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# Cancer-related hypercalcemia in oral cancer

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*Abstract.* Cancer-related hypercalcemia (CRH) is a critical paraneoplastic disorder in advanced cancer patients. In clinical practice, patients with CRH have a poor prognosis. The medical records of 3198 oral cancer patients with CRH diagnosed at Taichung Veterans General Hospital from 1 January 2003 to 31 December 2015 were reviewed. The criteria for patient enrolment were a diagnosis of hypercalcemia or the use of antihypercalcemia medication. Patients who met any of the following criteria were excluded: use of total parenteral nutrition, incomplete serum calcium data, and unknown date of death. The total incidence of CRH was 6.95‰ per year. A total of 91 patients were enrolled; their median survival time was 28 days. The patients were divided into two groups by survival time, with a cut-off point of 30 days. Reduced serum albumin, leucocytosis, and clodronate use had a statistically significant effect on survival in the univariate analysis (all $P < 0.05$). Forty-five patients (49.5%) had recurrence of CRH, of whom nine died within 30 days. These nine patients had a shorter interval to the first episode of CRH recurrence (median 13 days) than those who survived ≥30 days (median 28 days) ($P < 0.001$). It was observed that a short interval to the first episode of CRH recurrence is a poor prognostic factor.

Key words: oral cancer; hypercalcemia; survival.

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Cancer-related hypercalcemia (CRH) is a critical metabolic complication in patients with cancer, especially advanced cancer[1–4]. Previous studies have shown that CRH affects 20% to 44.1% of patients with cancer during their clinical course[2,5–9]. Humoral hypercalcemia of malignancy (HHM), which can be diagnosed by determining the concentration of parathyroid hormone-related protein (PTHrP), is the predominant cause of CRH, and accounts for 80% of CRH[2,6,10,11]. In squamous cell cancer (SCC), HHM is also the main cause of CRH[8,11].

The occurrence of CRH often leads to many symptoms, such as nausea, anorexia, constipation, lethargy, and confusion[8,11–13]. Studies have reported that elevated serum calcium also indicates a very poor prognosis with a short survival time[1,3,4,14–16]. The results of a retrospective study showed survival in patients with head and neck cancer diagnosed with hypercalcemia to range from 1 to 514+ days, with a median survival time of 33 days[16]. A Japanese study reported a median survival time of 54.9 ± 18.3 days (range 27–86 days) after the diagnosis of CRH in patients with oral SCC[11]. Adverse prognostic factors of survival time that have been identified include brain metastasis, corrected serum calcium >3 mmol/l (12 mg/dl), and hypoalbuminemia (albumin <3 mg/dl) in SCC patients, and leucocytosis (white blood cell (WBC) count $>15 \times 10^9$/l) in oral SCC patients[14,15,17].

It has been reported that the use of antihypercalcemic agents for CRH in oral SCC patients may improve the patient's clinical performance status, but has little effect on survival times[3]. For these cancer patients, early palliative care and hospice

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care can relieve symptoms and improve quality of life[18]. Furthermore, early palliative care and hospice care intervention have been shown to result in longer survival times in patients with malignancies[18,19].

In Taiwan, chewing betel nut is common among manual labourers and agricultural workers, and is a risk factor strongly linked to oral cancer. In 2013, oral cancer was the sixth most frequent malignancy among all cancers in Taiwan. Furthermore, the age-adjusted incidence rate of oral cancer was 14.92 per 100,000 people in the total population of Taiwan, and 27.41 per 100,000 in males[20]. Most affected patients receive anti-cancer treatment including surgery, chemotherapy, or radiotherapy during the course of the disease.

Oral cancer causes great physical and mental suffering, and the disease has a considerable impact on the patient's family. Patients typically experience a poor quality of life due to pain, nasogastric tube feeding, wound infections, and malodorous wounds, among others. Furthermore, some patients develop CRH in their clinical course. In clinical practice, the presentation of CRH often means a poor prognosis. However, few studies have investigated survival times in oral cancer patients with CRH. Thus, the present study was performed to evaluate survival among oral cancer patients in Taiwan who have developed CRH.

## Materials and methods

The medical records of patients diagnosed with oral cancer at Taichung Veterans General Hospital from 1 January 2003 to 31 December 2015 were reviewed. Taichung Veterans General Hospital is a tertiary medical centre in central Taiwan. The institutional review board of the hospital approved this study.

