Acta Med. Okayama, 2025
Vol. 79, No. 2, pp. 81–92

Acta Medica Okayama
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Original Article

Clinical Outcomes of Neoadjuvant Paclitaxel/Cisplatin/Gemcitabine Compared with Gemcitabine/Cisplatin for Muscle-Invasive Bladder Cancer

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We retrospectively evaluated the oncologic outcomes of paclitaxel, cisplatin, and gemcitabine (PCG) with those of gemcitabine and cisplatin (GC) as neoadjuvant chemotherapy in muscle-invasive bladder cancer (MIBC) patients. The primary outcome was efficacy: pathological complete response (pCR), ypT0N0; and pathological objective response (pOR), ypT0N0, ≤ypT1N0, or ypT0N1. Secondary outcomes included overall survival (OS), recurrence-free survival (RFS), predictive factors for pOR, OS, and RFS, and hematologic adverse events (AEs). Among 113 patients treated (PCG, n = 28; GC, n = 85), similar pOR and pCR rates were achieved by the groups (pOR: PCG, 57.1% vs. GC, 49. 4%; $p = 0.52$; pCR: PCG, 39.3% vs. GC, 29.4%; $p = 0.36$). No significant differences were observed in OS ($p = 1.0$) or RFS ($p = 0.20$). Multivariate logistic regression analysis showed that hydronephrosis (odds ratio [OR] 0.32, 95%CI: 0.11-0.92) and clinical node-positive status (cN+) (OR 0.22, 95%CI: 0.050-0.99) were significantly associated with a decreased probability of pOR. On multivariate Cox regression analyses, pOR achievement was associated with improved OS (hazard ratio [HR] 0.23, 95%CI: 0.10-0.56) and RFS (HR 0.30, 95%CI: 0.13-0.67). There were no significant between-group differences in the incidence of grade ≥ 3 hematologic AEs or dose-reduction required, but the PCG group had a higher incidence of grade 4 neutropenia.

Key words: urothelial carcinoma, paclitaxel, cisplatin, gemcitabine, neoadjuvant

Bladder cancer (BC) is the second most common urologic cancer (Lenis *et al.*, 2020). The mainstay of treatment for patients with muscle-invasive bladder cancer (MIBC) is a radical cystectomy (RC) with lymph node dissection, which is often preceded by neoadjuvant chemotherapy (NAC) (Witjes *et al.*, 2021). Historically, since the SWOG 8710 randomized phase III trial demonstrated that the median overall survival (OS) of its MVAC (methotrexate, vinblastine, adriamycin, and cisplatin) + cystectomy patient group was 77 months compared to 46 months in the cystectomy group ($p = 0.06$) (Grossman *et al.*, 2003), MVAC has been recommended as the standard of care NAC (*Neoadjuvant chemotherapy in invasive bladder cancer: update of a systematic review and meta-analysis of individual patient data advanced bladder cancer (ABC) meta-analysis collaboration*, 2005, Yin *et al.*, 2016, Galsky *et al.*, 2015).

Received April 15, 2024; accepted December 2, 2024.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

A later phase III trial compared the efficacy and safety outcomes of gemcitabine/cisplatin (GC) with those of MVAC, and the results showed comparable efficacy and better safety outcomes in the GC group (von der Maase *et al.*, 2000). The VESPER trial has demonstrated that the group of patients treated with dose-dense MVAC had a higher pathological complete response (pCR) rate but also a higher rate of severe adverse events compared to the GC group (Pfister *et al.*, 2021). However, due to the limited number of comparative studies evaluating the efficacy, tolerability, and cost-effectiveness of various NAC regimens, the optimal NAC regimen for patients with MIBC remains a matter of debate.

The first-line triplet regimen of paclitaxel, cisplatin, and gemcitabine (PCG) for advanced bladder cancer (BC) was reported in the randomized phase III study EORTC 30987 by Bellmunt *et al.* (Bellmunt *et al.*, 2000, Bellmunt *et al.*, 2012). In that study's intention-to-treat (ITT) population, the PCG group did not demonstrate significant differences in OS (hazard ratio [HR] 0.85, 95% confidence interval [CI]: 0.72-1.02, $p=0.075$) or progression-free survival (PFS) (HR 0.87, 95%CI: 0.74-1.03, $p=0.113$) compared to the GC group (Bellmunt *et al.*, 2012). However, in the eligible patient population with histologically confirmed stage IV locally advanced or metastatic urothelial carcinoma, the PCG group exhibited significantly improved OS (HR 0.82, 95%CI: 0.68-0.98, $p=0.03$) and a significantly higher objective response rate (55.5% vs. 43.6%, $p=0.0031$) compared to the GC group. Nevertheless, evidence supporting the use of PCG in a neoadjuvant setting for BC has not been reported. We thus conducted the present study to evaluate the efficacy and tolerability of PCG in a neoadjuvant setting.

