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Usefulness of palliative prognostic score in the treatment of patients with non-resectable gastric cancer

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Abstract. The aim of this study was to evaluate the clinical usefulness of the palliative prognostic (PaP) score in patients with non-resectable advanced gastric cancer. The PaP score was calculated prior to each course of chemotherapy in 44 consecutive patients with non-resectable advanced gastric cancer between 2003 and 2010 at the Tottori University Hospital, Yonago, Japan. The prognosis was evaluated according to the PaP score and the different chemotherapeutic agents. The median survival time (MST) was 10 months. The PaP score classified the heterogeneous patient sample into three isoprognostic groups with regard to the possibility of a 1-month survival period, with 28 patients in group A (>70% chance), 12 in group B (30-70% chance) and 4 in group C (<30% chance). The MST of the three groups was 11, 3 and 1 months for group A, B and C, respectively. In group A, chemotherapeutic regimens did not affect patient survival, although the docetaxel regimen prolonged survival of patients in group B. In conclusion, the PaP score may be useful in selecting the best chemotherapeutic regimen in patients with non-resectable gastric cancer.

Introduction

Outcomes are extremely poor in patients with non-resectable gastric cancer, with a median survival period ranging from 3 to 5 months, even with the best supportive care (1,2). S-1 is an oral anticancer drug that combines tegafur, a prodrug of fluorouracil, with 5-chloro-2,4-dihydropyrimidine (CDHP) and potassium oxonate at a molar ratio of 1:0.4:1 (Taiho Pharmaceutical Co., Ltd., Tokyo, Japan) (3). In a phase II study of S-1, an ~40% response rate was noted in patients with advanced gastric cancer (4,5). Thus, S-1 chemotherapy has been widely used as a basic treatment for patients with non-resectable gastric cancer. Findings from the SPIRIT trial identified S-1 plus cisplatin as a standard first-line treatment (6) and recommended its use in patients with an expected survival period of at least 3 months. However, due to the severe side effects, the S-1 plus cisplatin regimen [S-1: 40-60 mg/m^2; in a 5-week cycle (3 weeks on and 2 weeks off), in combination with 60 mg/m^2 cisplatin on day 8] was difficult to continue in patients with poor Eastern Cooperative Oncology Group Performance Status (ECOG PS). Additionally, a number of patients suffered from reduced quality of life (QOL) while undergoing this medical treatment (7). However, Casaretto *et al* (8) reported that chemotherapy increased the 1-year survival rate, provided a longer symptom-free period and improved the QOL of patients with non-resectable advanced gastric cancer. Clinically, it is important to select chemotherapeutic regimens that are most appropriate for the patient's condition.

The objective indicators determining suitable chemotherapy regimens for patients with non-resectable gastric cancer have been studied. The standard prognostic indicators in oncology, such as tumor size, grade and stage, or molecular biology, are less relevant in patients with advanced cancer. The palliative prognostic (PaP) score was developed in the 1990s, as a result of a series of prospective trials aimed to identify clinical and biologic factors associated with the prognosis of advanced cancer patients referred to hospice and to merge them into a prognostic index (9). The survival of patients with non-resectable or recurrent cancers can be estimated using the PaP score even during chemotherapy (10).

In this study, the usefulness of the PaP score in determining the first-line chemotherapy for patients with non-resectable gastric cancer was examined retrospectively.

Materials and methods

Patients. Between 2003 and 2010, 558 patients with gastric cancer were treated at the Tottori University Hospital, Yonago, Japan. Forty-four patients (7.9%) were diagnosed as non-resectable. Details of these 44 patients are shown in Table I. Patients were followed up at the hospital until March 2012. During this period, gastrectomy was performed on 3 patients (bleeding, 2 patients; perforation, 1 patient). All participants provided informed consent and the study design was approved by the Ethics Review Board of Tottori University.

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Key words: docetaxel, palliative prognostic score, non-resectable gastric cancer

Table I. Patient data (n=44).

Variables	No.
Age (range, mean; years)	23-92, 66.5
Gender (male/female)	24/20
Ascites (yes/no)	10/34
ECOG PS (0/1/2)	14/18/12
Non-resectable parameters	
Locally advanced	6
Lymph node	12
Hematogenic metastasis	19
Peritoneal metastasis	20
Surgical intervention	
No	29
Probe-laparotomy	1
Bypass operation	11
Gastrectomy	3

ECOG PS, Eastern Cooperative Oncology Group performance status.

Table II. PaP score.

Item	Score
Symptoms (presence/absence)	
Anorexia	1.0/0.0
Dyspnea	1.5/0.0
Karnofsky performance status	
≥50	0.0
30-40	0.0
10-20	2.5
Clinical prediction of survival (weeks)	
>12	0.0
11-12	2.0
9-10	2.5
7-8	2.5
5-6	4.5
3-4	6.0
1-2	8.5
Total white blood cells (/mm^3)	
Normal (4,800-8,500)	0
High (8,501-11,000)	0.5
Very high (>11,000)	1.5
Lymphocyte percentage	
Normal (20.0-40.0)	0
Low (12.0-19.9)	1.0
Very low (0-11.9)	2.5
PaP score groups	
A	0-5.5
B	5.6-11.0
C	11.1-17.5

PaP, palliative prognostic.

Chemotherapy. First-line chemotherapy was received by 41 patients (S-1, 7; S-1 plus cisplatin, 17; S-1 plus docetaxel, 13; other chemotherapy, 4). Chemotherapy was terminated in the case of 3 patients with poor performance status (PS) and advanced age, who then received best supportive care (BSC).

PaP score. The PaP score has four criteria: two symptoms (anorexia and dyspnea), performance status measured by the Karnofsky performance score, white blood cells (WBC) abnormalities (high total WBC count and lymphopenia) and a physician's survival prediction measured in weeks (Table II). Validated cut-off points based on the total PaP score were established to classify the patients into three prognostic groups for survival at 30 days: group A (>70% probability of a 1-month survival period), 0 to 5.5 points; group B (30-70% probability of a 1-month survival period), 5.6 to 11 points; group C (<30% probability of a 1-month survival), 11.1-17.5 points (10,11) (Table II).

Statistical analysis. The terminology used in this study conforms to the Japanese Classification of Gastric Carcinoma, 3rd English edition (12). Statistical analysis was carried out using χ^2 tests. Overall survival was calculated from the time of enrolment to death. Median survival time (MST) was calculated using the Kaplan-Meier non-parametric test, while comparison between the different patient cohorts was performed using the log-rank test. $P<0.05$ was considered to indicate a statistically significant difference.

Results

Median survival time. The MST of the 44 patients was 10 months. Patients were divided into 3 subgroups, according to their PaP score. The MST of 28 patients in group A (11 months) was much better compared to the 12 patients in group B (3 months) or the 4 patients in group C (1 month, $P<0.0001$, Fig. 1). In the 40 patients in groups A and B, the correlation between prognosis and factors considered to affect the prognosis was analyzed (Table III). The presence or absence of ascites or bypass surgery did not affect patient survival.

Correlation between the PaP score and the first-line chemotherapy regimens. The correlation between the PaP score and the first-line chemotherapy regimens are shown in Table IV. The S-1 plus cisplatin regimen was commonly used as first-line chemotherapy in PaP group A. However, due to renal dysfunction, cisplatin was not used in a number of patients in group B, thus S-1 plus docetaxel or S-1 alone was selected in this group instead. In the 28 patients in group A, the MST using the cisplatin regimen (10 months, n=16) did not differ from the other regimens (11 months, n=12, $P=0.221$). Although the difference was not significant ($P=0.062$), in the 12 patients

Table III. Prognosis of patients in PaP score groups A and B.

	N	MST (months)	P-value
PaP score group			
A	28	11	0.0045
B	12	3	
Ascites			
Absent	31	10	0.7548
Present	9	10	
Surgical intervention			
No	25	10	0.7238
Yes	15	11	

PaP, palliative prognostic; MST, median survival time.

