Local Regional Relapse Patterns Following Ipsilateral Postoperative Adjuvant Radiotherapy for Buccal Cancer

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To study the initial local regional relapse (iLRR) patterns following ipsilateral postoperative adjuvant radiotherapy (iPART) for primary buccal cancer as an aid in defining the clinical target volume (CTV) for buccal cancer.

From June 1991 through April 1999, forty-six patients with localized primary squamous cell carcinoma of the buccal/gingival mucosa were treated with complete iPART with two dimensional (2D) planning technique (generally due to negative clinical/imaging exam of contralateral neck). The median age of these 43 men and 3 women was 58 years. Stage III/IV cases composed the majority of the study group (41/46). The median dose at tumor bed was 60 Gy with range of 50-70Gy. Eight patients received chemotherapy.

After a median follow-up of 20 months (2-101 months), twenty-five patients had thirty-four iLRR (ipsilateral vs both side vs. contralateral only vs other = 19 vs. 3 vs. 2 vs. 1). Advanced stage (T4N2-3, 4/11 = 36%) was the most possible risk factor with statistical significance for contralateral iLRR. The risk of contralateral iLRR was 3% in non-T4N2-3 patients.

It might be appropriate to perform iPART only for non high-risk buccal cancer patients.

Key words: Buccal carcinoma; Local recurrence; Radiotherapy

In Taiwan, oral cancer was the 7th leading cause of cancer deaths of the entire population and the 5th leading cause of cancer deaths of men in 2000 [1]. The percentage of buccal cancer among patients with oral cancer was 17-52%, and the disease was highly associated with tobacco smoking, alcohol consumption, and betel nut chewing [2]. The majority of the patients presented in the advanced stages of disease (stage III/IV [3]) [2, 4]. The treatment of advanced buccal cancer requires a combination of surgery and radiotherapy (RT) as the principal treatment modalities [5, 6]. In the era of three-dimensional conformal radiotherapy (3DCRT) and intensity-modulated radiotherapy (IMRT), analysis of failure patterns is very helpful in delineation of clinical target volume (CTV) of radiotherapy (RT) [7]. Especially for lateralized oral cavity/oropharyngeal cancer (such as buccal cancer or tonsillar cancer), excluding contralateral neck in CTV may improve the complication such as xerostomia [8]. However, there have been few reports in the literature about the failure patterns of buccal cancer [9–13]. In addition, neck lymph node (LN) metastatic patterns (level I–VI [14]) were not mentioned in most of them [9–12]. In the present study, we reviewed the initial local regional relapse (iLRR) patterns (including the LN pattern level I–VI) of forty-six patients with buccal cancer treated with postoperative adjuvant RT to ipsilateral side only.

PATIENTS AND METHODS

1. Patient characteristics

According to cancer registry in our hospital, sixty-six consecutive patients with non-distant metastatic squamous cell carcinomas (SCC) of the buccal /gingival mucosa were treated with postoperative adjuvant radiotherapy after curative surgery at our institute from June 1991 through April 1999. Neighboring intra-oral lesion was only noted in one patient who received
incomplete RT. The contralateral neck status of these patients happened to be either clinically negative or pathologically negative. Chest x-rays, bone scan, liver sonography and post-operative head and neck computed tomography (CT) or magnetic resonance imaging (MRI) were routinely performed for every patient. RT record is incomplete for one patient. Among the remaining sixty-five patients, fifty patients were treated by two dimensional (2D) RT technique to tumor bed and ipsilateral neck. Two patients with incomplete RT and another two patients with history of previous local operation were excluded. The remaining forty-six patients (43 men and 3 women) constitute the study group. The decision not to treat the contralateral side was at the discretion of the treating physicians. Generally that was preserved for patients with neither suspicious metastatic lymph node in contralateral neck by clinical exam and post-operative CT/MRI nor obvious midline invasion. The median age at the initiation of RT was 58 years (range, 28 to 80 years). The percentage of smoker, betel nut user, and history of drinking were 67%, 72%, and 61% respectively. Bone and skin invasion were noted in seventeen and nine patients respectively. Infra-temporal fossa invasion and tonsillar invasion were noted in two different patients respectively. The status of lympho-vascular invasion and perineural invasion were unspecified in most of the cases except three positive cases and two negative cases. All patients were uniformly staged using complete medical history and pathological findings according to AJCC 5th edition in 1997 [3]. There were 5(11%) stage II patients, 5(11%) stage III patients, and 36(78%) stage IV patients. There were 3, 10, 3, and 30 patients for T1, T2, T3, and T4 classification respectively. There were also 17, 12, 15, and 2 patients for N0, N1, N2, and N3 classification respectively.