Patients and Methods

Patient selection. We identified 145 consecutive patients with histologically confirmed MIBC or high-risk non-muscle invasive bladder cancer (NMIBC) (cT1-4 and/or N1-3 and M0) who were treated with PCG at Okayama University Hospital or with GC at Hiroshima Citizens Hospital as NAC during the period from January 2012 to December 2020. We excluded patients who had been treated with regimens other than GC and PCG, whose treatment was changed from PCG to GC during their NAC, or who had concomitant upper urothelial carcinoma, high-risk NMIBC, or insufficient medical records regarding chemotherapy. We also excluded patients with visceral metastases or who were not eligible for NAC due to reasons such as severe chronic kidney disease (CKD) or poor performance status. The cases of the final total of 113 patients (PCG, n=28; GC, n=85) were retrospectively analyzed. This study was approved by the Institutional Review Board of Okayama University Hospital (Registration no. 2208-044).

Treatments. The PCG regimen consisted of 80 mg/m^2 paclitaxel and 1,000 mg/m^2 gemcitabine on days 1 and 8, and 70 mg/m^2 cisplatin every 28 days. The GC regimen consisted of 1,000 mg/m^2 gemcitabine on days 1, 8, and 15 and 70 mg/m^2 cisplatin on day 1. The cisplatin doses were adjusted by creatinine clearance (Ccr) based on the patient's 24-h Ccr or with the Cockcroft-Gault equation, estimated glomerular filtration rate (eGFR), or previous toxicity. In general, the cisplatin dose reduction criteria were as follows: when the Ccr or eGFR was 45-60 mL/min/1.73m^2, the dose was reduced to 75% of the initial dose; when the Ccr or eGFR was 30-45 mL/min/1.73m^2, the dose was reduced to 50% of the initial dose, and when the Ccr or eGFR was <30 mL/min/1.73m^2, the use of cisplatin was halted. However, the final decisions on dosing, including the number of cycles, were made at the treating physicians' discretion, accounting for the patient's general condition and tolerability to previous chemotherapy.

The radical cystectomy (RC) with an extensive pelvic lymphadenectomy included the obturator, external iliac, internal iliac, and distal primary iliac regions in general; however, some patients underwent a limited lymphadenectomy or no lymphadenectomy, in accord with their general condition.

Patient evaluation. We obtained patient characteristics (age, gender, tobacco smoking status, clinical stage of the tumor) and treatment characteristics (dose and number of cycles of chemotherapy, pathological characteristics after RC) from their medical records. Data regarding chemotherapy-related toxicity, specifically hematologic toxicity, were also extracted. The patients' responses to the NAC were assessed from the final pathological result from the RC. A pCR was defined as no evidence of residual tumor (ypT0N0), and a pathological objective response (pOR) was defined as the absence of residual muscle-invasive cancer and pathological lymph nodes (ypT0N0, $\leq$ypT1N0, or ypT0N1). Progression was defined as radiographic pro-

gression based on the Response Evaluation Criteria in Solid Tumors (RECIST), ver. 1.1. Adverse events (AEs) were assessed with the Common Terminology Criteria for Adverse Events (CTCAE) ver. 5.0.

Statistical analysis. The study endpoints were oncological and safety outcomes including the pCR, OS, RFS, and AE values. Overall survival was defined as the length of time from the RC to the date of any cause of death, and RFS was defined as the length of time from the RC to the date of recurrence or death. Patient and tumor characteristics are presented as the median with the interquartile range (IQR) for continuous variables and as the number (percentage) for categorical variables. Differences between the PCG and GC regimens were analyzed with the χ^2-test or Mann-Whitney *U*-test. Kaplan-Meier curves were applied to estimate the OS and RFS, and the log-rank test was used to examine survival differences between the PCG- and GC-treated patient groups.

We conducted univariate and multivariate logistic regression analyses to evaluate the association of clinical factors with the pCR and pOR values. Univariate and multivariate Cox hazard regression analyses were performed to evaluate the association of tumor status with OS and RFS. We conducted propensity score-matching and subgroup analyses to minimize the bias arising from differing patient demographics between the groups. In the propensity score-matching, all patients were matched 2 : 1 with the nearest neighbor propensity score. We used a caliper size 0.2 times the standard deviation of the logistic regression model of the propensity scores. After matching, Pearson's exact χ^2-test and Fisher's exact test were used to evaluate the efficacy outcomes with pCR and pOR, and Kaplan-Meier curves and log-rank tests were applied for survival outcomes analyses. The results were considered significant at $p < 0.05$. The statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, EZR is a modified version of R commander designed to add statistical functions that are frequently used in biostatistics.

Results

Patient and tumor characteristics. We analyzed the cases of 28 patients treated with PCG at Okayama University Hospital and 85 patients treated with GC at Hiroshima Citizens Hospital. The patients' characteristics, including pre- and post-operative status, are summarized in Table 1. The median age was 69.0 years for both groups. Male predominance was present in both groups. There were significant between-group differences in clinical node-positive status (PCG, 25.0%; GC, 8.2%; $p = 0.041$) and in the proportion of patients receiving more than three cycles of chemotherapy (PCG, 57.1%; GC, 12.9%; $p < 0.001$). Post-operatively, the PCG group had a significantly higher rate of pathological node-positive status (PCG, 37.0%; GC, 10.8%; $p = 0.003$) and positive surgical margin status (PCG, 10.7%; GC, 1.2%; $p = 0.043$). In contrast, the proportion of patients receiving adjuvant chemotherapy was significantly higher in the GC group compared to the PCG group (GC, 23.5%; PCG, 3.6%; p=0.023).

