Oral Oncology 50 (2014) 721–731

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Clinical evidence of field cancerization in patients with oral cavity cancer in a betel quid chewing area

Chun-Ta Liao [a,b,1], Christopher G. Wallace [a,b,c,1], Li-Yu Lee [b,d], Chuen Hsueh [b,d], Chien-Yu Lin [b,e], Kang-Hsing Fan [b,e], Hung-Ming Wang [b,f], Shu-Hang Ng [b,g], Chih-Hung Lin [b,c], Chung-Kan Tsao [b,c], I-How Chen [a,b], Shiang-Fu Huang [a,b], Chung-Jan Kang [a,b], Tzu-Chen Yen [b,h,*]

[a] Department of Otorhinolaryngology, Head and Neck Surgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC
[b] Department of Head and Neck Oncology Group, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC
[c] Department of Plastic and Reconstructive Surgery, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC
[d] Department of Pathology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC
[e] Department of Radiation Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC
[f] Department of Medical Oncology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC
[g] Department of Diagnostic Radiology, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC
[h] Department of Nuclear Medicine and Molecular Imaging Center, Chang Gung Memorial Hospital and Chang Gung University, Taoyuan, Taiwan, ROC

ARTICLE INFO

Article history:
Received 18 November 2013
Received in revised form 3 April 2014
Accepted 26 April 2014
Available online 29 May 2014

Keywords:
Oral cavity cancer
Squamous cell carcinoma
Betel quid chewing
Field cancerization
Prognosis

SUMMARY

Objectives: We sought to investigate whether there is evidence of field cancerization in patients with oral cavity squamous cell carcinoma (OSCC) enrolled in a betel quid chewing area. We also assessed whether betel quid chewing is an independent risk factor for field cancerization in OSCC patients.
Methods: We retrospectively examined the records of 1570 OSCC patients who underwent radical tumor resection between 1996 and 2011. A total of 1243 study participants (79%) had a positive history of betel quid chewing before surgery. Of the 767 patients treated with surgery alone, 599 (78%) were preoperative chewers, whereas a history of preoperative betel quid chewing was identified in 644 (80%) of the 803 patients who received adjuvant therapy. The 5-year control, survival, and second primary tumors (SPTs) rates served as the main outcome measures.
Results: Regardless of the treatment modality, more than 70% of the SPTs were located in the oral cavity or soft palate. Despite a similar risk profile in terms of tumor depth, lymph node metastasis, and pathological margin status, preoperative chewers showed a significantly higher incidence of 5-year SPTs and local recurrences compared with non-chewers. Moreover, multivariate analysis demonstrated that preoperative betel quid chewing was an independent prognostic factor for 5-year local control and SPTs occurrence rates.
Conclusions: Our results demonstrate that preoperative betel quid chewers had a higher incidence of local recurrence and SPTs than non-chewers, suggesting that field cancerization may occur in OSCC patients with a history of betel quid chewing.

Introduction

Oral cavity cancer is a major cause of cancer-related morbidity and mortality in areas where the habit of betel quid chewing is widespread. Oral cavity cancer ranks sixth in cancer incidence in Taiwan, and it is the most common malignancy diagnosed in Taiwanese men aged between 30 and 50 years [1]. Engagement in risky oral habits such as betel quid chewing (80%), cigarette smoking (85%), and alcohol drinking (65%) is common in Taiwanese patients with oral cavity cancer. Despite recent declines in the use of risky oral habits, the incidence of oral cavity cancer in Taiwan is still increasing (Fig. 1) [1,2].

Betel quid and areca nut chewing is considered a known human carcinogen by the International Agency for Research on Cancer [3]. We have previously shown that a history of betel chewing is independently associated with the risk of oral cavity squamous cell carcinoma (OSCC), the most common histological type of oral cavity cancer [4]. Moreover, betel chewers have a higher incidence of

* Corresponding author. Address: Department of Nuclear Medicine, Chang Gung Memorial Hospital at Linkou, No. 5, Fu-Hsing ST., Kwei-Shan, Taoyuan, Taiwan, ROC. Tel.: +886 3328 1200x2673; fax: +886 3211 0052.
E-mail address: yen1110@adm.cgmh.org.tw (T.-C. Yen).
[1] Chun-Ta Liao and Christopher G. Wallace contributed equally to this work.

