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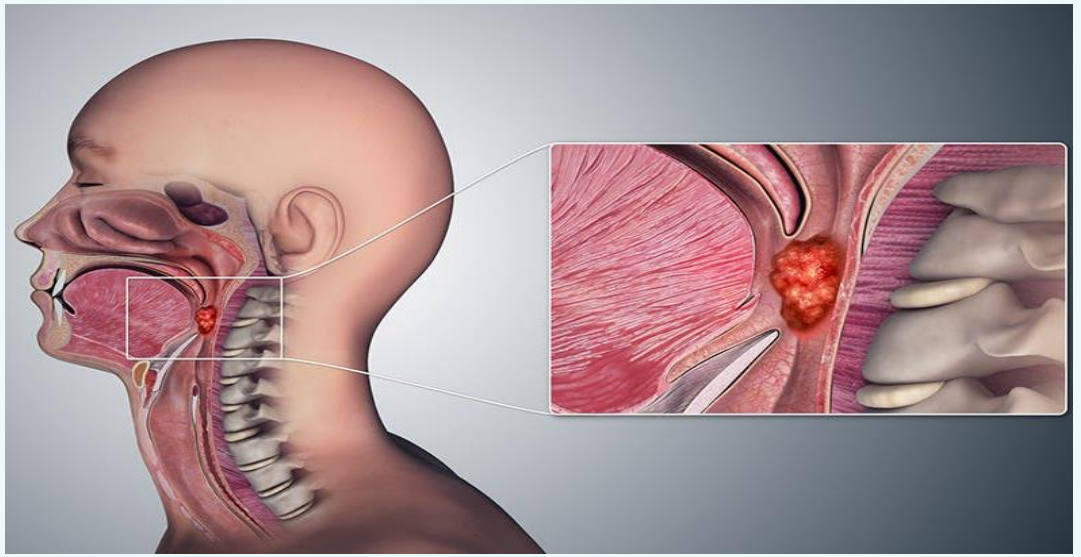


HPV related oropharyngeal squamous cell carcinoma

Dr Farshid Farhan

Outline

- What is HPV?
  - Epidemiology
  - Screening
  - Vaccination
- Diagnosis
- Staging
- Better prognosis is more for locoregional control than distant control.
  - *De-Escalation Strategys*

Traditional causes of H&N cancer

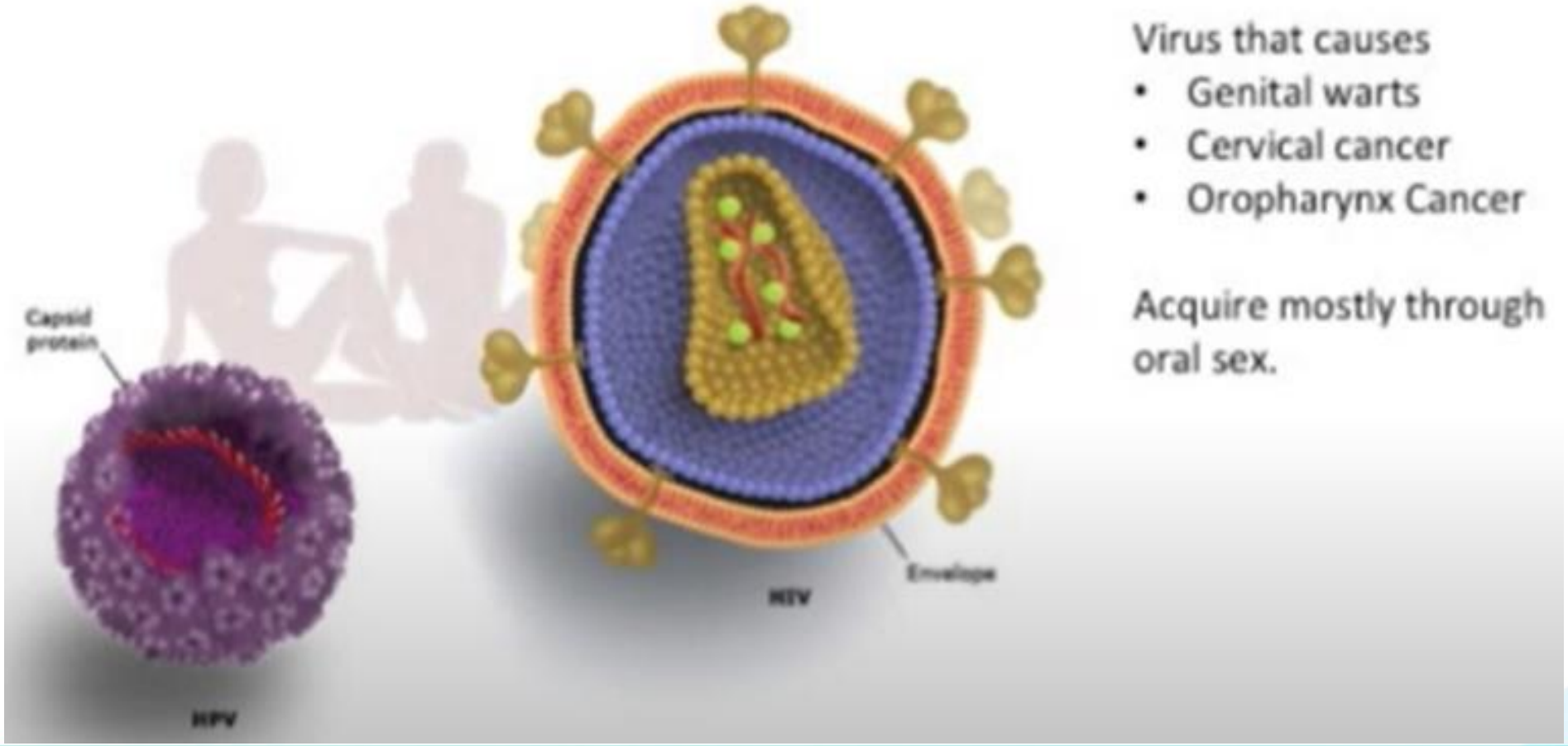
- Smoking
- Alcohol
- Betel nuts

Introduction

- With the global prevalence of HPV as a most common sexually transmitted infection, the incidence of HPV-associated head and neck squamous cell carcinoma (HNSCC), particularly oropharyngeal carcinoma, has dramatically increased over the past decades.

- Currently, HPV-associated oropharyngeal carcinoma accounts for 33% of all cases globally, with a highest prevalence reported in Lebanon (85%) and Sweden (70%).

HPV-associated head and neck squamous cell carcinoma (HNSCC)



Virus that causes

- Genital warts
- Cervical cancer
- Oropharynx Cancer

Acquire mostly through oral sex.

