Comparison of adjuvant gemcitabine plus S-1 with S-1 monotherapy for pancreatic ductal adenocarcinoma: Retrospective real-world data

Abstract

Background

S-1 has been recognized as one of the standard adjuvant chemotherapies for pancreatic ductal adenocarcinoma (PDAC) in East Asia, but the optimal adjuvant chemotherapy regimen has not been determined. We aimed to compare the efficacy and safety of adjuvant gemcitabine plus S-1 (GS) with S-1 monotherapy for PDAC.

Methods

Patients with resected PDAC who received adjuvant GS or S-1 chemotherapy in Peking Union Medical College Hospital between May 2014 and May 2022 were reviewed. Data retrieved from medical records were used to evaluate efficacy and toxicity.

Results

A total of 241 patients were included, with 167 receiving GS and 74 receiving S-1. The patients who received GS were generally younger (median [range] age: 62 [36-78] versus 64 [44-87] years, p = 0.004), but chemotherapy began later (median [range] interval between chemotherapy and surgery: 49 [17-125] versus 40 [16-100] days, p < 0.001). The median disease-free survival (DFS, 15.1 versus 15.9 months, p = 0.52) and overall survival (OS, 34.8 versus 27.1 months, p = 0.34) did not differ significantly between the GS and S-1 groups, even after adjustment for the biases. However, the chemotherapy completion rate was higher in the patients treated with S-1 (52.4% versus 75.7%, p = 0.006), while grade 3-4 neutropenia occurred more frequently in the GS group (49.5% versus 18.2%, p = 0.015).

Conclusions

Adjuvant S-1 monotherapy demonstrated noninferiority to the GS regimen in DFS and OS with better tolerability for PDAC following surgery.

Keywords: Pancreatic cancer, Adjuvant chemotherapy, S-1, Gemcitabine, Real-life data
Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and lethal cancers, and is speculated to be the second leading cause of tumor-related mortality in 2030, with a 5-9% five-year survival rate [1]. Surgery is the only potential curative way for PDAC, with a 20% five-year survival rate even after R0 resection [2]. Nevertheless, the recurrence rate after radical resection remains as high as 80%, since occult tumor metastasis may occur early in PDAC even if the patients are still asymptomatic [3]. Hence, adjuvant chemotherapy following surgery is the standard of care for PDAC, since studies have proved improved survival of patients with resectable PDAC treated with adjuvant chemotherapy [4–8].

In 2013, the CONKO-001 trial comparing gemcitabine as adjuvant therapy versus observation alone in patients undergoing complete resection of pancreatic cancer, showed a statistically superior disease-free survival (DFS) and overall survival (OS) for gemcitabine (13.4 and 22.8 months, respectively) than for observation (6.7 and 20.2 months, respectively) [5]. Subsequently, in 2016 the JASPAC 01 trial comparing oral S-1 versus intravenous gemcitabine as adjuvant chemotherapy in resected pancreatic cancer, indicated a prolonged DFS and OS in the S-1 group (22.9 and 45.5 months, respectively) than that in the gemcitabine group (11.3 and 25.5 months, respectively) [4]. S-1 is a fourth-generation oral fluoropyrimidine, consisting of tegafur, gimeracil, and oteracil potassium at a 1:0.4:1 molar ratio [9]. In East Asia, both S-1 and gemcitabine are standard adjuvant chemotherapy regimens for PDAC. Furthermore, a single-arm clinical trial has confirmed that patients with PDAC receiving adjuvant gemcitabine plus S-1 (GS) chemotherapy may achieve a desirable survival outcome [10]. However, there is no head-to-head comparison of adjuvant GS with other standard regimens, and the optimal adjuvant regimen for PDAC has not been determined [11]. In this study, we aimed to compare the efficacy and safety of adjuvant GS with S-1 monotherapy for PDAC at a single institution.

