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Original Article

The pattern of failure and predictors of locoregional control in lateralized buccogingival cancer after postoperative radiation therapy

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Abstract

Background: To evaluate the failure pattern and identify predictors of locoregional control in lateralized buccogingival cancer after postoperative radiotherapy (RT) at a single institution.

Methods: We retrospectively reviewed the clinical data of 150 patients with lateralized oral squamous cell carcinoma, including carcinoma of the buccal mucosa, gingiva and retromolar trigone. All patients underwent radical surgery followed by postoperative RT with or without concurrent chemotherapy. We registered planning computer tomography images with images obtained at recurrence and categorized the failure pattern as in-field, marginal, or out-field recurrence.

Results: The median follow-up duration was 47 months (range, 2−131 months). Twenty-eight patients (19%) experienced locoregional failure, including 20 local failure, 5 regional failure and 3 with both. Among the 24 patients who had image studies at recurrence, 15 patients had in-field recurrence, 5 were marginal recurrence and 4 were out-field recurrence. Seven patients (5%) had contralateral neck failure. Four of 5 patients with marginal failure had recurrent tumors in the infratemporal fossa. In multivariate analysis, extracapsular spread and positive or close surgical margin were associated with poor locoregional control.

Conclusion: Local in-field recurrence is the most common failure pattern in lateralized buccogingival cancer after postoperative RT. The infratemporal fossa is a risk area for marginal failure and should be encompassed adequately in the postoperative RT field. Extracapsular spread and positive or close margin are predictors of locoregional control for lateralized oral cancer. Patients exhibiting such adverse features require more aggressive treatment.

Keywords: Adjuvant radiotherapy; Locoregional neoplasm recurrence; Mouth neoplasm

1. Introduction

Oral cancer is highly prevalent in Taiwan, with an estimated 5000 cases newly diagnosed annually, contributing to 5.6% of all cancers in one year. Oral cancer of buccogingival origin is more common in Taiwan than in Western countries because Taiwan is an endemic area for betel nut chewing.[1−3]

Surgery is the primary treatment method for oral cancer when feasible. Postoperative radiotherapy (RT) with or

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without chemotherapy for high-risk patients may improve locoregional control and survival.[4,5] However, locoregional recurrence is not uncommon, and retreatment is challenging. In this study, we focused on lateralized buccogingival cancer and investigated the failure patterns and risk factors for locoregional recurrence after postoperative RT.

2. Methods

2.1. Patients

Between November 2002 and May 2012, 973 patients with oral cancer received RT at our department. We focus on tumors originating from the buccal mucosa, gingiva and retromolar trigone because they tend to be lateralized and often involve these neighboring subsites contiguously. We excluded patients with cancers originating from the tongue, mouth floor or palate because these regions are in close proximity to the oropharynx and their patterns of spread may be different from tumors of buccogingival origin. Lip cancers were excluded because they were associated with sun exposure and share many common features with skin cancers. Among 480 patients with buccal, gingival, or retromolar trigone cancers, 150 patients who had received radical surgery followed by postoperative RT with or without concurrent chemotherapy were included (Fig. 1). None of the cancers crossed the midline. Clinical and pathological characteristics of the patients are listed in Table 1. All patients were staged according to pathological findings using the American Joint Committee on Cancer staging system, seventh edition.[6] The present study was a retrospective analysis, so it was exempted from full review by the Institutional Review Board (No. 2016-06-002AC) and individual inform consent was waived.

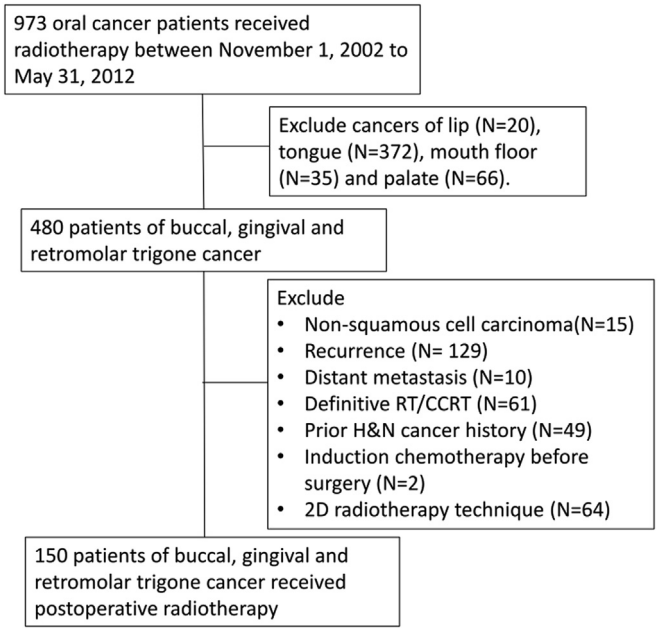

Fig. 1. Flowchart of study inclusion.