Efficacy analyses. As shown in Fig. 1, the pCR rate was 39.3% in the PCG group and 29.4% in the GC group ($p = 0.36$), and a pOR was achieved in 57.1% of the patients in the PCG group and 49.4% in the GC group ($p = 0.52$). Table 2 presents the results of the univariate and multivariate analyses of predictive factors for pOR. The NAC regimen was not associated with predicting pOR (odds ratio [OR] 2.0, 95%CI: 0.72-5.85; $p = 0.18$), but the presence of hydronephrosis (OR 0.32, 95%CI: 0.11-0.92; $p = 0.035$) and clinical node-positive status (OR 0.22, 95%CI: 0.05-0.99; $p = 0.049$) were independent predictors for pOR.

Survival outcomes. The median follow-up period was 22.0 months (IQR: 10.0, 39.5) in the PCG group and 39.0 months (IQR: 15.0, 75.0) in the GC group. Twelve (42.9%) patients in the PCG group and 30 (35.3%) patients in the GC group experienced cancer recurrence. The median OS and RFS were not reached in either group; the OS and RFS rates at 24 months were 80.8% (95%CI: 59.7-91.5%) and 53.9% (95%CI: 33.1-70.8%) respectively in the PCG group, and 74.7% (95%CI: 63.5-82.9%) and 66.3% (95%CI: 54.7-75.5%) respectively in the GC group. There were no significant between-group differences in OS (log-rank $p = 0.98$) or RFS (log-rank $p = 0.19$) (Fig. 2).

We conducted univariate and multivariate Cox regression analyses of predictive factors for OS and RFS based on the clinical data, including post-operative status (Table 3). The NAC regimen was not associated with predicting OS (HR 0.74, 95%CI: 0.29-1.86; $p = 0.52$) or RFS (HR 0.84, 95%CI: 0.39-1.83; $p = 0.67$).

Table 1 Patient demographics

	PCG	GC	*P*-value
	n=28	n=85	
Age (median, IQR)	69.0 (62.0, 72.0)	69.0 (63.0, 73.0)	0.45
Sex (%)			0.80
Male	21 (75.0)	66 (77.6)	
Female	7 (25.0)	19 (22.4)	
Smoking history (%)	17 (60.7)	56 (65.9)	0.65
Hydronephrosis (%)	9 (32.1)	15 (17.6)	0.12
BCG history (%)	5 (17.9)	10 (11.8)	0.52
cT (%)			0.39
cT2	16 (57.1)	40 (47.1)	
≥cT3	12 (42.9)	47 (52.9)	
cN+ (%)	7 (25.0)	7 (8.2)	0.041
Cycle (%)			<0.001
≤2	12 (42.9)	74 (89.2)	
≥3	16 (57.1)	11 (12.9)	
Surgical procedure			<0.001
Open (%)	3 (10.7)	67 (78.8)	
LRC (%)	6 (21.4)	0	
RARC (%)	19 (67.9)	18 (21.2)	
pT (%)			0.39
pT≥2	17 (60.7)	43 (50.6)	
pT<2	11 (39.3)	42 (49.4)	
pN+ (%)	10 (37.0)	9 (10.8)	0.003
Variant (%)	5 (17.9)	16 (18.8)	1.000
PSM (%)	3 (10.7)	1 (1.2)	0.043
No. of LND (median, IQR)	17.5 (10.8–22.8)	14.0 (9.0–20.0)	0.30
Adjuvant chemotherapy (%)	1 (3.6)	20 (23.5)	0.023
F/U period (months) (median, IQR)	22.0 (10.0, 39.5)	39.0 (15.0, 75.0)	0.040

PCG, Paclitaxel/Cisplatin/Gemcitabine; GC, Gemcitabine/Cisplatin; IQR, Interquartile range; BCG, Bacille Calmette-Guerin; LRC, laparoscopic radical cystectomy; RARC, Robot-assisted radical cystectomy; PSM, Positive surgical margin; LND, lymph node dissection.

In contrast, pOR (HR 0.23, 95%CI: 0.10-0.56; $p<0.01$) was an independent predictor of OS. The independent predictors of RFS were positive surgical margin status (HR 5.73, 95%CI: 1.59-20.7; $p<0.01$), pathological node-positive status (HR 3.03, 95%CI: 1.47-6.27; $p<0.01$), and pOR (HR 0.30, 95%CI: 0.13-0.67; $p<0.01$).

We performed subgroup analyses of the patients' 2-year OS and RFS rates after stratifying the patients according to their cycle number (≤2 and ≥3), pathological lymph node status, *i.e.*, pN(+) and pN(−), and adjuvant chemotherapy status (with and without). No significant differences between the PCG and GC groups were observed in any of the subgroup analyses (Fig. 3).

