Clinical Outcomes of Patients with Resected Oral Cavity Cancer and Simultaneous Second Primary Malignancies

Chun-Ta Liao1,2☯, Kang-Hsing Fan2,3☯, Chung-Jan Kang1,2, Chien-Yu Lin2,3, Joseph Tung-Chieh Chang2,3, Ngan-Ming Tsang2,3, Bing-Shen Huang2,3, Yin-Kai Chao2,4, Li-Yu Lee2,5, Chuen Hsueh2,5, Hung-Ming Wang2,6, Chi-Ting Liau2,6, Cheng-Lung Hsu2,6, Chia-Hsun Hsieh2,6, Shu-Hang Ng2,7, Chih-Hung Lin2,8, Chung-Kan Tsao2,8, Tuan-Jen Fang1,2, Shiang-Fu Huang1,2, Kai-Ping Chang1,2, Tzu-Chen Yen2,9*

1 Department of Otorhinolaryngology, Head and Neck Surgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC, 2 Head and Neck Oncology Group, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC, 3 Department of Radiation Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC, 4 Department of Thoracic and Cardiovascular Surgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC, 5 Department of Pathology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC, 6 Department of Medical Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC, 7 Department of Diagnostic Radiology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC, 8 Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC, 9 Department of Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC

☯ These authors contributed equally to this work.

* yen1110@adm.cgmh.org.tw

Abstract

Objectives

Simultaneous second primary tumors (SSPT) are not uncommon in patients with oral cavity squamous cell carcinoma (OSCC) living in areas where the habit of betel quid chewing is widespread. We sought to identify the main prognostic factors in OSCC patients with SSPT and incorporate them into a risk stratification scheme.

Methods

A total of 1822 consecutive patients with primary OSCC treated between January 1996 and February 2014 were analyzed for the presence of SSPT. The 18-month and 5-year overall survival (OS) rates served as the main outcome measures.

Results

Of the 1822 patients, 77 (4%) were found to have SSPT (i.e., two malignancies identified within one month of each other). The 18-month and 5-year OS rates in patients without SSPT and with SSPT were 82% and 69%, and 72% and 53%, respectively ($p = 0.0063$). Patients with SSPT were further divided into patients with either esophageal cancer or hepatocellular carcinoma (eso-HCC subgroup, n = 8) and other tumors (NO eso-HCC...
subgroup, n = 69). After multivariate analysis, neck nodal extracapsular spread (ECS, n = 18) and the presence of eso-HCC were identified as independent adverse prognostic factors. The 18-month OS rates of SSPT patients with both eso-HCC and ECS (n = 5) vs. the remaining patients (n = 72) were 0% and 78%, respectively (p < 0.0001).

Conclusion
OSCC patients with neck nodal ECS and esophageal cancer or hepatocellular carcinoma as SSPT have a dismal short-term prognosis.

Introduction
Simultaneous second primary tumors (SSPT) are not uncommon in patients with oral cavity squamous cell carcinoma (OSCC) [1], especially in areas where the habit of betel quid chewing is widespread [2]. We and others have previously shown that OSCC patients with SSPT generally have a poor prognosis [2–4]. However, the clinical outcomes of patients with first primary OSCC may be dependent on the presence of neck nodal extracapsular spread (ECS, a major adverse prognostic factor in OSCC) [5] and/or the site of second primary tumors (SPT; e.g., esophagus, hypopharynx, or lung) [6]. Radical surgery with or without postoperative adjuvant therapy (depending on the presence of pathological risk factors) remains the mainstay of treatment for OSCC patients. A secondary treatment strategy should be planned in OSCC patients who present with SSPT at the time of primary treatment [7,8].

According to the Taiwanese 2011 official statistics, liver, lung, hypopharyngeal, and esophageal malignancies rank first, second, fourth, and fifth, respectively, as the leading causes of cancer-related death in the male population [9]. Moreover, Taiwan is characterized by a markedly high incidence of HBV- and HCV-related hepatocellular carcinoma (HCC). Of note, approximately 5% of our OSCC patients present with concomitant HCC. However, the question as to whether OSCC patients with SSPT located at the liver or other at-risk sites should receive specific and/or targeted treatment approaches remains open [7,8]. In this scenario, we designed the current study to identify the main prognostic factors in OSCC patients with SSPT and incorporate them into a risk stratification scheme.

