INTRODUCTION

Pancreatic cancer is one of the most lethal human cancers. It is the fifth most common cancer and the fourth leading cause of cancer-related mortality worldwide, with a 5-year survival of rate less than 5% in all stages\(^1\).\(^2\).

Complete resection is essential for obtaining a cure for pancreatic cancer. However, patients with pancreatic cancer often develop tumor recurrence, even after complete curative resection. Therefore, it is important to identify prognostic factors for pancreatic cancer in order to select candidates for more aggressive treatment. Previously, clinicopathological factors, such as the tumor size and lymph node metastasis, were reported to be significant prognostic factors that may be used to predict survival in subjects with pancreatic cancer\(^3\).\(^4\).\(^5\).\(^6\).\(^7\).\(^8\).\(^9\).\(^10\).\(^11\). However, these reports only analyzed patients treated with surgery alone or surgery followed by adjuvant chemotherapy of unknown efficacy, as effective adjuvant chemotherapy regimens have not been verified in these patients.

Several investigators have conducted randomized controlled studies of adjuvant chemotherapy after pancreatic cancer resection. As a result of the European Study Group for Pancreatic Cancer (ESPAC)-1 and 3 trials and the Charite Onkologie 001 (CONKO-001) trial, adjuvant chemotherapy with gemcitabine (GEM) has become accepted as the standard treatment for patients with resected pancreatic cancer treated with surgery alone\(^8\).\(^9\).\(^10\).

Recently, Uesaka et al. reported the findings of a randomized phase III study of GEM vs S-1 in patients with pancreatic cancer treated with curative resection followed by adjuvant chemotherapy with S-1. The present results suggest that adjuvant chemotherapy with S-1 is not sufficient, especially in patients with relevant risk factors.

Key Words: pancreatic cancer, tumor size, adjuvant chemotherapy, S-1

(Received March 3, 2017; Accepted March 17, 2017)
S-1. As to the results of the JASAPC-01 trial, adjuvant chemotherapy with S-1 after curative surgery is now considered the standard therapy for such patients in Japan. Theoretically, adjuvant chemotherapy improves patient survival by inhibiting micrometastasis. In addition, the patterns and incidence of recurrence change after the administration of adjuvant chemotherapy\(^\text{10}\). Therefore, prognostic factors may be altered following treatment with S-1 adjuvant chemotherapy.

In this retrospective and exploratory study, we investigated prognostic factors in patients with pancreatic cancer who underwent curative resection followed by adjuvant chemotherapy with S-1.

**PATIENTS AND METHODS**

**Patients**

The subjects were selected based on the medical records of consecutive patients who underwent pancreatic surgery at Kanagawa Cancer Center between 2007 and 2014 according to the following criteria: (1) a diagnosis of a pathologically common type of pancreatic cancer according to the International Union Against Cancer TNM 6th edition\(^\text{12}\); (2) a history of extended radical resection for pancreatic cancer as the initial treatment, after which R0 or R1 resection was achieved; (3) treatment with S-1 adjuvant chemotherapy. The resected specimens were examined histopathologically and staged according to the TNM 6th edition. Patients with other pancreatic or periampullary neoplasms, such as intraductal papillary mucinous neoplasms, cystadenocarcinoma and endocrine tumors, were excluded.

**Adjuvant chemotherapy**

The patients received S-1 chemotherapy and were followed on an out-patient basis. Two groups of patients received S-1: (1) as a test arm of the JASPAC-01 trial and (2) as part of general clinical practice. The patients who were registered in the JASPAC-01 trial received 40 mg of S-1 per square meter of body surface area twice a day for four weeks, followed by two weeks of rest as one course (six-week schedule), and this regimen was continued for six months after surgery. The remaining patients received S-1 at the same dose as part of routine clinical practice for six months following the protocol of the JASPAC-01 trial after the results of the study were reported. Patients with a body surface area of < 1.25 m\(^2\) received 80 mg daily, those with a body surface area of 1.25 m\(^2\) or more and less than 1.5 m\(^2\) received 100 mg daily and those with a body surface area of 1.5 m\(^2\) or more received 120 mg daily. The need for a reduction in the starting dose, suspension or delay in treatment or dose reduction was determined according to the protocol for the clinical trial for patients registered in the JASPAC-01 trial\(^\text{10}\). The need for a reduction in the starting dose, delay in treatment or dose reduction in the patients who received S-1 in clinical practice was determined based on the findings of the JASPAC-01 trial.