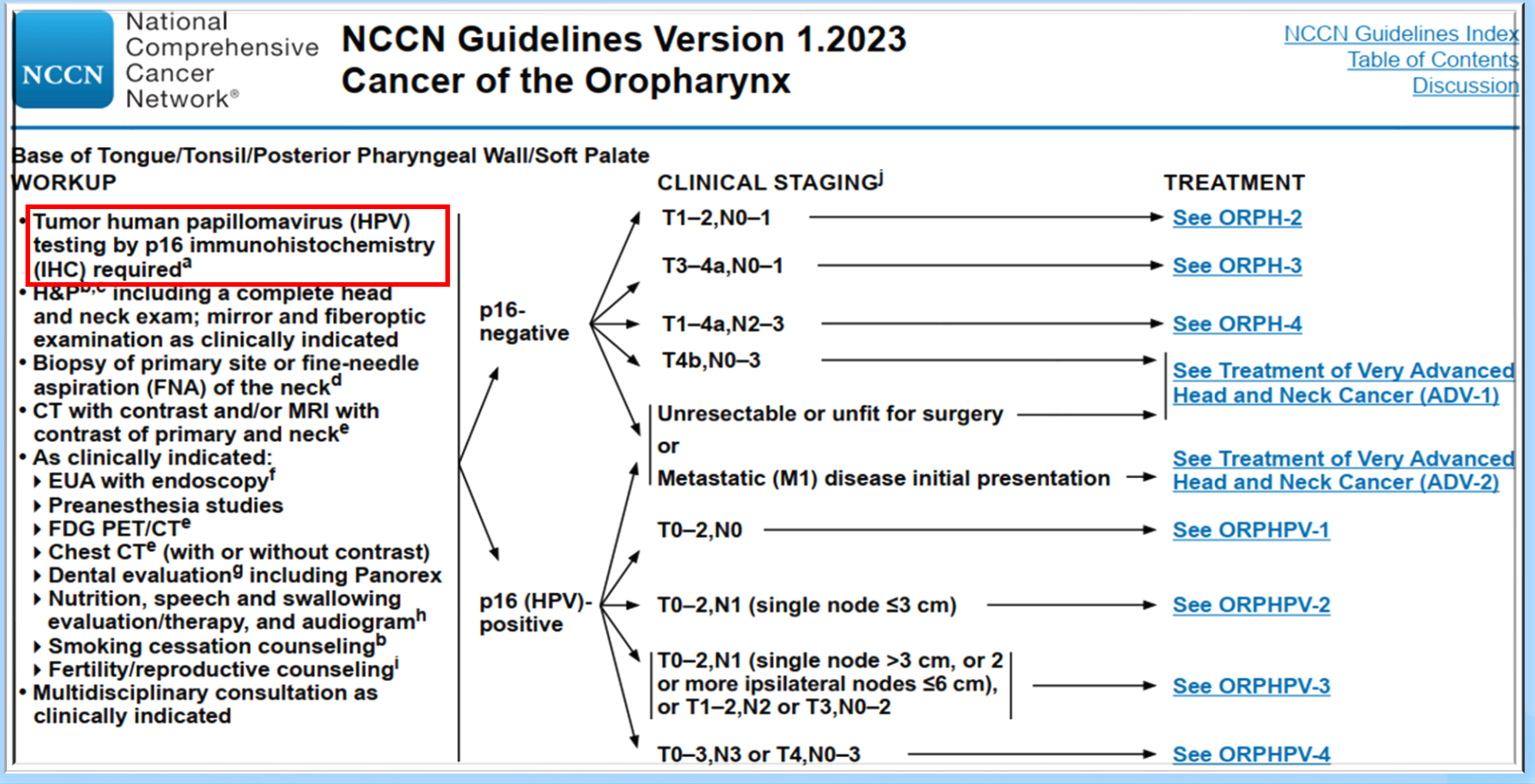
Features of HPV+ H&N cancer

- Location: Oropharynx
- Age: patients tend to be younger
- Gender: more men
- Less smoking
- Lower T stage, higher N stage
- Prognosis: better(highly curable cancers)
- *lower EGFR expression*
- Optimal treatment?

Introduction

- Seven weeks of treatment concurrent with chemotherapy has been the standard of care for H&N cancer for years.
- However, not all H&N cancers are the same.
- Patients with locoregionally confined HPV associated OPSCC typically have highly curable cancers and a better prognosis than those with non-HPV associated OPSCC.
- This favorable outcome was conceivably attributed to higher intrinsic sensitivity to radiation and chemotherapy , which prompted a plethora of strategies on treatment de-intensification to expand the therapeutic ratio in HPV-associated HNSCC.
- Research is looking into less toxic and just as effective treatment options **related to HPV infection**.

Should we routinely check for HPV infection?



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NCCN Guidelines Version 1.2023
Cancer of the Oropharynx

NCCN Guidelines Index
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Discussion

Base of Tongue/Tonsil/Posterior Pharyngeal Wall/Soft Palate

WORKUP

- Tumor human papillomavirus (HPV) testing by p16 immunohistochemistry (IHC) required[a]
- H&P[b,c] including a complete head and neck exam; mirror and fiberoptic examination as clinically indicated
- Biopsy of primary site or fine-needle aspiration (FNA) of the neck[d]
- CT with contrast and/or MRI with contrast of primary and neck[e]
- As clinically indicated:
  - EUA with endoscopy[f]
  - Preanesthesia studies
  - FDG PET/CT[e]
  - Chest CT[e] (with or without contrast)
  - Dental evaluation[g] including Panorex
  - Nutrition, speech and swallowing evaluation/therapy, and audiogram[h]
  - Smoking cessation counseling[b]
  - Fertility/reproductive counseling[i]
- Multidisciplinary consultation as clinically indicated

	CLINICAL STAGING[j]	TREATMENT
p16-negative	T1–2,N0–1	See ORPH-2
	T3–4a,N0–1	See ORPH-3
	T1–4a,N2–3	See ORPH-4
	T4b,N0–3	See Treatment of Very Advanced Head and Neck Cancer (ADV-1)
	Unresectable or unfit for surgery	See Treatment of Very Advanced Head and Neck Cancer (ADV-1)
	or Metastatic (M1) disease initial presentation	See Treatment of Very Advanced Head and Neck Cancer (ADV-2)
p16 (HPV)-positive	T0–2,N0	See ORPHPV-1
	T0–2,N1 (single node ≤3 cm)	See ORPHPV-2
	T0–2,N1 (single node >3 cm, or 2 or more ipsilateral nodes ≤6 cm), or T1–2,N2 or T3,N0–2	See ORPHPV-3
	T0–3,N3 or T4,N0–3	See ORPHPV-4

Staging

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Head and Neck Cancers

Table 3 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N)	
Clinical N (cN) - Oropharynx (p16-) and Hypopharynx	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* metastasis in any node(s) and clinically overt ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in any node(s) and clinically overt ENE(+)

Staging

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Head and Neck Cancers

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Table 3 — Continued
American Joint Committee on Cancer (AJCC)
TNM Staging System for the Oropharynx (p16-) and Hypopharynx (8th ed., 2017)
(Not included: P16-positive (p16+) oropharyngeal cancers and nasopharyngeal cancer)

Regional Lymph Nodes (N):

Pathological N (pN) - Oropharynx (p16-) and Hypopharynx

NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+) *or* larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); *or* metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); *or* in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); *or* a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastases in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastases in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); *or* in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); *or* a single contralateral node of any size and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); *or* multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+) *or* a single contralateral node of any size and ENE(+)

Note: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant Metastasis (M)

M0	No distant metastasis
M1	Distant metastasis

Histologic Grade (G)

GX	Grade cannot be assessed
G1	Well differentiated
G2	Moderately differentiated
G3	Poorly differentiated
G4	Undifferentiated

Prognostic Stage Groups

Stage 0	Tis	N0	M0
Stage I	T1	N0	M0
Stage II	T2	N0	M0
Stage III	T3	N0	M0
	T1	N1	M0
	T2	N1	M0
	T3	N1	M0
Stage IVA	T1	N2	M0
	T2	N2	M0
	T3	N2	M0
	T4a	N0,N1,N2	M0
Stage IVB	T4b	Any N	M0
	Any T	N3	M0
Stage IVC	Any T	Any N	M1