Table 1
Patient characteristics (n = 150).

Characteristic	No. of patients (%)
Male	143 (95)
Median age 50 (range 33–79) years	
Karnofsky performance status	
>70	119 (79)
≤70	31 (21)
Primary site	
Buccal mucosa	113 (75)
Gingiva	27 (18)
Retromolar trigone	10 (7)
Grade	
Well-differentiated	116 (77)
Moderately or poorly differentiated	34 (23)
Pathological T-classification	
T1	12 (8)
T2	39 (26)
T3	10 (7)
T4	89 (59)
Pathological N-classification	
N0	68 (45)
N1	28 (19)
N2	49 (33)
N3	1 (0.7)
Nx	4 (3)
Overall stage	
I	4 (3)
II	16 (11)
III	21 (14)
IV	109 (72)
Margin status	
Negative	105 (70)
Close (margin < 1 mm)	8 (5)
Positive	37 (25)
Extracapsular spread	
Yes	27 (18)
No	123 (82)
Lymphovascular invasion	
Yes	76 (51)
No	74 (49)
Perineural invasion	
Yes	75 (50)
No	75 (50)
Concurrent chemotherapy	
Yes	125 (83)
No	25 (17)
Neck irradiation	
Unilateral	82 (55)
Bilateral	68 (45)

2.2. Surgery

All patients underwent primary tumor resection. Ipsilateral or bilateral neck dissection was performed in 146 patients. One patient only had excisional biopsy of the neck lymph node, and three patients did not receive neck dissection because of clinical N0 disease.

2.3. Radiation therapy

Patients were referred for adjuvant RT if they had adverse pathological features, such as positive margins, extracapsular spread (ECS), ≥pT3 lesions, ≥N2 disease, perineural invasion

(PNI) or lymphovascular invasion (LVI). RT was planned to begin within 6 weeks after the operation. The median interval between surgery and RT was 39 days (range, 9−145 days). In 16 patients, RT was started more than 8 weeks after surgery, and most of them had poor wound healing or wound infection. The median interval of the radiation course was 44 days (range, 33−74 days). Treatment of the unilateral or bilateral neck was at the physician's discretion.

Our department started routine use of intensity-modulated radiotherapy (IMRT) in 2004. In this study, 47 and 103 patients were treated using 3D conformal radiotherapy and IMRT, respectively. CT simulation with IV contrast was performed for all patients. Image registration with preoperative CT, MRI or PET-CT was performed. The clinical target volume with a high dose (CTV-H) covered the primary tumor surgical bed, a positive surgical margin, or nodal lesions with ECS. The clinical target volume with a medium dose (CTV-M) covered a high-risk area, such as involved neck stations or anatomical structures adjacent to the primary tumor. The clinical target volume with a low dose (CTV-L) covered uninvolved nodal regions or the contralateral neck. A 3−5-mm margin was added to the CTV to form planning target volumes (PTVs), which were PTV-H, PTV-M, and PTV-L. Generally, for patients with positive surgical margins or ECS, 66 Gy was used for CTV-H, 59.4 Gy for CTV-M and 50.4 Gy for CTV-L. Patients with free margin and without ECS were prescribed 60 Gy, 54−60 Gy, and 50 Gy to CTV-H, CTV-M, and CTV-L, respectively. The fraction size was 1.8−2 Gy, and the fraction was delivered once per day, 5 days per week.

2.4. Chemotherapy

In our study, 125 patients (83%) received concurrent chemotherapy. The indications were positive surgical margins, ECS, or the presence of multiple risk factors. Most patients received cisplatin-based chemotherapy ($n = 119$). The regimens were either weekly cisplatin 25−30 mg/m^2 for 7 cycles plus daily tegafur 300 mg combined with uracil 672 mg in 3 dividing doses till RT completion or cisplatin 70 mg/m^2 and mitomycin C 7 mg/m^2, every four weeks for 2 cycles, plus daily tagafur 300 mg combined with uracil 672 mg in 3 dividing doses till RT completion. The remaining patients received carboplatin-based chemotherapy ($n = 3$) or concurrent cetuximab ($n = 3$). Among the 125 patients who received concurrent chemoradiotherapy (CCRT), 79 patients had post-CCRT adjuvant chemotherapy. The regimen was weekly fluorouracil 1000 mg/m^2 for 4 cycles after four weeks completion of RT.

