CHALLENGING CASES

Head and Neck Cancer

Prepared by: Cornerstone Specialty Network

Challenging Cases conducted: May 19, June 10, and August 21, 2025

Participating Practices

Challenging Cases in…
Head and Neck Cancer

Program conducted:
May–August 2025

Note: Aggregated results and high-level summary based on 3 practices (22 HCPs) and do not necessarily reflect the views and opinions of the moderator or Cornerstone Specialty Network unless otherwise stated. Clinical data, NCCN Guidelines, and FDA approvals current at time of presentation.

- **Georgia Cancer Specialists (n=7)** **May 19, 2025**
- **Multiple Practices (n=11)** **June 10, 2025**
- **Ironwood Cancer & Research Centers (n=4)** **August 21, 2025**

Overall Program Impact and Future Considerations

Most advisors manage a moderate volume of head and neck cancer patients using an MDT approach, prefer weekly cisplatin for its tolerability, and are beginning to integrate cfDNA/ctDNA for surveillance, though its role in guiding treatment remains exploratory

- Most advisors manage a moderate number of head and neck cancer patients and utilize a multidisciplinary team (MDT) approach or consult ENT surgical oncologists for treatment planning
- Concurrent weekly cisplatin 40 mg/m² + XRT 70 Gy is the standard of care for locally advanced disease, preferred for its balance of efficacy and tolerability over high-dose cisplatin
- The goal is a cumulative cisplatin dose of ≥200 mg/m², typically achieved over 7 weeks; dose modifications are made for patients with poor tolerance, though most complete therapy with minimal major toxicity
- Bolus cisplatin (100 mg/m² every 3 weeks) is generally avoided due to higher toxicity and lower completion rates, and is reserved for select patients
- Use of cfDNA/ctDNA is variable; about half of advisors integrate it for diagnosis and surveillance in HPV-related oropharyngeal cancer, but its role in guiding treatment decisions remains investigational
- Rising ctDNA levels may precede imaging evidence of recurrence, prompting closer monitoring, though no standardized response protocols are in place yet
- **Recommended actions:** *Invest in real-world data on cisplatin dose modifications and expand provider education on treatment protocols and emerging tools like ctDNA/cfDNA-guided decision-making to support broader adoption of well-tolerated regimens and enable earlier, more informed surveillance in HPV-associated head and neck cancers*

Georgia Cancer Specialists – High Level Summary

Community oncologists in Georgia use a multidisciplinary approach, favor cisplatin-based chemoradiation initial treatment of head and neck cancer, and are exploring cfDNA/ctDNA testing for HPV-related disease, though clinical application is still evolving

- Advisors report a moderate number of head and neck cancer patients seen in the past six months and typically use an MTD approach or consult with an ENT surgical oncologist for management decisions
- Concurrent weekly cisplatin 40 mg/m² + XRT 70 Gy remains the preferred initial regimen for most patients
  - The recommended dose is 40 mg/m² weekly; 30 mg/m² is not advised due to negative trial outcomes and the target cumulative cisplatin dose is ≥ 200 mg/m², typically achieved over 5–6 weeks
  - For patients with poor tolerance, dose intensity may be reduced, though most complete the full course of weekly cisplatin chemotherapy for 6 cycles with minimal major toxicity
- Circulating free-DNA (cfDNA) testing is a promising biomarker used for HPV-related head and neck cancers; most are more familiar with ctDNA for monitoring with numeric values appearing meaningful, but there are no clear therapeutic guidelines yet
  - Signatera was noted for all comers ctDNA testing whereas NavDX was noted as the preferred test for HPV-positive cancers
  - While ctDNA may detect recurrence early, more clinical validation is required before it guides treatment decisions in head and neck cancer

Multi-Practice – High Level Summary

Community oncologists predominantly manage head and neck cancer patients using a multidisciplinary approach, with cisplatin and XRT as the standard treatment for locally advanced disease, while emerging use of ctDNA is being explored for early recurrence detection, particularly in HPV-associated oropharyngeal cancer, with more limited adoption of cfDNA for p16 positive cases

- Most community oncologists have actively managed a moderate volume of new head and neck cancer patients in the past 6 months, with the majority utilizing a multidisciplinary approach or consulting ENT surgical oncologists for patient management
- Concurrent weekly cisplatin 40 mg/m² + XRT 70 Gy is the preferred first-line treatment for locally advanced disease
- Seven out of ten advisors do not currently use cfDNA for p16 positive oropharyngeal cancer
- ctDNA can indicate recurrence before imaging shows disease, particularly in HPV-associated oropharyngeal cancer
    - A rapid rise in ctDNA often predicts scan-positive recurrence within 2–3 months, while gradual increases may not indicate disease progression
    - Elevated HPV-related ctDNA may reflect other malignancies (e.g., anal or cervical) in patients with prior oropharyngeal cancer
    - If ctDNA rises but scans remain negative, careful monitoring and repeated imaging (including PET scans) are recommended

Ironwood Cancer & Research Centers – High Level Summary

Multidisciplinary decision-making and patient tolerance heavily influence treatment strategies for head and neck cancer, with weekly cisplatin favored over high-dose regimens due to lower toxicity, and emerging tools like cfDNA increasingly used for diagnosis and surveillance

