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**Date of Request**: August 13, 2019

**NCCN Guidelines Panel**: Head and Neck Cancers

The American Society for Radiation Oncology has reviewed the Head and Neck Cancers guideline for gaps relative to radiation therapy and offers seventeen recommendations supported by evidence-based rationales for your consideration.

We hope you find these recommendations useful to your panel as you review and update the guidelines.

Sincerely,

Laura I. Thevenot
Chief Executive Officer
American Society for Radiation Oncology

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**Recommendation 1**: Throughout the guideline, it should support IMRT as the standard-of-care in mucosal H&N cancers treated with curative intent. For example, although the guideline briefly mentions IMRT is preferred over 3D CRT on page ORPH-A, 1 of 2, it indicates both are acceptable. NCCN should dive deeper into the benefits of IMRT and state: "IMRT is preferred over 3D CRT because it decreases multiple acute and late toxicities, including the risk of xerostomia and prolonged dysphagia." Similarly, on page NASO-A, we recommend changing the wording to: "IMRT is recommended for cancers of the nasopharynx to minimize dose to critical structures. In clinics where these treatments are unavailable, 3D conformal RT may be used."

Rational: Multiple randomized trials have confirmed that IMRT is superior to either 2D or 3D in acute and late side effects. This improvement is particularly important for xerostomia. QOL, rates of skin or mucosal toxicity, feeding tube use, and stimulated parotid salivary flow between patients treated with IMRT vs. conformal treatment have also been studied prospectively and favor IMRT.

References:

- Ghosh-Laskar S, Yathiraj PH, Dutta D, Prospective randomized controlled trial to compare 3-dimensional conformal radiotherapy to intensity-modulated radiotherapy in head and neck squamous cell carcinoma: long-term results. Head Neck. 2016;38:1481-7.
- Rathod S, Gupta T, Ghosh-Laskar S, et al. Quality-of-life (QOL) outcomes in patients with head and neck squamous cell carcinoma (HNSCC) treated with intensity-modulated radiation therapy (IMRT) compared to three-dimensional conformal radiotherapy (3D-CRT): evidence from a prospective randomized study. Oral Oncol 2013;49(6):634-42.

- Gupta T, Agarwal J, Jain S, et al. Three-dimensional conformal radiotherapy (3D-CRT) versus intensity modulated radiation therapy (IMRT) in squamous cell carcinoma of the head and neck: A randomized controlled trial. Radiother Oncol 2012;104:343-384.
- Nutting CM, Morden JP, Harrington KJ, Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomized controlled trial. Lancet Oncol 2011;12(2):127-36.
- Braam PM, Terhaard CH, Roesink JM, et al. Intensity-modulated radiotherapy significantly reduces xerostomia compared with conventional radiotherapy. Int J Radiat Oncol Biol Phys. 2006;66(4):975-80.
- Ghosh G, Tallari R, Malviya A. Toxicity Profile of IMRT Vs. 3D-CRT in Head and Neck Cancer: A Retrospective Study. J Clin Diagn Res. 2016;10(9):XC01-XC03.


## Cancer of the Oral Cavity

**Recommendation 2**: On page OR-2, there is recommendation for resection of primary (without neck dissection). No detail is given in the decision tree on which patients this is appropriate for. A depth of invasion cut off should be considered. Page SURG-A, 6 of 9, indicates dissection should be strongly considered for >4 mm, only used in selective situations for < 2 mm, and be subject to clinical judgement for 2-4 mm, which should be reflected on page OR-2 as well.

Rational: In the Tata memorial trial, patients with cT1-T2N0 oral cavity cancer were randomized to elective neck dissection versus dissection at recurrence. There was a survival benefit to elective neck dissection, which was primarily seen in patients with DOI > 4 mm.


Reference: D'Cruz AK, Vaish R, Kapre N, et al. Elective versus Therapeutic Neck Dissection in Node-Negative Oral Cancer. N Engl J Med. 2015;373(6):521-9.


