ARS Appropriate Use Criteria

IPSILATERAL RADIATION FOR SQUAMOUS CELL CARCINOMA OF THE TONSIL

EXPERT PANEL ON TONSIL CANCER

Expert Panel on Head & Neck Cancer:  C. Jillian Tsai MD, PhD1; Thomas J. Galloway MD2; Danielle N. Margalit MD MPH3; Richard L. Bakst MD4; Beth M. Beadle MD, PhD5; Jonathan J. Beitler MD, MBA6; Steven Chang MD7; Allen Chen MD8; Jay Cooper MD9; Shlomo A. Koyfman, MD10; John A. Ridge MD, PhD12; Jared Robbins MD11; Minh Tam Truong MBBS12; Sue S. Yom MD, PhD13; Farzan Siddiqui, MD, PhD7

1 Principal Author, Memorial Sloan Kettering Cancer Center, New York, New York;
2 Fox Chase Cancer Center, Philadelphia, Pennsylvania;
3 Dana Farber Cancer Institute/Brigham & Women’s Cancer Center, Harvard Medical School, Boston, Massachusetts;
4 Mount Sinai Icahn School of Medicine, New York, New York;
5 Stanford University School of Medicine, Stanford, California;
6 Emory University School of Medicine, Atlanta, Georgia;
7 Henry Ford Cancer Institute, Detroit, Michigan;
8 University of California, Irvine, California;
9 Albert Einstein College of Medicine, Bronx, New York;
10 Cleveland Clinic, Cleveland, Ohio;
11 University of Arizona Cancer Center, Phoenix, Arizona;
12 Boston University School of Medicine, Boston, Massachusetts;
13 University of California San Francisco, San Francisco, California.

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CONFLICT OF INTEREST DISCLOSURE STATEMENT

Conflict of Interest Disclosure Statement

All panelists were required to declare all conflicts of interest for the previous 36 months prior to initiating work on this document. These complete disclosure forms are retained by the American Radium Society™ in perpetuity.

The ARS Appropriate Use Criteria Steering Committee reviewed these disclosures with the chair and co-chair of this document and approved participation of the panelists prior to starting development of this work.

Disclosures potentially relevant to the content of this guideline are provided.

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Methodology and Study Selection

For detailed methodology and study selection, please refer to the Supplemental Appendix. Briefly, a search of the medical literature from peer-reviewed journals was conducted through PubMed®. The search strategy and subject-specific keywords were developed based on the expert panel’s consensus. Articles published since January 2000 to May 2020 with full text available on PubMed® and restricted to the English language and human subjects were included. The following subject-specific keywords were used: (Tonsil/Palatine tonsil, Glossotonsillar sulcus, GTS, GT sulcus, Tonsillar, Glossopharyngeal sulcus) AND (Unilateral, Ipsilateral) AND (Squamous) AND (Cancer, Carcinoma, Malignancy) AND (Radiotherapy, Radiation, Radiation therapy, EBRT, Surgery, Transoral, TORS, Tonsillectomy, Radical, Intensity modulated radiation therapy, Intensity modulated radiotherapy, IMRT, Proton). The most recent search was performed in May 2020 to identify any additional evidence published since the ACR Appropriateness Criteria® Ipsilateral Tonsil Radiation recommendation was finalized in 2012.

The full bibliographies of identified articles were reviewed to exclude studies which were not relevant. Of the 46 citations returned from initial review, the authors added 3 citations from bibliographies, websites, or books not found in the literature search. Of the 49 citations, 30 citations were retained for further detailed review, and 14 of them were added to the evidence table. Articles were removed from the bibliography if they were not relevant or generalizable to the topic, focused on unknown primary disease, or were not otherwise deemed relevant for any form of citation in the revised narrative text.
Summary of Literature Review

Introduction

In 2012, the American College of Radiology (ACR) published the Appropriateness Criteria for Ipsilateral Radiation for squamous cell carcinoma (SCC) of the tonsil. In the interim, tonsil cancer incidence has increased, consistent with predicted epidemiologic trends, and an extraordinarily high long term survival rate for human papilloma virus (HPV)-related oropharynx cancer has been reported.

