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# Patterns of failure after postoperative intensity-modulated radiotherapy for locally advanced buccal cancer: Initial masticator space involvement is the key factor of recurrence

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## Abstract

**Background:** The purpose of this study was to determine failure patterns and clinicopathologic prognostic factors in patients with locally advanced buccal cancer after postoperative intensity-modulated radiotherapy (IMRT).

**Methods:** Eighty-two patients with locally advanced (American Joint Committee on Cancer [AJCC] stage III/IV) buccal cancer who underwent surgery followed by postoperative IMRT between January 2007 and October 2012 were retrospectively analyzed.

**Results:** Eighteen patients had local recurrences as the first recurrent site and 11 had supramandibular notch recurrences; the majority of recurrences were classified as marginal failures. The median time from the first local or regional recurrence to death was 5.9 months. In multivariate analyses of survivals, the initial masticator space involvement was the most important prognostic factor. Masticator space involvement, N classification, and maxillectomy were the significant prognostic predictors for supramandibular notch recurrences.

**Conclusion:** Postoperative IMRT for buccal cancer should not include the surgical beds alone, rather, it should be based on the potential patterns of spread.

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KEYWORDS
adjuvant radiotherapy, buccal cancer, oral cavity cancer, patterns of failure, postoperative intensity-modulated radiotherapy (IMRT)

## 1 | INTRODUCTION

Oral cavity cancer, especially locally advanced disease status, is characterized by high locoregional recurrence rates and poor survival,[1,2] although some improvement has been achieved during the past decade.[3] The leading treatment strategy for locally advanced oral cavity cancer is surgery followed by postoperative radiotherapy (RT) with or without chemotherapy. A major breakthrough in RT was the development of intensity-modulated radiotherapy (IMRT), which delivers highly conformal radiation doses to targets while sparing the surrounding normal tissues.[4–8]

Buccal cancer is a special type of oral cavity cancer that arises from the lining epithelial cells of the buccal space, which is adjacent to the retromolar trigone and masticator space, and is characterized by poor locoregional control and survival rates.[9,10]

Buccal cancer invading the masticator space, pterygoid plate, skull base, or internal carotid artery is defined as T4b disease and is considered very advanced local disease.[11] The masticator space, which includes the muscles of mastication (the medial and lateral pterygoids, masseter, and temporalis), ramus and posterior body of the mandible, mandibular nerve, and pterygoid venous plexus,[12,13] are bilateral suprahyoid cervical spaces that extend from the angle of the mandible to the parietal calvarium.[12] Locally advanced buccal cancer with initial involvement or encasement of the masseter muscle, mandibular ramus, or lower part of the medial pterygoid muscle, might be considered resectable disease with favorable outcomes.[14–17]

The aggressive behavior of buccal cancer, the resulting anatomic boundaries, and the change in lymphovascular drainage after surgery make the design of optimal RT very challenging. Some unexpected recurrences have been disclosed after postoperative IMRT. The purpose of this study was to analyze failure patterns and prognostic factors in patients with locally advanced buccal cancer after postoperative IMRT.

## 2 | MATERIALS AND METHODS

### 2.1 | Ethics statement

The Institutional Review Board at Chi Mei Medical Center approved this study. The Institutional Review Board waived the need for written informed consent from the participants because this was a retrospective chart review study.

### 2.2 | Study population

All consecutive patients with squamous cell carcinoma (SCC) of the buccal mucosa who had undergone curative surgery followed by postoperative IMRT between January 2007 and October 2012 at Chi Mei Medical Center (Tainan, Taiwan) were reviewed. Patients with a history of head and neck malignancy and oral cavity cancer of other subsites were excluded.

### 2.3 | Treatment

#### 2.3.1 | Surgery

The extent of curative surgery[18] included wide local excision of the primary tumor site and neck lymph node dissection. Bilateral neck dissection was performed in patients with suspected contralateral lymph node metastases. A marginal or segmental mandibulectomy or partial maxillectomy was performed if clinically indicated.

#### 2.3.2 | Radiotherapy

The high-risk clinical target volume (CTV) covered areas at risk of microscopic disease, including the primary tumor, surgical bed, and involved regional lymph nodes. For high-risk CTV, the standard of the upper boundary ended at the inferior part of the zygomatic arch and the upper boundary for high-risk CTV extended properly if clinically indicated. The involved regional lymph nodes encompassed the ipsilateral and/or bilateral upper neck at level IB, level II, and high-level III lymph nodes. The level IA lymph nodes were covered for anteriorly located tumors and those with pathologic involvement. The standard radiation dose to the high-risk CTV was 60 Gy in 30 fractions. In patients with suspicious nodular lesions on the postoperative CT scan, positive surgical margins, or nodal metastasis with extracapsular extension, the radiation dose to the area of concern was escalated to 63 to 70 Gy, whereas the remaining high-risk CTV region received 60 Gy. The low-risk CTV was the ipsilateral or contralateral uninvolved lower neck, including low-level III, level IV, and supraclavicular nodes. A standard radiation dose of 54 Gy was given to the low-risk CTV. Planning target volumes were generated by extending a 5-mm margin to all corresponding CTV volumes.