## Cancer of the Hypopharynx

**Recommendation 3**: On MS-28, the recommended fractionation schedule is 69.96 Gy in 33 fractions as used for these patients in RTOG 0615. However, the fractionation regimen with concurrent chemotherapy is typically 70 Gy in 35 fractions.

Rational: RTOG 0615 was a trial of nasopharyngeal cancer patients, not hypopharynx cancer. While 69.96 Gy in 33 fractions is reasonable, we are not aware of data in hypopharynx cancer supporting it.

## Cancer of the Oropharynx (p16 negative and positive)

**Recommendation 4**: In the Principles of Radiation Therapy (page ORPH-A 1 of 2), the guideline suggests 44-50 Gy (2.0 Gy/fraction) for low to intermediate risk disease. This should be broken down further to indicate that for IMRT a biologically equivalent dose of approximately 50 Gy in 2 Gy fractions or slightly higher should be prescribed (e.g., 50 Gy [2 Gy/fraction] or 54-56 Gy [1.54 Gy-1.63 Gy/fraction] in a dose-painting fashion where all target volumes receive 33-35 fractions), or 44 Gy in 22 fractions if using a low neck matched AP field.

Rational: RTOG 1016 was a trial of p16 positive oropharyngeal cancer. The ASTRO oropharyngeal guideline suggests "a biologically equivalent dose of approximately 50 Gy in 2 Gy fractions or slightly higher" as the appropriate dose for low risk disease.

References:


- Gillison ML, Trotti AM, Harris J, et al. Radiotherapy plus Cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): a randomized, multicenter, non-inferiority trial. Lancet. 2019;393(10166):40-50.
- Sher DJ, Adelstein DJ, Bajaj GK, et al. Radiation therapy for oropharyngeal squamous cell carcinoma: Executive summary of an ASTRO Evidence-Based Clinical Practice Guideline. Pract Radiat Oncol. 2017;7(4):246-53.


**Recommendation 5**: In footnote 6 on page ORPH-A 1 of 2, the guideline discusses altered fractionation with chemotherapy. It should be expanded to specifically include cetuximab, now level 2B for use concurrently with RT. Alternate fractionation should be suggested with concurrent cetuximab.

Rational: In the Bonner trial, 56% of patients received concomitant boost as part of high-dose radiation plus or minus cetuximab. In addition, all patients in RTOG 1016 received accelerated IMRT with cetuximab versus cisplatin.

References:


- Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. N Engl J Med. 2006;354(6):567-78.
- Gillison et al., 2019 (see recommendation 4)


## Cancer of the Nasopharynx

**Recommendation 6**: On page NASO-2, we suggest changing the bottom two treatment options for metastatic disease to focus on patients unsuitable for systemic therapy. They could be consolidated into: "For patients with limited-volume metastatic disease who cannot tolerate combination chemotherapy, concurrent systemic therapy/locoregional RT with SBRT or surgery to metastatic sites."

Rational: The bottom two options for "concurrent systemic therapy/RT" and "RT or surgery in select patients" are confusing since systemic chemotherapy followed by locoregional therapy is already listed as the second option. The benefits of systemic therapy are also particularly relevant now that we have two RCTs showing overall survival improvement with induction chemotherapy in the non-metastatic setting. Given evidence of improvement in overall survival for patients without metastatic disease, it seems reasonable to prioritize systemic chemotherapy for patients with known metastatic cancer.

References:


- Frikha M, Auperin A, Tao Y, et al. A randomized trial of induction docetaxel-cisplatin-5FU followed by concomitant cisplatin-RT versus concomitant cisplatin-RT in nasopharyngeal carcinoma (GORTEC 2006-02). Ann Oncol. 2018;29(3):731-6.
- Sun Y, Li WF, Chen NY, et al. Induction chemotherapy plus concurrent chemoradiotherapy versus concurrent chemoradiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: a phase 3, multicentre, randomised controlled trial. Lancet Oncol. 2016;17(11):1509-20.
- Zhang Y, Chen L, Hu GQ, et al. Gemcitabine and Cisplatin Induction Chemotherapy in Nasopharyngeal Carcinoma. N Engl J Med. 2019. [Epub ahead of print]

## Cancer of the Glottic and Supraglottic Larynx

**Recommendation 7**: On page GLOT-2, Since the guideline groups T1 and T2 tumors with T3 ones, systemic therapy and RT should be recommended as another option for post-operative patients with T1-T2, N0 or select T3, N0 tumors and positive surgical margins.