- Advisors indicate managing a wide range of head and neck cancer patients in the past 6 months
- Tumor boards and multidisciplinary team discussions discussions among surgical, medical, and radiation oncologists play a crucial role in determining whether upfront surgery or chemoradiation is most appropriate, aiming to minimize unnecessary treatments for patients
- Concurrent weekly cisplatin 40 mg/m^2 + XRT 70 Gy is the preferred first-line treatment
    - High-dose bolus cisplatin administered every 3 weeks is generally avoided due to high toxicity and difficulty completing the full course; only a very select group of patients can tolerate it
    - Weekly cisplatin is often preferred because it is better tolerated and more manageable, and efficacy may not differ significantly from high-dose bolus, with toxicity and patient tolerance strongly guiding scheduling decisions
- Half of respondents routinely integrate cfDNA for diagnosis and surveillance

Challenging Cases in… Head and Neck Cancer

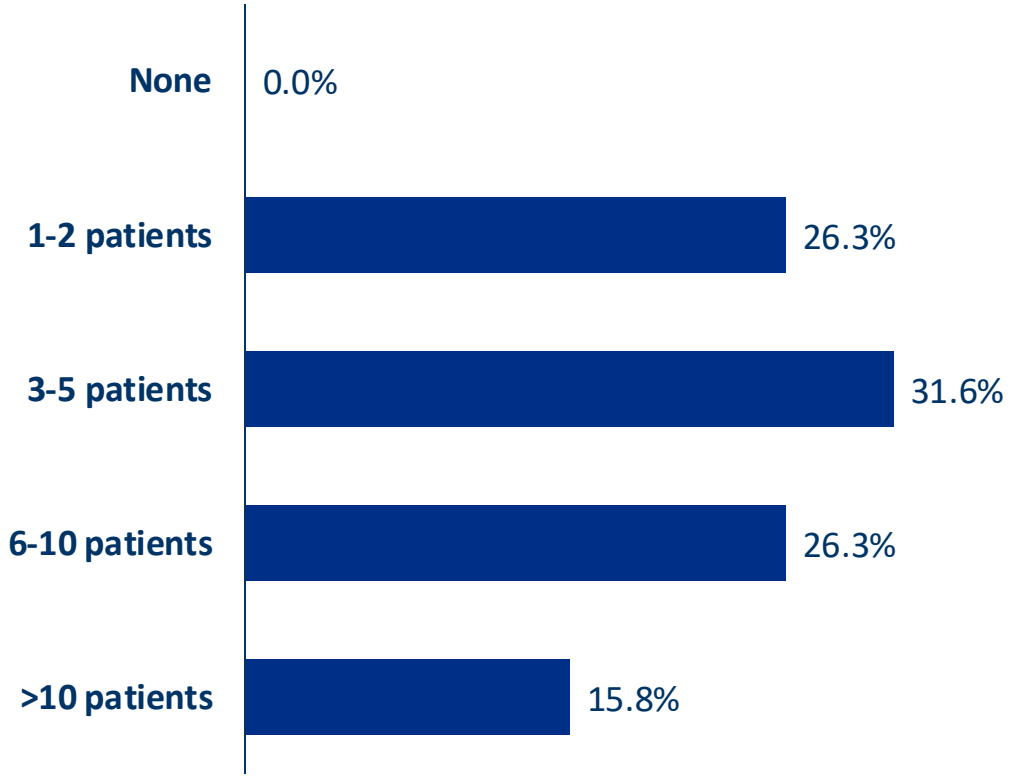
HPV-associated oropharyngeal carcinoma

Patient case: Early-stage

- *Role of confirmatory HPV testing (ddPCR/cfDNA or ISH)*
- *Awareness of clinical trial data and impact on treatment decisions?*
  - *Current status of adopting de-escalation therapy strategy for HPV-associated early-stage disease*
  - *Choice of radiosensitizing concurrent chemotherapy*
- *Impact of new approvals?*

ARS Results from HCP Participants

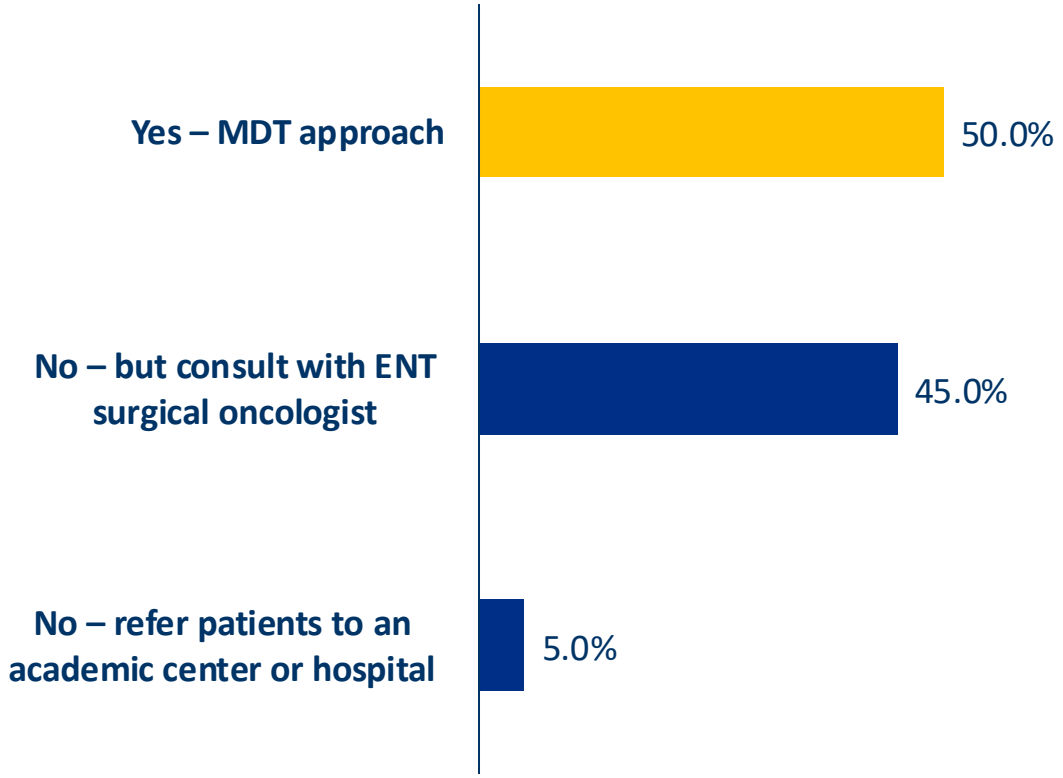
Considering the last 6 months, how many patients with previously untreated head and neck cancer are you actively treating?