Patients and Methods
Patients
Between January 1996 and February 2014, we identified a total of 1822 consecutive untreated patients presenting with first primary OSCC who were scheduled for radical surgery, either with or without neck dissection (ND). All of the participants underwent an extensive presurgical evaluation and staging workup. As of October 2002, the majority of the study patients underwent preoperative panendoscopy. Starting from August 2001, most patients with stage II-IV disease received whole-body FDG-PET for primary staging. Patients were staged according to the 1997 (5th) and 2010 (7th) staging criteria of the American Joint Committee on Cancer (AJCC). The 1997 criteria were used for patients enrolled before 2002, whereas the 2010 criteria were utilized for patients recruited after 2002. The major difference between the two staging systems is that some tumors with invasion of the masticator space/pterygoid plate would be classified as pT4b using the AJCC 2010 criteria, but only as pT2-T3 according to the 1997 criteria [10]. If two separated oral cavity
malignancies were detected simultaneously, the more advanced-staged tumor was considered as the index malignancy. The study protocol was approved by the Institutional Review Board of the Chang Gung Memorial Hospital (CGMH 101-4457B). Patient consent was waived due to the retrospective nature of the study.

Surgery and adjuvant therapy

The primary tumors were excised with safety margins of 1 cm or greater (both peripheral and deep margins). Level I–V NDs were performed in patients with cN+ disease, whereas cN- patients received level I–III NDs [2,5,10]. In general, post-operative radiotherapy (RT, 60 Gy) was performed for patients bearing pathological risk factors (RFs). RFs were classified according to the NCCN guidelines before 2008; thereafter, RFs classification was based on the Chang Gung guidelines outlined in our previous publications [11]. The main RFs for RT included: pT4, pT3N1, pT1-2N1 (N1 at levels IV/V), close margins ≤2 mm, poor differentiation with tumor depth ≥4 mm. Otherwise, the presence of at least 2 minor RFs (i.e., pN1, tumor depth ≥10 mm, close margins ≤4 mm, poor differentiation, perineural invasion, lymphatic invasion, vascular invasion) were required for RT. The radiation field included the entire tumor bed area (with 1- to 2-cm margins) as well as the regional lymphatics. Concomitant chemoradiation (CCRT, 66 Gy) with cisplatin-based regimens was administered to patients with ECS, multiple lymph node metastases, positive margins, or bearing at least three minor risk factors (i.e., the above-mentioned minor RFs plus pT4) [12–14]. The chemotherapy regimen consisted of intravenous cisplatin 50 mg/m² biweekly plus daily oral tegafur 800 mg and leucovorin 60 mg, cisplatin 40 mg/m² weekly, or cisplatin 100 mg/m² every 3 weeks [14].

Definitions and data analysis

SPT were defined as malignancies that were both distinct and anatomically separated (i.e., having at least 2 cm of normal tissue between each lesion). Metastases or local relapses were carefully excluded. Similarly, tumors occurring at the same site (regardless of the time elapsed from the patient’s first definitive treatment) were not considered as SPT. SSPT were defined as documented malignancies occurring within one month from OSCC diagnosis, whereas not-SSPT were considered to be present when tumors were identified after at least one month from the initial OSCC diagnosis. Follow-up was continued until February 2015. All of the study patients received follow-up examinations for at least 12 months after primary definitive treatment for OSCC or until death. The 18-month and 5-year overall survival (OS) rates served as the main outcome measure. OS was calculated from the date of surgery to the date of death or the last follow-up. Survival curves were plotted using the Kaplan—Meier method and compared with the log-rank test. Univariate and multivariate analyses (UVA and MVA) were used to identify the main prognostic factors. MVA was based on the Cox logistic regression method with a forward selection procedure. All calculations were performed using the SPSS 17.0 statistical software (SPSS Inc., Chicago, IL, USA). Two-tailed p values <0.05 were considered statistically significant. All relevant data are within the paper and its supporting information S1 and S2 Data.