Materials and methods

Patients

Patients who received adjuvant GS or S-1 chemotherapy after PDAC surgery in Peking Union Medical College Hospital (PUMCH) between May 2014 and May 2022 were reviewed using the Electronic Medical Record Analytical Database (PUMCH-EMERALD). Inclusion criteria were as follows: 1) patients with PDAC who had undergone curative-intent surgery (R0 or R1 resection); 2) received at least 1 cycle of adjuvant GS or S-1 chemotherapy; 3) age 18 years or older. The exclusion criteria were as follows: 1) died, tumor recurred, or lost of follow-up within one month after adjuvant chemotherapy initiation; 2) received any preoperative neoadjuvant therapy; 3) distant metastasis or malignant ascites was found before chemotherapy initiation; 4) survival outcomes could not be assessed; 5) combined with secondary primary tumors. Data retrieved from medical records and telephone follow-up was used to evaluate efficacy and toxicity. Consent to participate was not required due to the retrospective design and the anonymization of data.

Procedures and assessments

Testing results of carbohydrate antigen 19-9 (CA199) within one month before chemotherapy onset and after surgery were screened. R1 resection was defined as any margin ≤1 mm from tumor cells [12]. Eligibility criteria for the initiation of chemotherapy included an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1, and adequate bone marrow, liver, and renal function (leucocyte count ≥3000 cells/μL; hemoglobin concentration ≥8 g/dL; platelet count ≥100000/μL; total serum bilirubin concentration ≤3 mg/dL; serum creatinine concentration ≤1.5 mg/dL). After surgery, patients would receive adjuvant chemotherapy with 8 cycles of GS or S-1 monotherapy. Each cycle of adjuvant chemotherapy consisted of oral S-1 40 mg for body-surface area (BSA) <1.25 m², 50 mg for BSA ≥1.25 m² but <1.5 m², or 60 mg for BSA ≥1.5 m², twice per day for 14 consecutive days, followed by a 7-day pause (1 cycle). Patients in the GS group received additional intravenous gemcitabine (1000 mg/m²) on days 1 and 8 in each cycle of chemotherapy.

All patients were followed up until loss of contact or death, with a follow-up deadline of June 2022. To detect tumor recurrence, all patients were investigated by computed tomography (CT) scans and/or magnetic resonance imaging (MRI) every 3 to 6 months after surgery. OS was measured as the time from the initiation of adjuvant chemotherapy until death from any cause. DFS was defined as the time from chemotherapy onset to tumor recurrence, local-regional or distant metastases, or death due to any cause. Treatment-related adverse event (AE) severity was graded according to the Common Terminology Criteria for Adverse Events version 5.0.

Statistical analysis

Continuous or categorical variables were compared using Mann-Whitney U test or Pearson’s chi-square test and Fisher’s exact test. Survival outcome was estimated by the Kaplan-Meier method and compared using a log-rank test. Additionally, propensity-score matching (PSM) was utilized to minimize the impact of confounding factors. The propensity scores were calculated based on gender, age, tumor location, ECOG performance status score, CA199 level, histological grade, lymphovascular invasion (LVI), perineural invasion (PNI), resection margin status, and TNM stage. Furthermore, a Cox proportional hazard model was used to calculate the hazard ratios (HR) with 95% confidence intervals (CI) of variables associated with survival outcomes in patients. All statistical analyses were conducted using R software (version 3.6.1, https://www.r-project.org/). All the tests were two-sided, with statistically significant level set at p value < 0.05.