2.5. Follow-up and definition of relapse

The patients were evaluated every week for acute toxicities during RT. Common Terminology Criteria for Adverse Events version 4.0 was used for classifying toxicity severity. Regular follow-up every 2−3 months in the first two years was recommended and the interval was extended to 6 months after two years if no evidence of recurrence was noted. Clinical assessment included oral inspection, neck palpation and sometimes laryngoscopy at every visit. Post-radiation imaging was performed every 3−6 months in the first two years or when suspicious relapses occurred during any time of follow-up.

The failure pattern was documented by the first failure event, which was local, regional, or distant failure or a combination of these. Most patients with locoregional failure received CT, MRI or PET-CT at the time of relapse and had pathologically proven recurrent squamous cell carcinoma. When available, the images were registered with the planning CT images and the recurrence sites were contoured. We used the definition employed by Chao et al.[7]: failure was designated as in-field if >95% of the volume of the recurrent tumor was in the CTV, marginal if 20−95% of the volume was in the CTV, and out-field if <20% of the volume was in the CTV.

2.6. Statistics

Time-to-event intervals were calculated from the date of surgery to the event of interest. Overall survival was the interval until death from any cause. Disease-free survival was survival until the first event of recurrence (locoregional recurrence or distant metastasis) or death from any cause. Disease-specific survival was defined as the interval until cancer-related death. Duration of locoregional control was the time from surgery to local and/or regional recurrence. Distant metastasis-free survival was defined as the time from surgery to distant metastasis. Overall survival, disease-free survival, locoregional control, distant-metastasis free survival and disease-specific survival were calculated using the Kaplan−Meier method and log-rank test for univariate analyses. Cox proportional hazards model was used for multivariate analyses, in which the effects of age (>65 years vs. ≤65 years), Karnofsky performance status (>70 vs. ≤70), ECS, PNI, LVI, pathological N-classification (N0, N1, or N2−N3), T-classification (T1−3 vs. T4), overall stage (stage I−II vs. III−IV), margin status (positive or close, defined as <1 mm, vs. negative), unilateral or bilateral neck irradiation, the interval between surgery and RT (>6 weeks vs. ≤6 weeks), and total treatment time from the surgery to the end of RT (>100 days vs. ≤100 days)[8] on locoregional control were evaluated. All statistical analyses were performed using SPSS 22.0.

3. Results

The median follow-up duration was 47 months (range, 2−131 months). The median follow-up duration for living patients was 56 months (range, 3−131 months). The five-year overall survival, locoregional control, disease-free survival, distant metastasis-free survival and disease-specific survival were 70%, 79%, 65%, 85% and 79%, respectively.

The median doses prescribed for the tumor surgical bed and ipsilateral neck were 63.5 Gy (range, 54−70 Gy) and 50.4 Gy (range, 45−60 Gy), respectively. Eighty-two patients received unilateral neck irradiation, whereas 68 patients received bilateral neck irradiation. The median dose delivered to the contralateral neck was 54 Gy for patients who received bilateral neck irradiation.

3.1. Failure patterns

Twenty-eight patients (19%) experienced locoregional failure, with 20 having local failure, 5 having regional failure and 3 having both local and regional failure. Eight of the patients developed distant metastasis at the time of locoregional failure, and all of them died within one year. The median time from the end of RT to the occurrence of locoregional failure was 8.5 months (range, 1.0−80.0 months).

Four patients with local failure had no diagnostic images at the time of recurrence; two were lost to follow-up after biopsy confirmed recurrent disease, and the remaining two patients directly received salvage tumor excision. For the other 24 patients with locoreginal failure, CT images of recurrence were registered with planning CT images. There were 15, 5 and 4 patients who had in-field, marginal and out-field recurrence, respectively. Among patients with local failure, three patients had synchronous distant metastasis, two had regional failure, and one had both of these conditions at the time of local recurrence. Among those with in-field recurrence, 10 had recurrence in the CTV-H and CTV-M, and 5 patients had recurrence in the prophylactic radiation dose area (CTV-L). The most common local failure site was the original tumor bed. Four of 5 patients with marginal failure had recurrent tumors in the infratemporal fossa, which was covered by the CTV-L.

