CENTER FOR CLINICAL GUIDELINES | CANCER

Head and neck cancer of unknown primary

- Diagnostic work-up, treatment, and follow-up

Version 1.0

APPROVAL
Content approval
07.10.2025 DAHANCA
Administrative approval
08.05.2026 (Center for Clinical Practice Guidelines | Cancer)

REVISION
Planned: 01.01.2029

KEYWORDS
Cancer of Unknown Primary, Head and Neck, Squamous Cell Carcinoma

Content

Preface

This edition of the DAHANCA CUP guideline represents a substantial change in both diagnostic work-up and treatment compared with previous versions, reflecting contemporary epidemiology in which HPV-associated oropharyngeal carcinoma now predominates within CUP pathways. The diagnostic strategy is strengthened through accelerated, specialist-led pathways with senior multidisciplinary expertise at the forefront; targeted use of transoral robotic surgery to enhance diagnostic precision; and reduced volume radiotherapy to decrease late toxicity without compromising cancer control. Together, these changes set a new benchmark internationally.

A central strength of the guideline is its foundation in extensive analyses of national, real-world DAHANCA data. Accordingly, the recommendations are anchored in Danish clinical practice and observed outcomes, translating evidence directly into actionable clinical tools.

The guideline provides a shared national framework and a platform for continuous quality improvement across disciplines and regions. The working group gratefully acknowledges the contributions of colleagues involved in data collection, curation, analysis, and critical review, and encourages continued engagement and structured feedback to support future revisions.

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1. Anbefalinger – Dansk (Quick guide)

Udredning trin 1: Ambulant forundersøgelse

1. **Foretag en grundig anamnese, med fokus på relevante komorbiditeter og performancestatus, hvilket bl.a. anvendes til vurdering af patientens egnethed til kurativ behandling (D).**
2. **Foretag en systematisk ØNH-undersøgelse, inkl. trans-nasal video faryngo-laryngoskopi, med evaluering af slimhinden i cavum nasi, cavum oris, pharynx og larynx (D).**
3. **Anvend Narrow Band Imaging (NBI) eller tilsvarende modalitet, mhp. at øge detektionsraten af primærtumor (B).**
4. **Foretag en systematisk ultralydsscanning af halsen mhp. at evaluere halsens bløddele inkl. lymfeknuder, spytkirtler og skjoldbruskkirtel. Foretag N-staging: beskriv antal, topografi og karakteristika ved metastasesuspekte lymfeknuder herunder morfologi og tegn på perinodal vækst (D).**
5. **Foretag ultralydsvejledt finnålsaspiration af klinisk suspekte lymfeknuder og tumorer, mhp. cytologisk undersøgelse. Finnålsaspirat forberedes som udstrygninger på objektglas. Det anbefales, at den cytologiske analyse suppleres med HPV-DNA-analyse jf. # 20 (B).**
6. **Diagnostisk strategi skal vejledes af kliniske fund inkl. billeddiagnostik og cytologi (fx. HPV-DNA i FNA indikerer primærtumor i oropharynx). Hvis primærtumor identificeres i forbindelse med den indledende ØNH-undersøgelse, fortsættes udredningen iht. relevante guidelines. Dokumentér topografi og dimensioner, vurdér operabilitet og foretag biopsi (D).**

Udredning trin 2: Billeddiagnostik

7. **Foretag helkrops FDG-PET-CT mhp. at øge detektionsraten af primærtumor i eller udenfor hoved-halsregionen, evaluere omfanget af regionale lymfeknudemetastaser, samt identificere fjernmetastaser og synkron cancersygdom (B).**
8. **MR-hals anbefales mhp. at øge detektionsraten af primærtumor i hoved- og halsregionen og opnå større detaljegrad af primærtumor (såfremt den identificeres) samt lymfeknudemetastaser (B).**

Udredning trin 3: Plan for kirurgisk diagnostik

9. **Planlæg strategi for kirurgisk diagnostik i multidisciplinært regi, på et hoved-hals-onkologisk center, med involvering af hovedhals-kirurg, onkolog, nuklearmediciner og patolog (D).**

10. **Anvend kliniske prædiktorer for primærtumors lokalisation ved planlægningen af kirurgisk diagnostisk strategi, herunder særligt prædiktorer for HPV-associeret sygdom (HPV-DNA og p16) (B).**

Udredning trin 4: Kirurgisk diagnostik

11. **Brug en trinvis tilgang til at beslutte hvilke kirurgiske procedurer der er klinisk relevante. Dette styres af klinisk information fra hvert trin (Følg Work-up step 4.1) (D).**

12. **Kirurgisk diagnostik bør udføres af en hoved- og halskirurg, som kan vurdere operabilitet og udføre halsdissektion (D).**

13. **Foretag videoendoskopi under generel anæstesi. Anvend narrow band imaging eller lignende modalitet for at øge detektionsraten af primærtumor. Foretag systematisk evaluering af slimhinden i cavum nasi, cavum oris, pharynx, larynx og proximale øsofagus, med særlig opmærksomhed på det lymfoide væv i naso- og oropharynx eftersom disse steder er hyppige lokalisationer for små primære tumorer. Random biopsier frarådes (C).**

14. **Hvis primærtumor identificeres i forbindelse med endoskopi, fortsætter udredningen iht. relevante guidelines. Dokumentér topografi og dimensioner, vurdér operabilitet og foretag biopsi. Intraoperativ frysemikroskopi anbefales (D).**

15. **Hvis primærtumor IKKE identificeres i forbindelse med endoskopi OG forudgående diagnostik har bekræftet cervikal lymfeknudemetastase med planocellulært karcinom, udføres bilateral palatin tonsillektomi (B). Hvis patienten tidligere er tonsillektomeret, undlades biopsi medmindre der findes rest-tonsilvæv (B).**

16. **Hvis primærtumor IKKE identificeres i forbindelse med endoskopi OG forudgående diagnostik har bekræftet cervikal lymfeknudemetastase med**

planocellulært karcinom OG der påvises lymfoidt væv i nasopharynx, udføres endoskopisk vejledt biopsi herfra (C).

17. **Hvis primærtumor IKKE identificeres i forbindelse med endoskopi OG der IKKE foreligger en histolopatologisk diagnose på den/de suspekte cervikale lymfeknuder, udføres radikal excision af den mest suspekte lymfeknude mhp. at etablere en histopatologisk diagnose. I tilfælde af kliniske tegn på perinodal vækst, bør grovnålsbiopsi eller åben biopsi overvejes. Intraoperativ frysemikroskopi anbefales således at palatin tonsillektomi og halsdissektion kan foretages i samme seance, hvis indiceret. INDIKATION FOR INTRAOPERATIV HALSDISSEKTION: frysemikroskopi af suspekt lymfeknude viser planocellulært karcinom OG unilateral lymfeknudeinvolvering OG lymfeknudediameter ≤6 cm OG ingen tegn på perinodal vækst. Hvis frysemikroskopi af suspekt lymfeknude viser metastase fra andet end planocellulært karcinom, følges relevant guideline, baseret på histopatologi (D).**

18. **Hvis primærtumor IKKE identificeres i forbindelse med endoskopi og bilateral palatin tonsillektomi OG histopatologisk undersøgelse af excideret cervikal lymfeknude viser planocellulært karcinom, positiv for p16 og/eller HPV-DNA, udføres tungebasis mukosektomi ved transoral robotkirurgi, såfremt patienten vurderes operabel (B). Denne procedure foretages typisk som en separat procedure.**

19. **Hvis primærtumor IKKE identificeres i forbindelse med endoskopi og bilateral palatin tonsillektomi OG histopatologisk undersøgelse af excideret cervikal lymfeknude viser planocellulært karcinom, negativ for p16 og/eller HPV-DNA, overvejes tungebasis mukosektomi ved transoral robotkirurgi, såfremt patienten vurderes operabel (C). Denne procedure foretages typisk som en separat procedure.**

Udredning trin 5: Cytologi og histopatologi

20. **Finnålsaspirat fra suspekte cervikale lymfeknuder bør forberedes som udstrygninger på objektglas. Objektglas skal evalueres mikroskopisk af en patolog med ekspertise i hoved- og halspatologi. Følgende bør fremgå af patologirapporten: benign, malignitetssuspekte celler, maligne tumorceller, inkonklusiv. Ved maligne tumorceller bør subtypebestemmelse anføres. HPV-DNA-analyse med PCR anbefales (B).**

21. **Biopsimateriale fra suspekte primære tumorsites indsendes formalinfikseret eller ufikseret (til frysemikroskopi) mhp. histopatologisk undersøgelse ved hoved-hals patolog. Ektomi-præparater, f.eks. palatine tonsiller og tungebasis-resektater, skal orienteres og markeres af kirurgen forud for histopatologisk undersøgelse. Histopatologisk undersøgelse skal inkludere immunhistokemisk analyse, herunder p16-status. Analyse for HPV-DNA anbefales. Ektomi-præparater skal undersøges systematisk med tynde snit (max 2 mm) mhp. at identificere mikrofoci. Ved HPV-associeret cancer hvor primærtumor ikke identificeres, anbefales p16-farvning samt reevaluering af ektomi-præparaterne ved en anden patolog (D).**

22. **Hvis primærtumor identificeres i ektomi-præparatet, skal der foretages en detaljeret histopatologisk beskrivelse, inkl. tumorstørrelse, type, differentieringsgrad (hvis relevant) og resektionsrande (D).**

23. **Histopatologisk evaluering af exciderede cervikale lymfeknuder bør inkludere immunhistokemisk analyse med vurdering af p16-status. Ligeledes anbefales analyse for HPV-DNA. Ved halsdissektion bør evalueringen desuden indeholde: antal benigne lymfeknuder (level og total), antal metastaser (level og total), dimensioner på metastaser (OBS: intralymfatiske metastasemål), samt tilstedeværelse, udbredelse og morfologiske karakteristika af perinodal vækst (D).**

24. **Hvis histopatologisk evaluering af den exciderede cervikale lymfeknude viser p16/HPV negativ ikke-keratiniserende planocellulært karcinom eller udifferentieret karcinom, bør der udføres in situ hybridisering for Epstein-Barr Virus (B).**

Behandling: Kirurgi og (kemo-) strålebehandling

25. **Tilstræb tidlig planlægning af behandlingsstrategi, idet diagnostik og behandling ofte overlapper, og tid til behandlingsstart har prognostisk betydning (B). Behandling omfatter halsdissektion og/eller strålebehandling. Ved strålebehandling, foretrækkes ensidig og volumenreduceret behandling, medmindre der er bilaterale lymfeknudemetastaser eller N3-sygdom (C). Beslutning om behandlingsstrategi træffes på baggrund af multidisciplinær tumorkonference (D).**

26. **Volumenreduceret strålebehandling betegner unilateral strålebehandling af halsens lymfeknuder, typisk level II-IV uden samtidig bestråling larynx og pharynx. Volumenreduceret strålebehandling kan tilbydes patienter med**

unilaterale cervikale metastaser OG komplet gennemført udredning iht. aktuelle guidelines, i form af billeddiagnostik og kirurgisk diagnostisk (B).

27. **Ved EN cervikal lymfeknudemetastase ≤6 cm OG komplet gennemført udredning iht. aktuelle guidelines i form af billeddiagnostik og kirurgisk diagnostik anbefales ENTEN: 1) selektiv halsdissektion level 2-4 inkl. involverede levels HVIS metastase ≤3 cm (HPV-negativ) eller ≤4 cm (HPV-positiv) OG ingen perinodal vækst; ELLER 2) volumenreduceret strålebehandling +/- kemoterapi (B). Dog bør behandlingsplanen altid baseres på MDT-konsensus (D).**

28. **Ved FLERE cervikale lymfeknudemetastaser OG udelukkende unilaterale metastaser OG komplet gennemført udredning iht. aktuelle guidelines i form af billeddiagnostik og kirurgisk diagnostik anbefales følgende behandling: volumenreduceret strålebehandling +/- kemoterapi (C).**

29. **Ved bilaterale cervikale lymfeknudemetastaser ELLER N3 sygdom anbefales strålebehandling +/- kemoterapi med bilateral bestråling af halsens lymfeknuder samt pharynx og larynx (B).**

30. **Ved klinisk mistanke om Epstein-Barr virus-associeret nasopharyngeal primærtumor, anbefales behandling iht. guidelines for nasopharyngealt karcinom (A).**

Opfølgning

31. **Responsevaluering bør gennemføres ca. 3 mdr. efter afsluttet behandling og bør omfatte PET/CT eller MR og klinisk ØNH-undersøgelse inklusiv trans-nasal video faryngolaryngoskopi og ultralydsscanning af halsen. Undersøgelsen skal fokusere på at identificere primærtumor (emerging primary), ny primær tumor (second primary), lymfeknuderecidiv, funktionelle forhold og behandlingsrelateret morbiditet (D).**

32. **Opfølgning efter behandling bør foregå på et hoved-hals-onkologisk center på den afdeling, der har varetaget den endelige behandling, to uger, 2-3 mdr. og 6 + 12 + 18 + 24 + 36 + 42 + 60 mdr. efter endt behandling. Opfølgningen bør omfatte en grundig klinisk vurdering, herunder trans-nasal video faryngolaryngoskopi og ultralydsscanning af halsen (D).**

33. **Ved mistanke om recidiv og/eller ny primærtumor bør der udføres PET/CT. Afhængigt af lokalisationen af det suspekte tumorområde bør der desuden**

udføres MR-hals og/eller CT af ansigtsskelet for at understøtte planlægning af eventuel salvage-kirurgi (D).

34. **Definition af emerging primary: samme histologiske type OG samme p16-status og/eller HPV-DNA-status som lymfeknudemetastasen ved primære diagnose OG diagnosticeret inden for fem år efter primære diagnose (C).**

Rehabilitering

35. **Patienter med hoved- og halskræft af ukendt primærtumor udgør en meget heterogen gruppe. Omfanget af komplikationer og langtidseffekter er ofte tæt relateret til behandlingens type og intensitet. For en detaljeret gennemgang af mulige langtidseffekter og rehabiliteringsbehov henvises til de nationale retningslinjer for rehabilitering udstedt af Sundhedsstyrelsen (D).**

Salvage

36. **Muligheder for salvage-behandling drøftes i regi af multidisciplinær tumorkonference og kan omfatte kirurgi, strålebehandling, kemoterapi og immunterapi (D).**

Recommendations English (Quick guide)

Diagnostic work-up step 1: Office evaluation

1. **Obtain a comprehensive medical history, including an assessment of comorbidities and performance status, to evaluate the patient's suitability for curative treatment (D).**
2. **Perform a systematic ENT-examination including a trans-nasal video pharyngo-laryngoscopy with systematic evaluation of all anatomical subsites in the oral cavity, nasal cavities, pharynx and larynx (D).**
3. **Apply advanced visualization techniques, such as Narrow Band Imaging to increase the detection rate of a primary tumor (B).**
4. **Perform a systematic neck ultrasonography to evaluate soft tissues of the neck including lymph nodes, salivary and thyroid glands. Perform N-staging by specifying the number of suspicious lymph nodes and their corresponding neck levels. Additionally, provide a detailed characterization of suspicious lymph nodes, including dimensions, topography, morphology, and signs of extranodal extension (D).**
5. **Perform a fine-needle aspiration of clinically suspicious neck masses under ultrasonographic guidance. Fine-needle aspiration cytology should be prepared as smears on slides. HPV-DNA testing is recommended as part of the cytologic evaluation in accordance with #20 (B).**
6. **The diagnostic strategy should be guided by clinical findings, including imaging and cytology (i.e., the presence of HPV-DNA in FNA indicates a primary tumor in the oropharynx). If assessment of the upper aerodigestive tract reveals a primary tumor, conduct diagnostic work-up according to relevant guideline. Document topography and dimensions, assess whether it is suitable for surgical intervention, and perform targeted biopsies from suspicious areas (D).**

Diagnostic work-up step 2: Imaging

7. **Perform a whole-body FDG-PET-CT to increase the detection rate of a primary tumor within or outside the head and neck-region, and improve the assessment of nodal disease, and identify distant metastases and synchronous cancer (B).**

8. **Neck MRI is recommended to increase the detection rate of an occult primary tumor in the head and neck region and gain more detailed information on the primary tumor (if detected) as well as nodal disease in the neck (B).**

Diagnostic work-up step 3: Plan for surgical diagnostics

9. **The planning of a surgical diagnostic strategy should be guided by a multidisciplinary expert evaluation, incorporating the expertise of specialists in radiology, nuclear medicine, oncology, pathology, and head and neck surgery. The setting is a head and neck cancer center (D).**

10. **The diagnostic strategy should be guided by clinical predictors of the primary tumor site, with particular emphasis on predictors of HPV-associated disease (HPV-DNA and p16) (B).**

Diagnostic work-up step 4: Surgical diagnostics

11. **Use a stepwise approach, to decide which surgical procedures are clinically meaningful, guided by clinical information from each step (Follow Work-up step 4.1) (D).**

12. **Diagnostic surgery should be performed by a head and neck surgeon qualified to assess operability and perform a neck dissection (D).**

13. **Conduct a video-endoscopic evaluation of the upper aerodigestive tract under general anesthesia, with special emphasis on mucosal sites at risk: oral cavity, nasal cavities, nasopharynx, oropharynx, hypopharynx, larynx, and proximal esophagus. Apply advanced visualization techniques to identify potential primary sites. Special emphasis should be given to the examination of the pharyngeal lymphoid tissues, as these structures are common sites for small, often occult primary tumors. Random biopsies are not recommended (C).**

14. **If endoscopic evaluation of the upper aerodigestive tract identifies a primary tumor, conduct diagnostic work-up according to relevant guideline. Document topography and dimensions and assess whether it is suitable for surgical intervention. Conduct directed biopsies from any suspicious areas. Intraoperative frozen section is recommended (D).**

15. **If endoscopic evaluation of the upper aerodigestive tract FAILS to identify a primary tumor AND the cervical lymphadenopathy is confirmed to be squamous cell carcinoma, perform bilateral palatine tonsillectomy. In cases of previous**

palatine tonsillectomy and no signs of residual lymphoid tissue, random biopsies of the tonsillar fossa are not recommended (B).

16. **If endoscopic evaluation of the upper aerodigestive tract FAILS to identify a primary tumor, and the cervical lymphadenopathy is confirmed to be squamous cell carcinoma, perform endoscopic-guided directed biopsies of the nasopharynx IF lymphoid tissue is present in this region (C).**

17. **If endoscopic evaluation of the upper aerodigestive tract FAILS to identify a primary tumor AND a histopathological diagnosis on the cervical lymphadenopathy has NOT been established, perform a complete and oncologically safe excision of the most suspicious lymph node to establish a histopathological diagnosis. In cases with clinical extranodal extension, an open biopsy or core needle biopsy should be considered. Intraoperative frozen section is recommended to allow immediate extension to neck dissection and palatine tonsillectomy if indicated. INDICATION FOR INTRAOPERATIVE NECK DISSECTION: squamous cell carcinoma is confirmed by frozen section of the suspicious lymph node in the neck AND lymphadenopathy is unilateral AND nodal dimensions ≤6 cm AND no clinical extranodal extension. If non-squamous cell carcinoma is confirmed by frozen section of the suspicious lymph node, the subsequent approach should be guided by histopathology and relevant guideline (D).**

18. **If endoscopic evaluation of the upper aerodigestive tract, palatine tonsillectomy and directed biopsies FAIL to identify a primary tumor, AND the cervical lymphadenopathy is confirmed to be HPV-associated (HPV and/or p16-positive) squamous cell carcinoma, perform base of tongue mucosectomy by transoral robotic surgery, provided the patient is deemed suitable for surgery (B). This procedure is typically performed in a separate session.**

19. **If endoscopic evaluation of the upper aerodigestive tract, palatine tonsillectomy and directed biopsies FAIL to identify a primary tumor, and the cervical lymphadenopathy is confirmed to be HPV-independent (HPV/p16-negative) squamous cell carcinoma, consider base of tongue mucosectomy by transoral robotic surgery, provided the patient is deemed fit suitable for surgery (C). This procedure is typically performed in a separate session.**

Diagnostic work-up step 5: Cytology and histopathology

20. **Fine-needle aspiration cytology from suspicious cervical lymph nodes should be prepared as smears. Slides must be evaluated microscopically by a pathologist with**

expertise in head and neck pathology. Diagnostic findings should be classified as benign, cells suspicious of malignancy, malignant tumor cells, inconclusive. For malignant tumor cells, subtype determination should be stated. HPV-DNA analysis by PCR is recommended (B).

