

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

¹FARAZ AHMED TARIQ, BSc, BDS, MSc, Oral Medicine (London), C-Radiology (UK)

²OMER SEFVAN JANJUA, BSc, BDS, FCPS

³UMAIR KHAN, BDS, MSc, Oral Medicine (London), C-Radiology (UK)

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, out comes, 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 malignancies¹ with a 5-year survival rate of approximately 50%.²

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.^{3,4,5} OSCC is a

¹ Assistant Professor and Head of Oral Medicine Department, Islam Medical and Dental College, Sialkot

² Assistant Professor and Head of Department of Oral and Maxillofacial Surgery, Rawal Institute of Health Sciences, Islamabad

³ Assistant Professor and Head of Oral and Maxillofacial Medicine Department, Fatima Memorial College of Dentistry, Lahore

Correspondence: Dr Faraz Ahmed Tariq, House no 7, Lane no 1, Falcons Complex AFOHS, (Shaheen Housing), Tufail Road, Lahore Cantt, Pakistan, Email: faraz_tariq@yahoo.com, Contact number: Cell: 0333 4410538

devastating disease that can cause significant mortality, 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.⁶ 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).⁷ It is elevated in response to many inflammatory conditions like trauma, cancer, heart diseases and surgery.⁸ Elevated pre-operative serum CRP levels have been demonstrated as a prognostic indicator in many cancers like breast cancer⁹, oesophageal cancer¹⁰, colorectal cancer¹¹, renal cancer¹², cancer of the head of pancreas and multiple myeloma.¹³

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 OSCC 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 outcomes, 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 ± 19.68 mg/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-

TABLE 1: RELATIONSHIP OF CRP VALUES WITH OTHER VARIABLES

CRP levels	TNMStage				Lymph Node Recurrence		Distant Metastasis		5-year Survival	
	I	II	III	IV	Yes	No	Yes	No	Alive	Dead
Normal 0-5mg/L	3	4	0	0	0	7	0	7	7	0
High >5mg/L	0	1	7	16	10	14	9	15	2	22

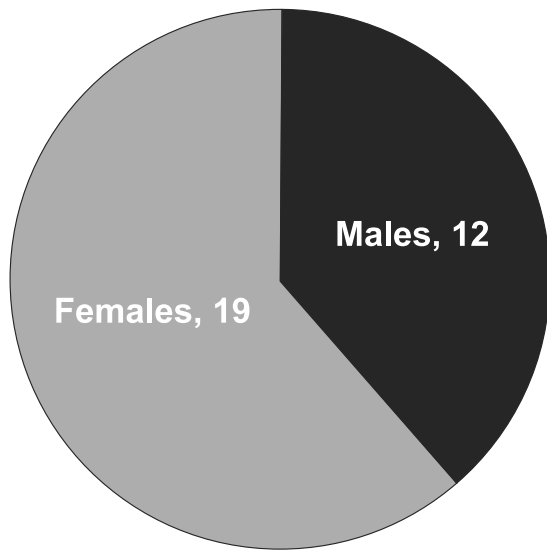


Fig 1: Distribution of patients according to gender

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 pre-operative 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.⁷ Its role is to activate the complement system by binding with the phosphocholine expressed on the surface of dead or dying cells.¹⁴ 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^{15,16,17} as well as produce a catabolic affect on host metabolism which further worsen the prognosis.¹⁸

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

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 al¹⁹ and Ki et al²⁰, 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 preoperative 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

- Chen YJ, Chang JT, Liao CT, Wang HM, Yen TC, Chiu CC *et al*. Head and neck cancer in the betel quid chewing area: recent advances in molecular carcinogenesis. *Cancer Sci* 2008; 99: 1507-14.
- Dias FL, Kligerman J, Matos de Sá G, Arcuri RA, Freitas EQ, Farias T, *et al*. Elective neck dissection versus observation in stage I squamous cell carcinomas of the tongue and floor of the mouth. *Otolaryngol Head Neck Surg* 2001;125:23-29.
- Johnson NW, Warnakulasuriya KA. Epidemiology and aetiology of oral cancer in the United Kingdom. *Community Dent Health* 1993;10 Suppl 1:13-29.
- Downer MC. Patterns of disease and treatment and their implications for dental health services research. *Community Dent Health* 1993;10 Suppl 2:39-46.
- Suzuki T, Wakai K, Matsuo K, Hirose K, Ito H, Kuriki K *et al*. Effect of dietary antioxidants and risk of oral, pharyngeal and laryngeal squamous cell carcinoma according to smoking and drinking habits. *Cancer Sci* 2006; 97: 760-67.
- Kim CH, Lee CH, Han SI. P201. The change of C reactive protein in oral cancer patients after resection and reconstructive surgery. *Oral Oncol* 2011;47:S139.
- Pepys MB, Hirschfield GM. C-reactive protein: A critical update. *J Clin Invest* 2003; 111:1805-12.
- Burtis CA, Ashwood ER, Bruns DE (2006). *Tietz, Textbook of Clinical Chemistry and Molecular Diagnostics* (ed 4). St Louis, MO, Elsevier Saunders
- Pierce BL, Ballard-Barbash R, Bernstein L, Baumgartner RN, Neuhauser ML, Wener MH *et al*. Elevated biomarkers of inflammation are associated with reduced survival among breast cancer patients. *J Clin Oncol* 2009;27:3437-44.
- Siewert JR, Ott K. Are squamous and adenocarcinomas of the esophagus the same disease? *Semin Radiat Oncol* 2007;17: 38-44.
- Nozoe T, Mori E, Takahashi I, Ezaki T. Preoperative elevation of serum C-reactive protein as an independent prognostic indicator of colorectal carcinoma. *Surg Today* 2008; 38: 597-602.
- Lamb GW, McMillan DC, Ramsey S, Aitchison M. The relationship between the preoperative systemic inflammatory response and cancer-specific survival in patients undergoing potentially curative resection for renal clear cell cancer. *Br J Cancer* 2006; 94:781-84.
- Kaneko M, Kanda Y, Oshima K, Nannya Y, Suguro M, Yamamoto M *et al*. Simple prognostic model for patients with multiple myeloma: a single-center study in Japan. *Ann Hematol* 2002; 81: 33-36.
- Thompson D, Pepys MB, Wood SP. The physiological structure of human C-reactive protein and its complex with phosphocholine. *Structure* 1999; 7: 169-77.
- Balkwill F, Mantovani A. Inflammation and cancer: back to Virchow? *Lancet* 2001; 357:539-45.
- Coussens LM, Werb Z. Inflammation and cancer. *Nature* 2002; 420:860-67.
- Miki S, Iwano M, Miki Y, Yamamoto M, Tang B, Yokokawa K, *et al*. Interleukin-6 functions as an in vitro autocrine growth factor in renal cell carcinomas. *FEBS Lett* 1989;250:607-10.
- Komai Y, Saito K, Sakai K, Morimoto S. Increased preoperative serum C-reactive protein level predicts a poor prognosis in patients with localized renal cell carcinoma. *BJU Int* 2007;99:77-80.
- Khandavilli SD, Ceallaigh PO, Lloyd CJ, Whitaker R. Serum C-reactive protein as a prognostic indicator in patients with squamous cell carcinoma *Oral Oncol* 2009;45:912-14
- Ki Y, Kim W, Nam J, Kim D, Park D, Kim D. C-reactive protein levels and radiation mucositis in patients with head and neck cancer. *Int J Radiat Oncol Biol Phys* 2009;75:393-98.