Eight patients experienced regional recurrence. Of these patients, only one had isolated contralateral neck lymphadenopathy as the first failure; the remaining patients had coexisting local or distant disease. Seven patients (5%) had contralateral neck failure, with three and four patients receiving unilateral and bilateral neck irradiation, respectively. Two of them received bilateral neck dissection. Only one patient had pathologically proven stage N2c disease. One patient who received bilateral neck irradiation was considered to have out-field failure because the recurrent lymphadenopathy was located at the junction of the contralateral supraclavicular fossa and upper mediastinum, which was not covered by the CTV_L.

3.2. Risk factors for locoregional recurrence

Univariate analyses revealed that the presence of ECS ($p < 0.0001$), LVI ($p = 0.043$) positive or close margin ($p = 0.031$) and N2−N3 disease ($p = 0.001$) were the factors that significantly correlated with poor locoregional control (Fig. 2). In multivariate analyses, ECS ($p = 0.047$; hazard ratio (HR), 2.61; 95% confidence interval (CI), 1.01−6.70) and positive or close margin ($p = 0.019$; HR, 2.63; 95% CI, 1.17−5.93) significantly predicted locoregional control (Table 2).

3.3. Toxicities

Grade 3 and grade 4 acute oral mucositis were observed in 38 and 5 patients, respectively; those with grade 4 acute oral mucositis all received systemic chemotherapy. Seven patients developed ≥grade 3 acute skin reactions; all of them underwent systemic chemotherapy. Grade 3 neutropenia was observed in 9 patients who received concurrent chemoradiation. The median weight loss during RT was 4% (range, −22% to 15%) of the baseline weight. Twenty patients had documented mandibular osteoradionecrosis that required sequestrectomy or hyperbaric oxygen therapy. A total of 33 and 56 patients had neck fibrosis and trismus, respectively.

4. Discussion

Oral cancer is a complicated disease because it comprises various anatomical subsites and the pattern of spread varies according to the tumor location. Surgery is the main treatment for operable cases, followed by RT with or without concurrent chemotherapy. However, locoregional recurrence remains the most common failure type. Several studies have discussed the treatment outcome of RT in oral cancer; most of them reported tumors originating in the tongue and included both definitive and postoperative RT approaches.[7,9,10] Literature review revealed that the incidence of contralateral neck recurrence in lateralized oral cancer varies, and that very few studies have examined this group.[11,12] In this study, we analyzed the failure patterns of 150 patients with buccal, gingival and retromolar trigone squamous cell carcinoma to evaluate the failure patterns and predictors of locoregional control.

In our study, the 5-year overall survival was 70%, which is comparable with that of the largest study on buccal cancer in Taiwan, in which the overall 5-year survival rates in surgically treated patients was 71%.[13]

Risk factors for locoregional recurrence have been identified and reported.[14−16] In our study, the presence of ECS and positive or close surgical margin were associated with poor locoregional control. Peters et al.[16] analyzed the risk factors for locoregional failure and reported ECS as the only independently significant variable. They suggested a boost dose of 63 Gy in the high-risk area. Bernier et al.[15] analyzed clinical and pathological risk factors in the EORTC 22931[4] and RTOG 9501 trials[5] and concluded that patients with ECS or microscopically involved surgical margins benefit the most from postoperative CCRT.

Regional failure is a rare event. In this study, eight patients had regional recurrence and only one of them was isolated regional recurrence. From the literature, the isolated regional relapse rate was low, ranging from 0% to 10%.[9,10,17,18] Duprez et al.[17] reported that of 16 patients with regional failure, seven experienced isolated regional relapse after elective nodal irradiation, with the 5-year isolated regional relapse rate being 5%. They concluded that increasing the dose to >51 Gy in the elective nodal area did not improve regional control. Of the 8 patients with regional failure in our study, two had local recurrence, four patients developed distant metastases and one had both of these conditions simultaneously. All of them had poor prognoses and died within 1 year after recurrence, with a median duration of 4.4 months from regional failure to death (range, 0.1−11.5 months).