Answered: 19

ARS Results from HCP Participants

Do you have a multidisciplinary team (MDT) approach for patients with head and neck cancer?

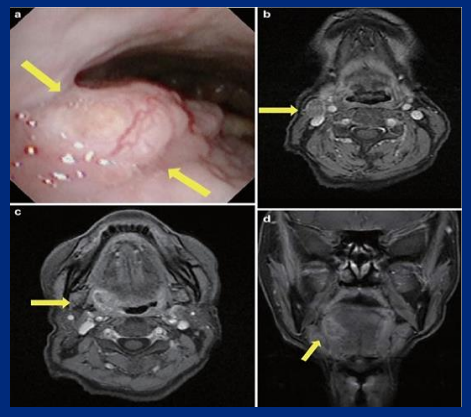


Answered: 20

Patient History

65-year-old male presenting with a tonsillar lesion and palpable neck mass

Patient is an active smoker but overall in great PS with ECOG 0-1



Diagnostics

2.5 cm R tonsillar mass with at least 2 ipsilateral cervical nodes up to 3 cm each. No contralateral nodal or distant metastatic disease

Path; **p16**+ moderatively differentiated squamous cell carcinoma

Baseline CrCl 65 without hearing impairment

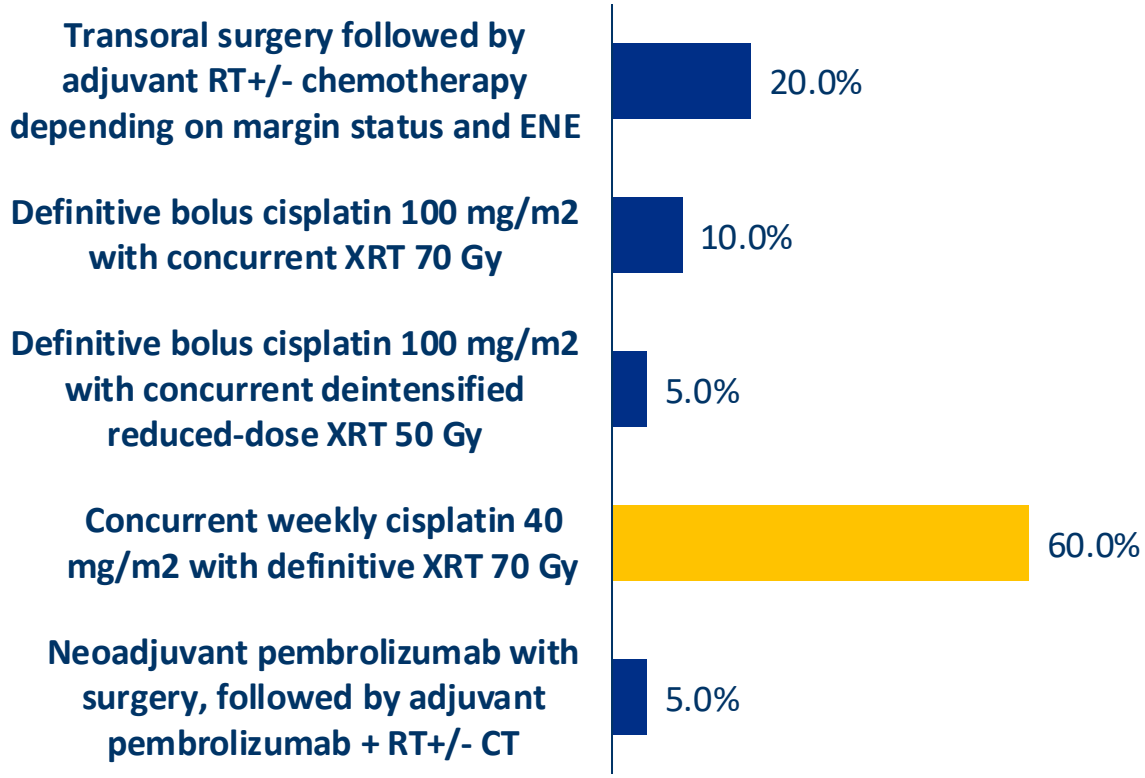
PD-L1 CPS 20%

What is your initial treatment recommendation?