**Follow-up**

The patients were followed up at outpatient clinics. Hematological tests and physical examinations were performed at least every two weeks during treatment with adjuvant chemotherapy and at least every three months for five years after completing the adjuvant chemotherapy regimen. The levels of the tumor markers CEA and CA19-9 were measured at least every three months for five years. All patients underwent CT examinations every three months during the first three years after surgery and then every six months until five years after surgery.

**Evaluations and statistical analysis**

Overall survival (OS) was defined as the period between surgery and death. Recurrence-free survival (RFS) was defined as the period between surgery and the occurrence of an event, recurrence or death, whichever came first. The data for patients who did not experience an event were censored as of the date of the final observation. OS and RFS curves were calculated according to the Kaplan-Meier method and compared using the log-rank test. In order to identify risk factors for oncological outcomes such as death or recurrence, the univariate and multivariate analyses using Cox proportional hazard model were performed; the analyses included several patients’ characteristics or clinicopathological findings as explanatory variables that could be potential risk for survival events. A P value of < 0.05 was defined as being statistically significant. The survival data were obtained from hospital records or the city registry system. The SPSS software package (v11.0 J Win, SPSS, Chicago, IL) was used for all statistical analyses. The study was approved by the Institutional Review Board Committee of Kanagawa Cancer Center.

**RESULTS**

**Patients**

Seventy-six patients were eligible for the present study. All patients had received S-1 as the standard therapy after 2013 when the results of the JASPAC-01 trial were presented or as the test treatment in the clinical trial of the JASPAC-01 study. The patients’ ages ranged from 46 to 81 years (median: 70 years); 45 patients were male and 31 were female. The type of surgery was distal pancreatectomy in 23 patients, pancreaticoduodenectomy in 46 patients and total pancreatic resection in seven patients. The pathological stage was IA in two patients, IB in one patient, IIA in 20 patients and IIB in 53 patients. The median follow-up period was 15.2 months (2.5–95.8 months). The S-1 treatment was continued for two
months in 61 patients, four months in 49 patients and six months in 44 patients.

**Overall survival analysis**

When the overall survival (OS) stratified according to the clinical factors was compared using the log-rank test, significant differences were observed in regard to the pathological tumor size (Table 1). The clinicopathological factors were categorized as shown in Table 2 and analyzed for prognostic significance. The univariate analyses of OS demonstrated the pathological tumor diameter to be a significant prognostic factor, whereas lymphatic invasion and lymph node recurrence were only marginally significant. The pathological tumor size was selected for the evaluation in the final model using a multivariate analysis (Table 2). The 1-year and 3-year overall survival rates were 83.7% and 40.5% in the pathological tumor size < 60 mm group and 30.0% and 0% in the pathological tumor size ≥ 60 mm group, respectively (p=0.010) (Fig. 1).

**Recurrence survival analysis**

The clinicopathological factors were categorized as shown in Table 3 and analyzed for prognostic significance. The univariate analyses of RFS identified the pathological tumor size as a significant prognostic factor, while age, lymph node metastasis and lymphatic invasion were only marginally significant. The pathological tumor size was selected for inclusion in the final model with a cutoff value of 40 mm for the tumor size. The authors found that overall survival rates and found that the tumor size was a significant prognostic factor, although it did not reach statistical significance in the multivariate analysis. The current results suggest that nodal metastasis may be an inferior prognostic factor compared to the pathological tumor size when the examination is limited to patients who receive S-1 adjuvant chemotherapy. However, the marginal significance might become more important if the number of patients and inter-institutional variability.

Lymph node metastasis is also considered to be a strong prognostic factor in pancreatic cancer patients. For example, Richter et al. examined 194 patients with pancreatic cancer and found that in cases of curative resection (R0), the presence of lymph node metastasis has prognostic significance according to a multivariate analysis. The 5-year survival rate for node-negative patients after curative resection is 37%, while that of node-positive patients is 19.9% (p=0.005). Moreover, Shimada et al. examined 88 patients with pancreatic cancer and found the presence of lymph node metastasis to have prognostic significance in both uni- and multivariate analyses. In the present study, nodal metastasis was found to be a marginally significant factor according to a univariate analysis, although it did not reach statistical significance in the multivariate analysis. The current results suggest that nodal metastasis may be an inferior prognostic factor compared to the pathological tumor size when the examination is limited to patients who receive S-1 chemotherapy. However, the marginal significance might become more important if the number of patients and inter-institutional variability.