Favorable oropharynx cancer survival rates led to increasing appreciation of toxicities associated with therapy. One way to potentially address toxicity is to limit bilateral neck therapy to those for whom it is truly required. This manuscript serves as an update to the ACR Appropriateness Criteria and the recommendations herein should supersede those of the previous effort.

Committee note: The literature review performed for this guideline did not return any titles that used the American Joint Committee on Cancer (AJCC) 8th Edition TNM Staging System. Therefore, this review uses descriptions of the nodes involved, rather than N categories, which entail aggregation. Multiple involved nodes ≤ 6 cm are common in these reports. Detailed literature search criteria are included in Appendix 1, where articles published up to May 2020 with full text available on PubMed and restricted to English language and human subjects were presented.

Topic 1. Updated Literature on Clinically Staged Tonsil Cancer (Variant 1)

Review and interpretation of the literature cited in the initial 2012 publication will not be repeated in this update. Studies published since 2012 are summarized in Table 1. The widespread adoption of pre-treatment PET/CT imaging has improved clinical detection of occult nodal metastases and potentially made physicians less concerned about otherwise occult adenopathy in the contralateral side of the neck. The recently published prospective ACRIN 6685 trial specifically affirmed the satisfactory negative predictive value (NPV) of PET/CT imaging for cN0 neck among 212 HNSCC patients (with 270 cN0 necks) with planned neck dissection, with a negative predictive value of 0.94 when using a variety of standardized uptake value maximum (SUVmax) cutoff values. Many of the cited studies here employed PET/CT staging for guiding clinical decision making, unlike those in the 2012 publication.

The largest case series of ipsilateral RT for tonsil SCC describes 185 patients with well-lateralized oropharyngeal tumors. Seventy percent of the patients had tumor confined to the tonsillar fossa, 25% had cancer of the soft palate (at least 1 cm away from the midline) and 5% had cancer of the lateral pharyngeal wall. Most patients had cN0 neck disease (50%), although a small proportion (17%) had multiple ipsilateral nodes. With a median follow-up of 4.1 years, 2 patients (1.1%) developed contralateral nodal failure. Both patients were successfully salvaged with surgery and postoperative radiation therapy resulting in an ultimate regional control rate of 100%.

Similar findings were observed in a previously cited series where 102 patients were treated with ipsilateral neck radiation. Both primary and nodal disease factors were taken into consideration and ipsilateral RT was delivered to patients with well-lateralized T1-T2 tonsillar primaries limited to the lateral one-third of the base of tongue or soft palate (≤ 1 cm of superficial mucosa of “hemistructure” extension, without muscle involvement or any suspicion of deeper penetration). Most patients were either
cN0 (54%) or had a single ipsilateral node not larger than 3 cm (26%), or larger than 3 cm (11%). Very few had multiple ipsilateral nodes (n=8, 8%).\textsuperscript{13} Practically this represents a limited sampling (~25%) of patients with tonsil cancer seen at their institution. Those who received ipsilateral RT had a 5-year contralateral progression rate of two percent (2% for p16+ and 3% for p16-) with no distant progression, both occurring in patients with T2 disease and a single node no larger than 3 cm.\textsuperscript{13} There was no association between contralateral disease development and p16 status.

A study of 37 patients (65% were p16+) with more generous, prospectively defined criteria for unilateral therapy (oropharyngeal cancers > 1 cm away from midline irrespective of T- or N-category designation) demonstrated no contralateral progression during a median follow-up of 32 months. In this series, 4/37 patients had T3 disease and 21/37 (62%) had multiple involved ipsilateral nodes ≤ 6 cm in diameter. The 3-year locoregional control, contralateral neck progression, distant metastasis, and disease-free survival rates were 96%, 0%, 7%, and 93%, respectively.\textsuperscript{14}