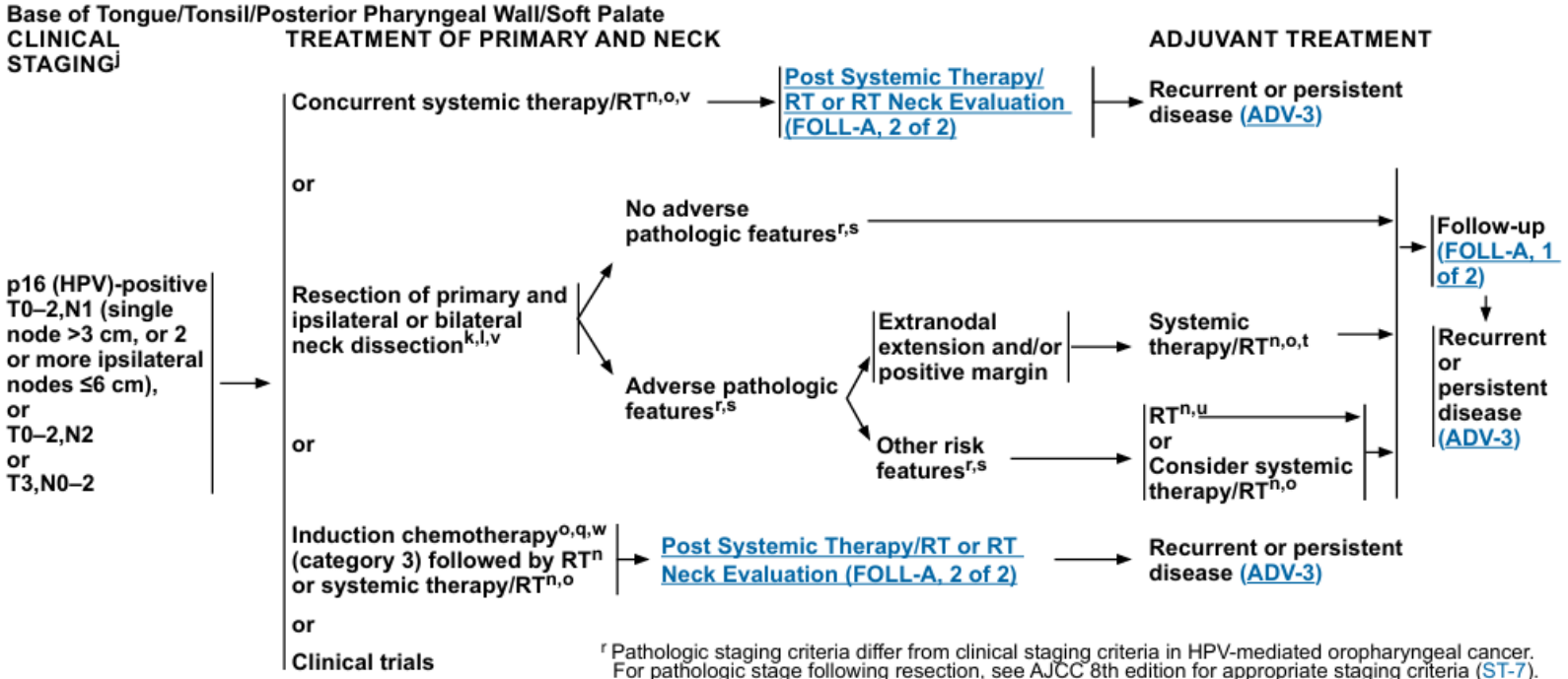
cornerstone specialty network™

ARS Results from HCP Participants

What is your initial treatment recommendation?



Answered: 20



[j] The clinical staging definitions are based on the AJCC 8th edition for oropharynx cancer (see ST-4 for p16-, and see ST-7 for p16+). Definitions for nodal staging criteria previously used in clinical trials (AJCC 7th edition) on the management of oropharynx cancer are included.
[k] 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.
[n] Principles of Radiation Therapy (ORPH-A).
[o] Principles of Systemic Therapy for Non-Nasopharyngeal Cancers (SYST-A).
[q] See Discussion on induction chemotherapy.