Result

Patient characteristics

A total of 241 patients were included. The baseline characteristics are shown in Table 1. Among those patients, 167 (69.3%) received GS as the adjuvant chemotherapy and 74 (30.7%) were treated with S-1 monotherapy. The median age was 63 years (range, 36-87), 54.8% of the patients were male, and 56.0/38.6% of the patients had ECOG performance status 0/1. Most patients underwent R0 resection (80.9%) and did not receive adjuvant radiotherapy after surgery (92.5%). Pathological results of surgical specimens demonstrated that 99 (41.1%), 112 (46.5%), and 30 (12.4%) patients were stage I, II, and III, respectively. Furthermore, patients treated with GS were generally younger (median [range] age: 62 [36-78] versus 64 [44-87] years, p = 0.004), but chemotherapy began later (median [range] interval between chemotherapy and surgery: 49 [17-125] versus 40 [16-100] days, p < 0.001) and the chemotherapy complete rate was lower (52.4% versus 75.7%, p = 0.006).

Efficacy

The median follow-up time was 16.7 months (range, 1.3-93.4). The median DFS (15.1 versus 15.9 months, HR 1.12 [95% CI 0.63-1.27], p = 0.524) did not differ significantly between the GS and S-1 groups (Fig. 1A). Consistently, the median OS was 34.8 months in the GS group and 27.1 months in the S-1 group (HR 0.81 [95% CI 0.53-1.24], p = 0.338) (Fig. 1B). By minimizing the influence of confounding factors using PSM, the DFS and OS were still comparable between the two treatment groups (Fig. 1C-D).
The results of the Cox analyses performed to estimate potential variables associated with DFS and OS for all 241 patients are presented in Tables 2 and 3, respectively. In the first univariate analysis for DFS, smoking history, resection margin, and CA199 concentration before chemotherapy began were associated with the DFS of patients with PDAC. Further multivariate analysis confirmed that R1 resection and elevated CA199 were independent indicators of poor DFS (Table 2). Likewise, multivariate analysis demonstrated smoking history, resection margin, and TNM stage were significantly associated with the OS of those patients (Table 3). However, adjuvant chemotherapy regimen choice (GS or S-1) was neither an independent predictor of DFS nor OS.

Subgroup analyses showed comparable DFS and OS between the adjuvant GS and S-1 groups in almost all subgroups (Fig. 2A-B). Intriguingly, patients with smoking history, positive LVI, or stage 1 PDAC receiving adjuvant GS chemotherapy may achieve prolonged OS than those receiving S-1 monotherapy (Fig. 2B). Moreover, considering some researchers are concerned that adjuvant chemotherapy is less effective in stage IA or node-negative PDAC [13, 14], survival analyses were performed after excluding patients with stage IA or nodal-negative PDAC, respectively. Nevertheless, adjuvant chemotherapy regimen choice (GS or S-1) was still not associated with survival outcomes (both DFS and OS) in patients with resected PDAC (Fig. 3A-B).

### Adverse Events

There were 117 patients with evaluable safety data. Grade 3 or 4 AEs reported in 64 of 95 (67.4%) patients receiving GS and 9 of 22 (40.9%) patients receiving S-1 monotherapy. Of those patients, grade 3 or 4 AEs frequently (≥5%) experienced in the GS group were abnormal neutrophil, leucocyte, hemoglobin, platelet, nausea, fatigue, vomiting, and rash. Grade 3 or 4 AEs frequently (≥5%) observed in the S-1 group were abnormal neutrophil, leucocyte, hemoglobin, platelet, nausea, fatigue, and vomiting (Table 4). Specially, the incidence of neutropenia in the GS group was

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**Table 1**

Baseline characteristics of all 241 included patients.