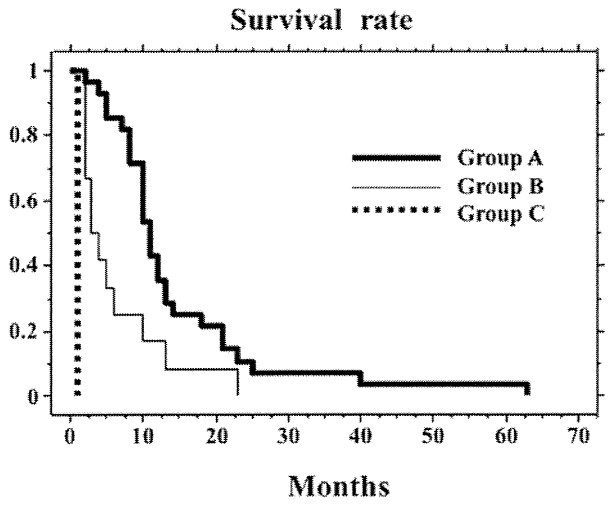

Figure 1. Survival of patients in group A was much better compared to patients in group B or C (P<0.0001).

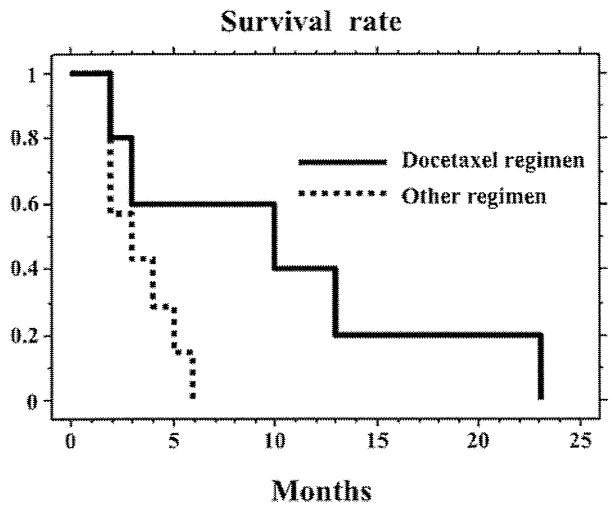

Figure 2. Survival of the 5 patients treated with docetaxel was better compared to the 7 patients treated with other regimens in the PaP group B, with no statistically significant difference (P=0.062).

Table IV. Correlation between PaP score and first-line chemotherapy.

	PaP score group		
First-line chemotherapy	A	B	C
S-1 plus cisplatin	16	1	0
S-1 plus docetaxel	8	5	0
S-1 plus CPT-11	2	2	0
S-1 only	2	4	1
BSC	0	0	3

PaP, palliative prognostic; BSC, best supportive care.

in group B, the docetaxel regimen prolonged the survival from 3 (other regimens, MST, 3 months, n=7) to 10 months (docetaxel regimen, MST, 10 months, n=5, Fig. 2).

Discussion

Large-scale randomized phase III clinical trials may reveal effective chemotherapeutic regimens for patients with advanced cancers, with the exception of those of advanced age or with poor PS. However, in clinical situations, it is difficult to decide the most suitable chemotherapeutic regimen for patients with short life expectancy or poor PS, such as patients with non-resectable gastric cancer. Identifying the patients that may benefit from palliative chemotherapy is quite difficult and its usefulness when controlling symptoms and maintaining QOL has not yet been proven (13,14).

The PaP score contains five parameters (symptom, PS, inflammation, immunity and physician's survival prediction) associated with cancer patient survival. Findings of previous studies have indicated that the PaP score may accurately estimate pre-terminal patient survival (15-17). Using the PaP score in 44 patients with non-resectable advanced gastric cancer, the correlation between PaP score groups and chemotherapeutic regimens was investigated. The findings showed that in the PaP score group A, the S-1 plus cisplatin regimen was commonly used and differences in chemotherapeutic regimens did not affect the survival of the patients in this group. In comparison, the survival of patients in PaP group B was extremely poor, although the S-1 plus docetaxel regimen prolonged the survival of these patients from 3 to 10 months. Although this study is retrospective and the number of objective cases is small, the docetaxel regimen may have a survival advantage in patients with a poor prognosis.

Docetaxel is reported to have a low rate of grade 3/4 leucopenia and neutropenia (19.4 and 10.6%) and rare, severe non-hematologic toxicities (18). Docetaxel chemotherapy with or without S-1 has been a suitable treatment for patients with advanced gastric cancer, advanced age or poor PS (19).

In conclusion, in the treatment of advanced non-resectable gastric cancer, the PaP score should be used to select patients and chemotherapeutic regimens. The S-1 plus docetaxel regimen is expected to improve outcomes in patients with a poor PS.

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Clinicopathologic Characteristics and Prognosis of Gastric Cancer in Young Patients

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To determine the clinicopathologic characteristics and prognosis of gastric cancer in young patients, a total of 1985 gastric cancer patients who had undergone gastrectomy at our hospital were reviewed. The male-to-female ratio was significantly lower in the young patients than in either the middle-aged ($P < 0.0001$) or elderly patients ($P < 0.0001$). Undifferentiated carcinoma was observed more frequently in the young patients compared with either the middle-aged ($P < 0.0001$) or elderly patients ($P < 0.0001$). Furthermore, peritoneal metastasis was observed more frequently in the young patients than in either the middle-aged ($P < 0.005$) or elderly patients ($P < 0.005$). Five-year survival rates were 61.0, 73.6 and 68.1% in the young, middle-aged and elderly patients, respectively. The prognosis of the middle-aged patients was significantly better than that of either the young or the elderly patients ($P < 0.05$). Multivariate analysis indicated that age was an independent prognostic factor. Peritoneal recurrence was more frequently observed in the young patients than either the middle-aged or the elderly patients ($P < 0.05$). Gastric cancer in young patients has unique characteristics, namely, a predominance of female patients and a high frequency of undifferentiated cancer and peritoneal metastasis and recurrence.

Key words: age; gastric cancer; prognosis

Gastric cancer is frequent in middle-aged and elderly populations. Although gastric cancer is rare in young populations (Okamoto et al., 1988; Mitsudomi et al., 1989), it has been reported that gastric cancer in young patients has some unique characteristics compared with that in middle-aged and elderly patients. For instance, the male-to-female ratio shows a predominance of females among younger patients (Bloss et al., 1980; Mori et al., 1985; Sandler and Holland, 1987; Tso et al., 1987). Furthermore, a significantly higher frequency of both Borrmann type 4 and poorly differentiated adenocarcinoma with a scirrhus growth pattern has been noted as a characteristic of gastric cancer in young patients (Bloss et al., 1980; Sandler and Holland, 1987; Tso et al., 1987; Okamoto et al., 1988; Mitsudomi et al., 1989). On the other hand, the prognosis of gastric cancer in young patients remains unclear thus far. The aim of the present study was to clarify the clinicopathologic characteristics and prognosis of gastric cancer in young patients.

Materials and Methods

Patients

The present study was based on a retrospective analysis of 1985 patients with gastric adenocarcinoma who underwent gastrectomy at our institution between January 1975 and December 2000. The clinicopathologic findings were determined according to the Japanese Classification of Gastric Carcinoma

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ORIGINAL ARTICLE

Increased apoptosis and elevated Fas expression in circulating natural killer cells in gastric cancer patients

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Abstract
Background Immune cells undergo extensive apoptosis in patients with cancer, which may be related to immune evasion by cancerous cells. The present study was designed to investigate the relationship between natural killer (NK) cell apoptosis and Fas expression in gastric cancer patients.
Methods NK cell apoptosis and Fas expression were evaluated by multicolor flow cytometry. Soluble Fas ligand (sFasL) was quantitated by enzyme-linked immunosorbent assay.
Results The frequency of apoptotic NK cells in gastric cancer patients was significantly higher than in normal controls ($p = 0.0016$). Moreover, their frequency was related to the progression of gastric cancer. Fas-positive NK cells were significantly more common in gastric cancer patients compared with normal controls ($p = 0.034$). Furthermore, Fas expression was closely related to the frequency of NK cell apoptosis ($r = 0.6$, $p < 0.0001$). The frequency of tumor-infiltrating NK cell apoptosis was significantly higher than that of circulating NK cell apoptosis ($p = 0.035$). Furthermore, Fas-positive NK cells in gastric cancer tissues occurred significantly more often than in peripheral blood ($p = 0.029$). FasL concentration in gastric cancer patients was lower than that in normal controls, and the difference tended to be significant ($p = 0.057$). Apoptotic circulating NK cells significantly decreased after surgery compared to before surgery ($p = 0.023$). Furthermore, Fas expression on circulating NK cells also significantly decreased after surgery compared with before surgery ($p = 0.021$).
Conclusions Upregulation of Fas expression on NK cells is related to increased apoptosis of circulating NK cells in gastric cancer patients.