Staging

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Head and Neck Cancers

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Table 4
American Joint Committee on Cancer (AJCC)
TNM Staging System for HPV-Mediated (p16+) Oropharyngeal Cancer (8th ed., 2017)
(Not including: P16-negative (p16-) cancers of the oropharynx)

Primary Tumor (T)
T0 No primary identified
T1 Tumor 2 cm or smaller in greatest dimension
T2 Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3 Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4 Moderately advanced local disease
Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond*
Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional Lymph Nodes (N)
Clinical N (cN)
NX Regional lymph nodes cannot be assessed
N0 No regional lymph node metastasis
N1 One or more ipsilateral lymph nodes, none larger than 6 cm
N2 Contralateral or bilateral lymph nodes, none larger than 6 cm
N3 Lymph node(s) larger than 6 cm

Pathological N (pN)
NX Regional lymph nodes cannot be assessed
pN0 No regional lymph node metastasis
pN1 Metastasis in 4 or fewer lymph nodes
pN2 Metastasis in more than 4 lymph nodes

Distant Metastasis (M)
M0 No distant metastasis
M1 Distant metastasis

Histologic Grade (G)
No grading system exists for HPV-mediated oropharyngeal tumors

Prognostic Stage Groups

Clinical

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3	N0,N1,N2	M0
Stage III	T0,T1,T2,T3	N3	M0
	T4	N0,N1,N2,N3	M0
Stage IV	Any T	Any N	M1

Pathological

Stage I	T0,T1,T2	N0,N1	M0
Stage II	T0,T1,T2	N2	M0
	T3,T4	N0,N1	M0
Stage III	T3,T4	N2	M0
Stage IV	Any T	Any N	M1

Diagnosis of HPV-Associated Head and Neck Cancer

- standard tissue-based biopsies
  - needle biopsy of a neck lymph node or a tissue biopsy from the oropharynx
  - invasive and painful
  - Time consuming

- liquid biopsy
  - Blood samples for circulating tumor HPV DNA

- Liquid Biopsy Provides Accurate, Fast Dx of HPV-Associated Head and Neck Cancer
  - The sensitivity and specificity were 98.4% and 98.6%, respectively

- Circulating tumor HPV DNA-based approach also less expensive than standard biopsy

Treatment approaches to deintensification

- de-escalation strategies:
  - Radiation or surgical deintensification?
  - tailored systemic therapies, or
  - use of biomarkers or imaging

- How we select appropriate patients?

How we select appropriate patients for surgery?

❑<u>minimally invasive transoral surgery</u>

- patients with well-lateralized T1-T2 disease with no clinical or radiographic evidence of multiple or bilateral nodes or extranodal extension that appears amenable to margin-negative resection

❑<u>or more invasive surgical techniques</u> (eg, transmandibular or transcervical open surgery)

- patients who are not eligible for minimally invasive approaches,
- we avoid the use of more aggressive surgical approaches, as ***these patients can be treated effectively using RT with or without chemotherapy with superior functional outcomes and high cure rates.***
- Unilateral or bilateral RT?
  - ***Unilateral RT may be an appropriate strategy in patients with well-lateralized tonsillar tumors that do not invade >1 cm beyond the mucosa of the soft palate or tongue base and do not extend to the posterior pharyngeal wall***

How we select appropriate patients for surgery?

❑ **patients with early-stage (T1-T2) disease with a single involved node ≤3 cm**

- ✓nonsmoking patients without adverse features on clinical evaluation and high-quality imaging (eg, no evidence of extranodal extension),
  - ➢ *we offer RT alone.*
  - ➢ ORATOR study: a randomized phase II trial directly comparing RT versus surgery suggested similar survival and functional outcomes.

- ✓patients who are active smokers, or have certain high-risk features such as:
  - endophytic,
  - ulcerated primary tumor,
  - radiographic evidence of extranodal extension,
  - retropharyngeal, level IV or V LN involvement and
  - patients where these features cannot be determined accurately on imaging,
  - ➢ *we offer definitive chemoradiation.*

How we select appropriate patients for surgery?

- patients with locoregionally advanced disease (eg,
  - clinical/radiographic evidence of T3-4 disease or
  - any T stage with one node greater than 3 cm,
  - multiple involved nodes, or evidence of extranodal extension),

➢ *we suggest definitive chemoradiation alone* rather than surgery followed by adjuvant chemoradiation , as this approach offers both organ preservation and excellent oncologic outcomes

How we select appropriate patients for surgery?

- Choice of sensitizing agent with chemoradiation
  - patients with HPV associated tumors treated with concurrent chemoradiation, ***cisplatin-based chemotherapy is preferred over cetuximab***.
  - patients with HPV associated OPSCC who are not cisplatin-eligible, an alternative option is a concurrent carboplatin-based regimen.

✓ *The fact that HPV positive Oropharyngeal carcinomas have lower EGFR expression than HPV-negative carcinomas is a possible explanation for the lower effectiveness of the combination of radiotherapy and EGFR inhibition in HPV-positive tumors.* Reimers N, Kasper HU, Weissenborn SJ et al (2007) Combined analysis of HPV-DNA, p16 and EGFR expression to predict prognosis in oropharyngeal cancer. IntJCancer120:1731–1738

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomised, multicentre, non-inferiority trial

Background Patients with human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma have high survival when treated with radiotherapy plus cisplatin. Whether replacement of cisplatin with cetuximab—an antibody against the epidermal growth factor receptor—can preserve high survival and reduce treatment toxicity is unknown. We investigated whether cetuximab would maintain a high proportion of patient survival and reduce acute and late toxicity.

Methods RTOG 1016 was a randomised, multicentre, non-inferiority trial at 182 health-care centres in the USA and Canada. Eligibility criteria included histologically confirmed HPV-positive oropharyngeal carcinoma; American Joint Committee on Cancer 7th edition clinical categories T1–T2, N2a–N3 M0 or T3–T4, N0–N3 M0; Zubrod performance status 0 or 1; age at least 18 years; and adequate bone marrow, hepatic, and renal function. We randomly assigned patients (1:1) to receive either radiotherapy plus cetuximab or radiotherapy plus cisplatin. Randomisation was balanced by using randomly permuted blocks, and patients were stratified by T category (T1–T2 *vs* T3–T4), N category (N0–N2a *vs* N2b–N3), Zubrod performance status (0 *vs* 1), and tobacco smoking history (≤10 pack-years *vs* >10 pack-years). Patients were assigned to receive either intravenous cetuximab at a loading dose of 400 mg/m² 5–7 days before radiotherapy initiation, followed by cetuximab 250 mg/m² weekly for seven doses (total 2150 mg/m²), or cisplatin 100 mg/m² on days 1 and 22 of radiotherapy (total 200 mg/m²). All patients received accelerated intensity-modulated radiotherapy delivered at 70 Gy in 35 fractions over 6 weeks at six fractions per week (with two fractions given on one day, at least 6 h apart). The primary endpoint was overall survival, defined as time from randomisation to death from any cause, with non-inferiority margin 1·45. Primary analysis was based on the modified intention-to-treat approach, whereby all patients meeting eligibility criteria are included. This study is registered with ClinicalTrials.gov, number NCT01302834.