Results

Patient characteristics and clinical outcomes

Table 1 depicts the general characteristics of the study participants. Of the 1822 patients, 426 (23%) were found to have SPT (77 [4%] SSPT, 349 (19%) not-SSPT), and 1396 (77%) no-SPT (Fig 1, upper panel). The rate of SPT within the first month of diagnosis (i.e., SSPT) of the
| Characteristics                      | Number of patients (%) |
|-------------------------------------|------------------------|
|                                     | n   | %   |
| Sex                                 |     |     |
| Male                                | 1701| 93.4|
| Female                              | 121 | 6.6 |
| Age at onset (years)                |     |     |
| Range: 25–89 (median 51)            |     |     |
| < 65                                | 1578| 86.6|
| ≥ 65                                | 244 | 13.4|
| Pathological T-status               |     |     |
| pT1                                 | 339 | 18.6|
| pT2                                 | 754 | 41.4|
| pT3                                 | 303 | 16.6|
| pT4                                 | 426 | 23.4|
| Pathological N-status               |     |     |
| pNx (no neck dissection)            | 125 | 6.9 |
| pN0                                 | 1044| 57.3|
| pN1                                 | 228 | 12.5|
| pN2                                 | 425 | 23.3|
| Pathological stagea                 |     |     |
| I                                   | 303 | 16.6|
| II                                  | 495 | 27.2|
| III                                 | 333 | 18.3|
| IV                                  | 691 | 37.9|
| Extracapsular spreadb               |     |     |
| No                                  | 1437| 79.0|
| Yes                                 | 382 | 21.0|
| Tumor differentiation               |     |     |
| Well                                | 698 | 38.3|
| Moderate                            | 964 | 52.9|
| Poor                                | 160 | 8.8 |
| Tumor depth (mm)b                   |     |     |
| < 10                                | 941 | 51.8|
| ≥ 10                                | 877 | 48.2|
| Margin status (mm)b                 |     |     |
| ≤ 4                                 | 190 | 10.5|
| > 4                                 | 1616| 89.5|
| Bone marrow invasion                |     |     |
| No                                  | 1569| 86.1|
| Yes                                 | 253 | 13.9|
| Skin invasion                       |     |     |
| No                                  | 1689| 92.7|
| Yes                                 | 133 | 7.3 |
| Perineural invasionb                |     |     |
| No                                  | 1261| 69.2|
| Yes                                 | 560 | 30.8|
| Lymphatic invasionb                 |     |     |
| No                                  | 1726| 94.8|

(Continued)
index OSCC was 4%, with an annual increase of approximately 3% (20%/5-year, 34%/10-year). The 18-month and 5-year OS rates in the entire cohort were 81% and 68%, respectively. The 18-month and 5-year OS rates in patients without SSPT (i.e., no-SPT plus not-SSPT, n = 1745) and with SSPT were 82% and 69%, and 72% and 53%, respectively (p = 0.0063, Fig 2-a).

Table 2 (left part) depicts the general characteristics of OSCC patients with SSPT. All of the 77 OSCC patients with SSPTs were male. The age at onset ranged between 29 and 73 years (mean: 53 years, median: 53 years). The distribution of risky oral habits was as follows: 61 patients (79%) had a history of preoperative alcohol drinking, 69 (90%) of preoperative betel chewing, and 69 (90%) of preoperative cigarette smoking. The sites of SSPT were as follows: oral cavity (n = 61, 79%), oral pharynx (n = 5, 7%), esophagus (n = 4, 5%), liver (HCC, n = 4, 5%), stomach (n = 1, 1%), colon (n = 1, 1%), and thyroid (n = 1, 1%). Regarding the treatment modality for the index OSCC, 31 patients (40%) had surgery alone, 29 (38%) received surgery plus RT, and 17 (22%) received surgery plus CCRT.

All of the 77 OSCC patients with SSPT were followed up for at least 12 months after primary surgery or until death (mean: 58 months, median: 34 months, range: 3–202 months). At the end of the study period, 37 patients (48%) were alive and 40 (52%) were dead. The patterns of recurrence for the index OSCC and rate of third primary tumors were as follows: local recurrence, 12% (n = 9); neck recurrence, 9% (n = 7); distant metastases, 10% (n = 8) and third primary tumors, 38% (n = 29). Salvage therapy for the primary OSCC was performed in six (40%) of the 15 patients with local and/or neck recurrences (one patient had both local and neck recurrence). Among the patients who were salvaged, two (33.3%) were still alive when the data were analyzed, whereas the remaining four (66.7%) were dead.

Fig 1 depicts the flow of the patients through the study and their clinical outcomes. All of the 77 OSCC patients with SSPT received radical primary tumor excision accompanied either by simultaneous removal of SSPT (n = 66; oral cavity [n = 61], oropharynx [soft palate, n = 4], liver [n = 1]) or subsequent treatment of SSPT at follow-up (n = 11; oropharynx [tongue base, n = 1], stomach [n = 1], colon [n = 1], thyroid [n = 1], esophagus [n = 4], liver [n = 3]).

Of the 61 patients who received simultaneous radical excision of both the index OSCC tumor and the SSPT in the oral cavity, 29 (47%) patients were alive at the time of analysis, whereas the remaining 32 (53%) were dead. Of the five patients with SSPT located in the

| Characteristics          | Number of patients (%) |
|--------------------------|------------------------|
|                          | n          | %      |
| Vascular invasionb       | 94         | 5.2    |
| No                       | 1776       | 97.6   |
| Yes                      | 44         | 2.4    |
| Treatment modality       |            |        |
| Surgery alone            | 886        | 48.6   |
| Surgery plus RT          | 506        | 27.8   |
| Surgery plus CCRT        | 430        | 23.6   |

Abbreviations: RT, radiotherapy; CCRT, concurrent chemoradiotherapy.