Lymph node metastasis was documented as level I (submental [Ia] and submandibular [Ib] lymphatics), level II (lymphatics between skull base and hyoid bone), level III (lymphatics between hyoid bone and cricothyroid membrane), level IV (lymphatics between cricothyroid membrane and clavicle), level V (lymphatics in posterior triangle of the neck), and level VI (lymphatics in anterior neck compartment), retrospectively according to medical record [14]. In some cases, clinical differentiation between level Ib and II was difficult, so the location was designated to be Ib-II. When metastatic carcinoma in lymph nodes was found in pathological specimen of clinical negative neck without detailed anatomic description, the metastatic pattern was designated to be level I-III (for supra-omohyoid neck dissection [SOHND]) or level I-V (for modified radical neck dissection [MRND]). The initial clinical and pathological LN metastatic patterns were shown in table 1.

2. Treatment

Surgical interventions at the primary sites included composite resection (with bony resection) in thirty-six patients and wide excision (without bony resection) in ten patients. Forty-one patients received ipsilateral neck dissection only. The choice of ipsilateral neck operations included suprathyroid neck dissection in three patients, supraomohyoid neck dissection (SOHND) in twelve patients, and modified radical neck dissection (MRND) in twenty-six patients. Bilateral neck dissection (ipsilateral MRND and contralateral SOHND) was done for two patients (one for prophylaxis and one for clinical suspicion). Reconstructions with soft tissue grafts (other than split thickness skin grafts) were performed in forty patients. The pathological diagnosis included twenty-one unspecified keratinizing SCC, twenty well-differentiated SCC, three moderately differentiated SCC, and two poorly differentiated SCC. The marginal status was positive in four patients, close in seven patients, negative in thirty patients, and unspecified in five patients.

The median interval between RT and operation was 35 days (range, 18-87 days). The RT schedule was 2 Gy per fraction, one fraction per day, 5 days per week, except planned treatment interruption (three weeks) in one patient. The median tumor bed dose was 60 Gy (50 Gy for two patients, 56 Gy for one patient, 60 Gy for forty-two patients, and 70 Gy for one patient).

In 2D planning, CTV generally consisted of the ipsilateral oral cavity and the ipsilateral level I, II, III and upper V lymphatics (usually up to skull base) [15]. Usually two or three portals were used. The main constraints were to keep cumulative spinal cord doses below 50 Gy. Generally 6 MV x-rays or 60Co were used. The dose was specified at the 85%-95% of isocenter. Radiotherapy was given for 33 to 70 days (median: 43 days).

Eight patients also received chemotherapy (C/T). Neoadjuvant chemotherapy was performed for six patients, adjuvant sequential chemo-radiotherapy was performed for one patient, and adjuvant concurrent chemo-radiotherapy (CCRT) was done for one patient. Generally cisplatin based chemotherapy was used.

3. Follow-up

Follow up schedule was once per 1-3 months in the first year then once per 6 months at least. For those
who lost follow-up, postcard communication to study their survival status was tried. During each follow-up visit, local examinations were performed, and laboratory or imaging study was done when recurrence was suspected clinically. Pathological proof of recurrence was done when it was felt to be necessary clinically. The iLRR was documented as primary, level Ia to IV [14-15], or others. When the mucosal recurrence developed out of the radiation field and developed 6 months after RT, it was designated as metachronous carcinoma as suggested by Erkal et al [16].