#### 2.3.3 | Chemotherapy

Patients with positive surgical margins or extracapsular extension received postoperative concurrent chemoradiotherapy. Chemotherapy was administered with a weekly cisplatin-based regimen (30 mg/M$^2$).

### 2.4 | Follow-up

Patient follow-up occurred regularly in the first, third, sixth, ninth, and twelfth months in the first year postsurgery. After the first year, follow-up occurred every 3 months in the second and third years, every 6 months in the fourth and fifth years, and annually after the fifth year. Image studies (CT scan or MRI) for follow-up were arranged in the first, sixth, and twelfth months in the first year postsurgery, then annually or as clinically indicated. Local or regional recurrence and distant metastasis were determined by various methods, such as physical examination, tissue biopsy, and serial imaging studies, including CT scan, MRI, or positron emission tomography/CT scan.

### 2.5 | Definition of failure pattern

Local failure was defined as the first recurrence at the primary site or tumor bed. Regional failure was defined as the first recurrence at the regional lymphatic drainage area, including the retropharyngeal and bilateral neck regions. The presence of distant metastases was defined as a recurrent lesion that had spread outside the head and neck region. Supramandibular notch recurrence was definite in cases in which the recurrent tumor extended above the axial planes of the mandibular notch on CT scan or MRI[15] into the suprazygomatic masticator space, skull base, or intracranial region.

### 2.6 | Dosimetric assessment of locoregional recurrent disease

The images of recurrence were fused with the original IMRT treatment plan to define the relationship between the failed tumor volume and the dosimetric distribution. For local and supramandibular notch recurrences, the in-field failure was determined as 95% of the failure volume at the primary site within 95% of the intended treatment dose (ie, for high-risk CTV, such as the tumor bed, the standard intended treatment dose was 60 Gy). Marginal failure was determined as 20%-95% of the failure volume within 95% of the intended treatment dose. Out-field failure was determined as <20% of the failure volume within 95% of the intended treatment dose. For regional recurrence, in-field, marginal, and out-field failures at the neck region were determined with the same criteria mentioned above.

### 2.7 | Clinicopathologic factors

Clinicopathologic factors, such as TNM classification (American Joint Committee on Cancer [AJCC] seventh edition), tumor size, tumor thickness, initial masticator space involvement, histologic grade, lymphovascular space invasion, perineural invasion (PNI), margin status, skin invasion, bone invasion, lymph node involvement with or without extracapsular spread, surgery-to-RT interval (interval between the operation date and the date RT started), and total package time (from the operation date to the date RT ended) were evaluated for survival analysis. Initial masticator space involvement was defined by the preoperative CT scan or MRI as involvement of at least one of the following components of the masticator space: the medial and lateral pterygoids; masseter muscle; temporalis muscle; posterior body and ramus of the mandible; and mandibular nerve.

### 2.8 | Statistical analysis

Statistical analyses were performed using SPSS software version 14 (SPSS, Chicago, IL). Estimates for supramandibular notch recurrence-free survival, local failure-free survival, regional failure-free survival, distant metastasis-free survival (DMFS), and overall survival (OS), were calculated using the Kaplan-Meier method with log-rank test. The multivariable analysis of supramandibular notch recurrence-free survival, local failure-free survival, regional failure-free survival, DMFS, and OS were estimated using the Cox proportional hazards model with the stepwise approach to select the statistical significant clinicopathologic factors from the univariate analysis. All tests were 2-tailed, with a probability value $< .05$ considered to be statistically significant.

## 3 | RESULTS

### 3.1 | Patient clinical characteristics

Eighty-two patients were enrolled retrospectively. All patients had locally advanced buccal cancer (AJCC stage III, 40 patients [49%]; stage IV, 42 patients [51%]). The median patient age was 49 years (range 32-77 years). The median duration of follow-up was 51 months (range 2-112 months). The clinical stages of patients with buccal cancer were determined by AJCC staging criteria and a multidisciplinary team meeting. There were 14 patients with initial masticator space involvement. Initial masticator space involvement was limited to the ramus of the mandible, the lower part of the medial pterygoid muscle, or masseter muscle in 7 of 14 patients. Twelve of 14 patients underwent wide excision of the tumor with a mandibulectomy and 6 patients received wide excision of the tumor and a partial maxillectomy. After surgery, 8, 3, and 1 of 14 patients were downstaged to pT4a, pT3, and pT1, respectively, according to the AJCC staging criteria. The pT4a referred to tumor invasion through the

cortical bone in our cases. These discrepancies might be due to peritumoral inflammatory changes mimicking tumor invasion on imaging or incomplete surgical information for pathologic evaluation. The patient and clinicopathologic characteristics are detailed in Table 1.

### 3.2 | Outcomes

The Kaplan-Meier method was used to estimate the local failure-free survival, regional failure-free survival, DMFS, and OS for all of the patients (Supporting Table S1). The estimated 5-year supramandibular notch recurrence-free survival, local failure-free survival, regional failure-free survival, DMFS, and OS rates were 85.5%, 76.4%, 78.2%, 84.4%, and 57.5%, respectively.