In clinical practice, the symptoms of hypercalcemia are obvious and noticeable, and antihypercalcemic agents are often administered if hypercalcemia is perceived. Thus, the criteria for enrolment of patients in this study were a diagnosis of hypercalcemia or the use of antihypercalcemia medication. Patients were included using the International Classification of Diseases ninth revision (ICD-9) codes 140, 141, 143, or 145, and any of the following criteria: first diagnosis of hypercalcemia or first use of an antihypercalcemic agent (pamidronate, calcitonin, clodronate, or zoledronic acid) during admission to the emergency department or a ward. Patients who met any of the following criteria were excluded: use of total parenteral nutrition, incomplete serum calcium data, and unknown date of death. Finally, 91 patients were enrolled in the study.

General data were recorded, including the primary location of the oral cancer, albumin, serum calcium, and the highest serum calcium values, WBC count, survival time, antihypercalcemic agent use, hospice care intervention, bone metastasis, interval to CRH recurrence (i.e. the time in days between the first and second episodes of hypercalcemia), and antibiotic use.

Oral cancers including lip, tongue, gingival, and buccal cancer were identified according to the ICD-9 codes 140, 141, 143, and 145, respectively. The primary tumour site was identified from the biopsy results in the formal pathology report. Hypercalcemia was defined as a total serum calcium $\geq$11.0 mg/dl. The serum calcium values were recorded and corrected based on the albumin level when the first diagnosis of CRH was made or antihypercalcemic agent was administered. Furthermore, the patients were categorized into three groups according to the level of serum calcium. A corrected calcium level of between 10.5 and 12.0 mg/dl or an ionized calcium level between 5.6 and 8.0 mg/dl was classified as mild hypercalcemia. A corrected calcium level between 12.0 and 14.0 mg/dl or an ionized calcium level between 8.0 and 10.0 mg/dl was classified as moderate hypercalcemia. A corrected calcium level $>$14.0 mg/dl or an ionized calcium level $>$10.0 mg/dl was classified as hypercalcemic crisis[21]. Moreover, all hypercalcemia was classified as CRH in this study. The highest corrected calcium and ionized calcium values were recorded during the clinical course after CRH was diagnosed.

Leucocytosis was defined as a WBC count $>15 \times 10^9$/l. Survival time was defined as the interval between the date that hypercalcemia was first diagnosed and the date of death. The use or non-use of antibiotics during the disease course after the first CRH occurrence was recorded. Whether the antihypercalcemic agent administered contained pamidronate, clodronate, calcitonin, or zoledronic acid was established by reviewing the medical records.

Hospice care interventions included hospitalization in a hospice unit, hospice shared care, and hospice home care. The number of days of hospice intervention was calculated by determining the interval between the date of consulting the hospice team and the date of death. Imaging examination by X-ray or bone scan study was used to determine the presence or absence of bony metastatic lesions. Recurrence of CRH was defined in the presence of a normal level of serum calcium recorded between the first and second episodes of hypercalcemia. The interval to CRH recurrence was calculated by determining the duration between the date of the first episode and the date of the second episode of hypercalcemia recorded in the same patient.

A previous study reported that most cancer patients died within 30 days after admission to a hospice facility[22]. Another study performed in China to predict the survival time in patients with incurable advanced cancer used survival time cut-off points of 7, 30, 90, and 180 days[23]. Thus, the survival time cut-off point was set at 30 days in the present study. The patients were divided into two groups based on a survival duration of $\geq$30 days or $<$30 days, and the differences in patient variables were compared.

### Statistical analysis

All analyses were performed using IBM SPSS Statistics version 22.0 software (IBM Corp., Armonk, NY, USA). Differences in categorical variables were assessed with the $\chi^2$ test or Fisher's exact test, as appropriate. The associations of individual variables were assessed using the Mann–Whitney *U*-test or the Kruskal–Wallis test. Spearman's rho model was used for correlations between prognostic factors and survival times. Logistic regression was used to evaluate the factors in a multivariate analysis. The Poisson regression model was used to check the difference in incidence according to sex. Laboratory results are presented as the median values.

## Results

During the study period 1 January 2003 to 31 December 2015, 3198 patients with oral cancer were admitted to Taichung Veterans General Hospital; 2938 were male and 260 were female. Among this group, 130 patients had a history of hypercalcemia during the course of their disease (125 male patients and five female patients). The total incidence of CRH was 6.95‰ per year. The incidence was 3.44‰ per year for female patients and 7.25‰ per year for male patients. Of the 130 oral cancer patients with CRH, 91 died during the study period and had complete laboratory data and details for the disease course.

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