Several other retrospective series reported low rates of contralateral nodal failure in select patients. In a series of 76 patients who received unilateral RT, with a median follow up of 7.1 years, there was a single contralateral neck recurrence in level III for a patient with cT1 tonsil cancer and multiple ipsilateral nodes ≤ 6 cm. This occurred 37 months after completion of treatment and the patient was successfully salvaged with neck dissection followed by adjuvant radiation therapy and concurrent cisplatin. In this series, 34% of the patients had multiple ipsilateral nodes ≤ 6 cm in size, 42% underwent a planned ipsilateral neck dissection, and 28% also received concurrent chemotherapy.\textsuperscript{15} In another series of 58 patients treated with unilateral RT, in which 33% had multiple ipsilateral nodes or nodes >3 cm in size, no contralateral nodal failure was noted even in those with advanced nodal category.\textsuperscript{16} A smaller study of 20 patients with well-lateralized tonsil SCC and < 1 cm invasion into the soft palate or BOT patients (1 with T3, and 8 with multiple involved nodes ≤ 6 cm) also found no contralateral failure at a median follow up of 64 months.\textsuperscript{17} In another series of 61 patients with well-lateralized cancer without any involvement of BOT or soft palate, with a median follow up of 37.2 months, only one contralateral nodal failure was seen. The authors reported a 5-year overall survival of 94% and disease-free survival of 86%.\textsuperscript{18}

The highest contralateral recurrence rates were reported in a recent single institution study of 53 patients in Norfolk, United Kingdom.\textsuperscript{19} The authors reviewed 133 patients with tonsil SCC treated with definitive 3D-CRT from 2004 to 2011, including 53 (40%) patients receiving ipsilateral neck RT.\textsuperscript{19} The majority of the patients had p16-positive disease (92.5%), and half of the patients had multiple nodes ≤ 6 cm (52.8%). During a median follow-up of 68 months, four (7.5%) patients developed contralateral nodal recurrence; all four had p16-positive T1 primaries with multiple nodes ≤ 6 cm at initial diagnosis. Two patients had successful salvage. The other two patients died from their disease; one succumbed to metastatic cancer, and the other developed progressive regional recurrence after salvage neck dissection and CRT, dying from the disease. All contralateral neck recurrences occurred among patients with multiple ipsilateral nodes ≤ 6 cm. In all, 14% (4/28) of patients with this node designation had contralateral nodal recurrences. However, the small sample size limited further evaluation of the significance of nodal burden or extent of spread across multiple nodal levels in this cohort.
Additional studies including patients with somewhat more advanced T- and N-categories (see Table 1) have been reported. Medial extension appears to be an important determinant for appropriately selecting patients for ipsilateral neck radiation in the published reports with low contralateral nodal failure rates; primary tumors need to be at least one cm from midline at the most medial extent\textsuperscript{14,16} or involve < 1 cm of involvement of base of tongue and/or soft palate\textsuperscript{15,17,18}.

Although the data is limited, the published experiences demonstrate low rates of contralateral failure in both p16-positive and p16-negative subsets, suggesting that a separate selection algorithm based on p16 status is not warranted. No other biologic or molecular criteria have been validated as predisposing for a risk of greater contralateral nodal spread. Therefore, the committee does not recommend distinguishing eligibility for ipsilateral radiation based on p16 status.

One should regard these reported series as composed of highly selected patients; even the patients with advanced primary or nodal disease were likely those judged to be the most favorable candidates based on the overall sense of their clinical team.

Based on the criteria which have been established and used to select patients for unilateral therapy, and similar to the recommendation that was issued in the earlier guideline, the committee maintains that unilateral therapy should be reserved for patients with tumors that are tonsil-confined or either > 1 cm from midline or involve ≤ 1 cm of the mucosa of the base of tongue and/or soft palate (including the glossotonsillar sulcus). The committee did not reach a consensus on the appropriate use of bilateral neck irradiation in cases of multiple ipsilateral nodes, lymph nodes with clinical ENE, or a single large (> 6cm) ipsilateral lymph node. There are insufficient data to comment on the relationship between clinical/radiographic/pathologic extranodal extension (ENE) and contralateral failure.