4. Statistical analysis

The primary endpoint of our study was the iLRR patterns. The secondary endpoint was the survival status. The period of overall survival (OS) was from the 1st day of RT to the day of the last follow-up, or the day of reply after postcard communication, or dead. The period of local control (LC) was from 1st day of RT to the day of local regional recurrence or the day of last follow-up without local regional recurrence. The Fisher’s exact test was used as measures of significance. The Kaplan-Meier method was used in the calculation of OS and LC. The Log Rank test was used to test the inter-group statistical difference.

RESULTS

1. Follow-up status

At the time of analysis, there are fifteen patients who are alive to our knowledge, which included fourteen patients with regular follow-up and one patient who lost his follow-up finally though postcard communication confirmed his aliveness initially. Thirty-one patients were dead. Twenty-three patients died of progressive local disease. Two patients died of complication (no evidence of recurrence in one patient and evidence of metachronous carcinoma in the other). Two patients died of isolated distant metastasis. Four patients were disease free in their last follow-up, then they lost their follow-up, and death of them was confirmed by postcard communication. Duration of follow-up was calculated from the initiation of RT to the day of last follow-up, or the reply of postcard communication, or death. The median follow-up was 20 months for all patients (range: 2-101 months), and 47 months for the survivors (range: 43-101 months).

2. Failure pattern

Thirty-four initial local regional relapses (iLRR) were noted in twenty-five patients. Pathological proof of iLRR was obtained in seventeen patients. All the other eight patients with clinical iLRR died of progressive disease during follow up. Seven patients were designated to have more than one iLRR. Nineteen patients had in-field failure only. Two patients had out-field failure only [iLRRs in contralateral site]. And three patients had both in-field and out-field failures [iLRRs in ipsilateral neck/level Ia/level VI and contralateral site]. The remaining one patient had iLRR in upper nasal ridge skin only. The median time to iLRR was 5 months (range: 1-45 months). The iLRR patterns are shown in Table 1.

Besides, metachronous carcinoma happened in one patient (contralateral maxillary sinus cancer). Isolated distant (lung) metastasis happened in two patients. For these twenty-eight patients with local relapse or distant metastasis or metachronous carcinoma, salvage treatment included operation in four cases, operation and C/T in six cases, operation and chemo-radiotherapy in one case, operation and RT in one case, chemo-radiotherapy in two cases, C/T in four cases, salvage in other hospital for one case, lost of follow-up in one case, and no salvage in eight cases. However, only two patients with LRR were survivors after salvage treatment with induction C/T plus operation and operation plus adjuvant CCRT respectively. The patient with metachronous carcinoma died from acute hepatitis after salvage C/T.

3. Complication

After operation and adjuvant RT, nine patients had complications that operation or hospitalization was needed while no active recurrent disease was

| Table 1. Initial clinical metastatic pattern, initial pathological metastatic pattern, and initial local regional relapse (iLRR) pattern |
|---|---|---|
| Number (percentage) | Clinical (n=46) | Pathological (n=43) | iLRR (n=25)* |
| Primary site |  – | – | 15(60) |
| Level Ia | 1(2) | 1(2) | 2(8) |
| Ipsilateral Level Ib | 15(33) | 16(37) | 2(8) |
| Ipsilateral Level Ib-2 | 4(9) | 3(7) | 0 |
| Ipsilateral Level II | 7(15) | 7(16) | 3(12) |
| Ipsilateral Level III | 0 | 2(5) | 1(4) |
| Ipsilateral Level IV | 1(2) | 1(2) | 1(4) |
| Ipsilateral Level V | 1(2) | 1(2) | 0 |
| Ipsilateral Level I-III | 0 | 2(5) | 0 |
| Ipsilateral Level I-V | 0 | 3(7) | 0 |
| Level VI | 0 | 0 | 1(4) |
| Contralateral Ib | 0 | 0 | 2(8) |
| Contralateral level II | 1(2) | 0 | 0 |
| Contralateral level III | 0 | 0 | 2(8) |
| Contralateral level IV | 0 | 0 | 3(12) |
| Skin | 0 | 0 | 2(8)# |

