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Failure rate in the untreated contralateral node negative neck of small lateralized oral cavity cancers: A multi-institutional collaborative study

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ABSTRACT

Objectives: The importance of treating the bilateral neck in lateralized small oral cavity squamous cell carcinoma (OCC) is unclear. We sought to define the incidence and predictors of contralateral neck failure (CLF) in patients who underwent unilateral treatment.

Materials and methods: We performed a multi-institutional retrospective study of patients with pathologic T1-T2 (AJCC 7th edition) OCC with clinically node negative contralateral neck who underwent unilateral treatment with primary surgical resection ± adjuvant radiotherapy between 2005 and 2015. Incidence of CLF was estimated using the cumulative incidence method. Clinicopathological factors were analyzed by univariate (UVA) and multivariate analysis (MVA) for possible association with CLF. Kaplan-Meier analysis was used to estimate overall survival (OS).

Results: 176 patients were evaluated with a median of 65.9 months of follow-up. Predominant pathologic T-stage was T1 (68%), 8.5% of patients were N1, 2.8% were N2b. Adjuvant radiotherapy was delivered to 17% of patients. 5-year incidence of CLF was 4.3% (95% CI 1.2–7.4%). Depth of invasion (DOI) > 10 mm and positive ipsilateral neck node were significant predictors for CLF on UVA. DOI > 10 mm remained significant on MVA (HR = 6.7, 95% CI 1.4–32.3, p = 0.02). The 2- and 5-year OS was 90.6% (95% CI 86.2–95.0%) and 80.6% (95% CI 74.5–86.8%), respectively.

Conclusion: Observation of the clinically node negative contralateral neck in small lateralized OCC can be a suitable management approach in well selected patients, however caution should be applied when DOI upstages small but deeply invasive tumors to T3 on 8th edition AJCC staging.

Introduction

Oral cavity cancers (OCC) associated with a high incidence of contralateral neck metastases include advanced T-stage tumors or tumors that abut or cross midline [1]. Elective neck dissection (END) to the clinically node negative (cN0) contralateral neck, as part of primary surgical management, may be offered for these primary tumors. In the absence of an END, radiotherapy (RT) to the contralateral neck should be delivered as a method of managing potential microscopic disease [2].

Recommended management of the cN0 contralateral neck in lateralized small, early T-stage OCC is less clear [2,3]. Contralateral neck management with END or RT in these tumors may add unnecessary

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morbidity without significant gains in tumor control or survival [4,5]. The lymphatic drainage pattern of predominantly lateralized (89%) T1/T2N0 OCC was demonstrated in the SENT trial [6]. The rate of drainage to the contralateral neck was 12% of cases [6]. However, of 415 patients in the SENT trial, only 7 patients (2%) had a clinically occult contralateral neck nodal metastases [6]. Pathological studies of END specimens from T1/T2 oral tongue squamous cell carcinoma (SCC) that did not cross midline also showed the rate of clinically occult contralateral neck nodal metastases to be < 5% [7–9]. Furthermore, studies that evaluated unilateral treatment outcomes for lateralized OCC have shown low rates of contralateral neck failure of < 10% [10–13]. Thus, treating the cN0 contralateral neck in these primary tumors is not routinely recommended [2,14].

However, practice variation exists in terms of managing the cN0 contralateral neck in lateralized small, early T-stage OCC as there is no high level evidence from randomized controlled trials (RCT) to recommend a standard of care [12,15]. Proponents of comprehensive neck management in OCC that recommend END and/or RT to the cN0 contralateral neck, provide the rationale that OCC, in particular oral tongue primary cancers, have rich lymphatic channels, that aberrant lymphatic drainage following ipsilateral neck dissection may occur to the contralateral neck following primary surgical management and successful salvage rates of regional recurrences are low [16–18].

We conducted a multi-institutional retrospective study of patients with OCC treated with primary surgical management to evaluate outcomes and assess for potential prognostic factors. As the importance of treating the bilateral neck in lateralized small OCC is unclear, the purpose of this study was to analyze the incidence of contralateral neck failure (CLF) and clinico-pathological predictors for CLF in these tumors treated unilaterally.