| Characteristics                                      | Adjuvant chemotherapy regimen | P-value |
|------------------------------------------------------|-------------------------------|---------|
|                                                      | GS (N = 167)                  | S-1 (N = 74) |
| Age, median (range), years                          | 62 (36, 78)                   | 64 (44, 87) | 0.004 |
| Sex, male                                           | 94 (56.3%)                    | 38 (51.4%) | 0.569 |
| ECOG performance status                             |                               |          |       |
| 0                                                    | 96 (57.5%)                    | 39 (52.7%) | <0.001|
| 1                                                    | 68 (40.7%)                    | 25 (33.8%) |          |
| Unknown                                              | 3 (1.8%)                      | 10 (13.5%) |          |
| Smoking history                                      |                               |          |       |
| Yes                                                  | 59 (35.3%)                    | 17 (23.0%) | 0.079  |
| No                                                   | 108 (64.7%)                   | 57 (77.0%) |          |
| Drinking history                                     |                               |          |       |
| Yes                                                  | 43 (25.7%)                    | 14 (18.9%) | 0.324  |
| No                                                   | 124 (74.3%)                   | 60 (81.1%) |          |
| Preoperative diabetes                                |                               |          |       |
| Yes                                                  | 51 (30.5%)                    | 22 (29.7%) | 1       |
| No                                                   | 116 (69.5%)                   | 52 (70.3%) |          |
| Tumor location                                       |                               |          |       |
| Head                                                 | 89 (53.3%)                    | 36 (48.6%) | 0.599  |
| Body or tail                                         | 78 (46.7%)                    | 38 (51.4%) |          |
| CA199, median (range), U/ml                          | 23.1 (0.6, 957)               | 18.9 (1, 278) | 0.594 |
| Histological grade                                   |                               |          |       |
| G1                                                    | 33 (19.8%)                    | 16 (21.6%) | 0.686  |
| G2                                                    | 80 (47.9%)                    | 31 (41.9%) |          |
| G3                                                    | 54 (32.3%)                    | 27 (36.5%) |          |
| Lymphovascular invasion                              |                               |          |       |
| Yes                                                  | 66 (39.5%)                    | 23 (31.1%) | 0.268  |
| No/unknown                                           | 101 (60.5%)                   | 51 (68.9%) |          |
| Perineural invasion                                  |                               |          |       |
| Yes                                                  | 123 (73.7%)                   | 57 (77.0%) | 0.693  |
| No/unknown                                           | 44 (26.3%)                    | 17 (23.0%) |          |
| Resection margin                                     |                               |          |       |
| R0                                                   | 134 (80.2%)                   | 61 (82.4%) | 0.824  |
| R1                                                   | 33 (19.8%)                    | 13 (17.6%) |          |
| TNM stage                                            |                               |          |       |
| I                                                     | 65 (38.9%)                    | 34 (45.9%) | 0.311  |
| II                                                    | 83 (49.7%)                    | 29 (39.2%) |          |
| III                                                   | 19 (11.4%)                    | 11 (14.9%) |          |
| Adjuvant radiotherapy                                |                               |          |       |
| Yes                                                  | 14 (8.4%)                     | 4 (5.4%)  | 0.585  |
| No                                                   | 153 (91.6%)                   | 70 (94.6%) |          |
| Gap between chemotherapy initiation and surgery, median (range), days | 49 (17, 125) | 40 (16, 100) | <0.001|
| Eight cycles of chemotherapy complete                | 75/143 (52.4%)                | 40/53 (75.7%) | 0.006  |
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Fig. 1. Kaplan-Meier curves of disease-free survival and overall survival in patients treated with adjuvant gemcitabine plus S-1 and S-1 monotherapy before (A, B) and after (C, D) propensity-score matching.

Table 2
Univariate and multivariate analyses of factors for disease-free survival.