21. **Tissue specimens from suspected primary tumor sites should be submitted either formalin-fixed or unfixed (for frozen section microscopy) for histopathological examination by a head and neck pathologist. Excision specimens (e.g. palatine tonsils and tongue base resections) must be oriented and marked by the surgeon prior to histopathological assessment. Histopathological evaluation must include immunohistochemical assessment, including p16 status. Likewise, testing for HPV-DNA is recommended. Excision specimens should be systematically examined using thin slicing, with a maximum slice thickness of 2 mm, in order to identify microfoci. In cases of HPV-associated disease where a primary tumor is not identified, staining for p16 and re-evaluation of the specimens by another head and neck pathologist is recommended (D).**

22. **If a primary tumor is identified in the resection specimen, a detailed histopathological description is essential, including tumor size, type, degree of differentiation (if relevant), and resection margins (D).**

23. **Histopathological evaluation of excised cervical lymph nodes should include immunohistochemical assessment of p16 status. Likewise, testing for HPV-DNA is recommended. The evaluation should also include: number of benign lymph nodes and lymph node metastases (per neck levels and total number), size of metastases (intranodal size of metastases), and the presence, extent, and morphological features of extranodal extension (D).**

24. **If histopathological evaluation of the excised cervical lymph node shows p16/HPV-negative non-keratinizing squamous cell carcinoma or undifferentiated carcinoma, in situ hybridization for Epstein-Barr Virus should be performed (B).**

Treatment: Surgery and (chemo-) radiotherapy

25. **Aim for early treatment planning, as diagnostic evaluation and therapy often overlap, and time to treatment has prognostic significance (B). Treatment involves neck dissection and/or radiotherapy. For radiotherapy, a unilateral and volume-reduced approach is preferred, unless bilateral lymph node involvement or N3 disease is present (C). Clinical decisions regarding the treatment strategy should be based on multidisciplinary team consensus (D).**

26. **Volume-reduced radiotherapy implies pharyngeal and laryngeal sparing and unilateral radiation treatment to neck levels II-IV and other involved levels. Volume-reduced treatment is feasible in cases with unilateral neck disease AND a complete diagnostic work-up according to this guideline, including imaging and diagnostic surgical procedures (B).**
27. **For ONE nodal metastasis in the neck ≤6 cm AND a complete diagnostic work-up according to this guideline, including imaging and diagnostic surgical procedures, the recommended definitive treatment is EITHER: 1) unilateral selective neck dissection IF neck metastasis ≤3 cm (HPV negative) or ≤4 cm (HPV positive) AND no extranodal extension; OR 2) volume-reduced radiotherapy +/- chemotherapy (B). However, treatment strategy should always be based on MDT-consensus (D).**
28. **For MULTIPLE nodal metastases in the neck AND unilateral neck involvement AND a complete diagnostic work-up according to this guideline, including imaging and diagnostic surgical procedures, the recommended definitive treatment is: volume-reduced radiotherapy +/- chemotherapy (C).**
29. **For bilateral nodal metastases OR N3 disease the recommended definitive treatment is: radiotherapy +/-chemotherapy with bilateral elective neck irradiation and irradiation of the pharyngeal and laryngeal mucosa (B).**
30. **In cases highly suggestive of an occult Epstein-Barr virus (EBV)-associated nasopharyngeal primary, treatment should adhere to the guideline concerning nasopharyngeal carcinoma (A).**

Follow-up

31. **Response evaluation should be conducted three months after end of treatment and include PET/CT or MRI, a clinical ENT-examination including trans-nasal video pharyngo-laryngoscopy and neck ultrasonography. The assessment should focus on identifying an emerging primary tumor, second primary tumors, recurrent neck disease, functional outcomes, and treatment-related morbidity (D).**
32. **Post-treatment follow-up should be conducted at a head and neck cancer center at the department responsible for the definite treatment, two weeks, 2-3 months, and 6 + 12 + 18 + 24 + 36 + 42 + 60 months post treatment. Surveillance should involve a comprehensive clinical evaluation, including trans-nasal video pharyngo-laryngoscopy with narrow-band imaging and neck ultrasonography (D).**
33. **In cases of recurrence or the emergence of a primary or second primary tumor, a PET-CT scan should be conducted. Depending on the location of the suspicious tumor area, a neck MRI and/or a CT of the facial skeleton should be performed to assist in planning potential salvage surgery (D).**

34. **Definition of an emerging primary: same histological type AND same p16 and/or HPV-DNA status as the nodal metastases at initial diagnosis AND diagnosis within five years of primary diagnosis (C).**

Rehabilitation

35. **Patients with head and neck cancer of unknown primary represent a highly heterogeneous group. The extent of morbidity and long-term effects is often closely related to the type and intensity of treatment. For a detailed review of potential long-term effects and rehabilitation needs, refer to the national rehabilitation guidelines issued by the Danish Health Authority (D).**

Salvage

36. **Salvage opportunities are discussed under multidisciplinary auspices and may include surgery, radiotherapy, chemotherapy, and immune therapy (D).**

2. Introduction

Objective

The overall objective of this guideline is to support evidence-based cancer care of high and consistent quality across the Danish healthcare system.
The specific objective of this guideline is to ensure an efficient diagnostic and treatment strategy of patients with suspected head and neck cancer of unknown primary, thereby guaranteeing thorough evaluation and rapid initiation of treatment with the least possible treatment related morbidity.

The guideline sets forth recommendations aiming for a uniform and efficient diagnostic assessment of all Danish clinical HNCUP patients, as well as for treatment and follow-up of true HNSCCUP patients. They also facilitate the appropriate referral of cHNCUP patients with cancer types other than SCC.

Target users

This guideline is developed to support clinical decision-making and quality improvement. Thus, the target users are healthcare professionals working in Danish cancer care, including private practicing oto-rhino-laryngologists, head and neck surgeons (hospital-employed oto-rhino-laryngologists), nurses, nuclear medicine physicians, neuroradiologists, pathologists, physicists and oncologists.

Target population

Cancer of unknown primary in the head and neck (HNCUP) is a diagnosis of exclusion. The designation includes all histological cancer types with the potential of metastasizing to the neck lymph nodes, with squamous cell carcinoma as the most prevalent – hence the term *head and neck squamous cell carcinoma of unknown primary (HNSCCUP)*. Accordingly, the following definitions are applied in the guideline:
cHNCUP = clinical head and neck cancer of unknown primary: the tentative diagnosis of patients with one or more suspected cervical lymph node metastases from an unknown primary tumor with or without verified cancer type, who have not yet completed the guideline-based work-up program.
cHNSCCUP = clinical head and neck squamous cell carcinoma of unknown primary: the tentative diagnosis of patients with one or more cervical lymph node metastases of squamous cell carcinoma type from an unknown primary tumor, who have not yet completed the guideline-based work-up program.
tHNCUP = true head and neck cancer of unknown primary: the final diagnosis of patients diagnosed with one or more cervical lymph node metastases from an unknown primary tumor, after completion of the guideline-based work-up program.
tHNSCCUP = true head and neck squamous cell carcinoma of unknown primary: the final diagnosis of patients diagnosed with one or more cervical squamous cell carcinoma lymph node metastases from an unknown primary tumor, after completion of the guideline-based work-up program.

The HNCUP population in Denmark

In Denmark, approximately 40 new tHNSCCUP cases are identified every year. However, the proportion of newly referred patients with one or more suspicious lymph nodes in the neck (cHNCUP) is significantly higher. In a yet unpublished report from the Central Denmark Region, the incidence of cHNSCCUP was 2.4 patients per 100 000 person-years, while the incidence of cHNCUP was 6.4 patients per 100 000 person-years(1). When extrapolated to a national scale, it indicates that 375 cases are referred to a Danish ENT department annually for cHNCUP, of which 144 represent cHNSCCUP.

With respect to patient demographics, the CUP population reflects the typical head and neck cancer profile of oropharyngeal cancer, characterized by an overrepresentation of males and current or previous of tobacco use. The median age among patients with tHNSCCUP is 64 years(2).

Comparing the incidence of tHNSCCUP from the period 2014-2020 to the most recent published national survey covering the period from 1975-1995, the incidence has doubled from 0.34 to 0.72 cases per 100 000 person-years(2, 3). It has been speculated, that this increase is associated with the rising incidence of HPV-associated oropharyngeal cancer, although the level of evidence is low(4).

TNM classification of tHNSCCUP

The 8th edition of the UICC TNM classification system, published in 2017, was the first to introduce a TNM classification specifically for cancer of unknown primary in the head and neck. See Table 1 for comparison of the 7th and the 8th classification system. In the current guideline, the 8th classification system is used.

Survival of Head and Neck CUP and the association with HPV

Based on a recent DAHANCA phase IV study evaluating the Danish national guidelines on HNCUP, the observed 5-year overall survival (OS) of patients with tHNSCCUP was 65% for all patients and 73% for patients treated with curative intent (Figure 1a). The 5-year OS was significantly better in patients with HPV-associated disease (85%) compared to HPV-independent disease (63%), using p16 immunohistochemistry as a surrogate marker (Figure 1b)(2). Data from this Danish national cohort convincingly demonstrate the prognostic importance of p16. Although the added prognostic value of HPV is likely, only a few smaller studies have evaluated the prognostic value of testing for both HPV and p16(5, 6).

The Danish results are in line with a Swedish national study from 2020 based on the Swedish Head and Neck Cancer Register (SweHNCR) with a 5-year OS of 71% in curatively treated tHNSCCUP patients(7). Two American studies reported 5-year OS rates of 79%(8) and 84%(9), respectively, which should be interpreted in the context of likely more selected patient populations and higher HPV incidence. A recently published UK study analyzing a larger retrospective cohort (n=965) reported a 5-year OS of 66% among all treated tHNSCCUP patients, and 85% among those with HPV-associated disease. The study utilized real-world binary HPV data from local institutions, employing various techniques such as p16 immunohistochemistry and HPV-DNA/-RNA in situ hybridization(10).

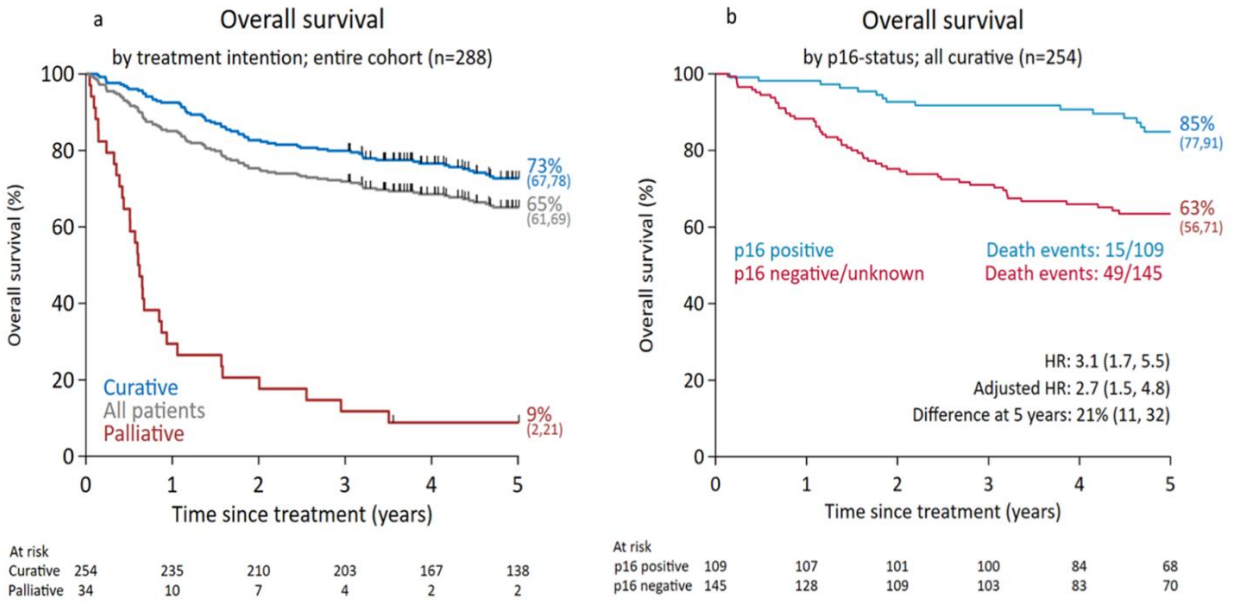


Figure 1. Five-year overall survival in a consecutive cohort of patients diagnosed with true head and neck cancer of unknown primary in the period 2014-2020. The overall survival estimates are stratified by a) treatment intention and b) HPV-status using p16 as a surrogate marker.

Time to diagnosis

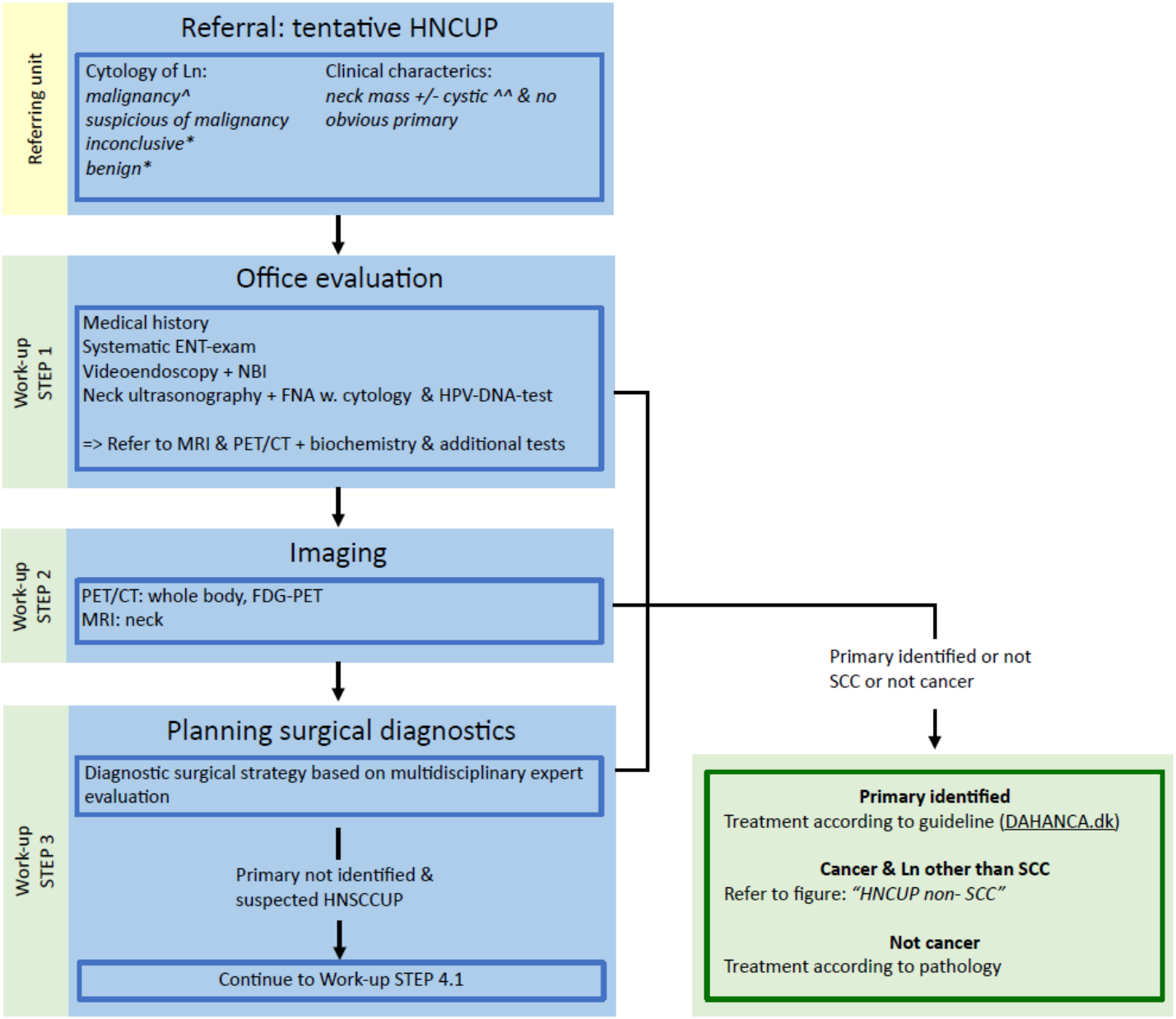
Time to diagnosis affects total tumor volume(11) and survival in cHNSCC patients, who after complete work-up are diagnosed with a known primary site(12). In cHNSCCUP diagnostic delays have only been addressed in two retrospective studies: one did not assess the implications on outcome(13), while the other found no statistically significant difference in OS(14). Based on our general knowledge on HNSCC, including the association between nodal tumor volume and prognosis(15), it is reasonable to assume that delayed initiation of treatment also negatively impacts outcomes in HNCUP patients. Therefore, the potential risk of treatment delay should be weighed against the potential benefits of identifying the primary tumor through comprehensive evaluation. To balance these considerations, the authors emphasize that the diagnostic process should not cause unnecessary delay and therefore place strong focus on streamlining the diagnostic program.

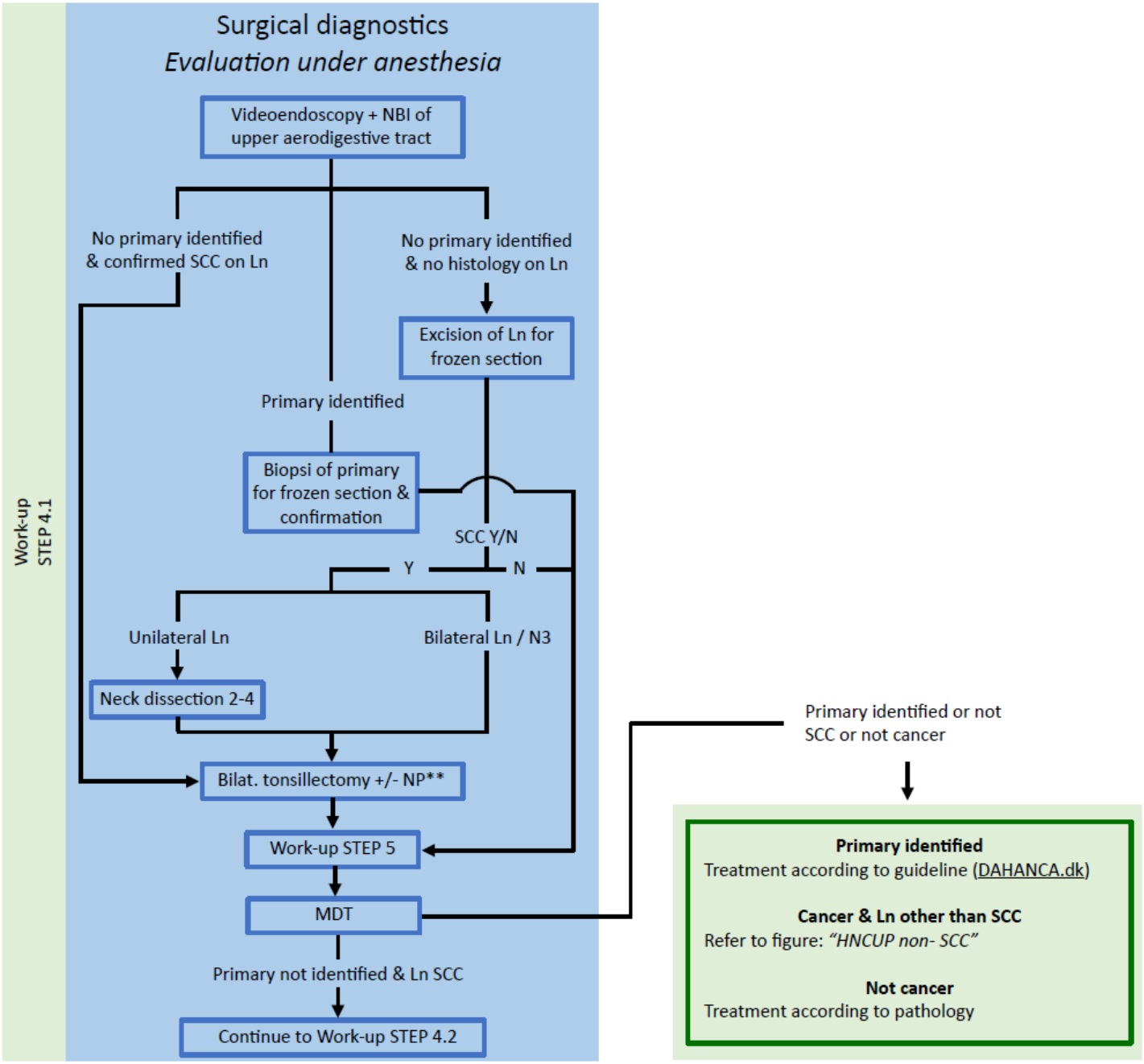
Morbidity/toxicity

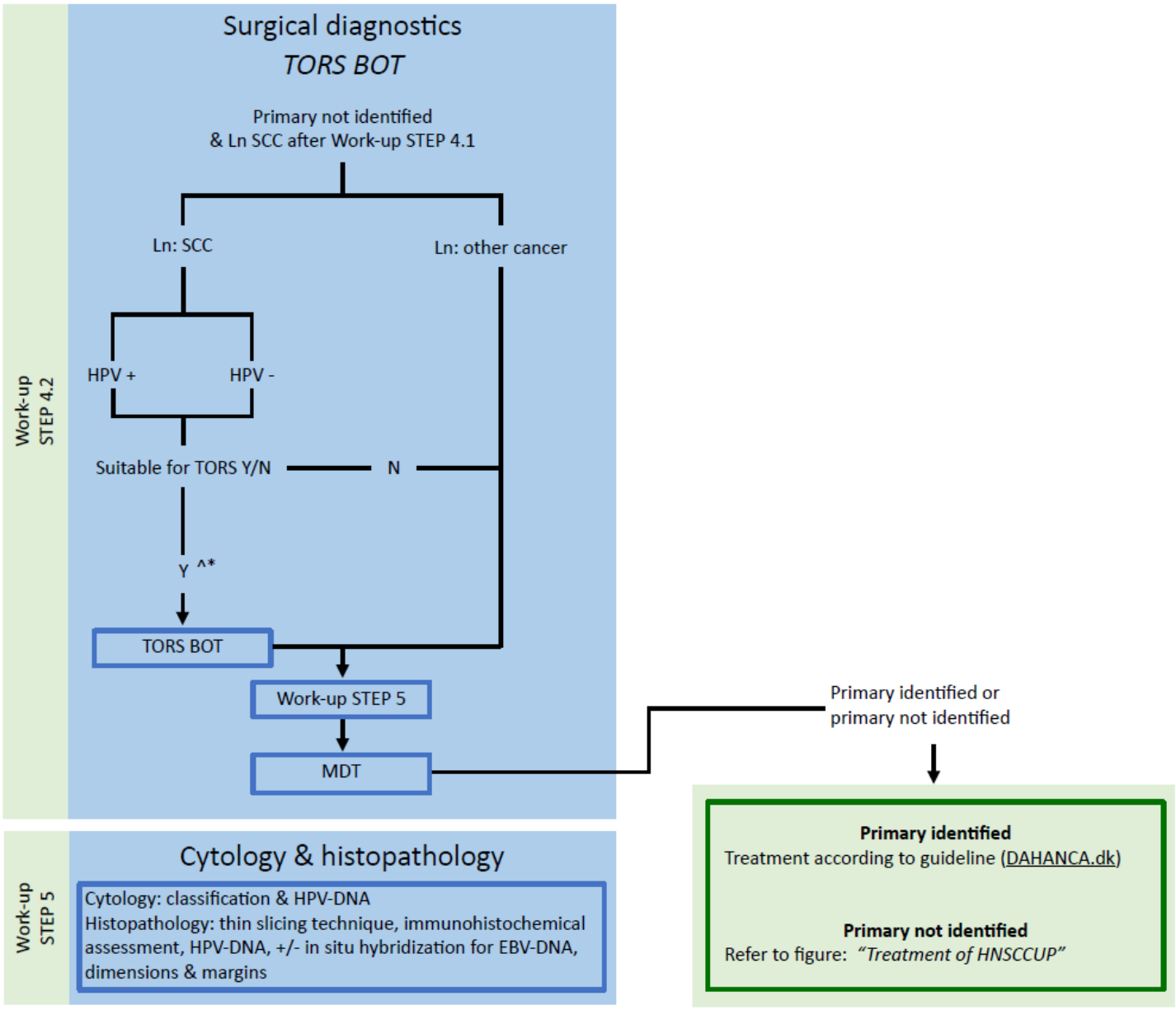
Treatment related morbidity is an important parameter when comparing different treatment options, especially considering that current guidelines often recommend multimodal treatment i.e. high-volume radiotherapy involving the entire neck as well as the pharyngeal-laryngeal axis. The associated acute and long-term toxicity of such high-volume therapy is well documented(16). Consequently, there has been an increasing interest in volume-reducing regimes such as laryngeal- and pharyngeal sparing radiotherapy(17-19).

