



## Reduced preoperative serum albumin and absence of peritoneal dissemination may be predictive factors for long-term survival with advanced gastric cancer with positive cytology test

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### Abstract

**Background:** Peritoneal lavage cytology cancer-positive (CY1) is a critical prognostic factor and is taken as representing stage IV in gastric cancer. There is no consensus treatment strategy for CY1-gastric cancer, and the detailed clinicopathological features remain obscure.

**Patients and methods:** Among 790 gastric cancer patients between 2005 and 2009, 52 cases of CY1 were identified (6.6%). A multivariate prognostic model was applied to the univariate prognostic factors to identify independent prognostic factors and factors associated with long-term survival in CY1-gastric cancer.

**Results:** (1) Five-year overall survival (OS) was 17.6% in CY1-gastric cancer as compared with 93.9% in CYX and 77.7% in CY0 (77.7%), where tumors with pT2 or beyond were included in 11% of CYX, 73% of CY0, and 98% of CY1 cases. (2) On univariate analysis, factors associated with a negative prognosis were the presence of peritoneal dissemination ( $p = 0.029$ ) and high preoperative serum albumin ( $p = 0.011$ ) in CY1-gastric cancer. The multivariate Cox proportional hazards and logistic regression model using propensity score identified preoperative albumin as a critical independent prognostic indicator. (3) Long-term survivors were identified and, were often characterized by long-term postoperative adjuvant treatment.

**Conclusion:** Reduced preoperative serum albumin and absence of peritoneal dissemination may be predictive factors for long-term survival in patients with advanced gastric cancer with positive cytology test. Long-term postoperative adjuvant therapy might improve survival of patients with CY1.

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**Keywords:** Gastric cancer; CY1; Prognosis; Albumin; Long-term postoperative therapy; Peritoneal dissemination; Propensity score

### Introduction

Gastric cancer is the fifth most common malignancy (952,000 cases in 2012) and the third leading cause of cancer-related death (723,000 deaths in 2012) worldwide.<sup>1</sup> Advanced gastric cancer continues to have poor survival outcomes despite progress in multidisciplinary therapy,<sup>2,3</sup> while early gastric cancer is largely a curable disease.<sup>4</sup>

In Japan, D2 gastrectomy followed by postoperative chemotherapy with S-1 is the standard treatment for pathological stage II/III advanced gastric cancer.<sup>2</sup> However, gastrectomy subsequent to postoperative chemotherapy has not proven to be effective against advanced gastric cancer with stage IV, and chemotherapy using S1/Cisplatin was established as a first line chemotherapeutic regimen of standard treatment for such metastatic gastric cancer.<sup>5–7</sup>

CY1 was considered stage IV disease in gastric cancer since 1999 in the Japanese Classification of Gastric Cancer (JCGC) stage, because the consensus meeting of the 70th Japanese Gastric Cancer Association (JGCA) confirmed

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that peritoneal lavage cytology testing could be performed in large portions (more than 90%) of the Japanese hospitals and it could be of prognostic significance, almost same as peritoneal dissemination.<sup>7,8</sup> On the other hand, the UICC (Union for International Cancer Control) also considered CY1 as stage IV disease in gastric cancer since 2009.<sup>9</sup> CY1 is likely to be a stage IV factor from a prognostic point of view in eastern countries other than Japan<sup>10</sup> and western countries.<sup>11</sup>

In the latest version of the Gastric Cancer Treatment Guidelines 2010 of the JGCA,<sup>12</sup> gastric resection is optional for gastric cancer with M1 including CY1. However, gastrectomy is practically performed because nobody knows whether it affects prognosis in gastric cancer with CY1. In this current study, the most recent clinical outcomes of gastric cancer with CY1 were investigated, and prognostic factors were explored.