| Variables                                      | Univariate analysis | Multivariate analysis |
|------------------------------------------------|---------------------|-----------------------|
|                                                 | HR (95% CI)         | P                     | HR (95% CI)         | P               |
| Age/years (years)                              | 1.01(0.99,1.03)     | 0.349                 | -                   | -               |
| Sex (Female vs. Male)                          | 0.77(0.55,1.09)     | 0.137                 | -                   | -               |
| ECOG Performance status (1 vs. 0)              | 1.12(0.78,1.62)     | 0.541                 | -                   | -               |
| Smoking history (Yes vs. No)                   | 1.44(1.01,2.05)     | **0.043**             | 1.43(0.99,2.09)     | 0.059           |
| Drinking history (Yes vs. No)                  | 1.27(0.87,1.86)     | 0.222                 | -                   | -               |
| Preoperative diabetes (Yes vs. No)             | 0.96(0.66,1.4)      | 0.827                 | -                   | -               |
| Tumor location (Head vs. Body or tail)         | 1.12(0.8,1.57)      | 0.518                 | -                   | -               |
| Elevated CA199 (Yes vs. No)                    | 1(1,1)              | **0.002**             | 1(1,1)              | **0.006**       |
| Histological grade (G2 vs. G1)                 | 1.16(0.72,1.86)     | 0.543                 | -                   | -               |
| Histological grade (G3 vs. G1)                 | 1.44(0.88,2.35)     | 0.145                 | -                   | -               |
| Lymphovascular invasion (Yes vs. No/unknown)   | 1.28(0.91,1.81)     | 0.159                 | -                   | -               |
| Perineural invasion (Yes vs. No/unknown)       | 1.2(0.81,1.77)      | 0.361                 | -                   | -               |
| Resection margin (R1 vs. R0)                   | 1.68(1.13,2.51)     | **0.011**             | 1.72(1.13,2.6)      | **0.011**       |
| TNM stage (II vs. I)                           | 1.33(0.92,1.91)     | 0.132                 | -                   | -               |
| TNM stage (III vs. I)                          | 1.08(0.6,1.93)      | 0.797                 | -                   | -               |
| Adjuvant radiotherapy (Yes vs. No)              | 0.47(0.21,1.06)     | 0.068                 | -                   | -               |
| Gap between chemotherapy initiation and surgery/days | 0.99(0.58,1)   | 0.262                 | -                   | -               |
| Regimen (GS vs. S-1)                           | 0.89(0.63,1.27)     | 0.524                 | -                   | -               |
Table 3

Univariate and multivariate analyses of factors for overall survival.

| Variables                        | Univariate analysis | Multivariate analysis |
|----------------------------------|---------------------|-----------------------|
|                                  | HR (95% CI)         | P                     | HR (95% CI)         | P   |
| Age/years                        | 1.01(0.99,1.03)     | 0.357                 | -                    | -   |
| Sex (Female vs. Male)            | 0.66(0.43,1.02)     | 0.063                 | -                    | -   |
| ECOG Performance status (1 vs. 0) | 1.44(0.92,2.29)    | 0.125                 | -                    | -   |
| Smoking history (Yes vs. No)     | 1.63(1.06,2.51)     | 0.027                 | 1.61(1.04,2.48)      | 0.031 |
| Drinking history (Yes vs. No)    | 1.01(0.62,1.63)     | 0.977                 | -                    | -   |
| Preoperative diabetes (Yes vs. No) | 0.820.5,1.33       | 0.414                 | -                    | -   |
| Tumor location (Head vs. Body or tail) | 1.33(0.87,2.02) | 0.183                 | -                    | -   |
| Elevated CA199 (Yes vs. No)      | 1(1.1)              | 0.304                 | -                    | -   |
| Histological grade (G2 vs. G1)   | 1.08(0.6,1.97)      | 0.792                 | -                    | -   |
| Histological grade (G3 vs. G1)   | 1.52(0.83,2.77)     | 0.177                 | -                    | -   |
| Lymphovascular invasion (Yes vs. No/unknown) | 1.35(0.89,2.07) | 0.163                 | -                    | -   |
| Perineural invasion (Yes vs. No/unknown) | 1.27(0.78,2.05) | 0.336                 | -                    | -   |
| Resection margin (R1 vs. R0)     | 2.5(1.56,4.02)      | <0.001                | 2.54(1.57,4.11)      | <0.001 |
| TNM stage (II vs. I)             | 1.62(1.01,2.59)     | 0.045                 | 1.66(1.03,2.67)      | 0.036 |
| TNM stage (III vs. I)            | 1.92(0.97,3.82)     | 0.062                 | 1.7(0.85,3.39)       | 0.13  |
| Adjuvant radiotherapy (Yes vs. No) | 0.78(0.32,1.92)    | 0.586                 | -                    | -   |
| Gap between chemotherapy initiation and surgery/days | 0.99(0.97,1) | 0.124                 | -                    | -   |
| Regimen (GS vs. S-1)             | 0.81(0.53,1.24)     | 0.338                 | -                    | -   |