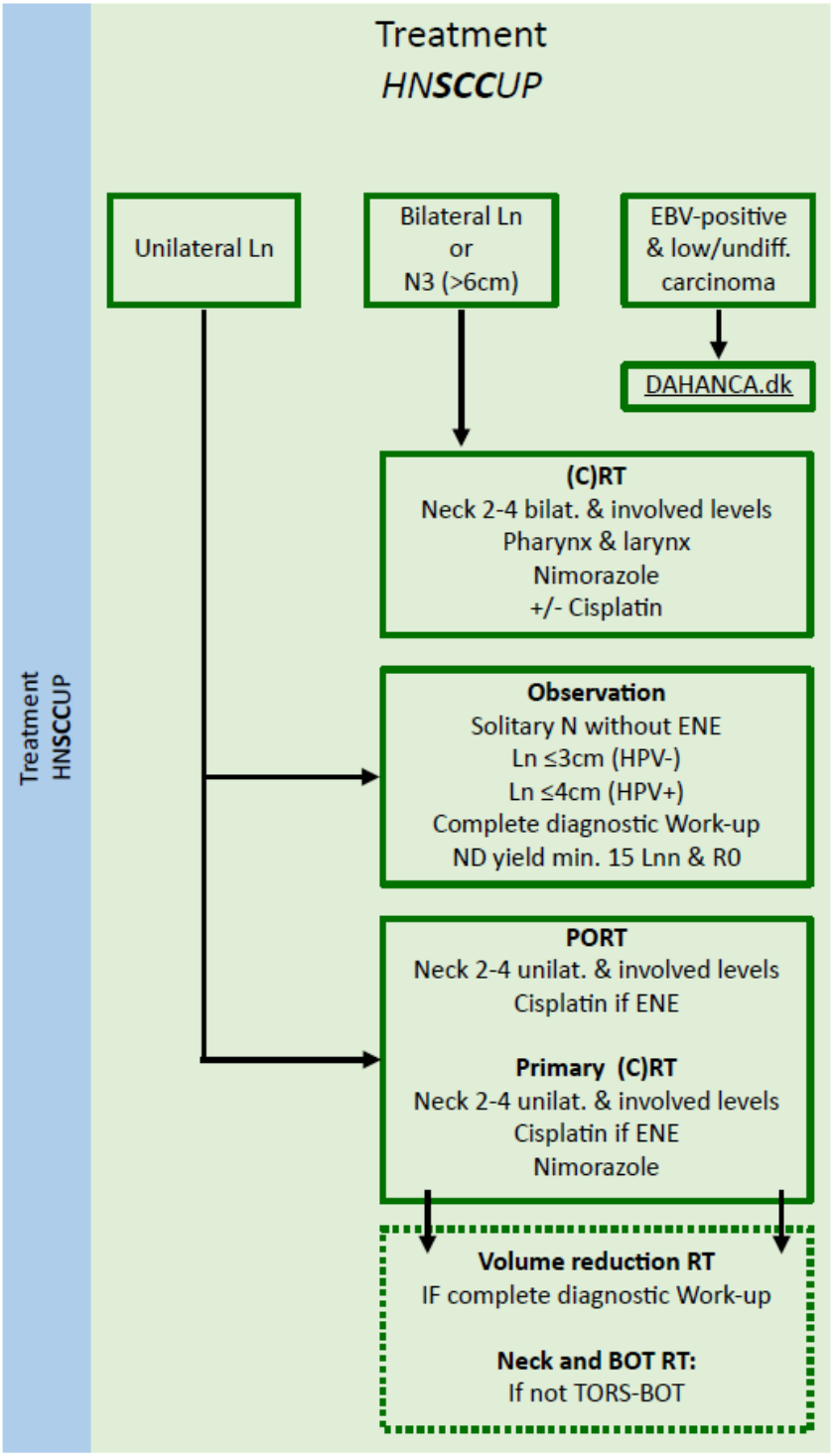
3. Scientific basis

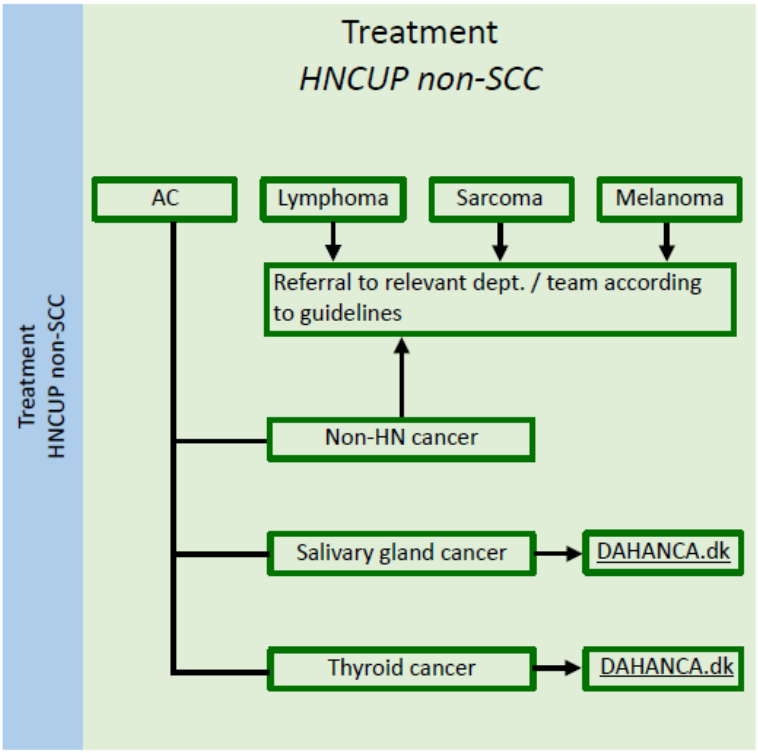
Work-up and treatment diagrams




Work-up
STEP 4.1
Surgical diagnostics
Evaluation under anesthesia
Videoendoscopy + NBI of upper aerodigestive tract
No primary identified & confirmed SCC on Ln
No primary identified & no histology on Ln
Excision of Ln for frozen section
Primary identified
Biopsi of primary for frozen section & confirmation
SCC Y/N
Y
N
Unilateral Ln
Bilateral Ln / N3
Neck dissection 2-4
Bilat. tonsillectomy +/- NP**
Work-up STEP 5
MDT
Primary not identified & Ln SCC
Continue to Work-up STEP 4.2
Primary identified or not SCC or not cancer
Primary identified
Treatment according to guideline (DAHANCA.dk)
Cancer & Ln other than SCC
Refer to figure: "HNCUP non- SCC"
Not cancer
Treatment according to pathology


Work-up STEP 4.2
Surgical diagnostics
TORS BOT
Primary not identified
& Ln SCC after Work-up STEP 4.1
Ln: SCC
Ln: other cancer
HPV +
HPV -
Suitable for TORS Y/N
N
Y ^*
TORS BOT
Work-up STEP 5
MDT
Primary identified or
primary not identified
Work-up STEP 5
Cytology & histopathology
Cytology: classification & HPV-DNA
Histopathology: thin slicing technique, immunohistochemical assessment, HPV-DNA, +/- in situ hybridization for EBV-DNA, dimensions & margins
Primary identified
Treatment according to guideline (DAHANCA.dk)
Primary not identified
Refer to figure: "Treatment of HNSCCUP"


Treatment
HNSCCUP
Treatment
HNSCCUP
Unilateral Ln
Bilateral Ln
or
N3 (>6cm)
EBV-positive
& low/undiff.
carcinoma
DAHANCA.dk
(C)RT
Neck 2-4 bilat. & involved levels
Pharynx & larynx
Nimorazole
+/- Cisplatin
Observation
Solitary N without ENE
Ln ≤3cm (HPV-)
Ln ≤4cm (HPV+)
Complete diagnostic Work-up
ND yield min. 15 Lnn & R0
PORT
Neck 2-4 unilat. & involved levels
Cisplatin if ENE
Primary (C)RT
Neck 2-4 unilat. & involved levels
Cisplatin if ENE
Nimorazole
Volume reduction RT
IF complete diagnostic Work-up
Neck and BOT RT:
If not TORS-BOT



Abbreviations and Comments

HNCUP: Head and Neck Cancer of Unknown Primary
HNSCCUP: Head and Neck Squamous Cell Carcinoma of Unknown Primary
SCC: Squamous Cell Carcinoma
AC: Adenocarcinoma
LN: Lymph Node
FNA: Fine-Needle Aspiration
TORS: Transoral Robotic Surgery
BOT: Base of Tongue
HPV: Human Papillomavirus
EBV: Epstein–Barr Virus
RT: Radiotherapy
ENE: Extranodal Extension
PORT: Postoperative Radiotherapy
ND: Neck Dissection

^ Cytology: squamous cell carcinoma, undifferentiated carcinoma, carcinoma not otherwise specified, HPV DNA-positive.
*If malignancy is suspected.
^^ If malignancy is suspected. For cystic neck masses: malignancy is suspected in patients aged ≥40 years
** If lymphoid tissue is present in the nasopharynx, biopsy is recommended. Random biopsies in the upper aerodigestive tract are not recommended
^* Consider TORS despite the diagnostic yield of TORS-BOT: HPV+ > HPV−

Diagnostic work-up step 1: Office evaluation

1. Obtain a comprehensive history, including an assessment of relevant comorbidities and performance status, to evaluate the patient's suitability for curative treatment (D).

Symptoms and medical history

The presence of a neck mass persisting for more than two weeks in adults, in the absence of an infection, is highly suggestive of malignancy and should be evaluated(12, 20). This also applies for cystic masses which may mimic benign conditions such as branchial cleft cysts. In adults above the age of 40, cystic masses in the lateral neck more likely represents HPV-associated oropharyngeal squamous cell carcinoma, with metastatic papillary thyroid cancer as a differential diagnosis. However, the age-limit is not absolute, as younger individuals may also present with malignant disease, although less likely(21). Lymphadenopathy is more commonly observed in OPSCC (55% HPV-associated; 22% HPV-independent) and hypopharyngeal cancer (26%) than in non-glottic laryngeal cancer(10%), glottic laryngeal cancer (1%) and oral cavity cancer (4%)(12).

Associated symptoms warranting attention include dysphagia, odynophagia, globus, ipsilateral otalgia, recent hearing loss, hoarseness, dyspnea, oral or pharyngeal ulcers, unilateral nasal obstruction, epistaxis, and unexplained weight loss(12). Details regarding social and past medical history including history of head and neck, immunodeficiency, genetic predispositions, as well as gender, age, life style factors such as tobacco and alcohol use and sexual history, and socioeconomic status should be noted(22-24).

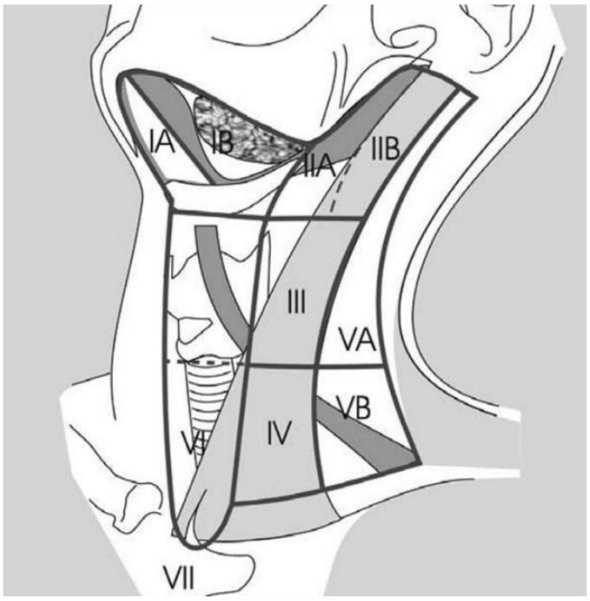
2. Perform a systematic ENT-examination including a trans-nasal video pharyngo-laryngoscopy with systematic evaluation of all anatomical subsites in the oral cavity, nasal cavities, pharynx and larynx (D).

Physical examination and trans-nasal pharyngo-laryngoscopy

The initial physical examination should include a systematic evaluation of the neck. Neck mass(-es) are described by tenderness, size, fixation to adjacent tissues, ulceration of the overlying skin, and involved neck level(-s). Lymph node levels and sublevels of the neck as defined by Robbins et al. (2008) are shown in Figure 2(25). Subsequent clarification of neck levels has been provided in a consensus statement by Gregoire et al. (2014), harmonizing the terminology and practice among surgeons, oncologists, and radiologists(26). The patient’s voice should be evaluated, and a thorough inspection of the skin in the head and neck region performed. The oral cavity should be assessed for findings such as trismus, restricted tongue mobility, ulcers, or masses, and the pharynx should be examined for asymmetry of the tonsils or soft palate. Furthermore, bimanual palpation of the floor of the mouth and palpation of the palatine tonsils is advised to detect masses or areas of induration.

An office-based flexible trans-nasal video pharyngo-laryngoscopy should be performed, to systematically evaluate all anatomical regions of the nasal cavities, pharynx and larynx. It is recommended to use video-endoscopy, as it offers a high definition and a magnified picture with enhanced detail. Furthermore, video-

endoscopy provides the opportunity for re-evaluation in collaboration with colleagues, and it enables the use of Narrow Band Imaging or similar types of filtered light, which improves the detection rate of malignancy and dysplasia(27).



Proposed nomenclature	Nomenclature recommended by AAO-HNS/AHNS
ND (I–V, SCM, IJV, CN XI)	Radical neck dissection
ND (I–V, SCM, IJV, CN XI, and CN XII)	Extended neck dissection with removal of the hypoglossal nerve
ND (I–V, SCM, IJV)	Modified radical neck dissection with preservation of the spinal accessory nerve
ND (II–IV)	Selective neck dissection (II–IV)
ND (II–IV, VI)	Selective neck dissection (II–IV, VI)
ND (II–IV, SCM)	NA
ND (I–III)	Selective neck dissection (I–III)
ND (I–III, SCM, IJV, CN XI)	NA
ND (II, III)	Selective neck dissection (II, III)
ND (IIA, III)	Selective neck dissection (IIA, III)
ND (VI)	Selective neck dissection (VI)
ND (VI, VII)	Selective neck dissection (VI, VII)

Figure 2. Lymph node levels and sublevels of the neck as of Robbins et al (2008); *Consensus Statement on the Classification and Terminology of Neck Dissection.* To the right, proposed terminology with the current widely used American terminology for different types of neck dissections as of Ferlito et al. (2010); *Proposal for a rational classification of neck dissections.*

3. Apply advanced visualization techniques, such as Narrow Band Imaging, to increase the detection rate of a primary tumor (B).

Narrow Band Imaging

Narrow Band Imaging (NBI) uses blue (415 nm) and green (540 nm) light, to enhance the mucosal capillary networks and subepithelial blood vessels, thereby revealing vascular patterns indicative of neoangiogenesis in neoplastic and preneoplastic lesions. A meta-analysis by Maio et al.(27) evaluated the diagnostic performance of Narrow Band Imaging in patients with cervical metastasis from head and neck squamous cell carcinoma of unknown primary. Five studies were included, with pooled sensitivity and specificity of Narrow Band Imaging in head and neck squamous cell carcinoma of unknown primary at 0.83 (99% CI, 0.54-0.95) and 0.88 (99% CI, 0.55-0.97), respectively. The pooled diagnostic odds ratio was 82.15 (99% CI, 7.06-955). Narrow Band Imaging had a detection rate of 0.35 (99% CI, 0.18-0.53), identifying the primary tumor in 61 of 169 patients not found by standard diagnostic methods. Narrow Band Imaging can also aid in defining surgical margins, thereby contributing to a higher rate of initial R0 resections(28).

4. **Perform a systematic neck ultrasonography to evaluate the soft tissues of the neck including lymph nodes, salivary and thyroid glands. Perform N-staging by specifying the number of suspicious lymph nodes and their corresponding neck levels. Additionally, provide a detailed characterization of suspicious lymph nodes, including dimensions, topography, morphology, and signs of extranodal extension (D).**

Ultrasonography

It is recommended that all patients undergo a systematic office-based neck ultrasonography. A special emphasis should be placed on assessing nodal metastases and identifying potential primary tumors in the salivary and thyroid glands as well as the palatine and lingual tonsils. The examination is preferably performed by an ENT specialist. The method offers high resolution imaging of the soft tissues in the neck and parts of the oropharynx. It also enhances the accuracy of fine needle aspiration cytology and core needle biopsy. Studies have shown that transcervical ultrasound can improve the detection of small tumors in the lingual tonsils. Currently, the value of transoral ultrasound is evaluated for the detection of sub-clinical primary tumors in the lingual and palatine tonsils, performed either in office-based settings or during panendoscopy in general anesthesia. Preliminary data are encouraging, but definitive evidence is still needed (22).

Technique: Systematic ultrasonographic evaluation of all neck levels should be performed, e.g. based on the seven sweeps technique(29).

Evaluation of suspicious neck lymph nodes includes:

- topography: number of pathological lymph nodes, involved level(s) and other sites (i.e., rethropaharyngeal)
- size in 3 dimensions (mm)
- signs of extra nodal extension
- morphology (i.e., necrosis, cystic appearance, infiltration into neighboring structures)

Evaluation of a suspicious primary tumor, amenable to ultrasonography should include:

- topography and involved structures
- size in 3 dimensions (mm)
- signs of infiltration into neighboring structures
- morphology (i.e., endophytic, exophytic)

5. **Perform a fine-needle aspiration of clinically suspicious neck masses under ultrasonographic guidance. Fine-needle aspiration cytology should be prepared as smears on slides. HPV-DNA testing is recommended as part of the cytologic evaluation in accordance with #20 (B).**

Fine-needle aspiration cytology, core needle biopsy

Fine-needle aspiration cytology is simple, safe, minimally invasive, and cost-effective. This method may be used for both neck masses and potential tumors in the oral cavity and oropharynx. FNA cytology plays a pivotal role and has substantial impact on the overall diagnostic strategy. In particular, the importance of HPV-DNA testing should be emphasized: detection of HPV-DNA in a lymph node, whether based on FNA material or histopathology, confirms malignancy and is strongly suggestive of an oropharyngeal primary tumor. Refer to section 20 for further information.

Technique: To enhance the diagnostic yield, it is recommended to perform ultrasound-guided fine needle aspiration whenever feasible, either as transcervical, enoral or transoral ultrasonography. Thus, both neck masses and tumors in the oral and oropharyngeal regions are amenable for ultrasonography targeted fine needle aspiration. Regarding neck masses, it is advised to target solid tissue areas, while avoiding regions with necrosis and cystic material, which often leads to inconclusive results. Fine-needle aspiration cytology should be prepared as smears on slides. Blood coagulum is optional, and should be preserved in a small amount of saline in a syringe (approximately 1:1), to enable the evaluation of coagulated material(30, 31). Core needle biopsy is primarily relevant in cases where fine-needle aspiration cytology is inconclusive and excisional biopsy from a suspicious lymph node is not feasible.