Methods and materials

Study population

This retrospective study was part of the Multi-institutional Oral Cavity Cancer Collaborative (MOCCC) effort to evaluate the outcomes of OCC treated definitively with surgery between January 2005 and January 2015. We evaluated outcomes of patients from five academic institutions with pathologic stage T1-2 (7th edition American Joint Committee of Cancer [AJCC]) OCC, treated with surgery ± ipsilateral neck treatment (neck dissection and/or RT). Patients were excluded if they had disease in the contralateral neck, underwent treatment to the contralateral neck (bilateral neck dissection/RT, adjuvant chemotherapy), unknown side of neck dissection/RT, or had high risk features (positive surgical margin or extranodal extension) that would typically warrant comprehensive neck treatment. We defined these inclusion and exclusion criteria to best represent patients who were thought to have small lateralized OCC at the time of treatment and were assessed to only require unilateral treatment.

This study was approved by Institutional Review Board/Human Research Ethics Committee at each respective institution.

Statistical analyses

The primary endpoint of this study was to assess the incidence of CLF as first site of regional disease recurrence. Secondary endpoints were to assess clinico-pathological predictors for CLF and to evaluate overall survival (OS) for the cohort.

The 2- and 5-year incidence of CLF was estimated using the cumulative incidence method, with ipsilateral neck failure as a competing event. Synchronous bilateral neck failure was considered a CLF. Local failure/s occurring prior to regional failure were not considered a competing or censored event. Univariate analysis (UVA) was performed to assess clinico-pathological predictors of CLF using Fine-Gray competing risk regression analysis, with ipsilateral neck failure as a competing event. Significant clinico-pathological predictors on UVA were included in multivariate analysis (MVA). OS of the cohort was estimated with the Kaplan-Meier method. Pathological staging was based on 7th edition AJCC system as this was recorded in the multi-institutional collaborative database. The cumulative incidence, hazard ratios and OS were reported with 95% confidence intervals (CI) and statistical significance was determined with p-value < 0.05. Statistical analysis was performed using SAS v9.4(SAS Institute, Cary, NC).

Results

Study cohort

Of 1282 patients in the multi-institutional database, 176 patients met inclusion criteria and were included in this study. The median follow-up was 65.9 months (range, 1–157). Median age was 59 years old (range, 22–93) and 60% were male. The most common primary site was oral tongue (82%).

The predominant pathological T-classification was T1 (68%). The majority of patients had node negative disease in the ipsilateral neck (pN0 – 81%). Adjuvant RT to the primary and/or ipsilateral neck was delivered in 17% of patients. Additional details of the study cohort are

Table 1
Study population.

Patient number	176
Median age in years (range)	59 (22–93)
Gender	
Male (%)	106 (60%)
Female (%)	70 (40%)
Tobacco/Betel Use	
Yes	127 (72%)
No	49 (28%)
Alcohol Use	
Yes	128 (73%)
No	44 (25%)
Unknown	4 (2%)
Tumor site	
Oral tongue (%)	145 (82%)
Floor of mouth (%)	31 (18%)
Pathological T-classification (7th edition AJCC)	
T1 (%)	119 (68%)
T2 (%)	57 (32%)
Depth of invasion	
≥4mm	39 (22%)
<4mm	84 (48%)
>10 mm	19 (11%)
≤10 mm	104 (59%)
Unknown	53 (30%)
Tumor differentiation	
Well	48 (27%)
Moderate	100 (57%)
Poor	22 (13%)
Unknown	6 (3%)
Lymphovascular space invasion	
Present	13 (7%)
Absent	154 (88%)
Unknown	9 (5%)
Perineural invasion	
Present	30 (17%)
Absent	137 (78%)
Unknown	9 (5%)
Ipsilateral neck involvement	
Pathological N0 (%)	143 (81%)
Pathological N+ (%)	21 (12%)
– N1*	15 (8%)
– N2b*	5 (3%)
– Unknown N-classification*	1 (1%)
Unknown	12 (7%)
Ipsilateral RT	
Yes	30 (17%)
No	146 (83%)

* N-classification was based on 7th edition AJCC staging.

summarized in Table 1.

