Title

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

Journal

Head & Neck, 43(1)

ISSN

1043-3074

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Publication Date

2021

DOI

10.1002/hed.26492

Peer reviewed

HHS Public Access

Author manuscript

Head Neck. Author manuscript; available in PMC 2022 May 24.

Published in final edited form as:

Head Neck. 2021 January ; 43(1): 392–406. doi:10.1002/hed.26492.

IPSILATERAL RADIATION FOR SQUAMOUS CELL CARCINOMA OF THE TONSIL: AMERICAN RADIUM SOCIETY APPROPRIATE USE CRITERIA

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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.[5] 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.[6–10]

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 June 2019 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.11 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 tumors confined to the tonsillar fossa (70%), the soft palate (25%), with at least one cm from the midline or the lateral pharyngeal wall (5%) received unilateral IMRT.12 Most patients were N0 (50%) although a small proportion (17%) had multiple ipsilateral nodes. During a median follow-up of 4.1 years, two developed contralateral nodal progression (1.1%) but both patient’s recurrences were successfully treated, and they remained disease free.

Similar findings were observed from a previously cited series where 102 patients with a lateralized T1-T2 tonsillar primary limited to the lateral one-third of the base of tongue

(BOT) or soft palate (≤ 1 cm of superficial mucosa of “hemistructure” extension, without muscle involvement or any suspicion of deeper penetration) and N0 to a single ipsilateral node not larger than 3 cm disease were treated with ipsilateral radiation.13 Practically this represents a limited sampling (~25%) of tonsil cancer patients seen at the 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.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 were T3 and 21/37 (62%) were N2b. The 3-year locoregional control, contralateral neck progression, distant metastasis, and disease-free survival were 96%, 0%, 7%, and 93%, respectively.[14]

In a series of 76 patients with a median follow up of 7.1 years who received unilateral RT, there was a single episode of contralateral neck disease in level III for a patient with cT1 tonsil cancer with multiple ipsilateral nodes ≤ 6 cm 37 months after completing treatment. This was successfully treated. In this series around 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.[15] Another series of 58 patients (33% N2-N3 disease) treated with unilateral RT demonstrated no contralateral disease progression even in those with advanced nodal category.[16] A smaller study of 20 patients (1 with T3 and 8 with multiple involved nodes ≤ 6 cm disease) with well-lateralized tonsil SCC and < 1 cm invasion into the soft palate or BOT also found no contralateral failure during a median follow up of 64 months.[17] In addition, for patients with well lateralized cancer without any involvement of BOT or soft palate, another series reported only one contralateral nodal progression out of 61 patients during a median follow up of 37.2 months, with a 5-year overall survival of 94% and disease-free survival of 86%.[18]

The highest contralateral recurrence rates came from a recent single institution study of 53 patients in Norfolk, United Kingdom.[19] The authors reviewed 133 tonsil SCC patients treated with definitive 3DCRT from 2004 to 2011, and included 53 (40%) patients receiving ipsilateral neck RT in the analysis.[19] The majority of the patients were p16-positive (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, and all four had p16-positive T1 primaries with multiple nodes ≤ 6 cm at initial diagnosis. Two patients were successfully salvaged, and the other two patients died from their disease; one succumbed to metastatic cancer and the other developed progressive local recurrence after salvage neck dissection and CRT, dying from the disease. All contralateral neck progression occurred among patients with multiple ipsilateral nodes ≤ 6 cm. In total 14% (4/28) of patients with this node designation progressed. 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 have reported outcomes including patients with somewhat more advanced T- and N-categories (see Table 1). Medial extension appears to be key – either primary tumors need to be at least one cm from midline at the most medial extent[14,16] or < 1 cm of involvement of base of tongue and/or soft palate.[15,17,18]