6. **The diagnostic strategy should be guided by clinical findings, including imaging and cytology (i.e., the presence of HPV-DNA in FNA indicates a primary tumor in the oropharynx). If assessment of the upper aerodigestive tract reveals a primary tumor, conduct diagnostic work-up according to relevant guideline. Document topography and dimensions, assess whether it is suitable for surgical intervention, and perform targeted biopsies from suspicious areas (D).**

Directed biopsies from potential primary site

Perform forceps biopsies from sites suspected of harboring a primary tumor, while avoiding excessive biopsies that may compromise subsequent tumor resection. Directed biopsies should be conducted in the outpatient clinic when feasible, and without delay, regardless of pending PET/CT and MRI scans. Document topography and dimensions of any suspicious sites, ideally with photographic documentation in the patient record. Frozen section analysis is recommended for rapid diagnosis.

Diagnostic work-up step 2: Imaging

7. **Perform a whole-body FDG-PET/CT to increase the detection rate of a primary tumor within or outside the head and neck-region, and improve the assessment of nodal disease, and identify distant metastases and synchronous cancer (B).**

^{18}F-FDG-PET/CT: Clinical Rationale

^{18}F-FDG-PET/CT combines metabolic and anatomical imaging, enabling detection of tumors with high glucose uptake. In HNCUP, PET/CT identifies up to 30% of primary tumors missed by CT or MRI, as shown in a systematic review(32) and a Danish prospective study(33). A large comparative study(34) reported

significantly higher detection rates by PET/CT (sensitivity 89%) versus MRI (75%), consistent with smaller series(35, 36). Further, whole-body PET/CT also increases detection rates of synchronous malignancies beyond the head and neck region. Current evidence supports combined use of PET/CT and MRI in HNCUP work-up, although PET/CT should be favored due to superior sensitivity and broader diagnostic scope.

Recommended evaluation of 18F-FDG-PET/CT include:

Interpretation of FDG-uptake:

- PET/CT is a valuable tool in identification of possible primary sites and should be evaluated by experts in nuclear medicine and radiology to ensure precise and reliable assessments.
- The grading of FDG uptake, such as using SUV-max, should not be considered in isolation but viewed as one component of a comprehensive, multifaceted diagnostic assessment.
- In specific instances, such as comparing uptake in paired organs like the palatine tonsils, grading can provide valuable insights(37).

Neck lymphadenopathy:

- An enlarged lymph node is defined as having a short-axis diameter of 15 mm in level 2 and 10 mm in other cervical levels. Other measures include exhibiting pathological FDG uptake or displaying suspicious morphological characteristicstopography: number of pathological lymph nodes, involved level(s) and other sites (i.e., retropharyngeal)
- size in 3 dimensions (mm, in any plane) of the largest lymph node bilaterally
- signs of extra nodal extension
- morphology (i.e., necrosis, cystic appearance, loss of ovoid shape, loss of hilum, infiltration into neighboring structures)
- FDG uptake

Head and neck primary:

- topography and involved structures
- size in 3 dimensions (mm)
- signs of infiltration into neighboring structures
- morphology (i.e., endophytic, exophytic)
- FDG-uptake

Pathology outside head and neck:

- involved organ(s), location and number of metastases
- largest dimension in mm
- pulmonary nodules >5mm: diagnostic work-up according to Danish national guidelines(38, 39)
- FDG-uptake

8. Neck MRI is recommended to increase the detection rate of an occult primary tumor in the head and neck region and gain more detailed information on the primary tumor (if detected) as well as nodal disease in the neck (B).

MRI: Clinical rationale

MRI provides superior soft tissue contrast compared to CT, making it valuable for delineating soft tissue tumors and assessing nodal disease. Although PET/CT shows higher overall sensitivity in HNCUP, MRI still detects additional primaries(34). Its particular strength lies in the detection of small or superficial lesions and by improving staging accuracy. Owing to its complementary value, MRI should be incorporated into the diagnostic work-up alongside PET/CT to improve detection rates and optimize treatment planning.

The MRI protocol should include T1-weighted (T1W) sequences both pre- and post-intravenous contrast administration. Post-contrast T1W fat-saturated sequences should be acquired to evaluate possible extra nodal extension, perineural spread and enhance visualization of a suspected primary tumor, which often exhibits a markedly high signal following contrast administration. T2-weighted (T2W) sequences provide excellent delineation of tumor involvement and pathological changes in lymph nodes.
MRI should be performed with, at a minimum, the following sequences:

- Coronal Short Tau Inversion Recovery (STIR)
- Axial T1-weighted (T1W) sequence prior to intravenous contrast administration
- Diffusion-weighted imaging (DWI)
- Axial T2-weighted (T2W) sequence
- Post-contrast T1-weighted fat-saturated (T1W FAT SAT) sequences, preferably in three planes (axial, coronal, and sagittal)

Recommended evaluation of MRI include:

Neck lymphadenopathy:
An enlarged lymph node is defined as having a short-axis diameter of 15 mm in level 2 and 10 mm in other cervical levels. Other measures include displaying suspicious morphological characteristics

- topography: number of pathological lymph nodes, involved level(s) and other sites (i.e., retropharyngeal)
- size in 3 dimensions (mm, in any plane) of the largest lymph node bilaterally
- signs of extra nodal extension
- morphology (i.e., necrosis, cystic appearance, loss of ovoid shape, loss of hilum, infiltration into neighboring structures)

Head and neck primary:

- topography and involved structures
- size in 3 dimensions (mm)
- signs of infiltration into neighboring structures
- morphology (i.e., endophytic, exophytic)

Diagnostic work-up step 3: Diagnostic surgical procedures

9. The planning of a surgical diagnostic strategy should be guided by a multidisciplinary expert evaluation, incorporating the expertise of specialists in radiology, nuclear medicine, oncology, pathology, and head and neck surgery. The setting is a head and neck cancer center (D).

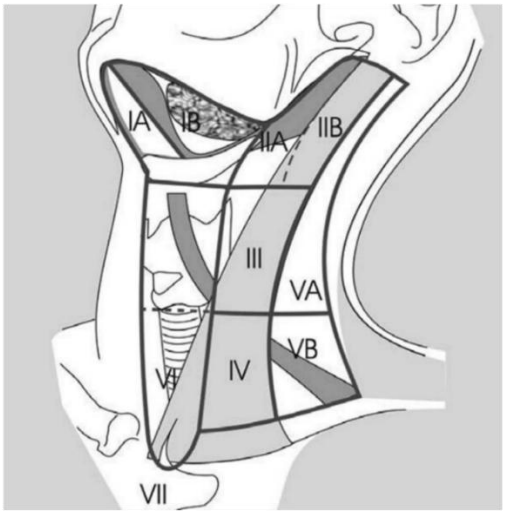
Clinical decision-making regarding strategy of diagnostic surgery

Expert evaluation of imaging, cytology, histopathology, and clinical findings should be conducted within a head and neck cancer center. Diagnostic surgery should be planned by an experienced head and neck surgeon. Despite limited direct evidence in HNCUP, expert consensus across different medical fields supports that complex decision-making benefits from specialized and multidisciplinary assessment. Such an approach ensures the most effective diagnostic strategy, while optimizing time, cost, and treatment planning(26).

10. The diagnostic strategy should be guided by clinical predictors of the primary tumor site, with particular emphasis on predictors of HPV-associated disease (HPV-DNA and p16) (B).

Predictors of primary tumor site

Topography: Knowledge of lymphatic drainage patterns can aid in localizing the primary tumor in HNCUP, though overlap between nodal levels—especially II and III—limits predictive accuracy(26, 40-44). (see Table 2: Drainage patterns). Unilateral lymphadenopathy is seen in ~93% of tHNCUP cases, while bilateral disease (7%) often suggests midline involvement (i.e., oral tongue, floor of the mouth, nasopharynx, base of the tongue, soft palate, posterior pharyngeal wall, supraglottic larynx, postcricoid area). The base of tongue, particularly on the side of the greater nodal burden, is the most frequent location of a primary; whereas a primary tumor in the contralateral palatine tonsil is rare and more likely represents synchronous disease(45). About half of cHNCUP patients present with single-level nodal involvement(1), which allows for a more targeted assessment. In multi-level nodal disease, predicting the location of the primary site becomes more challenging and should be guided by the dominant nodal level and predictive markers such as HPV status. Lower neck involvement may suggest a primary tumor outside the head and neck region, including lung, breast, gastrointestinal, or urogenital sites. Cobblestone appearance of nodes may indicate lymphoma(46). Involvement of the parotid gland may, aside from a primary salivary gland cancer, may represent metastatic skin cancer (squamous cell carcinoma) or rarely distant metastasis.



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ND (I–V, SCM, IJV, CN XI, and CN XII)	Extended neck dissection with removal of the hypoglossal nerve
ND (I–V, SCM, IJV)	Modified radical neck dissection with preservation of the spinal accessory nerve
ND (II–IV)	Selective neck dissection (II–IV)
ND (II–IV, VI)	Selective neck dissection (II–IV, VI)
ND (II–IV, SCM)	NA
ND (I–III)	Selective neck dissection (I–III)
ND (I–III, SCM, IJV, CN XI)	NA
ND (II, III)	Selective neck dissection (II, III)
ND (IIA, III)	Selective neck dissection (IIA, III)
ND (VI)	Selective neck dissection (VI)
ND (VI, VII)	Selective neck dissection (VI, VII)

Figure 2. Lymph node levels and sublevels of the neck as of Robbins et al (2008); *Consensus Statement on the Classification and Terminology of Neck Dissection.* To the right, proposed terminology with the current widely used American terminology for different types of neck dissections as of Ferlito et al. (2010); *Proposal for a rational classification of neck dissections.*

Morphology: Cystic morphology is a key distinguishing feature of nodal metastases in the neck and is strongly related with HPV-associated oropharyngeal squamous cell carcinoma, most commonly originating from the palatine tonsils or the base of the tongue. It should be noted, however, that papillary thyroid carcinoma may also present with cystic lymph node metastases(47). This warrants particular attention, especially among younger patients with cystic metastases in the neck, as distinguishing these from benign lateral neck cysts can be challenging(48, 49).

Biomarkers: Presence of HPV-DNA in a lymph node, either based on FNA or histopathology, verifies malignancy and is highly indicative of an oropharyngeal origin. p16 is considered a surrogate marker of HPV-associated malignancy. Concordance (p16+/HPV-DNA+) is believed to offer the highest specificity. In a national cohort of 318 CUP patients, >95% of primaries in HPV-positive disease arose from the oropharynx. By contrast, HPV-negative primaries were distributed across the pharynx and larynx without clear preference. Primary detection rates were also higher in HPV-positive than HPV-negative cases (67% vs. 58%, p=0.04)(1).

Proposed actions based on FNA-cytology from nodal neck metastases:

- squamous cell carcinoma, malignant tumor cells, cells suspicious for malignancy, tumor cells not otherwise specified, cyst (indeterminate type/morphology) and undifferentiated/anaplastic tumor cells: continue diagnostic investigation of cancer of unknown primary
- benign epithelial cells: continue diagnostic investigation of cancer of unknown primary, as this finding could represent metastatic squamous cell carcinoma
- lymphoma, malignant melanoma, thyroid cancer, salivary gland cancer, unspecified adenocarcinoma or other organ specific cancer: initiate diagnostic investigation in a non-squamous cell carcinoma cancer of unknown primary setting, according to other guidelines (Figure Treatment HNCUP non-SCC p.23)

Diagnostic work-up step 4: Surgical diagnostics

11. Use a stepwise approach, to decide which surgical procedures are clinically meaningful, guided by clinical information from each step (Follow Work-up step 4.1) (D).

Stepwise approach for diagnostic surgery

A structured, stepwise approach should be employed during diagnostic surgical procedures. Intraoperative decision-making should be guided by perioperative findings to determine the appropriate subsequent diagnostic steps. This assessment is based on a combination of endoscopic evaluation, palpation, ultrasonography, and intraoperative histopathological examination (frozen section), supplemented by preoperative imaging studies and any available cytological or histopathological results.

12. Diagnostic surgery should be performed by a head and neck surgeon qualified to assess operability and perform a neck dissection (D).

Expert level

Diagnostic surgery should be performed by a trained and experienced head and neck surgeon who is proficient in executing the necessary surgical procedures including neck dissection, and making informed clinical decisions based on sequential findings obtained perioperatively. Furthermore, the surgeon must be proficient in evaluating treatment strategies, including assessing operability and determining the appropriate surgical approach, such as exposure for transoral robotic surgery or other transoral techniques.

13. Conduct a video-endoscopic evaluation of the upper aerodigestive tract under general anesthesia, with special emphasis on mucosal sites at risk: oral cavity, nasal cavities, nasopharynx, oropharynx, hypopharynx, larynx and proximal esophagus. Apply advanced visualization techniques to identify potential primary sites. Special emphasis should be given to the examination of pharyngeal lymphoid tissues, as these structures are common sites for small, often occult primary tumors. Random biopsies are not recommended (C).

Video-endoscopic evaluation of the upper aerodigestive tract under general anesthesia

Video-endoscopic evaluation under general anesthesia is a key diagnostic step in HNCUP and should be the first procedure during diagnostic surgery. It typically includes rigid pharyngo-laryngoscopy and proximal esophagoscopy. While its standalone detection rate is difficult to quantify, operative endoscopy remains essential for thorough assessment(50-53).

Random biopsies from normal-appearing mucosa have low diagnostic yield and are no longer recommended. Historical studies reported low positivity rates (≤10% in nasopharynx and base of tongue)(52, 54). More recent data confirm minimal value of random biopsies, except for palatine tonsillectomy (19-39%)(52, 53, 55-57) which is NOT considered as a random biopsy and should still be conducted (**section 15**)(51). Importantly,

biopsies should be directed at any radiologic or clinical suspicion, including mucosal irregularities detected with narrow band imaging.

Technique: Video-endoscopy of the pharynx, larynx, and proximal esophagus should be performed using an operating laryngoscope or suspension system with straight and angled scopes. All subsites must be systematically examined, with emphasis on imaging-suspect areas. Video-endoscopy offers high-definition, magnified views, supports re-evaluation with colleagues, and enables the use of narrowband or filtered-light imaging to improve detection of malignancy. Oral and oropharyngeal soft tissues should also be palpated to identify tumors and assess infiltration depth. Biopsies from suspected sites must be submitted in full, with precise anatomical labeling, and resection specimens oriented for accurate margin assessment.

14. If endoscopic evaluation of the upper aerodigestive tract identifies a primary tumor, conduct diagnostic work-up according to relevant guideline. Document topography and dimensions and assess whether it is suitable for surgical intervention. Conduct directed biopsies from any suspicious areas. Intraoperative frozen section is recommended (D).

Identification of primary

When a primary tumor is identified, a thorough clinical assessment should document topography, extent, dimensions, and depth of infiltration. Surgical planning must consider exposure and suitability for transoral approaches, while biopsies should be representative yet avoid compromising future surgery through scarring or barrier disruption. If a primary tumor is identified in the palatine tonsil, a biopsy or ipsilateral palatine tonsillectomy, along with contralateral palatine tonsillectomy, should be conducted, as outlined in section 15.

All specimens should be submitted in full for histopathology, with resection specimens anatomically oriented for accurate margin assessment. Diagnostic work-up should follow current guidelines.

15. If endoscopic evaluation of the upper aerodigestive tract FAILS to identify a primary tumor AND the cervical lymphadenopathy is confirmed to be squamous cell carcinoma, perform bilateral palatine tonsillectomy. In cases of previous palatine tonsillectomy and no signs of residual lymphoid tissue, random biopsies of the tonsillar fossa are not recommended (B).

Palatine tonsillectomy

If endoscopic evaluation of the upper aerodigestive tract fails to reveal a primary tumor, and the cervical lymphadenopathy is confirmed to be squamous cell carcinoma, a bilateral palatine tonsillectomy is recommended, regardless of unilateral or bilateral nodal disease. If there is a high clinical suspicion of a tonsillar primary, targeted biopsies are recommended, as it reduces morbidity and improves feasibility for subsequent TORS. Ipsilateral tonsillectomy substantially increases detection, while contralateral tonsillectomy

offers some additional yield; although small contralateral primaries may instead indicate synchronous cancer(45) Reported rates of bilateral tonsillar carcinoma range from 3–10%, particularly in HPV-associated cases **(54, 58-62)**. Compared with deep random biopsies, tonsillectomy provides markedly higher diagnostic sensitivity (≈30% vs. 3%)(52). Given this evidence and the low morbidity, cost, and recovery burden, bilateral tonsillectomy should be included in the diagnostic work-up of cHNSCCUP. In patients with prior tonsillectomy and no residual lymphoid tissue, random biopsies should be avoided; instead, nasopharyngeal biopsy is recommended, according to **section 16.**

Surgical technique: Prior to performing a palatine tonsillectomy, thorough palpation and assessment of tonsillar mobility is mandatory. To optimize diagnostic yield, a complete bilateral tonsillectomy is recommended unless there is a high clinical suspicion of a tonsillar primary, in which case targeted biopsies is recommended, as it reduces morbidity and improves feasibility for subsequent lateral oropharyngectomy by transoral robotic surgery. Palatine tonsillectomy should be executed with precision to avoid damage to the peritonsillar tissue, including the anterior and posterior palatopharyngeal arches, the glossotonsillar sulcus, and superior pharyngeal constrictor muscle. Excessive scarification may compromise the feasibility of subsequent lateral oropharyngectomy by transoral robotic surgery. Moreover, breaching the superior pharyngeal constrictor muscle, which is considered a critical anatomical barrier, could hinder the ability to achieve clear surgical margins in subsequent resection.
Tissue specimens from suspected primary sites should be submitted in their entirety for histopathological analysis. Resection specimens must be anatomically oriented by the surgeon to ensure precise margin assessment. It is crucial to inform the pathologist that the case involves cancer of unknown primary origin, allowing them to adopt appropriate measures, including the use of fine sectioning techniques.

16. If endoscopic evaluation of the upper aerodigestive tract FAILS to identify a primary tumor, and the cervical lymphadenopathy is confirmed to be squamous cell carcinoma, perform endoscopic-guided directed biopsies of the nasopharynx IF lymphoid tissue is present in this region (C).

Nasopharyngeal biopsy

Nasopharyngoscopy with biopsy or rachlatio has been included in Danish guidelines since 1998, though supporting evidence was not cited. Today, the nasopharynx is routinely assessed with office-based trans-nasal video pharyngo-laryngoscopy. An American study(63) reported high-risk HPV DNA in a significant proportion of nasopharyngeal tumors. Directed biopsy is recommended if residual lymphoid tissue is present in the nasopharynx, particularly in cases with HPV and EBV-associated neck metastasis(64). Random biopsies from normal appearing mucosa should be avoided(51, 53, 57).

Surgical technique: Ideally, targeted transnasal biopsies should be obtained under guidance with a 0° video-endoscope.

17. If endoscopic evaluation of the upper aerodigestive tract FAILS to identify a primary tumor AND a histopathological diagnosis on the cervical lymphadenopathy has NOT been established, perform a complete and

oncologically safe excision of the most suspicious lymph node to establish a histopathological diagnosis. In cases with clinical extranodal extension, an open biopsy or core needle biopsy should be considered. Intraoperative frozen section is recommended to allow immediate extension to neck dissection and palatine tonsillectomy if indicated. INDICATION FOR INTRAOPERATIVE NECK DISSECTION: squamous cell carcinoma is confirmed by frozen section of the suspicious lymph node in the neck AND the lymphadenopathy is unilateral AND nodal dimensions ≤6 cm AND no clinical extranodal extension. If non-squamous cell carcinoma is confirmed by frozen section of the suspicious lymph node, the subsequent approach should be guided by histopathology and relevant guideline (D).

Excision of cervical lymph node / mass

If evaluation of the upper aerodigestive tract does not reveal a primary tumor and the cervical lymphadenopathy is not confirmed as carcinoma, the most suspicious lymph node should be excised for definitive diagnosis, since a cytological diagnosis obtained through fine-needle aspiration is currently considered insufficient to initiate oncological treatment. Excisional biopsy should adhere to surgical oncological principles (i.e. R0 resection) with the option to convert to neck dissection if indicated. In cases with clinical extranodal extension, open biopsy or core needle biopsy should be considered due to the risk of surgical sequela associated with excisional biopsy. Intraoperative frozen section is recommended, as it enables a "one-stop-shop" approach allowing direct progression to neck dissection and bilateral tonsillectomy if indicated. Consequently, thorough preoperative consent and planning is required.

Indications for neck dissection

If squamous cell carcinoma is confirmed based on excisional biopsy of the suspicious lymph node in the neck AND lymphadenopathy is unilateral AND nodal dimensions ≤ 6 cm AND no clinical extranodal extension, perform a selective neck dissection including at least levels 2-4. In addition, perform bilateral palatine tonsillectomy and biopsy from the nasopharynx, according to section 15 and 16.

The neck dissection should include levels II (a and b), III, IV, and any additional levels involved. Evidence and literature review is presented in **section 26**. Aiming to achieve an R0 resection and ensure an adequate nodal yield (≥10 lymph nodes) is of utmost importance, as failure to do so may necessitate adjuvant chemo-radiotherapy, potentially increasing treatment burden and morbidity.

Indications for avoidance of neck dissection

If squamous cell carcinoma is confirmed based on excisional or open biopsy of the suspicious lymph node in the neck AND clinical extranodal extension OR nodal dimensions > 6 cm OR lymphadenopathy is bilateral, avoid neck dissection. Proceed with bilateral palatine tonsillectomy and biopsy from the nasopharynx, according to section 15 and 16.

Neck dissection should be avoided in patients whose clinical presentation indicates a high probability of requiring adjuvant chemo-radiotherapy. This includes bilateral nodal disease, extranodal extension and nodal

dimensions exceeding 6 cm. The avoidance of trimodality therapy, comprising neck dissection, radiotherapy, and concurrent chemotherapy, is a key objective to reduce treatment-associated morbidity. Also, neck dissection should be avoided in cases where intraoperative frozen section of an excised suspicious neck node is inconclusive or indicates malignancy other than carcinoma, i.e. malignant melanoma and sarcoma. In these instances, awaiting the final histopathological diagnosis before proceeding is recommended.

