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Original Research Article

Patient-reported quality of life and toxicity in unilateral and bilateral radiotherapy for early-stage human papillomavirus associated tonsillar carcinoma

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ABSTRACT

Purpose: The purpose of this study was to compare self-reported health-related quality of life (QoL) and symptom burden in early stage tonsillar carcinoma patients treated with unilateral (URT) and bilateral radiotherapy (BRT).

Methods and materials: This is a secondary analysis of a larger study assessing patient reported outcomes in human papillomavirus (HPV) oropharyngeal cancer (OPC) patients. Recruited patients were ≥12 months from completion of radiotherapy. This analysis included only patients with T1-2, N1-2b tonsil cancer and excluded patients with base of tongue involvement or recurrent disease. QoL and patient reported toxicity was measured using the EORTC QLQ-C30 module and the MDASI-HN.

Results: Patients were enrolled from November 2018 to May 2019. Of the 136 patients recruited to the main study, 43 were eligible for this substudy (22 URT, 21 BRT), with a median age and follow up of 58.2 and 3.0 years respectively. The two groups were balanced with respect to patient, tumor and treatment factors with the exception of higher rates of T2 disease (27% v 71%, $p = 0.006$) and more extensive GTV nodal volumes (11.0 v 25.5cc, $p = 0.006$) in the BRT group.

BRT patients had lower global health status/QoL (84 v 69, $p = 0.0005$) and social functioning scores (93 vs 78, $p = 0.033$) on the EORTC QLQ-C30, and higher symptom severity (0.6 vs. 2.0, $p = 0.001$) and symptom interference scores (0.8 vs. 2.0, $p = 0.010$) on the MDASI-HN. Four of the six largest differences observed on MDASI-HN items were attributable to radiotherapy technique (dry mouth, mucous, difficulty swallowing/chewing and taste), with corresponding dose differences to the respective organs (contralateral parotid, oral cavity and pharyngeal constrictors). In every instance, severity of symptoms was worse on average for patients treated with BRT.

Conclusions: In the highly conformal radiotherapy era, BRT in early HPV tonsillar cancer survivors has an enduring impact on long-term QoL and toxicity.

1. Introduction

There is controversy regarding the appropriateness of unilateral radiotherapy (URT) in lateralized tonsillar tumors. ASTRO clinical practice guidelines [1] recommend URT in well-lateralized T1-T2 tonsillar tumors with N0-N1 disease (AJCC 7th edition [2]). In cases of N2a, shared-decision making was recommended, with consideration to the benefits of URT against the risk of contralateral nodal failure (CNF) and salvage therapy. However, in contemporary prac-

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tice the actual benefit of URT is largely unknown, having not been quantified using patient-reported outcome measures (PROMs), which include both quality of life (QoL) and toxicity measures. Thus the shared decision making relies largely on the treating clinician communicating their anecdotal experience to the patient.

The opposing argument for BRT is to reduce the risk of CNF. In the setting of a well-lateralized tonsillar tumour, low rates of CNF have been reported with URT where there are multiple ipsilateral neck nodes [3–14]. Following URT, these series also suggest that salvage is largely successful where CNF is isolated. While clinical trials continue to explore the optimal de-intensification strategy with various combinations of systemic, surgical and radiation treatments, increased utilization of URT may provide an alternative and effective strategy for selected patients.

The aim of this study was to provide an estimate of the long-term difference between URT and BRT based on patient-reported outcome measures (PROMs). We report the differences in an exclusive population of patients with human papillomavirus (HPV) associated, early stage tonsillar cancers treated with highly conformal radiotherapy.

2. Methods and materials

2.1. Participants

From November 2018 to May 2019 eligible patients were prospectively recruited to a larger study reporting QoL and exploring unmet needs in HPV-OPC survivors. The eligibility criteria for this secondary analysis were: (1) aged ≥18; (2) histologically confirmed HPV+ (determined by p16 status) lateralized tonsil carcinoma (limited to extension to the ipsilateral palate); (3) AJCC 7th edition T1-T2, N1-N2b disease [2]; (4) treated with curative intent intensity modulated radiotherapy (IMRT) ± chemotherapy; (5) English speaking; and (6) ≥12 months following treatment completion. Patients were excluded if they had base of tongue involvement, recurrent disease, another active malignancy or were enrolled on another study. The study was approved by our institutional ethics board (LNR/46990/PMCC-2018).