bPatients who did not undergo neck dissection were classified as pN0.

bUnavailable data: extracapsular spread (n = 3), tumor depth (n = 4), margin status (n = 16), perineural invasion (n = 1), lymphatic invasion (n = 2), vascular invasion (n = 2).

doi:10.1371/journal.pone.0136918.t001
oropharynx, four had their SSPT located in the soft palate removed alongside with the index OSCC tumor. In this subgroup of patients, three (75%) subjects were still alive, whereas the remaining one (25%) died. A patient with a SSPT arising at the tongue base received RT after radical excision of the primary OSCC. Unfortunately, the patient died 11 months after surgery because of distant relapse. All of the three patients with SSPT located in the stomach, colon, and thyroid received curative surgery followed by complete treatment of the index OSCC. Their survival following radical surgery was 90, 88, and 30 months, respectively. All of the four patients with SSPT located in the esophagus received sequential treatment. Two patients were treated with RT for both OSCC and SSPT in the esophagus (Table 3, cases 3 and 4). Treatment volume of RT included the tumor bed of OSCC, SSPT in esophagus, and regional lymphatics of OSCC and SSPT in the esophagus (neck, mediastinal, and upper abdominal lymphatics). Radiotherapy was performed according to two different treatment plans. Such plans were given sequentially and junction was carefully matched to avoid overlaps in radiation field and the occurrence of severe complications. One patient (25%) was still alive at the time of analysis.

* SPTs, Secondary primary tumors
* SSPTs, Simultaneous secondary primary tumors
* Index OSCC, First primary oral cavity squamous cell carcinoma

\[ \text{Fig 1. Clinical and demographic characteristics of the study patients summarizing the treatment modalities and the clinical outcomes of OSCC patients presenting with SSPT.} \]

doi:10.1371/journal.pone.0136918.g001
whereas the remaining three (75%) were dead. No recurrences or severe complications were observed at the junction between the two RT plans. Of the four patients with SSPT located in the liver, three received sequential treatment. Of them, one (33%) was still alive at the time of analysis, whereas the remaining two (67%) were dead. One patient underwent simultaneous radical excision of both the index OSCC and the simultaneous esophageal malignancy. This patient died of hepatic failure and gastrointestinal bleeding during RT.

### Independent prognostic factors for 5-year OS in OSCC patients with SSPT (n = 77)

The 5-year disease-free survival and disease-specific survival for the 77 patients with SSPT were 74% and 76% respectively. The 18-month and 5-year OS rates of the 77 patients were 72% and 53%, respectively. Table 2 depicts the results of UVA and MVA of 5-year OS including a total of 16 covariates. Cigarette smoking was not specifically analyzed as a risk factor.
Table 2. Univariate and multivariate analyses of 5-year overall survival in OSCC patients with SSPT (n = 77).

