Original Article

Contralateral neck nodal outcomes and recurrence pattern of small well-lateralized oral cavity carcinoma—a single institution experience

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Background: The administration of post-operative, contralateral neck nodal irradiation to patients with small, well-lateralized oral-cavity cancers is a controversial issue. We conducted a retrospective study to analyze the outcomes of these patients.

Methods: We performed a single-institution, retrospective study of patients with pT1-2, pN0-2b [American Joint Committee on Cancer (AJCC) 6th/7th edition] well-lateralized oral-cavity cancer who underwent primary surgical intervention with or without adjuvant therapy from 2007–2017. Contralateral nodal failure-free survival (cNFFS), overall survival (OS), and event-free survival (EFS) were estimated by the Kaplan-Meier method. Outcomes of ipsilateral and contralateral neck irradiation were compared by the log-rank test.

Results: One hundred and seventy-seven patients were evaluated with a median follow-up of 79.7 months. Adjuvant therapy was administered to 32.7% of patients. The 5-year cNFFS, OS, and EFS for all patients were 97.4%, 75.7%, and 67.9%, respectively. Of the 56 patients who received adjuvant radiotherapy (RT), no statistically significant differences between cNFFS, OS, and EFS were observed between ipsilateral and bilateral neck irradiation. Most (83.3%) local recurrence occurred prior to, or simultaneously with, contralateral neck recurrence.

Conclusions: For small, well-lateralized oral-cavity cancers, the contralateral neck nodal recurrence rate was low. No significant impacts of contralateral neck irradiation were found. Local failure should be treated with caution because it may indicate higher contralateral neck failure.

Keywords: Contralateral neck nodal outcome; well-lateralized oral cavity carcinoma; adjuvant radiotherapy (RT); neck treatment

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Introduction

Elective neck dissection on the contralateral side of well-lateralized oral-cavity cancers may not be performed during surgery, depending on the clinical tumor size or nodal status. Under some circumstances, post-operative radiotherapy (RT) is administered for pathologically proven high-risk head and neck malignancies, which are associated with increased local and regional nodal control (1). In past decades, the convention was to irradiate bilateral neck region lymph nodes once RT was administered; however, if contralateral nodal negativity is indicated by pathology, the necessity of contralateral neck irradiation remains controversial. Moreover, RT to the bilateral neck area is associated with acute and long-term adverse effects, reducing patient quality of life.

Previous studies revealed relatively low contralateral nodal recurrence rates of well-lateralized head and neck cancers (2-4). However, most of this research was based on oropharyngeal squamous cell carcinoma, and only a few cases of oral-cavity cancers have been reported (5,6). Whether the results of oropharyngeal cancer can be extrapolated to oral-cavity cancer remains a controversial question.

Thus, we conducted a retrospective study, analyzing small, well-lateralized oral-cavity cancers treated primarily with surgical intervention, to evaluate outcomes and patterns of contralateral nodal failure with/without contralateral neck irradiation.

Methods

Patients and staging workup

Between 2007 and 2017, patients with primary tumors of non-metastatic, well-lateralized oral-cavity cancers, mainly in the buccal, gingival, and retromolar regions, were identified. Well-lateralized was defined as tumor located more than 1 cm from midline of maxilla, mandible or hard palate. At a minimum, the pre-treatment staging workups included chest X-rays, contrast or non-contrast computed tomography (CT) or magnetic resonance imaging (MRI), and abdominal ultrasounds. If necessary, bone scans and/or positron emission tomography/CT (PET/CT) were used to rule out possible distant metastases. Patients whose pathology indicated pT1/2 or pN0-2b stage cancer according to the American Joint Committee on Cancer (AJCC) Staging Manual 6th/7th edition (7,8) were included in this study. Those simultaneously diagnosed with second primary cancers, with histories of cancer, or non-squamous cell histology oral-cavity cancer were excluded from the analysis.

Treatment

All patients underwent curative surgical excision as their first treatment, including composite tumor resection and/or neck dissection. Performance of ipsilateral or bilateral neck dissection was determined according to pre-operative CT or MRI and at the surgeon's discretion. Patients with pathological risk factors for possible recurrence, such as positive margins, involved nodes, or extranodal extension, received post-operative RT/chemotherapy [following National Comprehensive Cancer Network (NCCN) guidelines].