2.2. Demographic, disease and treatment variables

Patient demographic, disease and treatment variables were collected from patient medical records.

2.3. Patient reported outcome measures

Multiple patient-reported outcome measures (PROMs) were collected for the larger study. This study included the EORTC Quality of Life Questionnaire Core 30 (QLQ-C30) and the MD Anderson Symptom Inventory for head and neck cancer (MDASI-HN).

The EORTC QLQ-C30 is a 30-item inventory which maps to a global health status/QoL score, five functional scales, three symptom scales and six single-item scales [15]. Only the global health status/QoL and functional scales are reported in this study. Higher scores indicate better quality of life and functioning, respectively. Published guidelines were used to support the interpretation of differences in the QLQ-C30 domains [16].

The MDASI-HN assesses cancer symptoms (22 items) and their interference on daily activities (six items) [17]. The symptom items include 13 general and nine head and neck cancer symptoms. The mean symptom severity score is the average of the 22 symptom items and the mean symptom interference score is the average of the six interference items. The minimally important difference (MID) is estimated at 0.98–1.21 [17].

2.4. Statistical analysis

Descriptive statistics of baseline characteristics were reported and compared by treatment laterality using *t*-test, Fisher exact test and Wilcoxon rank sum test, as appropriate. Tobit regression was used to compare PROMs by laterality. This analysis was considered exploratory and no multiplicity adjustment was performed. All statistical analyses were performed in R version 3.6.0 (2015).

3. Results

In total, 136 patients were recruited to the main study. Forty-three (22 URT, 21 BRT) met the eligibility criteria for this substudy. Demographic, disease and treatment details are presented in Table 1. Of the patients receiving bilateral treatment in this study, all patients had disease limited to the ipsilateral hemi-palate, however the decision to treat bilateral was based on the extent of nodal disease in 11/21 (52%) and on soft palate invasion in 10/21 (48%).

The EORTC QLQ-C30 and MDASI-HN scores are presented in Tables 2 and 3. MDASI-HN severity ratings are presented in Table 4. In every instance scores were numerically favoured patients treated with URT.

The estimated clinical impact of the differences were considered medium for the global health status, cognitive and social functioning domains and trivial for the physical and role functioning domains.

MDASI-HN items were ranked in order of the magnitude of the difference between the URT and BRT groups (Table 3). Four of the six largest differences observed were attributable to radiotherapy technique: dry mouth, mucous, difficulty swallowing/chewing and taste. Correspondingly, dosimetric differences to the contralateral parotid, oral cavity and pharyngeal constrictors were significantly different between the URT and BRT cohorts (Table 1).

4. Discussion

To our knowledge this is one of the few studies to contrast self-reported, long-term QoL in early-stage tonsillar carcinoma patients treated with definitive URT and BRT in the IMRT era, suggesting worse long-term QoL and toxicity with BRT. In contrast to other series reporting toxicity outcomes [18–20], all our patients were confirmed cases of HPV + tonsillar carcinoma and all were treated with IMRT. This is a cross-sectional study, and while we accept some inevitable selection bias, this data illustrates the relative estimate of the long-term impact of BRT in patients with lateralized tonsillar carcinoma.

We noted medium-sized differences in global health status/QoL (84 v 69, $p = 0.0005$), social functioning (93 vs 78, $p = 0.033$) and cognitive function (86 v 75, $p = 0.129$), in favour of URT [16]. The differences in physical and role functioning were considered trivial. Differences in the MDASI-HN mean severity (0.6 vs. 2.0, $p = 0.001$) and mean interference scores (0.8 vs. 2.0, $p = 0.010$) were beyond the reported MID [17]. While patients treated with URT infrequently reported their symptoms as severe (≥7 on the MDASI-HN), this was numerically more frequent in the bilateral group, especially in the items considered most likely to be impacted by BRT (Table 4). When ranking the MDASI-HN items according to the largest difference in mean scores between the URT and BRT groups, four of the six items with the largest difference were primarily attributable to differences in radiotherapy technique, including dry mouth, problems with mucous, difficulty swallowing or chewing and taste. Although we did not have baseline PROM data to assess longitudinal changes, in the HPV-era, patients with small tonsillar tumors generally present with asymptomatic lymphadenopathy with relatively good QoL at baseline.