Propensity score-matching analyses for efficacy and survival outcomes. Patient characteristics before NAC such as age, sex, clinical stage, hydronephrosis, and Bacillus Calmette Guerin (BCG) treatment history were adjusted using propensity score-matching. Table 4 summarizes the patient demographics after the matching.

Efficacy outcomes. The pCR rate was 47.6% in the PCG group and 33.3% in the GC group ($p=0.29$). A pOR was achieved by 61.9% of the PCG group and 52.4% of the GC group ($p=0.59$) (Fig. 4).

Survival outcomes. The median follow-up period was 22.0 months (IQR: 10.0, 35.0) in the PCG group and 46.0 months (IQR: 18.5, 76.8) months in the GC group. Eight (38.1%) of the PCG-treated patients and 11 (26.2%) of the GC-treated patients experienced cancer recurrence. The median OS and RFS were not reached in either group; the OS and RFS rates at 24 months were 78.7% (95%CI: 52.4-91.5%) and 57.6% (95%CI: 32.4-76.3%) respectively in the PCG group and 82.3% (95%CI: 66.3-91.1%) and 77.7% (95%CI:

	PCG	GC	*P*-value
pCR	11/28 (39.3%)	25/85 (29.4%)	0.36
pPR	5/28 (17.9%)	17/85 (20.0%)	1.00
pOR	16/28 (57.1%)	42/85 (49.4%)	0.52

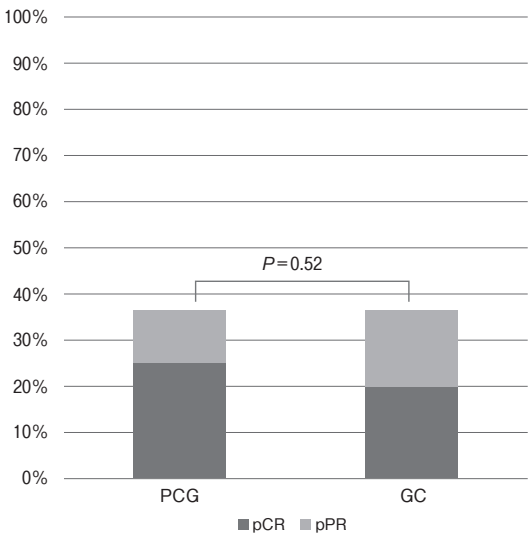

Fig. 1 The efficacy of paclitaxel, cisplatin, and gemcitabine (PCG) and gemcitabine and cisplatin (GC) in the neoadjuvant chemotherapy (NAC) setting in patients with muscle-invasive bladder cancer (MIBC).

Table 2 Univariate and multivariate analyses of predictive factors for pathological objective response (pOR)

	Univariate		Multivariate	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Age (continuous)	0.94 (0.89–0.99)	0.023	0.952 (0.90–1.01)	0.088
Male (Ref. Female)	2.44 (0.98–6.07)	0.056		
Smoking status	1.27 (0.59–2.74)	0.55		
Hydronephrosis	0.31 (0.12–0.81)	0.018	0.32 (0.11–0.92)	0.035
BCG history	0.59 (0.20–1.78)	0.35		
≥cT3 (Ref. cT2)	0.47 (0.22–1.00)	0.049	0.57 (0.25–1.28)	0.17
cN+ (Ref. cN−)	0.22 (0.057–0.83)	0.026	0.22 (0.050–0.99)	0.049
≥3 Cycle (Ref. ≤2)	0.85 (0.36–2.01)	0.71		
PCG (Ref. GC)	1.37 (0.58–3.23)	0.48	2.01 (0.72–5.85)	0.18

pOR, pathological objective response (ypT0N0 or ypT≤1N0 or ypT0N1); PCG, Paclitaxel/Cisplatin/Gemcitabine; GC, Gemcitabine/Cisplatin; BCG, Bacille Calmette-Guerin; OR, odds ratio.

61.5-87.7%) respectively in the GC group. As illustrated in Fig. 5, there were no significant between-group differences in OS (log-rank $p=0.47$) or RFS (log-rank $p=0.14$).

Adverse events. Overall, there were no significant differences in the incidence of CTCAE grade ≥3 hematologic AEs between the PCG and GC groups (78.6% vs. 65.9%, respectively). However, the incidence of grade 4 neutropenia was higher in the PCG group than in the GC group. The details of the hematologic AEs are summarized in Fig. 6. No significant differences between groups were identified in the proportion of patients who required a dose reduction due to AEs (Fig. 6).