Although the data is limited, the published experiences demonstrate low rates of contralateral failure in both p16+ and p16- subsets suggesting that based on the present evidence 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 being comprised of highly selected patients; 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 glossotonsillar sulcus). There is insufficient data to comment on the relationship between clinical/radiographic/pathologic extranodal spread (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.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 neck. In a manner 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 primary and cN0-N2b to single or multiple involved nodes ≤ 6 cm who underwent oncology tonsillectomy and ipsil/bilateral neck dissection followed by postoperative RT from 1997 to 2013. Beginning in 2007 patients with tonsil cancer > 1 cm

from midline were routinely treated unilaterally regardless of pathologic findings from the neck and as such 48 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. With a median follow up of 5.5 years, no contralateral neck recurrences developed among unilaterally treated patients. Unilateral IMRT reduced acute toxicity and improved patient-reported quality of life compared with bilateral IMRT.21

Another report reviewed 81 patients (51 p16+) with lateralized tonsil SCC (cT1–2, cN0 to single or multiple ipsilateral nodes ≤ 6 cm) treated with surgery (9 simple tonsillectomy 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. No contralateral recurrences ensued after a median follow-up of 5.7 years. 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. During 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 getting non-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 by a series of 136 patients (57% of them 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 at a median follow up of 4.2 years only 8/136 (5.9%) patients in this series had experienced a contralateral recurrence [25].

Surgical considerations for tonsil cancer may differ from those surrounding definitive ipsilateral RT. In addition to oncologic factors, functional outcomes, anatomic considerations, and comorbidity are important aspects for determining a proper surgical candidate.26 In many instances, the definitions of “well-lateralized” tonsil cancer from a surgeon’s perspective could be different from that of a radiation oncologist. Consequently, whether all surgically resected T1-T2 tonsil SCC with clinically node-negative contralateral side of the neck are candidates for ipsilateral adjuvant RT still warrants further discussion.

We strongly recommend multi-disciplinary evaluation before definitive surgery or radiation. Proper communication is crucial especially in a surgical case where the surgeon feels that the contralateral neck is at risk.

Topic 3. Role of Chemotherapy

Thus far, none of the aforementioned single-institutional case series have demonstrated an association between concurrent chemotherapy (most commonly cisplatin) used in conjunction with radiation therapy and a decreased or increased risk of contralateral nodal failure. Unfortunately, given the small size and heterogeneous nature of these datasets, it is unlikely that a valid analysis can be conducted on this question with the evidence that exists currently. At present, there is limited no high-quality evidence that supports the hypothesis that chemotherapy alone eradicates potential contralateral neck microscopic disease or that chemotherapy can eradicate microscopic disease outside the designated radiation treatment volumes. 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+ or p16- SCC. Therefore, given 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. As a consequence, most series with contralateral progression specifically report the outcomes of contralateral progression. Collectively, there are a total of 26 cases of contralateral disease progression. Of these, 19 were successfully treated and reported as controlled at time of publication. Thus, 73% of contralateral progression was 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. The result is similar to that from a prior review of 11 earlier studies of 1,116 patients with mean contralateral neck failure rate of 2.42% and salvage rate of 73%.27

Topic 5: Proton Therapy

The search did not return any literature specifically addressing ipsilateral radiation for tonsil cancer using proton therapy. Published retrospective ipsilateral proton therapy series often combined multiple histologic entities and subsites of head and neck cancer.28 However, prospective studies on proton therapy for ipsilateral treatment of tonsil/oropharyngeal cancer are under way (NCT01893307, NCT03829033).

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?

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	Reference	SQ	SOE	SOR
		1	2	3	4	5	6	7	8	9						
Ipsilateral RT						1	1	4	3	2	7					
Bilateral RT				1	4	4		3	1		5	X				

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?

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	Reference	SQ	SOE	SOR
		1	2	3	4	5	6	7	8	9						
Ipsilateral RT				4	1	1	3	2	2		6	X				
Bilateral RT					3	1	2	5	2		7	X				

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?

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	Reference	SQ	SOE	SOR
Ipsilateral RT			7	3	1		2				2					
Bilateral RT						2		1	6	2	8					

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?

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	Reference	SQ	SOE	SOR
Ipsilateral RT		1	5	4	1	2					3					
Bilateral RT		1		1		1		1	6	1	8					

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?

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	Reference	SQ	SOE	SOR
Ipsilateral RT			1	2	4	3		2		1	4	X				
Bilateral RT						3	1	3	6		7	X				

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?