There were 18 patients (22%) with local failure as the first recurrence site. Among the 18 patients, 11 patients had supramandibular notch recurrences, 7 patients had synchronous local and regional recurrences, and 2 patients had synchronous local, regional, and distant failures. Seventeen (21%) regional failures were detected; 5 patients had regional recurrences only, 3 patients had synchronous regional and distant recurrences, and 2 patients had sequential regional recurrences after the local recurrence. Thirteen patients (16%) presented with distant metastases. Only 3 patients had distant metastases without locoregional failure. Among the 13 patients with distant metastases, 8 had lung metastases, 2 had mediastinal lymph node metastases, 1 had thyroid metastases, 1 had massive peritoneal metastases, and 1 had right shoulder metastases. Twelve patients (15%) had >2 recurrent sites synchronously at the time of the first recurrence.

The median time from completion of treatment to the first local or regional recurrence was 6.8 months (range 1-33 months). The median time from the first local or regional recurrence to death was 5.9 months (range 1-20 months). The main salvage treatment for locoregional recurrence was salvage RT with or without chemotherapy to the recurrent tumor region. Thirty-two patients (39%) died; 26 patients died of progression of buccal cancer, 4 patients died of a second primary oral cancer, and 2 patients died of other diseases.

### 3.3 | Supramandibular notch recurrence

Of the 18 patients with local recurrences, 11 presented with supramandibular notch recurrences along the masticator space or with intracranial perineural spread outside the primary tumor bed. Seven of 14 patients with initial masticator space involvement experienced local recurrence were all classified as supramandibular notch recurrences. Details of the supramandibular notch recurrences and the involved regions are shown in Table 2. All 11 patients died of the disease with a median interval of 5.7 months from recurrence to death (range 1.7-11.1 months). Figure 1A,B show cases of supramandibular notch recurrences.

### 3.4 | Dose-volume analysis of failure patterns

Of the 18 local recurrences, 9 were in-field failures, 9 were marginal failures, and there were no out-of-field failures. The majority of the 11 supramandibular notch failures were marginal (8 patients), with 3 in-field failures (Figure 1C).

Five patients had regional failures as the first recurrent site. Two patients had in-field recurrences within the ipsilateral neck, 1 patient at level IB, and 2 patients at levels II and III. Two patients also had marginal recurrences (1 at the bilateral retropharyngeal region and 1 at the ipsilateral retropharyngeal region and level V). There was only 1 out-of-field failure in a patient treated with ipsilateral neck irradiation who had a recurrence in contralateral levels III and IV as the first recurrent site.

### 3.5 | Univariate and multivariate analysis for survival

The univariate relative survival risks of supramandibular notch recurrence-free survival, locoregional recurrence-free survival (LRFS), regional recurrence-free survival (RRFS), DMFS, and OS among all clinicopathologic factors are presented in Table 3. From the univariate analysis, T classification, N classification, bone invasion, maxillectomy, and initial masticator space involvement were important prognostic factors for supramandibular notch recurrence-free survival. In addition, N classification, lymphovascular invasion, maxillectomy, and initial masticator space involvement were critical factors of LRFS. For RRFS, the major predictors were N classification, extracapsular extension, lymphovascular invasion, chemotherapy, surgery to RT interval, and initial masticator space involvement. Moreover, the most significant prognostic predictors for DMFS and OS were N classification, lymphovascular invasion, surgery to RT interval, and initial masticator space involvement.

Based on the above significant prognostic predictors, Table 4 shows the multivariable analysis of clinicopathological factors for supramandibular notch recurrence-free survival, LRFS, RRFS, DMFS, and OS. The initial masticator space involvement identified the most significant prognostic predictors for supramandibular notch recurrence-free survival, LRFS, RRFS, DMFS, and OS, and the relative risk ratios were 14.40 (95% confidence interval [CI] 3.81-54.42; $P < .0001$), 3.59 (95% CI 1.69-7.63; $P = .0020$), 10.62 (95% CI 3.52-31.97; $P < .0001$), 9.88 (95% CI 2.99-32.67; $P = .0002$), and 4.85 (95% CI 2.19-10.73; $P < .0001$), respectively. Besides the initial masticator space involvement, the patients with N classification on N2 and maxillectomy presented, respectively, the 5.71-fold (95% CI 1.49-21.93; $P = .0111$) and 4.47-fold (95% CI 1.24-16.16; $P = .0225$) supramandibular notch recurrence-free survival risk compared with N classification on N0 to N1 and without

