10-17-2020

**Ipsilateral radiation for squamous cell carcinoma of the tonsil: American Radium Society appropriate use criteria executive summary**

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Funding information
Wayne State University School of Medicine; American College of Radiology; Springer Publishing; BioMimetix; Genentech; NCI PDQ Editorial Board; American Board of Radiology; Galera Therapeutics; Bristol Myers Squibb; Merck; UpToDate Inc; Varian Medical Systems; NIH/NCI Cancer Center, Grant/ Award Number: P30 CA008748

Abstract
Background: We conducted the current systemic review to provide up-to-date literature summary and optimal evidence-based recommendations for ipsilateral radiation for squamous cell carcinoma of the tonsil.

Methods: We performed literature search of peer-reviewed journals through PubMed. The search strategy and subject-specific keywords were developed based on the expert panel’s consensus. Articles published from January 2000 to May 2020 with full text available on PubMed and restricted to the English language and human subjects were included. Several prespecified search terms were used to identify relevant publications and additional evidence published since the initial American College of Radiology Appropriateness Criteria.
Ipsilateral Tonsil Radiation recommendation was finalized in 2012. The full bibliographies of identified articles were reviewed and irrelevant studies were removed.

**Results:** The initial search and review returned 46 citations. The authors added three 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, or focused on unknown primary disease. Several commonly encountered clinical case variants were created and panelists anonymously rated each treatment recommendation. The results were reviewed and disagreements discussed.

**Conclusions:** The panel provided updated evidence and recommendations for ipsilateral radiation for squamous cell carcinoma of the tonsil in the setting of primary radiation-based therapy and postoperative adjuvant radiotherapy. This committee did not reach agreements for some case variants due to a lack of strong evidence supporting specific treatment decisions, indicating a further need for research in these topics.

**KEYWORDS**
ipsilateral, radiation, radiotherapy, tonsil, unilateral

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## 1 | 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 unless truly necessary. 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) Eighth 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 S1, where articles published up to May 2020 with full English text available on PubMed and restricted to human subjects were presented.

