C-REACTIVE PROTEIN AS A PROGNOSTIC INDICATOR OF ORAL SQUAMOUS CELL CARCINOMA – A RETROSPECTIVE STUDY

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ABSTRACT

The objective was to determine Serum C- Reactive protein as a prognostic indicator for Oral Squamous Cell Carcinoma.

It was a retrospective cross sectional study, conducted in the Department of Oral Medicine, Eastman Dental Institute, University College London.

The medical records of the patients were reviewed by using NHS CDR (National Health Service Clinical Data Repository) and studying their hospital notes of the year 2005. All the patients who had histopathologically proven OSCC, being treated with surgery as primary treatment modality and had pre-operative CRP values were included in the study. Data collection included the pre-operative serum CRP values, treatment modalities, disease severity, outcomes, complications and the survival time period of the patients.

Thirty one patients with OSSC treated primarily with surgery were included in this study. Twenty four patients had elevated pre-operative serum CRP levels while seven patients had normal value of serum CRP. 12 were males and 19 females with male and female ratio of 1:1.6. The age of the patients ranged from 46-92 years with the mean age of 64.87±14.25 years. The pre-operative serum CRP levels ranged from 4-57.2 mg/L with the mean value of 35.94±19.68 mg/L. Higher values of CRP corresponded with higher TNM staging and poor overall 5-year survival.

The study showed that patients with elevated pre-operative serum CRP levels showed the worst prognosis and almost all of them died within five years while the patients with normal CRP were alive even after 5 years of surgical resection. Hence, it can be concluded that elevated pre-operative CRP levels are prognostic indicators in patients with OSCC.

Key words: Oral Cancer, Prognosis, C - Reactive Protein

INTRODUCTION

Oral squamous cell carcinoma (OSSC) is one of the most common cancers of the oral cavity and contributes to approximately 90% of all oral malignancies with a 5-year survival rate of approximately 50%. Overall, the prevalence of OSSC varies in different parts of the world and reflects exposure to different risk factors. Oral squamous cell carcinoma is one of the most common cancers in Central and South Asia due to large use of tobacco, betel nut, and pan. OSCC is a...
devastating disease that can cause significant mor-tality, morbidity and disfigurement of the patients. OSSC is a challenging disease in its nature and despite of improvement in the diagnostic and management methods, its prognosis is unpredictable. Therefore, there is a need of simple prognostic marker that can predict the possible behaviour of the disease before being treated with primary surgery.

A number of studies have investigated potential factors that may influence prognosis of OSSC patients and eventually predict the outcome of therapy. C-reactive protein (CRP) is an acute phase protein that is synthesized by hepatocytes in the liver and is regulated by pro-inflammatory and cancer related cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF). It is elevated in response to many inflammatory conditions like trauma, cancer, heart diseases and surgery. Elevated pre-operative serum CRP levels have been demonstrated as a prognostic indicator in many cancers like breast cancer, oesophageal cancer, colorectal cancer, renal cancer, cancer of the head of pancreas and multiple myeloma.

The aim of the present study was to determine an association between the pre-operative levels of serum C-reactive protein (CRP) in the insight of prognosis of OSSC patients and their 5-year survival treated with primary surgery at one major Head and Neck Cancer unit in University College London Hospital in the year 2005.

**METHODOLOGY**

This is a retrospective study of patients with pre-operative serum CRP and histopathologically proven OSSC in the year 2005. The medical records of the patients were reviewed by using NHS CDR (National Health Service Clinical Data Repository) and studying their hospital notes of the year 2005. All the patients who had histopathologically proven OSCC, being treated with surgery as primary treatment modality and had pre-operative serum CRP values were included in the study while patients with incomplete records, being treated with chemo/radio therapy primarily or who had oral dysplasia before OSCC were excluded from study.

42 patients with histopathologically proven OSSC who underwent primary surgical treatment were screened out of 210 patients with head and neck cancer treated in one major Head and Neck cancer unit in University College London Hospital in the year 2005. Out of these 42 patients, 11 patients were excluded because they did not have pre-operative serum CRP values. All the patients underwent primary surgery with/or without post-operative radiotherapy, chemotherapy and reconstruction.

Data collection included the pre-operative serum CRP values, clinical severity of the disease, surgery and other treatment modalities, treatment out comes, complications and the survival time period of the patients. Clinical and pathological factors like tumour size, lymph node involvement, metastasis and survival were correlated with pre-operative serum CRP levels.

Pre-operative CRP values were recorded from the patients notes. Serum CRP levels ranging from 0-5 mg/L were taken as normal while serum CRP levels greater than 5mg/L were considered to be high.

**RESULTS**

The study included 31 patients with the diagnosis of biopsy-proven oral squamous cell carcinoma (OSSC) of the year 2005 at University College London Hospital. These patients underwent primary surgical resection of the tumour with or without post-operative radiotherapy and/or chemotherapy. The pre-operative serum CRP values were recorded for each patient.

The patient sample consisted of 12 males and 19 females with male and female ratio of 1:1.6 (Figure 1). The age of the patients ranged from 46 to 92 years with the mean age of 64.87±14.25 years. The pre-operative serum CRP levels ranged from 4-57.2 mg/L with the mean value of 35.94±19.68mg/L. Out of these 31 patients, 24 patients had elevated pre-operative serum CRP levels while 7 had a normal serum CRP value (<5 mg/L).