Table 1
Demographic, disease and treatment characteristics.

Variable	Total (n = 43)	Unilateral (n = 22)	Bilateral (n = 21)	*p*-value
Mean Age (years, range)	58.2 [46.2–70.4]	59.1 [46.2–70.4]	57.3 [46.9–68.3]	0.232*
Partnered Relationship		16 (73%)	16 (76%)	1.000
Current Smoker	8 (18%)	3 (14%)	5 (24%)	0.457
Current Alcohol consumer	32 (74%)	18 (82%)	15 (71%)	0.488
Charlston Co-morbidity Score (range)	1.74 [0–6]	1.77 [0–5]	1.71 [0–6]	0.890
Mean Follow-up (years, SD)	3.2 (1.2)	3.3 (1.2)	3.1 (1.2)	0.445*
T stage				0.006†
T1	22 (51%)	16 (73%)	6 (29%)	
T2	21 (49%)	6 (27%)	15 (71%)	
N stage				0.714†
N1	10 (23%)	5 (23%)	5 (24%)	
N2a	4 (9%)	3 (14%)	1 (5%)	
N2b	29 (67%)	14 (64%)	15 (71%)	
No. of nodes				0.132‡
1	14 (33%)	8 (36%)	6 (29%)	
2	18 (42%)	11 (50%)	7 (33%)	
3	6 (14%)	3 (14%)	3 (14%)	
4	1 (2%)	0 (0%)	1 (5%)	
5	2 (5%)	0 (0%)	2 (10%)	
7	1 (2%)	0 (0%)	1 (5%)	
9	1 (2%)	0 (0%)	1 (5%)	
Median Nodal GTV Volume (cc, median, range)	13.4 [3.1–71.4]	11.0 [3.1–36.5]	25.5 [6.2–71.4]	0.006*
Radiotherapy Dose (Gy)				
66	3 (7%)	3 (14%)	0 (0%)	0.167†
68	1 (2%)	1 (5%)	0 (0%)	
70	39 (91%)	18 (82%)	21 (100%)	
Chemotherapy				
No	6 (14%)	5 (24%)	1 (5%)	0.184†
Yes	36 (86%)	16 (76%)	20 (95%)	
Mean Oral Cavity dose (Gy, SD)	35.3 (7.6)	30.2 (5.5)	40.9 (5.3)	<0.001*
Mean Pharyngeal constrictor dose (Gy, SD)	44.2 (6.5)	39.6 (5.0)	49.3 (3.3)	<0.001*
Mean Ipsilateral parotid dose (Gy, SD)	42.4 (10.3)	39.7 (9.8)	45.4 (10.3)	0.089*
Mean Contralateral parotid dose (Gy, SD)	17.6 (8.2)	10.3 (3.2)	25.8 (1.0)	<0.001*

GTV – Gross tumor volume, SD = standard deviation, **t*-test; †Fisher exact test; ‡Wilcoxon rank sum test.

Table 2
EORTC Global health status and functional domains and MDASI-HN summary scores.

Measure	Radiotherapy Technique		Estimate difference (95% CI)*	Clinical Impact of Difference [16]	*p*-value
	Unilateral (n = 22) Mean (SD)	Bilateral (n = 21) Mean (SD)			
EORTC QLQ-C30 domains					
Global health status	84 (17)	69 (21)	**16.4 (5.1, 27.7)**	Medium	**0.005**
Physical functioning	92 (12)	89 (15)	4.5 (−3.0, 11.9)	trivial	0.246
Role functioning	90 (25)	88 (21)	4.9 (−8.1, 18.0)	trivial	0.467
Emotional functioning	84 (19)	77 (19)	8.9 (−2.8, 20.5)	†	0.139
Cognitive functioning	86 (18)	75 (29)	11.2 (−3.2, 25.7)	medium	0.129
Social functioning	93 (13)	78 (30)	**16.0 (1.9, 30.0)**	medium	**0.033**
MDASI-HN Summary Scores					
Module Symptom Severity	0.6 (0.6)	2.0 (1.9)	**−1.3 (−2.0, −0.5)**	–	**0.001**
Symptom Interference	0.8 (1.5)	2.0 (2.1)	**−1.4 (−2.4, −0.4)**	–	**0.010**

*Marginal effect estimate from Tobit model, †emotional domain was omitted from the analysis by Cocks et al. [16].

