AMERICAN SOCIETY FOR RADIATION ONCOLOGY
251 18th St. South, 8th Floor
Arlington, VA 22202

Main: 703.502.1550 · Fax: 703.502.7852
www.astro.org · www.rtanswers.org

Email: Guidelines@astro.org

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The American Society for Radiation Oncology has reviewed the **2020 NCCN Head and Neck Cancers guideline** for gaps relative to radiation therapy and offers **5 key recommendations** supported by evidence-based rationales and 6 additional suggestions 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, IMRT should be emphasized over 3D-CRT as the standard-of-care in mucosal H&N cancers treated with curative intent.

Rationale: Multiple randomized trials have confirmed that IMRT is superior to 3D-CRT in multiple outcomes including xerostomia, quality of life, rates of skin or mucosal toxicity, feeding tube use, and stimulated parotid salivary flow.

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.

Recommendation 3: HYPO-A and MS-27 – The recommended fractionation scheme with concurrent chemotherapy in hypopharyngeal cancer is 70 Gy in 35 fractions, as no prospective data has validated other regimens with concurrent chemotherapy in the setting of hypopharyngeal cancer.

Rationale: Though the guideline cites RTOG 0615 and RTOG 0022 for alternative fractionation regimens, neither were a trial of hypopharynx cancer patients.

Recommendation 4: GLOT-2/SUPRA-2 – Select T3N0 patients should be removed from the decision tree, as there is no obvious reason why a subset of T3N0 disease should be treated with radiation alone over chemoradiation, given these patients were eligible for the VA Larynx and RTOG 91-11 trials, the latter of which showed improved locoregional control and laryngeal preservation outcomes with concurrent chemotherapy.

References:

- Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. The Department of Veterans Affairs Laryngeal Cancer Study Group. N Engl J Med 1991; 324: 1685–90.
- Forastiere AA, Goepfert H, Maor M, Pajak TF, Weber R, Morrison W et al. Concurrent Chemotherapy and Radiotherapy for Organ Preservation in Advanced Laryngeal Cancer. N Engl J Med 2003; 349: 2091–2098.
- Forastiere AA, Zhang Q, Weber RS, Maor MH, Goepfert H, Pajak TF 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: 845–52.

Recommendation 5: GLOT-3, GLOT-4, GLOT-6, SUPRA-3, 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.

Rationale: 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; further, both PARADIGM and DeCIDE trials showed no difference oncologic outcomes 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.

Additional Suggestions:

Recommendation 6: Hypofractionation should be marked as preferred for T2N0 (as it is for T1N0).

Rationale: 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 7: ETHM-2 – 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: Given the lack of a prospectively validated standard-of-care in sinonasal cancers, it is reasonable to offer upfront chemotherapy for these situations, as multiple retrospective series show favorable response rates for sinonasal squamous cell carcinomas and this is being investigated in the ongoing clinical trial EA3163.

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.

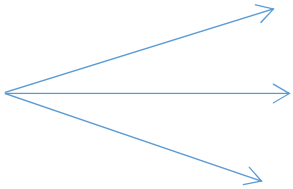
Recommendation 8: ETHM-2 – Anatomic location (including tumors located at the orbit/cribriform plate/pterygomaxillary fossa), perineural invasion and lymphovascular space invasion should be incorporated as additional considerations for post-op RT for T1-T2 tumors.

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

References:

- Dulguerov P, Jacobsen MS, Allal AS, Lehmann W, Calcaterra T. Nasal and paranasal sinus carcinoma: are we making progress? Cancer. 2001; 92 (12): 3012-29.
- Ang KK, Trotti A, Brown BW, Garden AS, Foote RL, Morrison WH, et al. Randomized trial addressing risk features and time factors of surgery plus radiotherapy in advanced head-and-neck cancer. Int. J. Radiat. Oncol. Biol. Phys. 2001

Recommendation 9: ADV-2 – We recommend re-structuring the algorithm for M1 disease by breaking off the first branch into:



Clinical trial preferred

Diffuse metastases: systemic therapy with consideration of palliative radiotherapy

Oligometastatic disease

PS 0-1 [systemic treatment] with surgery/RT/CRT for selected patients

PS 2-3: systemic treatment with consideration of palliative radiotherapy

Rationale: Patients with newly diagnosed metastatic head and neck cancer with limited systemic burden may benefit from aggressive locoregional therapy based on analogy from lung cancer data (such as SABR-COMET), but the data specific to head and neck cancers are limited.

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.

Recommendation 10: ADV-3 – The indications for consideration of postoperative chemoradiation should be specified for previously irradiated patients and should include patients with positive margins and extranodal extension.

Rationale: No direct specification on which patients should be reirradiated after surgery is mentioned and given the lack of prospective data in the reirradiation setting, reasonable analogy can be made using the features predictive for the benefit of adjuvant chemoradiation in the EORTC 22931 and RTOG 9501 trials (ECE and positive margins).

References:

- Bernier J, Cooper JS, Pajak TF, van Glabbeke M, Bourhis J, Forastiere A, 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 27:843–50.
- Bernier J, Domenge C, Ozsahin M, Matuszewska K, Lefèbvre J-L, Greiner RH, et al. Postoperative Irradiation with or without Concomitant Chemotherapy for Locally Advanced Head and Neck Cancer. N. Engl. J. Med. 2004 ;350:1945–52.
- Cooper JS, Pajak TF, Forastiere AA, Jacobs J, Campbell BH, Saxman SB, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. N. Engl. J. Med. 2004; 350:1937–44.

Recommendation 11: ADV-4 – Curative-intent reirradiation as part of initial therapy should not be initially recommended for patients with recurrent or persistent disease with distant metastases.

Rationale: High-dose reirradiation carries significant toxicities and should not be considered as part of the initial treatment paradigm if distant metastases are also present, though palliative reirradiation in this setting is reasonable.

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.