**DISCUSSION**

In this report, we first evaluated potential prognostic factors in patients undergoing curative resection followed by adjuvant chemotherapy with S-1 and clarified that the pathological tumor size is the most important prognostic factor based on the hazard ratio and p values.

Previous some authors have reported the significance of the pathological tumor size in terms of the prognosis of pancreatic cancer patients. For example, Benassai et al. examined 75 patients with pancreatic cancer and classified the subjects into groups with smaller tumors and those with larger tumors setting 30 mm as the cutoff value for the tumor size. The authors found that overall survival was markedly different between the patients with smaller and larger tumors. Mu et al. evaluated 35 patients with pancreatic cancer and divided the subjects into two groups using a cutoff value of 40 mm for the tumor size. The authors found that the prognosis of the patients with large tumors was significantly worse than that of the subjects with small tumors. Similar results have been observed in previous reports. Furthermore, analyses of 396 and 185 patients with pancreatic cancer showed that a tumor size of ≤ 2 cm is a significant prognostic factor. There are several possible ways by which larger tumors may negatively impact survival. The effect could be temporal in that larger tumors have an increased probability of micro-metastases and lymphatic spread at the time of surgery due to their long-term presence. It may also be that larger cancers reflect a more aggressive phenotype in faster growing de-differentiated tumors. Obtaining suitable oncological clearance in cases of larger tumors may also contribute to decreased survival. On the other hand, in the current study evaluating patients who received S-1 adjuvant chemotherapy, we set the cutoff value at 60 mm according to the 1- and 3-year overall survival rates and found that the tumor size was a strong independent prognostic factor. The optimal cutoff value is different between previous and the present report, which may be explained by the use of S-1 adjuvant chemotherapy, duration of the follow-up period, number of patients and inter-institutional variability.

Risk factor for pancreatic cancer followed by S-1化疗
Table 1  Comparison of survival rates stratified by patient characteristics

| Characteristics                  | No. of patients (%) | 1 year survival rate (%) | 3 year survival rate (%) | P value |
|----------------------------------|---------------------|--------------------------|--------------------------|---------|
| Age (years)                      |                     |                          |                          |         |
| < 70                             | 35 (46.0%)          | 75.2                     | 41.7                     | 0.8192  |
| ≥ 70                             | 41 (54.0%)          | 74.1                     | 47.8                     |         |
| Gender                           |                     |                          |                          | 0.6669  |
| Male                             | 45 (59.2%)          | 78.7                     | 29.2                     |         |
| Female                           | 31 (40.8%)          | 77.4                     | 23.2                     |         |
| ASA PS                           |                     |                          |                          | 0.1163  |
| 1                                | 7 (9.2%)            | 57.1                     | 57.1                     |         |
| 2-3                              | 69 (90.8%)          | 80.0                     | 37.0                     |         |
| Site of tumor                    |                     |                          |                          | 0.9672  |
| Head                             | 53 (69.7%)          | 77.3                     | 38.2                     |         |
| Body or tail                     | 23 (30.3%)          | 80.2                     | 33.4                     |         |
| Pathological tumor diameter (mm) |                     |                          |                          | 0.0242  |
| < 20                             | 6 (7.9%)            | 100                      | 100                      |         |
| ≥ 20 to < 40                     | 49 (64.5%)          | 86.2                     | 37.0                     |         |
| ≥ 40 to < 60                     | 10 (13.1%)          | 70.0                     | 35.0                     |         |
| ≥ 60                             | 11 (14.5%)          | 30.0                     | 0                        |         |
| Histological type                |                     |                          |                          | 0.3752  |
| well-mod                         | 65 (85.5%)          | 80.1                     | 36.0                     |         |
| poorly                            | 11 (14.5%)          | 70.7                     | 70.7                     |         |
| UICC T status                    |                     |                          |                          | 0.3523  |
| T1 or T2                         | 3 (3.9%)            | 100                      | 100                      |         |
| T3                               | 73 (96.1%)          | 77.1                     | 35.4                     |         |
| Lymph node metastasis            |                     |                          |                          | 0.1163  |
| N0                               | 23 (30.3%)          | 86.7                     | 74.3                     |         |
| N1                               | 53 (69.7%)          | 74.9                     | 28.1                     |         |
| Lymphatic invasion               |                     |                          |                          | 0.0807  |
| Negative                         | 38 (50.0%)          | 78.0                     | 43.3                     |         |
| Positive                         | 38 (50.0%)          | 73.3                     | 27.4                     |         |
| Vascular invasion                |                     |                          |                          | 0.2646  |
| Negative                         | 11 (14.5%)          | 90.0                     | 90.0                     |         |
| Positive                         | 65 (85.5%)          | 76.1                     | 28.2                     |         |