Surgical treatment of neck disease in non-squamous cell carcinoma

If NON-squamous cell carcinoma is confirmed based on excisional biopsy of the suspicious lymph node, the subsequent diagnostic approach should be guided by histopathology. If intraoperative frozen section reveals adenocarcinoma, carcinoma not otherwise specified, or undifferentiated carcinoma AND lymphadenopathy is unilateral AND nodal dimensions ≤6 cm in greatest dimension AND no signs of clinical extranodal extension, a selective neck dissection including levels II (a and b), III, IV, and any involved levels is recommended. Neck dissection should be avoided in cases with bilateral nodal involvement or when frozen section is inconclusive or reveals a non-carcinoma malignancy, such as malignant melanoma, lymphoma, or sarcoma. In these circumstances, awaiting the final histopathological diagnosis and proceeding with treatment according to disease-specific guidelines is recommended.

Surgical technique: Neuromonitoring is recommended. The incision should allow extension to neck dissection. The surgery must adhere to oncological principles, ensuring radical resection (R0) without breaching the lymph node to minimize the risk of tumor seeding. Close dissection should be avoided, and an adequate margin of healthy tissue should be preserved. In cases of clinical extranodal extension, neck dissection should be avoided because of the increased risk of surgical morbidity, including functional deficits and complications, as well as the potential need for trimodality therapy comprising neck dissection, radiotherapy, and concurrent chemotherapy. In such cases an open biopsy or core needle biopsy should be considered. Neck dissection is described in **section 25**.

18. If endoscopic evaluation of the upper aerodigestive tract, palatine tonsillectomy and directed biopsies FAIL to identify a primary tumor AND the cervical lymphadenopathy is confirmed to be HPV-associated (HPV and/or p16-positive) squamous cell carcinoma, perform base of tongue mucosectomy by transoral robotic surgery, provided the patient is deemed suitable for surgery (B). This procedure is typically performed in a sequential session.

Base of tongue mucosectomy by transoral robotic surgery

Base of tongue mucosectomy by transoral robotic surgery was first introduced by Weinstein and O´Malley in 2006(65). Since then, the method has been adopted in many institutions around the world(66-70), and varying results are being reported (see Table 3).

Detection rate: In a Danish national cohort study, the authors concluded that the addition of base of tongue mucosectomy by transoral robotic surgery to the contemporary Danish guideline-based work-up program(71, 72) (Danish 2013 guideline) significantly improved the primary tumor detection rate in head and neck squamous cell carcinoma of unknown primary, patients, especially in HPV-positive patients(72). Among 100

patients, primaries were identified in 49%, all in the oropharynx. Dual biomarker testing (p16 immunohistochemistry and HPV-DNA) yielded a detection rate of 64% in HPV-positive and 16% in HPV-negative patients. The positive and negative predictive value for HPV-positive/p16-positive nodal disease was 64% and 86%, respectively. These findings align with recent literature, which also emphasize the relevance of incorporating combined HPV-DNA and p16 testing(66, 72, 73).

Unilateral or total mucosectomy: The majority of base of tongue primaries are ipsilateral to the bulk of cervical nodal metastases. The risk of contralateral disease has been examined in two meta-analyses, reporting rates of 6% and 1.9%(68, 70), though both studies included patients with non-standardized work-up and partial base of tongue mucosectomy. In the Danish national study only one patient was diagnosed with synchronous bilateral disease in the base of tongue(72). Other studies have found contralateral primaries in 11–12% of cases, with HPV positivity rates of 72–96%(74, 75). The UK MOSES study reported 8.6% synchronous multifocal base of tongue tumors, while another series described a 7.7% rate of synchronous HPV-associated primaries in patients undergoing bilateral palatine tonsillectomy or base of tongue mucosectomy during head and neck squamous cell carcinoma of unknown primary, work-up(60, 76). Ongoing trials are evaluating transoral robotic surgery for head and neck squamous cell carcinoma of unknown primary, including Canadian (NCT03281499)(77) and UK (NCT04151134) studies. Until stronger evidence emerges, particularly in HPV-associated head and neck squamous cell carcinoma of unknown primary, total base of tongue mucosectomy is recommended due to the risk of synchronous or contralateral disease. Detected primaries are often small, with a mean size of 1.15 cm, and 57% <1 cm(70), with some primary tumors measuring only 1–2 mm(72, 76, 78).

Morbidity: Evidence on morbidity following base of tongue mucosectomy via transoral robotic surgery is limited(79). A retrospective study of base of tongue mucosectomy and/or palatine tonsillectomy reported temporary declines in speech and aesthetics (3-6 months), with recovery by 1 year, while eating and social scores worsened at 12 months compared to baseline(80). Another study found high functional QoL at 1 month, with scores lowest at 3 months post-adjuvant therapy and improving by 6-12 months, except for persistent eating difficulties(81). Both studies, however, were limited by small sample sizes. In a recent study of 231 transoral robotic surgery-treated oropharyngeal cancer patients, gastrostomy tube dependency at 3 and 12 months was linked to T-stage and feeding tube use at discharge, but not to tumor site or contralateral tonsillectomy(82). Based on a meta-analysis on patients undergoing transoral robotic surgery and other transoral approaches in the oropharynx, gastrostomy tube dependency was 0.4%(66). In the previously mentioned Danish national study (n=100) no long-term feeding tube dependency was registered(72). The main concern after base of tongue mucosectomy by transoral robotic surgery is postoperative hemorrhage, though reported rates are relatively low. An American study examining complications after base of tongue mucosectomy found a 30-day readmission rate of 8.2%, with bleeding (1.9%) and dysphagia (1.7%) as the most frequent causes for readmission, and no registered deaths(83). In the Danish national study(72), the complication rate was found to be low, with postoperative hemorrhage necessitating readmission occurring in 4% of cases, well in line with previous systematic reviews (5%)(66, 68) and similar reports(84), and with no fatalities observed(72). A standardized pain management protocol, including dexamethasone, used in a Danish cohort, has previously been associated with effective pain control(85).

Surgical technique: The surgical technique regarding base of tongue mucosectomy by transoral robotic surgery in patients with head and neck squamous cell carcinoma of unknown primary is debated in the literature, with some centers performing concurrent base of tongue mucosectomy and palatine tonsillectomy, and some centers only perform ipsilateral palatine tonsillectomy and base of tongue mucosectomy. Furthermore, the current evidence is based on quite limited cohorts(66, 68, 70, 86, 87). Herein we advise against performing simultaneous bilateral palatine tonsillectomy and total base of tongue mucosectomy due to the risk of extensive scarring and pharyngeal stenosis.
We recommend that base of tongue mucosectomy should be performed only as a transoral robotic surgical procedure. Further, in head and neck squamous cell carcinoma of unknown primary, a total base of tongue mucosectomy is recommended (i.e. resection of both halves of the base of tongue lymphoid tissue)(88) as stated above. A full-length incision is made along the terminal sulcus, followed by a midline division through the base of the tongue, extending from the terminal sulcus to the medial glosso-epiglottic junction at the base of the epiglottis, without traumatizing the underlying deep musculature. Dissection proceeds along the level between the lymphoid tissue and muscle, starting at the terminal sulcus, with lateral boundaries defined by the lateral pharyngeal wall and medial boundaries by the prior midline incision, extending inferiorly to the level of the epiglottic vallecula. The procedure entails *en bloc* removal of the entire base of tongue lymphoid tissue in two separate specimens (left and right). Tissue specimens should be submitted in their entirety for histopathological analysis. Resection specimens should be anatomically oriented by the surgeon to ensure precise margin assessment. The pathologist should be informed that the case involves cancer of unknown primary to ensure appropriate processing and fine sectioning(72).

19. If endoscopic evaluation of the upper aerodigestive tract, palatine tonsillectomy and directed biopsies FAIL to identify a primary tumor, and the cervical lymphadenopathy is confirmed to be HPV-independent (HPV/p16-negative) squamous cell carcinoma, consider base of tongue mucosectomy by transoral robotic surgery, provided the patient is deemed fit suitable for surgery (C). This procedure is typically performed in a separate session.

Base of tongue mucosectomy in HPV-independent disease by transoral robotic surgery

As previously described, the primary tumor detection rate using base of tongue mucosectomy via transoral robotic surgery is significantly lower in HPV-independent head and neck carcinoma of unknown primary (around 11-13%)(72, 89) compared to HPV-associated head and neck carcinoma of unknown primary (58%)(72). Consequently, selection criteria for base of tongue mucosectomy in patients with HPV/p16-negative nodal metastases should be more stringent and primarily limited to those with a clinical suspicion of a base of tongue primary, based on symptoms, imaging and involved neck levels.

Diagnostic work-up step 5: Cytology and histopathology

20. Fine-needle aspiration cytology from suspicious cervical lymph nodes should be prepared as smears. Slides must be evaluated microscopically by a pathologist with expertise in head and neck pathology. Diagnostic findings should be classified as benign, cells suspicious of malignancy, malignant tumor cells, inconclusive. For malignant tumor cells, subtype determination should be stated. HPV-DNA analysis by PCR is recommended (B).

Fine-needle aspiration cytology

Fine-needle aspiration (FNA) of suspected metastatic lymph nodes carries a high false negative rate, particularly in cystic squamous cell carcinoma metastases (up to 42%)(90). Ultrasound guidance improves sensitivity to ~80%(91). In a recent study of 148 patients with HPV-associated oropharyngeal squamous cell carcinoma, initial FNA diagnosed malignancy in 74%(92, 93).

Immediate evaluation by a cytopathologist including assessment for high-risk HPV testing enhances speed and accuracy of the diagnostic work-up(93). HPV status can also be assessed from nodal FNA samples using techniques such as p16 immunohistochemistry on cell blocks. However, defining a reliable cutoff is difficult, and the lower specificity of p16 compared to HPV-DNA or mRNA testing may be a diagnostic pitfall. Consequently, p16 analyses on FNA are no longer routinely employed, whereas HPV-DNA analysis has become the preferred method. HPV-DNA can be detected by PCR from fine-needle aspiration samples of cervical lymph node metastases, which may help guide the subsequent diagnostic work-up(92, 94-97). A Danish study reported sensitivity of 86.7%, specificity of 92.0%, positive predictive value of 96.3%, and negative predictive value of 74.2% for HPV-DNA testing on FNA. The relatively low negative predictive value indicates a risk of false negatives, suggesting that repeat HPV testing may be relevant when FNA is negative, whereas positive results generally do not require confirmation.(93) (dvs. uafhængigt om der laves HPV DNA)?

21. Tissue specimens from suspected primary tumor sites should be submitted either formalin-fixed or unfixed (for frozen section microscopy) for histopathological examination by a head and neck pathologist. Excision specimens (e.g. palatine tonsils and tongue base resections) must be oriented and marked by the surgeon prior to histopathological assessment. Histopathological evaluation must include immunohistochemical assessment, including p16 status. Likewise, testing for HPV-DNA is recommended. Excision specimens should be systematically examined using thin slicing, with a maximum slice thickness of 2 mm, in order to identify microfoci. In cases of HPV-associated disease where a primary tumor is not identified, staining for p16 and re-evaluation of the specimens by another head and neck pathologist is recommended (D).

Relevance and methodology of HPV-testing

HPV-associated squamous cell carcinoma frequently manifests as metastatic disease in cervical lymph nodes. In a regional retrospective cohort study conducted in the Central Denmark Region (n=318) with suspected head and neck squamous cell carcinoma of unknown primary, 212 (67%) patients were HPV positive (p16 positivity used as a surrogate marker), 81 (25%) were HPV negative, and 25 (8%) had an unknown HPV status(1). Additionally, a national cohort study of 254 curatively treated patients with head and neck squamous cell carcinoma of unknown primary, found that 44% were HPV positive(2). The association between HPV status and lymph node involvement was particularly strong for level II and III lymph nodes and HPV positive metastases were ultimately traced to the oropharynx, specifically the palatine tonsils and the base of tongue(1). Accordingly, HPV testing is recommended for all cases of head and neck squamous cell carcinoma of unknown primary. A variety of methods are commonly employed in combination to enhance the accuracy and reliability of HPV detection in oropharyngeal cancers, with p16 immunohistochemistry typically serving as the initial screening approach. Further, testing for HPV-DNA or -mRNA is advised to establish a definitive diagnosis of HPV-associated oropharyngeal carcinoma(73). Recently, a national study on circulating tumor DNA in HPV-associated oropharyngeal cancer has been initiated (DAHANCA42), aiming to investigate whether measurement of HPV-DNA in blood can enhance standard follow-up by enabling earlier or concurrent detection of recurrence compare with routine clinical and radiologic evaluation.

p16 immunohistochemistry:. p16 serves as a surrogate marker for high-risk HPV, as it is overexpressed in HPV-positive squamous cell carcinoma, although it may also be expressed in other carcinoma types. In high-prevalence settings, p16 is considered a reliable surrogate marker for high risk-HPV in oropharyngeal cancer with low discordance to HPV DNA testing(98). While p16 immunohistochemistry is highly sensitive, its specificity can be limited in low-prevalence settings, such as in the context of lung or skin squamous cell carcinoma. In the Danish population, p16 immunohistochemistry is regarded as a reliable diagnostic tool. Within a Danish cohort of 318 patients with suspected head and neck squamous cell carcinoma of unknown primary, 13 patients (4%) were ultimately diagnosed with cutaneous squamous cell carcinoma, two of whom were p16 positive(1). However, it is important to acknowledge the discordance that may occur between p16 status and HPV-DNA status. This discrepancy has been shown to hold significant prognostic value in relation to overall survival in patients with oropharyngeal cancer. Although the same has not been established within head and neck squamous cell carcinoma of unknown primary, it seems reasonable to assume that HPV-DNA may inform the interpretation of p16 with respect to the topographical origin of a primary tumor(73). Accordingly, supplementary analysis of HPV-DNA is recommended.

Polymerase Chain Reaction: PCR testing can detect HPV DNA and is a highly sensitive and specific method for identifying HPV infection. PCR can be used to determine the presence of specific high-risk HPV strains, such as HPV 16 and 33, in oropharyngeal cancer tissue.

RNA in Situ Hybridization: This method detects viral RNA transcripts from HPV, associated with the expression of the E6 and E7 oncogenes, which are crucial for HPV-driven carcinogenesis. RNA-ISH offers more direct evidence of active HPV infection compared to DNA-based methods.

High-Risk HPV DNA PCR and Genotyping: Specific genotyping tests can identify high-risk HPV types, such as HPV 16, which is most associated with oropharyngeal cancer. These tests are often used for confirming the type of HPV present in a tumor sample.

Thin slice-technique in ectomy specimen: In the verification of primary tumors, the thoroughness of pathological tissue assessment is of importance. Thin slice-techniques and re-evaluation of pathological tissue specimens by a second pathologist are possibilities in this setting and have been evaluated in the MOSES study, amongst others(76, 99), in which especially re-evaluation was found useful. Histological examination should include thin slice sections of maximum 2 mm to identify small tumors. Mean size for identified primaries have been reported to be 1.15 cm in diameter with 57% being less than 1 cm in diameter(70), and some reports have described tumors as small as 1-4 mm(55, 72, 100).

Frozen section: Frozen section analysis in head and neck cancer is a valuable intraoperative diagnostic tool used to assess resection margins, confirm lymph node metastases, and evaluate suspicious tissue for malignancy. Its primary benefit is providing rapid feedback to guide surgical decision-making, allowing for immediate re-excision if tumor-positive margins are detected, thereby improving oncologic outcomes. However, its accuracy may be limited by sampling errors and freezing artifacts, necessitating confirmation by permanent histopathology.

22. If a primary tumor is identified in the resection specimen, a detailed histopathological description is essential, including tumor size, type, degree of differentiation (if relevant), and resection margins (D).

Recommended evaluation of an identified primary tumor in resection specimens

- **Tumor Type and Differentiation Grade:** Keratinizing squamous cell carcinoma graded as well-differentiated, moderately differentiated, or poorly differentiated according to the WHO 2023 classification(101). HPV-associated non-keratinizing squamous cell carcinoma is not graded. The invasive tumor front should be described as either cohesive or non-cohesive.

- **Deepest Tumor Infiltration:** Metric: millimeters (mm). Tumor dimensions: length × width × depth. Vascular and perineural invasion: Presence of tumor invasion into blood vessels and nerve pathways. Surgical resection margins (in ectomy specimens): The shortest distance from the tumor to resection margins.

- **Dysplasia/Carcinoma In Situ, margins:** The shortest distance from dysplasia or carcinoma in situ to all examined mucosal resection margins (measured in mm).

23. Histopathological evaluation of excised cervical lymph nodes should include immunohistochemical assessment of p16 status. Likewise, testing for HPV-DNA is recommended. The evaluation should also include: number of benign lymph nodes and lymph node metastases (per neck levels and total number), size of metastases (intranodal size of metastases), and the presence, extent, and morphological features of extranodal extension (D).

Recommended histopathological evaluation of neck nodes

Neck dissection specimens should be submitted in a manner that allows precise identification of individual neck levels, either by sending each level in separate containers or by using clear marking methods. For each

anatomical level, the number of lymph nodes must be recorded, and key structures such as the salivary glands, sternocleidomastoid muscle, and internal jugular vein should be identified, with documentation of the relationship between metastases and these structures. The size and level of the largest metastatic lymph node must be reported, and sections should represent the maximal extent of the metastasis, divided across multiple tissue blocks if required. Areas showing macroscopic suspicion of extranodal extension should always be sampled. Smaller lymph nodes should be bisected through the hilum unless they measure less than 2 mm, in which case they should be embedded whole; lymph nodes of similar size from the same level may be embedded together. A level II–VI neck dissection specimen typically yields at least ten lymph nodes; if fewer are found - particularly on the tumor bearing side - all remaining adipose tissue should be submitted for histopathological examination. According to the 2025 Danish national oral cavity cancer guideline (DAHANCA), extranodal extension is defined histologically as unequivocal invasion of the lymph node capsule by viable tumor cells into extranodal soft tissue, with or without a desmoplastic reaction. This definition is based on recently updated international consensus recommendations(102). The presence of extranodal extension must be noted in the description and indicated with the extent in mm measured perpendicular to the lymph node capsule. Studies have demonstrated that extranodal spread of <1.7 mm does not have a significant impact on disease-specific survival(103, 104). However, any micro metastases (< 2 mm) and isolated tumor cells (< 0.2 mm) are noted and counted as metastases(105). This is despite the fact that the 8th edition of the IUCC TNM classification generally considers micro metastases and isolated tumor cells as pN0 for other types of cancer(106).

If extranodal extension is present, the extent should be measured on HE-stained sections perpendicular to the estimated lymph node capsule. Additionally, the number of foci where the tumor extends beyond the lymph node capsule should be recorded(107, 108). Soft tissue metastasis is defined as a tumor mass in the connective tissue or fat of the neck without any residual lymph node or lymph node capsule(109).

Recommendations for the pathology report:

- Number of lymph nodes in each level
- Number of positive lymph nodes in each level
- Largest diameter of largest metastasis (if only two metastases, then largest diameter of both metastases)
- Presence and extent of extranodal tumor extension
- Micro metastasis (0,2-2 mm. in diameter)
- Isolated tumor cells
- Vascular invasion
- Soft tissue metastasis
- Vascular invasion.
- TNM-classification should refer to the 8th edition of the UICC TNM classification

24. If histopathological evaluation of the excised cervical lymph node shows p16/HPV-negative non-keratinizing squamous cell carcinoma or undifferentiated carcinoma, in situ hybridization for Epstein-Barr Virus should be performed (B).

Testing for Epstein-Barr Virus

EBV-associated squamous cell carcinomas are mainly associated with the undifferentiated type of nasopharyngeal carcinoma. This is a rare condition in most European and North American populations. Within the Kingdom of Denmark, the disease is not considered endemic—except in Greenland, which, although part of the Danish Realm, has a distinct epidemiological profile. The differences in the natural history and treatment response between neck metastases from EBV-related nasopharyngeal carcinoma and EBV-unrelated head and neck cancers are well-documented. This distinction has led to the introduction of T0 for EBV-positive head and neck squamous cell carcinoma of unknown primary (HNSCCUP) in the 8th edition of the AJCC staging manual for nasopharyngeal carcinoma. EBV testing is recommended for poorly differentiated or undifferentiated squamous cell in lymph nodes. A positive EBV test would suggest a nasopharyngeal or salivary origin, although it may occasionally indicate other head and neck or non-head and neck sites. Epstein-Barr encoding region in situ hybridization is the preferred method for testing(110-112). Non-keratinizing squamous cell carcinoma is found in both HPV-associated cancers and EBV-associated cancers and therefore cannot be used to decide which patients to test for EBV. Additionally, co-infection with HPV and EBV is increasingly reported(64, 113). Therefore, a positive HPV result does not rule out the need for EBV testing in a metastatic lymph node. However, very little is known about the most likely primary site in cases of double-positivity.