Discussion

NAC has been a standard treatment strategy for patients with MIBC since the establishment of level I evidence for neoadjuvant MVAC for patients with MIBC prior to RC was established (Grossman *et al.*, 2003). Various regimens have been explored as NAC for

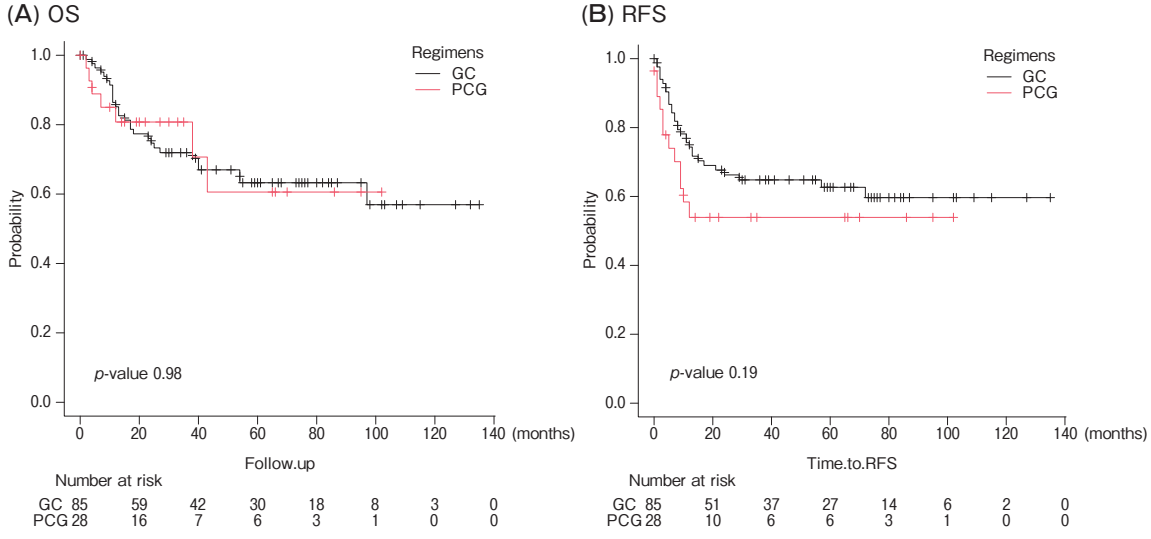

Fig. 2 Oncological outcomes comparing PCG and GC as NAC in patients with MIBC.

Table 3 Univariate and multivariate analyses of predictive factors for survival outcomes

	OS				RFS			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (continuous)	1.035 (0.99–1.09)	0.17			1.01 (0.97–1.06)	0.55		
Male (Ref. Female)	0.86 (0.40–1.83)	0.69			0.70 (0.36–1.37)	0.30		
Smoking status	0.95 (0.48–1.89)	0.88			0.71 (0.39–1.32)	0.28		
Hydronephrosis	1.99 (0.95–4.18)	0.069			2.48 (1.30–4.74)	<0.01	1.75 (0.86–3.57)	0.12
BCG history	2.45 (1.05–5.68)	0.037	2.06 (0.87–4.90)	0.101	3.0 (1.47–6.15)	<0.01	2.02 (0.92–4.46)	0.081
PSM	2.59 (0.62–10.8)	0.19			3.52 (1.09–11.4)	0.036	5.73 (1.59–20.7)	<0.01
pN+	3.13 (1.51–6.47)	<0.01	1.87 (0.82–4.27)	0.14	5.04 (2.64–9.60)	<0.01	3.03 (1.47–6.27)	<0.01
pOR	0.184 (0.079–0.42)	<0.01	0.23 (0.10–0.56)	<0.01	0.19 (0.089–0.39)	<0.01	0.30 (0.13–0.67)	<0.01
PCG (Ref. GC)	0.99 (0.43–2.28)	0.98	0.74 (0.29–1.86)	0.52	1.56 (0.79–3.04)	0.20	0.84 (0.39–1.83)	0.67

PCG, Paclitaxel/Cisplatin/Gemcitabine; GC, Gemcitabine/Cisplatin; OS, Overall survival; RFS, Recurrence-free survival; HR, hazard ratio; CI, confidential interval; BCG, Bacille Calmette-Guerin; PSM, Positive surgical margin; pOR, pathological objective response (ypT0N0 or ypT≤1N0 or ypT0N1).

MIBC from both efficacy and safety perspectives, but the optimal regimen remains uncertain. We conducted the present study to compare the efficacy and safety outcomes of PCG and GC in a neoadjuvant setting in patients with MIBC. Our analyses revealed no significant differences in the rates of pCR, pOR, or OS between the patients treated with PCG and those treated with GC. In the safety analysis, PCG was not associated with a higher incidence of CTCAE grade ≥3 hematologic AEs compared to GC.

Historically, paclitaxel has been among the most frequently used taxane agents for patients with advanced urothelial cancer (aUC) (Roth *et al.*, 1994), and as a result, combination strategies incorporating taxane agents have been extensively researched (Terakawa *et al.*, 2014, Vaishampayan *et al.*, 2005, Suyama *et al.*, 2009, Kanai *et al.*, 2008, Kaya *et al.*, 2012). Based on the results of a phase III trial, our research group has highlighted the utility of PCG as a first-line therapy (Katayama *et al.*, 2021) and as a salvage therapy after first-line therapy (Hirata *et al.*, 2018) for patients with aUC. In accord with the results of the phase III trial in the first-line setting in patients with advanced BC (Bellmunt *et al.*, 2012), our present analyses revealed