Findings Between June 9, 2011, and July 31, 2014, 987 patients were enrolled, of whom 849 were randomly assigned to receive radiotherapy plus cetuximab (n=425) or radiotherapy plus cisplatin (n=424). 399 patients assigned to receive cetuximab and 406 patients assigned to receive cisplatin were subsequently eligible. After median follow-up duration of 4·5 years, radiotherapy plus cetuximab did not meet the non-inferiority criteria for overall survival (hazard ratio [HR] 1·45, one-sided 95% upper CI 1·94; p=0·5056 for non-inferiority; one-sided log-rank p=0·0163). Estimated 5-year overall survival was 77·9% (95% CI 73·4–82·5) in the cetuximab group versus 84·6% (80·6–88·6) in the cisplatin group. Progression-free survival was significantly lower in the cetuximab group compared with the cisplatin group (HR 1·72, 95% CI 1·29–2·29; p=0·0002; 5-year progression-free survival 67·3%, 95% CI 62·4–72·2 *vs* 78·4%, 73·8–83·0), and locoregional failure was significantly higher in the cetuximab group compared with the cisplatin group (HR 2·05, 95% CI 1·35–3·10; 5-year proportions 17·3%, 95% CI 13·7–21·4 *vs* 9·9%, 6·9–13·6). Proportions of acute moderate to severe toxicity (77·4%, 95% CI 73·0–81·5 *vs* 81·7%, 77·5–85·3; p=0·1586) and late moderate to severe toxicity (16·5%, 95% CI 12·9–20·7 *vs* 20·4%, 16·4–24·8; p=0·1904) were similar between the cetuximab and cisplatin groups.

Interpretation For patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin. Radiotherapy plus cisplatin is the standard of care for eligible patients with HPV-positive oropharyngeal carcinoma.

- *For patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin.*
- *Radiotherapy plus cisplatin is the standard of care for eligible patients with HPV-positive oropharyngeal carcinoma.*

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): an open-label randomised controlled phase 3 trial

Background The incidence of human papillomavirus (HPV)-positive oropharyngeal cancer, a disease affecting younger patients, is rapidly increasing. Cetuximab, an epidermal growth factor receptor inhibitor, has been proposed for treatment de-escalation in this setting to reduce the toxicity of standard cisplatin treatment, but no randomised evidence exists for the efficacy of this strategy.

Methods We did an open-label randomised controlled phase 3 trial at 32 head and neck treatment centres in Ireland, the Netherlands, and the UK, in patients aged 18 years or older with HPV-positive low-risk oropharyngeal cancer (non-smokers or lifetime smokers with a smoking history of <10 pack-years). Eligible patients were randomly assigned (1:1) to receive, in addition to radiotherapy (70 Gy in 35 fractions), either intravenous cisplatin (100 mg/m² on days 1, 22, and 43 of radiotherapy) or intravenous cetuximab (400 mg/m² loading dose followed by seven weekly infusions of 250 mg/m²). The primary outcome was overall severe (grade 3–5) toxicity events at 24 months from the end of treatment. The primary outcome was assessed by intention-to-treat and per-protocol analyses. This trial is registered with the ISRCTN registry, number ISRCTN33522080.

Findings Between Nov 12, 2012, and Oct 1, 2016, 334 patients were recruited (166 in the cisplatin group and 168 in the cetuximab group). Overall (acute and late) severe (grade 3–5) toxicity did not differ significantly between treatment groups at 24 months (mean number of events per patient 4·8 [95% CI 4·2–5·4] with cisplatin *vs* 4·8 [4·2–5·4] with cetuximab; p=0·98). At 24 months, overall all-grade toxicity did not differ significantly either (mean number of events per patient 29·2 [95% CI 27·3–31·0] with cisplatin *vs* 30·1 [28·3–31·9] with cetuximab; p=0·49). However, there was a significant difference between cisplatin and cetuximab in 2-year overall survival (97·5% *vs* 89·4%, hazard ratio 5·0 [95% CI 1·7–14·7]; p=0·001) and 2-year recurrence (6·0% *vs* 16·1%, 3·4 [1·6–7·2]; p=0·0007).

Interpretation Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control. Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.

- *Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control.*
- *Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.*

Is there a role for treatment deintensification?

- Deintensification is an emerging treatment approach for patients with HPV associated oropharyngeal squamous cell carcinoma (OPSCC) that aims
  - to preserve superior oncologic outcomes
  - while minimizing treatment-related toxicity.

- encouraging results in various phase II trials conducted in both the ***definitive*** and ***adjuvant*** settings

Is there a role for treatment deintensification?

- different approaches have been studied
  - surgical resection,
  - a lower dose of adjuvant RT,
  - induction chemotherapy to de-escalate definitive RT dosing,
  - dose-reduced definitive RT alone, or
  - substitution of a potentially less toxic drug than cisplatin

Is there a role for treatment deintensification?

- **<u>Surgical resection,</u>**
- One randomized phase II trial (ORATOR) comparing surgery versus definitive RT in patients with HPV associated OPSCC suggested similar survival and functional outcomes.

- 68 patients with mostly HPV related (88 percent, T1-2N0-2, with nodal disease ≤4 cm) resectable disease were randomly assigned to initial treatment with either definitive RT (70 Gy) or transoral robotic surgery (TORS) plus elective neck dissection

- among those treated with TORS in this study, a majority still received full-dose adjuvant RT (71 percent) for intermediate- to high-risk pathologic features, so whether TORS could effectively allow for overall deintensification remains unclear.

Is there a role for treatment deintensification?

- **<u>A lower dose of adjuvant RT,</u>**
- Is there clinical benefit from standard adjuvant therapy in the presence of high-risk pathologic findings on postoperative pathology?
- randomized phase II trial (**<u>ECOG 3311</u>**) of 519 patients
  - ❑**low-risk disease:** negative margins [>3 mm], no nodes or one node without extranodal extension and no perineural invasion or lymphovascular invasion
  - ❑**intermediate-risk disease:** close margins [<3 mm], two to four positive nodes or a single node >3 cm and ≤6 cm, extranodal extension ≤1 mm, or perineural/lymphovascular invasion
  - ❑**high-risk disease** (eg, positive margins, five or more positive nodes, one node >6 cm, or extranodal extension >1 mm

➢ These trial support the potential use of

➢ *TORS alone in surgically eligible patients with low-risk disease and*

➢ *TORS plus deintensified adjuvant RT (ie, 50 Gy) in those with intermediate-risk disease.*

Is there a role for treatment deintensification?

- **Dose-reduced definitive RT alone,**
- randomized phase II trial (ORATOR-2) of 61 patients with HPV associated OPSCC compared dose-reduced definitive radiation (60 Gy of RT given concurrently with weekly cisplatin) with TORS plus neck dissection and dose-reduced adjuvant RT
  - compared with TORS plus dose-reduced adjuvant RT, dose-reduced definitive RT improved two-year OS (100 versus 89 percent) and PFS (100 versus 84 percent).
  - the trial was closed early due to two treatment-related deaths from TORS (one oropharyngeal bleed and one cervical osteomyelitis following adjuvant RT)

Is there a role for treatment deintensification?

- **Radiation versus chemoradiation** In a phase II trial (NRG-HN002), 306 patients with seventh edition AJCC stage III or locoregionally advanced stage IV OPSCC were randomly assigned to either

❑dose-reduced accelerated RT alone (60 Gy in five weeks) or

❑dose-reduced RT (60 Gy in six weeks) administered concurrently with weekly cisplatin (40 mg/m^2).