## 2 | PATIENTS AND METHODS

### 2.1 | Study selection

For detailed methodology and study selection, refer to the Appendix S1. 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
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<tr>
<th>Reference</th>
<th>Study type</th>
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<th>Contralateral neck failure (CNF) and salvage therapy</th>
<th>Level of evidence</th>
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<tr>
<td>Al-Mamgani et al9</td>
<td>Single-institution case series</td>
<td>185 patients Ipsilateral RT criteria: T1-3N0-2b tumors confined to the tonsillar fossa, the soft palate with at least 1 cm from the midline or the lateral pharyngeal wall Staging imaging: CT and/or MRI PET/CT if needed</td>
<td>Median follow up: 4.1 y Contralateral neck failure rates: 2/185 (1.1%) N0: 1/92 (11 mo post RT) N1: 0/43 N2a: 0/18 N2b: 1/32 (3 mo post RT) 5-y LC rates: 90% 5-y RC rates: 96% 5-y DFS rates: 84%</td>
<td>Patient #1: initial T1N2b, salvage ND + brachytherapy boost; NED Patient #2: initial T2N0, salvage ND + RT; NED</td>
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<td>Lynch et al10</td>
<td>Single-institution case series</td>
<td>136 patients Ipsilateral RT criteria: T1-3N0-2b No tumor in tongue base or middle and medial 1/3 of the soft palate Staging imaging: CT and/or MRI 57% of patients underwent an ipsilateral neck dissection pre-radiotherapy</td>
<td>Median follow-up: 4.2 y rates: 8/136 (5.9%) N0: 1/28 N1: 1/20 N2a: 0/31 N2b: 6/55 N3: 0/2</td>
<td>Patient #1: T3N0, initial tonsillectomy + RT alone; not salvageable due to tonsil recurrence and CNF. DOD. Patient #2: T2N1, initial tonsillectomy + ND + CRT; failed in contralateral tonsil and neck. Salvaged ND + RT; NED Patient #3: T2N2b, initial tonsillectomy + ND + CRT; salvage ND + RT; NED Patients #4-8: T2N2b, initial tonsillectomy + ND + CRT; salvage ND + RT; NED</td>
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<td>Huang et al11</td>
<td>Single-institution case series</td>
<td>102 patients (96 with p16 stain; 62 p16+) Ipsilateral RT criteria: T1-2N0-2b ≤1/3 of “hemistructure” of BOT or soft palate with ≤1 cm superficial mucosa of “hemistructure” extension No muscle involvement or deeper penetration Staging imaging: CT MRI if BOT invasion PET/CT not routinely used</td>
<td>Median follow up: 6 y CNF rates: 2/96 (2.1%) N0: 0/52 N1: 2/25 N2a: 0/11 N2b: 0/8 5-y LC rates: p16+: 95% p16−: 90% 5-year RC rates: p16+: 98% p16−: 94%</td>
<td>Both CNF had T2N1 disease and received RT alone 60Gy/25 fractions with homolateral wedge pairs. Patient #1 (HPV+): salvage ND; NED 12 y later Patient #2 (HPV−): salvage ND + RT; NED for 8 y</td>
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<td>Liu et al12</td>
<td>Single-institution case series</td>
<td>58 patients (9 p16+, 6 p16−, rest unknown) Ipsilateral RT criteria: Tumor within the tonsillar fossa or ≥ 1 cm from midline Staging imaging: Information not available</td>
<td>Median follow-up: 5.3 y CNF rates: 0/58 N0: 0/25 N1: 0/14 N2a: 0/10 N2b: 0/4 N3: 0/5 5-y LC rates: 91% 5-y RC rates: 87%</td>
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<td>Kennedy et al.13</td>
<td>Single-institution case series</td>
<td>76 patients (p16 missing in 88%) Contralateral neck failure (CNF) and salvage therapy</td>
<td>Median follow-up: 7.1 y CNF rates: 1/76 (1.3%) N0: 0/27 N1: 0/15 N2a: 0/8 N2b: 1/26 (37 mo post-RT)</td>
<td>Patient #1: initial T1N2b; salvage ND + CRT with cisplatin; NED</td>
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<td>Dan et al.14</td>
<td>Single-institution case series</td>
<td>61 patients T1-3N0-2b/3 Well-lateralized primary without involvement of the base of the tongue, soft or hard palate</td>
<td>Median follow-up: 3.1 y CNF rates: 1/61 (1.6%) N0: 0/0 N1: 0/15 N2a: 0/14 N2b: 1/31 (6 mo post-RT) N3: 0/1</td>
<td>Patient #1: initial T2N2b, salvage ND + RT; NED</td>
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<td>Hu et al.15</td>
<td>Single-institution case series</td>
<td>37 patients (23 p16+) &gt;1 cm from midline</td>
<td>Median follow-up: 2.7 y CNF rates: 0/37 N0: 0/4 N1: 0/9 N2a: 0/3 N2b: 1/21</td>
<td>3-y LRC rates: 96%</td>
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<tr>
<td>Ye et al.16</td>
<td>Single-institution case series</td>
<td>70 patients (53 p16+) Physician discretion</td>
<td>Median follow-up: 5.7 y CNF rates in p16+: 4/53 (7.5%) N0: 0/15 N1: 3/18 N2a: 1/7 N2b: 0/11 N3: 0/2</td>
<td>No detail on each patient Patient #1: also had DM; palliative RT; DOD Patients #2-4: salvage ND only; one NED, one DOD, one died from another cause</td>
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<td>Koo and Wu17</td>
<td>Single-institution case series</td>
<td>20 patients T1-3N0-2b not cross midline and &lt;1 cm of tumor invasion into the soft palate or BOT</td>
<td>Median follow-up: 5.3 y CNF rates: 0/20 N0: 0/2 N1: 0/8 N2a: 0/2 N2b: 0/8</td>
<td>5-y LC rates in p16+: 83%</td>
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<td>Gottumukkala et al18</td>
<td>Single-institution case series</td>
<td>34 patients (25 p16+; 1 p16−; rest unknown)</td>
<td>Median follow up: 2.8 y&lt;br&gt;CNF rates: 1/34&lt;br&gt;N1: 1/6&lt;br&gt;N2a: 0/8&lt;br&gt;N2b: 0/19&lt;br&gt;N2: 0/1&lt;br&gt;5-y LC rates: 95%</td>
<td>Patient #1: pT2cN1 initially; postop PET/CT showed a borderline contralateral level 2 node with SUV of 3.3. Patient underwent ipsilateral IMRT to 70 Gy in 35 fractions. CNF at 1-y post-RT in the prior suspicious lymph node. Received salvage ND alone. NED for 7 y</td>
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<td>Maskell et al19</td>
<td>Single-institution case series</td>
<td>53 patients (49 p16+)</td>
<td>Median follow up: 5.7 y&lt;br&gt;CNF rates: 4/53 (7.5%)&lt;br&gt;N0: 0/10&lt;br&gt;N1: 0/10&lt;br&gt;N2a: 0/5&lt;br&gt;N2b: 4/28</td>
<td>All 4 patients had p16+ T1N2b tumors. 3 had 3 or more multi-level nodes&lt;br&gt;Patient #1: recurred 18 mo after RT; salvage ND + CRT; DOD&lt;br&gt;Patient #2: recurred 43 mo after RT; salvage ND + CRT; NED&lt;br&gt;Patient #3: recurred 23 mo after RT; salvage ND + CRT; DOD&lt;br&gt;Patient #4: recurred 34 mo after RT; definitive CRT; NED</td>
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<td>Chin et al20</td>
<td>Single-institution case series</td>
<td>154 patients treated with postoperative IMRT&lt;br&gt;107 with lateralized primary and cN0-2b disease: Group 1: 48 received unilateral IMRT&lt;br&gt;Group 2: 59 received bilateral IMRT&lt;br&gt;47 patients had nonlateralized primary or N2c to N3 disease and received bilateral IMRT (group 3)</td>
<td>5-y LC rates: Group 1: 100%&lt;br&gt;Group 2: 96%&lt;br&gt;Group 3: 94%&lt;br&gt;(no difference)</td>
<td>5-y OS rates: Group 1: 85%&lt;br&gt;Group 2: 79%&lt;br&gt;Group 3: 76%&lt;br&gt;(no difference)</td>
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<td>Rackley et al21</td>
<td>Single-institution case series</td>
<td>81 patients (51 p16+) with lateralized tonsil SCC (cT1-2, cN0-2b per AJCC seventh) treated with surgery and unilateral adjuvant (chemo) radiotherapy&lt;br&gt;N0 = 18 patients (22%)&lt;br&gt;N1 = 3 patients (4%)&lt;br&gt;N2a = 12 patients (15%)&lt;br&gt;N2b = 48 patients (59%)</td>
<td>Of 67 patients who underwent neck dissection: 18 (27%) extranodal extension (ENE)&lt;br&gt;30 (45%) had ≥3 involved lymph nodes&lt;br&gt;29 (43%) had a node ≥30 mm&lt;br&gt;5-y LC rates: 95%&lt;br&gt;5-y PFS rates: 93%&lt;br&gt;5-y OS rates: 91%&lt;br&gt;No contralateral failure after a median follow-up of 5.7 y</td>
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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.