Keywords Apoptosis · Fas · Fas ligand · Gastric cancer · Natural killer cells

Introduction

Natural killer (NK) cells are effector lymphocytes of the innate immune system that respond to several types of tumors and microbial infections by limiting their spread and subsequent tissue damage [1]. Because NK cells exhibit natural cytotoxicity against a broad range of human solid tumors in the absence of major histocompatibility complex molecules on target cells [2–5], they play an important role in host anticancer defense mechanisms in vitro [6] and in vivo [7, 8]. Nonetheless, NK cell immune responses are not sufficient to eradicate tumors in cases of clinical cancer because tumors develop a mechanism to escape host immune responses [9, 10]. In fact, defects in NK cell activity have been found in various cancers [11].

Gastric cancer is one of the most common malignancies. Although prognoses of patients with gastric carcinoma have improved because of better diagnostic techniques and better intraoperative and postoperative care, death from gastric cancer still ranks second among all cancer deaths worldwide [12]. Decreased NK cell activity has been observed in gastric cancer patients. Furthermore, Takeuchi et al. demonstrated that lower NK cell activity was an independent prognostic indicator in gastric cancer patients,

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suggesting a potential role for NK cells in preventing progression of gastric cancer [13]. However, the mechanism responsible for defective NK cell function in gastric cancer has yet to be defined. One possible mechanism responsible for dysfunction of immune cells in cancer patients is extensive apoptosis, such as T cells [14, 15] and NK cells [16]. Tumor cells express FasL [17], receptor-binding cancer antigen expressed on SiSo cells (RCAS1) [18], and B7-H1 [19], which induce T-cell apoptosis. It has been suggested that the Fas/Fas ligand (Fas/FasL) system plays an important role in establishing tumors with a privileged immune status by inducing Fas-mediated apoptosis in tumor-specific lymphocytes. A number of studies have demonstrated that tumor cells express FasL, which induces Fas-mediated apoptosis in T cells [17, 20, 21]. Furthermore, we have previously demonstrated that Fas expression on CD8+ T cells is closely related to the frequency of CD8+ T-cell apoptosis in gastric cancer patients [22]. On the other hand, Fas expression on NK cells remains relatively undetermined in patients with cancer. In the current study, we therefore sought to assess a potential role of Fas expression on NK cell apoptosis.

Materials and methods

Gastric cancer patients and normal donors

Thirty-eight patients treated at Tottori University Hospital (Yonago, Japan) and pathologically diagnosed with gastric cancer were enrolled in this study. None of the patients received radiotherapy, chemotherapy, or other medical interventions before surgery. International review boards at Tottori University approved the study, and informed consent for blood donations was obtained from all individuals. Patient characteristics are shown in Table 1. Healthy controls ($n = 17$) were age-matched (62.7 ± 16.1 years for the controls vs. 65.5 ± 9.9 years for patients), and each experiment was performed in parallel for controls and patients.

Table 1 Clinicopathological parameters of gastric cancer patients enrolled in the current study

	Gastric cancer patients	Normal controls
Gender		
Male	20	8
Female	18	9
Age	48–82 (65.5)	44–88 (62.7)
Depth of invasion		
T1 (early)	18	
T2/T3/T4 (advanced)	20	
Lymph node metastasis		
Absent	23	
Present	15	

Preparation of peripheral blood mononuclear cells (PBMCs)

Peripheral blood (30 ml) was drawn from each donor before surgery and centrifuged using a Ficoll-Paque (Pharmacia, Uppsala, Sweden) gradient. In 10 of the 33 patients, 30 ml peripheral blood was also drawn 1–2 months after surgery.

Isolation of tumor-infiltrating NK cells

Freshly excised tumor tissues were minced and digested with 1.5 mg/ml collagenase D (Wako Pure Chemical Industries, Osaka, Japan). The resulting cell suspensions were filtered through a mesh filter (BD, Franklin Lakes, NJ, USA). Because it is necessary to get a large piece of tissue sample to have enough tumor-infiltrating NK cells for flow cytometry analysis, tumor-infiltrating NK cells were not available for analysis from most early gastric cancer patients. Therefore, tumor-infiltrating NK cells were available in 7 patients of 38 patients in the current study.

Flow cytometry analysis

Fluorescence-activated cell sorting (FACS) analysis was performed on a FACSCalibur (BD Pharmingen, Franklin Lakes, NJ, USA), and cells were classified using the following antibodies: anti-CD3-PE-Cy5, anti-CD56-PE, and anti-CD95-FITC (BD Pharmingen).

Apoptosis in peripheral NK cells

The percentage of apoptotic cells was calculated by scoring annexin V-binding cells after back-gating of CD3−/CD56+ cells. All gated mononuclear cell subpopulations were visualized on forward angle scatter/side angle scatter (FSC/SSC) dot plots. To include all apoptotic cells and avoid debris with a high SCC signal, the gate was set to include a wide boundary of mononuclear cells because apoptotic cells accumulate mainly in the lower FSC/SSC channels. A cutoff was set using unstained control cells.

Measurement of soluble Fas ligand (sFasL)

sFasL in human sera was measured by enzyme-linked immunosorbent assay (ELISA) using human Fas ligand/TNFSF6 immunoassay (R&D Systems, Minneapolis, MN, USA).

Statistical analysis

Either paired t tests or Mann–Whitney U tests were used to determine statistical differences between groups. Correlations between NK cell apoptosis and Fas expression were analyzed using the Spearman rank correlation coefficient. $p < 0.05$ was considered significant. GraphPad Prism software (GraphPad Software, La Jolla, CA, USA) was used for statistical analyses.

Results

Apoptosis of circulating NK cells in gastric cancer patients

We first determined the frequency of apoptotic circulating NK cells in both normal controls and gastric cancer patients. The frequency of apoptotic cells in gastric cancer patients (21.3 ± 11.6 %) was significantly higher than that in normal controls (11.2 ± 5.2 %) ($p = 0.0016$; Fig. 1). The frequency of apoptotic circulating NK cells was 17.4 ± 9.8 % and 24.8 ± 12.2 % in early and advanced gastric cancer patients, respectively, and the differences were significant between early and advanced gastric cancer patients ($p = 0.037$). Furthermore, there were significant differences in the frequency of apoptotic circulating NK cells between node-negative (17.0 ± 8.4 %) and node-positive (28.0 ± 12.8 %) gastric cancer patients ($p = 0.0086$).

Fas expression on NK cells in gastric cancer patients

To determine the mechanism responsible for increased apoptosis in circulating NK cells in gastric cancer patients, we compared Fas expression on NK cells obtained from gastric cancer patients with that from normal controls. The mean (±SD) number of Fas-positive NK cells was 41.2 ± 16.9 % in gastric cancer patients compared with 29.5 ± 13.0 % in normal controls ($p = 0.034$; Fig. 2). Furthermore, Fas expression was closely related to the frequency of NK cell apoptosis ($r = 0.6$, $p < 0.0001$; Fig. 3). These findings indicate that upregulation of Fas expression on circulating NK cells may be responsible for increased NK cell apoptosis in gastric cancer patients.