Regional failure rate

Regional failure was seen in 32 patients (18%). Ipsilateral neck failure occurred in 23 patients (13%) and 9 patients had CLF (5%). Of these 9 patients, 2 had synchronous bilateral neck failure (1%). Of the patients who had CLF, the pathological features, any local failure and treatment for CLF are summarized in Table 2. Four patients with CLF had experienced a local failure; two local failures occurred prior to CLF and two local failures were synchronous with CLF. The number of patients with any local, loco-regional, or regional disease failure are summarized in Supplementary Table 1.The estimated cumulative incidence of CLF at 2 years was 3.6% (95% CI 0.8–6.5%) and at 5 years was 4.3% (95% CI 1.2–7.4%) (Fig. 1). The estimated cumulative incidence of ipsilateral neck failure at 2 years was 11.9% (95% CI 7.0–16.8%) and at 5 years, was 13.3% (95% CI 8.1–18.5%).

Clinico-pathological predictors of contralateral neck failure

On UVA, pathological predictors for CLF was depth of invasion (DOI) > 10 mm and ipsilateral neck node positive status (Table 3). There were no significant clinical predictors of CLF. On MVA, DOI > 10 mm remained a statistically significant predictor for CLF ($p = 0.02$) with an adjusted hazard ratio of 6.7 (95% CI 1.4–32.3) for risk of CLF compared to tumors with DOI ≤ 10 mm.

Overall survival

The estimated 2- and 5- year OS for the entire cohort was 90.6% (95% CI 86.2–95.0%) and 80.6% (95% CI 74.5–86.8%), respectively (Fig. 2). For patients who had no regional failure, the estimated 5-year OS was 85.1% (95% CI 78.9–91.3%) (Fig. 3). For patients who had a regional failure, the estimated 5-year OS for ipsilateral neck failure was 63.8% (95% CI 43.7–83.9%), and for CLF was 55.5% (23.1–88%), respectively.

Discussion

This multi-institutional study represents the largest series to report the incidence of CLF in lateralized, small early T-stage OCC that underwent unilateral treatment (Table 4). In our cohort with favorable prognosis and 5-year OS of 80.6%, the 5-year incidence of CLF was low at 4.3%, providing support that omitting treatment to the contralateral cN0 neck is a reasonable approach in well selected patients. For small but deeply invasive tumors with DOI > 10 mm however, caution should be applied with consideration of treating the bilateral neck comprehensively.

In T1/T2 cN0 OCC lateralized to one side of midline, RCT data supports the use of ipsilateral END due to improved OS and disease free survival compared to therapeutic neck dissection at the time of nodal relapse [19]. However, there is no RCT data to guide standard of care management of the contralateral cN0 neck in this subgroup. Whilst the RCT performed by D'Cruz et al. demonstrated a survival benefit with ipsilateral END in early stage OCC, it is unclear what the role of contralateral END is in this setting [19]. There was an 11.9% nodal recurrence rate in the END group (N = 29/243), although the side (ipsilateral vs. contralateral) of neck recurrence was not reported [19]. Furthermore, adjuvant RT to the neck was delivered in 28.4% of patients in the END group with parallel opposed fields, so the contralateral neck is presumed to have received some dose.