Contralateral neck failure in oral cancer treatment has been investigated.[11,12,19,20] Lymphatic drainage differs according to

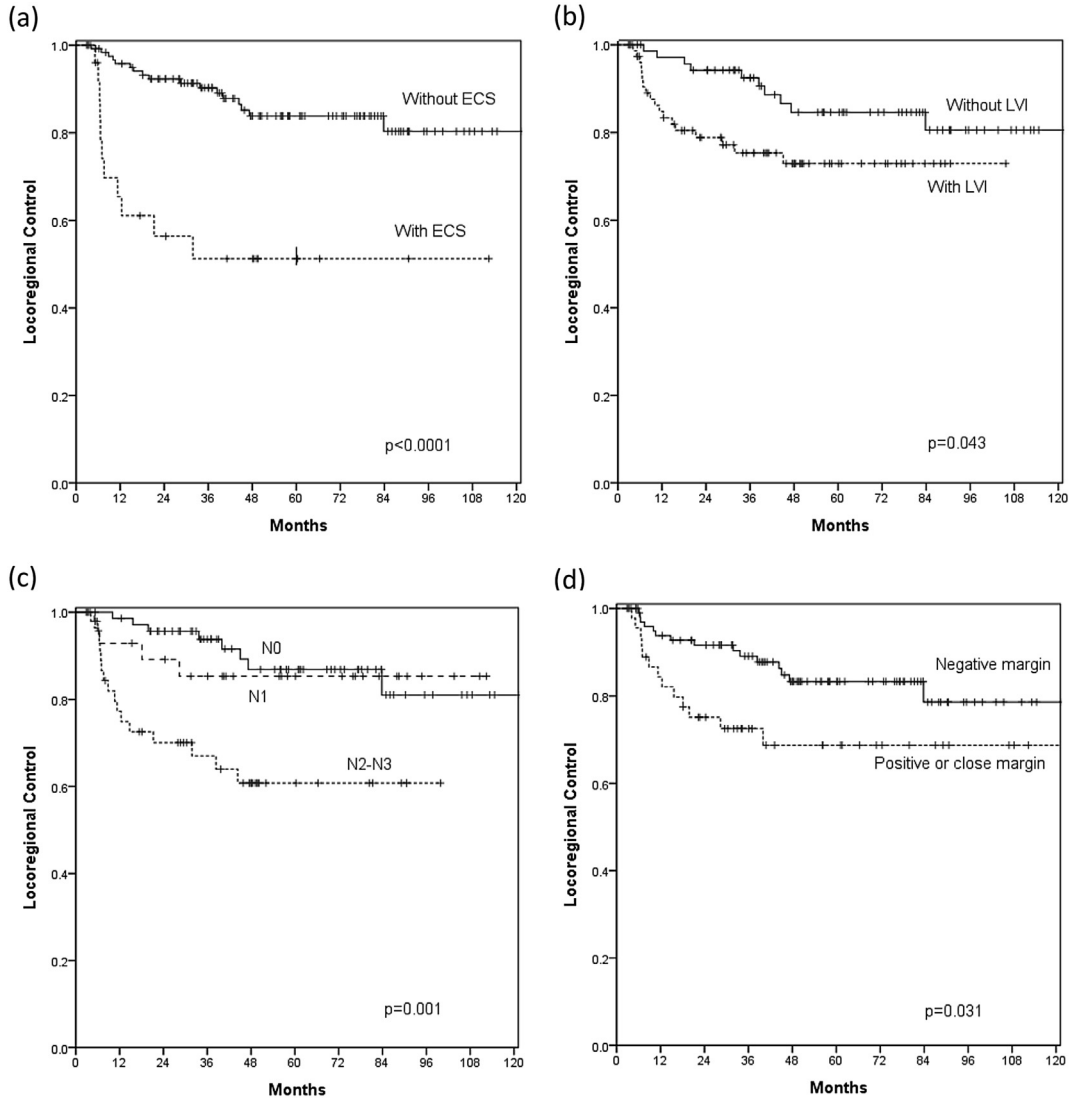

Fig. 2. Kaplan−Meier estimates of locoregional control according to (a) the presence of extracapsular extension (ECS), (b) the presence of lymphovascular invasion (LVI), (c) N-classification, and (d) margin status.