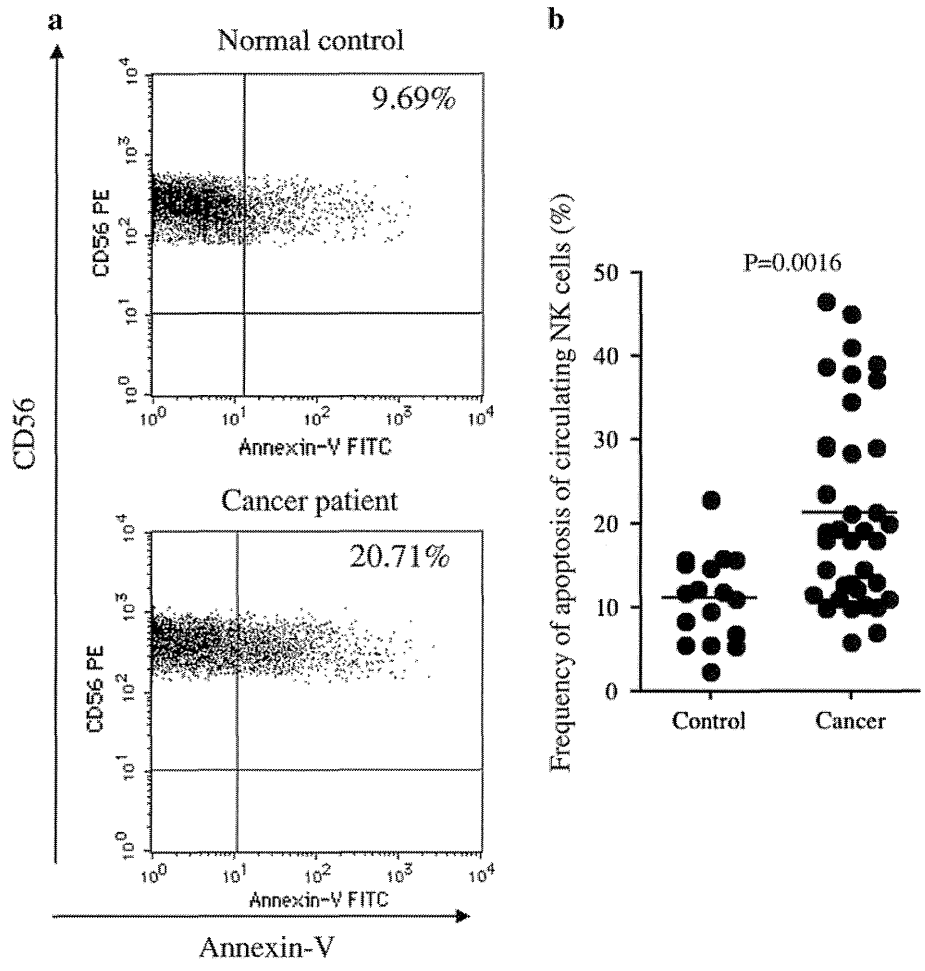

Fig. 1 **a** A representative fluorescence-activated cell sorting (FACS) result showing the frequency of apoptotic natural killer (NK) cells in normal controls and gastric cancer patients. The percentage of apoptotic cells was calculated by scoring annexin V-binding cells after back-gating of CD3−/CD56+ cells. **b** The frequency of apoptotic NK cells in gastric cancer patients was significantly higher than that in normal controls ($p = 0.0016$)

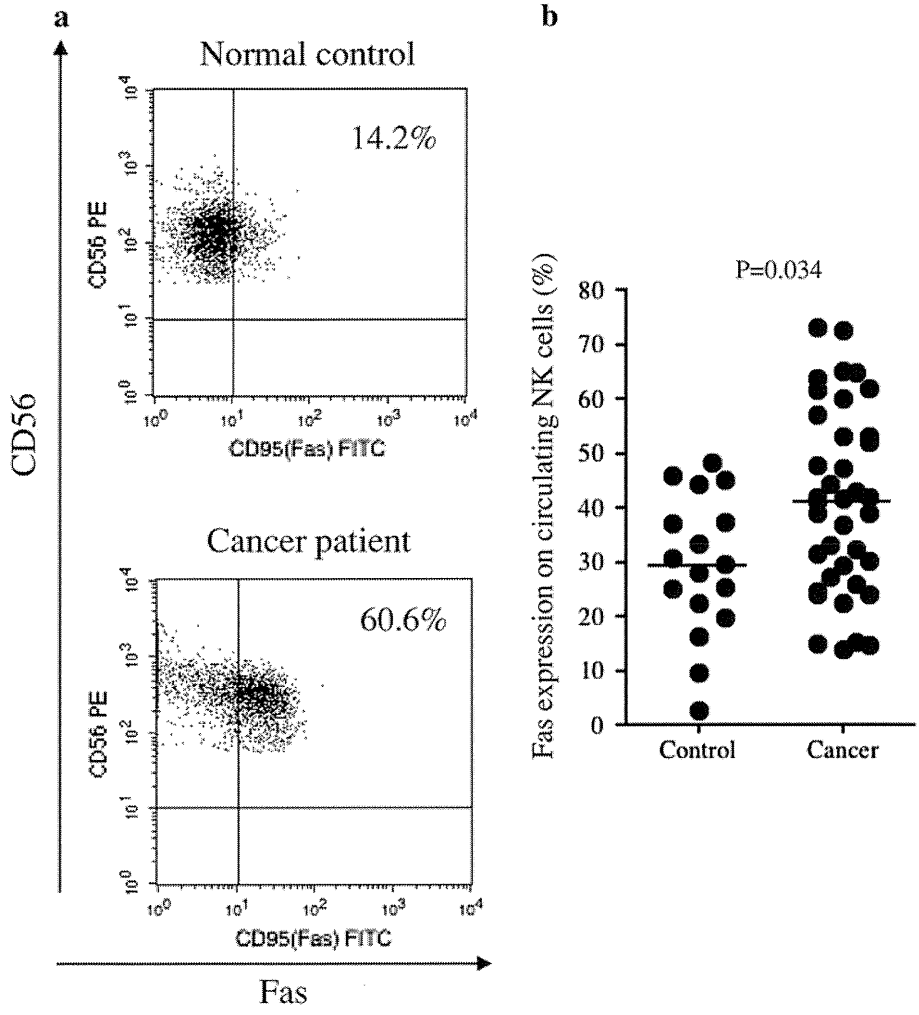

Fig. 2 **a** A representative FACS result showing Fas expression on NK cells from normal controls and gastric cancer patients. **b** Fas+ NK cell frequency in gastric cancer patients was significantly higher than that in normal controls ($p = 0.034$)

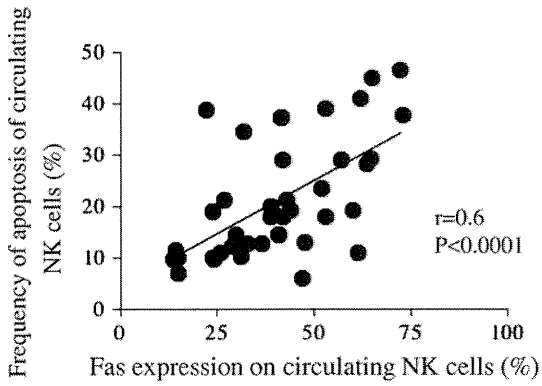

Fig. 3 The frequency of apoptotic NK cells was significantly correlated with Fas expression on NK cells ($r = 0.6$, $p < 0.0001$)