The treatment of the cN0 neck in head and neck SCC is typically recommended when the risk of occult metastases is >20% [20]. For the cN0 contralateral neck, expert guidelines suggest that there is substantial risk of occult metastases in oral tongue/floor of mouth tumors that are T3/T4 (8th edition AJCC) or approach midline and thus the bilateral neck should be treated comprehensively either with END or RT [2]. In lateralized small, early T-stage OCC however, the role of treating the neck comprehensively with inclusion of the contralateral cN0 neck is less clear. Our data suggests that omitting treatment to the contralateral cN0 neck in this subgroup is acceptable given the low 5-year incidence of CLF of 4.3%. Furthermore, upon CLF, 7 of 9 patients underwent salvage neck dissection (78%). It is important to note however, that the cohort presented here were well selected patients that predominantly had T1 (68%) and node negative (81%) disease. The cohort was considered low risk to warrant RT in 17% of cases, and was associated with favourable prognosis as demonstrated by the high OS rates. Nonetheless, regional recurrences can have detrimental impact on OCC prognosis [3]. Thus, considerable thought in the setting of a multidisciplinary tumor board should be performed for both patient selection and minimizing unnecessary morbidity when managing the contralateral cN0 neck. Our results are consistent with published reports of CLF < 10% as detailed in Table 4, and is likely a reflection of well selected patient cohorts as the studies listed were all retrospective in nature. The SENT trial however, provides prospective data of the low risk of clinically occult metastases in the contralateral neck. In this prospective observational trial of early T-stage, cN0 OCC evaluating the role of sentinel node biopsy, 369 patients had lateralized tumors [6]. Of these lateral tumors, the drainage pattern was 10.8% to the bilateral neck and 2.4% exclusively to the contralateral neck. However, a positive contralateral sentinel node was only detected in 1.9% of cases (N = 7/369). For early T-stage OCC including midline tumors that did present with occult metastases, the contralateral neck was involved in 6% of cases (N = 7/109) [6]. Thus, watchful waiting can be a reasonable management approach to the contralateral cN0 neck in small lateralized OCC.

The challenge of clinical decision making in managing the

Table 2
Patients with contralateral neck failure.

Patient no.	Age	Primary site	Pathological T-classification*	DOI (mm)	pN status	LVSI	PNI	Adjuvant RT	Local failure and relation to CLF	Salvage surgery for CLF?	Adjuvant RT post salvage surgery
1	57	OT	T1	17	NA	Neg	Neg	No	Yes, prior to CLF	Yes	Yes
2	55	OT	T1	3	Pos	Pos	Neg	No	Yes, synchronous with CLF	Yes	Yes
3	62	OT	T1	NA	Pos	Neg	Neg	No	Yes, synchronous with CLF	No	NA
4	60	FOM	T2	4	Neg	Neg	Neg	No	No	Yes	Yes
5	51	OT	T1	0.8	Neg	Neg	Neg	No	Yes, prior to CLF	Yes	Yes
6	44	OT	T2	13	Pos	Neg	Pos	Yes	No	Yes	No
7	58	OT	T2	12	Neg	Pos	Pos	Yes	No	No	NA
8	58	OT	T2	13	Pos	Neg	Neg	Yes	No	Yes	Yes
9	61	OT	T2	20	Neg	Neg	Neg	Yes	No	Yes	Yes

*Pathological T-classification based on 7th edition AJCC; DOI = depth of invasion (measured in millimeters); pN status = pathological node status; LVSI = Lymphovascular space invasion; PNI = perineural invasion; RT = radiotherapy; NA = not available; Pos = positive for pathological feature; Neg = negative for pathological feature; CLF = contralateral neck failure.

