論　文　内　容　要　旨

Impact of Secreted Protein Acidic and Rich in Cysteine (SPARC) Expression on Prognosis After Surgical Resection for Biliary Carcinoma

（胆道癌切除例におけるSPARC発現の予後に与える影響について）

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Background: Biliary carcinoma is currently one of the most lethal human cancers. Although the only way to cure patients with biliary carcinoma is surgical resection, its outcome is still unsatisfactory. Therefore, some adjuvant chemotherapeutic regimens were recently considered for improving the prognosis of patients with biliary carcinoma. Indeed, our previous reports have demonstrated a favorable postoperative prognosis on adjuvant gemcitabine-based chemotherapy. Nonetheless, its therapeutic effect was different among individuals. Identification of predictive biomarkers for adjuvant chemotherapy for biliary carcinoma is attractive to improve survival after surgery for biliary carcinoma. Secreted protein acidic and rich in cysteine (SPARC) is a member of the matricellular family of proteins, which are expressed and affects at development, wound repair, and tissue remodeling. The reported functions of SPARC include modulating apoptosis, cell cycle progression, angiogenesis, matrix cell adhesion, proliferation, and migration. These roles of SPARC in tumor tissue were likely related to carcinogenesis and supposed to affect prognosis and sensitivity to chemotherapy of patients with several types of cancer. However, predictive value and impact on chemotherapy of SPARC in biliary carcinoma is still unclear.

Aim: The aim of this study is to investigate whether cytoplasmic and/or stromal SPARC expression can predict the postoperative survival of patients treated with surgical resection and adjuvant gemcitabine-based chemotherapy for biliary carcinoma.

Method: A single-institutional retrospective cohort study was performed. All patients underwent surgical resection with curative intent (R0 or R1 resection) for biliary carcinoma at the Department of Surgery, Hiroshima University Hospital, Hiroshima, Japan from 1998 to 2014. Cytoplasmic and stromal SPARC expressions in resected specimen were investigated immunohistochemically. The relationship between SPARC expression and clinicopathological factors were compared. In addition, risk factors for poor prognosis after surgery were evaluated. Immunohistochemistry was performed using the streptavidin-peroxidase technique and the Dako EnVision+ System (Dako, Carpinteria, CA, USA). To evaluate SPARC expression, a monoclonal mouse antibody directed against SPARC (clone ON1-1; TaKaRa Bio, Inc., Otsu, Japan) was used. Staining of sections was evaluated based on the proportion of positively stained tumor cells and the intensity of staining. Relationships between SPARC expression and clinicopathological factors were evaluated using the χ^2 test. The Kaplan-Meier method and the log-rank test were performed to examine differences in overall survival (OS) between two groups. Those factors found to be significant using univariate analysis were entered into multivariate analysis using a Cox proportional hazards model. A P value less than 0.05 was considered statistically significant.

All statistical analyses were carried out using JMP statistical software (version 12, SAS Institute, Cary, NC, USA).

Result: 175 patients with resected stage II - IV biliary carcinoma (19 with intrahepatic cholangiocarcinoma, 62 with hilar cholangiocarcinoma, 51 with distal cholangiocarcinoma, 25 with carcinoma of the gallbladder, and 18 with ampullary carcinoma) were eligible for this study. High SPARC expression in cytoplasmic and stromal cells was found in 50 (28.6%) and 61 patients (34.9%), respectively. In all 175 enrolled patients, adjuvant gemcitabine-based chemotherapy ($P < 0.001$), lymph node metastasis ($P < 0.001$), and stromal SPARC expression ($P = 0.006$) were significantly associated with OS, whereas cytoplasmic SPARC expression was not ($P = 0.94$). Multivariate analysis revealed that absence of postoperative adjuvant chemotherapy ($P < 0.001$; hazard ratio [HR], 2.76; 95% confidence interval [CI], 1.81-4.17), lymph node metastasis ($P < 0.001$; HR, 2.38; 95% CI, 1.55-3.71), and high stromal SPARC expression ($P = 0.006$; HR, 1.81; 95% CI, 1.19-2.71) were identified as independent risk factors for poor OS. In the subset of 118 patients who received adjuvant gemcitabine plus S-1 chemotherapy, lymph node metastasis ($P = 0.005$) and high stromal expression ($P = 0.003$) were associated with poor prognosis. In the multivariate analysis of this same group, lymph node metastasis ($P = 0.010$; HR, 2.03; 95% CI, 1.18-3.59) and high stromal SPARC expression ($P = 0.010$; HR, 2.04; 95% CI, 1.19-3.46) were independent risk factors for poor OS. On the other hand, stromal expression did not significantly correlate with OS in the subset of 57 patients who did not received adjuvant gemcitabine plus S-1 chemotherapy ($P = 0.21$).

Conclusion: Analysis of stromal SPARC expression enables the stratification of biliary adenocarcinoma patients treated with adjuvant gemcitabine plus S-1 chemotherapy based on their likelihood of OS, and may have a potential to optimize adjuvant chemotherapy for resected biliary carcinoma.