Rational: The grouped analysis of RTOG 95-01 and EORTC 22931 showed a benefit for systemic therapy and radiation in this patient population.

Reference: Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). Head Neck. 2005;27(10):843-50.

**Recommendation 8**: On pages GLOT-3, GLOT-4, GLOT-6, SUPRA-3, and SUPRA-8 for T3 tumors requiring (amenable to) total laryngectomy (N0-N3) and selected T4a patients who decline surgery, the algorithm should reflect that chemoradiation is preferred over induction chemotherapy.

Rational: Although long-term follow up of RTOG 91-11 showed similar laryngectomy-free survival between chemoradiation and induction chemotherapy followed by radiation, there was higher local control and laryngeal preservation with chemoradiation. Both the PARADIGM and DeCIDE trials showed no difference in OS or PFS, but worse Grade 3/4 toxicity with induction chemotherapy followed by chemoradiation versus chemoradiation alone.

References:

- Forastiere AA, Goepfert H, Maor M, et al. Concurrent chemotherapy and radiotherapy for organ preservation in advanced laryngeal cancer. N Engl J Med. 2003;349(22):2091-8.
- Forastiere AA, Zhang Q, Weber RS, et al. Long-term results of RTOG 91-11: a comparison of three nonsurgical treatment strategies to preserve the larynx in patients with locally advanced larynx cancer. J Clin Oncol. 2013;31(7):845-52.
- Haddad R, O'Neill A, Rabinowits G, et al. Induction chemotherapy followed by concurrent chemoradiotherapy (sequential chemoradiotherapy) versus concurrent chemoradiotherapy alone in locally advanced head and neck cancer (PARADIGM): a randomised phase 3 trial. Lancet Oncol. 2013;14(3):257-64.
- Cohen EE, Karrison TG, Kocherginsky M, et al. Phase III randomized trial of induction chemotherapy in patients with N2 or N3 locally advanced head and neck cancer. J Clin Oncol. 2014;32(25):2735-43.

**Recommendation 9**: On page GLOT A, 1 of 2, for patients with Tis, N0 tumors, 56.25 Gy in 2.25 Gy fractions should also be included as a suitable fractionation scheme.

Rational: This regimen was used as part of the studies by Sengupta et al and Yamazaki et al.

References:

- Sengupta N, Morris CG, Kirwan J, Amdur RJ, Mendenhall WM. Definitive radiotherapy for carcinoma in situ of the true vocal cords. Am J Clin Oncol. 2010;33(1):94-5.

- Yamazaki H, Nishiyama K, Tanaka E, Koizumi M, Chatani M. Radiotherapy for early glottic carcinoma (T1N0M0): results of prospective randomized study of radiation fraction size and overall treatment time. Int J Radiat Oncol Biol Phys. 2006;64(1):77-82.

**Recommendation 10**: Hypofractionation should be marked as preferred for T2N0 (as it is for T1N0).

Rational: Multiple non-randomized studies have shown not only improved local control, but also improved survival when hypofractionated RT is compared to conventional RT.

References:
- Bledsoe TJ, Park HS, Stahl JM, et al. Hyperfractionated Radiotherapy for Patients with Early-Stage Glottic Cancer: Patterns of Care and Survival. J Natl Cancer Inst.2017;109(10).
- Le QT, Fu KK, Kroll S. Influence of fraction size, total dose, and overall time on local control of T1-T2 glottic carcinoma. Int J Radiat Oncol Biol Phys.1997;39:115-26.