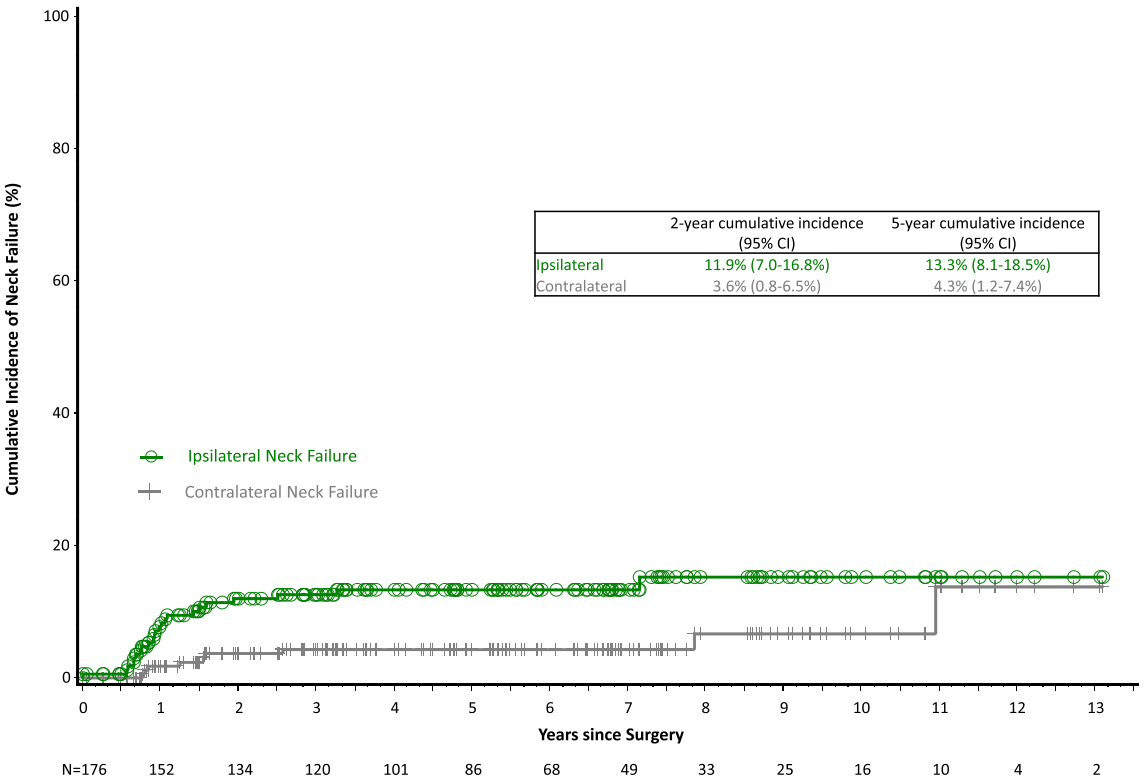

Fig. 1. Cumulative incidence of regional failure following unilateral treatment for lateralized, small oral cavity cancers.

Table 3
Clinico-pathological predictors for contralateral neck failure.

	Univariate analysis		Multivariate analysis	
Clinical factor	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
Tobacco/Betel Use Yes vs. No	3.4 (0.4–27.0)	0.26		
Alcohol Use Yes vs. No	3.1 (0.4–23.3)	0.26		
Pathological factor	Hazard ratio (95% CI)	p-value	Hazard ratio (95% CI)	p-value
pN + vs. pN0	9.5 (2.5–37.0)	**<0.01**	3.6 (0.7–16.9)	0.11
pT2 vs. pT1	3.0 (0.8–10.6)	0.09		
LVSI present vs. absent	4.0 (0.8–19.6)	0.09		
DOI ≥ 4 mm vs. < 4 mm	1.6 (0.3–8.1)	0.54		
DOI > 10 mm vs. ≤ 10 mm	10.3 (2.5–41.7)	**<0.01**	6.7 (1.4–32.3)	**0.02**
PNI present vs. absent	1.5 (0.3–7.1)	0.61		
PD vs. WD/MD	0.8 (0.1–6.6)	0.81		

pN+ = pathological neck node positive; pN0 = pathological neck node negative; pT2 = pathological T2 classification (7th edition AJCC); pT1 = pathological T1 classification (7th edition AJCC); LVSI = lymphovascular space invasion; DOI = depth of invasion; PNI = perineural invasion; PD = poorly differentiated; WD/MD = well/moderately differentiated.

contralateral cN0 neck is performing risk stratification beyond characteristics of small and lateralized OCC in the absence of RCT data. We assessed for potential clinico-pathological predictors associated with CLF in our cohort, however similar to previous published series (Table 4), CLF events were low and likely to impact the power to detect associations. Ipsilateral nodal status has been reported as a predictor for CLF in patients with lateralized OCC undergoing unilateral treatment, although overall CLF events were low [11,13]. Our cohort had 9 CLF events as first site of regional disease recurrence and ipsilateral node positive status was significantly associated with CLF on UVA. This factor did not remain statistically significant on MVA, which may relate to the low number of CLF events. In comparison, a study of 243 patients with OCC at high risk of contralateral nodal metastasis (predominantly advanced T-stage OCC, with all lesions abutting or cross midline) found 29% had contralateral nodal metastasis, and ipsilateral node positive status was the most significant factor associated with contralateral nodal metastasis on MVA [1]. The DOI of the primary lesion however, was not evaluated. As our cohort was predominantly node negative (81%), in the setting of pathologically positive ipsilateral node/s, we would recommend discussion at a multidisciplinary tumor board when considering a watchful waiting approach to the contralateral cN0 neck.