**Topic 2. Updated Literature on Pathologically Staged Tonsil Cancer (Variant 2)**

The initial 2012 analysis reviewed three publications of primary tonsil cancer managed with bilateral neck dissections. The current manuscript includes three additional publications (Table 1) and an additional surgical-only series (not included in Table 1) specifically evaluating bilateral neck dissections for tonsil cancer.\textsuperscript{20} This analysis included relatively few patients but revealed that 4/14 (29%) of patients treated with a bilateral neck dissection had occult disease in the contralateral side of the neck. The only predictive factor suggestive of occult contralateral disease on the MVA was multi-level involvement of the ipsilateral neck (p = 0.007).

Similar to the management principles commonly employed for patients treated with primary radiation therapy, most patients managed with primary surgery who have medial extension of the primary tumor (to within one cm of the midline) are either managed with bilateral neck dissections or elective radiation given postoperatively to the contralateral side of the neck. Similar to reports of patients treated with primary radiation, there have been surgically-oriented publications evaluating the outcomes of patients who initially present with >1 node and/or extra-nodal extension (ENE) who are managed with unilateral therapy.

*Subtopic 1: Patients with multiple pathologic nodes*
One series examined 107 patients with lateralized tonsil cancers and cN0 to single or multiple involved nodes ≤ 6 cm who underwent surgery followed by unilateral or bilateral IMRT. Beginning in 2007, patients with tonsil cancer > 1 cm from midline were routinely treated unilaterally regardless of pathologic findings from the neck. Consequently, 48 patients received unilateral IMRT and 59 received bilateral IMRT.21 Of patients in the unilateral RT group, 23 (48%) had 2-5 positive nodes, 5 (10%) had > 5 positive nodes, and 77% had pathologic ENE. These numbers were comparable to the bilateral RT group. The 5-year locoregional control rates and survival were similar between the two groups of patients (5-year local-regional control of 100% for unilateral and 96% for bilateral treatments). With a median follow up of 5.5 years, no contralateral neck recurrences developed among patients treated unilaterally. Unilateral IMRT reduced acute toxicity and improved patient-reported quality of life compared with bilateral IMRT.21

Another report reviewed 81 patients (n=51, p16-positive) with lateralized tonsil SCC (cT1-2, cN0 to single or multiple ipsilateral nodes ≤ 6 cm) treated with surgery (9 simple tonsillectomies without further surgery to the oropharynx, 64 transoral laser microsurgery, and 8 cases lip split mandibulotomy with a free tissue/pedicle flap) and unilateral adjuvant radiotherapy. Of 67 patients, who underwent neck dissection, 30 (45%) had three or more involved lymph nodes, 29 (43%) had a node ≥ three cm, and 18 (27%) had ENE. With a median follow-up of 5.7 years, there were no contralateral recurrences reported. Five-year overall survival, progression-free survival, and locoregional control were 91.0%, 93.0%, and 95.4%, respectively.22

In a propensity-score matched, pooled analysis of 241 patients from 16 institutions who underwent various forms of tonsillectomy (without neck dissection) from 2001-2012 followed by adjuvant radiation, 70 selected patients who received ipsilateral adjuvant radiation were matched to another 70 patients with bilateral adjuvant radiation.23 Of note, the authors did not specifically state if the surgical procedure was simple tonsillectomy or oncologic radical tonsillectomy. The two groups of patients had similar survival outcomes. There was no contralateral neck recurrence in 61 patients with pathologic T1-2 and clinical N0 to a single node ≤ 6 cm. Among 79 patients with clinical multiple nodes ≤ 6 cm, 38 received ipsilateral RT and 41 bilateral RT. Contralateral neck recurrence was 3/38 (7.9%) in ipsilateral RT group vs. 0 in bilateral RT group (p=0.107). Notably, two of the three patients with contralateral neck failures also experienced local recurrence. With a median follow-up of 55 months, a total of 11 patients (15.7%) with pathologic T1-2, clinical N0 disease in the ipsilateral RT group experienced local recurrence, whereas only three patients (4.3%) developed recurrence in the bilateral RT group; this was primarily attributable to a high rate of local failure and not to a single isolated contralateral neck failure. It is unclear if the recurrence was related to treatment with less than radical tonsillectomy.