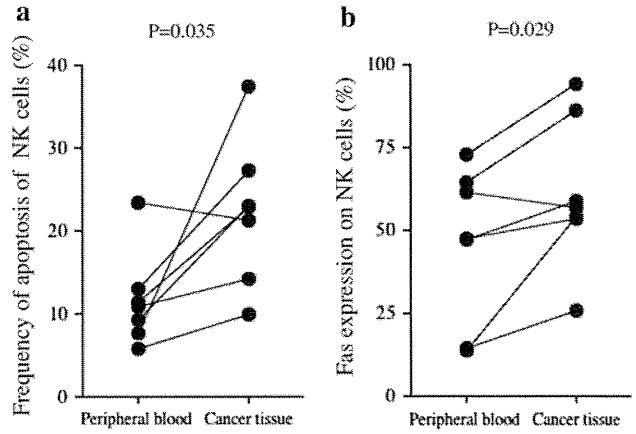

Fig. 4 **a** The frequency of tumor-infiltrating NK cell apoptosis was significantly higher than that of circulating NK cell apoptosis ($p = 0.035$). **b** Fas expression of tumor-infiltrating NK cells was significantly higher than that of circulating NK cells ($p = 0.029$)

Apoptosis and Fas expression of tumor-infiltrating NK cells

We then determined the frequency of tumor-infiltrating NK cell apoptosis and found that the frequency of tumor-infiltrating NK cell apoptosis (22.4 ± 8.9 %) was significantly higher than that of circulating NK cell apoptosis (11.7 ± 5.7 %) ($p = 0.035$; Fig. 4a). Furthermore, the mean (±SD) number of Fas-positive NK cells was

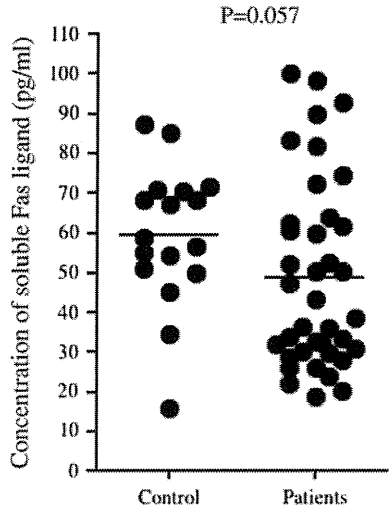

Fig. 5 The concentration of sFasL in patients with gastric cancer tended to be lower than that in normal controls ($p = 0.057$)

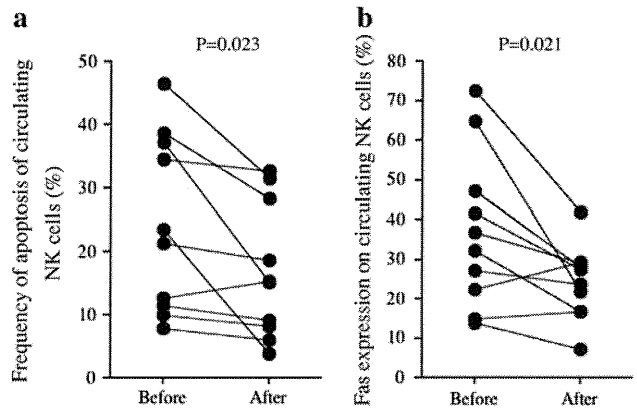

Fig. 6 **a** A significant decrease in the percentage of apoptotic NK cells was observed after surgery compared with that before surgery ($p = 0.023$). **b** A significant decrease in Fas expression on circulating NK cells was observed after surgery compared with that before surgery ($p = 0.021$). The *connecting lines* represent specimens from the same patient

61.6 ± 22.4 % in tissue of gastric cancer compared with 46.2 ± 23.6 % in peripheral blood ($p = 0.029$; Fig. 4b).

Serum concentrations of soluble Fas ligand in gastric cancer patients

To evaluate the contribution of the Fas/FasL pathway to circulating NK cell apoptosis, sFasL concentration was determined. Serum concentrations of sFasL were 48.9 ± 23.7 pg/ml and 59.4 ± 17.7 pg/ml in gastric cancer patients and controls, respectively, and the difference tended to be significant ($p = 0.057$; Fig. 5).

Decreased apoptosis and Fas expression of circulating NK cells after tumor removal

Decreased apoptosis of circulating NK cells was observed after surgery (16.9 ± 10.7 %) compared with before surgery (24.4 ± 14.0 %) ($p = 0.023$; Fig. 6a). Furthermore, Fas expression on circulating NK cells also significantly decreased after surgery (24.2 ± 9.4 %) compared with before surgery (37.4 ± 19.7 %) ($p = 0.021$; Fig. 6b).

Discussion

NK cells use inhibitory receptors to monitor constitutively expressed "self" molecules on susceptible target cells. In particular, NK cells express MHC class I-specific receptors and 'lose' inhibitory signals when encountering MHC class I-deficient hematopoietic cells in several in vitro and in vivo models [23, 24]. Because most cancer cells downregulate MHC class I expression, tumor cells are recognized as NK cell targets [1]. In fact, NK cells may participate in tumor immune surveillance, particularly in leukemia [25], neuroblastoma [26], and gastrointestinal stromal tumors [27]. However, NK cell function is suppressed in gastric cancer patients, even though gastric cancer cells exhibit decreased MHC class I expression [28]. This result suggests other mechanisms are responsible for the NK cell dysfunction observed in gastric cancer.

In the current study, we determined the frequency of NK cell apoptosis to assess one potential mechanism of immune evasion by gastric cancer cells. We observed more frequent NK cell apoptosis in PBMCs obtained from gastric cancer patients than from normal donors. To examine the mechanism responsible for increased apoptosis of NK cells in more detail, we examined Fas expression in these cells. Fas, a member of the tumor necrosis factor (TNF) receptor family, is a type I membrane protein expressed by a variety of cell types. Upon cross-linking by either FasL or an agonistic anti-Fas monoclonal antibody, the Fas-associated death domain and caspase-8 form a death-inducing signaling complex; this activates the caspase cascade, resulting in apoptosis and cell death [29]. In the current study, Fas expression on circulating NK cells from gastric cancer patients was more frequent than that from normal controls. Furthermore, Fas expression was closely related to the frequency of NK cell apoptosis, indicating that increased apoptosis of circulating NK cells might be caused by elevated Fas expression.

Binding of FasL is indispensable for inducing apoptosis of Fas-positive cells. FasL is a type II transmembrane protein expressed by NK cells and activated T cells and within immune-privileged sites, such as the eye and brain [30, 31]. FasL is a member of the TNF family, which also includes TNF-α and CD40 ligand [32]. Membrane-bound FasL is expressed on the cell surface as a 37- to 42-kDa

protein that is proteolytically cleaved by matrix metalloproteinase (MMP) to generate its 26-kDa soluble form (sFasL) [33]. Song et al. [34] demonstrated that sFasL induces apoptosis of Fas+ T lymphocytes in patients with cancer. Moreover, studies have demonstrated that sFasL concentration in cancer patients is elevated compared with normal controls [35, 36]. Therefore, we examined sFasL concentration in the current study. In contrast to previous reports, we observed that sFasL concentration in patients with gastric cancer trended to be lower than that in normal controls. We therefore suspected that sFasL of these patients might be consumed by binding to Fas expressed on circulating NK cells. This result is in line with a previous report on head and neck squamous cell carcinoma, demonstrating that increased lymphocytic apoptosis is associated with low-level sFasL in the serum [14]. To our knowledge, this is the first report to show that Fas upregulation on NK cells, but not an increase in sFasL concentration, correlates with apoptosis of circulating NK cells in gastric cancer patients. Fas expression significantly decreased after surgery. Furthermore, Fas expression in tumor-infiltrating NK cells was significantly higher than that in circulating NK cells. These findings indicate that gastric cancer affects Fas expression in NK cells. However, the factor responsible for upregulating Fas on NK cells remains unclear in gastric cancer patients. In this regard, we added supernatant obtained from five different gastric cancer cell lines and serum from advanced gastric cancer patients to the culture of PBMC to determine the alteration of Fas expression on NK cells and observed no alteration of Fas expression on NK cells, indicating that soluble factor including cytokines might not be responsible for the upregulation of Fas expression on NK cells (data not shown). Further investigations to clarify the mechanisms responsible for Fas upregulation on NK cells in gastric cancer patients are urgently required.