An interesting finding of this study was the significant association between DOI > 10 mm and CLF on MVA in our cohort of small, lateralized OCC. These small tumors would now be upstaged to T3 disease on the 8th edition AJCC staging [21], raising the question of whether these tumors require the same comprehensive neck treatment as tumors that meet the T3 criterion based on greatest surface dimension. Based on T-classification alone, expert guidelines would suggest treating the bilateral neck comprehensively [2]. DOI in OCC has been shown to correlate significantly with OS, disease specific survival and risk of nodal metastases [22–24]. However, the risk of contralateral nodal metastases have not been addressed in OCC studies of DOI. Although prior studies of lateralized OCC that included T3/T4 disease reported low rate of CLF in the untreated contralateral neck [11,13,17], this subgroup accounted for a minority of the study cohort. Staging systems prior to the incorporation of DOI in the 8th edition AJCC staging were used in these studies, and as extrinsic tongue muscle infiltration is no longer a criterion for T4 disease, it is possible that the reported T4 cohort could now be downstaged based on DOI. A RCT would best guide standard of care for the management of the contralateral cN0 neck in small but deeply invasive lateralized tumors, however such a trial would be difficult to initiate and accrue. Patients presenting with these tumors are uncommon and the management of the contralateral cN0 neck with END, RT or

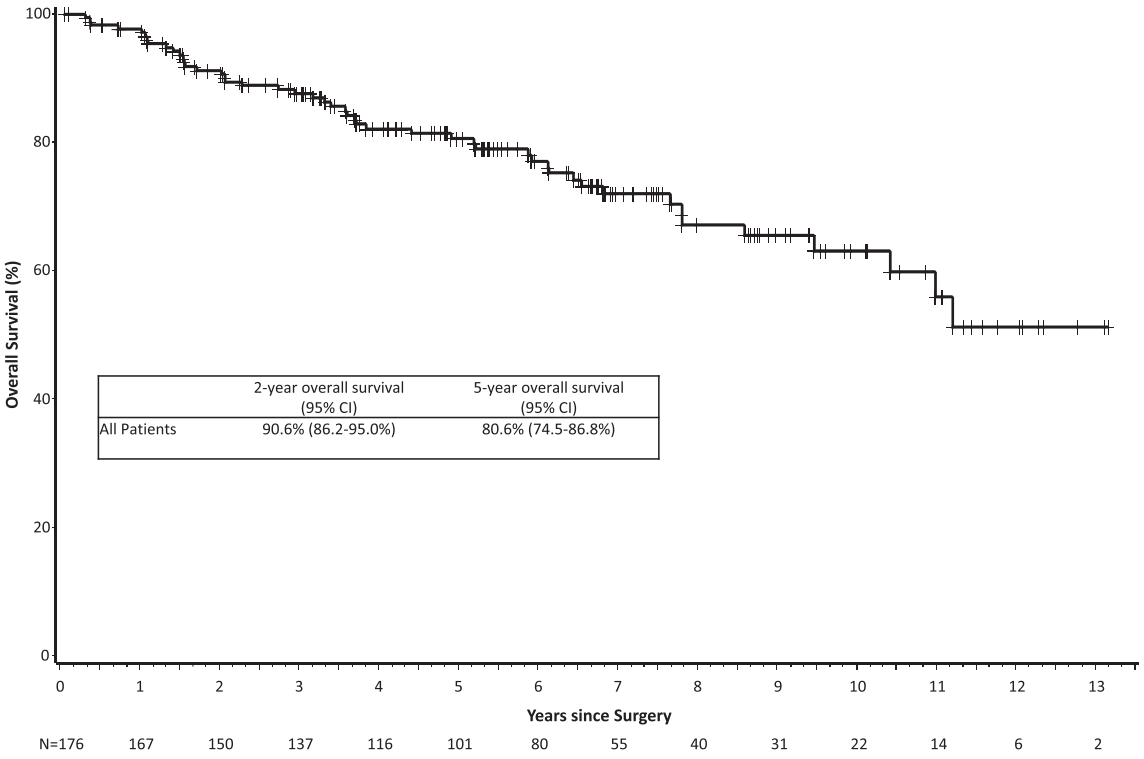

Fig. 2. Overall survival estimate following unilateral treatment for lateralized, small oral cavity cancers.