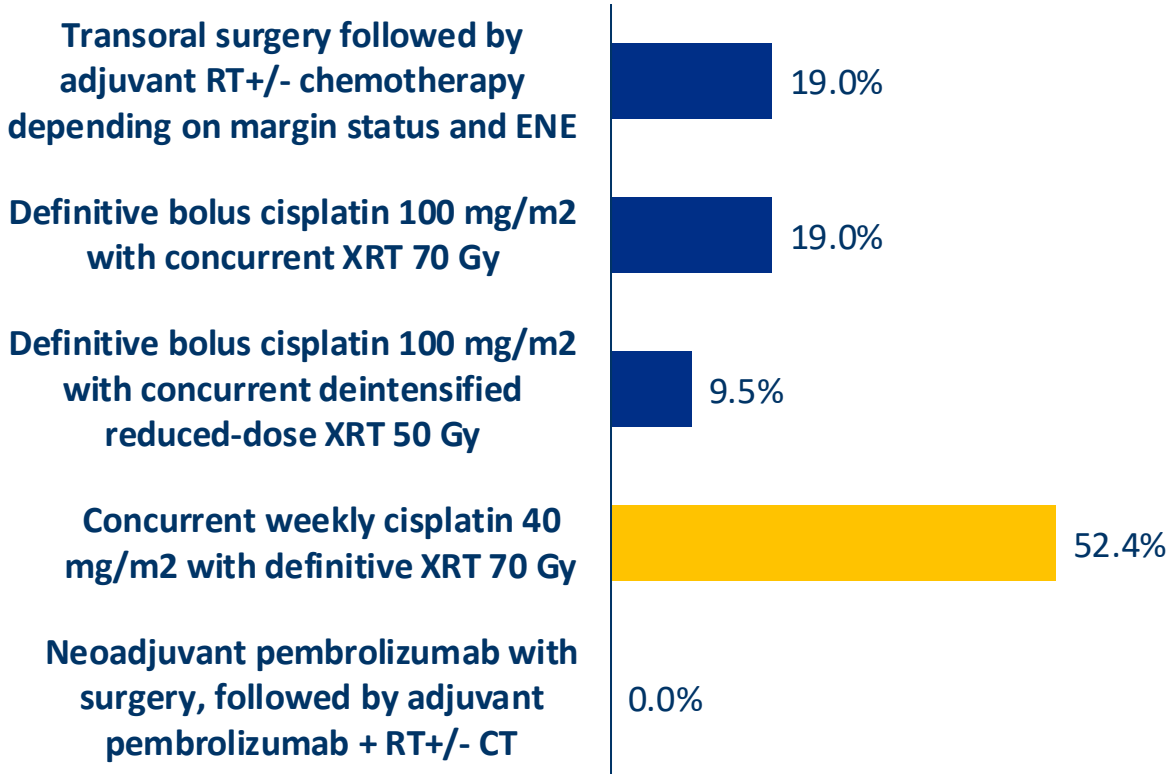
[r] Pathologic staging criteria differ from clinical staging criteria in HPV-mediated oropharyngeal cancer. For pathologic stage following resection, see AJCC 8th edition for appropriate staging criteria (ST-7).
[s] Adverse pathologic features: extranodal extension, positive margins, close margins (<3 mm), pT3 or pT4 primary, one positive node >3 cm or multiple positive nodes, nodal disease in levels IV or V, perineural invasion, vascular invasion, and lymphatic invasion (Discussion). The definition of an adverse pathologic feature in the context of HPV+ disease is an area of active research. This includes the presence and extent of extranodal extension, and the number of involved nodes.
[t] The recommendations for patients at high risk with extranodal extension + positive margins are based on randomized studies involving patients for whom the HPV status of their tumors was not specified.
[u] De-escalation to 50 Gy may be considered in patients with p16 (HPV)-positive oropharynx cancer who have ≤4 positive lymph nodes, T1–T2 resected to negative or close margins (<3 mm), and/or N1–N2 disease (excluding bilateral disease based on ECOG 3311 criteria) with ≤1 mm extranodal extension (Ferris RL, et al. J Clin Oncol 2022;40:138-149) (category 2B).
[v] For those with clinical evidence of fixed or matted nodes or obvious extranodal extension, resection is not recommended and concurrent systemic therapy/RT is preferred.
[w] Surgical intervention may be an option for select patients with disease that does not respond to induction chemotherapy.

Note: All recommendations are category 2A unless otherwise indicated.

[U] De-escalation to 50 Gy may be considered in patients with p16 (HPV)-positive oropharynx cancer who have ≤4 positive lymph nodes, T1–T2 resected to negative or close margins (<3 mm), and/or N1–N2 disease (excluding bilateral disease based on ECOG 3311 criteria) with ≤1 mm extranodal extension (Ferris RL, et al. J Clin Oncol 2022;40:138-149) (category 2B).

ARS Results from HCP Participants

What is your initial treatment recommendation? (post review of the ECOG-ACRIN E3311 and NRG-HN005 data)



Answered: 21

NCCN Guidelines: Version 5.2025 — August 12, 2025

The current preferred treatment for resectable HPV-associated oSCC is surgery followed by adjuvant RT+/- CT vs definitive cCRT after multidisciplinary discussion

Primary Systemic Therapy + Concurrent RT

Preferred Regimens
- High-dose cisplatin (category 1)[3,4]
- Carboplatin/infusional 5-FU (category 1)[5,6]

Other Recommended Regimens
- Weekly cisplatin (40 mg/m2)[7,8,9,10]
- Carboplatin/paclitaxel (category 2B)[11]

Useful in Certain Circumstances
- Docetaxel (if cisplatin ineligible)[12]
- 5-FU/hydroxyurea (category 2B)[13]
- Cetuximab (category 2B)[14]
- Cisplatin/infusional 5-FU (category 2B)[15]
- Cisplatin/paclitaxel (category 2B)[13]

Select ethmoid/maxillary sinus cancers (ie, small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features):
- Carboplatin/etoposide ± concurrent RT[16]
- Cisplatin/etoposide ± concurrent RT[16,17]

Induction[a]/Sequential Systemic Therapy and Neoadjuvant immunotherapy

Preferred Regimens
- Docetaxel/cisplatin/5-FU[18-21] (category 1 if induction is chosen)