➢RT alone had similar PFS (two-year PFS 88 and 91 percent) and OS (two-year OS 97 percent each), but ***higher rates of locoregional failure at two years*** (10 versus 3 percent).

Is there a role for treatment deintensification?

- **<u>Dose-reduced chemosensitizing agent with radiation</u>**
- single-arm, nonrandomized phase II trial, 114 patients with seventh edition AJCC stage I to IVA (T0 to T3, N0 to N2, clinical M0) were treated with definitive RT (60 Gy over six weeks) with or without concurrent weekly cisplatin at a reduced dose of 30 mg/m^2 for six doses.

➢Data suggest that a subset of patients with low-volume, low-risk HPV associated OPSCC may have good disease control

Is there a role for treatment deintensification?

- **<u>Induction chemotherapy</u>**
- **ECOG 1308,** Phase II Trial of Induction Chemotherapy(IC) Followed by Reduced-Dose Radiation
  - For IC responders, reduced-dose IMRT with concurrent cetuximab is worthy of further study
- **UCLA/UC-Davis study**
- **OPTIMA,** a phase II dose and volume de-escalation

➢Given the toxicities, it is unknown to what extent induction chemotherapy constitutes deintensified treatment.

➢Further data are needed to determine the optimal induction regimen, dosing of RT, and concurrent chemosensitizing agent regimen.

Evaluation of Substantial Reduction in Elective Radiotherapy Dose and Field in Patients With Human Papillomavirus–Associated Oropharyngeal Carcinoma Treated With Definitive Chemoradiotherapy, Nancy Y. Lee,

JAMA Oncol. 2022;8(3):364-372. doi:10.1001/jamaoncol.2021.6416

- This retrospective cohort study included 276 consecutive patients with HPV-positive OPC receiving CCRT
- About a third had cT3-cT4 disease, 23.5% had cN2-cN3 disease
- 62.3% completed 300-mg/m^2 high-dose cisplatin therapy
- Interventions
  - ❑lower dose of elective nodal radiotherapy delivered to smaller field,
  - ❑while sparing selected negative neck, retropharyngeal, level Ib, and level V nodal basins.
  - ❑reduced radiotherapy volume and dose of 30 Gy to the elective treatment regions over 15 fractions, followed by a cone down of 40 Gy in 20 fractions to gross disease for a total dose of 70 Gy

De-Escalation Strategy Appears Feasible in HPV+ Oropharyngeal Cancer, Nancy Y. Lee

- de-escalation strategy was associated with:
  - 24-month locoregional control rate of 97.0%,
  - progression-free survival, 88.0%
  - distant metastasis-free survival of 95.2%, and
  - overall survival of 95.1%

- *This cohort study found that the evaluated de-escalation strategy for elective regions showed favorable clinical outcomes and QOL profiles.*

- *Long-term follow-up data will help affirm the efficacy of this strategy as a care option for treating HPV-associated OPC with primary CCRT.*

Treatment de-escalation for HPV+ oropharyngeal cancer: A systematic review and meta-analysis

Fausto Petrelli MD, Andrea Luciani MD, Antonio Ghidini MD, Sara Cherri MD, Paolo Gamba
https://doi.org/10.1002/hed.27019

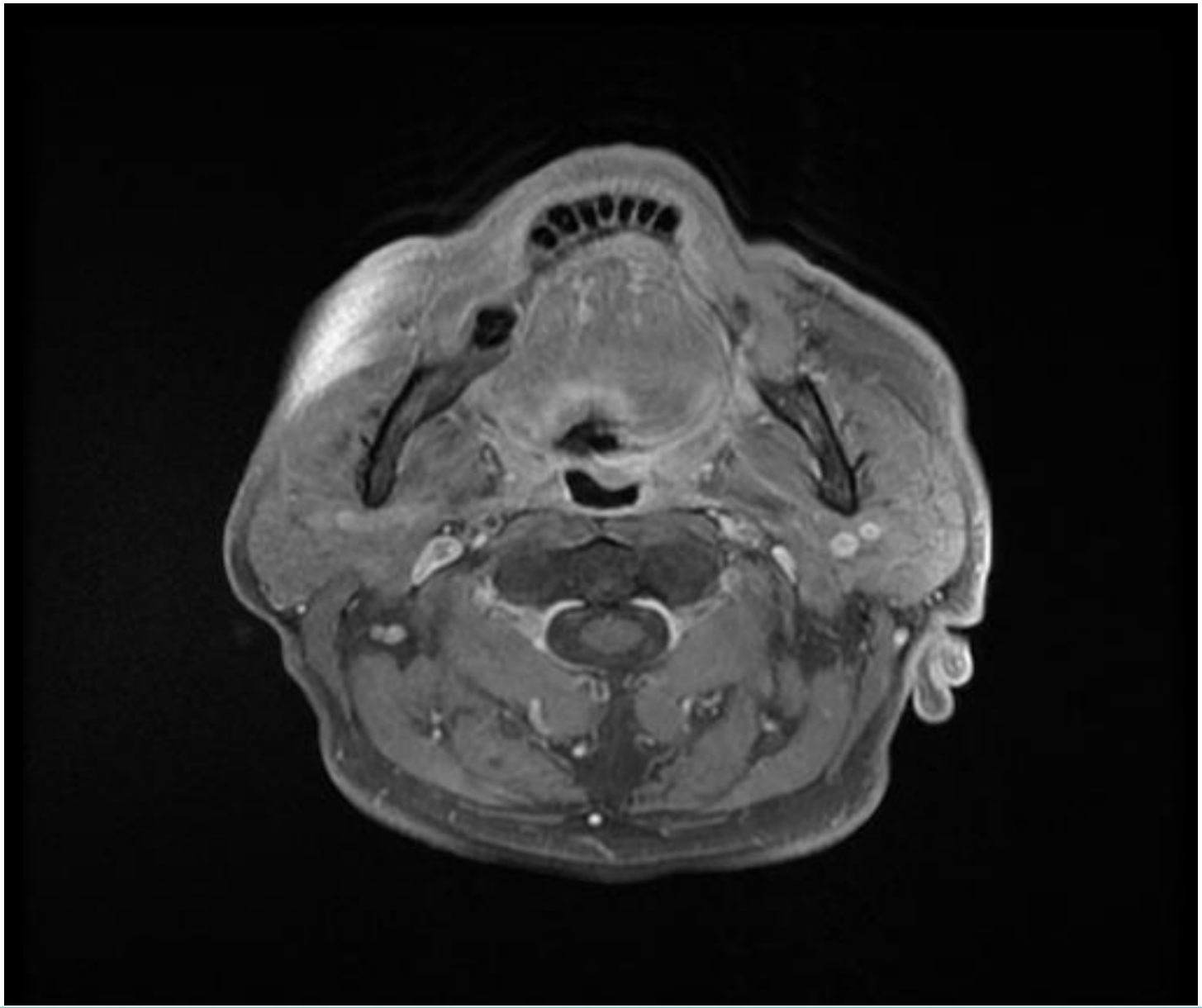
- A total of 55 studies (from 1393 screened references) were employed for quantitative synthesis for 38 929 patients.
- Among *n* = 48 studies with data available, ***de-intensified treatments reduced OS in HPV+ OPCs*** (HR = 1.33; $p < 0.01$).
- In de-escalated treatments, ***PFS was also decreased*** (HR = 2.11; $p < 0.01$).
- Compared with standard ***treatments,*** ***reduced intensity approaches were associated with reduced locoregional and distant disease control*** (HR = 2.51; $p < 0.01$; and HR = 1.9; $p < 0.01$).
- *Chemoradiation improved survival in a definitive curative* setting compared with radiotherapy alone (HR = 1.42; $p < 0.01$).
- *When adjuvant treatments were compared, standard and de-escalation strategies provided similar OS.*

