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Prognostic value of hypercalcaemia and leucocytosis in resected oral squamous cell carcinoma

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Abstract

Hypercalcaemia and leucocytosis are common in our patients with progressive oral squamous cell carcinoma (SCC). However, the precise incidence, prognostic value, and correlation with the condition of the tumour remain obscure. A total of 618 patients with oral SCC who were treated primarily between 2007 and 2012 and had serum calcium concentrations and white blood cell count (WCC) measured postoperatively were included in the study. Primary TNM stage, pathological features, and the presence of locoregional recurrence or distant metastasis after comprehensive surgical treatment were recorded. The incidence of hypercalcaemia was 9.1% and that of leucocytosis 7.2%. Hypercalcaemia correlated significantly with size of primary tumour (T status), nodal involvement (N status), TNM stage, perineural invasion, lymphovascular permeation, and recurrence or metastasis of disease. Leucocytosis, however, correlated only with T status, lymphovascular permeation, and recurrence or metastasis. In multivariate analysis of survival, recurrence, metastasis, hypercalcaemia, and leucocytosis were strong independent prognostic factors. Median survival was low if the patient had hypercalcaemia or leucocytosis (179 (range 3–73) days if the patient had distant metastasis, and 43 (range 3–102) days if the patient had locoregional recurrence). The incidence of hypercalcaemia and leucocytosis was high during the course of the disease, and both conditions have an adverse impact on survival from oral SCC. Periodic evaluation of serum calcium concentrations and WCC should be routine during the postoperative period.

Keywords: Hypercalcaemia; Leucocytosis; Oral squamous cell carcinoma; Survival

Introduction

Cancer-related hypercalcaemia[1–4] and leucocytosis[5,6] have been reported to be poor prognostic signs in patients with advanced disease or who require palliative care. Hypercalcaemia is defined as a serum calcium concentration above 2.55 mmol/L. The incidence of cancer-associated hypercalcaemia varies widely according to different sites and stages of malignancy, and is most common in patients with lung, breast, head and neck, and kidney cancer.[7] The incidence of hypercalcaemia in early-stage head and neck cancer is low, but it may become high during the advanced stages.[8] Hypercalcaemia was not detected in our patients with oral cancer at the time of the first examination, but was subsequently detected in 2.6–7.2% of these patients, developing as the disease progressed.[1,2,9,10] Patients with oral squamous cell carcinoma (SCC) and hypercalcaemia failed to respond

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to resection, radiotherapy, or chemotherapy, and had a poor life expectancy.

One study reported that the median survival time after diagnosis of hypercalcaemia in stage IV oral SCC was 55.8 ± 19.9 days (range, 27–86 days).[11] However, some authors have hypothesised that early recognition of hypercalcaemia could aid the proper treatment of occult neoplasms and so prolong survival.[8,12] Concentrations of calcium in serum should therefore be monitored in patients with oral SCC regardless of the stage of the disease.[8]

Leucocytosis is defined as a raised white blood cell count (WCC $> 15 \times 10^9$/L). The causes of leucocytosis in patients with cancer vary, and include infection, corticosteroids, intoxication, severe haemorrhage, bone marrow metastases, and paraneoplastic leukemoid syndrome.[13] The latter syndrome can be diagnosed only after excluding the above diagnoses, and is characterised by persistent neutrophilic leucocytosis above 50×10^9/L immature white blood cells.[6] We have found that leucocytosis is quite common in patients with oral cancer in the terminal stage, although the WCC count is seldom above 50×10^9/L. Nevertheless, the incidence and importance of leucocytosis in oral cancer are not yet established.[10]

Leucocytosis and hypercalcaemia sometimes occur simultaneously. The single study on combined hypercalcaemia–leucocytosis syndrome in oral SCC reported the incidence as 225 patients.[14] A possible explanation for this is that granulocytes and osteoclasts have a common haematopoietic precursor by which the tumour may therefore stimulate the formation of osteoclasts as well as granulocytes.[14]

We know of only a few reports about the role of hypercalcaemia and leucocytosis in oral cancer. Previous such studies were evaluated without consideration of stage of primary cancer, the current condition of the tumour (recurrence or metastasis, or neither), or the treatment given.[15] As the evidence is scarce, the strength of association between these syndromes and oral cancer and their roles in the prognosis of oral SCC cannot be established.[10] In the present study we have sought to evaluate the incidence of hypercalcaemia and leucocytosis in oral SCC, their association with stages of the primary tumour, and their impact on survival.

Patients and methods

Study group

The records of a total of 618 patients with oral SCC who were treated surgically between 2007 and 2012 in Taipei Veterans General Hospital and who had postoperative measurements of calcium and WCC were retrieved from our hospital's cancer registry and were enrolled in the study. The inclusion criteria were: newly diagnosed cancer with no previous history of treatment, and resection with curative intent. Patients who had either more than one primary cancer; cancer of the posterior one-third of the tongue (base of tongue); un-resectable tumours that were mainly treated by radiation with or without chemotherapy; or distant metastases; were excluded.

All the patients included were treated according to our protocol. Patients with advanced oral SCC or with adverse pathological features (lymphovascular permeation, perineural invasion, or tumour emboli) were given either standard postoperative radiotherapy or concurrent chemoradiotherapy.

All patients were regularly followed up every 1–2 months during the first 2 years postoperatively and at least every

Table 1
Personal details and clinical characteristics of patients ($n = 618$). Data are number (%) except where otherwise stated.

Variable	No (%)
Median (range) age (years)	
Sex: male/female	552: 66
Site of primary tumour:	
Lip	20 (3.2)
Anterior tongue	238 (38.6)
Gingiva	109 (17.6)
Floor of mouth	21 (3.4)
Palate	26 (4.2)
Buccal mucosa	204 (33)
AJCC T status:	
T1	193 (31.2)
T2	209 (33.8)
T3	36 (5.9)
T4	180 (29.1)
AJCC N status:	
N0	472 (76.4)
N1	50 (8.1)
N2	92 (11.9)
N3	4 (<1)
AJCC TNM stage:	
Stage I	174 (28.1)
Stage II	166 (26.9)
Stage III	52 (8.4)
Stage IV	226 (36.6)
Tumour recurrence or metastasis:	
None	497 (80.4)
Local recurrence	22 (3.6)
Regional recurrence	54 (8.7)
Distant metastasis:	45 (7.3)
Lung	29
Bone	24
Liver	10
Miscellaneous	9
No hypercalcaemia or leucocytosis	538 (87.1)
Hypercalcaemia alone	35 (5.7)
Leucocytosis alone	23 (3.7)
Hypocalcaemia and leukocytosis	22 (3.5)
Time interval[a]	
Median (range) (months):	2.95 (0–38.5)
≤3	23
3–6	7
>6	10

AJCC = American Joint Committee on Cancer.

[a] Time interval between the episode of hypercalcaemia or leucocytosis and recurrence of tumour or metastasis.