Gunn et al. have reported long-term MDASI-HN outcomes in survivors of early stage tonsillar fossa cancers, (T1-2, N0-N2b) treated with IMRT [18]. In contrast to our findings, the only significant differences between URT and BRT (in patients treated with RT alone) was the mean score of the skin-related item and higher rates of moderate to severe dry mouth (40% v 25%, $p = 0.03$). The reason for the discordance to our findings is not obvious. While our series included patients treated mostly with concurrent chemoradiotherapy (86%), the Gunn et al. series compared only patients treated with RT alone (62%) in the URT/BRT analysis. Another contributing factor may be differences by HPV/p16 status, an independent factor for QoL outcomes [21]. While our study exclusively recruited patients with HPV+/p16 + disease, the status in the majority of cases (78/139; 56%) in their series was unknown, although it was positive in the majority where the status was known (57/61). We also noted that the assessment time was longer in their cohort (mean 5.1 versus 3.2 years), although in general it would be expected that for most, the toxicity profile would remain stable over this interval. A small series (n = 30; 15 URT, 15 BRT) from Roswell Park has also been presented in abstract form, reporting sim-

Table 3
MDASI-HN items ranked by difference between unilateral and bilateral treatment.

MDASI-HN item	Technique		Numerical Difference (bilateral – unilateral)
	Unilateral (n = 22) Mean (SD)	Bilateral (n = 21) Mean (SD)	
Mean Symptom items			
Dry mouth	3.0 (3.1)	5.4 (3.6)	2.4
Difficulty swallowing/chewing	1.2 (1.8)	3.5 (3.4)	2.3
Fatigue	2.2 (2.5)	4.5 (2.8)	2.3
Mucus in your mouth and throat	0.8 (1.7)	3.0 (3.5)	2.2
Sleep	2.0 (2.5)	4.1 (3.1)	2.1
Taste	1.1 (1.6)	3.0 (3.9)	1.9
Drowsy	1.6 (2.3)	3.3 (3.0)	1.7
Appetite	1.0 (2.0)	2.6 (3.5)	1.6
Mouth/throat sores	0.1 (0.4)	1.7 (2.8)	1.6
Teeth or Gums	0.9 (1.7)	2.4 (3.4)	1.5
Pain	0.5 (1.4)	2.0 (2.6)	1.5
Shortness of breath	0.7 (1.5)	2.2 (2.9)	1.5
Remembering things	1.8 (2.2)	3.2 (3.3)	1.4
Voice/speech	0.2 (0.5)	1.2 (1.6)	1.0
skin pain/burning/rash	0.2 (0.9)	1.1 (2.7)	0.9
choking/coughing	0.2 (0.4)	1.1 (1.7)	0.9
Distress	1.5 (2.7)	2.4 (3.0)	0.9
Numbness or tingling	0.8 (1.8)	1.6 (2.2)	0.8
Sad	1.2 (2.0)	2.0 (2.6)	0.8
Constipation	0.7 (1.9)	1.3 (2.7)	0.6
Nausea	0.2 (1.1)	0.6 (1.9)	0.4
Vomiting	0.1 (0.4)	0.5 (1.5)	0.4
Interference items			
Relations with other people	0.8 (1.7)	2.6 (2.9)	1.8
Enjoyment of Life	0.9 (1.9)	2.3 (2.6)	1.4
General activity	0.6 (1.6)	1.8 (2.5)	1.2
Mood	0.9 (1.7)	2.0 (2.3)	1.1
Work	1.0 (1.8)	2.1 (2.6)	1.1
Walking	0.7 (1.6)	1.3 (2.3)	0.6

Table 4
MDASI-HN symptom severity ratings.