Treatment: Surgery and (chemo-) radiotherapy

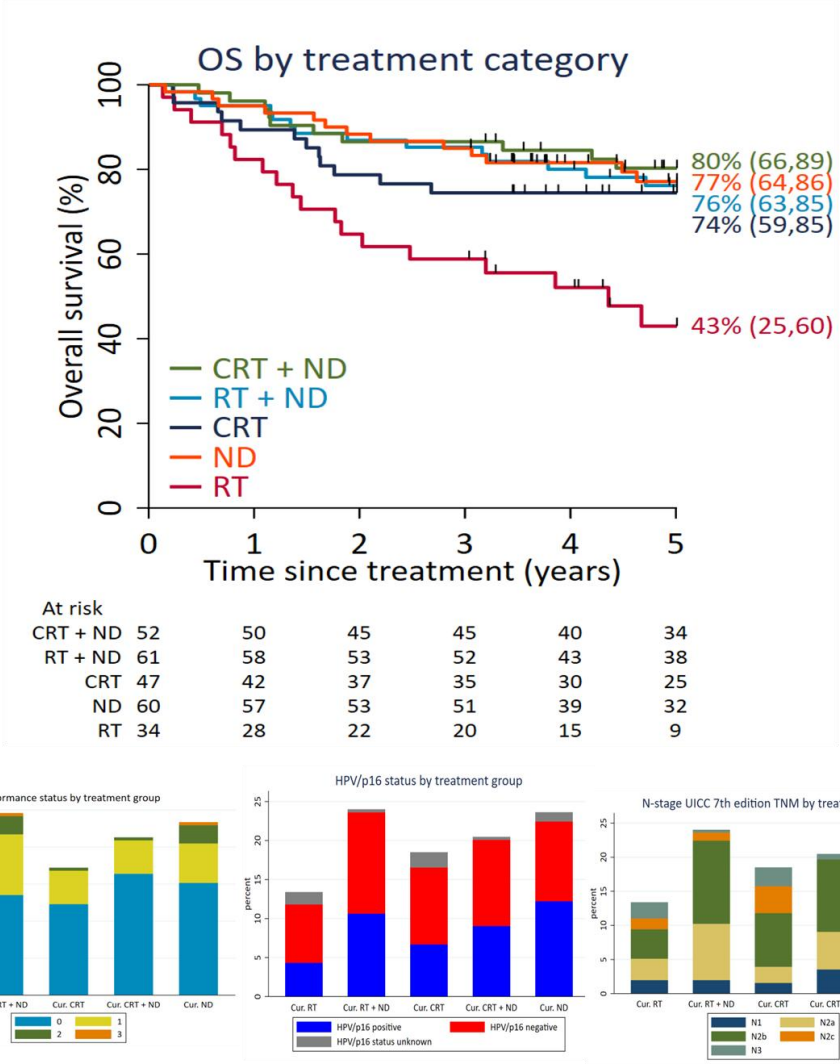


Figure 3. 5-year overall survival by treatment category in the Danish head and neck cancer of unknown primary cohort from 2014-2020. Below histograms of performance status, HPV-status and N-stage by treatment category. Abbreviations: CRT = chemoradiotherapy; ND = neck dissection; RT = radiotherapy.

25. **Aim for early treatment planning, as diagnostic evaluation and therapy often overlap, and time to treatment has prognostic significance (B). Treatment involves neck dissection and/or radiotherapy. For radiotherapy, a unilateral and volume-reduced approach is preferred, unless bilateral lymph node involvement or N3 disease is present (C). Clinical decisions regarding the treatment strategy should be based on multidisciplinary team consensus (D).**

Treatment of tHNSCCUP, general considerations

Treatment planning for head and neck squamous cell carcinoma of unknown primary should commence early, as diagnostic evaluation and therapy are closely interconnected. Management commonly includes neck dissection and/or radiotherapy, which should be considered in parallel with diagnostic investigations to avoid unnecessary delays. All treatment decisions should be made through multidisciplinary team consensus to ensure coordinated, evidence-based, and expert-driven care.

When surgery is indicated, the following principles apply: careful patient selection to minimize the risk of trimodality therapy (neck dissection, radiotherapy, and chemotherapy); selective neck dissection including levels 2–4 and any involved levels; a minimum nodal yield of 10 lymph nodes; achievement of R0 resection; and efforts to reduce morbidity and complications, including the use of intraoperative neurostimulation.

When radiotherapy is indicated, patient selection should aim for volume-reduced fields when feasible to limit toxicity, with wide-field radiotherapy reserved for advanced disease. Concurrent chemotherapy and nimorazole may be added in selected cases.

26. Volume-reduced radiotherapy implies pharyngeal and laryngeal sparing and unilateral radiation treatment to neck levels II-IV and other involved levels. Volume-reduced treatment is feasible in cases with unilateral neck disease AND a complete diagnostic work-up according to this guideline, including imaging and diagnostic surgical procedures (B).

Background and key considerations for volume-reduced radiotherapy

The treatment of patients with head and neck squamous cell carcinoma of unknown primary remains controversial. Treatment strategies differ among cancer centers worldwide, and no international consensus on the optimal management approach has been established. Most published studies are small and retrospective and the lack of randomized studies makes it difficult to draw firm conclusions from literature. Furthermore, the low incidence of head and neck squamous cell carcinoma of unknown primary makes it hard to imagine that data supporting one treatment over another, such as the effect of chemoradiotherapy versus radiotherapy alone, unilateral versus bilateral irradiation and inclusion/exclusion of various mucosal areas in radiotherapy, will emerge in the near future. Recommendations regarding treatment are therefore primarily based on published retrospective patient series and extrapolations from studies of head and neck cancer with a known primary site.

Until now, the Danish strategy has built on extensive bilateral elective irradiation of the lymph nodes of the neck including the mucosa of the larynx and pharynx(3). Over the years imaging strategies have improved with the standard use of CT, MRI and later PET-CT in the diagnostic evaluation(33) as well as a more targeted treatment and reirradiation of the neck has become possible with intensity-modulated radiotherapy (IMRT) and Volumetric Modulated Arc Therapy (VMAT). A recent evaluation of the Danish DAHANCA experience from Nielsen SB et al.(2) showed and 5-year locoregional failure rate of 22% and a 5-year overall survival of 73% - fully comparable to the general Danish outcome for patients with known head and neck cancer(114). However, the prize is toxicity due to the extensive irradiated volume. The experience from recent retrospective studies(115), the Danish DAHANCA experience(2) and emerging Danish data on recurrence patterns(116) suggests that the radiotherapy strategy for head and neck squamous cell carcinoma of unknown primary can be further stratified, which has resulted in the current decision tree (Figure *Treatment HNSCCUP*).

Concomitant chemotherapy

There are no randomized studies on the effect of concomitant chemotherapy for patients with head and neck squamous cell carcinoma of unknown primary. However, there is strong evidence supporting concomitant chemotherapy for patients with squamous cell carcinoma in the head and neck region with a known primary tumor. This applies to both primary radiotherapy(117) and postoperative radiotherapy in patients with a high risk of recurrence: lymph node with extracapsular extension, or non-radical surgery(118). There is reason to believe that a similar benefit would be seen in head and neck squamous cell carcinoma of unknown primary. The rationale for concomitant chemotherapy is thus based on the proven effect in cases with known primary tumors, as well as the predominantly positive outcomes reported in the literature as well as the results of the Danish experience 2014-2022, with a 5-year loco-regional control of 78%(2). Arguments against concomitant chemotherapy include the increased morbidity, which is exacerbated by a large treatment volume.
Concomitant cisplatin chemotherapy is recommended for patients undergoing primary radiotherapy with extranodal extension or a non-radical (R1/R2) resection following surgery for squamous cell carcinoma metastasis to the neck from an unknown primary. These high-risk patients should receive chemotherapy only if medically suitable and no contraindications. The most appropriate regimen is weekly cisplatin, consistent with recommendations from the national Danish SundK-DAHANCA guidelines(119).
As neoadjuvant and adjuvant chemotherapy have not found a role in the treatment of head and neck cancer in general, these modalities cannot be recommended for head and neck squamous cell carcinoma of unknown primary(117).

Concomitant nimorazole

In primary radiotherapy, nimorazole is recommended in accordance with DAHANCA's guidelines for the treatment of head and neck squamous cell carcinoma of unknown primary, preferably after testing of the hypoxic gene profile as indicated in the SundK-DAHANCA guideline "Treatment with the hypoxic radiosensitizer Nimorazole in squamous cell carcinoma of the head and neck"(119).

Immunotherapy or other targeted treatments in the curative setting

A few smaller retrospective studies have been published the recent years, indicating a possible effect of PD-L1 inhibition as a part of the treatment for head and neck squamous cell carcinoma of unknown primary(120, 121). So far, no data indicate PD-L1 inhibtors or other targeted drugs should be incorporated as a part of the treatment of head and neck squamous cell carcinoma of unknown primary outside clinical protocols.

Recommendations on (chemo-)radiotherapy

Radiotherapy for patients with head and neck squamous cell carcinoma of unknown primary is recommended to be administered according to the following principles:

- For unilateral disease, elective lymph node areas include levels II, III, and IV unilaterally, while levels I and V are only irradiated if there are metastases in those levels.
- For bilateral disease and N3 disease, elective lymph node areas include levels II, III, and IV bilaterally, while levels I and V are only irradiated if there are metastases in those levels.

- Elective mucosal areas of the larynx and pharynx are only included in case of bilateral or N3 disease due to the technical difficulties in reirradiation in these situations if a primary tumor emerges at a later stage.
- The base of tongue is only included in case where base of tongue mucosectomy by TORS has not been performed as a part of the diagnostic work-up
- In case of EBV-positive and low/undifferentiated carcinoma, the patient is treated according to to DAHANCA guidelines for nasopharyngeal carcinoma.
- Radiotherapy is preferably given as VMAT or IMRT alternatively as proton therapy in case of patients younger than 40 of age due to the risk of secondary cancer.
- Postoperative radiotherapy is precribed according to the SundK-DAHANCA radiotherapy guidelines; typically 60-66gy/30-33 fractions, 5 fx/wk.
- Primary radiotherapy is prescribed according to the SundK-DAHANCA radiotherapy guideline; typically as 66-68Gy/33-34fx, 5fx/wk.
- Concomitant chemotherapy is used in patients in good general condition who have undergone elective neck dissection for tHNSCCUP with high risk of recurrence: extranodal extension or non-radical surgery (R1 and R2), or patients who are receiving primary radiotherapy.
- Chemotherapy is recommended as weekly concomitant cisplatin according to DAHANCA's guidelines.
- Nimorazole is recommended in patients receiving radiotherapy, in accordance with DAHANCA's guidelines for the treatment of squamous cell head and neck cancer with a known primary site (Level of evidence 5).

27. For ONE nodal metastasis in the neck ≤ 6cm AND a complete diagnostic work-up according to this guideline, including imaging and diagnostic surgical procedures, the recommended definitive treatment is EITHER: 1) unilateral selective neck dissection IF neck metastasis ≤ 3cm (HPV negative) or ≤ 4 cm (HPV positive) AND no extranodal extension; OR 2) volume-reduced radiotherapy +/- chemotherapy (B). However, treatment strategy should always be based on MDT-consensus (D).

Treatment of solitary nodal neck disease, pT0N1M0

Historically, several retrospective studies have evaluated the efficacy of primary neck dissection(122-124) (see Table 4). Likewise, definitive intensity-modulated radiotherapy has achieved regional control rates exceeding 90%(9, 19, 125, 126). Comparative analyses further indicate no significant differences in regional control or overall survival between surgical and radiation-based treatment approaches(127, 128). Moreover, in cases involving a solitary nodal metastasis without extranodal extension, with a maximum diameter of 3 centimeters and an adequate nodal yield (defined as a minimum of 10 lymph nodes in the neck dissection specimen), neck dissection as a sole intervention demonstrates comparable overall survival to radiotherapy(1, 129-131). Although the results in the Danish DAHANCA based study(1) were not statistically significant, they suggest

caution when considering the omission of postoperative radiotherapy in cases of more advanced lymph node disease (>1 nodal metastasis or extranodal extension). These findings underscore the importance of evaluating the comparative morbidity profiles of each strategy to inform treatment decisions.

Neck dissection in solitary unilateral neck disease

Neck dissection may be conducted as a part of the primary diagnostic surgery or as an elective procedure, following MDT. Considerations regarding neck dissection as a part of diagnostic surgery are specified above.

Preconditions for neck dissection as single modality in squamous cell carcinoma of unknown primary: A solitary neck metastasis based on histopathology AND maximum diameter of 3 cm in HPV negative disease and 4 cm in HPV positive disease based on histopathology AND no extranodal extension based on histopathology AND R0 AND nodal yield of minimum 10 lymph nodes AND sufficient neck dissection including levels 2a, 2b, 3, 4 in addition to involved neck levels AND sufficient diagnostic work-up according to the current guideline, **sections 1-22**. In case of stage migration, postoperative adjuvant radiotherapy +/- chemotherapy is recommended, as described in **section 26** and below.

Surgical technique: It is recommended that the revised nomenclature for the surgical management of cervical lymph nodes be implemented, wherein the neck dissection procedure is systematically described. The specific lymph node levels or sublevels resected should be documented and denoted. i.e. numerals I through VII and subdivided into sublevels A and B for levels I, II, V. Any resection of non-lymphatic structures should be clearly indicated using standardized acronyms (e.g., IJV: internal jugular vein; SCM: sternocleidomastoid muscle; CN XI: spinal accessory nerve; CN XII: hypoglossal nerve, etc.)(132, 133) (Figure 2). Neck dissection should always include levels II - IV. In addition, levels with involved disease should be included. Several studies have demonstrated that the number of lymph nodes retrieved (nodal yield) during both elective and therapeutic neck dissection is an independent prognostic factor for both overall and disease-specific survival. The underlying mechanism is likely that a higher nodal yield reflects greater surgical and pathological thoroughness, which is associated with increased likelihood of removing subclinical nodal disease. Various cut-off values have been evaluated. The 8th edition of the UICC TNM classification states that, in general for head and neck cancers, the expected number of harvested lymph nodes is ≥10 for elective and ≥15 for radical or modified radical neck dissections. Based on current evidence, a threshold of ≥10 lymph nodes is recommended for optimal prognostic reliability.

Radiotherapy in solitary unilateral neck disease

Volume-reduced radiotherapy is considered equivalent to neck dissection in patients with solitary neck metastasis ≤ 3 cm in HPV negative disease / ≤ 4 cm in HPV positive disease and no extranodal extension, as stated above. Volume-reduced radiotherapy is recommended in favor of neck dissection in cases of advanced solitary nodal disease: metastases >3 cm in HPV-negative disease and >4 cm in HPV-positive disease, extranodal extension, insufficient nodal yield after neck dissection, and non-radical resection (R1-2). In addition, radiotherapy may be preferred when surgery is contraindicated or not feasible or based on patient preference. Radiotherapy for unilateral solitary as well as multinodal disease is guided by the same principles of volume-reduced treatment planning. Please refer to section 26, for comprehensive information.

28. For MULTIPLE nodal metastases in the neck AND unilateral neck involvement AND a complete diagnostic work-up according to this guideline, including imaging and diagnostic surgical procedures the recommended definitive treatment is: volume-reduced radiotherapy +/- chemotherapy (C).

Treatment of unilateral multinodal neck disease

As presented previously, up-front neck dissection is recommended in unilateral neck disease (see section 17), in conjunction with the initial surgical diagnostic procedure **sections 18-19 + 29-30**. Although the management of patients with unilateral multinodal disease is somewhat contentious, there is sufficient evidence to support this strategy. Some advocate for surgery followed by radiotherapy or chemoradiotherapy, while others have reported satisfactory results with radiotherapy or chemoradiotherapy alone, reserving surgery as a salvage option. Primary surgery followed by adjuvant radiotherapy and chemotherapy has been associated in some studies with a reduced risk of complications and improved prognosis. Primary surgical resection with selective neck dissection and subsequent pathological assessment provides more accurate staging, including evaluation of extranodal extension.

Some studies suggest that neck dissection is associated with improved overall survival and progression-free survival compared to radiotherapy alone. This benefit appears consistently across nodal stages, although it diminishes with more advanced nodal disease. As all studies are of retrospective nature the trend may be due to selection bias. Lou et al. reported a 5-year overall survival of 67.1% (median survival: 70 months) for their cohort, with higher overall survival in the neck dissection group (71.3%) compared to the non-dissection group (53.2%) ($p = 0.061$). Multivariate analysis identified N stage ($p = 0.000$), bilateral metastases ($p = 0.001$), extranodal extension ($p = 0.016$), and neck dissection ($p = 0.028$) as independent prognostic factors for overall survival. Locoregional failure occurred in 18.8% of patients, with significantly lower rates in the neck dissection group (13.5%) compared to the non-dissection group (37.9%) ($p = 0.003$). Higher N stage was an independent risk factor for locoregional failure ($p = 0.015$)(134). Similar findings were reported by Abu-Shama et al. in a cohort of 322 patients: 16.5% underwent no neck dissection, 10.2% had lymph node resection, 36.0% had selective dissection, and 37.3% underwent radical or modified radical dissection. The 3-year nodal relapse rate was 12.5%, with a progression-free survival of 69.1%. After adjustment for nodal stage, all forms of dissection were associated with reduced risk of nodal relapses or progression, although no effects on overall survival were seen. Notably, patients who underwent lymph node resection or neck dissection experienced significantly better progression-free survival and a lower incidence of nodal relapse in the N1 + N2a group. However, this improvement was not significant for patients in the N2b or N2c + N3c groups. Severe toxicity rates exceeded 40% in patients undergoing radical neck dissection(135). This aligns with other institutional reports indicating improved regional control in patients with head and neck squamous cell carcinoma of unknown primary who undergo neck dissection compared to those treated with radiotherapy alone(122, 136). Data from the national cohort of patients with head and neck squamous cell carcinoma of unknown primary from 2014-2020 show a similar tendency with worse prognosis in terms of 5-year overall survival in patients treated with primary radiotherapy compared to patients undergoing neck dissection followed by radiotherapy (Figure 3), as patients with better performance and less advanced disease were selected to undergo surgery first, which has been the main rule in the Danish 2013 guideline strategy. Surgical resection of nodal disease may also obviate the need for chemotherapy in the absence of extranodal extension and may provide enhanced locoregional control, particularly in patients with bulky or advanced nodal involvement.

Neck dissection in unilateral multinodal neck disease

Neck dissection is performed either in extension to the surgical diagnostic procedure (section 13-22) or as an elective procedure, following the recommendations of a multidisciplinary tumor board decision. The surgical technique has been addressed in **section 27.**

Radiotherapy in unilateral multinodal neck disease

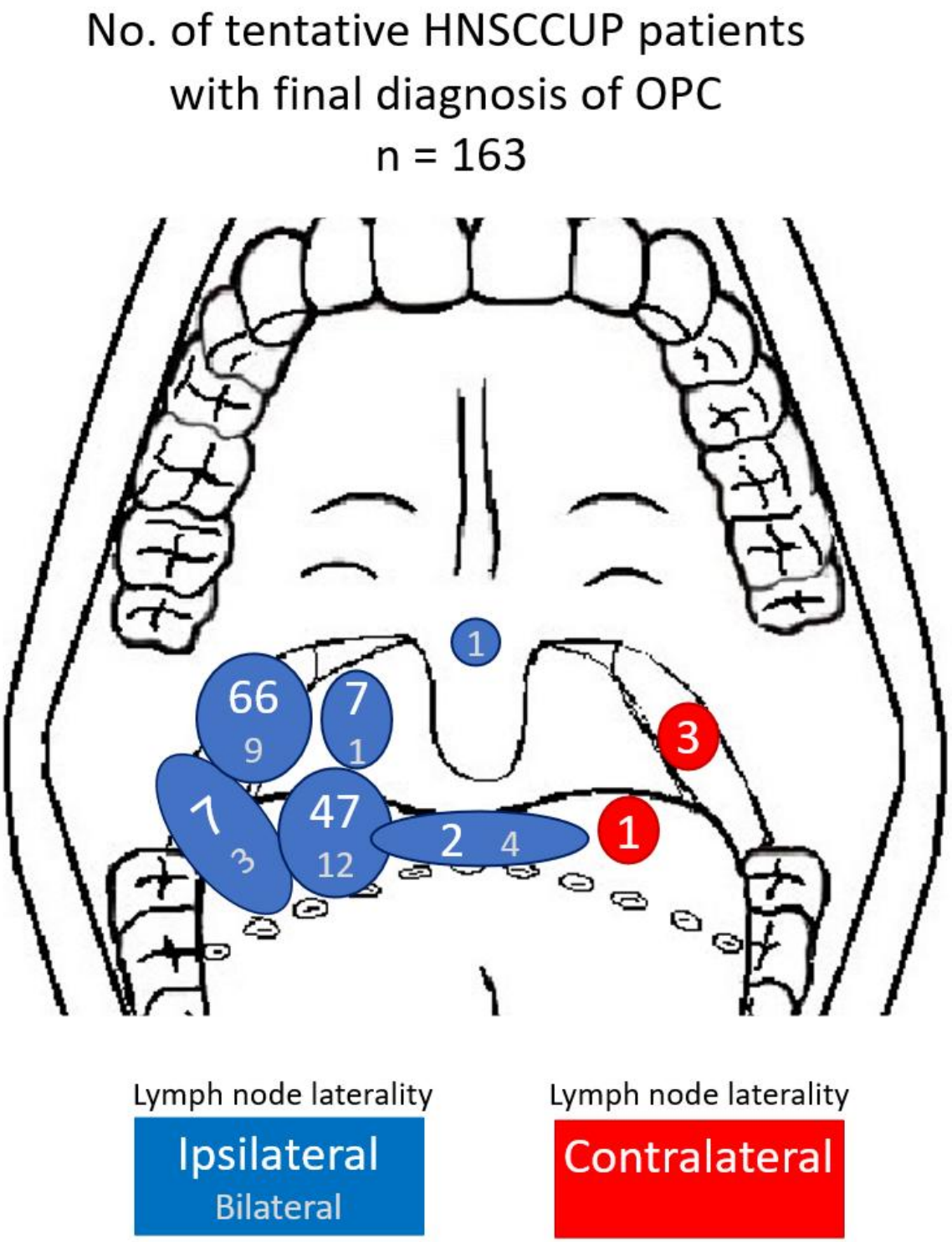
Despite improved diagnostic abilities, the fraction of head and neck squamous cell carcinoma of unknown primary among all head and neck cancer cases has not decreased over the years. Instead, the absolute number seems to have increased along with a bigger proportion being p16 positive(2, 3, 137).Thus, for assessing the risk of contralateral lymph node involvement it seems reasonable to extrapolate from T1 oropharyngeal cancer. A study from Zurich and Lyon showed that the risk of contralateral lymph node involvement were 8%, but the risk of pathological infiltration (after contralateral neck dissection) were less than 2% in T1 oropharyngel carcinomas(138). This was confirmed when evaluating 879 patients with T1 oropharynx cancer from the Danish quality database DAHANCA between 2007 and 2022 where 9% had clinical suspicious contralateral metastases – however in the Danish cohort contralateral neck dissection was not performed and thus the true risk of pathological infiltration could not be assessed. Nevertheless, it is reasonable to assume that the risk for contralateral metastases is not substantially high.