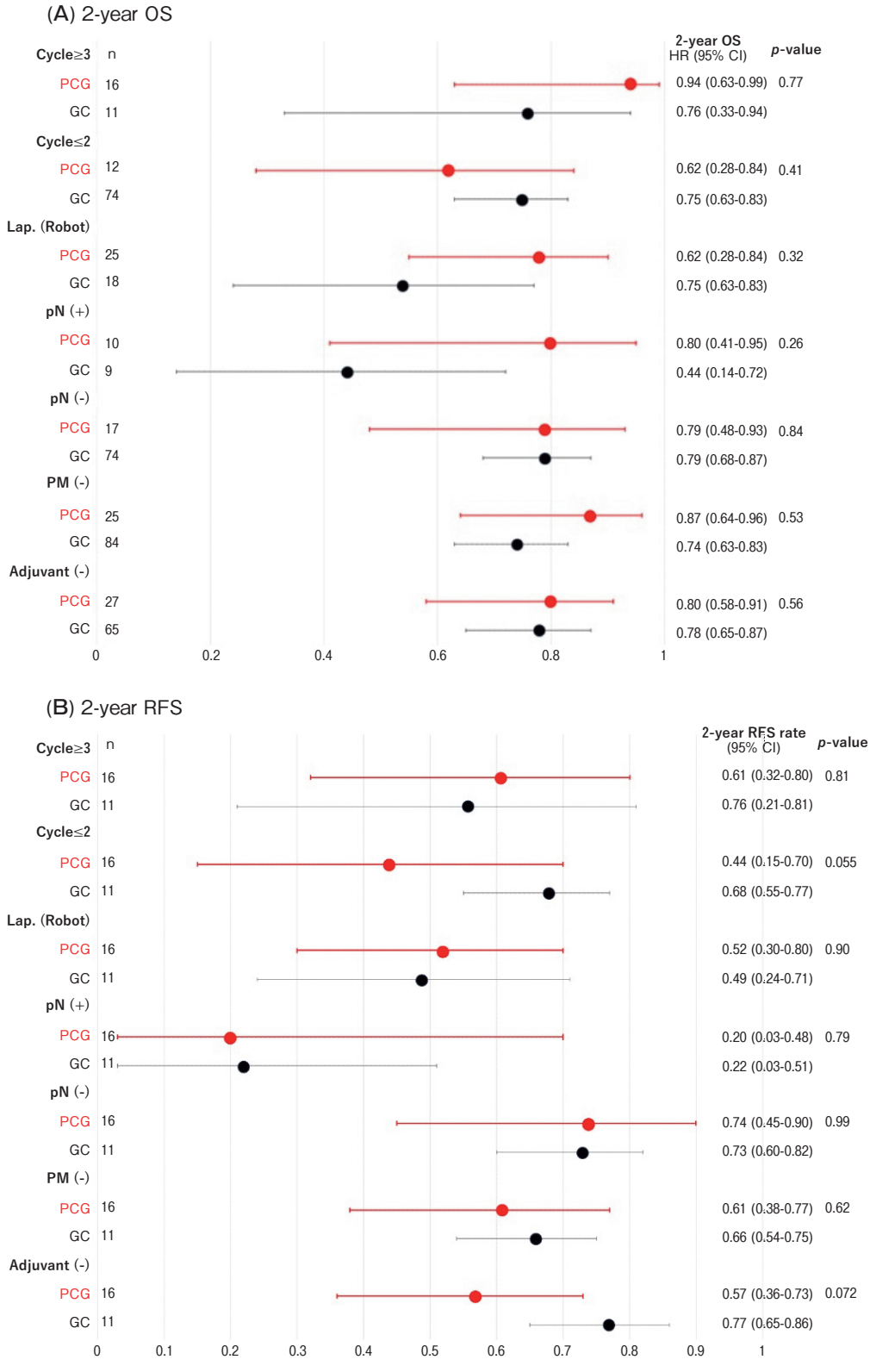

Fig. 3 Subgroup analyses for (A) 2-year overall survival (OS) and (B) 2-year recurrence-free survival (RFS).

Table 4 Patient characteristics after the propensity score-matching

	PCG	GC	*P*-value
	n=21	n=42	
Age (median, IQR)	69.0 (62.0, 70.0)	67.0 (61.0, 71.8)	0.77
Sex (%)			0.75
Male	16 (76.2)	34 (81.0)	
Female	5 (23.8)	8 (19.0)	
Smoking history (%)	14 (66.7)	31 (73.8)	0.57
Hydronephrosis (%)	5 (23.8)	9 (21.4)	1.0
BCG history (%)	2 (9.5)	6 (14.3)	0.71
cT (%)			1.0
cT2	11 (52.4)	23 (54.8)	
≥cT3	10 (47.6)	19 (45.2)	
cN+ (%)	2 (9.5)	4 (9.5)	1.0
Cycle (%)			<0.001
≤2	9 (42.9)	36 (85.7)	
≥3	12 (57.1)	6 (14.3)	
Surgical procedure			<0.001
Open (%)	1 (4.8)	33 (78.6)	
LRC (%)	6 (28.6)	0	
RARC (%)	14 (66.7)	9 (21.4)	
pT (%)			0.59
pT ≥2	8 (38.1)	20 (47.6)	
pT <2	13 (61.9)	22 (52.4)	
pN+ (%)	7 (35.0)	9 (21.4)	0.003
Variant (%)	4 (19.0)	10 (23.8)	0.76
PSM (%)	2 (9.5)	1 (2.4)	0.26
No. of LND (median, IQR)	17.0 (11.0–21.0)	14.5 (9.0–20.8)	0.37
Adjuvant chemotherapy (%)	1 (4.8)	7 (16.7)	0.25
F/U period (months) (median, IQR)	20.0 (10.0, 35.0)	46.0 (18.5, 76.8)	0.022