MDASI-HN Item	Unilateral (n = 22)			Bilateral (n = 21)		
	None-mild (0–4)	Moderate (5–6)	Severe (7–10)	None-mild (0–4)	Moderate (5–6)	Severe (7–10)
Symptom Items						
Dry mouth	15 (68%)	3 (14%)	4 (18%)	11 (52%)	0 (0%)	10 (48%)
swallowing/chewing	20 (91%)	2 (9%)	0 (0%)	14 (67%)	1 (5%)	6 (29%)
Fatigue	16 (73%)	5 (23%)	1 (5%)	9 (43%)	5 (24%)	7 (33%)
Mucus mouth/throat	21 (95%)	0 (0%)	1 (5%)	15 (71%)	2 (10%)	4 (19%)
Sleep	18 (82%)	1 (5%)	3 (14%)	12 (57%)	4 (19%)	5 (24%)
Taste	20 (91%)	2 (9%)	0 (0%)	15 (71%)	1 (5%)	5 (24%)
Drowsy	18 (82%)	3 (14%)	1 (5%)	14 (67%)	3 (14%)	4 (19%)
Appetite	19 (86%)	3 (14%)	0 (0%)	16 (76%)	1 (5%)	4 (19%)
Mouth/throat sores*	21 (100%)	0 (0%)	0 (0%)	17 (81%)	2 (10%)	2 (10%)
Teeth or Gums†	20 (91%)	2 (9%)	0 (0%)	16 (80%)	1 (5%)	3 (15%)
Pain	21 (95%)	1 (5%)	0 (0%)	18 (86%)	0 (0%)	3 (14%)
Shortness of breath	20 (91%)	2 (9%)	0 (0%)	16 (76%)	2 (10%)	3 (14%)
Remembering things	19 (86%)	3 (14%)	0 (0%)	14 (67%)	2 (10%)	5 (24%)
Voice/speech	22 (100%)	0 (0%)	0 (0%)	20 (95%)	1 (5%)	0 (0%)
skin pain/burning/rash	22 (100%)	0 (0%)	0 (0%)	19 (90%)	2 (10%)	0 (0%)
choking/coughing	22 (100%)	0 (0%)	0 (0%)	20 (95%)	1 (5%)	0 (0%)
Distress	19 (86%)	0 (0%)	3 (14%)	15 (71%)	4 (19%)	2 (10%)
Numbness or tingling	21 (95%)	0 (0%)	1 (5%)	19 (90%)	1 (5%)	1 (5%)
Sad	19 (86%)	3 (14%)	0 (0%)	16 (76%)	3 (14%)	2 (10%)
Constipation	21 (95%)	0 (0%)	1 (5%)	18 (86%)	1 (5%)	2 (10%)
Nausea‡	21 (95%)	1 (5%)	0 (0%)	18 (95%)	0 (0%)	1 (5%)
Vomiting	22 (100%)	0 (0%)	0 (0%)	19 (90%)	2 (10%)	0 (0%)
Interference items						
Relations with other people	20 (91%)	2 (9%)	0 (0%)	15 (71%)	2 (10%)	4 (19%)
Enjoyment of Life	19 (86%)	3 (14%)	0 (0%)	17 (81%)	2 (10%)	2 (10%)
General activity	20 (91%)	2 (9%)	0 (0%)	17 (81%)	2 (10%)	2 (10%)
Mood	20 (91%)	2 (9%)	0 (0%)	18 (86%)	2 (10%)	1 (5%)
Work	20 (91%)	2 (9%)	0 (0%)	16 (76%)	3 (14%)	2 (10%)
Walking	20 (91%)	2 (9%)	0 (0%)	18 (86%)	1 (5%)	2 (10%)

*1 patient did not answer from unilateral group; †1 patient did not answer from bilateral group; ‡2 patients did not answer from bilateral group.

Table 5
Reported contralateral outcomes in well-lateralized tonsillar tumors treated with unilateral radiation limited to results in patients with multiple ipsilateral neck nodes (N2b).