A few retrospective studies support the omission of contralateral elective irradiation and mucosal sparing. The studies from Pflumio and Brenet are among the most substantial: A retrospective French study from 2019 involving 350 patients, 74.5% had unilateral disease, and more than two-thirds underwent bilateral irradiation. The study aimed to explore the role of nodal and mucosal irradiation, hypothesizing that unilateral irradiation would result in 15% more recurrences compared to bilateral irradiation. Their findings indicated that the regional control rate and the occurrence of mucosal primaries were similar between patients who received unilateral and bilateral irradiation. However, treatment related morbidity was more common following bilateral irradiation(139).

In 2022 Brenet et al. published a retrospective study of 138 head and neck squamous cell carcinoma of unknown primary patients who all underwent neck dissection and postoperatively were treated with either unilateral radiotherapy to the neck (44%) or bilateral neck irradiation and panmucosal irradiation (66%). The group found no statistical difference in overall survival, disease specific survival and loco-regional recurrence free survival at 5 years(140).

Recent data suggests that a substantial group of patients with head and neck squamous cell carcinoma of unknown primary has p16/HPV positive carcinomas and these carcinomas are predominantly located in the base of the tongue (82%) when base of tongue mucoal resection is performed. In contrast, this is only the case in 12% with p16/HPV negative carcinomas(66). A similar Danish study found that the majority (1 out of 41 patients) were found in the ipsilateral part of the base of the tongue(72). Based on that, it seems safe to omit base of tongue mucosal irradiation in patients where base of tongue mucosal resection has been performed.

Figure 4



While reduced volume irradiation has the potential to significantly decrease treatment-related toxicity, it should be noted that insufficient upfront diagnostic work-up may increase the risk of undertreating an occult primary

tumor. Therefore, comprehensive upfront diagnostic evaluation as described in this guideline is essential prior to the implementation of unilateral and mucosal-sparing irradiation in patients with head and neck squamous cell carcinoma of unknown primary. With the implementation of the current guidelines the DAHANCA group commits itself to follow the situation and secure that an increased frequency of recurrences is not observed.

29. For bilateral nodal metastases OR N3 disease the recommended definitive treatment is: radiotherapy +/- chemotherapy with bilateral elective neck irradiation and irradiation of the pharyngeal and laryngeal mucosa (B).

Treatment of bilateral nodal disease or N3 disease

In case of bilateral nodal involvement or N3 disease, the recommended treatment is (chemo-)radiotherapy. See the following two sections.

Neck dissection in bilateral nodal disease or N3 disease

Neck dissection is generally not indicated in bilateral nodal disease and N3 disease and should only be offered in cases where patients are either not suitable for curatively intended (chemo-) radiotherapy or insist on surgical treatment only. Surgical approach is described in **section 27** for detailed information on the surgical approach.

Radiotherapy in bilateral nodal disease or N3 disease

In case of bilateral nodal involvement or nodal metastases > 6 cm in diameter, the risk of recurrence is estimated by the DAHANCA working group to be too high to recommend reduced elective fields. Furthermore, in these situations the possibility to perform reirradiation seems to be more complex. Accordingly, the recommended treatment strategy aligns with the previous approach described in the 2013 DAHANCA guideline, involving bilateral elective irradiation and mucosal coverage of the pharynx and larynx. Please refer to **section 26** for detailed information on treatment regimes.

30. In cases highly suggestive of an occult Epstein-Barr virus (EBV)-associated nasopharyngeal primary, treatment should adhere to the guideline concerning nasopharyngeal carcinoma (A).

Treatment of Epstein-Barr Virus associated disease

If cervical lymphadenopathy is confirmed EBV-positive and histopathology shows low/undifferentiated carcinoma and regardless of size, it is suggested to treat the patient as having nasopharyngeal cancer and according to the SundK-DAHANCA national radiotherapy guideline(119).

Follow-up

31. Response evaluation should be conducted three months after end of treatment and include PET/CT or MRI, a clinical ENT-examination including trans-nasal video pharyngo-laryngoscopy, and neck ultrasonography. The assessment should focus on identifying any emerging primary tumor, second primary tumors, recurrent neck disease, functional outcomes, and treatment-related morbidity (D).

Detection of emerging primary and recurrence by PET-CT

Post-treatment ^{18}F-FDG PET/CT or MRI approximately 12 weeks after therapy is recommended for all patients with head and neck squamous cell carcinoma of unknown primary, regardless of initial treatment modality, to evaluate response and identify emerging primary tumor, second primaries, and residual or recurrent disease. This early post-therapy visit is aimed at confirming disease control and detecting any residual or recurrent cancer while salvage treatment is most feasible(141-143). In particular, careful endoscopic examination (e.g. trans-nasal video pharyngo-laryngoscopy) of all potential mucosal sites – supplemented by Narrow Band Imaging (NBI) – enhances visualization of subtle lesions and can uncover small primary tumors that were not evident initially(27). Indeed, studies show that a previously occult primary may become clinically apparent on follow-up in a subset of patients treated for head and neck squamous cell carcinoma of unknown primary (often in the oropharynx or hypopharynx), underscoring the need for diligent surveillance(116, 144, 145). Equally, the 3-month evaluation allows assessment of functional outcomes and treatment-related morbidity(145). Common sequelae of HNCUP therapy such as dysphagia, xerostomia, trismus, or shoulder dysfunction (e.g. from spinal accessory nerve injury) should be actively evaluated at this visit, with early referral to rehabilitative services (swallowing therapy, physiotherapy, etc.) as needed(145).

A 3-month post-therapy PET/CT offers high negative predictive value (~95%) for persistent cancer, enabling clinicians to confidently avoid unnecessary invasive procedures (e.g. planned neck dissection) when the scan shows complete metabolic response(146). Conversely, if PET/CT reveals abnormal FDG uptake suspicious for residual disease, further evaluation (biopsy and assessment of salvage options) is warranted to confirm and manage recurrence(146). Timing is critical – imaging at ~12 weeks maximizes accuracy, as PET/CT performed too early (<3 months) often yields false-positive findings from post-therapy inflammation(146).

32. Post-treatment follow-up should be conducted at a head and neck cancer center at the department responsible for the definite treatment, two weeks, 2-3 months, and 6 + 12 + 18 + 24 + 36 + 42 + 60 months post treatment. Surveillance should involve a comprehensive clinical evaluation, including trans-nasal video pharyngo-laryngoscopy with narrow-band imaging and neck ultrasonography (D).

Sequence of post-treatment follow-up

This guideline recommends that follow-up of patients who have received treatment for head and neck squamous cell carcinoma of unknown primary is conducted at a head and neck cancer center, ideally by a head and neck surgeon or an oncologist, experienced in the use and interpretation of trans-nasal video

pharyngo-laryngoscopy with Narrow Band Imaging. This applies to patients regardless of the treatment received, considering that the physician has specialized expertise in distinguishing mucosal radiation effects in irradiated patients and identifying any emerging primaries or new mucosal primaries. While there is a higher likelihood of emerging primaries among patients treated exclusively with surgery, the risk exists in both groups(116, 147). Danish studies have shown that recurrences can be both symptomatic and asymptomatic. Therefore, it is crucial for patients to be seen by physicians with specialized expertise in recognizing alarm symptoms and conducting clinical examinations(148, 149).
In addition to the benefit of detecting symptoms and relevant clinical findings indicative of potential recurrences and emerging tumors, the follow-up process also has the advantage of managing treatment morbidity, which can partly involve referring the patient to the appropriate specialist at the right time(149).
Additionally, the follow-up aims to achieve quality control through registration in clinical databases, documentation of any protocol-related parameters, and the education of healthcare professionals. The effectiveness of the 2013 guideline was evaluated using prospectively collected data in the DAHANCA database in a phase-IV study(2). The goal is to similarly evaluate national data on the effectiveness and toxicity resulting from the current guideline's strategy after an appropriate follow-up period. Current recommendation of follow-up intervals is: 2 weeks, 2-3 months, 6 + 12 + 18 + 24 + 36 + 42 + 60 months post treatment.

33. In cases of recurrence or the emergence of a primary or second primary tumor, a PET-CT scan should be conducted. Dependent on the location of the suspicious tumor area, a neck MRI and/or a CT of the facial skeleton should be performed to assist in planning potential salvage surgery (D).

Imaging and evaluation of suspected recurrence or emerging primary

In patients previously treated for head and neck squamous cell carcinoma of unknown primary who develop signs of recurrence or a new primary tumor, prompt imaging is critical. A fluorodeoxyglucose PET-CT scan should be obtained without delay to assess for locoregional and distant disease, as most guidelines recommend using PET-CT when new symptoms or findings suggest relapse(142). Additional anatomic imaging is then selected based on the suspected site of recurrence to guide surgical planning. For example, a contrast-enhanced neck MRI is preferred for evaluating soft-tissue recurrence (e.g. tongue/base of skull or intracranial extension), whereas a high-resolution CT of the skull base or facial skeleton is useful if bony involvement is suspected(150). Early involvement of the multidisciplinary tumor board is strongly advised upon suspicion or confirmation of recurrence(151). The multidisciplinary team board should review the case and imaging findings to evaluate all treatment options – such as salvage surgery, re-irradiation, and/or systemic therapy – and determine an optimal, individualized salvage strategy. This approach is supported by current international guidelines, including recent updates from ASCO, NCCN, and ESMO, which emphasize timely imaging and coordinated multidisciplinary evaluation in the follow-up of head and neck cancer patients(141, 142, 150, 152).

34. Definition of an emerging primary: same histological type AND same p16 and/or HPV-DNA status as the nodal metastases at initial diagnosis AND diagnosis within five years of primary diagnosis (C).

Definition of recurrence and emerging primary

In the Odense–Birmingham classification for head and neck squamous cell carcinoma, an emerging primary is defined as a tumor arising in the same or adjacent subsite within ~3 years of treatment and within ~3 cm of the original site. Such tumors may reflect field cancerization rather than a completely unrelated malignancy. A new (second) primary is anatomically distinct (beyond adjacent subsites or >3 cm away), often appears after a longer disease-free interval, and may differ in p16 status for oropharyngeal cancers, indicating a separate pathogenic origin. This classification helps differentiate recurrence from new tumors, with implications for prognosis and treatment(153). However, this classification is not directly to applicable to head and neck squamous cell carcinoma of unknown primary, and thus, an emerging primary is defined as stated above(1).

Rehabilitation

35. Patients with head and neck cancer of unknown primary represent a highly heterogeneous group. The extent of morbidity and long-term effects is often closely related to the type and intensity of treatment. For a detailed review of potential long-term effects and rehabilitation needs, refer to the national rehabilitation guidelines issued by the Danish Health Authority (D).

Morbidity and functional outcome after treatment

Comprehensive post-treatment rehabilitation is recommended for patients with head and neck squamous cell carcinoma of unknown primary, encompassing speech/swallowing therapy, nutritional support, psychosocial care, and physical rehabilitation. Both Danish and international guidelines (DAHANCA, NCCN, ASCO, ESMO) underscore that a coordinated multidisciplinary approach – integrating speech/swallow therapists, dietitians, psychosocial services, and physical therapy – is essential to optimize functional outcomes and quality of life after treatment for head and neck squamous cell carcinoma of unknown primary(2, 141, 154-156).
Patients with head and neck cancer represent a highly heterogeneous group. Some patients are treated for small, often curable cancers, while others suffer from highly aggressive cancer types requiring extensive treatment with surgery, radiotherapy, and/or chemotherapy, or combinations of these modalities. The extent of complications and late effects is often closely related to the type and intensity of treatment. For a detailed review of potential late effects and rehabilitation needs, refer to the Danish Health Authority's publications " Opfølgningsprogram for hoved- og halskræft 2015" and "Pakkeforløb for hoved- og halskræft", and the Danish Multidisciplinary Cancer Groups' "Tværgående retningslinjer for senfølger efter kræft og kræftbehandling"(157-159). Rehabilitation is planned as described in the section above, based on an individual needs assessment and ongoing follow-up of the described late effects. Additionally, non-specific needs should be assessed for potential intervention. Interventions are targeted based on professional judgment following the individual needs assessment.
The primary responsibility for rehabilitation lies with the municipalities, while the responsibility for palliative care depends on the nature of the intervention. The hospital is responsible for rehabilitation and palliation if the patient requires diagnosis-specific rehabilitation that necessitates a specialist (see the Danish Health Authority's "Program for Rehabilitation and Palliation in Connection with Cancer, 1028; pp. 34-36"). It is the responsibility of the hospitals/treating departments to refer the patient to municipal rehabilitation. Several forms can be used for patient needs assessment, such as the PCI (Patient Concern Inventory), which has been translated and tested on the Danish population, revealing more "unmet needs" than standard follow-up.

Psychosocial care: (e.g. counseling or support groups) should be offered to address depression, anxiety, body image, or social isolation, which are common in head/neck cancer survivors(155).

Dental Rehabilitation: After surgery and/or radiotherapy for head and neck cancer, patients may be eligible for subsidies for dental treatment. Refer to the Danish Health Authority's guidelines in their brochure "Tilskud til tandbehandling" (2019)(160). The brochure only covers patients who have received chemotherapy and/or radiotherapy. If teeth are removed as part of the surgical treatment, the patient is only eligible for dental rehabilitation in the public sector if bone surgery is performed simultaneously with tooth removal. If teeth are

removed solely during surgery, the patient is not entitled to public dental rehabilitation and must pay for it themselves. However, practices may vary between regions.

Salvage

36. Salvage opportunities are discussed under multidisciplinary auspices and may include surgery, radiotherapy, chemotherapy, and immune therapy (D).

Approach to salvage therapy

There is limited knowledge regarding salvage therapy for patients with head and neck squamous cell carcinoma of unknown primary. A Danish study explored the effectiveness of the primary treatment strategies as outlined in the 2013 national guideline and included the effects of salvage. The study revealed acceptable long-term outcome in patients treated with definitive neck dissection, interpreted by the authors as an indication that salvage of primary tumors could be looked upon as a deferred part of the primary treatment. Thus, primary treatment, follow-up and salvage are closely related in head and neck cancer of unknown primary. A dose planning study comparing the ΔNTCP for proton versus photons concluded that re-irradiation for emerging primaries might be a suitable indication for intensity modulated proton therapy, as it may minimize the accumulated high dose volumes(161).

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5. Method

The development of these guidelines was initiated through two interdisciplinary meetings with nationwide participation. The first meeting was held in 2022, during which a dedicated working group was appointed under the auspices of DAHANCA to lead the guideline development process. These meetings were facilitated by the guideline lead, Thomas Kjærgaard, who also conducted a Delphi analysis to support the consensus-building process.

Consensus was reached on the overall framework and direction of the guidelines during these meetings. However, it quickly became evident that there was a lack of robust evidence—particularly Danish data—to support several of the clinically reasonable choices being considered. As a result, a series of research projects were undertaken, primarily based on data from the DAHANCA database. These studies focused on the period following the publication of the previous guidelines and were structured as phase IV studies, evaluating the real-world effectiveness of the former recommendations.

The insights gained from this research, combined with other contemporary national and international evidence, have been used to inform and substantiate the present guideline. The aim has been to provide a clinically relevant and evidence-based framework for the diagnosis and treatment of a heterogeneous disease entity.

Literature search

Because terminology and definitions in this field are heterogeneous, we used a structured multi-database search strategy to balance sensitivity and precision. Searches were conducted in PubMed, Embase, and Scopus. The initial search was performed in December 2021 with no lower date limit, and searches were updated at intervals, most recently in October 2025, to ensure inclusion of new evidence. Language filters allowed publications in English, Danish, German, and other Nordic languages.
Search strategies combined controlled vocabulary (MeSH/Emtree) with free-text terms spanning both diagnostic work-up and treatment of the condition, covering patients with clinical HNSCCUP as well as true HNSCCUP. In Scopus, proximity operators linked head and neck cancer terms with descriptors for unknown or occult primary tumours, SCC histology, and diagnostic and therapeutic interventions (e.g., imaging modalities, endoscopic and transoral techniques, tonsillectomy, tongue-base procedures, fine-needle biopsy, and oncologic treatments). In PubMed, MeSH terms were integrated with Title/Abstract terms reflecting the same domains. Reference lists of key papers were screened, and recognised national experts were consulted to minimise the risk of missing essential studies.

Literature review

All records were screened using predefined criteria focusing on relevance to diagnostic evaluation and therapeutic management in patients with suspected or confirmed HNSCCUP, methodological quality, and clinical applicability. We included original quantitative studies providing data that informed either evaluation or treatment pathways. Publications with very small samples, insufficient methodological reporting, or limited transferability were excluded, as were non-peer-reviewed materials.

Eligible full texts underwent critical appraisal regarding study design, risk of bias, and applicability. Evidence was graded using the Oxford Centre for Evidence-Based Medicine (OCEBM) Levels of Evidence (1–5), which formed the basis for assigning recommendation strength (A–D).

Formulation of the recommendations

Recommendations were developed by integrating the OCEBM-graded evidence with structured expert consensus. Each recommendation received a strength grade (A–D) consistent with the underlying evidence and its reliability, using more directive wording for Grades A–B and more qualified language for Grades C–D. Draft recommendations and their proposed grades were refined through iterative discussion, including a Delphi process, to ensure coherence between evidence level, recommendation strength, and clinical applicability.

Stakeholder involvement

Patients or patient representatives were not formally involved in the development of this guideline (e.g. through participation in the steering committee or structured consultation processes). However, patient perspectives have been actively considered throughout the guideline development based on the multidisciplinary group's extensive clinical experience and continuous interaction with patients in routine clinical practice.

In particular, the guideline development has taken into account patient-reported concerns commonly expressed by patients with cHNSCCUP and tHNSCCUP, notably the uncertainty related to the underlying diagnosis, the true anatomical origin of the disease, and the implications of diagnostic findings for subsequent treatment. The recommendations reflect a balance between patients' expressed need for a timely diagnostic clarification and their equally important wish for diagnostic accuracy, in order to avoid both diagnostic delay and unnecessary or excessive treatment.

Furthermore, attention has been paid to patients' concerns regarding receiving treatment that is appropriately targeted to sites with confirmed malignancy, while minimizing exposure of non-involved tissues. These considerations have informed the diagnostic and therapeutic pathways outlined in the guideline.

Hearing

The draft guideline was circulated for hearing among clinicians and stakeholders affiliated with DAHANCA through the DAHANCA mailing list, thereby providing all relevant parties with an interest in head and neck cancer the opportunity to review the guideline and submit comments. Feedback received during the hearing was considered by the guideline development group and incorporated into the final version where appropriate.

Approval

Content approval:

The guideline was formally approved by the DAHANCA group. The approval reflects consensus within the multidisciplinary cancer group and was obtained with representation from relevant professional groups, including otorhinolaryngologists, head and neck–specialized oncologists, nuclear medicine physicians, radiologists, pathologists, and patient representatives.

Administrative approval:
08.05.2026

Recommendations that entail significant additional costs

The recommendations are not expected to entail significant additional costs requiring management-level assessment. They primarily represent an optimization and streamlining of the diagnostic work-up based on existing clinical experience. Transoral robotic surgery is already integrated into parts of head and neck oncology and is therefore not considered an additional cost. Improved diagnostic precision is expected to enable identification of more primary tumors, allowing for more targeted treatment and potentially reducing overtreatment and treatment-related toxicity.

Need for further research

There is a lack of controlled studies addressing the diagnosis and treatment of HNSCCUP, which limits the ability to conduct systematic reviews and draw evidence-based conclusions.

Authors and conflicts of interest

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For detailed cooperative relationships, please refer to the declaration via the Danish Medicines Agency's website: List of proprietary pharmacists, doctors, nurses, dentists, proprietary pharmacists and prescribing pharmacists who have a relationship with a company

Plan for revision

The DAHANCA group is responsible for revision of the guideline. A formal revision process will be initiated no later than 01 January 2029 and will include updated literature searches and review of the available evidence in relevant areas. In addition, the guideline will be subject to ongoing updates based on emerging evidence and new literature within the field, with adjustments made as appropriate to maintain clinical relevance and validity.

Version of guideline template

The guideline has been developed in the 3.0 version of the template.

6. Monitoring

Standards and indicators

Development of quality in this area is supported by knowledge from DAHANCA under the auspices of the Danish Healthcare Quality Institute (SundK), as the indicators in the database must illuminate relevant clinical guidelines.