The distribution of the 24 patients according to the size of tumour having elevated pre-operative serum CRP levels showed that 16 patients had stage IV disease, 7 had stage III and only 1 patient has stage II disease. No patient had stage I disease. 12 patients with high pre-operative serum CRP levels showed further neoplastic events (second primary tumour and/or dysplasia) and distant metastasis was also evident in these patients. In contrast the 7 patients with normal pre-
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The operative serum CRP level had a small sized tumour, with no lymph node and distant metastasis and the disease was in early stage i.e. stage I or II.

The results also showed positive correlation between elevated pre-operative serum CRP levels and decreased survival time. The patients with high preoperative serum CRP levels died earlier than the patients with normal pre-operative serum CRP levels. The 5-year survival rate in patients with elevated pre-operative serum CRP was only 8%, with the mean survival time of 27.5 months (2 years & 3.5 months) while the patients with normal pre-operative CRP levels were able to survive for 5-years. (Table 1)

**DISCUSSION**

The present study is sought to establish the possible association between preoperative levels of serum C-reactive protein (CRP) and outcomes of oral squamous cell carcinoma (OSSC) affecting individuals attending one major Head and Neck Cancer unit in University College London Hospital.

Several tumour markers have been studied in the spectrum of their prognostic and predictive importance in oral squamous cell carcinoma patients. They include staging, differentiation, tumour thickness, extracapsular spread, perineural invasion and resection margin status. However, all these parameters can only be assessed post-operatively and none of them can be used in day to day practice because of the high laboratory costs. So, attempts are made to use C-reactive protein as a simple prognostic indicator for oral squamous cell carcinoma as it is very simple to measure is repeatable and the laboratory cost is also minimal.

CRP is an acute phase protein that is synthesized in the liver and is regulated by cytokines like interleukin-1 (IL-1), interleukin-6 (IL-6) and tumour necrosis factor. Its role is to activate the complement system by binding with the phosphocholine expressed on the surface of dead or dying cells. Several theories have been proposed to explain that serum CRP levels can affect the survival of the patients. It has been suggested that the inflammatory response to tumour cells results in a tumour microenvironment rich in pro-inflammatory cytokines, angiogenic, lymphogenic factors and chemokine creating conditions that favour tumour growth, angiogenesis and metastasis as well as produce a catabolic affect on host metabolism which further worsen the prognosis.

The results of the present study suggest that serum CRP may indeed be an indicator of the poor outcome of OSSC. In this study, the pre-operative levels of CRP ranged from 4-57.2 mg/L with the mean value of 36.88 mg/L.

Among the 31 patients, 24 patients (77%) had elevated levels of pre-operative CRP. The mean size of the primary tumour in patients with elevated pre-operative CRP levels was significantly larger and 75% of these patients showed lymph node involvement resulting in more advanced disease i.e. stage III-IV while the primary tumour size in the patients with

<table>
<thead>
<tr>
<th>CRP levels</th>
<th>TNMStage</th>
<th>Lymph Node Recurrence</th>
<th>Distant Metastasis</th>
<th>5-year Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I  II III IV</td>
<td>Yes No</td>
<td>Yes No</td>
<td>Alive Dead</td>
</tr>
<tr>
<td>Normal 0-5mg/L</td>
<td>3 4 0 0</td>
<td>0 7</td>
<td>0 7</td>
<td>7 0</td>
</tr>
<tr>
<td>High &gt;5mg/L</td>
<td>0 1 7 16</td>
<td>10 14</td>
<td>9 15</td>
<td>2 22</td>
</tr>
</tbody>
</table>

Fig 1: Distribution of patients according to gender.

TABLE 1: RELATIONSHIP OF CRP VALUES WITH OTHER VARIABLES
normal serum CRP was smaller, there was no involvement of lymph nodes and the disease was in stage I and II. The survival of patients with elevated pre-operative serum CRP levels was worse than the patient with normal pre-operative serum CRP value. 5-year survival rate was 8.3% in patients with elevated pre-operative serum CRP levels as compared to 100% where serum CRP was normal. These results agree with the study conducted by Sunil et al and Ki et al, showing that pre-operative elevation of serum CRP is an independent prognostic indicator and can be used as an indicator for malignant potential of tumours and unfavorable prognosis of the patients with oral squamous cell carcinoma.

This study is clearly limited by the small number of patients that have been included. The limited number of patients reflects the difficulties that were encountered in retrieving the data of patients with pre-operative serum CRP. The study did not include the control group as the intention was that the investigation to be a pilot study. Clearly, there is a need for an appropriate control group that takes into account possible causes, other than OSSC, for serum CRP elevation. Possible control groups might comprise individuals with the same risk factors and systemic status as those with OSSC (for example those with oral epithelial dysplasia). The present study thus only provides a snapshot of the possible association of the pre-operative CRP levels with OSSC. There is a need for much more rigorous investigation to establish if pre-operative serum CRP levels predict outcomes of patients with OSSC.

CONCLUSION

The results of this small sample indicate that elevated pre-operative serum CRP level is independently associated with the poor prognosis and reduced survival of the patients and can be used as an independent prognostic indicator in patients with OSSC.

REFERENCES