Adjuvant RT was administered by either intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) using a megavoltage linear accelerator. Planning CT was obtained after the patient was immobilized with a thermoplastic mask. The following radiation doses were administered: 45–54 Gy to neck regional lymph nodes and 59.4–72 Gy to surgical tumor beds and high-risk nodal areas, which were all in 1.8–2 Gy per fraction. Administration of ipsilateral or bilateral neck irradiation was at the radiation oncologist's discretion according to the pathology report, such as tumor stage, nodal status, or extranodal extension status. Concurrent chemotherapy was administered at the medical oncologist's discretion.

Follow-ups

Regular follow-ups were arranged every 2–3 months in the first two years and then every 4–6 months afterwards. On each visit, oral inspection with neck palpation and the occasional endoscopic examination were done regularly. Imaging studies (CT or MRI) were done every 3–6 months during the follow-up period. Tissue pathology proof would be obtained if clinically or radiologically recurrence were suspected.

Statistical analysis

The primary end point of this study was contralateral nodal failure-free survival (cNFFS). The crude rate of contralateral neck failure was also demonstrated. Secondary end points included overall survival (OS) and event-free survival (EFS).

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Failure on the ipsilateral or contralateral side was well-documented, so cNFFS could be defined as the amount of time between the day of operation and the day of contralateral nodal failure at the first failure site. OS was defined as the amount of time between the day of operation and the day of death from any cause or the last follow-up. EFS was defined as the amount of time between the day of operation and the day of local recurrence, nodal failure, or distant metastasis, whichever came first. For patients who received adjuvant RT, we conducted subgroup analyses of cNFFS, OS, and EFS.

The Kaplan-Meier method was used to estimate all the survival endpoints. The survival between treatment groups was compared with a stratified log-rank test. All statistical analysis was performed using Statistical Product and Service Solutions (SPSS) software, version 22.0 (SPSS Inc., Chicago, IL, USA) and R software (version 3.6.1; R Foundation for Statistical Computing, Vienna, Austria). Two-tailed P<0.05 was considered statistically significant.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of National Cheng Kung University Hospital (IRB number: A-ER-111-181). The requirement for informed consent from the study subjects was waived due to the retrospective study design.

Results

Study population

From May 2007 to December 2017, 177 patients in our institution were analyzed. The median follow-up was 79.7 months (range, 2.2–178.1 months). The median age at diagnosis was 54 years (range, 31–91 years).

Patient and tumor characteristics are listed in *Table 1*. The main tumor sites included buccal (139, 78.5%), gingival (31, 17.5%), and retromolar (7, 4.0%) subsites. The pathological stages were II (115, 65%), III (22, 12.4%), and IVA (40, 22.6%) with tumor stages of T1 (18, 10.1%) and T2 (159, 89.9%) and nodal stages of N0 (115, 65%), N1 (22, 12.4%), and N2 (40, 22.6%). One hundred forty-five (81.9%) patients received ipsilateral neck dissections, 20 (11.3%) patients received adjuvant RT alone, and 36 (20.3%) patients received concurrent chemoradiotherapy (CCRT).

Patient and tumor characteristics of those received ipsilateral and bilateral neck RT are listed in *Table 2*. Thirty-one patients received ipsilateral neck nodal RT, while 25 patients received bilateral neck nodal irradiation. All characteristics showed no statistical difference between two subgroups except pathological and nodal stage (P=0.015), and neck dissection side (P=0.011).

Outcomes

The primary endpoint, 5-year cNFFS, was 97.4% (*Figure 1A*), and the crude rate of contralateral neck failure was 3.4%. Patients received post-operative RT or not showed no statistical significance in cNFFS (*Figure 1B*). The 5-year OS and EFS were 75.7% and 67.9%, respectively (*Figure 2A,2B*); the survival difference between patients received post-operative RT or not were also shown in *Figure 2C,2D*.

Regional neck recurrence was observed in 20 patients (11.3%); recurrences were in the ipsilateral, contralateral, and bilateral neck for 14, 4, and 2 patients, respectively. Of the 6 patients with contralateral/bilateral regional neck recurrence, 4 had local recurrence prior to regional recurrence, 1 experienced simultaneous local and regional neck recurrence, and 1 had regional neck recurrence prior to local recurrence.

Subgroup analysis

Of the 56 patients who had received RT, there was no statistically significant difference in cNFFS (92.6% *vs.* 93.3%; P=0.703), 5-year OS rate (67.2% *vs.* 60.0%; P=0.259), and EFS rate (69.5% *vs.* 54.0%; P=0.210) in patients receiving ipsilateral and bilateral neck irradiation (*Figure 3*).