ASA-PS: ASA physical status, UICC: Union for International Cancer Control

Fig. 1  Comparison the overall survival between the pathological tumor size < 60 mm group and the pathological tumor size ≥ 60 mm group.
### Table 2: Uni and Multivariate Cox proportional hazards analysis of clinicopathological factors for overall survival

| Factors                                      | Number | Univariate analysis | Multivariate analysis |
|----------------------------------------------|--------|---------------------|-----------------------|
|                                             |        | OR                  | 95% CI                | P value   | OR                  | 95% CI                | P value   |
| **Age (years)**                              |        |                     |                       |           |                     |                       |           |
| 70 ≤ -                                       | 41     | 1.000               |                       | 0.819     |                     |                       |           |
| - < 70                                       | 35     | 1.036               | 0.476-2.557           |           |                     |                       |           |
| **Gender**                                   |        |                     |                       | 0.667     |                     |                       |           |
| Male                                         | 45     | 1.000               |                       |           |                     |                       |           |
| Female                                       | 31     | 1.207               | 0.512-2.848           |           |                     |                       |           |
| **ASA PS**                                   |        |                     |                       | 0.138     |                     |                       |           |
| 1                                            | 7      | 1.000               |                       |           |                     |                       |           |
| 2-3                                          | 69     | 3.278               | 0.683-15.737          |           |                     |                       |           |
| **Pathological Tumor diameter (mm)**         |        |                     |                       | 0.100     |                     | 1.000                 | 0.100     |
| - < 60                                       | 65     | 1.000               |                       |           |                     |                       |           |
| 60 ≤ -                                       | 11     | 4.291               | 1.427-12.904          |           |                     | 4.291                 | 1.427-12.904 |
| **Site of tumor**                            |        |                     |                       | 0.967     |                     |                       |           |
| Head                                         | 53     | 1.000               |                       |           |                     |                       |           |
| Body or Tail                                 | 23     | 1.020               | 0.397-2.618           |           |                     |                       |           |
| **Histological type**                        |        |                     |                       | 0.381     |                     |                       |           |
| Well-mod                                     | 65     | 1.000               |                       |           |                     |                       |           |
| Por                                          | 11     | 1.742               | 0.503-6.029           |           |                     |                       |           |
| **UICC T status**                            |        |                     |                       | 0.540     |                     |                       |           |
| T1-T2                                        | 3      | 1.000               |                       |           |                     |                       |           |
| T3                                           | 73     | 21.789              | 0.000-N/A             |           |                     |                       |           |
| **Lymph node metastases**                    |        |                     |                       | 0.130     |                     |                       |           |
| Negative                                     | 23     | 1.000               |                       |           |                     |                       |           |
| Positive                                     | 53     | 2.568               | 0.758-8.701           |           |                     |                       |           |
| **Lymphatic invasion**                       |        |                     |                       | 0.088     |                     |                       |           |
| Negative                                     | 38     | 1.000               |                       |           |                     |                       |           |
| Positive                                     | 38     | 2.117               | 0.896-5.003           |           |                     |                       |           |
| **Vascular invasion**                        |        |                     |                       | 0.277     |                     |                       |           |
| Negative                                     | 11     | 1.000               |                       |           |                     |                       |           |
| Positive                                     | 65     | 2.245               | 0.522-9.654           |           |                     |                       |           |

ASA-PS: ASA physical status, UICC: Union for International Cancer Control

### Table 3: Uni and Multivariate Cox proportional hazards analysis of clinicopathological factors for recurrence free survival

