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Editorial

Refining Guidelines Regarding Unilateral Treatment in Patients With Well-lateralized Squamous Cell Carcinoma of the Palatine Tonsil and Multiple Positive Nodes or Extranodal Extension

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The general topic of this editorial is the extent to which the status of the ipsilateral neck should determine the need for elective treatment of the contralateral neck in patients with head and neck cancer. We focus the discussion on patients with well-lateralized squamous cell carcinoma of the palatine tonsil because recently published guidelines appear to mandate contralateral neck treatment in all patients with more than 1 positive node or extranodal extension of tumor (ENE), regardless of node number, node size, or extent of ENE. In our opinion, these requirements may encourage overtreatment and result in increased toxicity in patients who are at low risk of contralateral neck recurrence.[1] Toxicity reduction is especially important in the era of increasing incidence of cancer associated with human papillomavirus (HPV), in which cure is likely in the great majority of cases.

The importance of this discussion goes beyond early-stage tonsil cancer, because questions from colleagues around the country and on social media show that clinicians are wondering if the same indications for bilateral neck treatment should apply to other situations that have historically been treated with unilateral treatment, such as lateralized cancer of the oral cavity, skin, and salivary gland.

This editorial will review major publications and present our opinion about the need for elective treatment of the contralateral neck in patients with multiple positive nodes or ENE in the ipsilateral neck from a well-lateralized squamous cell carcinoma of the palatine tonsil. For this discussion, *well-lateralized* means stage T1-2 and less than 1.0-cm extension to the soft palate, tongue base, or posterior pharyngeal wall. Elective treatment refers to either neck dissection or radiation therapy (RT), usually limited to stations 2 to 4. Nodal stage is as defined in the seventh edition of the American Joint Commission on Cancer staging manual, in which definitions are the same for tumors associated with and not associated with HPV, and N2b is defined as more than 1 positive node on 1 side of the neck, with all nodes <6.0 cm.

Consensus Guidelines

Table 1 summarizes major consensus guidelines with recommendations about elective treatment of the contralateral neck based on the extent of adenopathy in the ipsilateral neck in patients with well-lateralized squamous cell carcinoma of the palatine tonsil.[2-8] We make 3 main observations from this summary.

N2b and ENE are discussed as binary parameters

In the guidelines that discuss general policy regarding contralateral neck treatment, N2b and ENE are discussed as binary parameters. Limiting the discussion to "multiple positive nodes, yes or no" does not distinguish between 2 small positive nodes in a single station and a large number of nodes filling multiple stations. Likewise, "ENE, yes or no" does not distinguish between a single node with a few millimeters of ENE and multiple nodes with extensive ENE into surrounding structures. As in many areas of oncology, the degree to which the status of the ipsilateral neck influences the risk of subclinical metastasis to the contralateral neck is a continuum, such that guidelines that treat N2b and ENE as binary factors will not be optimal for some clinical situations.

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Table 1 Consensus guidelines regarding elective treatment of the contralateral neck based on the extent of adenopathy in the ipsilateral neck in patients with well-lateralized squamous cell carcinoma of the palatine tonsil*

Guideline†	Radiographic or pathologic status	HPV status	Multiple positive nodes‡ (AJCC, seventh Edition, N2b)	ENE
ARS Margalit et al, 2021[2]	Pathologic	Positive	Not mentioned	Equal weighting: Recommended and not recommended (single node with 0.2-cm ENE)
ARS Tsai et al, 2021[3]	Both	Not mentioned	Consensus not reached	Consensus not reached
National Comprehensive Cancer Network, version 2, 2020[4]	Not mentioned	Not mentioned	Not mentioned	Not mentioned
International Consensus Biau et al, 2019[5]	Radiographic	Not mentioned	Recommended (but unilateral discussed)	Not mentioned
ASTRO Sher et al, 2017[6]	Not mentioned	Not mentioned	Not mentioned	Not mentioned
ASCO Quon et al, 2017[7]	Not mentioned	Not mentioned	Recommended (after careful discussion)	Not mentioned
ACR Yeung et al, 2012[8]	Not specified		Bilateral neck irradiation recommended for all N2b	Not mentioned

Abbreviations: ACR = American College of Radiology; AJCC = American Joint Committee on Cancer; ARS = American Radium Society; ASCO = American Society of Clinical Oncology; ASTRO = American Society of Radiation Oncology; ENE = extranodal extension; HPV = human papillomavirus; N2b = more than 1 positive node on 1 side of the neck, with all nodes <6.0 cm.