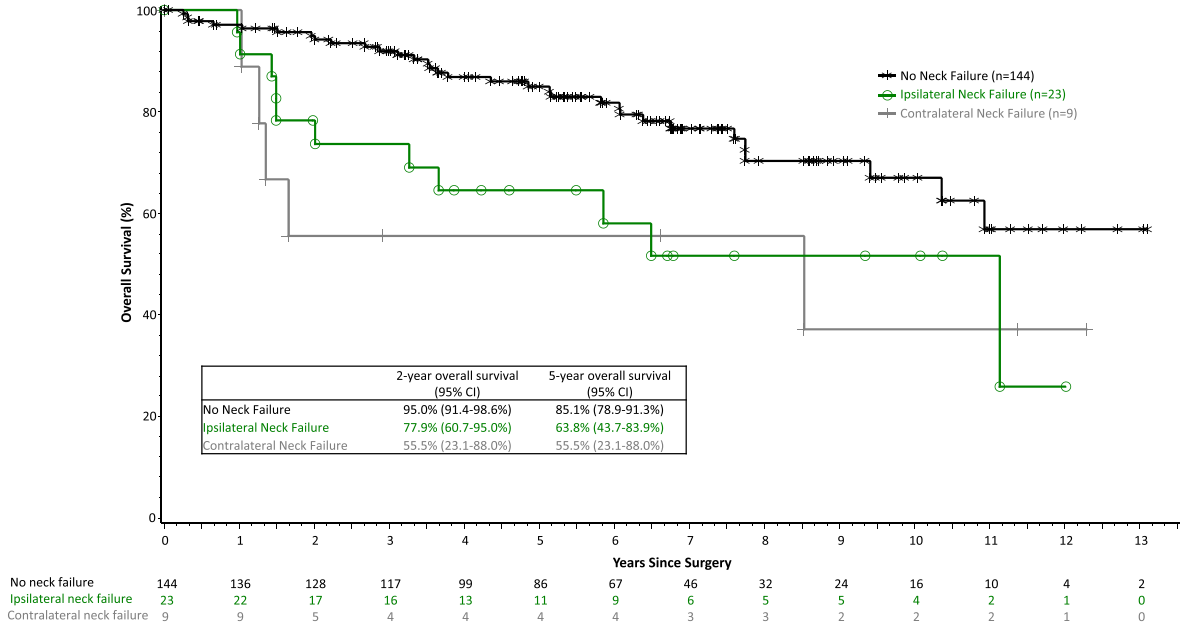

Fig. 3. Overall survival estimate by regional disease status.

END and postoperative RT to cover the surgically perturbed bed could prove difficult to standardize and maintain study compliance. Thus, in the absence of RCT data, a cautious approach in the management of a small but deeply invasive OCC is recommended, with consideration of treating the bilateral neck comprehensively. Future studies evaluating outcomes of the untreated contralateral cN0 neck in small, lateralized OCC should exclude deeply invasive lesions.

We acknowledge there are limitations to this study. Due to the retrospective and multi-institutional nature of this study, we could not reliably define the histopathological distance of the primary tumor from midline and thus this was not recorded at the outset of developing this multi-institutional database. Our inclusion and exclusion criteria included those who best represented patients thought to have small lateralized OCC at the time of treatment and were assessed to only require unilateral treatment. Due to limited study numbers, we could not compare outcomes of patients that had lateralized early T-stage OCC, who received bilateral neck treatment with our current cohort. However, as there was a low number of contralateral neck events seen in the present study, such a comparison would unlikely yield additional data on managing the contralateral cN0 neck. Nonetheless, this study

Table 4
Literature review of failure rate in the node negative contralateral neck of oral cavity cancers.