The clinical quality database's steering group has the mandate to decide on the database's indicator set, including which specific processes and results are monitored in the database.

Diagnostic hit-rates, overall survival, emerging primaries, loco-regional recurrence, disease-specific survival.

Plan for audit and feedback

Minor revision of the guidelines is planned every second year from the publication date.

7. Appendices

Appendix 1 – Search protocol

A specific search string cannot be provided, as the relevant literature was not retrieved through conventional database searches, but rather identified through extensive review and critical appraisal of available sources.

Appendix 2 – Table 1

Table 1. TNM classification of true head and neck squamous cell carcinoma of unknown primary

7th edition*		8th edition^	
Primary tumor (T)			
T0	No evidence of primary tumor	T0	No evidence of primary tumor
Regional lymph nodes (N)			
Classification regardless of EBV and HPV/p16 status		EBV or HPV/p16 negative or unknown	
N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension	N1	Metastasis in a single ipsilateral lymph node, 3 cm or less in greatest dimension
N2	Metastasis as described below:	N2	Metastasis as described below:
N2a	Metastasis in a single ipsilateral lymph node, more than 3 cm but not 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 without extranodal extension
N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension	N2b	Metastasis in multiple ipsilateral lymph nodes, none more than 6 cm in greatest dimension, without extranodal extension
N2c	Metastasis in bilateral or contralateral 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, without extranodal extension
N3	Metastasis in a lymph node more than 6 cm in greatest dimension	N3a	Metastasis in a lymph node more than 6 cm in greatest dimension without extranodal extension
		N3b	Metastasis in a single or multiple lymph nodes with clinical extranodal extension[¤]
Note: Midline nodes are considered ipsilateral nodes.		HPV/p16 positive	
		N1	Unilateral metastasis, in cervical lymph node(s), all 6cm or less in greatest dimension
		N2	Contralateral or bilateral metastasis in cervical lymph node(s), all 6 cm or less in greatest dimension
		N3	Metastasis in cervical lymph node(s) greater than 6cm in dimension
		EBV positive	
		N1	Unilateral metastasis, in cervical lymph node(s), and/or unilateral or bilateral metastasis in retropharyngeal lymph nodes, 6 cm or less in greatest dimension, above the caudal border of cricoid cartilage
		N2	Bilateral metastasis in cervical lymph node(s), 6 cm or less in greatest dimension, above the caudal border of cricoid cartilage.
		N3	Metastasis in cervical lymph node(s) greater than 6 cm in dimension and/or extension below the caudal border of cricoid cartilage.
Distant metastases (M)			
M0	No distant metastases	M0	No distant metastases
M1	Distant metastases	M1	Distant metastases

*7th edition: Typically, the classification for oropharyngeal cancers was applied in the lack of a specific classification of HNSCCUP.
^8th edition: A specific classification of HNSCCUP was added to this edition of the classification. According to this "There should be histological confirmation of squamous cell carcinoma with lymph node metastases but without an identified primary carcinoma". Histological methods should be used to identify EBV and HPV/p16-related tumors. If there is evidence of EBV, the nasopharyngeal classification is applied. If there is evidence of HPV and positive immunohistochemistry p16 overexpression, the p16-positive oropharyngeal classification is applied".
Abbreviations: UICC: Union for International Cancer Control

Appendix 3 – Table 2

Table 2. Drainage patterns	
Lymph node level	Possible primary cancer site and efferent lymphatics
I (Ia and Ib)	Ia: floor of mouth, anterior tongue, anterior mandibular alveolar ridge, lower lip. Ib: oral cavity, lips, anterior nasal cavity, hard and soft palate, maxillary and mandibular alveolar ridges, cheeks, upper and lower, anterior tongue, submandibular gland, submental lymph nodes (Ia).
II	Nasal cavity, oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, and major salivary glands. Efferents from face, parotid gland, autitory canal, submandibular, submental and retropharyngeal nodes. Level IIb (posteriorly to the posterior edge of internal jugular vein) more likely oropharynx or nasopharynx, and less likely oral cavity, larynx and hypopharynx.
III	Oral cavity, nasopharynx, oropharynx, hypopharynx, larynx, thyroid gland. Efferents from levels II and V, and retropharyngeal pretracheal and recurrent laryngeal nodes.
IV (IVa and IVb)	Hypopharynx, larynx, thyroid, trachea, cervical esophagus. Efferents from levels III and V, pretracheal nodes Rarely: anterior oral cavity with minimal or no proximal nodal disease.
V	Nasopharynx, oropharynx, thyroid gland, cutaneous posterior scalp. Efferents from occipital, retroauricular, parietal scalp, skin of lateral and posterior neck, shoulder, and infraclavicular structures.
VI	Lower lip, oral cavity (floor of mouth and tip of tongue), thyroid gland, glottic and subglottic larynx, piriform sinus, and cervical esophagus. Cutis and subcutis of lower face and anterior neck.

Drainage pattern and possible primary tumor site, modified from Grégoire et al (2014); *Delineation of the neck node levels for head and neck tumors: a 2013 update. DAHANCA, EORTC, HKNPCSG, NCIC CTG, NCRI, RTOG, TROG consensus guidelines*. The table is simplified by omitting subdivision into all sublevels as stated in the article. Likewise, not all lymph node levels are included. The table can serve as a guide in the diagnostic process. It indicates possible primary sites to investigate based on known lymph node involvement. Therefore, it can be used right after the initial examination of the patient with an ultrasound of the neck.

Appendix 4 – Table 3

Table 3. Overview over systematic reviews of transoral robotic surgery in HNSCCUP

Author (year)	Search period	No. of patient/studies	Country/ state	Detection-rate (%) (TORS)	Other main findings
Fu (2016) (162)	Inception to 2015	139/8	Canada	67%	- In 49/60 identified primaries, tumor site specified; 94% ipsilateral BOT; 6% contralateral BOT.
Meccariello (2019) (87)	Inception to 2015	349/12	Italy	71% (range 53;90)	- Positive margins: 23% (range15;49) - Rate of HPV+ PT: 75% (249/334) - BOT main site of PT - Positive correlation between HPV status and detection of PT. - HPV infection not related to primary tumor.
Farooq (2019)(68)	Inception to 2018	566/21	UK, Canada, Switzerland, USA	78% (95% CI 41-92) HPV+: 75%	- Hit-rate TORS: 74% (95% CI 68;79) - Hit-rate TLM: 91% (95% CI 85;98) - Hit-rate by TBM: 53% (95% CI 43;63) - Hit-rate in patients with negative CT/MRI, PET/CT, EUA and tonsillectomy pre-TORS: 78% (95% CI 41;92) (on the basis of 3 studies) - Pooled proportion 78% (95% CI 72;84) (=total lingual and palatine tonsils).
van Weert (2020)(86)	2013-2018	274/12	The Netherlands	72% (range 17;90)	- Negative margins achieved in 60% (range 0;85)
Al-Iami (2022)(66)	Inception to 2020	777 (30 studies)	UK	HPV+: 82% (178/216) HPV-: 12% (7/59)	- Hit-rate TORS: 60% (95% CI 49;70) - Hit-rate TLM: 80% (95% CI 0.6;1.0) - Hit-rate TOEC: 41% (95% CI 0.05, 0.8)

Appendix 5 – Table 4

Table 4. Studies on definitive neck dissection

REFERENCE FIRST AUTHOR (YEAR)	STUDY PERIOD ORIGIN	NO. (SURGERY-ONLY/TOTAL CURATIVE)	DESIGN; METHODS, COMPARISON	RESULTS
Jesse (1973)(163)	1948-1968 MD Anderson Hospital	104/210	Histology; SCC (62%), UDC (28%), glandular carcinoma (red. ADC) (10%). N-stages by treatment category presented in bar-chart: Surgery (n=104); 36% Nx, 8% N1, 22% N2, 33% N3 (estimated from bar chart)	LF rate: 18 % (fail any time, min. 3-yr FU) RF rate ipsilat. neck: 13% (Nx-1) 32% (N2-3) RF rate contralat. neck: (16/97) 16% 3-yr DFS in surgically treated: Nx (79%), N1 (67%), N2 (45%), N3 (38%) all surgically treated (57%) NB. Not possible to distinguish histological types in the results section. Also, a high rate of Nx limits applicability of results.
DeSanto (1985)(164)	1970-1980 Mayo Clinic	41	Comparative, retrospective; surgery-only (n=15) vs. bilateral neck and mucosal PORT (n=18), pre-operative RT (n=8).	Surgery only (n=15, low grade, fewer with advanced disease and 27% with N0 disease). LF rate: 0% (FU range 3-13 years). 5-yr OS 72% and cause-specific survival 74%. Note: It is important to point out that the literature at the time was very diverse, as many included, for example, subclavian lymph node metastases and different histology, which result in a significantly worse prognosis.
Coster (1992)(131)	1965-1987 Mayo Clinic	24 (curative surgery)	Retrospective cohort study. 100% SCC. AJCC1988: N1 (n=14), N2a (n=6), N2b (n=3), N3 (n=1). FU 8.5 years (range 3.3-20 years). Endpoints: recurrence within dissected neck, contralateral metastases in dissected neck, emerging primary in H&N region, loco-regional control, cause-specific survival and OS.	LF rate: 3/24 (13%) (1 within 5-yrs FU; 1.5 years, larynx). The other two after +9.5 yrs (both larynx). RF ipsilat. neck: 6/24 (25%) 5 of which with ECE. Only 1 received salvage. RF contralat. neck: 2 pts DF: 1 patient with N1 + ECE (3.3 months) NB: one of three mentioned in 2013 Danish guidelines, forming the evidence base for definitive ND as treatment option in N1 -pENE.

Jakobsen (1992)(165)	1975-1986	12/37 (22 curatively treated)	12 patients received surgery only. Unfortunately, only 8 were epidermoid carcinoma (=SCC), 2 adenocarcinoma and 2 anaplastic carcinomas in the surgery only group.	Outcome only presented for the whole population and graphically stratified by N-stage. NB: one of three (Jakobsen 1992, Coster (1992)(131) and Nguyen (1994)(166) (last mentioned included only one patient treated with definitive ND)) mentioned in 2013 Danish guidelines, forming the evidence base for definitive ND as treatment option in N1 -pENE.
Wang (1990)(130)	1953-1988 MDACC, Houston	57 /157 (surgery only/entire cohort)	Single centre, retrospective cohort study. 36% (n=57) receiving primary surgery. Note a high proportion of clinical Nx. By AJCC1980: Nx (38%), N1 (14%), N2a (13%), N2b (9%), N3a (15%) and N3b (11%).	Entire cohort: 5-yr OS 55%, DSS 76%. 5-yr actuarial DSS in treatment groups; surgery, RT, combined: 86%, 74%, 63%. RF rate: 11% for surgery only, 9% for RT and 20% in the combined group (PORT).
Grau (2000)(3)	1975-1995	23/273	National observational, historical cohort. Comparing actuarial estimates of being free of emerging primary in head and neck; surgery (n=23) vs. RT neck vs. unilateral neck RT (n=26) + mucosa (n=224). Surgery alone = either lymph node excision or modified radical neck dissection (not further specified). UICC87: N1 (n=9), N2 (n= 2), N2a (n=8), N2b (n = 2), N2c (n=1), Nx (n=1)	5-yr/10-yr free of emerging primary estimates; 46/46% (surgery), 77/77% (unilat. neck RT), 87/75% (bilat. neck RT+mucosa). 5-yr actuarial probabilities; Neck control: 58% Mucosal control (H&N):46% Loco-regional control: 29% Cause-specific survival: 76% Overall survival: 65% Patients treated with surgery alone not included in cox proportional hazards analysis (univariate) with death from any cause as endpoint.
Iganej (2002)(167)	1969-1994	29 ND (+12 excisional biopsy) /106	Total 106 HNSCCUP patients; excisional biopsy (n=12), definitive ND (n=29), primary RT (n=24), excisional biopsy plus RT (n=15) and PORT (n=26).	LR tumor control of definitive surgery i.e. ND/excisional biopsy (incl. salvage, definitive surgery): 81% ultimate LR tumor control for N1-N2a.
Lou J (2015)(123)	2001-2012 Zhejiang Cancer Hospital, China	46/133 (intention of treatment unknown)	Single center cohort study. Not reported whether only curative/palliative intention of treatment. 7 N1; 5 N2a; 30 N2b; 3 N2c; 1 N3	Emerging primary sites in surgery only group: nasopharynx (n=6), hypopharynx (n=6), oropharynx (n=3), larynx (n=3).

Mizuta (2018)(129)	2006-2015	27/80	Retrospective; 12 centres in Japan. Surgery only (AJCC, 7th ed.); N1 (n=9), N2a (n=6), N2b (n=11), N2c(n=1).	3-yr OS 72.5%, DSS 80.3%. No patients in the N1-N2a developed distant metastasis or died of HNSCCUP within 3 years (i.e. 3-yr DSS of 100%). All patients with N1-N2a treated with ND only (n=15) were alive without local failure at 3 yrs. 20% of the 15 patients developed ipsilateral nodal failure; all cured by salvage. Six patients in the ND only group developed an emerging primary; all underwent salvage therapy, of which 4 with RT; all obtained local disease-free status.
Axelsson (2020)(7)	2008-2012	7/216 (7 curative primary surgery/total curative)	Patients allocated to surgery: Patients that refused (C)RT or judged not to withstand postoperative RT (NB potential selectionbias). Median age 84 (66–89) years. Comparing OS between 3 treatment groups; primary surgery, PORT-(C) and primary (C)RT. HPV-/p16-status available in 44% of patients.	HR univariate analysis; 3.07 (1.20–7.87) and HR, multivariate analysis 0.63 (0.20–1.97) with PORT(C) as comparator. OBS; the subgroup analysis is not reliable due to the small number of patients treated with definitive ND. Also, the results are most likely subject to selection bias (patients refusing (C)RT or weak physical condition).

8. About this clinical guideline

This clinical practice guideline is developed in collaboration between the Danish Multidisciplinary Cancer Groups (DMCG.dk) and the Danish Healthcare Quality Institute (SundK). The development is part of an intensified guideline effort launched in relation to the National Cancer Plan IV. The aim is to support high-quality cancer care across the Danish healthcare system. The guideline content is approved by the disease-specific Multidisciplinary Cancer Group, whereas the format is approved by the Center for Clinical Practice Guidelines | Cancer. Further information about clinical practice guidelines concerning cancer treatment in Denmark can be found here: www.dmcg.dk/kliniske-retningslinjer

The guideline targets clinically active healthcare professionals in the Danish healthcare system and contains systematically developed statements that can be used as decision support by professionals and patients when deciding on appropriate and correct healthcare services in specific clinical situations.

Clinical practice guidelines concerning Danish cancer care is characterized as professional advice. The guidelines are not legally binding and professional judgment in the specific clinical context will always determine what the appropriate and correct medical care is. Adherence to the guideline recommendations is no guarantee for a successful outcome. Sometimes care corresponding to a lower level of evidence will be preferred due to the individual patient's situation.

The guideline includes, in addition to the central recommendations (chapter 1 – quick guide), a description of the basis for the recommendations – including the underlying evidence (chapter 3), references (chapter 4), and applied methods (chapter 5).
Recommendations marked A are based on the strongest evidence, while recommendations marked D are based on the weakest evidence. For further information on strength of evidence see the ”Oxford Centre for Evidence-Based Medicine Levels of Evidence and Grades of Recommendations**”,**
https://www.cebm.net/2009/06/oxford-centre-evidence-based-medicine-levels-evidence-march-2009/

The basis for the Oxford level grading in the present guideline is detailed below for each numbered section.

1 — Oxford level: 5 — A thorough history focusing on comorbidities and lymph node characteristics is considered general good clinical practice based on expert consensus rather than comparative evidence.
2 — Oxford level: 5 — Systematic ENT examination including flexible endoscopy is recommended by standard diagnostic practice, not by controlled studies comparing examination vs. no examination.
3 — Oxford level: 2a — Narrow Band Imaging (NBI) improves detection of the primary tumor, supported by a systematic review and meta-analysis of diagnostic studies.
4 — Oxford level: 5 — Routine neck ultrasound for lymph node assessment and staging is mainly supported by consensus practice; the referenced evidence is a study protocol rather than outcome data.
5 — Oxford level: 2b — Ultrasound-guided FNA with HPV-DNA testing is supported by observational diagnostic validation studies of HPV/p16 markers in cytology samples.

6 — Oxford level: 5 — Tailoring the diagnostic strategy according to clinical findings and suspected tumor origin reflects clinical consensus rather than specific primary studies.
7 — Oxford level: 2a — FDG-PET/CT increases primary tumor detection and identifies distant metastases; supported by systematic reviews and prospective multicenter diagnostic studies.
8 — Oxford level: 2b — MRI of the neck for detecting the primary tumor is supported by a diagnostic cohort study comparing MRI with PET/CT.
9 — Oxford level: 5 — Planning surgical diagnostic strategies in a multidisciplinary team reflects organizational consensus rather than evidence from comparative studies.
10 — Oxford level: 2b — Clinical predictors of the likely primary site (e.g., HPV status or nodal level) are derived from observational cohort studies analyzing metastatic patterns and biomarkers.
11 — Oxford level: 5 — A stepwise surgical diagnostic algorithm represents consensus-based clinical workflow guidance.
12 — Oxford level: 5 — Recommendation that surgical diagnostics be performed by a head-and-neck surgeon is an organizational/competence consensus statement.
13 — Oxford level: 4 — Evidence that targeted biopsies during endoscopy are superior to random biopsies mainly comes from retrospective series and heterogeneous observational studies.
14 — Oxford level: 5 — If a primary tumor is detected during endoscopy, management should follow existing disease-specific guidelines; this is a procedural statement rather than evidence-tested intervention.
15 — Oxford level: 2b — Bilateral tonsillectomy when endoscopy is negative is supported by retrospective comparative studies showing higher detection rates than deep biopsy alone.
16 — Oxford level: 4 — Nasopharyngeal biopsy in selected cases is supported mainly by observational and virological marker studies rather than direct comparative trials.
17 — Oxford level: 5 — Excision of the involved lymph node when the primary tumor remains unidentified is a consensus-based surgical recommendation.
18 — Oxford level: 2a — TORS base-of-tongue mucosectomy for HPV-associated CUP is supported by a large systematic review/meta-analysis, but heterogeneity of included studies lowers the confidence.
19 — Oxford level: 4 — Base-of-tongue mucosectomy in HPV-negative CUP is supported by small retrospective series with low detection rates.
20 — Oxford level: 2b — PCR-based HPV-DNA testing on FNA cytology is supported by prospective diagnostic evaluations and laboratory validation studies.
21 — Oxford level: 5 — Detailed pathological processing of biopsies (e.g., thin slicing or total embedding) is based on pathology practice standards and consensus.
22 — Oxford level: 5 — Standardized reporting of tumor size, margins, and depth in resection specimens reflects guideline-based pathology reporting standards.
23 — Oxford level: 5 — Histopathological evaluation of nodal metastases including HPV, EBV, and extranodal extension follows consensus-based staging and pathology standards.
24 — Oxford level: 2b — EBV testing for p16/HPV-negative non-keratinizing SCC metastases is supported by observational cross-sectional and laboratory studies linking viral markers to likely primary sites.
25 — Oxford level: 5 — Early treatment planning is a process recommendation based on clinical consensus rather than direct outcome comparisons.

26 — Oxford level: 2b — Volume-reduced radiotherapy for unilateral disease is supported by cohort and registry analyses (e.g., national database studies) rather than randomized trials.
27 — Oxford level: 2b — Selective neck dissection or reduced-volume radiotherapy for a single nodal metastasis ≤6 cm is supported by large retrospective cohorts and registry analyses.
28 — Oxford level: 2b — Reduced-volume radiotherapy with consideration of chemotherapy for multiple nodal metastases is supported mainly by observational cohort and registry data.
29 — Oxford level: 5 — Bilateral radiotherapy for bilateral nodal disease or N3 stage reflects consensus extrapolated from staging principles rather than comparative trials.
30 — Oxford level: 5 — EBV-associated CUP should be treated as nasopharyngeal cancer according to disease-specific guidelines, representing consensus practice.
31 — Oxford level: 5 — Response evaluation at 3 months using clinical examination and imaging (MRI/PET-CT) is guideline-based with heterogeneous supporting evidence.
32 — Oxford level: 5 — Follow-up frequency and duration after treatment are largely determined by guideline consensus rather than randomized studies.
33 — Oxford level: 5 — Evaluation of suspected recurrence with clinical examination, biopsy, and PET/CT follows standard guideline principles rather than CUP-specific comparative evidence.
34 — Oxford level: 4 — The concept of an “emerging primary” within five years is derived from observational follow-up data and classification arguments.
35 — Oxford level: 5 — Rehabilitation recommendations reflect general principles derived from observational toxicity and quality-of-life literature and expert consensus.
36 — Oxford level: 5 — Salvage treatment decisions (surgery, radiotherapy, chemotherapy, immunotherapy) are recommended to be made by an MDT due to limited comparative evidence across strategies.

This guideline also includes information on the target population (chapter 2) and the method of development (chapter 5) is also included in the guideline. See the table of contents for page references.

The guideline template has been prepared based on international quality requirements for the development of clinical guidelines as described by AGREE II, GRADE, and RIGHT.
For information on the Danish Health Authority’s cancer packages – descriptions of the entire standard patient pathway specifying requirements for timelines and content – refer to the relevant disease area at: https://www.sst.dk/en/english

The Danish Health Authority (National Cancer Plan IV) and the Danish Healthcare Quality Institute (SundK) funded the development of this clinical practice guideline.