In patients who had received RT, regional neck recurrence was noted in 4 patients (7.1%); the recurrences were in the ipsilateral, contralateral, and bilateral neck regions in 1, 2, and 1 patients, respectively. Of the 3 patients who suffered from contralateral/bilateral neck recurrence, 2 had local recurrence prior to neck recurrence, and 1 had local recurrence after neck recurrence during follow-up. One of the 3 patients who experienced contralateral neck nodal recurrence received post-operative bilateral neck irradiation.

Discussion

This retrospective cohort study indicated a 5-year cNFFS of 97.4%, with a crude rate of contralateral neck recurrence

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Table 1 Patient and tumor characteristics

Characteristics	OP	OP + RT	P value
Patient number	121	56	
Median age in years [range]	53 [31–86]	50 [32–91]	0.272
Gender, n (%)			0.578
Male	110 (90.9)	53 (94.6)	
Female	11 (9.1)	3 (5.4)	
Tumor site, n (%)			0.111
Buccal	91 (75.2)	48 (85.7)	
Gingival	26 (21.5)	5 (8.9)	
Retromolar	4 (3.3)	3 (5.4)	
Tumor stage, n (%)			<0.001
1	5 (4.1)	13 (23.2)	
2	116 (95.9)	43 (76.8)	
Nodal stage, n (%)			<0.001
0	104 (86.0)	11 (19.6)	
1	12 (9.9)	10 (17.9)	
2	5 (4.1)	35 (62.5)	
Stage, n (%)			<0.001
II	104 (86.0)	11 (19.6)	
III	12 (9.9)	10 (17.9)	
IVA	5 (4.1)	35 (62.5)	
Neck dissection side, n (%)			0.009
Ipsilateral	98 (81.0)	47 (83.9)	
Bilateral	9 (7.4)	9 (16.1)	
No neck dissection	14 (11.6)	0 (0.0)	
Tumor differentiation, n (%)			0.001
Well	68 (56.2)	15 (26.8)	
Moderate	48 (39.7)	35 (62.5)	
Poor	4 (3.3)	6 (10.7)	
Data missing	1 (0.8)	0 (0.0)	
Tumor size, n (%)			0.221
≤2 cm	14 (11.6)	12 (21.4)	
>2 cm, ≤4 cm	103 (85.1)	42 (75.0)	
>4 cm	3 (2.5)	2 (3.6)	
Data missing	1 (0.8)	0 (0.0)	

Table 1 *(continued)*

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Table 1 *(continued)*

Characteristics	OP	OP + RT	P value
Perineural invasion, n (%)			<0.001
Yes	20 (16.5)	28 (50.0)	
No	98 (81.0)	28 (50.0)	
Data missing	3 (2.5)	0 (0.0)	
Lymphovascular invasion, n (%)			<0.001
Yes	12 (9.9)	25 (44.6)	
No	106 (87.6)	31 (55.4)	
Data missing	3 (2.5)	0 (0.0)	
Extracapsular spread, n (%)			<0.001
Yes	4 (3.3)	20 (35.7)	
No	114 (94.2)	36 (64.3)	
Data missing	3 (2.5)	0 (0.0)	
Margin status, n (%)			0.013
≤1 mm or involved (inadequate)	2 (1.7)	7 (12.5)	
1–3 mm (close)	53 (43.8)	26 (46.4)	
>3 mm (free)	65 (53.7)	22 (39.3)	
Data missing	1 (0.8)	1 (1.8)	
Adjuvant chemotherapy, n (%)			<0.001
No	119 (98.3)	20 (35.7)	
Yes	2 (1.7)	36 (64.3)	

OP, operation; RT, radiotherapy.

Table 2 Patient and tumor characteristics of those receive ipsilateral and bilateral radiotherapy

Characteristics	Ipsilateral RT	Bilateral RT	P value
Patient number	31	25	
Median age in years [range]	50 [37–91]	49 [32–65]	0.499
Gender, n (%)			0.316
Male	28 (90.3)	25 (100.0)	
Female	3 (9.7)	0 (0.0)	
Tumor site, n (%)			0.538
Buccal	28 (90.3)	20 (80.0)	
Gingival	2 (6.5)	3 (12.0)	
Retromolar	1 (3.2)	2 (8.0)	
Tumor stage, n (%)			0.657
1	6 (19.4)	7 (28.0)	
2	25 (80.6)	18 (72.0)	