| Characteristics                  | Number of patients (%) | 5-year overall survival |        | Multivariate |        |
|----------------------------------|------------------------|-------------------------|--------|--------------|--------|
|                                  | n         | %          | Univariate | 5-year % | Number of events | p      | p, HR (95% CI) |        |
| Esophagus or liver subsites      |           |            |            |          |                |        | 0.0062 | 0.030, 2.829 (1.108–7.220) |
| No                               | 69        | 89.6       | 56         | 59      | 34             |        |        |        |
| Yes                              | 8         | 10.4       | 19         | 15      | 6              |        |        |        |
| Sex                              | 77        | 100.0      |            |          |                |        |        |        |
| Male                             |            |            |            |          |                |        | 0.9162 | ns        |
| Age at onset (years)             |           |            |            |          |                |        |        |        |
| < 65                             | 64        | 83.1       | 52         | 53      | 33             |        |        | 0.2838 | ns        |
| ≥ 65                             | 13        | 16.9       | 53         | 53      | 7              |        |        |        |
| Pathological T-status            |           |            |            |          |                |        |        |        |
| pT1                              | 2         | 2.6        | 50         |          | 1              |        |        |        |
| pT2                              | 31        | 40.3       | 63         |          | 13             |        |        |        |
| pT3                              | 21        | 27.3       | 52         |          | 10             |        |        |        |
| pT4                              | 23        | 29.9       | 40         |          | 16             |        |        |        |
| Pathological N-status            |           |            |            |          |                |        | 0.0113 | ns        |
| pN0                              | 49        | 66.2       | 64         |          | 21             |        |        |        |
| pN1                              | 7         | 9.5        | 38         |          | 4              |        |        |        |
| pN2                              | 18        | 24.3       | 24         |          | 14             |        |        |        |
| Pathological stage*              |           |            |            |          |                |        | 0.1971 | ns        |
| I                                | 2         | 2.6        | 50         |          | 1              |        |        |        |
| II                               | 21        | 27.3       | 71         |          | 7              |        |        |        |
| III                              | 22        | 28.6       | 50         |          | 11             |        |        |        |
| IV                               | 32        | 41.6       | 44         |          | 21             |        |        |        |
| Extracapsular spread             |           |            |            |          |                |        | 0.0051 | 0.018, 2.273(1.153–4.483) |
| No                               | 59        | 76.6       | 61         |          | 26             |        |        |        |
| Yes                              | 18        | 23.4       | 24         |          | 14             |        |        |        |
| Tumor differentiation            |           |            |            |          |                |        | 0.3190 | ns        |
| Well                             | 29        | 37.7       | 61         |          | 13             |        |        |        |
| Moderate                         | 43        | 55.8       | 47         |          | 25             |        |        |        |
| Poor                             | 5         | 6.5        | 60         |          | 2              |        |        |        |
| Tumor depth (mm)                 |           |            |            |          |                |        | 0.4392 | ns        |
| < 10                             | 32        | 41.6       | 61         |          | 15             |        |        |        |
| ≥ 10                             | 45        | 58.4       | 46         |          | 25             |        |        |        |
| Margin status (mm)*              |           |            |            |          |                |        | 0.0717 | ns        |
| ≤ 4                              | 10        | 13.2       | 30         |          | 8              |        |        |        |
| > 4                              | 66        | 86.8       | 57         |          | 31             |        |        |        |
| Bone marrow invasion             |           |            |            |          |                |        | 0.1038 | ns        |
| No                               | 57        | 74.0       | 56         |          | 26             |        |        |        |
| Yes                              | 20        | 26.0       | 42         |          | 14             |        |        |        |
| Skin invasion                    |           |            |            |          |                |        | 0.3956 | ns        |
| No                               | 69        | 89.6       | 55         |          | 35             |        |        |        |
| Yes                              | 8         | 10.4       | 38         |          | 5              |        |        |        |
| Perineural invasion              |           |            |            |          |                |        | 0.2312 | ns        |
| No                               | 54        | 70.1       | 54         |          | 26             |        |        |        |

(Continued)
because of the small number of non-smokers (n = 8). Patients with SSPT were further examined in relation to the presence of either esophageal cancer or HCC (due to their poor outcomes when compared with other SSPT subsites; Figs 1 and 2-b) (eso-HCC subgroup, n = 8) vs. other tumors (NO eso-HCC subgroup, n = 69). The results of UVA demonstrated that eso-HCC subgroup, pN status, ECS, and lymphatic invasion were significant poor prognostic factors for 5-year OS. After allowance for potential confounders, MVA demonstrated that the eso-HCC subgroup (Fig 2-b) and ECS (Fig 2-c) retained their independent prognostic significance for 5-year OS (Table 2).

Table 2 summarizes the general characteristics of the eight OSCC patients who presented with SSPT located at the esophagus (n = 4) or the liver (n = 4). Of them, five presented with ECS (two cases with esophageal cancer and three with HCC). All of them died either of disease or disease-related causes (i.e., primary OSCC or simultaneous eso-HCC; Table 3, footnote). Of the three cases without ECS, one died of third primary cancer of the tongue base 29 months after treatment of the primary OSCC (case 1). The remaining two patients are still alive after a follow-up of 18 and 36 months, respectively (cases 2 and 5, Table 3).

**Prognostic scoring system for OSCC patients with SSPT**

We developed a 3-point prognostic scoring system by summing up the two independent prognostic factors identified in MVA (i.e. eso-HCC subgroup and ECS). A score of 0 was assigned when the risk factor was absent, whereas a score of 1 was given in presence of the risk factor. As expected, high-risk patients with a score of 2 showed the worst prognosis. Moreover, intermediate-risk patients with a score of 1 had worse 5-year OS rates than low-risk patients who scored 0 (Fig 2-d).

**Discussion**

The choice of the optimal therapeutic modality for OSCC patients who present with SSPT remains problematic. When SSPTs are surgically resectable, it is still unclear whether simultaneous or sequential removal should be pursued [7,8]. In cases treated in a sequential manner,
the order by which tumors should be removed (primary OSCC vs. SSPT) has not been clearly established. Similarly, there is a lack of consensus on the priority for RT or CCRT in non-surgical cases. Finally, the question as to whether patients with an expected 2-year OS of less than 10% should receive treatment with curative intent or palliation remains open. Starting from these premises, we designed the current study to identify the main prognostic factors in OSCC patients presenting with SSPT and incorporate them into a risk stratification scheme.