Another study of 34 patients with well-lateralized, node-positive tonsillar SCC treated with either definitive or adjuvant radiation to the primary site and ipsilateral side of the neck showed only one (3%) contralateral failure during a median follow-up of 34 months.24 Of the 34 patients, 16 (47%) had transoral resection before radiation and 10 (29%) of them also underwent neck dissections. All patients received definitive or adjuvant radiation to the primary site and ipsilateral neck. The 5-year local control rate was 95%.
The highest rate of contralateral failure after adjuvant unilateral RT for lateralized tonsil cancer was described in a series of 136 patients (57% of whom underwent an ipsilateral neck dissection pre-radiotherapy) treated with unilateral RT. Although the contralateral node recurrences were infrequent and a univariate/multivariate analysis was not performed, the authors comment that among the 8 patients with contralateral progression, 6 had multiple positive ipsilateral nodes, most had pathologic ENE, and most had >10 pack years smoking. However, the number of cases used to reach these conclusions was small and only 8/136 (5.9%) patients in this series had experienced a contralateral recurrence, at a median follow up of 4.2 years. 

Surgical considerations for tonsil cancer may differ from those regarding definitive ipsilateral RT. In addition to oncologic factors, functional outcomes, anatomic considerations, and comorbidity are important aspects for determining a proper surgical candidate. In many instances, the definitions of “well-lateralized” tonsil cancer from a surgeon’s perspective could be different from that of a radiation oncologist. Hence, the appropriateness of post-operative ipsilateral neck RT in T1-2 tonsil SCC still warrants further evaluation.

We strongly recommend that a multi-disciplinary review and discussion of these cases be performed prior to initiation of therapy. Proper communication is crucial in selecting the initial treatment modality and in optimal management of the contralateral neck.

**Topic 3. Role of Chemotherapy**

At present, there is limited evidence supporting the hypothesis that chemotherapy alone eradicates potential microscopic disease outside the radiation treatment fields. Furthermore, it is unclear what doses of radiation are needed with or without concurrent chemotherapy to successfully eradicate microscopic disease in the ipsilateral or contralateral neck for either p16+ -positive or p16-negative SCC. Therefore, with the paucity of evidence, the committee does not take a position on the usefulness of planned concurrent chemotherapy in determining a patient’s eligibility for ipsilateral radiation therapy.

**Topic 4: Salvage of Contralateral Progression in the Unirradiated Contralateral Neck**

The retrospective reports cited in this guideline all demonstrated low rates of contralateral recurrence. Collectively, there are a total of 26 cases of contralateral disease progression. Of these, 19 cases were successfully treated and reported as controlled at time of publication. Thus, 73% cases with contralateral progression were reported as successfully managed with a variety of treatment regimens and <1% (7 of 1,031) of patients managed unilaterally experienced contralateral progression that was not successfully treated. These results are similar to a prior review of 1,116 patients with mean contralateral neck failure rate of 2.42% and salvage rate of 73.

**Topic 5: Proton Therapy**

The search did not return any literature specifically addressing ipsilateral radiation for tonsil cancer using proton therapy. A published retrospective ipsilateral proton therapy series combined multiple histologic entities and subsites of head and neck cancer. Prospective studies on proton therapy for ipsilateral treatment of tonsil/oropharyngeal cancer are underway (NCT01893307, NCT03829033).
SUMMARY OF RECOMMENDATIONS