Other Recommended Regimens
- Paclitaxel/cisplatin/infusional 5-FU[22]
- Stage III-IVa cancer of the oral cavity (with PD-L1 (CPS) ≥1):
  - Neoadjuvant pembrolizumab followed by adjuvant pembrolizumab/RT (with cisplatin if extranodal extension and/or positive margin) followed by adjuvant pembrolizumab[23,24]

Useful in Certain Circumstances
- Carboplatin/paclitaxel (category 2B)[25,26]
- Carboplatin/paclitaxel/cetuximab[27] (induction only) (category 2B)
- Stage III-IVa cancer of p16-negative oropharynx, hypopharynx, and larynx (with PD-L1 (CPS) ≥1):
  - Neoadjuvant pembrolizumab followed by adjuvant pembrolizumab/RT (with cisplatin if extranodal extension and/or positive margin) followed by adjuvant pembrolizumab[23,24]

For Newly Diagnosed T3, T4a Ethmoid Sinus Tumor

Other Recommended Regimen
- Docetaxel/cisplatin/5-FU

Useful in Certain Circumstances
- Cisplatin/etoposide

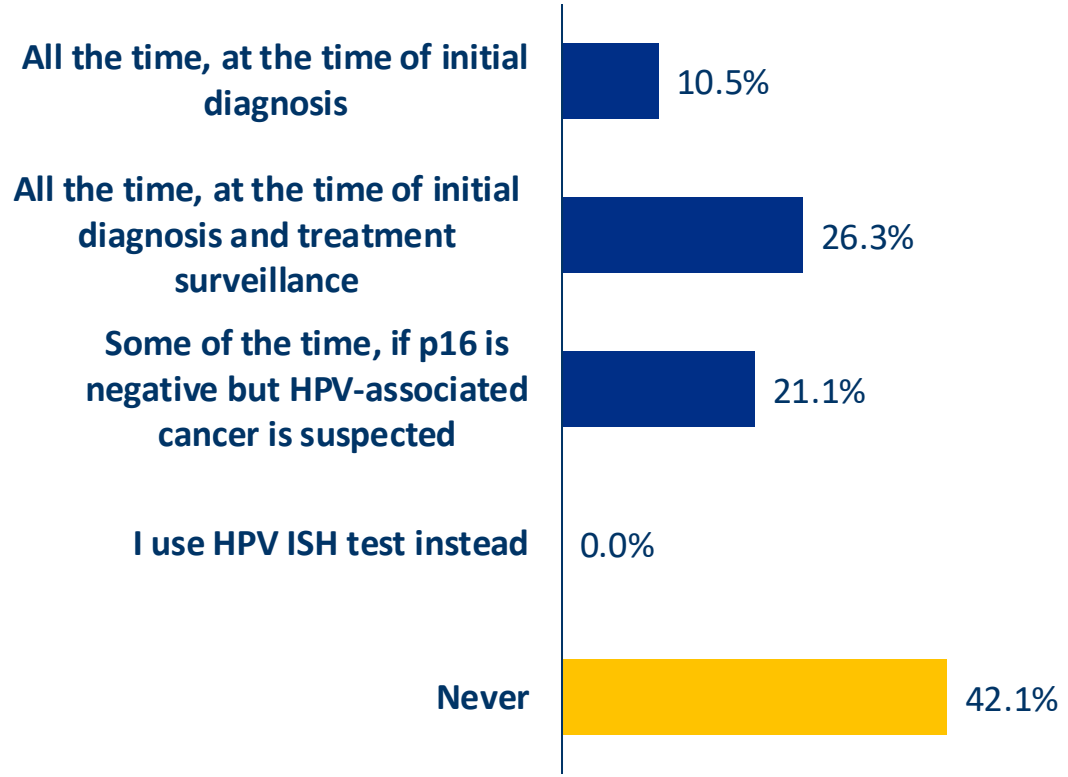
Select ethmoid/maxillary sinus cancers (ie, small cell, SNEC, high-grade olfactory esthesioneuroblastoma, SNUC with neuroendocrine features):
- Cyclophosphamide/doxorubicin/vincristine[28] (followed by RT-based treatment)

To what extent do NCCN Guidelines impact your treatment decisions ? Pathways? Patient performance status? Risk factors? Goals of therapy?