* Stage T1-2 with <1 cm extension to the soft palate or tongue base.

† These guidelines do not discuss HPV status or they explain that data are insufficient to make different recommendations based on HPV status.

‡ *Recommended* means the guideline clearly recommends elective treatment of the contralateral neck in all cases with stage N2b or with ENE. *Not mentioned* means the guideline does not explicitly state a policy regarding elective treatment of the contralateral neck. However, several guidelines indirectly suggest that the contralateral neck should be electively treated in all N2b or ENE cases by not describing any situation in which unilateral radiation therapy is permitted (ASTRO for N2b and ENE, and ASCO for ENE).

Most guidelines discourage unilateral treatment in all N2b cases, and several imply that it is unacceptable

The American Society of Clinical Oncology and International Consensus guidelines permit unilateral treatment in N2b cases but discourage it with statements that emphasize the risk of this decision. The American Society for Radiation Oncology (ASTRO) and American College of Radiology guidelines imply that unilateral treatment is unacceptable in all N2b cases by not mentioning any scenario where unilateral treatment is permissible. One American Radium Society (ARS) appropriate-use paper is specific to the question of unilateral RT for tonsil cancer, summarizing major studies and ending with a determination of "consensus not reached" regarding the use of unilateral RT in patients with nodal stage N2b.[3]

Only 1 guideline presents a scenario that permits unilateral treatment with ENE

Recent ARS guidelines on postoperative RT for squamous cell carcinoma of the head and neck describe a case in which it is "usually appropriate" to limit RT to the ipsilateral neck with ENE.[2] The case relevant to this issue is that of an early-stage p16 positive tonsil cancer with a single positive node with 0.2 cm ENE. For this case, both unilateral and bilateral neck treatment received a rating of "unusually appropriate." The ARS appropriate-use paper[3] ends with a determination of "consensus not reached" regarding the use of unilateral RT with ENE.

The ASTRO and American Society of Clinical Oncology guidelines indirectly prohibit unilateral treatment in all cases with ENE because they discuss ENE as a risk factor and then do not describe a scenario wherein unilateral treatment is acceptable with ENE. The other

Table 2 Examples of series that report the rate of contralateral neck recurrence in selected cases with well-lateralized squamous cell carcinoma of the palatine tonsil and neck stage N2b or with ENE in the ipsilateral neck*

Series	Unilateral neck treatment		Isolated contralateral neck recurrence with unilateral treatment
	Patients with N2b†, No.	Patients with ENE, No.	
Huang et al, 2017[9]	9	Not evaluated	None (0 of 9) with N2b
Toronto, Canada	Radiographic		
Kim et al, 2017[10]	38	22	2.6% (1 of 38) with N2b
Goyang, Korea	Radiographic	Radiographic	≤4.5% (1 of 22) with ENE‡
Rackley et al, 2017[11]	48	18	None (0 of 48) with N2b
Cardiff, United Kingdom	Pathologic	Pathologic	None (0 of 18) with ENE
Kennedy et al, 2016[12]	26	Not evaluated	3.8% (1 of 26) with N2b
Gainesville, Florida	Radiographic		
Lynch et al, 2014[13]	55	30	10.9% (6 of 55) with N2b
London, United Kingdom	Both radiologic and pathologic; exact numbers not stated	Pathologic	16.7% (5 of 30) with ENE

Abbreviations: ENE = extranodal extension; N2b = more than 1 positive node on 1 side of the neck, with all nodes <6.0 cm.

* Stage T1-2 with <1cm extension to the soft palate or tongue base.

† American Joint Committee on Cancer, seventh edition, N2b. *Pathologic* means the neck was staged from microscopic examination of a neck dissection specimen. *Radiologic* means the neck dissection was not performed and the neck was staged by imaging.