2.2 | Consensus voting

The lead author and panelists created and reviewed several clinical variants with corresponding treatment options representing commonly encountered clinical scenarios. Panelists anonymously rated each treatment using a score of “1 to 9,” representing “usually not appropriate” (1-3), “may be appropriate” (4-6), and “usually appropriate” (7-9). The results were reviewed and disagreements discussed, then a second round of voting was performed and results were finalized after another round of discussion. We then calculated the median score and determined the level of agreement based on the BIOMED Concerted Action on Appropriateness definition. The strength of recommendations was graded using the GRADE system.

3 | RESULTS

3.1 | 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 pretreatment Positron Emission Tomography - Computed Tomography (PET/CT) imaging has improved clinical detection of occult nodal metastases and potentially made physicians less concerned about otherwise occult adenopathy in the

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<td>Kim et al22</td>
<td>Multi-institution case series</td>
<td>241 patients cT1-2 and cN0-2b tonsil SCC from 16 institutions</td>
<td>All patients underwent tonsillectomy and postop RT</td>
<td>Ipsi vs Bilateral RT- 5-y DMFS rates: 93% vs 97% ($P = .08$) 5-y LRRFS rates: 88% vs 97% ($P = .37$) 5-y DFS rates: 81% vs 94% ($P = .08$) 5-y OS rates: 93% vs 94% ($P = .99$)</td>
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<td>No contralateral neck recurrence in 61 patients with T1-2N0-2a regardless of the treatment groups</td>
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<td>For 79 patients with N2b, contralateral neck recurrence was more common in the ipsi RT group than in the bilateral RT group (7.9% vs 0.0%), but the difference was not significant ($P = .107$)</td>
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Note: Level of evidence key: (1) The conclusions of the study are valid and strongly supported by study design, analysis and results. (2) The conclusions of the study are likely valid, but study design does not permit certainty. (3) The conclusions of the study may be valid but the evidence supporting the conclusions is inconclusive or equivocal. (4) The conclusions of the study may not be valid because the evidence may not be reliable given the study design or analysis.