Fig. 2. Forest plot of the treatment effect on disease-free survival (A) and overall survival (B) in selected subgroups.

Discussion

More than one-quarter of all new pancreatic cancer-related diagnoses and deaths occur in China, making it the country most affected by the disease [15, 16]. Adjuvant chemotherapy has been repeatedly shown to improve prognosis in patients with resected PDAC, but the optimal adjuvant chemotherapy regimen for PDAC remains controversial [17]. The PRODIGE24 trial reported the longest survival outcome in pancreatic cancer patients who received adjuvant mFOLFIRINOX (oxaliplatin, irinotecan, leucovorin, and fluorouracil) regimen following surgery, but with a higher incidence of AEs, particularly neutropenia and diarrhea [8]. Therefore, mFOLFIRINOX is regarded as the best adjuvant regimen in very fit and well-selected patients [18]. Notably, some meta-analyses argued that S-1 adjuvant chemotherapy provides DFS and OS similar to or better than mFOLFIRINOX, and S-1 is better for overall and hematologic grade 3 or 4 toxicities [11, 19]. Considering that S-1 and gemcitabine are both standard regimens for adjuvant chemotherapy in resected PDAC, and that the GS regimen (gemcitabine plus S-1) has shown promising effects in advanced PDAC [20], we compared the efficacy and safety of adjuvant GS and S-1 monotherapy for PDAC.

In this study, we included 241 patients who underwent curative-intent surgery, and found that patients treated with GS were younger, but chemotherapy began later. This may be because the GS regimen is usually administered after hospitalization, which leads to a slight delay in the start time of chemotherapy. Moreover, with highly selected patients, the completion rate of chemotherapy in clinical trials ranges from 54 to 79% [21]. We reported a similar completion rate of chemotherapy, but those...
of GS were lower than those of S-1 monotherapy. The JASPAC 01 trial showed the median DFS and OS in patients with PDAC receiving curative-intent surgery and adjuvant S-1 monotherapy were 22.9 and 46.5 months [4], whereas median DFS and OS in another trial using the GS regimen as adjuvant chemotherapy were 23.8 and 35.4 months, respectively [10]. In unresectable pancreatic cancer, the GEST trial demonstrated a non-inferior survival outcome of S-1 to GS in the first-line setting [20]. Likewise, our result suggested that the median DFS (15.1 versus 15.9 months, \( p = 0.52 \)) and OS (34.8 versus 27.1 months, \( p = 0.34 \)) were comparable between the GS and S-1 groups, even after adjustment for the impact of confounding factors using PSM. Furthermore, the safety profiles of GS and S-1 chemotherapy in this study are consistent with those reported in previous studies [4, 20]. Notably, the incidence of neutropenia in the patients receiving adjuvant GS was higher than that in the S-1 group. Intriguingly, subgroup analyses showed that patients with smoking history, positive LVI, or stage I PDAC receiving adjuvant GS chemotherapy achieved better OS than those treated with S-1 monotherapy, suggesting adjuvant GS regimen may be advisable in selected and fit patients with resected PDAC.