‡ Data for ENE were not presented in a manner that allows exact calculation, but because there was only 1 isolated contralateral neck recurrence after unilateral treatment, the isolated contralateral neck failure rate in the 22 patients with ENE was 0% to 5%.

guideline documents do not mention ENE in their discussions.

Contralateral Neck Recurrence After Unilateral Treatment in Selected Cases With N2b or ENE

Table 2 summarizes a selection of studies that report the rate of contralateral neck recurrence after unilateral treatment in patients with lateralized tonsil cancer and nodal stage N2b and/or ENE in the neck.[9-13] Although not comprehensive, this list is representative of the published experience. The authors of these series all emphasize that their N2b and ENE cases were selected for unilateral treatment based on favorable prognostic factors, but specific criteria usually are not described. We report the rate of isolated contralateral neck recurrences because the main question is whether unilateral treatment compromises recurrence-free survival. For the endpoints of recurrence-free survival, locoregional control, and regional control, patients who recurred simultaneously at the primary site or ipsilateral neck in addition to the contralateral neck were not disadvantaged by unilateral treatment.

If we define a favorable risk tradeoff in this setting to be a contralateral recurrence rate of <5%, all but 1 of these series support the conclusion that unilateral treatment is acceptable in selected patients with multiple positive nodes, and 2 of the 3 series that evaluated ENE show favorable results. The range of results, from 0% to 16.7%, shows the importance of selection.

The HPV Issue

Most studies of unilateral treatment do not evaluate the influence of HPV association on the risk of recurrence of contralateral neck cancer. The main study of the HPV issue is from Huang et al from the Princess Margaret Cancer Centre (Toronto, Ontario, Canada).[9] These authors compared outcomes in 379 patients with known HPV status and T1-2 N0-2b tonsil cancer treated with unilateral versus bilateral neck RT. The rate of contralateral neck failure after unilateral treatment was the same and very low (2%) in HPV-positive and HPV-negative cases. Additional studies are needed to confirm these results, but they suggest that HPV status should not influence criteria for the unilateral neck.

Our Opinions

Most treatment decisions in oncology involve a tradeoff between cancer control and toxicity. We will always want better data to inform their decisions, and reasonable people will disagree about trade-offs in specific clinical situations. Given these qualifications, we present several opinions on the indications for elective treatment of the contralateral neck in general and specifically in well-lateralized tonsil cancer.

Primary tumor characteristics are the dominant determinant of risk for spread to the contralateral neck

The volume, histology, and precise anatomic location of the primary tumor related to drainage to the

contralateral lymphatics are the major factors that determine the need for elective treatment of the contralateral neck. Well-lateralized cancers of the skin and salivary gland with multiple positive nodes or ENE in the ipsilateral neck rarely need elective treatment of the contralateral neck, and the same is likely true for oropharyngeal cancer confined to the palatine tonsil.

Clinical versus pathologic ipsilateral neck stage

The burden and aggressiveness of metastatic cancer is often greater with clinical as opposed to pathologic staging. From the available data, it is not clear how to apply the risk estimates from studies based on pathologic stage to clinical staging.

Selection is the handmaiden of success

We cannot emphasize enough the importance of selection in interpreting data on the need for elective treatment of the contralateral neck. In all studies of this subject, the treating physicians made a judgment decision to limit ipsilateral treatment to patients they believed were at very low risk of contralateral neck failure. The details of selection factors are rarely described to the degree that is needed to be confident in establishing treatment guidelines. For example, the use of positron emission tomography scanning to increase the accuracy of cN0 staging is not uniform or not described.

Although we think that many published guidelines are too strict, every clinician should be cautious about ignoring the risk and morbidity of contralateral neck recurrence. A specialized situation is a history of prior neck surgery that could cause aberrant lymphatic drainage patterns with direct drainage to the contralateral neck. In this situation, bilateral neck treatment may be warranted regardless of other risk factors.

