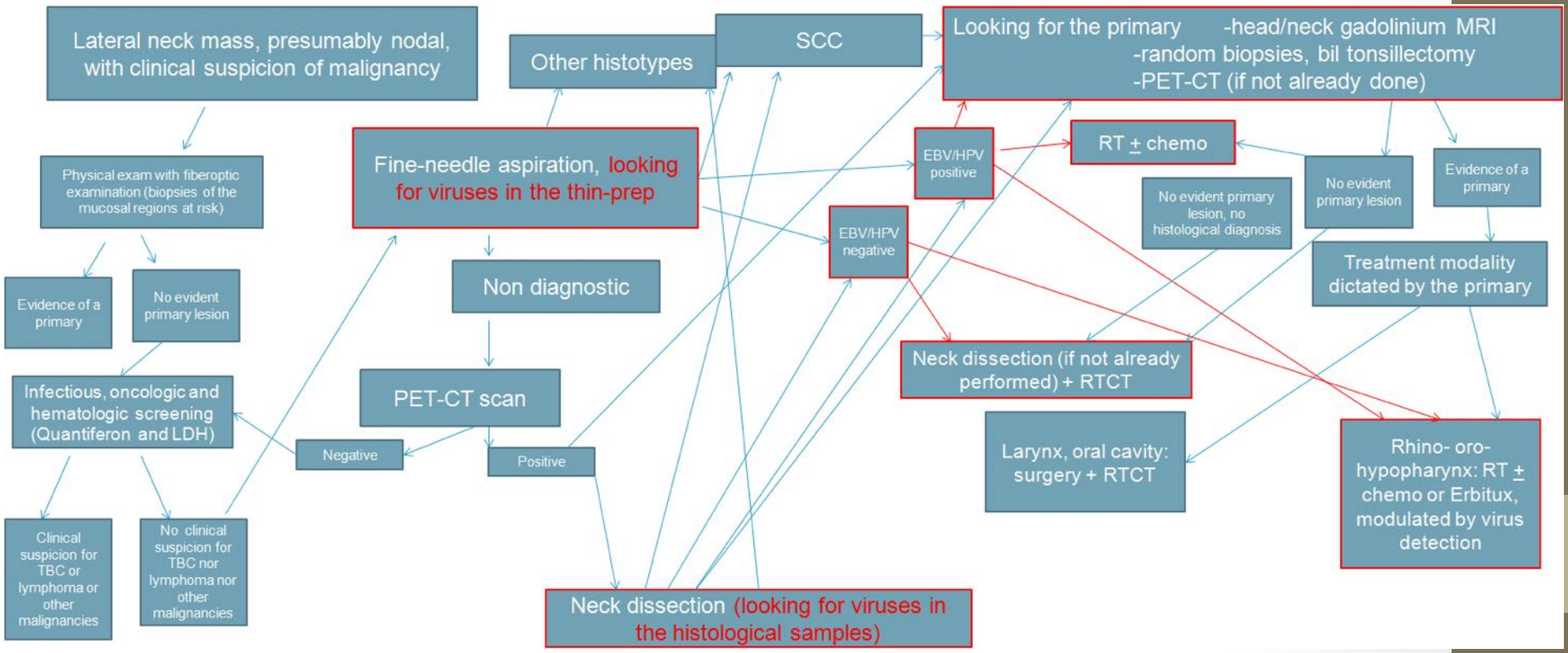
Viruses in occult T

- The only acknowledged etiologic genotype for head and neck (oropharynx) carcinogenesis is HPV16
- HPV18 has never been found in our 40 oropharyngeal cases
- Nevertheless HPV18 is the most frequently detected genotype in our series of nodal SCC
- Is it a specific etiologic factor for metastases from occult T?

Clinical implications of virus related neck metastases from unknown primary

- The evaluation of impact viral infection on prognosis and on sensitivity to different treatment modalities (are virus related forms more sensitive to non surgical modalities as in the oro- and rhinopharynx?) could modify our recommendations for adjuvant treatment
- Detecting the viruses in the FNAB would have a more decisive impact on the diagnostic algorythm
  - Evaluate the reliability of the detection methods on FFPE samples (RNA extraction very expensive and not reliable) and on thin-prep samples from FNAB

Nodal metastases from virus induced head and neck SCC should be always be considered in the diagnostic/ therapeutic algorythm



Thank you