**TABLE 1** Patient characteristics

| Characteristics | No. of patients | Percentage |
|---|---|---|
| Sex | | |
| Male | 81 | 99 |
| Female | 1 | 1 |
| Age, years | | |
| Median | 49 | |
| Range | 32-77 | |
| T classification (pT) | | |
| T1 | 10 | 12 |
| T2 | 24 | 29 |
| T3 | 22 | 27 |
| T4a | 24 | 29 |
| T4b | 2 | 3 |
| N classification (pN) | | |
| N0 | 35 | 43 |
| N1 | 28 | 34 |
| N2 | 19 | 23 |
| Stage | | |
| III | 40 | 51 |
| IV | 42 | 49 |
| Extracapsular extension | | |
| Present | 16 | 20 |
| Absent | 66 | 80 |
| Histological grade | | |
| Well differentiated | 25 | 31 |
| Moderately differentiated | 48 | 59 |
| Poorly differentiated | 9 | 11 |
| Lymphovascular invasion | | |
| Present | 4 | 5 |
| Absent | 78 | 95 |
| PNI | | |
| Present | 10 | 12 |
| Absent | 72 | 88 |
| Margin status | | |
| Negative | 74 | 90 |
| Close | 2 | 3 |
| Positive | 6 | 7 |
| Chemotherapy | | |
| None | 68 | 93 |
| Concurrent | 14 | 7 |
| Neck irradiation | | |
| Unilateral | 76 | 93 |
| Bilateral | 6 | 7 |
| Surgery to RT interval | | |
| <6 wk | 43 | 52 |
| ≥6 wk | 39 | 48 |
| Total package time | | |
| <12 wk | 38 | 46 |
| ≥12 wk | 44 | 54 |
| Mandibulectomy | | |
| Yes | 61 | 76 |
| No | 21 | 24 |

(*Continues*)

**TABLE 1** (Continued)

| Characteristics | No. of patients | Percentage |
|---|---|---|
| Maxillectomy | | |
| Yes | 25 | 70 |
| No | 57 | 30 |
| Masticator space involvement | | |
| Yes | 14 | 17 |
| No | 68 | 83 |

Abbreviations: PNI, perineural invasion; RT, radiotherapy.

maxillectomy. Moreover, the final estimated predictors of LRFS were initial masticator space involvement and N classification (hazard ratio [HR] 2.75; 95% CI 1.35-5.61; $P$ = .0223). Furthermore, not only initial masticator space involvement but also extracapsular extension (HR 4.97; 95% CI 1.77-13.98; $P$ = .0024), lymphovascular invasion (HR 5.72; 95% CI 1.34-24.38; $P$ = .0184), and surgery to the RT interval (HR 8.97; 95% CI 2.35-34.22; $P$ = .0013) were independent prognostic factors for RRFS based on the multivariable analysis. For DMFS, the initial masticator space involvement, lymphovascular invasion, and surgery to the RT interval were indicated as the significant risk at 9.88 (95% CI 2.99-32.67; $P$ = .0002), 13.42 (95% CI 3.20-56.30; $P$ = .0004), and 5.99 (95% CI 1.51-23.72; $P$ = .0108), respectively. Finally, besides the initial masticator space involvement, the final model of OS show that patients with N classification on N2, lymphovascular invasion, and surgery to the RT interval ≥6 weeks had 2.27-fold, 5.45-fold, and 2.45-fold risk of OS compared with N classification on N0 to N1, without lymphovascular invasion, and surgery to the RT interval <6 weeks, respectively. In summary, masticator space involvement is the most important prognostic factor in patients with SCC of the buccal mucosa.

## 4 | DISCUSSION

Current treatment for advanced oral cavity cancer remains a challenge. Several clinical studies have evaluated outcomes for oral cavity cancer treated with surgery and postoperative IMRT.[4–6,8,19] The 2- to 3-year rates of local control, locoregional control, and OS range from 67% to 92%, 53% to 82%, and 60% to 74%, respectively. In the current study, the 5-year local failure-free survival, regional failure-free survival, and OS rates were 76.4%, 78.2%, and 57.5%, respectively. Compared with the previous series described above, the disease control rate in the current study was moderately inferior. There are 2 reasons that might account for this outcome: initial masticator space involvement; and the notably different failure pattern.

### 4.1 | Masticator space involvement is the most important prognostic factor

The optimal management of very advanced local buccal cancer with initial masticator space involvement is still unknown. With modern surgical techniques, tumors in the masticator space are resectable, however, whether or not the disease is really curable is questionable.[20,21] Liao et al[14,15] reported favorable surgical outcomes in patients who underwent tumor resection with masticator space involvement or

**TABLE 2** Patterns of supramandibular notch recurrence

| Involved recurrent region | Suprazygomatic masticator space | Masticator space | Retromolar trigone | Foramen rotundum / V2 | Foramen ovale / V3 | PPF | Parapharyngeal space | Optic canal/ Mackles' cave/ cavernous sinus | Synchronous regional recurrence |
|---|---|---|---|---|---|---|---|---|---|
| Patient 1[a] | + | + | + | + | + | + | - | +/+/+ | + |
| Patient 2[a] | - | + | + | - | - | - | - | - | - |
| Patient 3 | + | + | - | - | - | - | - | - | - |
| Patient 4[a] | + | + | + | - | - | + | + | - | + |
| Patient 5[a] | + | + | + | - | - | - | + | - | + |
| Patient 6 | - | + | + | - | - | - | - | - | + |
| Patient 7[a] | + | + | + | + | + | + | + | +/+/- | + |
| Patient 8[a] | + | + | + | + | + | + | + | -/-/- | + |
| Patient 9 | + | + | + | - | - | - | + | - | - |
| Patient 10 | - | + | - | + | + | + | + | +/+/+ | - |
| Patient 11[a] | + | + | + | - | - | - | - | - | + |

Abbreviations: PPF, pterygopalatine fossa; V2, the maxillary division of the trigeminal nerve; V3, the mandibular division of trigeminal nerve; Synchronous regional recurrence, recurrence with neck lymph metastasis concurrently.
[a] The patients with initial masticator space involvement.