Policies that go beyond N2b and ENE as binary factors

As explained in multiple publications, the binary yes-or-no classifications of "multiple positive nodes" or "ENE positive" are far too broad to define indications for important treatment decisions such as neck dissection or RT to the contralateral neck.[5,9,14] We do not know of data on more detailed guidelines, and the policy in our groups is constantly under discussion.

Multiple reviewers asked that we explain what we currently do in our practices regarding elective treatment of the contralateral neck based on nodal status of the ipsilateral neck. As shown by the literature review in this editorial, there are no definitive data on this subject, and as such, we do not present our policy as a recommendation; in the absence of an indication for contralateral neck treatment based on characteristics at the primary tumor site or a history of neck surgery that would disrupt the cervical lymphatics, our current indications for contralateral neck treatment are as follows: >8 positive nodes of any size, multiple nodes >3 cm, a single node >6 cm, or ENE invading a structure (eg, the dermal lymphatics) in an area that carries risk to drain to the contralateral neck.

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References

1. Chin RI, Rao YJ, Hwang MY, et al. Comparison of unilateral versus bilateral intensity-modulated radiotherapy for surgically treated squamous cell carcinoma of the palatine tonsil. *Cancer*. 2017;123:4594-4607.
2. Margalit DN, Sacco AG, Cooper JS, et al. Systematic review of postoperative therapy for resected squamous cell carcinoma of the head and neck: Executive summary of the American Radium Society appropriate use criteria. *Head Neck*. 2021;43:367-391.
3. Tsai CJ, Galloway TJ, Margalit DN, et al. Ipsilateral radiation for squamous cell carcinoma of the tonsil: American Radium Society appropriate use criteria executive summary. *Head Neck*. 2021;43:392-406.
4. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines). Head and Neck Cancers. Version 2.2020. June 9, 2020. Available at: https://www.nccn.org/professionals/physician_gls/pdf/head-and-neck.pdf. Accessed November 2, 2020.
5. Biau J, Lapeyre M, Troussier I, et al. Selection of lymph node target volumes for definitive head and neck radiation therapy: A 2019 update. *Radiother Oncol*. 2019;134:1-9.
6. 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;7:246-253.

7. Quon H, Vapiwala N, Forastiere A, et al. Radiation therapy for oropharyngeal squamous cell carcinoma: American Society of Clinical Oncology endorsement of the American Society for Radiation Oncology evidence-based clinical practice guideline. *J Clin Oncol*. 2017;35:4078-4090.
8. Yeung AR, Garg MK, Lawson J, et al. ACR Appropriateness Criteria® ipsilateral radiation for squamous cell carcinoma of the tonsil. *Head Neck*. 2012;34:613-616.
9. Huang SH, Waldron J, Bratman SV, et al. Re-evaluation of ipsilateral radiation for T1-T2N0-N2b tonsil carcinoma at the Princess Margaret Hospital in the human papillomavirus era, 25 years later. *Int J Radiat Oncol Biol Phys*. 2017;98:159-169.
10. Kim Y, Cho KH, Moon SH, et al. Comparison of the clinical outcomes of patients with squamous cell carcinoma of the tonsil receiving postoperative ipsilateral versus bilateral neck radiotherapy: A propensity score matching analysis (KROG 11-07). *Cancer Res Treat*. 2017;49:1097-1105.
11. Rackley TP, Namelo WC, Palaniappan N, et al. Unilateral radiotherapy for surgically resected lateralized squamous cell carcinoma of the tonsil. *Head Neck*. 2017;39:17-23.
12. Kennedy WR, Herman MP, Deraniyagala RL, et al. Ipsilateral radiotherapy for squamous cell carcinoma of the tonsil. *Eur Arch Otorhinolaryngol*. 2016;273:2151-2156.
13. Lynch J, Lal P, Schick U, et al. Multiple cervical lymph node involvement and extra-capsular extension predict for contralateral nodal recurrence after ipsilateral radiotherapy for squamous cell carcinoma of the tonsil. *Oral Oncol*. 2014;50:901-906.
14. Mermod M, Tolstonog G, Simon C, et al. Extracapsular spread in head and neck squamous cell carcinoma: A systematic review and meta-analysis. *Oral Oncol*. 2016;62:60-71.