Table 2 *(continued)*

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Table 2 *(continued)*

Characteristics	Ipsilateral RT	Bilateral RT	P value
Nodal stage, n (%)			0.015
0	10 (32.3)	1 (4.0)	
1	3 (9.7)	7 (28.0)	
2	18 (58.1)	17 (68.0)	
Stage, n (%)			0.015
II	10 (32.3)	1 (4.0)	
III	3 (9.7)	7 (28.0)	
IVA	18 (58.1)	17 (68.0)	
Neck dissection side, n (%)			0.011
Ipsilateral	30 (96.8)	17 (68.0)	
Bilateral	1 (3.2)	8 (32.0)	
Tumor differentiation, n (%)			0.359
Well	6 (19.4)	9 (36.0)	
Moderate	21 (67.7)	14 (56.0)	
Poor	4 (12.9)	2 (8.0)	
Tumor size, n (%)			0.897
≤2 cm	6 (19.4)	6 (24.0)	
>2 cm, ≤4 cm	24 (77.4)	18 (72.0)	
>4 cm	1 (3.2)	1 (4.0)	
Perineural invasion, n (%)			1
Yes	16 (51.6)	12 (48.0)	
No	15 (48.4)	13 (52.0)	
Lymphovascular invasion, n (%)			0.206
Yes	11 (35.5)	14 (56.0)	
No	20 (64.5)	11 (44.0)	
Extracapsular spread, n (%)			0.378
Yes	9 (29.0)	11 (44.0)	
No	22 (71.0)	14 (56.0)	
Margin status, n (%)			0.23
≤1 mm or involved (inadequate)	6 (19.4)	1 (4.0)	
1–3 mm (close)	14 (45.2)	12 (48.0)	
>3 mm (free)	10 (32.3)	12 (48.0)	
Data missing	1 (3.2)	0 (0.0)	
Adjuvant chemotherapy, n (%)			0.054
No	15 (48.4)	5 (20.0)	
Yes	16 (51.6)	20 (80.0)	

RT, radiotherapy.

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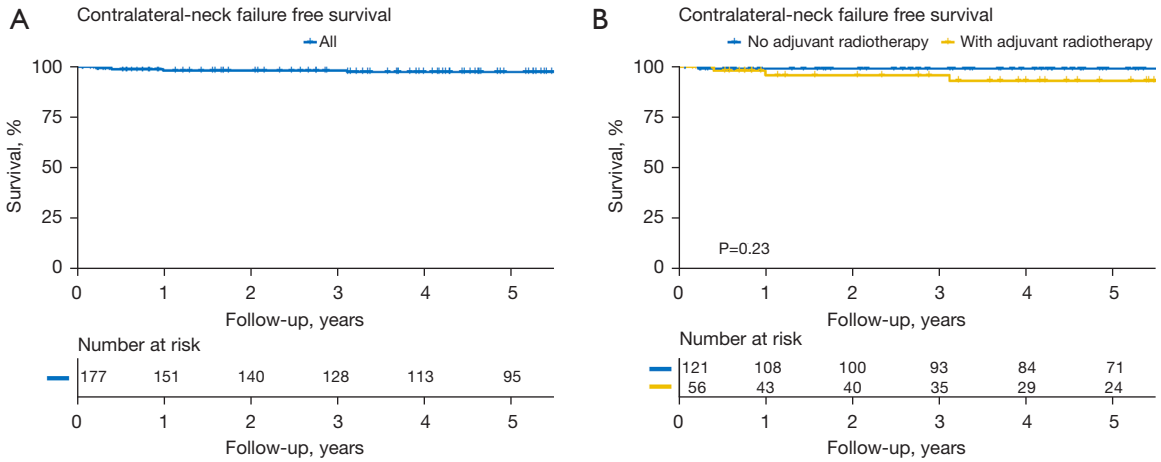

Figure 1 Kaplan-Meier plots of cNFFS of all patients (A) & patients received radiotherapy versus those who did not received radiotherapy (B). cNFFS, contralateral nodal failure-free survival.