| Factors                                      | Number | Univariate analysis | Multivariate analysis |
|----------------------------------------------|--------|---------------------|-----------------------|
|                                             |        | OR                  | 95% CI                | P value   | OR                  | 95% CI                | P value   |
| **Age (years)**                              |        |                     |                       |           |                     |                       |           |
| 70 ≤ -                                       | 41     | 1.000               |                       | 0.077     | 1.000               | 1.000                 | 0.027     |
| - < 70                                       | 35     | 1.889               | 0.933-3.824           |           | 2.297               | 1.000                 | 1.100-4.797 |
| **Gender**                                   |        |                     |                       | 0.348     |                     |                       |           |
| Male                                         | 45     | 1.000               |                       |           |                     |                       |           |
| Female                                       | 31     | 1.395               | 0.696-2.794           |           |                     |                       |           |
| **ASA PS**                                   |        |                     |                       | 0.481     |                     |                       |           |
| 1                                            | 7      | 1.000               |                       |           |                     |                       |           |
| 2-3                                          | 69     | 2.057               | 0.276-15.325          |           |                     |                       |           |
| **Pathological Tumor diameter (mm)**         |        |                     |                       | 0.042     |                     |                       | 0.008     |
| - < 60                                       | 65     | 1.000               |                       |           | 1.000               | 1.000                 |           |
| 60 ≤ -                                       | 11     | 2.629               | 1.035-6.675           |           | 4.242               | 1.469-12.251          |           |
| **Site of tumor**                            |        |                     |                       | 0.122     |                     |                       |           |
| Head                                         | 23     | 1.000               |                       |           |                     |                       |           |
| Body or Tail                                 | 53     | 2.019               | 0.829-4.917           |           | 3.221               | 1.169-8.870           |           |
| **Histological type**                        |        |                     |                       | 0.130     |                     |                       |           |
| Well-mod                                     | 65     | 1.000               |                       |           |                     |                       |           |
| Por                                          | 11     | 1.995               | 0.817-4.872           |           | 2.731               | 1.005-7.422           |           |
| **UICC T status**                            |        |                     |                       | 0.535     |                     |                       |           |
| T1-T2                                        | 3      | 1.000               |                       |           |                     |                       |           |
| T3                                           | 73     | 1.881               | 0.256-13.844          |           |                     |                       |           |
| **Lymph node metastases**                    |        |                     |                       | 0.089     |                     |                       |           |
| Negative                                     | 23     | 1.000               |                       |           |                     |                       |           |
| Positive                                     | 53     | 2.160               | 0.889-5.245           |           |                     |                       |           |
| **Lymphatic invasion**                       |        |                     |                       | 0.054     |                     |                       | 0.061     |
| Negative                                     | 38     | 1.000               |                       |           | 1.000               | 1.000                 |           |
| Positive                                     | 38     | 1.975               | 0.988-3.949           |           | 3.229               | 0.947-11.016          |           |
| **Vascular invasion**                        |        |                     |                       | 0.436     |                     |                       |           |
| Negative                                     | 11     | 1.000               |                       |           |                     |                       |           |
| Positive                                     | 65     | 1.519               | 0.530-4.351           |           |                     |                       |           |

ASA-PS: ASA physical status, UICC: Union for International Cancer Control
of patients is increased or the assessment includes long-term follow-up.

Comparing the results of the JASPAC-01 trial and the present study, there are differences in the backgrounds of the patients. First, the patient characteristics were different. The median age was 66 years in the JASPAC-01 trial, while the median age was 70 years in the present study. Moreover, there were no patients with a performance status over 2 in the JASPAC-01 trial. Second, the pathological findings were different. The T status was greater in the present study (pT3, pT4, 73/76; 95%) than in the JASPAC0-1 trial (pT3, pT4, 165/187; 88%). Additionally, the incidence of nodal metastasis was higher in the present study (pN1, 53/76; 70%) than in the JASPAC0-1 trial (pN1, 120/164; 64%). However, the surgical procedure, interval from surgery to the start of adjuvant S-1 chemotherapy and resection status were similar between the present study and the JASPAC-01 trial.

There are many limitations associated with the current study. First, this was a retrospective single-center study with a small sample size. Our findings may have been observed by chance alone in this series. Second, the median follow-up period was only 15.2 months, which is not adequate to draw definitive conclusions. Third, the optimal cutoff value is unclear. In the present study, the cutoff value was set at 60 mm considering the 1- and 3-year survival rates. However, the appropriate cutoff value should be determined in further validation studies.

In conclusion, in this study, the pathological tumor size was found to be the only significant independent prognostic factor in patients treated with curative resection followed by adjuvant S-1 chemotherapy. The value of prognostic factors may therefore be altered by the use of effective adjuvant chemotherapy.

ACKNOWLEDGMENT
This work was supported, in part, by the Kanagawa Prefectural Hospitals Cancer Fund and Yokohama Foundation for the Advancement of Medical Science.

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