http://dx.doi.org/10.1016/j.oraloncology.2014.04.010
1368-8375/

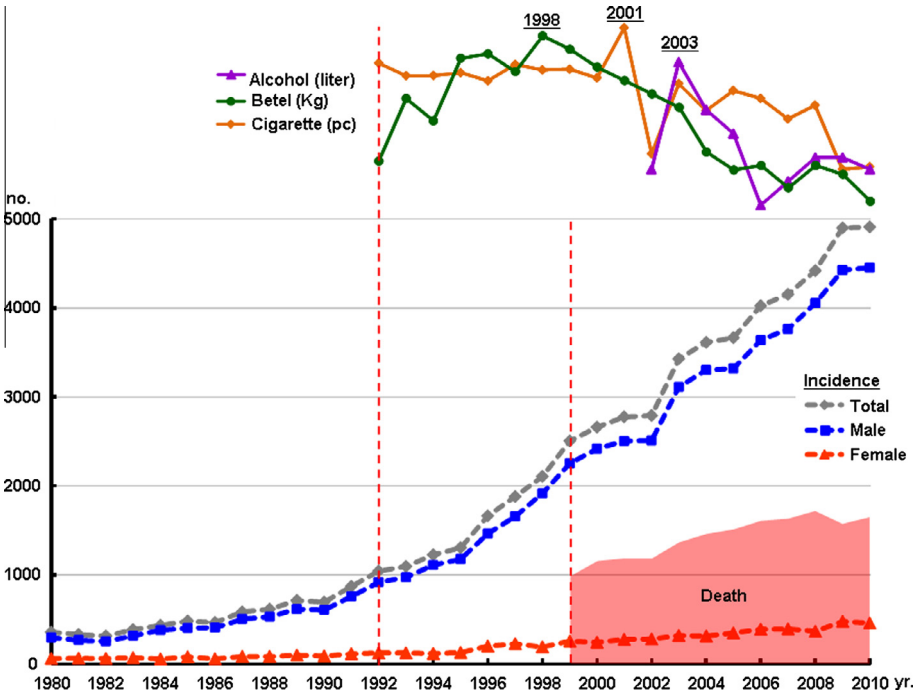

Fig. 1. Taiwan official statistics of (1) risky oral habits, (2) incidence of oral cavity cancer, and (3) mortality from oral cavity cancer.

local tumor recurrences and second primary tumors (SPTs) after surgical resection compared with non-chewers [5,6]. Importantly, cumulative and prolonged exposure to betel chewing can result in oral submucosal fibrosis with trismus, which may limit surgical field exposure and make radical surgery difficult [4]. We hypothesized that the high incidence of local tumor recurrences and SPTs in resected OSCC patients with a history of betel chewing may be due to the presence of field cancerization (FC). FC is characterized by the presence of synchronous or metachronous subclinical field changes in the oral mucosa, with one or more areas of genetically altered cells that may develop into invasive cancer in a stepwise fashion, from benign hyperplasia to dysplasia, and then from carcinoma in situ to invasive cancer [7–12]. Under these circumstances, it is possible that radical resection of OSCC will not result in a complete elimination of the genetically altered field. Because data on the prognostic impact of betel chewing on OSCC outcomes remain scanty [13–16], we designed the current study to investigate whether a history of betel chewing may be an independent risk factor for FC in OSCC patients. To this aim, we retrospectively examined the impact of betel chewing on 5-year control, survival, and SPTs rates in 1570 patients with previously untreated first primary OSCCs who underwent radical tumor resection between January, 1996 and July, 2011.

Patients and methods

Patients

All of the participants underwent an extensive presurgical evaluation before the primary surgery [4–6]. The pathological findings of the study participants were thoroughly reviewed by two head-and-neck pathologists using a checklist provided by our interdisciplinary tumor board. Patients were staged according to the staging criteria of the 1997 (5th) and 2010 (7th) 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 masticator space/pterygoid plate would be classified as pT4b using the AJCC 2010 criteria, but only as pT2–T3 tumors according to the 1997 criteria. The retrospectively review of tumor specimens collected before 2002 in order to re-stage such malignancies as pT4b was not feasible for the purpose of this study. In line with previous investigations [6,17]. We defined SPTs according to the Warren and Gates criteria. Multiple primary tumors were defined as distinct malignant tumors that were topographically separate (with the presence of at least 2 cm of normal epithelium between each other) [6]. 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). Classic radical or modified neck dissections (levels I–V) were performed in patients with clinically positive lymph node disease. Supraomohyoid neck dissections (levels I–III) were performed in clinically node-negative patients [4–6]. Postoperative radiotherapy (60 Gy) was performed for patients carrying pathological risk factors. The radiation field included the entire tumor bed area (with 1–2 cm margins) as well as the regional lymphatics. Concomitant chemoradiation (66 Gy) with cisplatin-based regimens was administered to patients with extracapsular nodal spread, multiple lymph node metastases, and positive margins [18–20].

Salvage therapy for locoregional recurrence

Patients with local tumor recurrence underwent radical surgical excision with safety margins of 1.5 cm or greater (both peripheral and deep margins). Patients with cervical lymph node recurrences