Abbreviations: BOT, base of tongue; CNF, contralateral neck failure; CRT, chemoradiation; CT, computed tomography; DFS, disease-free survival; DM, distant metastasis; DMFS, distant metastasis-free survival; DOD, dead of disease; IMRT, intensity-modulated radiotherapy; LC, local control; LRRFS, locoregional recurrence-free survival; MRI, magnetic resonance imaging; ND, neck dissection; NED, no evidence of disease; OS, overall survival; PET, positron emission tomography; PFS, progression-free survival; RC, regional control; RT, radiation therapy; SUV, standard uptake value.
contralateral side of the neck. The recently published prospective ACRIN 6685 trial specifically affirmed the satisfactory negative predictive value of PET/CT imaging for cN0 neck among 212 head and neck squamous carcinoma cancer patients (with 270 cN0 necks) undergoing planned neck dissection, with a negative predictive value of 0.94 when using a variety of standardized uptake value maximum (SUV_{max}) 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 radiation therapy (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 RT 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 to 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%). 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 recurrence rate of 2% (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. 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. 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 RT 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. 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. A smaller study of 20 patients with well-lateralized tonsil SCC and <1 cm invasion into the soft palate or base of tongue (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. 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 1 contralateral nodal failure was seen. The authors reported a 5-year overall survival of 94% and disease-free survival of 86%.

The highest contralateral recurrence rates were reported in a recent single institution study of 53 patients in Norfolk, UK. The authors reviewed 133 patients with tonsil SCC treated with definitive 3D-conformal RT from 2004 to 2011, including 53 (40%) patients receiving ipsilateral neck RT. 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 1 cm from midline at the most medial extent\textsuperscript{12,15} or involve <1 cm of involvement of base of tongue and/or soft palate.\textsuperscript{13,14,17}

Although the data are 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 that 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 glosso-tonsillar 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 extranodal extension (ENE), or a single large (>6 cm) ipsilateral lymph node. There are insufficient data to comment on the relationship between clinical/radiographical/pathological ENE and contralateral failure.

3.2 | 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{24} 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 multivariable analysis was multilevel involvement of the ipsilateral neck.

Similar to the management principles commonly employed for patients treated with primary RT, most patients managed with primary surgery who have medial extension of the primary tumor (to within 1 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 ENE who are managed with unilateral therapy.

3.2.1 | 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.\textsuperscript{20} Of patients in the unilateral RT group, 23 (48%) had 2 to 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.\textsuperscript{20}

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 mandibulectomy 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 ≥3 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.\textsuperscript{21}

In a propensity-score matched, pooled analysis of 241 patients from 16 institutions who underwent various forms of tonsillectomy (without neck dissection) from 2001 to 2012 followed by adjuvant radiation, 70 selected
patients who received ipsilateral adjuvant radiation were matched to another 70 patients with bilateral adjuvant radiation. 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 = .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 to T2, 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. 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 postoperative ipsilateral neck RT in T1 to T2 tonsil SCC still warrants further evaluation.

We strongly recommend that a multidisciplinary 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.

### 3.3 | 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 oropharyngeal carcinoma. 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 RT.

### 3.4 | 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 1031) of patients managed unilaterally experienced contralateral progression that was not successfully treated. These results are similar to a prior review of 1116 patients with mean contralateral neck failure rate of 2.42% and salvage rate of 73%.

### 3.5 | 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 to 2 involved lymph nodes discussed in 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 did not reach a consensus on the appropriate use of ipsilateral neck irradiation 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 (>6 cm) ipsilateral lymph node (variants 1, 2, and 5).
  - The panel 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 lymphovascular 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 (<1 mm) 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 (Data S1).

ACKNOWLEDGMENTS
The authors thank Dr. Nancy Lee and the ARS AUC Steering Committee for critically reviewing the manuscript and Ms. Andrea Taylor for administrative support. This study was supported in part through the NIH/NCI Cancer Center Support Grant P30 CA008748.