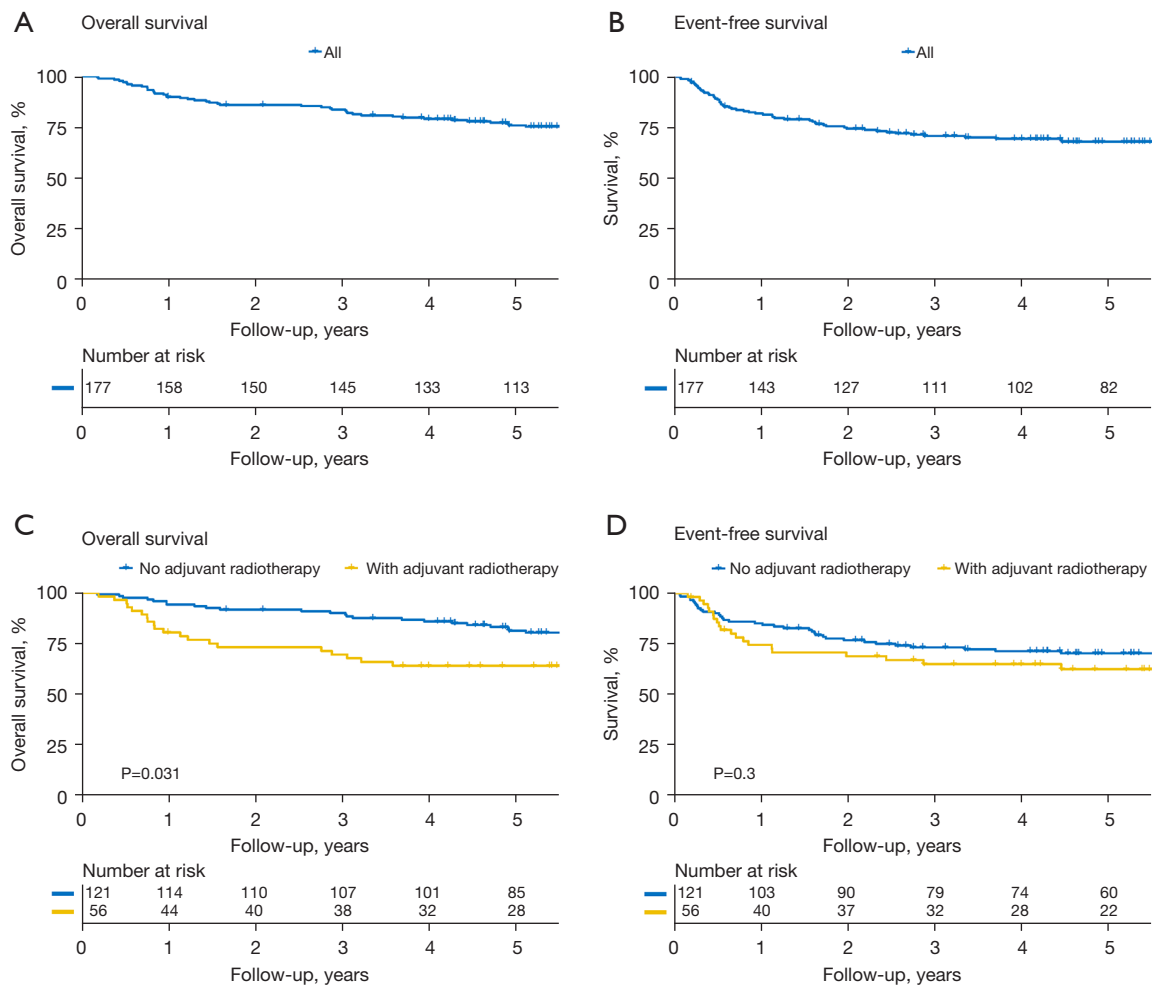

Figure 2 Kaplan-Meier plots of the OS and EFS of all patients (A,B, respectively) & patients received radiotherapy versus those who did not received radiotherapy (C,D, respectively). OS, overall survival; EFS, event-free survival.

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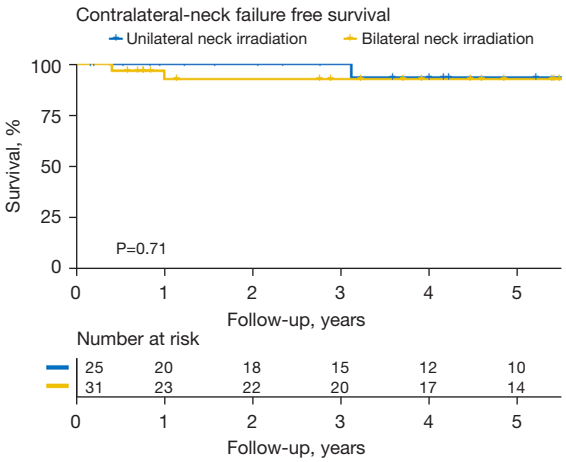

Figure 3 Kaplan-Meier plot of the 5-year cNFFS in patients received ipsilateral and bilateral neck radiotherapy. cNFFS, contralateral nodal failure-free survival.

of 3.4% in the patients with small, well-lateralized oral-cavity cancers. Previous retrospective studies had shown relatively low contralateral recurrence rates in lateralized head and neck patients of 5% (2), 6.1% (3), and 3% (9), which supports our study results. However, these studies included various subsites for head and neck cancer. This heterogeneity might have impacted the determined contralateral recurrence rates.