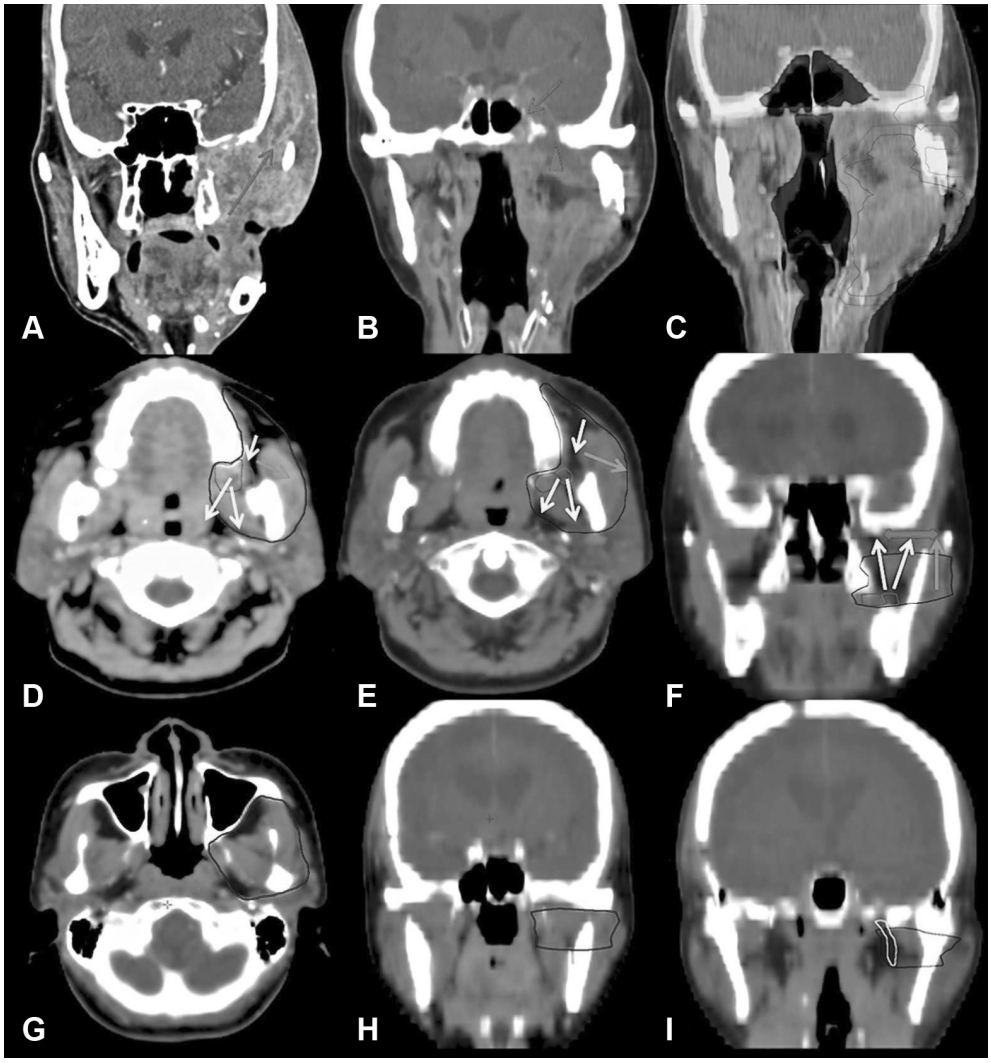


**FIGURE 1** A, Patient 8 in Table 2. The arrow indicates tumor spread to the suprazygomatic masticator space; B, patient 1 in Table 2. The tumor spreads to the foramen rotundum (arrow) and foramen ovale (arrowhead); C, fused treatment plans of patient 1, the marginal failure case. The red line shows the initial clinical target volume (CTV); the magnet lines show the initial planning target volume. The orange color wash shows the recurrent tumor; D-I, the yellow arrows show medial spreading patterns of buccal cancer; the orange arrows show lateral spreading routes; and the red arrows show spreading across mandibular notch. Red lines indicate the retromolar trigone; pink lines indicate the pterygomandibular raphe; blue lines indicate CTV; and yellow line indicates part of the mandibular nerve

cT4b disease; however, some patients still had rapid disease progression within the first few years. Liao et al[14,15] did not report how the disease failed or progressed. The extent of surgery in patients with SCC of the buccal mucosa with masticator space involvement remains controversial. A clinical trial in India suggested radical compartment resection yields more safe margins and improved survival.[17] In the previous study, when the masticator space was involved by SCC of the retromolar trigone, the patients did poorly despite radical surgery and adjuvant therapy.[20] Currently, there are no clinical trials comparing surgical intervention and definitive RT or concurrent chemoradiotherapy in patients with cT4b disease. No evidence exists suggesting which modality is superior in patients with initial masticator space involvement.