The role of adjuvant radiotherapy in patients with PDAC after surgery remains controversial. The ESPAC-1 trial suggested adjuvant radiotherapy might even be harmful [22]. Nevertheless, the RTOG 9704 trial demonstrated that patients treated with chemoradiotherapy followed by chemotherapy had a lower local recurrence rate than those receiving chemotherapy alone [11]. Furthermore, a study based on National Cancer Database showed that patients with R0 resection of node-positive PDAC could benefit from adjuvant radiotherapy [23]. The meta-analysis involving 5 randomized trials concluded that adjuvant chemoradiotherapy provides survival benefits in patients with R1 resection [24]. Regrettably, in our study, radiotherapy was mainly conducted (13/18, 72.2%) in patients undergoing R1 resection, and due to limited sample size, the prognostic effects of radiotherapy could not be analyzed separately in patients with different resection margin statuses. Intriguingly, a previous retrospective study at our institution included 266 PDAC patients with a node-positive disease or R1 resection and found that adjuvant chemotherapy followed by chemoradiotherapy was associated with prolonged OS and lower local recurrence rate compared to chemotherapy alone (HR 0.284, \( p = 0.014 \)) [25].

Our results suggested that the adjuvant chemotherapy regimen (GS or S-1) had no significant effect on prognosis. We also noticed that elevated CA199 and R1 resection indicated poor DFS in patients with resected PDAC, and smoking history, resection margin, and TNM stage were associated with OS. However, the factors that influence survival after surgery in patients with PDAC are also controversial. For example, the ESPAC-1 trial reported that current smoking, R1 resection, and node-positive disease indicated worse OS [22], whereas the CONKO-001 trial and other studies showed lymph node metastasis was associated with DFS and OS, but resection margin was not [5, 26]. In contrast, most studies support CA199 level and tumor stage as prognostic indicators for patients with PDAC [6, 27, 28]. Furthermore, gene expression (such as MLH1) and circulating tumor DNA as prognostic factors of chemotherapy also deserve further exploration [29, 30].

To the best of our knowledge, this is the first study to compare the efficacy and safety of GS with S-1 in patients with resected PDAC in the adjuvant setting. Unexpectedly, the addition of gemcitabine to S-1 did not confer more survival benefits but increased toxicity. Our study adds to novel evidence supporting the use of S-1, rather than GS, in patients with resected PDAC as adjuvant chemotherapy. However, this study has some limitations.

Fig. 3. Kaplan-Meier curves of disease-free survival and overall survival in patients treated with adjuvant gemcitabine plus S-1 and S-1 monotherapy after excluding patients with stage IA (A, B) or nodal-negative (C, D) pancreatic ductal adenocarcinoma.
First, inherent selection bias cannot be eliminated due to the retrospective nature. Moreover, the incidence of AEs might be affected by monitoring bias. Second, we failed to analyze the effect of gene mutation profiles or expression levels on tumor prognosis. Third, similar to the JASPAC 01 trial, our study was conducted on the Chinese population. Given the pharmacokinetics and pharmadynamics of S-1 [31], the results of our study may cannot be generalizable to Caucasian patients.

**Conclusion**

In summary, the results of this study suggested that adjuvant S-1 monotherapy demonstrated noninferiority to the GS regimen in DFS and OS, with a lower incidence of neutropenia. Further prospective studies are warranted to determine the optimal adjuvant chemotherapy regimen for patients with resected PDAC.

**Ethics approval and consent to participate**

This study was approved by the Medical Ethics Committee of Peking Union Medical College Hospital (S-K2099) and carried out following the Helsinki Declaration on experimentation involving human subjects. Consent to participate and publication were not required due to the retrospective design and the anonymization of data.

**Consent for publication**

Not applicable.

**Availability of data and materials**

All inquiries can be directed to the corresponding authors.

**Authors’ contributions**

HT, YW conceived the research. HT and CQ carried out literature search. HT, JL, YC, DH, TZ, and JG conducted data collection and analysis. HT and CQ participated in data visualization. HT and YW drafted the manuscript, and YC, CB and YW reviewed the manuscript. All authors read and approved the submitted version.

**Competing interests**

The authors declare that no competing interest exists.

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