*: Some patients were designated to have more than one metastatic/failure sites; #: one ipsilateral occipital area skin and one upper nasal skin
noted. One patients had more than one episode of complications. These included contracture in three cases, plate extrusion in two cases, osteoradionecrosis in two cases, periodontitis in one case, aspiration pneumonia in one case, and septic shock in one case (which leads to the only mortality due to complication alone).

4. Risk factors for in-field failures:

As to the twenty-two patients with in-field failures, no statistical significant differences were found within stage (stage II/III vs stage IV), gender (male vs female), differentiation (poorly/moderately vs well/keratinization), margin (close/positive vs negative/unspecified), and usage of chemotherapy or not. As to the relationship between RT dosage and the nineteen patients with in-field failures only, all the three patients with less than 60 Gy RT dose had in-field failures, and there were sixteen in-field failures among the forty-two patients with RT dose of 60 Gy, and the only patient with RT dose of 70 Gy had contralateral iLRR only. RT dosage less than 60 Gy is a borderline risk factor for in-fields failures only (p-value of Fisher’s exact test: 0.06).

5. Risk factors for contralateral relapse

Some clinical pathological features for the five patients with contralateral iLRR were shown in table 2. 67% (2/3) female patients and 36% (4/11) advanced stage (T4N2-3) patients had contralateral iLRR. The p-values of Fisher’s exact tests were 0.02 and 0.008 respectively. No statistical significance was found for poorly/moderately-differentiation histology, pathological close or positive margin, and history of chemotherapy.

6. Survival and local control

The 3 year OS and 5-year OS were 41% and 30% respectively. The 2-year LC for stage II/III and stage IV patients were 50% and 43% respectively without statistical significant differences.

DISCUSSION

Radiotherapy is an important modality for treating patients with buccal cancer [4-6]. In the era of 3DCRT and IMRT, the optimal CTV for head and neck cancer has still not been well established [15]. It is important to analyze the metastatic patterns or relapse patterns of buccal cancer in establishing the optimal CTV for buccal cancer, so as to keep the therapeutic benefit while lowering the complication rate.

The lymphatic drainage of buccal regions is sub-mental, submandibular, jugulodigastric, and high jugular LN [18]. There were some reports about the neck LN metastatic pattern, although most discussions about buccal cancer were mixed with other neighboring subsites of the oral cavity [15, 19].

Another approach was to identify the relapse patterns of patients with buccal cancer, especially in term of detailed anatomic location such the distribution of “levels” instead of “neck” only. The detailed relapse patterns following RT for buccal cancer was especially useful in establishing CTV. The failure pattern of patients with buccal cancer has been mentioned in some reports [4,9-13]. However, the local regional failure patterns were only defined as “primary” and “neck” in most of these studies.

Gregoire et al made a proposal for CTV of head and neck cancer [15]. However, buccal cancer was not a unique entity discussed in this review. For well localized oral cavity cancer, primary site and ipsilateral level I, II, III was the recommended CTV for N0-1 patients, and primary site and bilateral level I, II, III, IV, V was the recommended CTV for N2b patients. For neck failures after adjuvant RT, Fang et al [4] reported 14% neck failures rate (8/57), which included four failures in the ipsilateral neck, two failures in the contralateral neck, and two failures on both sides. Half of the neck failures were isolated neck failures, which included three within the ipsilateral upper and middle neck and one in the contralateral upper neck. For neck failure after surgery alone, Pradhan et al [12] reported that supra-omohyoid dissection (clearance of level I-III LN) was an adequate therapeutic procedure for T3/4 buccal-gingival cancer. The results were similar to radical neck dissection (clearance of level I-V LN) and better than suprahyoid dissection (clearance of level I LN).