In this retrospective study examining the records of 1822 resected OSCC patients enrolled between 1996 and 2014, we identified 77 cases with SSPT treated with curative intent because

Table 3. Clinicopathological characteristics of oral cavity cancer patients presenting with SSPT located at the esophagus or the liver (n = 8).

| No | Age, years | Primary treatment | Site | Stage | ECS | Interval between primary surgery and clinical events |
|----|------------|-------------------|------|-------|-----|---------------------------------------------------|
|    |            |                   |      |       |     | Tumor recurrence | Neck recurrence | DM | Tumor salvage | DOD | AND |
| 1  | 50         | S to tongue, + CCRT (6600 cGy) to eso. | Tongue | pT2N0 | -   | -   | -   | - | - | - | - |
|    |            |                   |      |       |     | 18 |
| 2  | 60         | S to tongue, + S to eso., + RT (6000 cGy) to tongue | Tongue | pT2N1 | -   | -   | -   | - | - | - | - |
|    |            |                   |      |       |     | 18 |
| 3  | 44         | S+CCRT (6600 cGy) to bucca, + RT (3000+3000 cGy) to eso. | Buccal | pT2N2b | +   | -   | -   | - | - | - | - |
|    |            |                   |      |       |     | 18 |
| 4  | 70         | S to mouth floor, + CCRT (6600 cGy) to mouth, floor and eso. | Mouth floor | pT4N2c | +   | 4   | -   | - | - | - | 13 |
|    |            |                   |      |       |     | 13 |
| 5  | 69         | S+RT (6000 cGy) to tongue, + TACE to liver | Buccal | pT2N0 | -   | -   | -   | - | - | - | 36 |
|    |            |                   |      |       |     | 36 |
| 6  | 54         | S+CCRT (4000 cGy) to bucca, No treatment for liver | Buccal | pT4N2b | +   | 9   | -   | - | - | - | 14 |
|    |            |                   |      |       |     | 14 |
| 7  | 49         | S+CCRT (6600 cGy) to tongue, + TACE to liver | Tongue | pT2N2b | +   | -   | -   | - | - | - | - |
|    |            |                   |      |       |     | 11 |
| 8  | 55         | S to retromolar and liver, + RT (3000cGy) to retromolar | Retromolar | pT4N2b | +   | -   | -   | - | - | - | - |
|    |            |                   |      |       |     | 3 |

(a)(case 1) Died of third primary squamous cell carcinoma of the tongue base 29 months after primary surgery for OSCC.
(b)(case 3) Died of malignant pleural effusion related to the second primary tumor.
(c)(case 6) Incomplete CCRT due to chemotherapy and liver cirrhosis-induced pancytopenia.
(d)(case 7) Died of upper gastrointestinal bleeding.
(e)(case 8) Incomplete RT due to jaundice and ascites, died of hepatic failure and gastrointestinal bleeding.

Abbreviations: SSPT, simultaneous secondary primary tumor; eso., esophagus; TACE, transcatheter arterial chemoembolization; DM, distant metastases; ECS, extracapsular spread; S, surgery; RT, radiotherapy; CCRT, concurrent chemoradiotherapy; DOD, died of disease or disease-related causes; AND, alive without disease.

doi:10.1371/journal.pone.0136918.t003
of the absence of distant metastases at their primary staging. First, our data demonstrate that OSCC patients presenting with SSPT had a lower 5-year OS rate than those without SSPT (53\% vs. 69\%, respectively). Notably, eso-HCC subgroup, pN status, ECS, and lymphatic invasion were identified as significant adverse prognostic factors for 5-year OS. However, only eso-HCC subgroup and neck nodal ECS retained their independent prognostic significance in MVA. According to unpublished data from the Taiwanese National Health Institute (released solely to Taiwan tertiary hospitals and not publicly available), the 3- and 5-year overall survival rates for Taiwanese patients with esophageal cancer and HCC alone are 17%/14% and 39%/28\%, respectively (2007–2009). No survival data are currently available for patients with esophageal cancer or HCC according to the presence or absence of co-occurring OSCC. In this study, we identified four patients with co-occurrence of OSCC and esophageal cancer. Only one patient was alive at the date of last follow-up (18 months). Notably, we also identified one patient with co-occurring OSCC and HCC who survived at 36 months. Although the number of cases included was small, it appears that SSPT subsites are critical determinants of survival. According to our prognostic scoring system based on the two independent risk factors, the worst OS rate (0\% at 2 years) was observed for patients presenting with both SSPT located at the esophagus or the liver and ECS.