CONFLICT OF INTERESTS
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. Dr. Tsai reports consulting fees/honorarium from Varian Medical Systems; Dr. Galloway reports personal fees from Varian Medical Systems, personal fees from UpToDate Inc, outside the submitted work; Dr. Ridge has nothing to disclose; Dr. Robbins has nothing to disclose; Dr. Bakst has nothing to disclose; Dr. Beadle has nothing to disclose; Dr. Chang has nothing to disclose; Dr. Cooper has nothing to disclose; Dr. Koyfman reports grants from Merck, grants from Bristol Myers Squibb, other from Varian Medical Systems, other from UpToDate, outside the submitted work; Dr. Margalit reports personal fees from Galera Therapeutics in 2018, outside the submitted work;
Dr. Truong reports travel expenses from the American Board of Radiology and honoraria from the NCI PDQ Editorial Board; Dr. Yom reports grants from Genentech, grants from Bristol-Myers Squibb, grants from Merck, grants from BioMimeticx, personal fees from Springer, personal fees from UpToDate, outside the submitted work; Dr. Siddiqui reports grants, personal fees, and non-financial support from Varian Medical Systems, Inc, other from American College of Radiology, other from American College of Radiology, other from American College of Radiology. Dr. Siddiqui reports grants, personal fees, and non-financial support from Varian Medical Systems, Inc, other from American College of Radiology, other from American College of Radiology. Dr. Siddiqui reports grants, personal fees, and non-financial support from Varian Medical Systems, Inc, other from American College of Radiology, other from American College of Radiology.

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**REFERENCES**


SUPPORTING INFORMATION
Additional supporting information may be found online in the Supporting Information section at the end of this article.

APPENDIX: 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>Group median rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral RT</td>
<td>A</td>
<td>7</td>
<td></td>
<td>13-15,19,20,24-26</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>M</td>
<td>5</td>
<td>×</td>
<td>13-15,19,20,24-26</td>
<td>M</td>
<td></td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating category</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>
<td>M</td>
<td>6</td>
<td>×</td>
<td>-</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>M</td>
<td>7</td>
<td>×</td>
<td>-</td>
<td>L</td>
<td></td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating category</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>
<td>U</td>
<td>2</td>
<td></td>
<td>12,13,16-19,24-25</td>
<td>S</td>
<td>↑</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>A</td>
<td>8</td>
<td></td>
<td>12,13,16-19,24-25</td>
<td>S</td>
<td>↑</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating category</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>
<td>U</td>
<td>3</td>
<td></td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>A</td>
<td>8</td>
<td></td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
</tbody>
</table>

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?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating category</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>
<td>M</td>
<td>4</td>
<td>×</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>M</td>
<td>7</td>
<td>×</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
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?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating category</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>
<td>M</td>
<td>3</td>
<td>×</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>A</td>
<td>8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
</tbody>
</table>

**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 lateralized tumor impact the decision of unilateral therapy?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating category</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>
<td>A</td>
<td>7</td>
<td>×</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>M</td>
<td>5</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

Variant 8: Patient with resected primary tumor with 0.5 cm soft palate and/or tongue base invasion, five 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>Group median rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral RT</td>
<td>M</td>
<td>5</td>
<td>×</td>
<td>21-23</td>
<td>L</td>
<td>-</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>A</td>
<td>8</td>
<td>21-23</td>
<td>M</td>
<td>↑</td>
<td></td>
</tr>
</tbody>
</table>

Variant 9: Patient with significant medical comorbidity with resected primary tumor with <1 cm of soft palate/BOT involved, two 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>Group median rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral RT</td>
<td>M</td>
<td>6</td>
<td>×</td>
<td>22</td>
<td>L</td>
<td>-</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>A</td>
<td>7</td>
<td>22</td>
<td>L</td>
<td>↑</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 LVI influence a recommendation of bilateral neck therapy?

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Rating category</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>
<td>A</td>
<td>7</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>↑</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>M</td>
<td>4</td>
<td>-</td>
<td>-</td>
<td>-</td>
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</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>Group median rating</th>
<th>Disagree</th>
<th>Reference</th>
<th>SOE</th>
<th>SOR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ipsilateral RT</td>
<td>M</td>
<td>6</td>
<td>×</td>
<td>21,22</td>
<td>L</td>
<td>-</td>
</tr>
<tr>
<td>Bilateral RT</td>
<td>M</td>
<td>6</td>
<td>×</td>
<td>21,22</td>
<td>L</td>
<td>-</td>
</tr>
</tbody>
</table>

Abbreviations: EC, expert consensus; EO, expert opinion; L, limited; M, moderate; RT, radiation therapy; S, strong; SOE, strength of evidence; SOR, strength of recommendation; †, strong recommendation; ‡, weak recommendation; -, not strong, not weak.

**Note**: Refer to the supporting documentation for a more complete discussion of the concepts and their definitions below. Rating categories: A, usually appropriate; M, may be appropriate; U, usually not appropriate. Disagreement: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation (see the narrative text). Group median rating is set automatically to 5. References show the lists of the references associated with the recommendation.