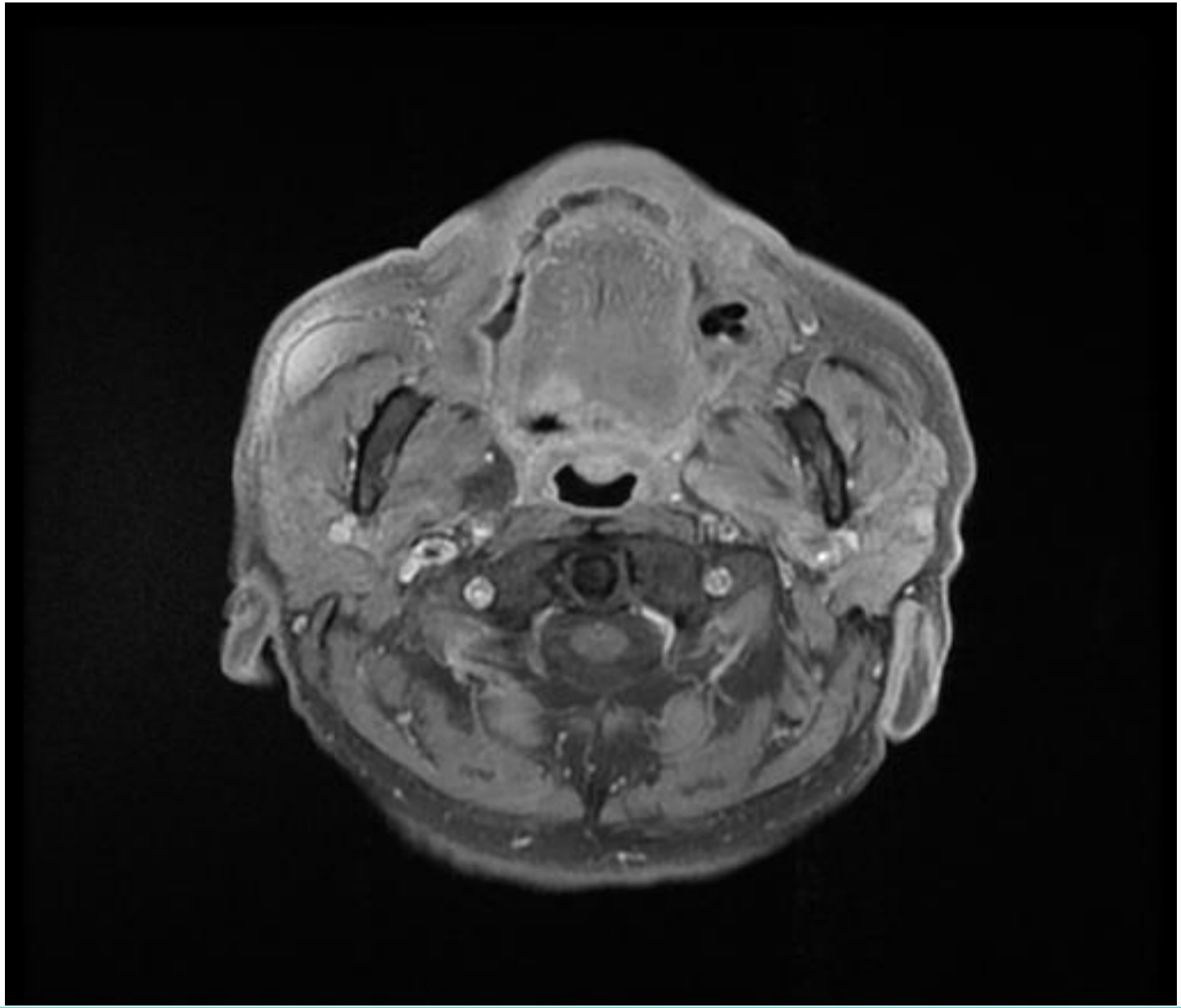
- *In conclusion, in patients with HPV+ OPC, de-escalation treatments should not be widely and agnostically adopted in clinical practice, as therein lies a concrete risk of offering a sub-optimal treatment to patients.*

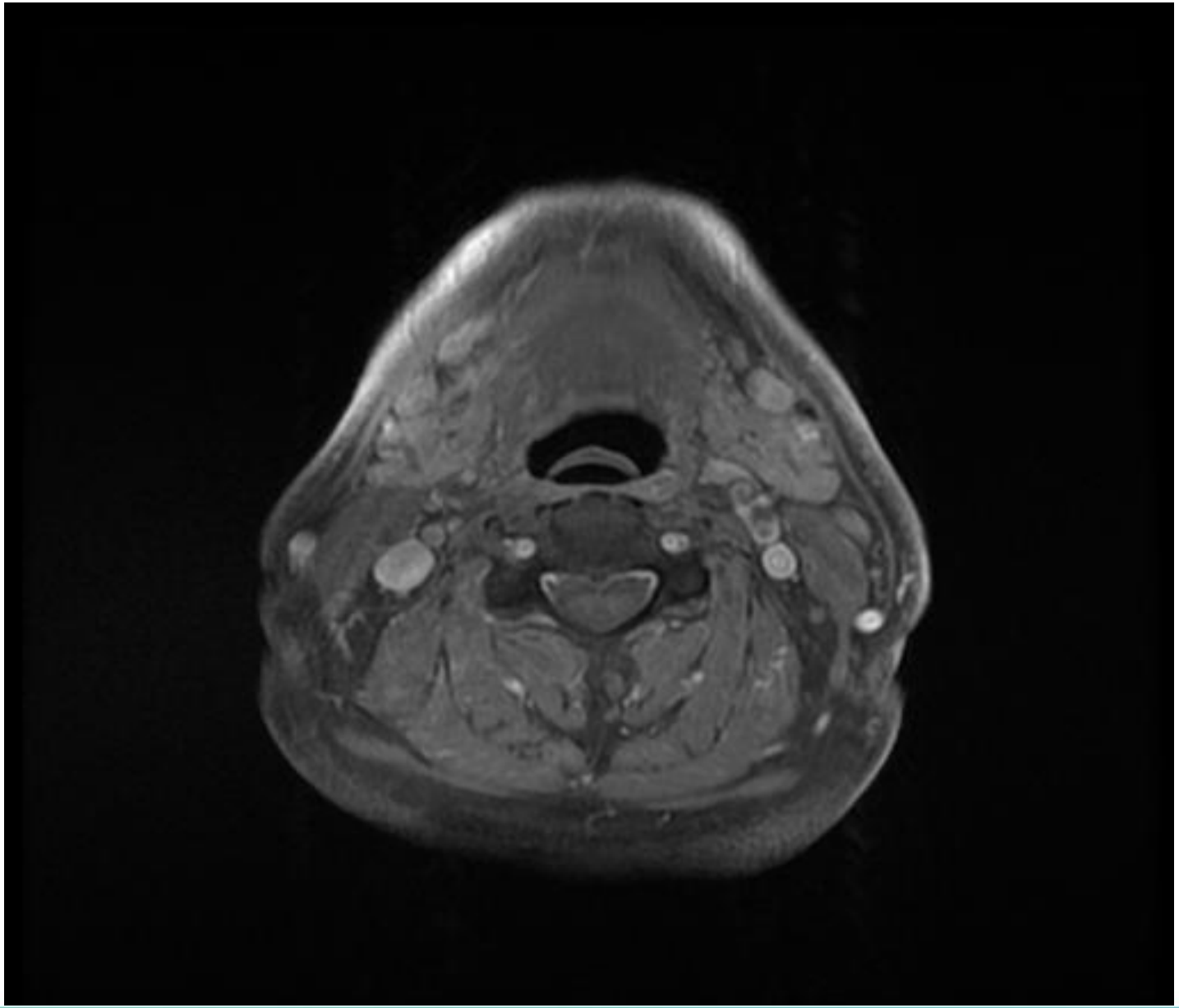
De-Escalation Strategy Appears Feasible in HPV+ Oropharyngeal Cancer

