The impact of elevated C-reactive protein level on the prognosis for oro-hypopharynx cancer patients treated with radiotherapy

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The purpose of this study was to investigate an association between the prognosis for oro-hypopharynx squamous cell carcinoma treated with radiation therapy and the pre-therapeutic level of C-reactive protein (CRP). Patient with oro-hypopharyngeal squamous cell carcinoma who underwent definitive radiotherapy in our institution from January 2002 to August 2016 were enrolled. The patient were divided into elevated CRP (over 0.3 mg/dl) group and normal CRP groups, according to pre-treatment serum levels. There were 276 evaluable patients, and the median follow up was 41 months, ranging from 2 to 171 months. The 3-year OS and CSS for all enrolled patients were 67.0% and 72.8%, respectively. The OS and CSS rates were significantly worse in the elevated CRP group than in the normal CRP group, according to Kaplan-Meier survival curves analysed by a Log-rank test (p = 0.005 and p < 0.001, respectively). Multivariate analyses indicated that serum CRP levels remained independent predictors for both OS (HR: 1.588, p = 0.022) and CSS (HR: 1.989, p = 0.005). The pre-treatment CRP level is an independent predictor of treatment prognosis in patients with oro-hypopharyngeal cancer who underwent definitive radiotherapy. Especially, it is curious that an elevated CRP serum level is a significant predictor of loco-regional recurrence.

C-reactive protein (CRP) belongs to a family of acute-phase proteins whose plasma concentrations increase in response to inflammation. When inflammation or destruction of tissue cells occurs in the body, CRP is secreted from the liver into the blood. From the Virchow’s hypothesis in 1863 it has been revealed that there is a close relationship between inflammation and cancer. It is known that chronic inflammation causes carcinogenesis and progression of cancer. Parkin et al. suggested that about 20% of malignant tumours are closely related to chronic inflammation associated with infection. In particular, the relationship between Helicobacter pylori, Epstein-Barr virus, human papilloma virus, hepatitis virus and cancer is well known. Many studies have shown the elevation of pre-treatment CRP to be a significant prognostic indicator in patients with esophageal cancer, non-small cell lung cancer, hepatocellular carcinoma, renal cell cancer and prostate cancer. Although various factors have been suggested as prognostic indicators in cancer patient, measurements of CRP seem to be a fast, simple and cost-effective predictor in clinical practice.

Radiation therapy is a feasible and effective modality in the treatment of head and neck squamous cell cancer, especially in regard to organ preservation. Platinum-based chemo-radiotherapy, which is regarded as standard treatment in locally advanced cases, may be administered in two ways: induction or concurrent chemotherapy. As induction chemotherapy, a combination of cisplatin and 5-fluorouracil (CF regimen) has long been regarded as a standard in locally advanced head and neck cancer, however, in the TAX323 trial evaluating docetaxel, platinum plus 5-fluorouracil (DCF regimen) was superior to the CF regimen in survival and function preservation. Concurrent chemotherapy is also beneficial in all tumor subsites in head and neck cancer. The results of the Radiation Therapy Oncology Group 91-11 study revealed that cisplatin-radiotherapy is superior in loco regional...
control and larynx preservation compared with induction chemotherapy. Nevertheless, severe late toxicity and high treatment-related deaths after concurrent chemotherapy are important issues to overcome. Conclusive recommendations for chemo-radiotherapy in head and neck cancer have not been well established. It is important to quickly elucidate the factors that determine the prognosis because it will allow choosing the most appropriate treatment modality.

The prognostic role of CRP in patients with head and neck cancer is not fully understood. The purpose of this study was to investigate the relationship between serum CRP level and prognosis in oro-hypopharynx cancer patients treated by radiotherapy.

**Materials and Methods**

We included oro-hypopharyngeal squamous cell carcinoma patients treated with definitive radiotherapy in our hospital from January 2002 to August 2016. Written informed consent was obtained from all subjects. This study was performed in accordance with the guidelines approved by the institutional review board at the University of Tokyo Hospital. Clinical staging was performed according to the 7th edition of American Joint Committee on Cancer (AJCC) staging in oropharyngeal and hypopharyngeal cancer. All patients enrolled in this study satisfied the following eligibility criteria: (a) histologically confirmed primary squamous cell carcinoma; (b) no evidence of distant metastasis; (c) radiotherapy for definitive intent, excluding palliative intent cases; and (d) no history of previous radiotherapy to oropharynx or hypopharynx.