PCG, Paclitaxel/Cisplatin/Gemcitabine; GC, Gemcitabine/Cisplatin; IQR, Interquartile range; BCG, Bacille Calmette-Guerin; LRC, laparoscopic radical cystectomy; RARC, Robot-assisted radical cystectomy; PSM, Positive surgical margin; LND, lymph node dissection.

	PCG	GC	*P*-value
pCR	10/21 (47.6%)	14/42 (33.3%)	0.29
pPR	3/21 (17.9%)	8/42 (20.0%)	0.74
pOR	13/21 (61.9%)	22/42 (49.4%)	0.59

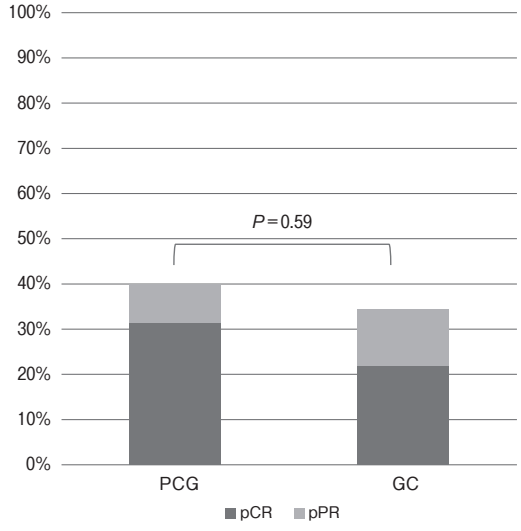

Fig. 4 Efficacy analyses after the propensity score-matching.

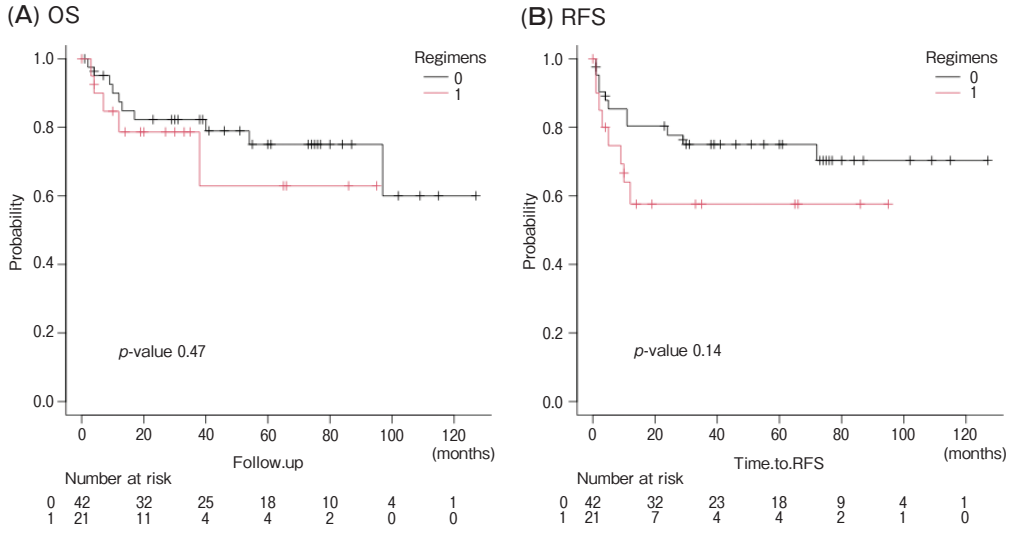

Fig. 5 Survival outcomes after the propensity score-matching.

(A) Hematological AEs

	PCG		GC	
	Grade III	Grade IV	Grade III	Grade IV
Neutropenia	7 (25.0%)	14 (50.0%)	25 (29.4%)	10 (11.7%)
Febrile neutropenia	5 (17.9%)	1 (3.6%)	6 (7.1%)	1 (1.2%)
Thrombocytopenia	6 (21.4%)	1 (3.6%)	23 (27.1%)	3 (3.5%)
Anemia	0	0	5 (5.9%)	0
Renal toxicity	0	0	0	0
Hepatic toxicity	1 (3.6%)	0	0	0