Study	N	Primary site	Pathological T-classification[α]	Lateralized primary	Lateralized treatment	N status	Adj Rx	Incidence of contralateral neck failure	Predictors of contralateral neck failure
MOCCC	176	OT (82%) FOM (18%)	T1 (68%) T2 (32%)	Y	100% UNI	N+ (12%) N0 (81%) UNK (7%)	RT (17%)	2 year incidence 3.6% 5 year incidence 4.3% Crude rate 5%	DOI > 10 mm
Habib [11]	481	OT (50%) FOM (17%) ALV (12%) BUC (10%) RMT (9%)	T1 (41%) T2 (32%) T3 (8%) T4 (19%)	Y	100% UNI	N+ (33%) N0 (67%)	RT (34%) CTX (3%)	Crude rate 2.9%	pN+ Poor differentiation
Ganly [10]	164	OT (100%)	T1 (46%) T2 (54%)	NR	90% UNI 7% BL 3% NR	N+ (13%)[β] N0 (87%)	None	Crude rate 7%	NR
Nobis [7]	150	OT (100%)	T1 (71%) T2 (29%)	Y	70% UNI 30% BL	N+ (23%) N0 (77%)	RT (19%) CRT (6%) CTX (1%)	Crude rate 2.7%	NR
Vergeer [13]	104	OT (25%) FOM (8%) ALV (48%) BUC (19%)	T1 (24%) T2 (30%) T3 (10%) T4 (36%)	No, 9% close/ cross midline	100% UNI	NR	RT (100%)	5 year contralateral neck control 92%	Number of positive nodes
Waldram [17]	101	OT (51%) FOM (17%) ALV (15%) RMT (10%) BUC (7%)	T1 (11%) T2 (40%) T3 (9%) T4 (40%)	NR	73% UNI 27% BL	N+ (72%) N0 (28%)	RT (75%) CRT (25%)	Crude rate 5%	NR
Wirtz [25]	74	NR	NR but includes T1-T4	Y	NR	NR	NR	5 year contralateral neck control 93.5% Crude rate 6.7%	None
Lim [9]	54	OT (100%)	T1 (19%) T2 (81%)	Y	42% UNI 58% BL	N+ (28%) N0 (72%)	RT (34%)	Crude rate 0%	NR
O'steen [12]	32	OT (72%) FOM (28%)	T1 (47%) T2 (41%) T3 (9%) T4 (3%)	Y	66% UNI 22% BL 12% NR	N+ (19%) N0 (81%)	RT (62%) CRT (38%)	Crude rate 0%	NR

MOCCC = Multi-institutional Oral Cavity Collaborative group (present study). OT = oral tongue. FOM = floor of mouth. ALV = alveolus. BUC = buccal. RMT = retromolar trigone. [α]Pathological T-classification based on 7th edition AJCC. UNI = unilateral treatment. BL = bilateral treatment. N status = neck nodal status. Adj Rx = adjuvant treatment. DOI = depth of invasion. pN+ = pathological node positive. NR = not reported. UNK = unknown. RT = radiotherapy. CRT = chemo-radiotherapy. CTX = chemotherapy. [β]micrometastases detected of available lymph node dissection specimen (n = 52).

reports on the incidence of CLF in the largest cohort series to date of small lateralized OCC receiving unilateral treatment and provides support for omitting treatment to the contralateral cN0 neck in well selected patients.

Conclusion

For small lateralized OCC with a clinically uninvolved contralateral neck, we found the incidence of CLF to be low when undergoing unilateral treatment. Omission of treatment to the contralateral neck with close surveillance can be a suitable management approach in well selected patients, however treating the bilateral neck should be considered in small but deeply invasive tumors.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jimmy Caudell discloses the following relationship with Varian Medical Systems for grants, honoraria and consulting. Farzan Siddiqui discloses the following relationship with Varian Medical Systems: honorarium for talks and lectures, with American College of Radiology: honorarium for

site surveys.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.oraloncology.2021.105190.

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