All patients underwent radiotherapy with 6–10 MV photon linear accelerators. The prescription dose to primary lesions or positive nodes ranged from 57 to 72 Gy (median 66 Gy). Prophylactic nodal areas were irradiated at doses of 40–56 Gy. The dose-fractionation regimen is either once daily, twice daily or concomitant boost. The radiation method was either three-dimensional conformal radiotherapy (IMRT), including volumetric modulated arc therapy (VMAT). Radiotherapy was combined with induction and/or concurrent chemotherapy, mostly consisting of a platinum-based regimen, although targeted therapy such as cetuximab was also used. We excluded post-operative radiotherapy cases, such as total laryngectomy or pharyngo-laryngectomy with thyroidecction resulting in positive resection margins, or extra-capsular extension of lymph nodes or partial resections such as trans-oral surgery. Unilateral or bilateral neck dissections alone were included in our study, according to previous report criteria. Pre-therapeutic CRP levels and hemoglobin concentration were measured in peripheral venous blood samples. Anemia was defined as hemoglobin concentration < 11 g/dL, known as a predictor of tumor hypoxia. The normal serum level of CRP was defined as 0.3 mg/dL or lower, according to several references. Comparisons between two groups were calculated with chi-square or fisher exact test for qualitative data. For prognosis analysis, we examined the factors of the primary site, age, gender, KPS, smoking history, current smoking status, clinical stages, anemia, pre-therapeutic CRP level and radiation treatment modalities.

All statistical analyses were performed with the R statistical package (The R Foundation for Statistical Computing, Vienna, Austria). Overall survival (OS) and cause-specific survival (CSS) were measured from the first day of initial therapy. Loco-regional control (LRC) was measured from the first day of initial therapy until the date of local or regional relapse, even if distant metastasis occurred with no evidence of local-regional failure. Cases lost to follow-up or death from any cause were regarded as censored cases. Distant metastasis control (DMC) was defined as the period until detection of first distant metastasis without considering loco-regional relapse. The OS, CSS, LRC and DMC rates were calculated by the Kaplan–Meier method using the Log-Rank test. Univariate and multivariate analyses were considered significant at p < 0.05. We conducted a multivariate Cox proportional hazard analysis by using covariates with p < 0.10 in the univariate analysis.

**Results**

Among 303 consecutive eligible patients, we excluded 27 cases (8.9%) without any predictor, smoking data were missing for 3 patients, and CRP data were missing for 24 patients. We conducted statistical analyses on the remaining 276 patients. All patients had no evidence of active infection, inflammatory disease, trauma and heart attack at the time of CRP evaluation.

**Patient characteristics.** There were 141 oropharynx patients and 135 hypopharynx patients. TNM staging of each cancer is presented in supplementary table 1. The median age of patients was 65 years, ranging from 21 years to 93 years. The patients were predominantly male (92%) with a 10 pack-year smoking history (75%). Induction chemotherapy consisted mainly of the DCF (docetaxel, platinum plus 5-fluorouracil) regimen followed by the CF (platinum plus 5-fluorouracil) regimen and other regimens, such as CDDP alone, the DC (platinum plus docetaxel) regimen and oral S-1 administration. Concurrent chemotherapy, consisting of the DCF regimen, CF regimen, platinum alone or other regimens, including intra-arterial CDDP, cetuximab, and weekly docetaxel/platinum-based regimens. Other patient characteristics and treatment modalities are summarized in Table 1. The median value of normal CRP was < 0.29 mg/dL (interquartile range: 0.08–0.90 mg/dL). A total of 132 patients (48%) were grouped into an elevated CRP group, and 144 patients (52%) were grouped into a normal CRP group.