In the current postoperative IMRT series with the 14 patients with initial masticator space involvement, 9 patients had locoregional recurrences; 1 patient had distant failure only; and 4 patients remained disease-free despite aggressive treatment. Among the 9 patients with locoregional recurrences, 6 patients had synchronous local and regional recurrences, 1 patient had local recurrence alone, and 2 patients had regional recurrence alone. All of the 7 patients with initial masticator space involvement experienced local recurrences and were supramandibular notch recurrences, which led to lethal events in a short period of time. Initial masticator space involvement was the most important prognostic factor in the all survival analyses in the current study (Table 4 and Supporting Figure S1).

### 4.2 | Patterns of failure and radiotherapy field

The previous postoperative IMRT study reported some unexpected regional failures, which were classified as

**TABLE 3** The univariate analysis of clinicopathological factors for prognosis

| | Supramandibular notch recurrence-free survival | | LRFS | | RRFS | | DMFS | | OS | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Factors, no. of patients** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| Age, years | | | | | | | | | | |
| >40 vs ≤40 (ref.) | 0.44 (0.10-2.07) | .3004 | 0.48 (0.14-1.67) | .2493 | 0.42 (0.12-1.47) | .1750 | … | … | 0.42 (0.17-1.01) | .0519 |
| T classification | | | | | | | | | | |
| T3-4 vs T1-2 (ref.) | **7.84 (1.00-61.25)** | **.0497** | 1.18 (0.46-3.04) | .7354 | 1.39 (0.52-3.76) | .5149 | 1.15 (0.38-3.21) | .8101 | 1.51 (0.78-2.92) | .2208 |
| N classification | | | | | | | | | | |
| N2 vs N0-1 (ref.) | **3.95 (1.20-13.00)** | **.0240** | **3.04 (1.17-7.85)** | **.0221** | **4.31 (1.65-11.21)** | **.0028** | **3.05 (0.99-9.40)** | **.0526** | **2.34 (1.18-4.65)** | **.0149** |
| Stage | | | | | | | | | | |
| IV vs III (ref.) | 2.92 (0.77-11.00) | .1144 | 1.31 (0.52-3.31) | .5742 | 1.99 (0.74-5.38) | .1761 | 1.68 (0.55-5.14) | .3625 | 1.50 (0.80-2.83) | .2078 |
| Extracapsular extension | | | | | | | | | | |
| Present vs absent (ref.) | 2.96 (0.86-10.18) | .0842 | 1.43 (0.47-4.34) | .5304 | **5.22 (2.01-13.57)** | **.0007** | 2.43 (0.74-7.93) | .1421 | 1.48 (0.68-3.22) | .3274 |
| Histological grade | | | | | | | | | | |
| Well vs poorly differentiated (ref.) | … | … | … | … | 2.77 (0.34-22.49) | .3411 | 1.51 (0.17-13.54) | .7111 | 2.45 (0.55-10.84) | .2388 |
| Moderately vs poorly differentiated (ref.) | … | … | … | … | 1.98 (0.25-15.66) | .5161 | 1.81 (0.23-14.46) | .5773 | 2.80 (0.66-11.84) | .1624 |
| Lymphovascular invasion | | | | | | | | | | |
| Present vs absent (ref.) | 2.99 (0.37-24.10) | .3027 | **5.39 (1.16-25.10)** | **.0318** | **8.30 (2.30-29.95)** | **.0012** | **13.46 (3.38-53.51)** | **.0002** | **6.15 (2.12-17.86)** | **.0008** |
| Perineural invasion | | | | | | | | | | |
| Present vs absent (ref.) | 0.80 (0.10-6.24) | .8282 | 1.03 (0.24-4.51) | .9648 | 1.79 (0.51-6.26) | .3617 | 2.52 (0.69-9.19) | .1605 | 1.85 (0.77-4.43) | .1676 |
| Margin status | | | | | | | | | | |
| Close vs negative (ref.) | 1.34 (0.17-10.57) | .7818 | 0.71 (0.09-5.36) | .7399 | 0.78 (0.10-5.92) | .8119 | 1.13 (0.15-8.75) | .9076 | 0.67 (0.16-2.78) | .5803 |
| Positive vs negative (ref.) | 6.20 (0.78-49.27) | .0844 | 3.50 (0.46-26.45) | .2253 | 3.66 (0.48-27.83) | .2097 | 4.59 (0.59-35.72) | .1456 | 1.30 (0.18-9.53) | .7960 |
| Skin invasion | | | | | | | | | | |
| Present vs absent (ref.) | 2.27 (0.60-8.55) | .2276 | 1.17 (0.34-4.05) | .8010 | 1.30 (0.37-4.53) | .6791 | 1.67 (0.46-6.06) | .4387 | 1.06 (0.45-2.54) | .8881 |
| Bone invasion | | | | | | | | | | |
| Present vs absent (ref.) | **3.70 (1.13-12.12)** | **.0309** | 1.64 (0.58-4.60) | .3476 | 1.74 (0.61-4.93) | .2992 | 1.81 (0.56-5.88) | .3235 | 1.46 (0.69-3.11) | .3228 |
| Chemotherapy | | | | | | | | | | |
| Adjuvant concurrent CRT vs none (ref.) | 2.15 (0.63-7.37) | .2235 | 1.03 (0.34-3.13) | .9580 | **3.75 (1.44-9.73)** | **.0067** | 2.49 (0.81-7.65) | .1103 | 1.23 (0.58-2.58) | .5949 |
| Neck irradiation | | | | | | | | | | |
| Bilateral vs unilateral (ref.) | 0.66 (0.20-2.15) | .4859 | 0.68 (0.27-1.72) | .4119 | 1.32 (0.46-3.74) | .6060 | 1.20 (0.37-3.90) | .7614 | 1.31 (0.66-2.59) | .4424 |
| Tumor size | | | | | | | | | | |
| ≥4 cm vs <4 cm (ref.) | 2.27 (0.66-7.75) | .1917 | 1.01 (0.40-2.57) | .9782 | 1.50 (0.58-3.90) | .4017 | 1.48 (0.50-4.39) | .4841 | 1.52 (0.81-2.86) | .1954 |