In conclusion, a significant proportion of circulating NK cells in gastric cancer patients is eliminated by apoptosis, thus potentially weakening the antitumor defense in these patients. Our results provide new data suggesting that Fas overexpression on NK cells, but not sFasL secreted from tumor cells, is related to increased apoptosis of circulating NK cells.

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ORIGINAL ARTICLE

The central vein access port and catheter in outpatient chemotherapy for colorectal cancer: a retrospective study of 101 patients

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Abstract
Purpose The central venous access port (CV-port) system was examined in a series of colorectal cancer (CRC) patients.
Methods One hundred and one CRC patients underwent chemotherapy with the 5-fluorouracil + oxaliplatin (FOLFOX) or 5-fluorouracil + irinotecan regimen. The complications of the CV-port system were retrospectively assessed.
Results The CV-port system was placed in a total of 101 patients. The patients received a total of 1035 courses of these regimens. Eight complications occurred in the 101 patients (7.9%). The complications included three instances of catheter rupture, two thrombotic events around the catheter, and three infections at the site of the port or catheter. The complications were identified after a median of nine courses (range 6–16) and 135 days after the placement of the CV-port system. Sixty-six of the 101 patients switched their regimen from FOLFOX to another regimen, and 4 of these 66 patients (6.1%) experienced complications associated with the CV-port system. There were 25 subjects who were admitted to the hospital emergency wing during the chemotherapeutic regimens, and 4 of these patients (16%) had complications associated with the CV-port system.
Conclusions The complications of the CV-port system occurred at a defined rate, therefore the early diagnosis and the appropriate treatment to address these complications is crucial.

Keywords Colorectal cancer · Outpatient chemotherapy · Central venous access port · Complication · Pinch-off

Introduction

Completely implantable port systems were first introduced in the early 1980s. A variety of anticancer agents have been administered while using the devices without difficulty, and the patient acceptance of this system is excellent [1]. Late complications may occur, including catheter rupture and embolization, venous thrombosis, pocket infection, and port-related bacteremia. However, these devices have a long working life and a low rate of patient complications, and are of great value to patients who require long-term or cyclic intravenous treatments [2]. These data support the increasing use in current oncologic medical practices. The gastrointestinal division originally used the central venous access port (CV-port) system, either for administering chemotherapy to patients with gastric cancer, to provide nourishment to patients with short bowel syndrome, or for the treatment of patients with other conditions. The CV-port system has been extensively used since its introduction in colorectal cancer (CRC) patients receiving the 5-fluorouracil + oxaliplatin (FOLFOX) or 5-fluorouracil + irinotecan (FOLFIRI) + bevacizumab [3] chemotherapy.

A summary of this study was presented at the 108th Annual Meeting of the Japan Surgical Society in 2008 and the 46th Annual Meeting of the Japan Society of Clinical Oncology in 2008.

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Patients and methods

Patients and chemotherapeutic regimens

One hundred and three CRC patients underwent FOLFOX or FOLFIRI chemotherapy between April 2005 and March 2008 at our institution. One hundred and one of the 103 patients (98%) underwent CV-port system placement. Two patients could not receive the CV-port, because one patient had a mechanical valve and the other experienced difficulty in the placement of the CV-port. The 101 remaining patients (range 27–82 years of age, with a median age of 62 years) underwent chemotherapy for unresectable metastatic CRC, and also underwent adjuvant chemotherapy following hepatectomy. The regimens consisted of the modified FOLFOX-6 (m-FOLFOX 6), FOLFOX-4, or FOLFIRI regimens. The regimens consisted of a continuous infusion of 5-fluorouracil (5-FU) using a portable disposable pump, which was manufactured by Baxter (Deerfield, IL, USA).

Ports and routes of access to the central vein and maintenance of ports

Central venous access ports were placed by surgeons in the CRC patients. An indwelling catheter was inserted from the right subclavian vein at the lateral side using diagnostic imaging guidance and fluoroscopy to confirm that the catheter was placed in the superior vena cava. The ports were placed at the jugular vein or the inguinal vein if the surgeon experienced difficulty placing it in the subclavian vein. All 101 patients had a single-lumen Groshong 8-F catheter and an MRI-Port (CR Bard, Summit, NJ, USA) implanted. The first one or two courses of the regimen were administered while the patients were hospitalized in order to monitor any adverse events. The CV-port was put in place, and the patients were educated about the chemotherapy. After one or two courses of chemotherapy in the hospital, the patients underwent chemotherapy every 2 weeks as outpatients. Their ports were punctured by a doctor with a Huber-pointed needle. The doctor confirmed whether there was redness, swelling, or pain around the port, and confirmed that the natural drip was smooth before the patient was connected to the pump. The state of the catheter was regularly checked with chest X-rays every 3 months. The needle was removed without a saline flush after chemotherapy by the patients themselves or their family doctor.

The frequency and types of complications involving CV-ports and catheters were retrospectively evaluated. We also examined the instances of emergency hospital outpatient admission during chemotherapy and the reasons for changing to other regimens. The purpose of the present study was to demonstrate the placement methods and maintenance of the CV-port system for preventing and identifying late complications.

Results

A total of 101 patients underwent the FOLFOX regimen, and a total of 750 courses were administered (median 8 courses per patient). Forty of the 101 patients also received the FOLFIRI regimen, and a total of 270 courses were administered (median 6 courses). An overall total of 1035 courses were administered (median 10). Eight patients had central vein access port and catheter complications (7.9%). The complications associated with the central vain access port and catheter occurred at a median of 9 courses (range 6–16) and at a median time of 135 days after putting the CV-port system in place (Table 1).

Table 1 Complications of the central venous access port and catheter

	Total patients	Patients with complications
Number of patients	101	8
Sex, male/female	66/35	6/2
Age, median (range)	62 (27–82)	69 (65–81)
Courses of chemotherapy, median (range)	10 (1–25)	9 (6–16)

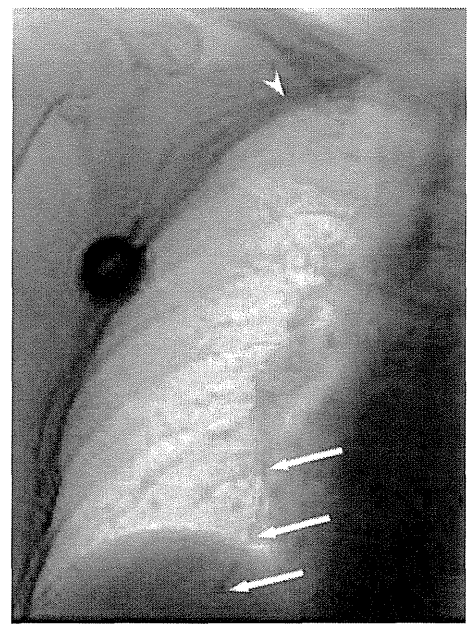

Fig. 1 Pinch-off syndrome and fracture of the catheter. The catheter was transected between the clavicle and the first rib (*arrowhead*), and the tip of the catheter was wedged into the pulmonary artery (*arrow*)