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	Reference	SQ	SOE	SOR
Ipsilateral RT			4	3	1	2		3			3	X				
Bilateral RT					2			2	4	3	8					

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

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, … etc.)

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the references associated with the recommendation.

SQ: Study Quality (1, 2, 3, or 4) of the references listed

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

SOR: ↑ 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 lateralized tumor impact the decision of unilateral therapy?

Treatment	Rating Category	Final Tabulations 1	2	3	4	5	6	7	8	9	Group Median Rating	Disagree	Reference	SQ	SOE	SOR
Ipsilateral RT					1		1	4	4	1	7					
Bilateral RT		1	1	3	1	4	1		2		5	X				

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?

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	Reference	SQ	SOE	SOR
		1	2	3	4	5	6	7	8	9						
Ipsilateral RT				3	3	2	2	2	1		5	X				
Bilateral RT						1		2	6	2	8					

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?

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	Reference	SQ	SOE	SOR
		1	2	3	4	5	6	7	8	9						
Ipsilateral RT			2		2	2	3	4			6	X				
Bilateral RT		1					1	5	3	1	7					

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?

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	Reference	SQ	SOE	SOR
		1	2	3	4	5	6	7	8	9						
Ipsilateral RT			1					6	3	1	7					
Bilateral RT			1	3	4		2	3			4	X				

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?

Treatment	Rating Category	Final Tabulations									Group Median Rating	Disagree	Reference	SQ	SOE	SOR
		1	2	3	4	5	6	7	8	9						
Ipsilateral RT			1	3			3	3	2	1	6	X				
Bilateral RT			1	1	2	2	2	3	2		6	X				

KEY: RT = Radiation Therapy; ENE = Extranodal Extension

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

Final Tabulations: A histogram of the number of panel members who rated the recommendation as noted in the column heading (ie, 1, 2, 3, … etc.)

Disagree: The variation of the individual ratings from the median rating indicates panel disagreement on the final recommendation.

References: Lists the references associated with the recommendation.

SQ: Study Quality (1, 2, 3, or 4) of the references listed

SOE: S Strong; M Moderate; L Limited; EC Expert Consensus; Expert Opinion

SOR: ↑ Strong Recommendation; ↓ Weak Recommendation; - Not strong, not weak

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

The authors thank Dr. Nancy Lee for critically reviewing the manuscript and Ms. Andrea Taylor for administrative support.

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. Beitler has nothing to disclose; Dr. Chang has nothing to disclose; Dr. Chen has nothing to disclose; Dr. Cooper has nothing to disclose; Dr. Koyfman reports grants from Merck, grants from Bristol Myers Squib, 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 BioMimetix, 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 Wayne State University School of Medicine, outside the submitted work.

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Methodology and Study Selection

For detailed methodology and study selection, please refer to the Supplemental Material. Briefly, a search of 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 year 2000 to May 2020 with full text available on PubMed® and restricted to 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 bibliographies of full articles were reviewed to exclude studies which were not relevant. Of the 46 citations returned from the search, 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 they were no longer cited in the revised narrative text. The most recent search was done in May 2020 to identify additional evidence published since the ACR Appropriateness Criteria® Ipsilateral Tonsil Radiation topic was finalized.

SUMMARY OF RECOMMENDATIONS

- Definitive (chemo)radiotherapy:

  Primary disease burden

  - The committee strongly recommends the use of ipsilateral radiation only for a tonsil-confined tumor or when there is ≤ 1 cm of tumor invasion into the soft palate or base of tongue.
  - The committee strongly recommends that the assessment of eligibility should be based on careful clinical examination and imaging including contrast-enhanced CT or MRI as well as PET/CT.
  - 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. For these patients, the committee strongly recommends that bilateral neck irradiation is usually appropriate due to the increased risk of occult contralateral nodal spread.