## Patients and methods

### Patients

Between 2005 and 2009, 790 patients with histologically confirmed primary gastric cancer underwent surgery at the Department of Surgery, Kitasato University School of Medicine, Sagamihara, Japan. During this time, peritoneal lavage cytology testing was principally performed for gastric cancer with cT2 or beyond, while it was omitted for cT1 gastric cancer. As a result, among the 790 patients, 458 patients (58.0%) underwent peritoneal lavage cytology testing, and 52 patients (11.4%) had a diagnosis of CY1 among those with gastric cancer of cT2 or beyond.

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Research Ethics Committee of Kitasato University School of Medicine. The requirement for informed consent was waived because of the retrospective study design.

### Clinicopathological factors

Prognostic analyses were performed to identify independent prognostic factors in the 52 gastric cancer patients who underwent gastrectomy. Pathological tumor depth (pT) and pathological lymph-node metastasis (pN) were classified according to the Japanese Classification of Gastric Cancer staging system, 14th edition.<sup>13</sup> The results of cytological examinations of either ascites or peritoneal lavage fluid (CY; cytology test) were evaluated according to the Japanese Classification of Gastric Cancer (JGCG) and were classified as CY1 (positive cytology test), CY0 (negative cytology test), CYX (not assessed by cytology test). No genetic techniques were used during the cytology testing.

The results of the cytology testing could actually affect the surgical procedure. In our institute, positive cytology together with other stage IV factors, such as peritoneal dissemination, liver metastasis, or distant lymph node metastasis, was not a

basic indication for gastrectomy, but the final judgment was made by the attending surgeons. CY1-gastric cancer with no other stage IV factor could be indicated for gastrectomy, because of the small potential for cure after gastrectomy. Either D1+ or D1 lymph node dissection was permitted, because the efficacy of D2 lymph node dissection has not been proven for stage IV gastric cancer.

The preoperative value of serum albumin was taken as the value just prior to surgery, and a log-rank plot analysis was used to determine the best cut-off to maximize risk ratio for deaths.

### Chemotherapy

The adjuvant Chemotherapy Trial of S-1 for Gastric Cancer (ACTS-GC) showed in 2007,<sup>2</sup> that S-1 is effective as adjuvant chemotherapy, and we participated actively in that trial. Since then, it has been recommended that patients with stage II/III advanced gastric cancer receive adjuvant chemotherapy with S-1. CY1-gastric cancer represents stage IV in the JGCG staging system, so postoperative chemotherapy was inevitably recommended for all such patients, if feasible. There has been, however, no consensus chemotherapeutic regimen for post-gastrectomy patients with stage IV gastric cancer in Japan. Among the 52 CY1-gastric cancer patients, postoperative administration of either S1 or other chemotherapeutic regimens was done as the initial chemotherapy in 31 and 9 (CPT11/CDDP,  $n = 1$ ; Taxotere,  $n = 3$ ; UFT,  $n = 1$ ; and Docetaxel/S1,  $n = 4$ ), respectively, and the remaining 12 cases did not undergo postoperative chemotherapy due to low activities of daily living (ADLs), advanced age, or rapid disease progression.

The Institutional Review Board of Kitasato University Hospital approved the use of Docetaxel/Cisplatin/S1 (DCS) regimen for the management of far advanced gastric cancer since 2009.<sup>14</sup> DCS was used as neoadjuvant chemotherapy (NAC) ( $n = 5$ ), and the only other NAC regimen was CDDP/S1 (CS) ( $n = 1$ ).

### Statistical analysis

Continuous variables were evaluated by Student's *t*-test; categorical variables were evaluated by Fisher's exact test or the chi-square test, as appropriate. Survival was calculated by the Kaplan–Meier method. Univariate analyses of prognostic factors for overall survival (OS) were performed using the log-rank method. OS was defined as the time from surgery to death from any causes, and data on surviving patients were censored at the last follow-up. The median follow-up was 38 months (range: 3–75 months). Factors with  $P < 0.05$  on univariate analysis were subjected to multivariate analysis using Cox proportional hazards and logistic regression model to identify independent prognostic factors. Multivariate regression adjustment was also applied to the CY1-gastric cancer

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