(*Continues*)

**TABLE 3** (Continued)

| Factors, no. of patients | Supramandibular notch recurrence-free survival | | LRFS | | RRFS | | DMFS | | OS | |
|---|---|---|---|---|---|---|---|---|---|---|
| | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| Tumor thickness | | | | | | | | | | |
| >4 mm vs ≤4 mm (ref.) | … | … | … | … | 2.11 (0.28-15.95) | .4680 | … | … | 1.79 (0.55-5.81) | .3344 |
| Surgery to RT interval | | | | | | | | | | |
| ≥6 wk vs <6 wk (ref.) | 3.15 (0.84-11.88) | .0904 | 2.36 (0.89-6.30) | .0858 | **3.88 (1.26-11.90)** | **.0178** | **4.00 (1.10-14.53)** | **.0354** | **2.32 (1.20-4.47)** | **.0121** |
| Total package time | | | | | | | | | | |
| ≥12 wk vs <12 wk (ref.) | 1.52 (0.45-5.21) | .5017 | 1.33 (0.52-3.45) | .5510 | 2.10 (0.74-5.95) | .1643 | 2.02 (0.62-6.55) | .2436 | 1.66 (0.86-3.20) | .1299 |
| Mandibulectomy | | | | | | | | | | |
| Yes vs no (ref.) | 3.56 (0.46-27.78) | .2265 | 2.86 (0.66-12.44) | .1613 | 1.67 (0.48-5.81) | .4202 | 0.54 (0.18-1.65) | .2808 | 1.10 (0.53-2.25) | .8008 |
| Maxillectomy | | | | | | | | | | |
| Yes vs no (ref.) | **4.28 (1.25-14.64)** | **.0203** | **2.51 (1.00-6.32)** | **.0513** | 1.70 (0.65-4.47) | .2813 | 0.72 (0.20-2.62) | .6199 | 1.72 (0.90-3.28) | .1016 |
| Initial masticator space involvement | | | | | | | | | | |
| Yes vs no (ref.) | **13.08 (3.76-45.55)** | **< .0001** | **4.55 (1.75-11.86)** | **.0019** | **7.07 (2.69-18.56)** | **< .0001** | **6.11 (2.03-18.43)** | **.0013** | **3.26 (1.58-6.74)** | **.0014** |

Abbreviations: CI, confidence interval; CRT, chemoradiotherapy; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, local recurrence-free survival; OS, overall survival; ref., reference; RRFS, regional recurrence-free survival; RT, radiotherapy.

The figures in bold represent …

**TABLE 4** Multivariate analyses of clinicopathological factors for prognosis of patients with buccal cancer

| | Supramandibular notch recurrence-free survival | | LRFS | | RRFS | | DMFS | | OS | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Factors, no. of patients** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** | **HR (95% CI)** | ***P* value** |
| Initial masticator space involvement | | | | | | | | | | |
| Yes vs no (ref.) | 14.40 (3.81-54.42) | < .0001 | 3.59 (1.69-7.63) | .0020 | 10.62 (3.52-31.97) | < .0001 | 9.88 (2.99-32.67) | .0002 | 4.85 (2.19-10.73) | < .0001 |
| N classification | | | | | | | | | | |
| N2 vs N0-1 (ref.) | 5.71 (1.49-21.93) | .0111 | 2.75 (1.35-5.61) | .0223 | | | | | 2.27 (1.11-4.64) | .0243 |
| Extracapsular extension | | | | | | | | | | |
| Present vs absent (ref.) | | | | | 4.97 (1.77-13.98) | .0024 | | | | |
| Lymphovascular invasion | | | | | | | | | | |
| Present vs absent (ref.) | | | | | 5.72 (1.34-24.38) | .0184 | 13.42 (3.20-56.30) | .0004 | 5.45 (1.84-16.14) | .0022 |
| Surgery to RT interval | | | | | | | | | | |
| ≥6 wk vs <6 wk (ref.) | | | | | 8.97 (2.35-34.22) | .0013 | 5.99 (1.51-23.72) | .0108 | 2.45 (1.21-4.93) | .0124 |
| Maxillectomy | | | | | | | | | | |
| Yes vs no (ref.) | 4.47 (1.24-16.16) | .0225 | | | | | | | | |

Abbreviations: CI, confidence interval; DMFS, distant metastasis-free survival; HR, hazard ratio; LRFS, local recurrence-free survival; OS, overall survival; ref., reference; RRFS, regional recurrence-free survival; RT, radiotherapy.

marginal failures due to the parotid-sparing IMRT technique.[8,22–24] Some unexpected local recurrences have been shown as the result of retrograde invasion through perineural spread.[4,7,8,25] In the current study, there were 11 patients who experienced supramandibular notch recurrences, and each supramandibular notch recurrence originated from local recurrences. The majority of supramandibular notch recurrences were marginal failures (8 of 11). This pattern of failure is different from the previous report about these unexpected recurrences.