  Nodal burden

  - The committee recommends a high degree of caution in managing patients with multiple positive ipsilateral nodes, where ipsilateral radiation may be appropriate based on individualized evaluation that takes into consideration of primary disease burden and the extent of nodal disease.
  - The committee strongly recommends ipsilateral RT for patients with small primary tonsil cancer without soft palate or base of tongue involvement and with 0–1 node and this is ranked as usually appropriate.
  - There are conflicting results regarding patients with multiple positive ipsilateral nodes. We recommend individualized evaluation that considered primary disease burden, its extent and the burden of nodal disease.

  HPV status

  - The panel does not recommend consideration of HPV status in determination of eligibility for ipsilateral radiation.

- Adjuvant (chemo)radiotherapy:

  - With pT1, with single or multiple ipsilateral nodes ≤ 6 cm disease: for patients with clearly documented well-lateralized primary disease (< 1 cm of tumor invasion into the soft palate or base of tongue) it is appropriate to use unilateral adjuvant RT in this setting. The committee advise against ipsilateral adjuvant radiation if there was no clear documentation of detailed location of the primary site (and involvement of midline structures) before surgical resection.

- For pT2 disease: we caution against unilateral adjuvant RT. Individualized decision must be made after carefully evaluating pre-operative extent of the primary disease.

- Role of chemotherapy:
  - The committee does not recommend consideration of chemotherapy in the decision to offer ipsilateral radiation.

Table 1

Evidence Table

Reference	Study Type	Study Population	Results	Contralateral Neck Failure (CNF) and Salvage Therapy	Study Quality
Definitive (chemo)radiation					
Al-Mamgani A, van Rooij P, Fransen D, Levendag P. Unilateral neck irradiation for well-lateralized oropharyngeal cancer. *Radiother Oncol* 2013; 106(1): 69–73.	Single-institution case series	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	Median follow up: 4.1 yrs CNF 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-year LC rates: - 90% 5-year RC rates: - 96% 5-year DFS rates: - 84%	Patient #1: initial T1N2b, salvage ND + brachytherapy boost; NED Patient #2: initial T2N0, salvage ND+ RT; NED	2
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(9): 901–6.	Single-institution case series	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	Median follow-up: 4.2 yrs CNF rates: 8/136 (5.9%) - N0: 1/28 - N1: 1/20 - N2a: 0/31 - N2b: 6/55 - N3: 0/2	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 + RT alone; salvage ND+RT; NED Patients #4–8: T2N2b, initial tonsillectomy+ND+CRT; salvage ND+RT; NED	3
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(1): 159–69	Single-institution case series	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	Median follow up: 6 yrs CNF rates: 2/96 (2.1%) - N0: 0/52 - N1: 2/25 - N2a: 0/11 - N2b: 0/8 5-year LC rates: - p16+: 95% - p16−: 90% 5-year RC rates: - p16+: 98% - p16−: 94%	Both CNF had T2N1 disease and received RT alone 60Gy/25fx with homolateral wedge pairs. Patient #1 (HPV+): salvage ND; NED 12 years later Patient #2 (HPV−): salvage ND+RT; NED for 8 years	2
Liu C, Dutu G, Peters LJ, Rischin D, Corry J. Tonsillar cancer: the Peter MacCallum experience with unilateral and bilateral irradiation. *Head Neck* 2014; 36(3): 317–22.	Single-institution case series	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	Median follow up: 5.3 yrs CNF rates: 0/58 - N0: 0/25 - N1: 0/14 - N2a: 0/10 - N2b: 0/4		2

