New ASTRO guideline establishes standard of care for curative treatment of oropharyngeal cancer with radiation therapy

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The American Society for Radiation Oncology (ASTRO) today issued a new clinical guideline for the management of oropharyngeal cancer. The guideline, "Radiation therapy for oropharyngeal squamous cell carcinoma: An ASTRO Evidence-based Clinical Practice Guideline," is available as a free access article in *Practical Radiation Oncology*, ASTRO's clinical practice journal.

Drawing on data from clinical trials and other prospective studies, recommendations address the use of radiation therapy (RT), also known as radiotherapy, to treat tumors of the oropharynx in a variety of scenarios. The new clinical practice guideline covers optimal radiation dose and fractionation schedules, the integration of chemotherapy with RT and the role of induction chemotherapy.

Oropharyngeal squamous cell cancer (OPSCC) is rapidly becoming the most commonly diagnosed head and neck malignancy. The demand for radiation oncologists to treat head and neck cancer is projected to increase nearly 20 percent by 2020 over 2010 rates. (1) The profile of the typical OPSCC patient has changed in the past several decades. From 1988 to 2004, the rates of human papillomavirus (HPV)-associated OPSCC rose more than 200 percent, while the rates of HPV-negative disease dropped by half. (2) The estimated risk of death for HPV-positive OPSCC patients is 50 percent lower than for those with HPV-negative disease, in large part due to the more favorable biology of HPV-

driven disease, but also because these patients tend to be younger and healthier when they are diagnosed. (3)

"Advances in treatment planning and technology, as well as a shift in the 'typical' oropharyngeal cancer patient over the past several decades, have led to a significant improvement in treatment outcomes for these patients," said David J. Sher, MD, MPH, co-chair of the task force that authored the guideline and a radiation oncologist at the University of Texas Southwestern in Dallas. "Despite these advances, however, treatment in this sensitive and complex region of the head and neck often leads to short-term, long-term and potentially lifelong side effects—which become even more salient as this patient population trends younger."

"Radiation therapy is the most commonly used curative option for the primary treatment of oropharynx tumors," said Avraham Eisbruch, MD, also co-chair of the task force and a radiation oncologist at the University of Michigan in Ann Arbor, Michigan. "We developed the current guideline to address critical topics facing radiation oncologists who treat oropharyngeal cancer, including when to use chemotherapy, as well as appropriate dose and fractionation schedules for definitive and post-surgical RT settings."

The guideline first addresses the addition of chemotherapy to curative RT for oropharyngeal cancer, recommending concurrent chemoradiation for patients with stage IV disease or stage III disease with large-volume tumors, but not for patients with stage I-II disease. Recommendations by disease stage are as follows:

- Stage IV: Patients with stage IVA-B tumors receiving definitive RT should receive concurrent high-dose intermittent cisplatin. Advanced-stage patients who are medically unfit for high-dose cisplatin should receive concurrent cetuximab or carboplatin-

fluorouracil; weekly cisplatin may be considered for these patients with the caveat that there is limited prospective evidence to support its use. Concurrent cetuximab should not be co-delivered to patients receiving definitive chemoradiation (CRT), nor should intra-arterial chemotherapy be used in this population.

- Stage III: Patients with stage III OPSCC receiving definitive RT should receive concurrent systemic therapy for T3 N0-1 tumors. CRT may be considered for larger volume T1-T2 N1 tumors that are at substantial risk for locoregional recurrence. Systemic therapy for other stage III patients may convey unnecessary toxicity.
- Stage I-II: Concurrent systemic therapy is not recommended for patients with stage I-II OPSCC receiving definitive RT, due to a lack of evidence supporting its use for early-stage disease.