**Recommendation 11**: On pages GLOT A and SUPRA-A, 1 of 2, recommendation dose for low to intermediate risk starts at 44 Gy in 2 Gy fractions, when it should start at 50 Gy.

Rational: RTOG 91-11 indicates no more than 44 Gy to midplane because of max spinal cord dose, but clearly states neck needs to get at least 50 Gy. This is also the case in RTOG 0129.

References:
- Forastiere et al., 2003 (see recommendation 8)
- Nguyen-Tan, Zhang Q, Ang KK, et al. Randomized phase III trial to test accelerated versus standard fractionation in combination with concurrent cisplatin for head and neck carcinomas in the Radiation Therapy Oncology Group 0129 trial: long-term report of efficacy and toxicity. J Clin Oncol. 2014;32(34):3858-66.

## Ethmoid and Maxillary Sinus Tumors

**Recommendation 12**: For sinonasal cancers (ethmoid and maxillary sinus tumor sections), induction/neoadjuvant chemotherapy should be added as an option for T3-T4 tumors where upfront surgery or radiation would compromise organ function (i.e., the orbit or skull base is involved such that there would sacrifice of structures surgically or to exceed dose tolerances with radiation).

Rationale: Many institutions offer upfront chemotherapy as an option in these situations based on retrospective series showing favorable response rates for squamous cell carcinoma. Retrospective data is the best information available to date to guide therapy for sinonasal cancers in most situations, although an ongoing clinical trial, EA3163, is exploring the use of neoadjuvant chemotherapy.

References:
- Licitra L, Locati LD, Cavina R, et al. Primary chemotherapy followed by anterior craniofacial resection and radiotherapy for paranasal cancer. Ann Oncol. 2003;14(3):367-72.
- Hanna EY, Cardenes AD, DeMonte F, et al. Induction chemotherapy for advanced squamous cell carcinoma of the paranasal sinuses. Arch Otolaryngol Head Neck Surg. 2011;137(1):78-81.
- LoRusso P, Tapazoglou E, Kish JA, et al. Chemotherapy for paranasal sinus carcinoma. A 10-year experience at Wayne State University. Cancer. 1988;62(1):1-5.

- Rosen A, Vokes EE, Scher N, Haraf D, Weichselbaum RR, Panje WR. Locoregionally advanced paranasal sinus carcinoma. Favorable survival with multimodality therapy. Arch Otolaryngol Head Neck Surg. 1993;119(7):743-6.
- Brasnu D, Laccourreye O, Bassot V, et al. Cisplatin-based neoadjuvant chemotherapy and combined resection for ethmoid sinus adenocarcinoma reaching and/or invading the skull base. Arch Otolaryngol Head Neck Surg. 1996;122(7):765-8.
- Björk-Eriksson T, Mercke C, Petruson B, Ekholm S. Potential impact on tumor control and organ preservation with cisplatin and 5-fluorouracil for patients with advanced tumors of the paranasal sinuses and nasal fossa. A prospective pilot study. Cancer. 1992;70(11):2615-20.


**Recommendation 13**: On page ETHM-2 for ethmoid sinus cancers, the use of postop RT for T1-2 cancers is based on features including negative margins, favorable histology, central tumors, and low-grade tumors. Anatomic location should be incorporated as another consideration. The inclusion of "central" tumors may be meant to do this, but the term is not specific and this consideration should be explained further. Perineural or lymphovascular invasion should also be considered.

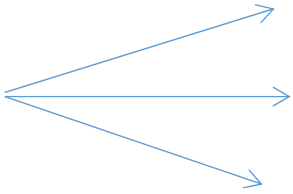
Rationale: Tumors at the orbit/cribiform plate may be at higher risk for recurrence after surgery alone.

## Very Advanced H&N Cancer

**Recommendation 14**: On page ADV-1, re-define "very advanced head and neck cancer" to change it to metastatic disease. Nasopharynx cancer should also be excluded from this population.