Reference	Study Type	Study Population	Results	Contralateral Neck Failure (CNF) and Salvage Therapy	Study Quality
			- N3: 0/5 5-year LC rates: - 91% 5-year RC rates: - 87%		
Kennedy WR, Herman MP, Deraniyagala RL, et al. Ipsilateral radiotherapy for squamous cell carcinoma of the tonsil. *European archives of oto-rhino-laryngology: official journal of the European Federation of Oto-Rhino-Laryngological Societies (EUFOS): affiliated with the German Society for Oto-Rhino-Laryngology - Head and Neck Surgery* 2016; 273(8): 2151–6.	Single-institution case series	76 patients (p16 missing in 88%) Ipsilateral RT criteria: - Information not available Staging imaging: - Information not available 32 (42 %) underwent a planned neck dissection and 21 (28 %) patients received concomitant chemotherapy.	Median follow-up:7.1 years CNF rates: 1/76 (1.3%) - N0: 0/27 - N1: 0/15 - N2a: 0/8 - N2b: 1/26 (37mo post RT) 5-year LC rates: - 97% 5-year RC rates: - 93%	Patient #1: initial T1N2b; salvage ND + CRT with cisplatin; NED	2
Dan TD, Raben D, Schneider CJ, et al. Freedom from local and regional failure of contralateral neck with ipsilateral neck radiotherapy for node-positive tonsil cancer: updated results of an institutional clinical management approach. *Oral Oncol* 2015; **51**(6): 616–21.	Single-institution case series	61 patients Ipsilateral RT criteria: - T1-3N0-2b/3 - well-lateralized primary without involvement of the base of the tongue, soft or hard palate Staging imaging: - CT and/or MRI - PET/CT in majority (51/61) 44 (72%) had tonsillectomy and 34 patients (56%) had ipsilateral neck dissection. 54 patients (89%) received concurrent systemic therapy.	Median follow-up: 3.1 yrs CNF rates: 1/61 (1.6%) - N0: 0/0 - N1: 0/15 - N2a: 0/14 - N2b: 1/31 (6 mos post RT) - N3: 0/1	Patient #1: initial T2N2b, salvage ND +RT; NED	2
Hu KS, Mourad WF, Gamez M, et al. Low rates of contralateral neck failure in unilaterally treated oropharyngeal squamous cell carcinoma with prospectively defined criteria of lateralization. *Head Neck* 2017; 39(8): 1647–54.	Single-institution case series	37 patients (23 p16+) Ipsilateral RT criteria: - >1 cm from midline Staging imaging: - PET/CT required	Median follow-up: 2.7 yrs CNF rates: 0/37 - N0: 0/4 - N1: 0/9 - N2a: 0/3 - N2b: 1/21 3-year LRC rates: - 96%		2
Ye A, Bradley KL, Kader H, Wu J, Hay JH. Patterns of Relapse in Squamous Cell Carcinoma of the Tonsil - Unilateral vs. Bilateral Radiation in the HPV-Era. *Cureus* 2015; 7(9): e322.	Single-institution case series	70 patients (53 p16+) Ipsilateral RT criteria: - Physician discretion Staging imaging: - CT - PET/CT (<10%)	Median follow-up: 5.7 yrs CNF rates in p16+: 4/53 (7.5%) - N0: 0/15 - N1: 3/18 - N2a: 1/7 - N2b: 0/11 - N3: 0/2 CNF rates in p16−: 1/17 (6%; no details given) 5-year LC rates in p16+: - 89% 5-year RC rates in p16+: - 83%	No details on each patient Patient #1: also +DM; palliative RT; DOD Patients #2–4: salvage ND only; one NED, one DOD, one died from another cause.	3

Head Neck. Author manuscript; available in PMC 2022 May 24.