cornerstone specialty network™

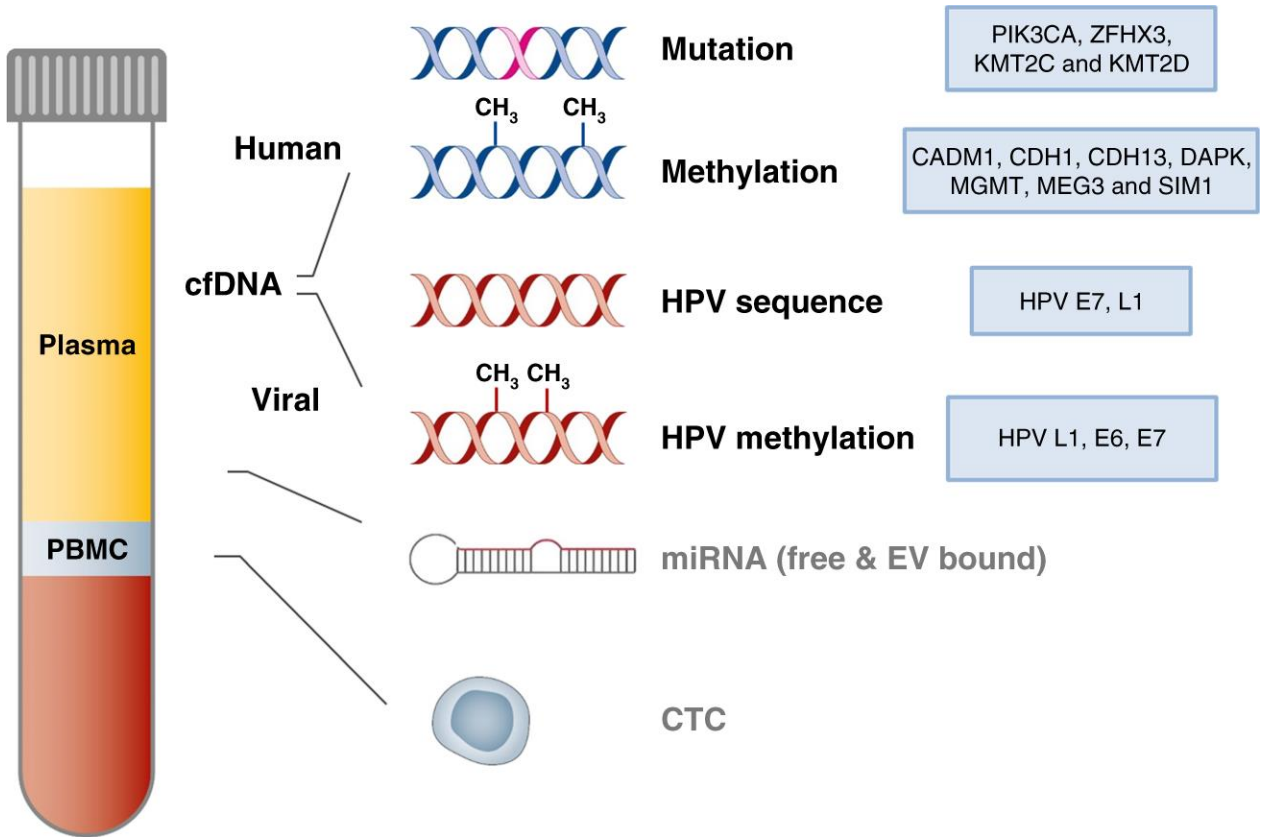
ARS Results from HCP Participants

Do you utilize cfDNA for p16 positive oropharyngeal cancer?