Rational: The definition driving this first tree bifurcation does not seem reasonable. Standard treatment paradigms for patients with "unresectable nodal disease" or who are unfit for surgery should not deviate from prior, standard-of-care treatment approaches. (In addition, these scenarios are very different than T4b disease.) At a minimum, PS 0-1 patients should be treated according to the standard treatment paradigm from earlier in the guideline. Some include induction chemotherapy at the same recommendation strength as chemoradiation (like larynx) and some do not (like oropharynx). NCCN recently made induction chemotherapy equal to definitive CRT, but there is no rationale for this change.

**Recommendation 15**: On page ADV-2, we recommend re-imagining the algorithm for M1 disease. It is not clear what physicians should do for distant metastases. The key question for radiation oncology is when to use local therapy to the head and neck. We recommend breaking off the first branch into:



Clinical trial preferred

Multiple metastases (systemic therapy regardless of PS)

Limited number of metastases
- PS 0-1 [systemic treatment] but surgery/RT/CRT for selected patients
- PS 2-3: systemic treatment

In addition, patients who only receive systemic treatment should be candidates for palliative radiotherapy, and that is not currently mentioned in the guideline. Patients who only receive local therapy and not systemic treatment should have oligometastatic ablation with SBRT/surgery.

Rational: There is a separate section for nasopharynx metastatic disease so it should not be addressed here. Patients with newly diagnosed metastatic head and neck cancer with limited systemic burden may benefit from aggressive locoregional therapy, but the data are limited. NCCN currently accepts this concept but does not clarify the population. There is also no discussion of palliative radiotherapy, which may be extremely beneficial for all patients with newly diagnosed metastatic disease with locoregional symptoms (there is footnote about palliative therapy on pages ADV-3 and ADV-4, but not on ADV-2). Finally, it is not clear how metastatic sites are treated if patients receive systemic treatment only. Consistent with studies in other disease sites, presumably they need SBRT or other local treatment.

References:


- Lok BH, Jiang G, Gutiontov et al, Palliative head and neck radiotherapy with the RTOG 8502 regimen for incurable primary or metastatic cancers. Oral Oncol 2015; 51(10):957-62.
- Iyengar P, Wardak Z, Gerber DE. Consolidative radiotherapy for limited metastatic non-small cell lung cancer: a phase II randomized clinical trial. JAMA Oncol 2018;4(1):e173501.
- Gomez DR, Tang C, Blumenschein GR et al. Local consolidative therapy vs maintenance therapy or observation for patients with oligometastatic non-small cell lung cancer: long-term results of a multi-institutional phase II randomized study." J Clin Oncol 2019;37(18):1558-65.


**Recommendation 16**: On page ADV-3, specify when postoperative chemoradiation should be given for previously irradiated patients.

Rational: The guideline quotes Janot et al to explain why "reirradiation should be limited to a highly select subset of patients." However, this study was published over 10 years ago and techniques are vastly different. There should be careful selection of patients for reirradiation and we recommend changing the wording to: "patients with positive margins and/or extranodal extension should be strongly considered for reirradiation," because the risk of recurrence in these scenarios is so high.

**Recommendation 17**: On page ADV-4, reirradiation as part of first-line therapy should not be initially recommended for patients with recurrent or persistent disease with distant metastases.

Rational: Reirradiation carries significant toxicities and should not be considered as part of the first-line treatment paradigm if distant metastases are also present. Palliative reirradiation is reasonable, but surgery or RT should not be considered in the beginning of treatment, even for PS 0-1 patients.

References:


- Ward M, Lee N, Caudell J, et al. A competing risk nomogram to predict severe late toxicity after modern re-irradiation for squamous carcinoma of the head and neck. Oral Oncol. 2019;90:80-6.
- Ling DC, Vargo JA, Ferris RL, et al. Risk of Severe Toxicity According to Site of Recurrence in Patients Treated With Stereotactic Body Radiation Therapy for Recurrent Head and Neck Cancer. Int J Radiat Oncol Biol Phys. 2016;95(3):973-80.