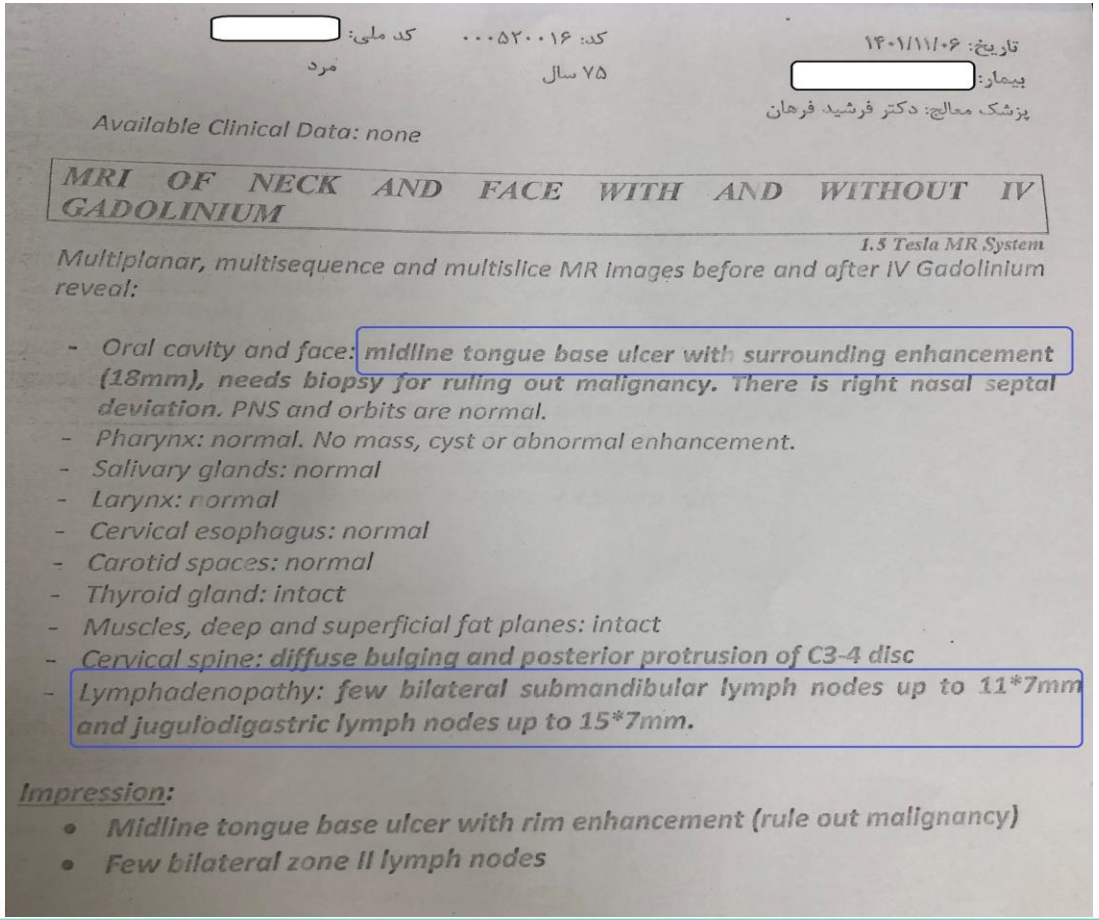
- the concept of substantially reducing elective dosing should be further integrated into prospective trial design.

- The role of treatment deintensification remains investigational, and patients interested in this approach should enroll in clinical trials, where available.









کد ملی: [redacted]
مرد

کد: ۰۰۰۵۲۰۰۱۶
۷۵ سال

تاریخ: ۱۴۰۱/۱۱/۰۶
بیمار: [redacted]
پزشک معالج: دکتر فرشید فرهان

Available Clinical Data: none

MRI OF NECK AND FACE WITH AND WITHOUT IV GADOLINIUM

1.5 Tesla MR System

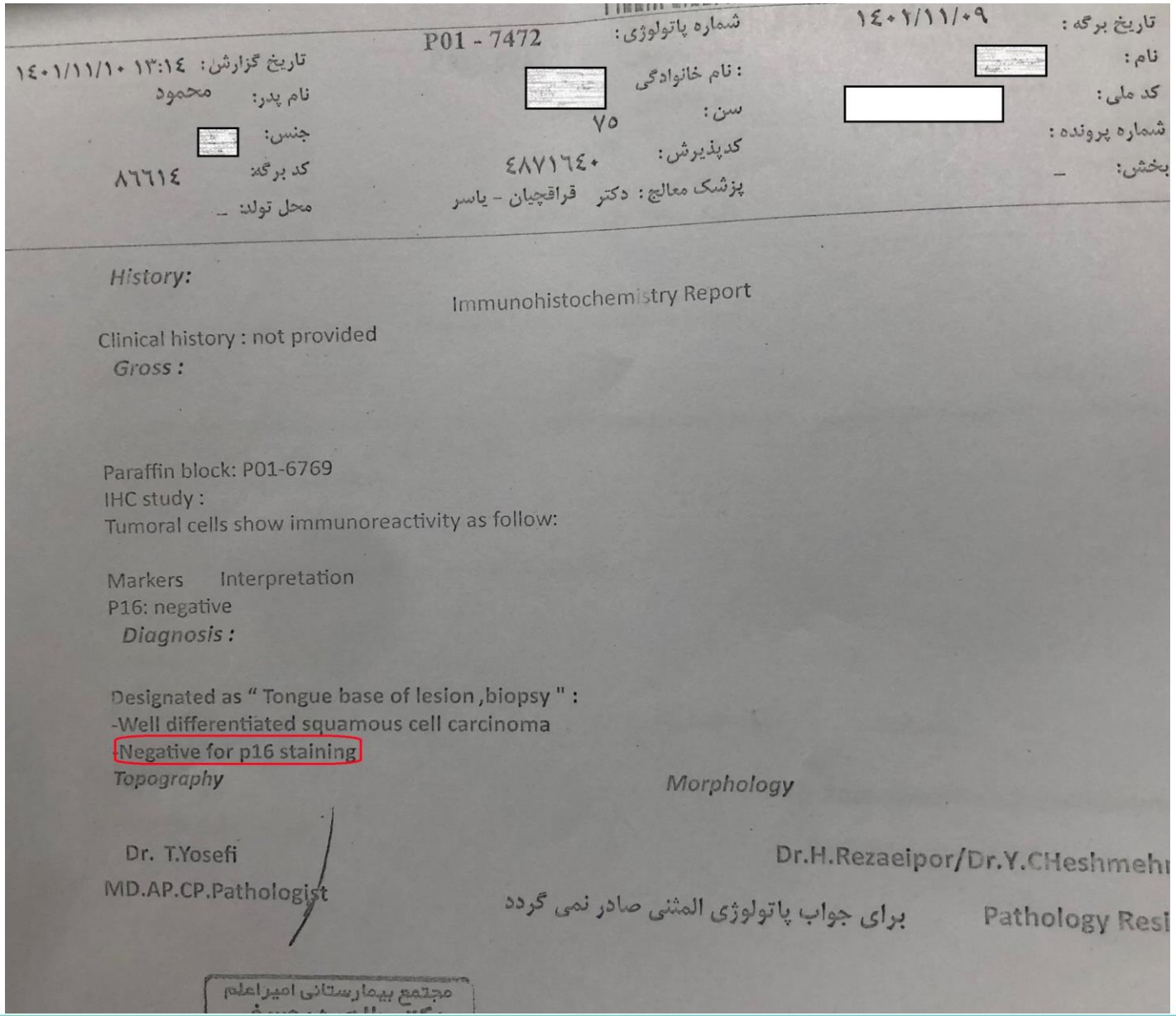
Multiplanar, multisequence and multislice MR images before and after IV Gadolinium reveal:

- Oral cavity and face: **midline tongue base ulcer with surrounding enhancement (18mm), needs biopsy for ruling out malignancy. There is right nasal septal deviation.** PNS and orbits are normal.
- Pharynx: normal. No mass, cyst or abnormal enhancement.
- Salivary glands: normal
- Larynx: normal
- Cervical esophagus: normal
- Carotid spaces: normal
- Thyroid gland: intact
- Muscles, deep and superficial fat planes: intact
- Cervical spine: **diffuse bulging and posterior protrusion of C3-4 disc**
- **Lymphadenopathy: few bilateral submandibular lymph nodes up to 11*7mm and jugulodigastric lymph nodes up to 15*7mm.**

Impression:

- **Midline tongue base ulcer with rim enhancement (rule out malignancy)**
- **Few bilateral zone II lymph nodes**

- P16+: Stage II (T1N2)
- P16-: Stage IVA (T1N2)



تاریخ برگه : ۱۴۰۱/۱۱/۰۹
نام :
کد ملی :
شماره پرونده :
بخش: _

شماره پاتولوژی : P01 - 7472
: نام خانوادگی
سن : ۷۵
کدپذیرش : ۴۸۷۱۶۴۰
پزشک معالج : دکتر قراقچیان - یاسر

تاریخ گزارش : ۱۴۰۱/۱۱/۱۰ ۱۳:۱۴
نام پدر: محمود
جنس:
کد برگه: ۸۶۶۱۴
محل تولد: _

Immunohistochemistry Report

History:

Clinical history : not provided

Gross :

Paraffin block: P01-6769
IHC study :
Tumoral cells show immunoreactivity as follow:

Markers Interpretation
P16: negative

Diagnosis :

Designated as " Tongue base of lesion ,biopsy " :
-Well differentiated squamous cell carcinoma
-Negative for p16 staining

Topography *Morphology*

Dr. T.Yosefi
MD.AP.CP.Pathologist

Dr.H.Rezaeipor/Dr.Y.CHeshmehr

برای جواب پاتولوژی المثنی صادر نمی گردد Pathology Rest

مجتمع بیمارستانی امیراعلم

NCCN Guidelines Version 1.2023
Cancer of the Oropharynx (p16-negative)

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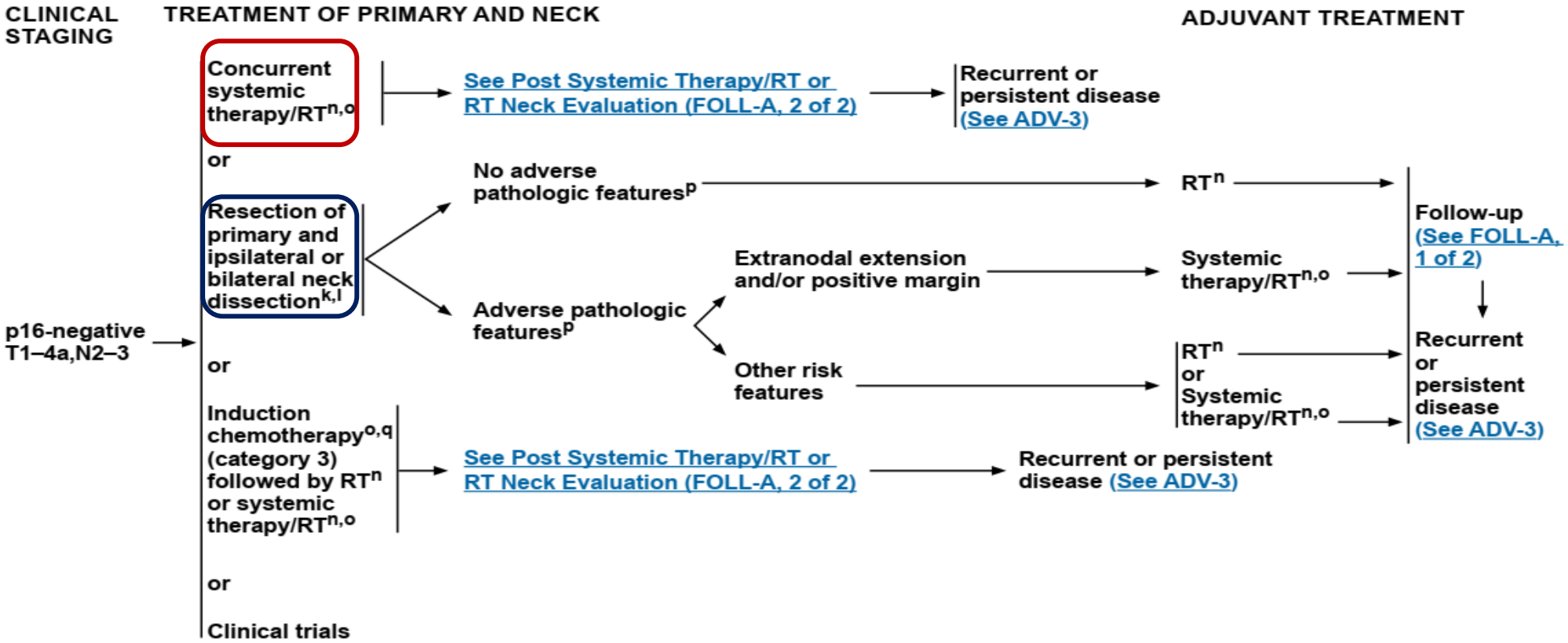

[k] See Principles of Surgery (SURG-A).

[l] Tumors in the base of tongue, posterior pharyngeal wall, and soft palate require consideration of bilateral neck treatment as do tumors of the tonsil invading the tongue base.

[p] Adverse pathologic features: extranodal extension, positive margins, close margins, pT3 or pT4 primary, pN2 or pN3 nodal disease, nodal disease in levels IV or V, perineural invasion, vascular invasion, and lymphatic invasion (See

Take Home Message

- Treatment de-escalation should be performed exclusively in prospective studies and can currently not be recommended in clinical routine.

- Replacement of cisplatin with cetuximab or omission of cisplatin with definitive radiotherapy have not been successful.

- The addition of immunotherapy to definitive radiation-based treatment has not demonstrated a benefit thus far.