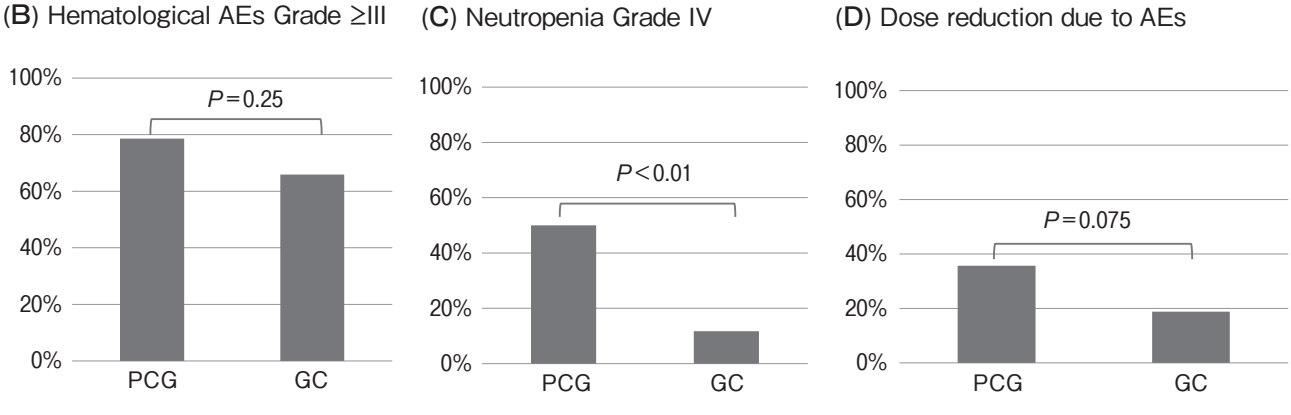

Fig. 6 Safety outcomes comparing PCG and GC as NAC in patients with MIBC.

no significant differences in efficacy between PCG and GC in the NAC setting for patients with MIBC (pCR: PCG, 39.3% and GC, 29.4%, $p=0.36$; and pOR: PCG, 57.1% and GC, 49.4%, $p=0.52$). Notably, the pCR rate afforded by the GC regimen in our patient population was lower than that in the phase III trial (GC, 36% and dose-dense [dd]MVAC, 42%). Although these results cannot be compared directly due to the different set-

tings and regimens, a potential reason for the lower pCR rate in our study is our inclusion of more patients with ≥ cT3 stage disease and lymph node-positive status.

In addition to the non-negligible complications during NAC, some clinical features raise questions regarding which patients would be good candidates for NAC. Few studies have assessed predictive and prognostic clinicopathological features in patients treated with NAC followed by an RC, and they have obtained differing results (D'Andrea *et al.*, 2020, Gild *et al.*, 2020, Pokuri *et al.*, 2016, Soria *et al.*, 2021, Ravi *et al.*, 2021). Our present findings demonstrate that the presence of hydronephrosis and clinical lymph node-positive status were independent predictive factors for a decreased probability of pOR in our patient population, with significant implications regarding clinical decision-making and patient counseling. Given that pOR and pCR have been considered surrogate markers for survival outcomes (Petrelli *et al.*, 2014, Peyton *et al.*, 2018, Ravi *et al.*, 2021), in light of our present findings, patients with advanced features including hydronephrosis and clinical lymph node-positive status should receive preoperative counseling.

Tolerability is one of the most important elements for considering an optimal regimen for NAC. Despite no high-level evidence supporting NAC with GC, NAC with GC has been widely adopted after the non-inferiority phase III trial in the aUC setting which reported that GC was associated with less toxicity without compromising the survival benefit (von der Maase *et al.*, 2000). In the present study, which showed relatively high frequencies of AEs compared to earlier international studies (Bellmunt *et al.*, 2012, Griffiths *et al.*, 2011, Yuh *et al.*, 2013), possibly due to ethnic differences in drug toxicity (O'Donnell & Dolan, 2009), there were no significant differences in the rate of grade ≥ 3 hematologic AEs between the PCG and GC groups. However, grade 4 neutropenia was more common in the PCG group, similar to the EORTC 30987 trial, which reported more major hematotoxicity (especially neutropenia) in the PCG arm compared to the GC arm. However, there were no significant differences in the rates of dose reduction between the two regimens in our study. A possible explanation for this might be that our patient selection for NAC included patients with better performance status and less comorbidity compared to the late-stage setting.

This report is the first regarding the efficacy and tolerability of PCG in a neoadjuvant setting. However, several study limitations must be addressed. The study population was small and could not be adjusted for patient characteristics. Selection bias is another potential concern because aspects of the treatment strategy such as the dose, the number of chemotherapy sessions, and surgical procedures depends on the treating physicians' discretion. To minimize bias, we carried out subgroup analyses for survival outcomes that stratified the patients according to cycle number, pathological lymph node status, and adjuvant chemotherapy, and we conducted propensity score matching analyses for efficacy and survival outcomes. There were no significant differences between groups, as in the whole cohort analysis. In addition, group bias due to the data from each regimen coming from different hospitals may have reduced the study's statistical power. Lastly, because of the retrospective nature of this study, the toxicity could have been underestimated.

In conclusion, our comparison of PCG with GC for the first time in the NAC setting revealed no significant between-regimen differences in oncologic outcomes but a higher incidence of severe neutropenia in the PCG-treated patients. The use of PCG in NAC settings is worthy of further controlled trials with more patients to confirm its utility.

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