Reference	Study Type	Study Population	Results	Contralateral Neck Failure (CNF) and Salvage Therapy	Study Quality
Koo TR, Wu HG. Long-term results of ipsilateral radiotherapy for tonsil cancer. *Radiat Oncol J* 2013; 31(2): 66–71.	Single-institution case series	20 patients Ipsilateral RT criteria: - T1-3N0-2b - not cross midline and <1 cm of tumor invasion into the soft palate or BOT Staging imaging: - CT and/or MRI - PET/CT in 14/25 Surgery +adj RT: 14 patients (4 received chemotherapy)	Median follow-up: 5.3 yrs CNF rates: 0/20 - N0: 0/2 - N1: 0/8 - N2a: 0/2 - N2b: 0/8 5-year LC rates: - 95%		
Gottumukkala S, Pham NL, Sumer B, et al. Risk of contralateral nodal failure following ipsilateral IMRT for node-positive tonsillar cancer. *Oral Oncol* 2017; 75: 35–8.	Single-institution case series	34 patients (25 p16+; 1 p16−; rest unknown) Ipsilateral RT criteria: - T1-4N0-2b/3 - Disease confined to tonsillar fossa or ≤ 1/3 of the soft palate Staging imaging: - CT and/or MRI - PET/CT in 14/25 16 (47%) had transoral resection before radiation and 10 (29%) of them also underwent neck dissections. All received definitive or adjuvant radiation to the primary site and ipsilateral neck	Median follow up: 2.8 yrs CNF rates: 1/34 - N1: 1/6 - N2a: 0/8 - N2b: 0/19 - N2: 0/1 5-year LC rates: - 95%	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 one year post RT in the prior suspicious lymph node. Received salvage ND alone. NED for 7 years.	2
Maskell D, Buckley H, Sission K, Roques T, Geropantas K. Ipsilateral neck radiotherapy in N2b well-lateralized tonsil cancer - Approach with caution. *Head Neck 2019*.	Single-institution case series	53 patients (49 p16+) Ipsilateral RT criteria: - T1-2N0-2b - Not extending to ≤1 cm from midline; not invading the BOT, posterior pharyngeal wall or >1/3 of the soft palate Staging imaging: - CT and/or MRI - PET/CT in challenging cases	Median follow up: 5.7 yrs CNF rates: 4/53 (7.5%) - N0: 0/10 - N1: 0/10 - N2a: 0/5 - N2b: 4/28	All 4 patients had p16+ T1N2b tumors. 3 had 3 or more multi-level nodes. Patient #1: recurred 18 mo after RT; salvage ND+ CRT; DOD Patient #2: recurred 43 mo after RT; salvage ND+ CRT; NED Patient #3: recurred 23 mo after RT; salvage ND+ CRT; DOD Patient #4: recurred 34 mo after RT; definitive CRT; NED	
Postoperative radiation					
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**(23): 4594–607.	Single-institution case series	154 patients treated with postoperative IMRT 107 with lateralized primary and cN0-2b disease: Group 1: 48 received unilateral IMRT Group 2: 59 received bilateral IMRT 47 patients had nonlateralized primary or N2c to N3 disease and received bilateral IMRT (Group 3)	5-year LC rates: - Group 1: 100% - Group 2: 96% - Group 3: 94% (no difference) 5-year OS rates: - Group 1: 85% - Group 2: 79% - Group 3: 76% (no difference) No contralateral neck recurrences among unilaterally treated patients.		2
Rackley TP, Namelo WC, Palaniappan N, Cole N, Owens DM, Evans M. Unilateral radiotherapy for surgically resected lateralized	Single-institution case series	81 patients (51 p16+) with lateralized tonsil SCC (cT1-2, cN0-2b per AJCC 7th) treated with surgery and unilateral adjuvant (chemo)radiotherapy.	Of 67 patients who underwent neck dissection: - 18 (27%) ENE - 30 (45%) had ≥ involved lymph nodes		2

Reference	Study Type	Study Population	Results	Contralateral Neck Failure (CNF) and Salvage Therapy	Study Quality
squamous cell carcinoma of the tonsil. *Head Neck* 2017; **39**(1): 17–23.		N0 = 18 patients (22%) N1 = 3 patients (4%) N2a = 12 patients (15%) N2b = 48 patients (59%).	- 29 (43%) had a node ≥30 mm. 5-year LC rates: 95% 5-year PFS rates: 93% 5-year OS rates: 91% No contralateral failure after a median follow-up of 5.7 years.		
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**(4): 1097–105.	Multi-institution case series	241 patients cT1-2 and cN0-2b tonsil SCC from 16 institutions All had tonsillectomy (no neck dissection) and postop RT 84 ipsilateral 157 bilateral 70 patients were identified from each group by propensity score matching	Ipsi vs Bilateral RT – 5-year DMFS rates: 93% vs 97% (p=0.08) 5-year LRRFS rates: 88% vs 97% (p=0.37) 5-year DFS rates: 81% vs 94% (p=0.08) 5-year OS rates: 93% vs 94% (p=0.99) No contralateral neck recurrence in 61 patients with T1-2N0-2a regardless of the treatment groups. 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=0.107).		2