In addition, a retrospective study reported that midline involvement in oropharyngeal carcinomas was a significant prognostic factor in contralateral regional failure (5). Therefore, we chose to focus on patients with relatively lateralized tumors without midline involvement, such as buccal, gingival, and retromolar tumors.

To date, there is still no compelling evidence indicating whether contralateral neck dissection or irradiation should be administered in patients who are negative in the contralateral neck. In conventional clinical practice, once adjuvant RT is administered, it is unclear whether contralateral irradiation should be administered to these patients, especially in those with adverse pathological features [e.g., extracapsular spread (ECS)-positive or inadequate surgical margin status]. Our study results suggest that neither pathological factors nor ipsilateral/contralateral neck irradiation was significantly associated with cNFFS. However, we could not address the true impacts of contralateral neck radiation on outcomes because there were few events of contralateral neck recurrence in our subgroup analysis. The opportunity to omit unnecessary treatments without compromising cure rates prompts further investigation.

The pathological features, neck radiation sites, and relationships between local and contralateral neck failures for the 6 patients who experienced contralateral neck failure in our study are summarized in *Table 3*.

All these 6 patients underwent ipsilateral neck dissection during surgery. All were classified as pathological stage T2, and 4 had positive neck lymph node metastases. There was no obvious correlation between the characteristics mentioned above and contralateral neck nodal recurrence after analysis. Only 1 had characteristics of ECS, which is currently regarded as a mainly adverse feature of prognosis. Another patient developed contralateral neck nodal recurrence even after receiving bilateral neck irradiation, which could be due to the relatively low treatment dose (45 Gy). It was noteworthy that 5 of 6 (83.3%) contralateral neck nodal recurrences occurred after, or simultaneously with, local failure. Only 1 patient suffered from isolated contralateral neck nodal recurrence prior to local failure. Consequently, better local control might result in lower contralateral nodal recurrence rates, and more intense follow-ups or image studies should be considered once local recurrence has occurred.

The study is limited because it is a single-institution, non-randomized, and retrospectively reviewed cohort study. The small sample size and low primary endpoint events during follow-up could contribute to inconclusive results and insufficient study power to detect risk factors for contralateral neck recurrence. Therefore, extrapolation of the results from a wider, well-lateralized oral-cavity cancer population, including patients with more advanced tumor stages (T3–4), is warranted in the future.

Conclusions

For small, well-lateralized oral-cavity cancers, low contralateral neck nodal recurrence rates were observed. The benefit of contralateral neck irradiation cannot be well established according to our study. Once local failure occurs, cautionary follow-up is necessary because it may indicate a higher likelihood of contralateral neck failure. Further prospective, multi-center randomized controlled trials are warranted.

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Table 3 Characteristics of contralateral/bilateral neck nodal failure patients

No.	Age (years old)	T stage	N stage	Tumor site	Margin (mm)	PNI	LVI	ECS	RT site	Chemotherapy	cNF time (years)	Local failure and relation to cNF
1	37	2	1	Retromolar	10	+	–	–	–	–	6.3	Prior to cNF
2	44	2	2b	Buccal	10	+	+	+	Ipsilateral	Cisplatin	0.4	cNF occurred first
3	53	2	0	Gingival	6	–	–	–	–	–	5.6	Prior to cNF
4	64	2	0	Buccal	2	+	–	–	Ipsilateral	–	1.0	Prior to cNF
5	41	2	1	Buccal	5	–	–	–	–	–	0.2	At the same time
6	56	2	1	Retromolar	10	–	–	–	Bilateral	–	3.1	Prior to cNF

PNI, perineural invasion; LVI, lymphovascular invasion; ECS, extra-capsular spread; RT, radiotherapy; cNF, contralateral nodal failure.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://tro.amegroups.com/article/view/10.21037/tro-22-27/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by Institutional Review Board of National Cheng Kung University Hospital (IRB number: A-ER-111-181). The requirement for informed consent from the study subjects was waived due to the retrospective study design.

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