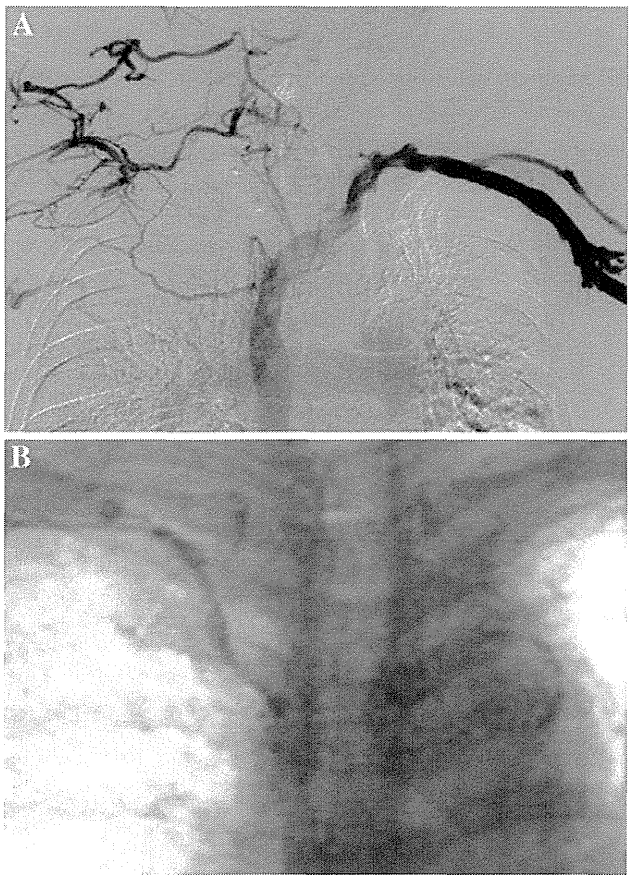

Fig. 2 A case of thrombosis around the site of the catheter (fibrin-sheath formation). **a** Contrast medium was injected from the bilateral median veins; however, the contrasting effect was not seen in the right subclavian vein, and it was concluded that a collateral pathway had developed. **b** There was no outflow of contrast media from the catheter tip, and a light contrasting effect was observed around the catheter

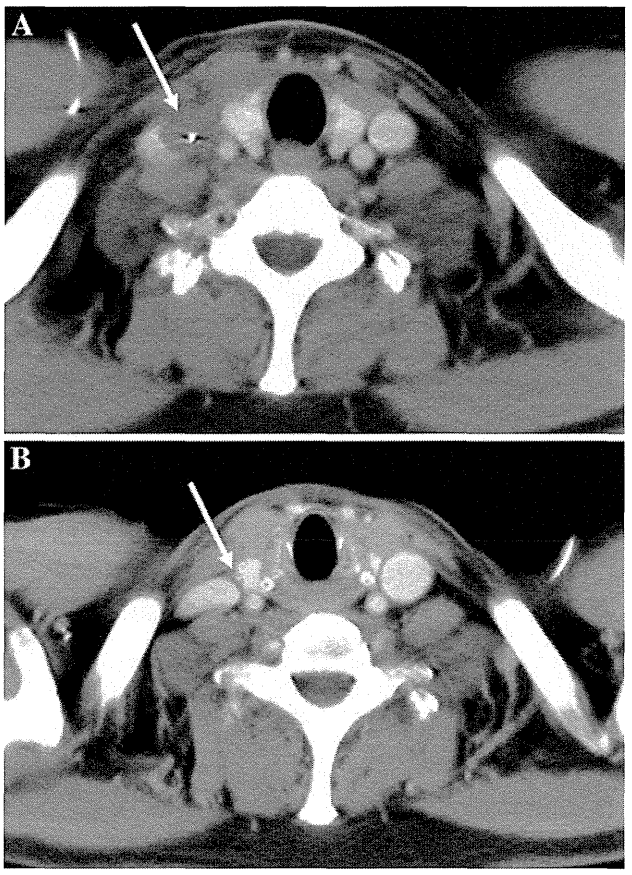

Fig. 3 Cases of thrombosis in the internal jugular vein. **a** The tip of the catheter was detected in an internal jugular vein and there was thrombosis around the catheter (*arrow*), as observed on contrast computed tomography. **b** Thrombosis in the internal jugular vein improved (*arrow*) after 5 months of warfarin treatment

The incidents involved catheter pinch-off syndrome (POS) and fracture of the catheter ($n = 1$, Fig. 1), thrombosis around the catheter ($n = 2$, Figs. 2, 3), the connection portion of the port and catheter coming off ($n = 1$, Fig. 4), the flexure of the catheter ($n = 1$, Fig. 5), and the infection of the site of the port or catheter ($n = 3$) (Table 2).

Sixty-six of the 101 patients changed their regimen from FOLFOX to other regimens. Thirty-seven subjects were switched because of progressive disease (56.1%), 22 patients switched due to an adverse event (33.3%), and 4 patients were switched because of complications associated with the CV-port system (6.1%). The adverse events included peripheral neuropathy in 13 patients (19.7%), allergy in 5 patients (7.6%), and myelosuppression, interstitial pneumonia, and one patient's request (Table 3).

There were 25 patients admitted to the emergency department during the FOLFOX or FOLFIRI chemotherapeutic

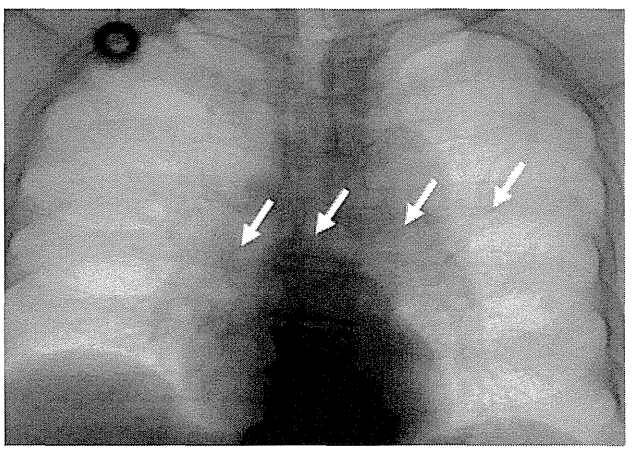

Fig. 4 Port connector rupture, connection portion coming off. The catheter was wedged into the pulmonary artery (*arrow*). The catheter was not fractured, and the rupture was judged to be caused by the catheter separating from the port connector

regimen, and 3 of 25 patients (12.5%) had adverse effects including pyrexia with neutropenia, severe anorexia, and acute exacerbation of interstitial pneumonia. However,

4 subjects (16.7%) required an emergency hospital admission due to complications associated with the CV-port system (Table 4).

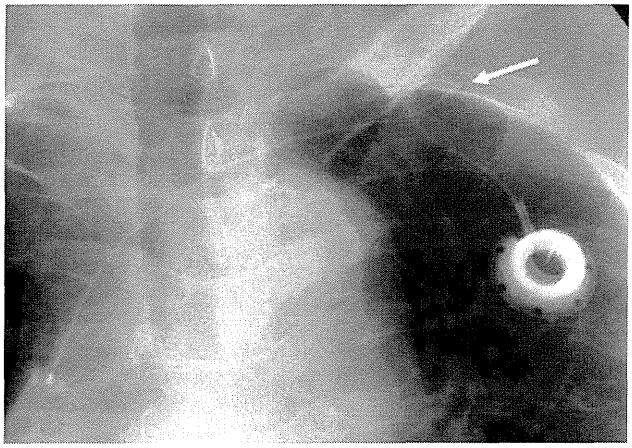

Fig. 5 Flexure and obstruction of the catheter. The catheter was bent in the subcutis (*arrow*), not in the subclavian vein, and was therefore manually repositioned

Discussion

FOLFOX or FOLFIRI regimen administration with a continuous infusion of 5-FU may be switched to a combination of an oral anticancer drug, such as S-1 or capecitabine, with irinotecan or oxaliplatin (IRIS, XELOX, etc.) [4–6]. However, the FOLFOX and FOLFIRI regimens are administered to CRC patients because there is a large amount of evidence indicating the efficacy, safety, and feasibility of these regimens.