The clinical outcomes of the 77 OSCC patients presenting with SSPT are summarized in Fig 1. After the exclusion of high-risk patients with SSPT located in the esophagus (n = 4) or the liver (n = 4), we found that 79\% (61/77) of SSPT were located in the oral cavity, whereas 5\% (4/77) originated from the soft palate. All of these patients received simultaneous radical treatment. The remaining four patients with SPT located at the tongue base, thyroid, stomach, and colon were treated with sequential definitive treatment. At the time of the last follow-up, 51\% of these patients (n = 35) were alive, whereas the remaining 49\% (n = 34) were dead.

One of the main clinical issues for patients in eso-HCC subgroup was that the definite diagnosis of ECS requires ND and subsequent pathological examination. In this scenario, the selection of the optimal treatment strategy (simultaneous vs. sequential; definitive vs. palliative) poses major challenges. Because of the higher 2-year OS in patients without ECS (66.7\% [1/3] vs. 0\% [5/5], Table 3), we propose a sequential treatment comprising ND to confirm or exclude the presence of neck nodal ECS. In the absence of ECS, definitive treatment with radical surgery should be pursued in eco-HCC subgroup patients. In presence of ECS, the prognosis is dismal and supportive care should be recommended. A reliable imaging or biomarker of ECS is eagerly awaited for OSCC patients with clinically suspected neck nodal metastases and SSPT located at the esophagus or the liver. Interestingly, a previous small-sized FDG-PET study from our group demonstrated that 38 (95\%) of the 40 patients with a preoperative maximum standardized uptake value of the neck lymph nodes (SUVnodal-max) ≥5.7 had ECS [15]. Such an imaging biomarker would avoid unnecessary radical neck surgery and promote the use of the best supportive care for patients with poor prognosis.

Some limitations of our study merit comment. First, its retrospective single-center nature limits the generalizability of the results. Although this study is the largest to date in which SSPT has been analyzed in a homogenously treated cohort of OSCC patients enrolled in a single institution, there were no commonly reported lung or hypopharynx SSPT identified in this series. Although primary lung cancer is frequently associated with head and neck malignancies, we believe that there are at least two reasons that may explain its unusually low frequency in our study. First, all of the study participants were scheduled for radical surgery and patients presenting with lung lesions (either primary or metastatic) were excluded. Second, we identified 29 patients as having a second primary lung cancer after at least one month from the initial OSCC diagnosis. However, they were included in the Not-SSPT subgroup and not among patients presenting SSPT (Fig 1) based on the definition used for the current study (i.e., SSPT...
Fig 3. Flowchart of treatment selection in OSCC patients presenting with SSPT.

- Index OSCC, First primary oral cavity squamous cell carcinoma
- SSPTs, Simultaneous secondary primary tumors
- ECS, Neck nodal Extra-capsular spread

For citation:
doi:10.1371/journal.pone.0136918.g003
defined as two independent cancers identified within one month of each other). Another caveat is that we did not collect the occurrence of malnourishment, a major factor influencing OS. In addition, our OSCC patients without ECS had earlier-stage esophageal cancer when compared with those showing ECS (Table 3). Finally, all of the participants came from an area in which betel quid chewing is endemic; therefore, the findings might not be applied to patients in different geographic locations.

In summary, the results of our study indicate that radical surgery (either with simultaneous or sequential definitive treatment) should be recommended for OSCC patients who present with SSPT but who do not carry adverse risk factors (neck nodal ECS or eso-HCC subgroup). In the eso-HCC subgroup, the presence or absence of ECS should be investigated by means of ND or other reliable methods. In the absence of ECS, sequential definitive treatment should be recommended. Because the presence of ECS portends a poor prognosis, the use of best supportive care (instead of sequential definitive treatment) is indicated to improve the quality of life unless other novel treatments are discovered in the next future (Fig 3).

Supporting Information

S1 Data. Dataset.
(XLS)

S2 Data. Dataset specification.
(XLS)

Acknowledgments

This study did not receive any specific funding. We appreciate the contribution and the valuable assistance of the Linkou Chang Gung Memorial Hospital Cancer Center databank and case managers.

Author Contributions

Conceived and designed the experiments: CT. Liao KHF TCY. Performed the experiments: CT. Liao KHF CJK CYL JTCC NMT BSH YKC LYL CH HMW CT. Liau CLH CHH SHN CHL CKT TJF SFH KPC TCY. Analyzed the data: CT. Liao KHF TCY. Contributed reagents/materials/analysis tools: CT. Liao KHF CJK CYL JTCC NMT BSH YKC LYL CH HMW CT. Liau CLH CHH SHN CHL CKT TJF SFH KPC TCY. Wrote the paper: CT. Liao KHF CJK CYL JTCC NMT BSH YKC LYL CH HMW CT. Liau CLH CHH SHN CHL CKT TJF SFH KPC TCY.