- Definitive (chemo)radiotherapy:
  - The committee strongly recommends that the use of ipsilateral radiation is usually appropriate for a tonsil-confined tumor with a minimal burden of nodal disease such as 0-2 involved lymph nodes (Variant 1). However, there were differing perspectives on the precise number and size of clinically involved nodes that constitute a ‘minimal burden of disease.’ There was agreement that unilateral therapy is usually appropriate for a tonsillar fossa-based tumor with ≤ 1 cm of tumor invasion into the soft palate or base of tongue (Variant 1). The committee acknowledges the importance of the clinical exam and variation in individual anatomy when quantifying the amount of soft palate and base of tongue involvement.
  - The committee does not recommend ipsilateral therapy for patients with > 1 cm of tumor extension into the mucosa of the base of tongue and/or soft palate. Instead, the committee strongly recommends bilateral neck irradiation in these cases, deemed as usually appropriate due to the increased risk of occult contralateral nodal spread (Variant 3).
  - The committee strongly recommends the use of bilateral neck irradiation as usually appropriate in cases with tumor extension to the posterior pharyngeal wall and in the presence of ipsilateral retropharyngeal lymphadenopathy (Variants 4 and 6). However, the committee did not reach a consensus regarding the appropriate use of ipsilateral neck irradiation for a tonsil-confined tumor with a single ipsilateral retropharyngeal node (Variant 6).
  - The committee did not reach a consensus on the appropriate use of bilateral neck irradiation in cases of multiple ipsilateral nodes, lymph nodes with clinical ENE or a single large (> 6cm) ipsilateral lymph node (Variants 1, 2 and 5).
  - The committee does not recommend consideration of HPV status or the use of concurrent chemotherapy in determining a patient’s eligibility for ipsilateral neck irradiation.

- Adjuvant (chemo)radiotherapy:
  - The committee recommends the use of ipsilateral neck irradiation as usually appropriate after resection of a well-lateralized tonsil primary tumor with a single ipsilateral pathologically positive node, regardless of microscopic ENE in the node or perineural invasion and lympho-vascular space invasion in the primary specimen (Variants 7 and 10). The committee did not reach a consensus on the appropriate use of bilateral neck irradiation for these pathologic features.
  - The committee strongly recommends the use of bilateral neck irradiation as usually appropriate after neck dissection in cases of multiple pathologically positive ipsilateral lymph nodes and in the presence of macroscopic extranodal extension (Variants 8 and 9).
The committee did not reach a consensus on the appropriate use of ipsilateral neck irradiation in this setting.

- The committee did not reach a consensus on the appropriate use of ipsilateral or bilateral neck irradiation in patients with a close (< 1mm) mucosal margin at the base of tongue (Variant 11).

- Committee note: for many of the case variants, the committee did not reach agreement, likely due to a lack of level 1 evidence supporting specific treatment decisions. This indicates an unmet need for higher-quality research specifying the exact criteria for unilateral radiation in future prospective clinical trials.

SUPPORTING DOCUMENTS

For additional information on the ARS Appropriate Use Criteria methodology and other supporting documents go to http://www.americanradiumsociety.org/page/aucmethodology.
CASE VARIANTS

Clinical condition: Primary radiation-based therapy

Variant 1: Patient with primary tumor 2 cm, confined to the tonsillar fossa, one 3 cm mobile ipsilateral node in level 2 and one mobile 1 cm ipsilateral node in level 3.

*Issues raised: what is the maximum number of nodes for which unilateral therapy is appropriate?*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
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<th>Reference</th>
<th>SOE</th>
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<td>12, 13, 16-19, 24-25</td>
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Variant 2: Patient with primary tumor 1.8 cm confined to the tonsillar fossa, single 4 cm lymph node on exam growing through skin.

*Issues raised: does clinical ENE trigger a recommendation of bilateral therapy in a well lateralized tumor?*

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<tr>
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<td>7</td>
<td>X</td>
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Variant 3: Patient with primary tumor 2.5 cm, invading 1.5 cm into the soft palate and/or tongue base, no lymph nodes bilaterally.

*Issues raised: does proximity to midline trigger bilateral therapy when the ipsilateral neck is cN0?*

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<th>Treatment</th>
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<th>Final Tabulations</th>
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Variant 4: Patient with primary tumor 2.5 cm, invading posterior pharyngeal wall, no lymph node bilaterally.

*Issues raised: does involvement of posterior pharyngeal wall trigger a recommendation of bilateral therapy when the ipsilateral neck is cN0?*

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<th>Treatment</th>
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<th>Final Tabulations</th>
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Variant 5: Patient with primary tumor 1.5 cm, confined to the tonsillar fossa, single 7 cm mobile ipsilateral node.

**Issues raised:** what is the largest single node for which unilateral therapy is appropriate?

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<th>Treatment</th>
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<th>Final Tabulations</th>
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Variant 6: Patient with primary tumor 2 cm, confined to the tonsillar fossa, single ipsilateral 1.5 cm lateral retropharyngeal node seen on cross-sectional imaging.