Herein, we demonstrated that supramandibular notch recurrences are associated with the initial masticator space involvement and the anatomic changes after surgery, especially maxillectomy. The pattern of failure is more likely directly spread. The buccal space is anterior to the masticator space and there is no complete fasciae separating it from the adjacent spaces.[26] The buccal fat pad is continuous with the fat anterior to the mandibular ramus and provides a communication with the masticator space.[27] During surgical interventions, soft tissues around the primary tumor, such as the pterygomandibular raphe, retromolar trigone, and masticator space, are usually dissected to achieve a 5- to 10-mm safe margin. When these continuous boundaries are disrupted, recurrent tumor cells can directly invade the supramandibular notch region (Table 2). Figure 1D-F shows the possible routes of direct invasion by recurrent tumors.

If recurrent cancer cells invade the medial side of the mandibular ramus, the very first site of invasion would be the pterygomandibular raphe.[28,29] When cancer cells invade the pterygomandibular raphe, tumor cells can then spread superiorly to the medial pterygoid plate, pterygopalatine fossa, and the maxillary nerve (V2). Subsequent to invasion of the pterygomandibular raphe, tumor cells can then spread into the retromolar trigone. At the retromolar trigone, tumor cells can invade medially and posteriorly into the masticator space, pterygoid plate, and retropharyngeal space, which can be explored during a partial maxillectomy, and up to the foramen ovale, Mackles' cave, or cavernous sinus with or without mandibular nerve (V3) involvement.

Anterior spreading from the retromolar trigone may occur along the alveolar ridge, maxillary bone, and V2 to the foramen rotundum. Inferior spreading occurs along the mandible and inferior alveolar nerve, followed by a retrograde spread pattern through the foramen ovale.[30] Laterally, recurrent cancer cells can directly invade the masticator space through the temporalis muscle into the suprazygomatic masticator space (Figure 1A).

None of the patients with supramandibular notch recurrences was initially diagnosed with PNI clinically or histopathologically; however, in patients with supramandibular notch recurrences, 5 were shown to have perineural spreading (Table 2). Possible reasons for perineural spread include the following: true PNI may not have been initially identified because of histopathologic sampling; or perineural spread may have been a result of direct invasion or infiltration after recurrence.

The results of this study showed that after buccal cancer recurrence, cancer cells spread widely. Therefore, delineation of high-risk CTV should not only include the tumor or surgical bed alone but should also be based on the potential patterns of spread.

In the current study, we showed that lymph node involvement (pN2) is a significant adverse factor in patients with buccal cancer for 5-year supramandibular notch recurrence-free survival, LRFS, DMFS, and OS. Detection of cancer cells in the lymph nodes is a crucial step in disease progression and systemic dissemination of cancer.[31,32] Previous studies also showed that pN2 disease is associated with poor disease control, and local survival, regional survival, disease-specific survival, or OS.[7,10,14,15] Thus, pN2 buccal cancer might exhibit more aggressive tumor behavior and requires more intense adjuvant therapies. Due to our limited number of patients and relatively large CI, pN2 could also be a confounding factor for supramandibular notch recurrence. The analysis of a larger patient cohort or national database is warranted.

### 4.3 | Study limitations and treatment recommendations

Although oral cancer is usually deemed a single disease entity, the tumors have heterogeneous behaviors and local extension. The literature with a focus on buccal cancer alone is sparse. This is the first report to address the recurrence pattern with initial masticator space involvement in buccal cancer after postoperative IMRT; however, there were some limitations to our study. First, this was a retrospective study with a relatively small sample size of a special type of patient with oral cancer treated in a single institution. Thus, the conclusions should be interpreted cautiously. Second, no complete assessment of late toxicities and quality of life has been performed, which could have an important impact on survival. Even with these limitations, we still recommend prophylactically covering the superior end of the infrazygomatic masticator space (including the V3 at the posterior part of the masticator space; Figure 1D-I) for patients with initial masticator space involvement, N2 disease, maxillectomy, and escalating doses of high-risk CTV to 66 Gy. Well-designed prospective trials and further research are needed to provide better disease control for buccal cancer.

## 5 | CONCLUSION

In conclusion, buccal cancer is an aggressive type of oral cancer with a high locoregional failure rate, especially with initial masticator space involvement. For most patients, locoregional recurrences are lethal. Delineation of high-risk CTV should not only include surgical beds but should also

be based on the patterns of recurrences. Improvements in high-risk CTV definition, especially for patients with initial masticator space involvement, might translate into better locoregional control.

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