References

1. Fukuzawa K, Noguchi Y, Yoshikawa T, Saito A, Doi C, Makino T, et al. High incidence of synchronous cancer of the oral cavity and the upper gastrointestinal tract. Cancer Lett. 1999; 144(2):145–51. PMID: 10529014.
2. Liao CT, Kang CJ, Chang JT, Wang HM, Ng SH, Hsueh C, et al. Survival of second and multiple primary tumors in patients with oral cavity squamous cell carcinoma in the betel quid chewing area. Oral Oncol. 2007; 43(8):811–9. PMID: 17174143.
3. Qaisi M, Vorrasi J, Lubek J, Ord R. Multiple primary squamous cell carcinomas of the oral cavity. J Oral Maxillofac Surg. 2014; 72(6):1511–6. doi: 10.1016/j.joms.2014.03.012 PMID: 24813779.
4. Hsu SH, Wong YK, Wang CP, Wang CC, Jiang RS, Chen FJ, et al. Survival analysis of patients with oral squamous cell carcinoma with simultaneous second primary tumors. Head Neck. 2013; 35 (12):1801–7. doi: 10.1002/hed.23242 PMID: 23489643.
5. Liao CT, Lee LY, Huang SF, Chen IH, Kang CJ, Lin CY, et al. Outcome analysis of patients with oral cavity cancer and extracapsular spread in neck lymph nodes. Int J Radiat Oncol Biol Phys. 2011; 81(4):930–7. doi: 10.1016/j.ijrobp.2010.07.1988 PMID: 20934267.

6. Lim H, Kim DH, Jung HY, Gong EJ, Na HK, Ahn JY, et al. Clinical significance of early detection of esophageal cancer in patients with head and neck cancer. Gut Liver. 2015; 9(2):159–65. doi: 10.5009/gnl13401 PMID: 25167869.

7. Boute P, Page C, Biet A, Cuvelier P, Strunski V, Chevalier D. Epidemiology, prognosis and treatment of simultaneous squamous cell carcinomas of the oral cavity and hypopharynx. Eur Ann Otorhinolaryngol Head Neck Dis. 2014; 131(5):283–7. doi: 10.1016/anor.2013.10.003 PMID: 25288121.

8. Morita M, Kawano H, Otsu H, Kimura Y, Saeki H, Ando K, et al. Surgical Resection for Esophageal Cancer Synchronously or Metachronously Associated with Head and Neck Cancer. Ann Surg Oncol. 2013; 20(7):2434–9. doi: 10.1245/s10434-013-2875-z PMID: 23358793.

9. Cancer registry annual report, Taiwan, 2011. Available: http://www.bhp.doh.gov.tw/. Accessed 8 April 2015.

10. Liao CT, Lee LY, Hsueh C, Lin CY, Fan KH, Wang HM, et al. Comparative outcomes in oral cavity cancer with resected pT4a and pT4b. Oral Oncol. 2013; 49(3):230–6. doi: 10.1016/j.oraloncology.2012.09.010 PMID: 23063612.

11. Liao CT, Lin CY, Fan KH, Wang HM. The optimal treatment modality for Taiwan oral cavity cancer patients—Experience of a medical center. J Cancer Res Pract. 2015; 2(2):103–16. doi: 10.6323/JCRP.2015.2.2.01.

12. Lin CY, Wang HM, Kang CJ, Lee LY, Huang SF, Fan KH, et al. Primary tumor site as a predictor of treatment outcome for definitive radiotherapy of advanced-stage oral cavity cancer. Int J Radiat Oncol Biol Phys. 2010; 78(4):1011–9. doi: 10.1016/j.ijrobp.2009.09.074 PMID: 20434273.

13. Fan KH, Wang HM, Kang CJ, Lee LY, Huang SF, Lin CY, et al. Treatment results of postoperative radiotherapy on squamous cell carcinoma of the oral cavity: coexistence of multiple minor risk factors results in higher recurrence rates. Int J Radiat Oncol Biol Phys. 2010; 77(4):1024–9. doi: 10.1016/j.ijrobp.2009.06.064 PMID: 20610038.

14. Wang HM, Liao CT, Chang TC, Chen JS, Liaw CC, Chen IH, et al. Biweekly paclitaxel, cisplatin, tegafur, and leucovorin as neoadjuvant chemotherapy for unresectable squamous cell carcinoma of the head and neck. Cancer. 2004; 101(8):1818–23. PMID: 15386306.

15. Liao CT, Chang JT, Wang HM, Ng SH, Hsueh C, Lee LY, et al. Preoperative 18F-FDG PET standardized uptake value of neck lymph nodes predicts neck control and survival rates in patients with oral cavity squamous cell carcinoma and pathologically positive lymph nodes. Int J Radiat Oncol Biol Phys. 2009; 74(4):1054–61.