**Issues raised:** does involvement of a retropharyngeal node trigger a recommendation for bilateral therapy?

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<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
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**KEY:** RT = Radiation Therapy

*Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.*

**Rating Categories:**
- U Usually not appropriate;
- M May be appropriate;
- A Usually appropriate

**Disagreement:**
- i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**References:**
- Lists the references associated with the recommendation.

**SOE:**
- Strength of Evidence. S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

**SOR:**
- Strength of Recommendation. ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
Clinical condition: Adjuvant radiation-based therapy

Variant 7: Patient with resected primary tumor confined to tonsillar fossa and single ipsilateral node with ENEmi (ENE 1 mm).

Issues raised: does microscopic ENE in an otherwise well lateraledized tumor impact the decision of unilateral therapy?

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<th>Treatment</th>
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<th>Final Tabulations</th>
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<th>Reference</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
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<tr>
<td>Bilateral RT</td>
<td>M</td>
<td>1 1 3 1 4 2</td>
<td>5</td>
<td>X</td>
<td>22-23</td>
<td>L</td>
<td>-</td>
</tr>
</tbody>
</table>

Variant 8: Patient with resected primary tumor with 0.5 cm soft palate and/or tongue base invasion, 5 ipsilateral nodes, no ENE.

Issues raised: does number of positive nodes pathologically impact the decision of unilateral therapy?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral RT</td>
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<td>22-23</td>
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<td>8</td>
<td></td>
<td>22-23</td>
<td>M</td>
<td>↑</td>
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</table>

Variant 9: Patient with significant medical comorbidity with resected primary tumor with < 1 cm of soft palate/BOT involved, 2 ipsilateral nodes, + ENEma (5 mm of ENE)

Issues raised: does major ENE in a lateralized tumor trigger a recommendation of bilateral therapy? Do age/comorbidities of the patient matter?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SOE</th>
<th>SOR</th>
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</thead>
<tbody>
<tr>
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<tr>
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<td>1 5 3 1</td>
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<td>22</td>
<td>L</td>
<td>↑</td>
</tr>
</tbody>
</table>

Variant 10: Patient with resected primary tumor with < 1 cm of soft palate/BOT involved, PNI and LVSI on specimen, single 2 cm ipsilateral lymph node with no ENE.

Issues raised: do PNI and LVSI influence a recommendation of bilateral neck therapy?

<table>
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<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
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<th>Reference</th>
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<th>SOR</th>
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</thead>
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<td>2 3</td>
<td>4</td>
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<td></td>
<td></td>
</tr>
</tbody>
</table>

Variant 11: Patient with T1N1 tonsil cancer with <0.5 cm BOT invasion clinically. Underwent radical tonsillectomy + limited tongue base resection and ipsilateral neck dissection and final pathology reveals 2.2 cm primary tumor with < 1 mm margin on BOT and single 1.5 cm ipsilateral lymph node with no ENE.

Issues raised: should we irradiate the contralateral neck based on the close margin?
<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating Category</th>
<th>Final Tabulations</th>
<th>Group Median Rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SOE</th>
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</thead>
<tbody>
<tr>
<td>Ipsilateral RT</td>
<td>M</td>
<td>1 3 3 2 1</td>
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<td>X</td>
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<td>L</td>
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<td>Bilateral RT</td>
<td>M</td>
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<td>6</td>
<td>X</td>
<td>21-22</td>
<td>L</td>
<td>-</td>
</tr>
</tbody>
</table>

**KEY:** RT = Radiation Therapy

*Please refer to the supporting documentation for a more complete discussion of the concepts and their definitions below.*

**Rating Categories:**
- U Usually not appropriate
- M May be appropriate
- A Usually appropriate

**Disagreement:**
- i.e., the variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see narrative text). Group median rating is set automatically to 5.

**References:**
- Lists the references associated with the recommendation.

**SOE:**
- Strength of Evidence. S Strong; M Moderate; L Limited; EC Expert Consensus; EO Expert Opinion

**SOR:**
- Strength of Recommendation. ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak
References