the location within the oral cavity. Tongue and mouth floor cancer have rich lymphatics across the midline, thus carrying a high risk of contralateral neck failure. Therefore, it is prudent to irradiate the neck bilaterally. However, whether the contralateral neck must be included in lateralized oral cancer remains controversial. Lin et al.[11] analyzed 120 buccal mucosa cancer patients who had undergone unilateral neck irradiation, of whom only 3 (2.1%) developed contralateral neck recurrence. By contrast, none of the 23 patients who received bilateral neck irradiation had contralateral neck failure. Lin et al. reported that locoregional control and disease-specific survival did not differ significantly between patients receiving unilateral and bilateral neck irradiation. Vergeer et al.[12] evaluated the contralateral nodal control rate in 123 well-lateralized oral cancer patients after surgery and ipsilateral neck RT. Contralateral neck failure developed in 7 patients (6%), and the 5-year contralateral nodal control rate was 92%. The number of metastatic lymph nodes was the most significant predictor of contralateral nodal control, and the authors proposed that bilateral neck RT be applied in patients with multiple metastatic lymphadenopathy. Kurita et al.[20] suggested that patients with T4 tumors, multiple ipsilateral neck nodes, and high-histological-grade tumors were high-risk groups for contralateral neck metastasis. Furthermore, they stated that contralateral neck metastasis is unlikely in N0 neck or in T1−T3 lateralized oral carcinoma, except in tongue cancer. In our study, the contralateral neck recurrence rate was 5%. Most patients who had contralateral neck metastasis were at advanced tumor stage or had ipsilateral positive neck node. Generally, the incidence of contralateral neck lymph node recurrence is low, and unilateral neck irradiation may be sufficient to cover microscopic disease in lateralized oral cancer. Bilateral neck irradiation could be considered for patients with multiple metastatic lymph nodes or locally advanced disease.

The infratemporal fossa is a risk area for recurrence. Yao et al.[10] reported that oral cancer could spread retrograde along the inferior alveolar nerve to the infratemporal fossa. They suggested that the infratemporal fossa be included in the

Table 2
Multivariate analyses for locoregional recurrence.

Variable	Hazard ratio (95% CI)	p*
Age >65 (vs. ≤65)	1.91 (0.54−6.84)	0.318
KPS >70 (vs. ≤70)	0.40 (0.12−1.39)	0.149
T-classification T4 (vs. T1−T3)	1.42 (0.47−4.29)	0.529
N-classification N2−N3 (vs. N0)	2.78 (0.63−12.23)	0.175
Stage III−IV (vs. stage I−II)	0.75 (0.12−4.56)	0.757
Positive or close margin (vs. negative)	2.63 (1.17−5.93)	0.019
Presence of ECS (vs. no ECS)	2.60 (1.01−6.70)	0.047
Presence of LVI (vs. no LVI)	1.43 (0.58−3.53)	0.432
Presence of PNI (vs. no PNI)	1.21 (0.48−3.05)	0.690
Interval between surgery and RT >6 weeks (vs. ≤6 weeks)	0.64 (0.21−1.94)	0.433
Total treatment time >100 days (vs. ≤100 days)	2.90 (0.73−11.50)	0.130
Bilateral neck irradiation (vs. unilateral neck)	0.98 (0.33−2.86)	0.968

CI, confidence interval; ECS, extracapsular spread; KPS, Karnofsky performance status; LVI, lymphovascular invasion; PNI, perineural invasion; RT, radiotherapy.
*p value < 0.05 is considered significant.

radiation field in cases with PNI of the mental nerve or inferior alveolar nerve and in those whose tumors are close to these nerves. In our study, 5 patients had recurrence in the infratemporal fossa. All of them exhibited adverse features of PNI, and 4 patients had positive or close surgical margins. One patient had in-field failure at the dose of 60 Gy. The other 4 patients had a marginal miss at doses of 50−54 Gy, meaning that the region of the infratemporal fossa was not fully covered in the radiation field. The primary tumor sites of these 4 patients were in the retromolar trigone or the upper gingiva. Two of them were T4 tumors. No patient had direct tumor extension to the infratemporal fossa before treatment. Therefore, encompassing the entire infratemporal fossa in the postoperative radiation field for patients with retromolar trigone or upper gingiva cancer should be considered.

The limitations of this study are its retrospective nature and relatively small sample size. Nevertheless, the study results regarding the failure pattern and risk factors for locoregional control are consistent with those of previous studies.

In conclusion, in lateralized buccogingival cancer after postoperative RT, local in-field failure remains the predominant failure pattern. ECS and positive or close surgical margin were predictors of poor locoregional control. The infratemporal fossa is a risk area for marginal miss in upper gingival or retromolar trigone cancer and careful target delineation is required.

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