**Survival.** The median follow-up for censored cases was 41 months (range: 2–171). The 3-year OS and CSS for all enrolled patients were 67.0% (95% CI: 60.5–72.7%) and 72.8% (95% CI: 66.4–78.2%), respectively. No significant differences were detected between oropharyngeal and hypopharyngeal cancer in OS (p = 0.69) and CSS (p = 0.71), as shown in Table 2. The OS and CSS rates were significantly worse in the elevated CRP group than in the normal CRP group, according to a comparison of Kaplan–Meier curves analysed by a Log-rank test (p = 0.005 and p < 0.001) (Fig. 1). Elevated CRP at pre-treatment was significantly correlated with advanced TNM staging by Fisher’s exact test (Supplementary Table 2). Relationship of pre-treatment CRP value and the same T or N stage of the treatment modalities were summarized in Supplementary Table 3. In a univariate analysis, KPS, smoking
| Variables                      | Number (Total 276) | Percentage |
|-------------------------------|--------------------|------------|
| **Patient characteristics**   |                    |            |
| Site of primary lesion        |                    |            |
| Hypopharynx                   | 135                | 49%        |
| Oropharynx                    | 141                | 51%        |
| Age                           |                    |            |
| >65 years old                 | 128                | 46%        |
| ≤65 years old                 | 148                | 54%        |
| Gender                        |                    |            |
| Male                          | 253                | 92%        |
| Female                        | 23                 | 8%         |
| Karnofsky Performance Scale   |                    |            |
| ≥90                           | 205                | 74%        |
| <90                           | 71                 | 26%        |
| Current smoker                |                    |            |
| Yes                           | 119                | 43%        |
| No                            | 157                | 57%        |
| Smoking history               |                    |            |
| ≥10 packs year                | 208                | 75%        |
| <10 packs year                | 68                 | 25%        |
| Clinical T stage              |                    |            |
| 4                             | 43                 | 16%        |
| 3                             | 79                 | 29%        |
| 2                             | 113                | 41%        |
| 1                             | 41                 | 15%        |
| Clinical N stage              |                    |            |
| 3                             | 23                 | 8%         |
| 2                             | 126                | 46%        |
| 1                             | 41                 | 15%        |
| 0                             | 86                 | 31%        |
| **Treatment modality**        |                    |            |
| Radiation method              |                    |            |
| IMRT                          | 53                 | 19%        |
| Conventional 3D-CRT           | 223                | 81%        |
| Radiation fractionation       |                    |            |
| Once daily                    | 244                | 88%        |
| Twice daily                   | 8                  | 3%         |
| Concomitant boost             | 24                 | 9%         |
| Neck dissection               |                    |            |
| Yes                           | 41                 | 15%        |
| No                            | 235                | 85%        |
| Concurrent chemotherapy       |                    |            |
| Yes                           | 112                | 41%        |
| DCF                           | 36                 | 13%        |
| CF                            | 43                 | 16%        |
| Platinum alone                | 20                 | 7%         |
| Other regimens                | 13                 | 5%         |
| No                            | 164                | 59%        |
| Induction chemotherapy        |                    |            |
| Yes                           | 93                 | 34%        |
| DCF                           | 80                 | 29%        |
| CF                            | 31                 | 4%         |
| Other regimens                | 3                  | 1%         |
| No                            | 182                | 66%        |

Table 1. Patient characteristics and treatment modality of 276 patients with oropharyngeal and hypopharyngeal squamous cell carcinoma.
respectively. The 3-year LRC and DMC for all enrolled patients were 66.8% (95% CI: 60.3–72.4%) and 82.4% (95% CI: 76.6–86.9%), respectively. The Kaplan–Meier analysis was used to calculate LRC and DMC rate curves. The log-rank test was used to detect significant differences between the elevated CRP group and the normal CRP group in LRC and DMC rate curves (p \(< 0.001\)).

### Discussion

This is the first study to show a significant correlation between elevated serum CRP levels and cancer prognosis in oro-hypopharynx cancer patients treated by radiotherapy. Moreover, our 3-year overall survival rate, progression-free survival rate and loco-regional control rate are comparable to those in previous reports\(^2\). Especially, it is curious that an elevated CRP serum level is a significant predictor of loco-regional recurrence. Nakamura et al. also reported the pre-operative CRP level as an independent predictor of local control\(^2\). Sun et al. reported that the tumor microenvironment plays an essential role in therapeutic resistance in cancer treatment\(^2\).
In the present study, the pretreatment CRP elevation is significantly correlated with KPS and advanced clinical stage (Supplementary Table 2). These results are consistent with previous reports which reveals the positive relationship between CRP level and TNM tumor staging. The production of CRP is affected by inflammatory cytokines, such as interleukin-6 (IL-6), interleukin-1 (IL-1) and tumour necrosis factor (TNF)-alpha, which are secreted by monocytes or macrophages due to inflammation or cancer. Especially, interleukin-6 is one of the multifunctional cytokines that control humoral immunity and are involved in inflammation, infection responses, and metabolic regulation. Serum concentrations of IL-6 and CRP are positively correlated, and recent evidence suggests that IL-6 also affects cancer cell biology. It has been confirmed that an IL-6 signalling pathway stimulates cancer progression through the IL-6 receptor on the cancer cell surface in prostate cancer. Shinriki et al. revealed that the IL-6 signalling system in human oral squamous cell carcinoma may be involved in the development of cancer by controlling angiogenesis and lymphangiogenesis. In addition, the size and efficiency of tumor formation were dependent on IL-6 secretion in human ovarian cancer cells. Other inflammatory cytokines, such as IL-1 and TNF-alpha, are also related to the immune-expression increases in cancer patients. The prognostic relationship with serum CRP levels in cancer patients is probably a complicated and multifactorial process that is still not well understood, but it seems likely that inflammatory cytokines might mediate the relationship.