In our analysis, twenty-five patients developed thirty-four iLRRs. The risk of isolated contralateral iLRR and all iLRR with contralateral iLRR were 4%(2/46) and 11%(5/46) respectively. In the study by Fang et al [4], the risk of contralateral neck failure was

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<th>Table 2. Clinical pathological features of the five patients with initial local-regional relapse (iLRR) in contralateral side</th>
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T = T stage; N = N stage; Diff = differentiation; K = keratinizing; m: male; f: female; WD = well differentiation; PD = poorly differentiation; u = unspecified; a+b: initial LRR in both side; b = initial LRR only in contralateral side
7% (4/57). Weiss et al [20] proposed that treatment of the N0 neck is warranted if the probability of occult neck metastasis is higher than 20%, whereas Gregoire et al suggested that treatment of the N0 neck is warranted if the probability of occult neck metastasis is higher than 5-10% [15]. Thus, the proposal (treat primary and ipsilateral neck only) made by Gregoire et al [15] seems applicable to our patient population. As to prediction of contralateral neck recurrence, female or advanced stage (T4/N2-3) carried high risk, though the limited number of female patients (3 patients) in our study made this risk factor less conclusive. Maybe some new technologies such as sentinel lymph node study or positron emission tomography can provide better predictive power toward neck recurrence in the future [21-22]. In view of the present study, the contralateral neck should be included in the CTV for pT4N2-3 patients.

The locoregional control in our study (21/46=46%) is somehow inferior to other endemic reports (35/57=61%) [4]. More aggressive treatment seems needed. However, higher adjuvant RT dose may not be helpful [23], although RT dose may be inadequate if it was less than 60 Gy. CCRT had now been favored in definitive treatment for inoperable head and neck cancer [24]. Currently Taiwan Cooperative Oncological Group (TCOG) had started a phase III trial of adjuvant CCRT for advanced oral cancer. Maybe it can tell whether adjuvant CCRT can also improve the result in the future. Molecular targeted treatment may also play a role in the future [24].

CONCLUSION

For buccal cancer patients with neither suspicious metastatic lymph node in contralateral neck by clinical exam and post-operative CT/MRI nor obvious initial midline invasion, our retrospective analysis showed that the overall risk of contralateral iLRR of patients with buccal cancer receiving ipsilateral postoperative adjuvant RT was about 11% (5/46), and even lower [3%] in non-T4N2-3 patients. Thus, it might be appropriate to exclude the contralateral neck from the clinical target volume of postoperative adjuvant RT except for high risk (T4/N2-3) buccal cancer patients so as to decrease the irradiated volume and possibly to lower the complication rate.

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颊癌病患接受同側術後輔助性放療之局部復發情形探討

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研究頰癌經同側術後輔助性放療之局部復發模式，以協助決定術後輔助性放療之適當靶體積。

自1991-1999，共收集連續46位因原發性頜癌於本院接受完整同側術後輔助性放療（以電腦做治療計畫）之病人。通常以臨牀上及術後電腦斷層上對側頸部正常者為接受同側放療之原則。共有43位男性及3位女性，中位年齡為52歲。多數病人為第三或第四期（41/46）。腫瘤床處之中位放療劑量為60格雷（範圍：50-70格雷）。

在中位追蹤20個月後（範圍：2-101個月）共有25個病人發生34處局部復發（同側：雙側：對側：其他＝19：3：2：1）。期別（T4N2-3，4/11＝36%）為最可能導致對側復發之危險因子。

除高危險性之頜癌病患外，術後輔助性放療可以治療同側為原則。

關鍵詞：頜鱗狀細胞癌，腫瘤局部復發，放射治療