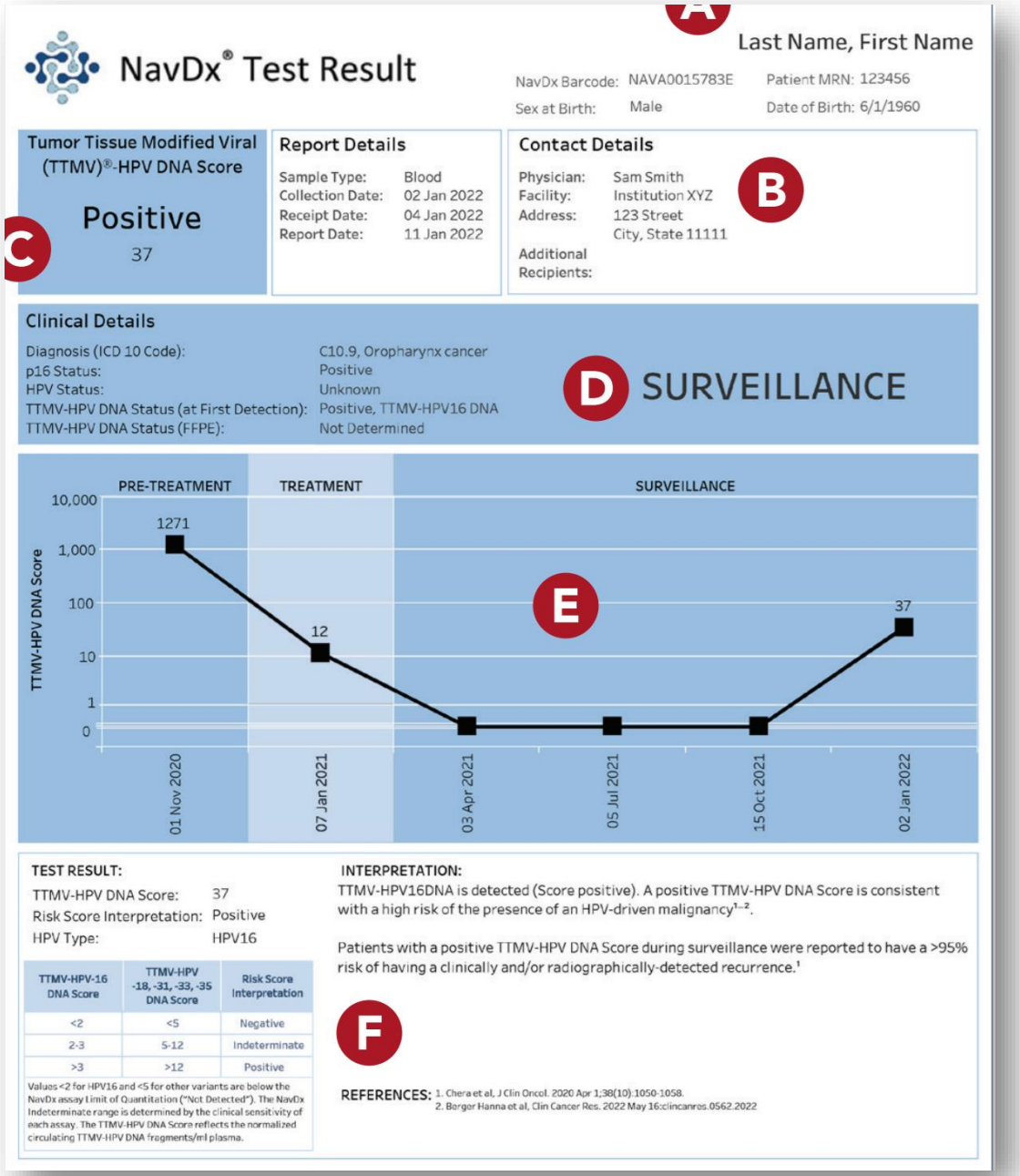


Answered: 19

cfDNA for p16 positive oropharyngeal cancer



Slide credit: Herbst, *British Journal of Cancer* 2022



Prognostic Implications of HPV cfDNA After Curative-Intent Treatment

V. Salati et al. / Clinical Oncology 41 (2025) 103807

- Dynamic biomarker right after curative therapy and surveillance tool.
- Negative predictive value of 99% to detect the absence of disease in serial testing.
- Biomarker of residual disease in equivocal treatment responses on post-treatment PET/CT.
- Positive predictive value of 100% with two consecutive positive tests.
- Detection of recurrences earlier than traditional follow-up protocols.

cornerstone specialty network™

Review Question

What is your initial treatment recommendation?

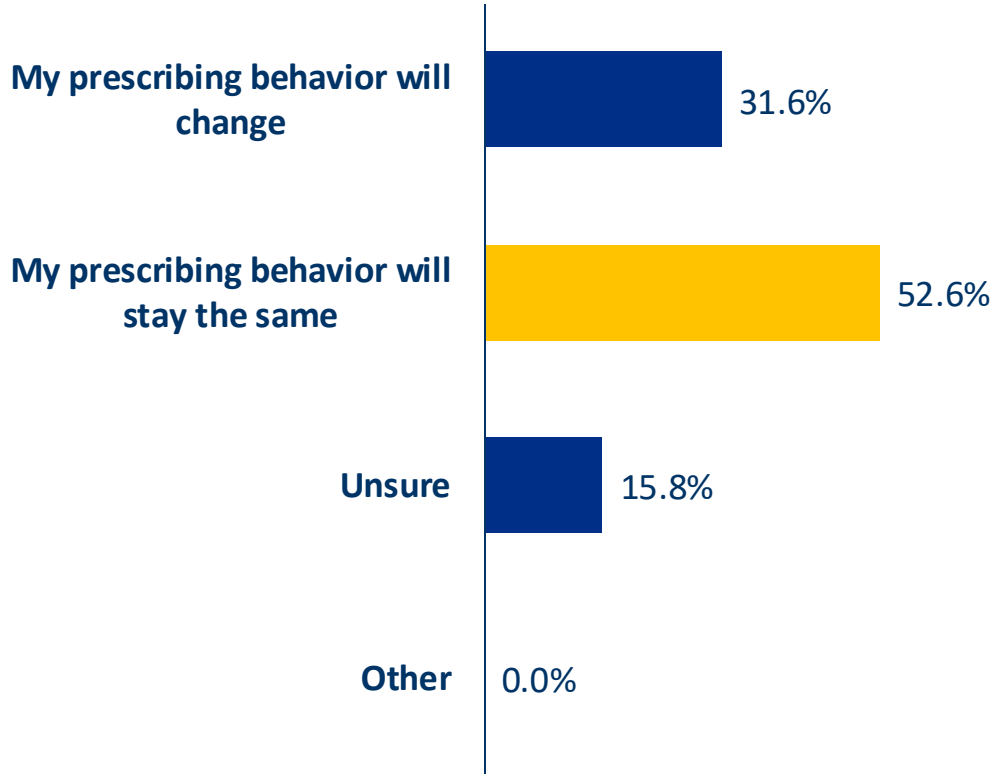
1. Transoral surgery followed by adjuvant RT+/- chemotherapy depending on margin status and ENE
2. Transoral surgery followed by cfDNA biomarker testing
3. Definitive bolus cisplatin 100 mg/m2 with concurrent XRT 70 Gy
4. Definitive bolus cisplatin 100 mg/m2 with concurrent deintensified reduced-dose XRT 50 Gy
5. Concurrent weekly cisplatin 40 mg/m2 with definitive XRT 70 Gy

→ Perioperative/neoadjuvant pembrolizumab with surgical intent

cornerstone specialty network™

ARS Results from HCP Participants

How will the presented challenging case impact your current prescribing behavior for early-stage HPV-associated oropharyngeal carcinoma?



Answered: 19

Key Takeaways

HPV-associated oropharyngeal carcinoma

Patient case: Early-stage

- *Awareness of clinical trial data for de-escalation treatment strategy for locally advanced HPV-associated oropharyngeal cancer*
- *Prognostic implications of HPV cfDNA after curative-intent treatment and as an adjunctive surveillance tool*
- *Recent approval and updated NCCN guidelines impactful*