Recently, the relationship between serum CRP level and head and neck cancer was gradually uncovered. Zeng et al. reported that the degree of inflammation is a marker predicting the prognosis for 79 Patients with locally advanced nasopharyngeal carcinoma. They found that patients treated by chemo-radiotherapy had a poor prognosis if they had elevated serum CRP before treatment. Multivariate analysis showed that CRP was an independent prognostic indicator of CSS, with a hazard ratio of 3.04 (95% confidence interval: 1.22 to 7.55; p = 0.017). Chen et al. analyzed pre-treatment combinations of serum squamous cell carcinoma antigen (SCC-Ag) and CRP levels in relation to prognosis for patients with pharyngo-laryngeal cancer. They reported that elevated levels of SCC-Ag and CRP were associated with a high metabolic rate as well as proliferative activity measured by 18F-fluorodeoxyglucose positron emission tomography. In contrast, Astrid et al. reported no significant correlation between pre-treatment CRP levels and prognosis in patients with head and neck cancer treated by surgery.

Elimination of inflammation might be an effective strategy in cancer treatment. The mechanisms underlying the effects of anti-inflammatory drugs are gradually being elucidated. Wang et al. reported that long-term oral administration of non-steroidal anti-inflammatory drugs such as aspirin significantly reduced the risk of carcinogenesis leading to colorectal cancer. Administration of non-steroidal anti-inflammatory drugs could be beneficial in enhancing chemotherapy effects in conventional cancer treatment. Although it is probably premature to begin using these drugs at the present time to enhance cancer treatment, anti-inflammatory drugs might bring new insight into cancer therapy. Many studies are still necessary in order to elucidate which lesion or cell type is suitable for cancer prevention or treatment with anti-inflammatory agents.

There were several limitations of our study to mention. First, this was a retrospective analysis with a limited number of cases and possible selection bias because of the retrospective nature of the study. Second, patients were evaluated during considerable long period, which was correlated with various treatment strategy regarding radiation technique and chemotherapy regimens. In addition, the ambiguities about criteria of the different treatment strategies could not be resolved. Despite a large variety of treatments were applied, relatively low patient number was included. Moreover, sufficient relevant prognostic factors were not considered in the statistical analysis. Third, the each clinical endpoint (OS, CSS, LRC and DMC) was not fully independent of each other, type I error inflation might have existed. Fourth, limited information was available regarding pretreatment patients’ characteristic. We need further consideration of relevant factors that affect the pre-treatment CRP value.

Figure 1. Kaplan-Meier curves for overall survival (A) and cause-specific survival (B). A vertical bar indicates a censored case.
In conclusion, the pre-treatment CRP level was an independent predictor of prognosis in patients with oro-hypopharyngeal squamous cell carcinoma undergoing definitive radiotherapy. An elevated CRP level might be useful to identify candidates for more active surveillance and potential adjuvant therapy. However, since the sample size in this study was limited, a confirmatory prospective cohort study with a larger number of patients and a long follow-up period should be carried out. In addition, treatment responsiveness should be stratified in the patients’ background information.

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| Variables                     | OS HR [95% CI]     | p value | CSS HR [95% CI] | p value |
|-------------------------------|--------------------|---------|-----------------|---------|
| Age >65 vs ≤ 65 years old     | 1.760 [1.176–2.635] | 0.006   | 2.033 [1.261–3.279] | 0.004   |
| KPS < 90 vs ≥ 90              | 1.755 [1.139–2.705] | 0.011   | 1.696 [1.026–2.804] | 0.039   |
| Current smoking Yes vs No     | 1.447 [0.939–2.230] | 0.094   | 1.460 [0.880–2.420] | 0.143   |
| Smoking history ≥ 10 vs <10 vs 10 packs year | 1.471 [0.822–2.632] | 0.194   | 1.779 [0.853–3.711] | 0.125   |
| T stage 123 vs 4              | 1.263 [0.758–2.104] | 0.371   | 1.495 [0.850–2.629] | 0.163   |
| N stage 123 vs 0              | 1.519 [0.968–2.383] | 0.069   | 2.095 [1.170–3.752] | 0.013   |
| CRP > 0.3 vs ≤ 0.3 mg/dl      | 1.588 [1.069–2.359] | 0.022   | 1.989 [1.235–3.203] | 0.005   |
| Induction chemotherapy Yes vs No | 0.715 [0.463–1.103] | 0.129   | —               | —       |

Table 3. Multivariate Cox regression analysis of OS and CSS.

Figure 2. Kaplan-Meier curves for loco-regional control rate (A) and distant metastasis control rate (B). A vertical bar indicates a censored case.
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**Author Contributions**

M.A., M.Y. and Y.S. recruited the patients and collected their clinical data. A.K., K.Y. and W.T. analysed and interpreted the clinical data. A.K. was a major contributor in writing this report. H.Y. conceived of this study and participated in its design and coordination. H. Y. revised this report critically for important intellectual content. O.A. and K.N. supervised this study. All authors have read and approved the final manuscript.

**Additional Information**

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