Study	Number of N2b cases	Any CNF	Isolated CNF	Salvage	True Unsalvagable CNF rate	Salvage/CNF Notes
Lynch [3]	55	8	6	6/6 (100%)	0%	Six true CNFs were all salvaged; 2/8 other CNF: 1. One patient with CNF also had a contralateral tonsil primary at 4 years and was salvaged; 2. One patient with T3 disease recurred in ipsilateral primary site and contralateral neck and died of disease
Al-Mamgani [4]	32	1	1	1/1 (100%)	0%	
Dan [5]	31	1	1	1/1 (100%)	0%	
Maskell [6]	28	4	4	2/4 (50%)	7.1%T	1. One patient underwent salvage ND and CRT then devloped a local relapse in the tongue and died of disease; 2. One patient underwent ND and CRT with subsequent development of pulmonary metastases and died of disease
Kennedy [7]	26	1	1	1/1 (100%)	0%	One patient developed CNF, was treated with salvage ND and adjuvant CRT and died two years later without evidence of disease
Chronowski [8]	22	0	0	NA	0%	
Hu [9]	21	0	0	NA	0%	
Gottumukkala [10]	19	0	0	NA	0%	
Rusthoven [11]	13	0	0	NA	0%	
Koo [12]	8	0	0	NA	0%	
Huang [13]	8	0	0	NA	0%	
Liu [14]	4	0	NA	NA	0%	

CNF = contralateral nodal failure; ND = neck dissection; CRT = chemoradiotherapy; BOT = base of tongue.

ilar findings to ours, in that URT may be associated with an improved toxicity profile (EORTC QLQ-C30 and H&N35 modules), but details about staging, selection criteria for URT and BRT and use of chemotherapy were not included in the abstract [20].

A comprehensive study of clinician-scored toxicity by Jensen et al. with field based radiotherapy treatment showed a more favourable toxicity profile with URT over BRT [19]. Lower mean scores and rates of moderate to severe toxicity were seen with respect to xerostomia, dysphagia, hoarseness, atrophy, fibrosis and oedema. However, patients were treated with opposed laterals in the BRT group and a wedge pair in the URT cases. While this data is not necessarily applicable in the highly conformal radiotherapy era, our series consisting exclusively of IMRT-treated patients demonstrated similar findings.

The available literature suggests a low CNF rate with URT in N2b disease (approximating 5%) and a lower unsalvageable rate of patients who truly experience an isolated CNF (Table 5). A contemporary systematic review of URT outcomes reported a CNF rate of 1.47% (9/325), 4.15% (11/265) and 4.84% (9/186) in N0, N1 and N2b disease, respectively [22]. While these series reported "N2b" outcomes, it is possible that the majority of included cases consisted of reasonably low volume N2b disease. In series where URT is delivered following surgical management of the lateralized tonsil, similar findings have been demonstrated [11,23]. While the rationale to pursue BRT may reduce the risk of CNF in some, it will not safeguard against locoregional failure in all cases, even where maximal intensity therapy is undertaken. An important consideration in the decision-making process is also the increasing risk of distant metastases with an increasing burden of nodal disease in the ipsilateral neck and in the presence of either radiological extracapsular extension or a matted nodal mass [24–26]; risks that may be in excess of the CNF rate.

Our study has several limitations including its small sample size, non-randomised groups and selection bias, absence of pre-treatment PROM assessment and heterogeneity in PROM time-point assessment. This led to some imbalance between the groups, evidenced in differences by T-stage and GTV nodal volume between the URT and BRT groups. There was an approximate even distribution of patients receiving bilateral treatment on the basis of nodal disease and soft palate invasion, although all had disease limited to the ipsilateral hemi palate. However, this report is not designed to determine the efficacy of treatment, rather to provide an estimate of the potential toxicity of contralateral treatment; we would suggest that the impact of extending prophylactic coverage across the midline is likely to have more of an impact on toxicity than slightly larger volumes of primary tumour coverage. There were other factors, such as the prescribed dose and chemotherapy utilisation which were not statistically different between the two groups, but numerically favoured the URT group. We did also not find any differences in social (partner status; alcohol and smoking status) and medical factors (medical comorbidity). However, even with these limitations, this data adds to the limited body of literature in estimating the patient perspective in the URT vs BRT debate, and appears to be consistent with the clinical experience in long-term outcomes of patients treated with URT and BRT.

In summary, our study estimates the potential impact of BRT on QoL and toxicity in patients with early stage tonsillar tumours. This should be factored into clinical decision making and provides impetus for prospectively evaluating the efficacy of URT as method of treatment de-intensification in patients with lateralised tonsillar tumors with more extensive nodal disease.

5. Conclusions

In the highly conformal radiotherapy era, the decision to the treat the contralateral neck may impact patients' long-term QoL and toxicity. In the setting of low CNF rates and high salvageability, prospective evaluation of unilateral RT in more advanced ipsilateral neck disease is warranted.

6. Funding statement

None.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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