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Prognostic impact of elevated preoperative C-reactive protein on patients with differentiated thyroid carcinoma

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ABSTRACT

Background: C-reactive protein (CRP) has been reported to be associated with poorer prognosis in various malignancies. However, the relationship between CRP and differentiated thyroid carcinoma (DTC) remains to be elucidated.

Methods: A total of 45 patients, including 32 patients with preoperative DTC and 13 DTC patients with metastatic disease, were included in the study. The relationships between CRP levels and clinicopathological features were retrospectively analyzed.

Results: Analysis using a receiver operating characteristic curve revealed a preoperative CRP cutoff value of 0.155 mg/dL. Patients with preoperative CRP $\geq$ 0.155 mg/dL, those with T3 + T4, those with extrathyroidal invasion, or those with stage II, showed a statistically shorter recurrent-free survival than those with preoperative CRP $<$ 0.155 mg/dL, those with T1 + T2, those without extrathyroidal invasion, or those with stage I ($P = 0.001$, $P = 0.004$, $P = 0.024$, and $P = 0.025$, respectively). Preoperative CRP $\geq$ 0.155 mg/dL was an independent prognostic factor for recurrent-free survival in the DTC patients (hazard ratio = 6.334, 95% confidence interval: 1.023-39.234, $P = 0.037$). The proportion of patients aged $\geq$55 y, and those with T3 + T4, was statistically higher in those with preoperative CRP $\geq$ 0.155 mg/dL than in those with preoperative CRP $<$ 0.155 mg/dL ($P = 0.037$ and $P = 0.038$, respectively).

Conclusions: Higher preoperative CRP levels have a robust prognostic impact on recurrence-free survival in DTC patients. In addition, higher preoperative CRP levels were associated with age $\geq$ 55 y and T3 + T4.

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Introduction

One percent of all neoplasms are thyroid tumors, 80%-85% of which are differentiated thyroid tumors (papillary and follicular type).[1-4] Differentiated thyroid carcinoma (DTC) is subdivided into papillary and follicular thyroid carcinoma. Although patients with DTC usually show a favorable prognosis with a 10-y survival rate exceeding 90%,[5] recurrent disease occurs in some cases. Various scoring systems, such as AGES (patient age, histologic grade of the tumor, tumor extrathyroidal invasion or distant metastasis, and the size of the tumor),[6] MACIS (metastasis, patient age, completeness of surgical resection, local invasion, and tumor size),[7] AMES (patient age, presence of distant metastasis, and extent and size of the primary tumor),[8] and EORTC (the European Organization for Research and Treatment of Cancer),[9] have been reported for prognosis stratification. On the other hand, the prognostic impact of lymph node metastasis remains controversial.[3,8,10,11]

Clinical translational research on thyroid carcinoma has been progressing, with one study focusing galectin-3, β-galactoside binding lectin, as a diagnostic molecular marker.[12] Recently, galectin-3 was reported to induce secretion of angiogenic factors, such as interleukin (IL)-6, vascular endothelial growth factor (VEGF), granulocyte colony-stimulating factor (G-CSF), granulocyte macrophage colony-stimulating factor, and soluble intercellular adhesion molecule (sICAM)-1, from blood vascular endothelial cells *in vitro*.[13] Systemic chronic inflammation, in combination with angiogenesis, has been reported to play roles in the suppression of tumor immunity, carcinogenesis, and tumor progression.[14,15] On the other hand, C-reactive protein (CRP), which was named for its capacity to precipitate C-polysaccharide of *Streptococcus pneumoniae*, is a sensitive and widely used inflammatory marker produced primarily in the liver, in response to IL-1, IL-6, tumor necrosis factor-α, and IL-17.[16,17] Recently, CRP has been reported to be associated with poorer prognosis in nasopharyngeal,[18] breast,[19] hepatocellular,[20] pancreatic,[21] colorectal,[22] renal,[23] urothelial,[24] ovarian,[25] and prostate carcinoma.[26] However, the relationship between CRP and DTC remains to be elucidated. Thus, we aimed to evaluate the prognostic impact of CRP on DTC patients, in conjunction with angiogenic, inflammatory, immunological, and nutritional parameters.

Materials and methods

Patients

Fifty-one patients with DTC were enrolled between June 1, 2011, and March 31, 2013. Among the 51 patients, six were excluded from the analyses because of having anaplastic cancer. Thus, a total of 45 DTC patients, including 32 preoperative patients (30 papillary and two follicular cancer) and 13 postoperative patients with recurrence (11 papillary and two follicular cancer), were included in the study. If a patient had a tumor <10 mm in size localized in the hemithyroid without obvious lymph node swelling nor tumor extension beyond the thyroid capsule (Ex), thyroid lobectomy with prophylactic lymph node dissection was performed. Otherwise, total thyroidectomy with therapeutic lymph node dissection was performed. Following surgery, the cancer stage of each patient was determined pathologically, according to the TNM classification system of malignant tumors published by the Union for International Cancer Control, eighth edition.[27] The study protocol was approved by the ethics committee of Fukushima Medical University, and written informed consent was obtained from all enrolled patients.

Measurements of parameters

Blood samples were collected before starting treatment. Regarding the angiogenic factors, serum concentrations of galectin-3, IL-6, VEGF, sICAM-1, and G-CSF were measured using an enzyme-linked immunosorbent assay (ELISA; R&D Systems, Minneapolis, MN) according to the manufacturer's instructions. As for the inflammatory parameters, CRP, white blood cell count, neutrophil and lymphocyte counts, and the neutrophil-to-lymphocyte ratio, were used. With regard to immunological cytokines, the productivity of IL-10, 12, and 17 were examined. Peripheral blood mononuclear cells were separated on Ficoll-Hypaque (Pharmacia Biotech, Uppsala, Sweden) columns and washed twice using RPMI-1640 (Wako Pure Chemical Industries Ltd, Osaka, Japan). The isolated peripheral blood mononuclear cells were then incubated in 1 mL of RPMI-1640 at a concentration of 10^6 cells/mL with 10% heat-inactivated fetal calf serum (Gibco BRL, St. Louis, MO) in 5% CO_2 at 37°C for 24 h with the following stimulations: 20 μg/mL phytohemagglutinin for IL-10 and IL-17 production assays and 0.01% of *Staphylococcus aureus* Cowan-1 for IL-12 production assays. Aliquots of these supernatants were then frozen and stored at −80°C until use. The measurements of IL-10, IL-12, and IL-17 concentrations were performed using ELISA (R&D Systems). Each sample was used only once after thawing and not all blood samples were of sufficient volume for all measurements.

Statistical analysis

Data are presented as frequencies or percentages for categorical variables and mean ± SD for continuous variables, unless otherwise indicated. For categorical clinical variables, differences between groups were evaluated using Fisher's exact test. The differences in mean values between the groups were analyzed using the Mann–Whitney *U* test. A receiver operating characteristic (ROC) curve was used to evaluate the usefulness of the examined parameters as a prognostic factor, and associations between the two variables were quantified using Spearman's rank correlation coefficient. The mean observation period was 67.0 mo (range: 54.1-82.3), and the final assessment of disease status was made on December 12, 2017. Overall survival (OS) and recurrence-free survival (RFS) were calculated using the Kaplan–Meier method, and differences between the groups were assessed by using the log-rank test. Factors found to be significant in the univariate analysis were subjected to multivariate analysis using a Cox proportional hazard model to identify independent predictors of prognosis.