Complications have been associated with the long-term placement of a CV-port and catheter [7–10]. The current series demonstrated complications in 8 of 101 patients (7.9%). The frequency of complications that occurred in association with the CV-port system during the chemotherapeutic treatment of outpatients in the present study was consistent with past reports. Several CRC patients required hospitalization for complications associated with the catheter. Furthermore, the complications of the CV-port and catheter caused some patients to change to another regimen (6.1%) or to require emergency treatment (16.7%). Outpatient chemotherapy was safely performed for the

Table 2 Summary of complications of central venous access-ports or catheters, excluding three patients with a catheter infection

Age (years)/sex	Chief complaint	Complication	Treatment
71/F (9)[a]	Pain around the port	Pinch off syndrome	Extraction of the catheter by interventional radiology
		Fracture of the catheter	Change to IRIS regimen
68/M (5)	Pain around the port	Thrombosis	Extraction of the catheter
		Fibrin sheath formation	Change to IRIS regimen
62/M (9)	Right neck pain	Thrombosis, dislocation	Extraction of the catheter
		Right internal jugular vein	Anticoagulant and change to the IRIS regimen
73/M (11)	Swelling around port	Port connector rupture	Extraction of the catheter by interventional radiology
		Connection portion coming off	Catheter replacement
81/M (13)	Poor infusion	Flexure of the catheter	Repositioning: stretch the catheter out
		Bent in subcutis	

IRIS regimen: combination therapy of S-1 and irinotecan

[a] Courses of chemotherapy in parentheses

Table 3 Reasons for changing from the FOLFOX regimen to another regimen

Reason ($n = 66$)	Number	Percentage	Age (years) Median	Sex M/F	Courses of chemotherapy
Progressive disease	37	56.1	61	24/13	8
Adverse events	22	33.3			
Peripheral neuropathy	13	19.7	63	10/3	10
Allergy	5	7.6	55	2/3	10
Myelosuppression	2	3.0	58	2/1	4
Interstitial pneumonia	1	1.5	75	1/0	8
Patient's request	1	1.5	44	0/1	2
Complication of CV-port system	4	6.1	69	3/1	12
Others	3	4.5	61	2/1	10

FOLFOX 5-fluorouracil + oxaliplatin, *CV-port* central venous access port

Table 4 Emergency hospital admissions during FOLFOX or FOLFIRI chemotherapy

Reason ($n = 25$)	Number	Percentage
Progressive disease	9	36
Adverse events	3	12
Peripheral neuropathy	0	0
Allergy	0	0
Myelosuppression	0	0
Interstitial pneumonia	1	4
Pyrexia with the neutropenia	1	4
Severe anorexia	1	4
Complication of CV-port system	4	16
Surgical site infection	2	8
Others	7	28

FOLFOX 5-fluorouracil + oxaliplatin, *FOLFIRI* 5-fluorouracil + irinotecan, *CV-port* central venous access port

majority of cases in our hospital. However, some issues remained, such as the occurrence of complications associated with the CV-port system, which led to changes to either another treatment regimen or to emergency hospital admission. These complications associated with the port and catheter included three instances of catheter rupture and embolization, venous thrombosis, and infection. We herein discuss the placement methods, the appropriate maintenance of CV-ports, and the measures taken to address these complications when they occur.

Catheter rupture and embolization

Pinch-off syndrome occurs when the CV access devices placed via the subclavian vein become obstructed due to thrombosis, impingement against a vein wall, or compression between the clavicle and the first rib. Luminal narrowing and complete catheter fracture occur in approximately 1% of catheter placements [11]. One case of catheter pinch-off was experienced at our institution during the study period. The patient did not report an active exercise history, but the subject had a small physique, weighed 45 kg, and was 145 cm in height. A catheter tip measuring 5 cm in length caused an embolus to a pulmonary artery. The catheter was withdrawn with a snare from the right inguinal vein by a radiologist. A puncture point is important to avoid pinch-off points. The catheter should be preferentially placed on the lateral side of the subclavian vein or in the internal jugular vein to avoid a pinch-off point [12]. Peripheral arm ports have been implanted in some CRC patients with no incidences of catheter POS [13]. The supraclavicular technique provides the best results with regard to the percutaneous introduction of large-bore central venous catheters [14]. At our institution, the most general approach from the right subclavian vein is the first choice of a puncture. There are no reports of cases that have an increased tendency to have pinch-offs, but we perform a puncture from another portion; namely, the right supraclavian vein or left subclavian vein, not the right subclavian vein, due to the fact that patients who actively exercise or have a small physique may experience POS.

Port connector rupture is usually caused by the method used to place the CV-port device. The method for connecting a port and catheter varies with the CV-port device, and the surgeon must confirm the type of CV-port device and the method used to ensure a proper connection.

Venous thrombosis

Catheter-related central venous thrombosis (CRCVT) occurs at a rate of 12–66% [15, 16]. In a prospective study, CRCVT was observed in 63 of 95 (66%) patients; however, it was symptomatic in only 4 of 63 (6%) of these patients [15]. There is no prognostic marker for venous thrombotic complications [16]. Three recent clinical trials investigated the effects of prophylactic anticoagulation with either low molecular weight heparin or low dose warfarin in cancer patients who had central venous devices [17–19]. However, these studies did not support the routine use of prophylactic anticoagulation in cancer patients with venous catheters to prevent catheter-induced thrombosis. Based on these results, routine anticoagulation is not recommended [20]. Anticoagulant administration just after the placement of the CV-port system is not used in our hospital. Two thrombosis cases were detected at our institution during the study period. These patients were diagnosed by injecting contrast media from the port and median vein on the port insertion side. The IRIS regimen (a combination therapy of the oral anticancer drug S-1 and irinotecan) was administered for the current patient series when the CV-port could not be replaced due to thrombosis. In the present study, thrombosis improved after the administration of anticoagulant therapy. Both patients had the CV-port system put in place again, and the FOLFOX regimen was restarted.

Infection

A diagnosis of a catheter-related infection might be difficult in the absence of local signs of inflammation [21]. Routine device removal is not recommended for most patients. Empirical antibiotics are administered when the patient presents with sepsis or septic shock. Port systems must be removed in case of a persistent relapse of infection after antibiotic treatment, at signs of port or catheter tunnel infection, for unstable patients, or after the development of systemic complications [22, 23]. However, CRC patients undergoing perioperative chemotherapy have had highly

invasive surgery, and the general opinion is that these guidelines do not apply to most of these patients. A high fever after CRC resection is usually attributable to an infection at the surgical site or an infection of the CV-port system. In our hospital we experienced a patient who demonstrated complications associated with a biliary fistula after hepatectomy, who continued to have a high fever after antibiotic treatment. The CV-port system was withdrawn, but no bacteria were detected on the catheter. However, we thought that the CV-port system should be withdrawn in such a case, contrary to popular opinion.

In conclusion, the management of the CV-port system is an important factor in the administration of chemotherapy to outpatients with CRC. We have described proper CV-port system placement and have summarized a recent report about the tendencies of port complications. We have also explained measures that were used to treat the complications in our experimental cases. The chemotherapeutic treatment of outpatients with the CV-port system is therefore best performed when the physicians are aware of these complications and how to best treat patients for CV-port complications without compromising their anticancer treatment.

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ORIGINAL ARTICLE

A randomized phase-II trial comparing sequential and concurrent paclitaxel with oral or parenteral fluorinated pyrimidines for advanced or metastatic gastric cancer

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Abstract
Background The purpose of this study was twofold: (1) to compare S-1 with infusional 5-fluorouracil (FU) to determine which would be a better partner of paclitaxel (PTX), and (2) to compare a concurrent strategy with a sequential one, the latter strategy being the one that is widely used in Japanese general practice.
Methods The 161 eligible patients were randomized into four arms to receive the following regimens: A (sequential), intravenous 5-FU at 800 mg/m^2 for 5 days every 4 weeks followed by weekly PTX at 80 mg/m^2; B (sequential), S-1 at 80 mg/m^2 for 4 weeks and 2-week rest followed by PTX; C (concurrent), intravenous 5-FU at 600 mg/m^2 for 5 days and weekly PTX at 80 mg/m^2 every 4 weeks; and D (concurrent), S-1 for 14 days and PTX at 50 mg/m^2 on days 1 and 8 every 3 weeks. The primary endpoint was the overall survival (OS) rate at 10 months.
Results The ten-month OS rates in arms A, B, C, and D were 63, 65, 61, and 73%, respectively. The OS was best in the concurrent S-1/PTX arm, with a mean survival time of

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