The guideline also provides guidance for the use of radiation and chemoradiation following primary surgery for OPSCC. Post-operative, or adjuvant, RT is recommended for patients who show pathologic risk factors for disease recurrence, such as positive surgical margins or positive lymph nodes following surgery, although concurrent chemoradiation is strongly recommended only for high-risk patients. Recommendations by treatment type and risk level are as follows:

- Concurrent systemic therapy for high-risk patients: Systemic therapy, specifically high-dose intermittent cisplatin, should be delivered with post-surgical RT for patients with positive surgical margins and/or extracapsular extension. Weekly cisplatin may be delivered to post-operative patients who are unable to tolerate high-dose cisplatin. Post-operative patients who are unable to tolerate cisplatin-based chemoradiotherapy should not routinely receive concurrent chemotherapy. Existing prospective data do not support the use of cetuximab, concurrent weekly carboplatin or routine concurrent weekly docetaxel with post-operative RT,

although clinical trials are underway to examine these alternative agents.

- Adjuvant therapy for lower-risk patients: Concurrent chemoradiation should not be routinely used in intermediate-risk disease. Adjuvant RT is strongly recommended for post-operative OPSCC patients at significant risk of locoregional recurrence but only conditionally recommended in scenarios (e.g. pathologic N1 disease, perineural invasion, lymphovascular invasion) with a more uncertain risk of locoregional failure. Adjuvant radiotherapy may be delivered to patients without conventional adverse pathologic risk factors only if the clinical and surgical findings imply a particularly significant risk of locoregional recurrence.

The guideline also outlines optimal dosing and fractionation schedules based on treatment approach, disease profile and risk of recurrence. Recommendations by treatment setting are as follows:

- Definitive RT: Patients with stage III-IV OPSCC should receive a cumulative dose of 70 Gray (Gy) delivered to the primary tumor site and positive nodes in 2-Gy daily fractions over seven weeks, as well as an equivalent dose of 50 Gy delivered in 2-Gy daily fractions to the surrounding region at risk for tumor spread. For stage IV A-B patients not receiving concurrent systemic therapy, altered fractionation schedules (either accelerated or hyperfractionated) are recommended. For Stage IV A-B patients undergoing concurrent CRT, either standard or accelerated fractionation may be implemented. Altered fractionation also should be used for patients with T3 N0-1 disease not receiving concurrent chemoradiation, and it may be used for patients with T1-2 N1 or T2 N0 disease at high risk for recurrence.
- Post-surgical/Adjuvant RT: Post-operative OPSCC patients at high risk for recurrence (e.g., those with positive surgical

margins) should receive a total dose of 60 to 66 Gy delivered to the positive margins and region of extranodal extension in 2-Gy daily fractions. High-risk patients not undergoing concurrent systemic therapy should receive the upper limit of this range, while the 60-Gy total dose is recommended for patients with negative margins following surgery.

- Early T-stage tonsillar carcinoma: Ipsilateral RT, which involves treating only one side of the oropharyngeal area, is strongly recommended for the subset of OPSCC patients with early-stage tonsillar cancer, specifically well-lateralized T1-2 N0-1 tumors. It is conditionally recommended for patients with lateralized T1-2 N0-2a disease without evidence of extra-capsular extension.

The guideline also addresses the role of induction chemotherapy (IC) in treating OPSCC, examining the three existing published randomized trials examining IC followed by CRT for the disease. Because none of these trials found an improvement in overall survival yet all found increased toxicity following IC, the guideline strongly recommends that IC should not be delivered routinely to patients with OPSCC.

The guideline was based on a systematic literature review of studies published from January 1990 through December 2014. A total of 2,615 abstracts were retrieved from PubMed, and the 119 articles that met inclusion criteria were abstracted into evidence tables and evaluated by a 16-member task force of experts in oropharyngeal cancer, including radiation oncologists, medical oncologists, otolaryngologists and a patient representative. The Clinical Practice Statement was approved by ASTRO's Board of Directors following a six-week period of public comment. The guideline has been endorsed by the European Society for Radiotherapy & Oncology (ESTRO) and the American Society of Clinical Oncology (ASCO).

More information: David J. Sher et al, Radiation therapy for

oropharyngeal squamous cell carcinoma: Executive summary of an ASTRO Evidence-Based Clinical Practice Guideline, *Practical Radiation Oncology* (2017). DOI: 10.1016/j.prro.2017.02.002